Autorità Garante della Concorrenza e del Mercato

THE AUTHORITY GUARANTEE OF COMPETITION AND THE MARKET

IN ITS MEETING of May 17, 2022;

HEARD the Supervisor Professor Michele Ainis;

GIVEN Article 102 of the Treaty on the Functioning of the European Union (TFEU);

GIVEN the Regulation (EC) n. 1/2003 of the Council of 16 December 2002, concerning the application of the competition rules referred to in articles 81 and 82 of the EC Treaty (today articles 101 and 102 TFEU);

HAVING REGARD to the Communication from the Commission on cooperation within the network of competition authorities of 27 April 2004;

GIVEN the law of 10 October 1990, n. 287;

GIVEN the DPR 30 April 1998, n. 217;

GIVEN its provision no. 27940 of 8 October 2019, with which a proceeding to ascertain the existence of a violation of Article 102 of the TFEU;

GIVEN its provision no. 28325 of 4 August 2020, with which the commitments presented by the companies Essetifin SpA, Leadiant Biosciences SpA, Leadiant Biosciences Ltd., Leadiant GmbH and Sigma-Tau Arzneimittel GmbH in liquidation were rejected;

GIVEN its own provisions n. 28377 of 13 October 2020, n. 29704 of 8 June 2021, n. 29855 of 19 October 2021 and no. 29982 of 8 February 2022 with which the deadline for closing the preliminary proceedings was lastly extended to 20 May 2022, in order to ensure the Parties the widest exercise of the right of defense and to fully guarantee the right to be heard. ;

GIVEN the Communication of the Investigation Results, sent to the Parties on 22 September 2021, pursuant to article 14 of the Presidential Decree of 30 April 1998, no. 217;

GIVEN the final briefs of the companies Essetifin SpA, Leadiant Biosciences Ltd., Leadiant GmbH and Sigma-Tau Arzneimittel GmbH in liquidation, and of Altroconsumo, received on January 28, 2022;

HEARD in the final hearing the representatives of the companies Essetifin SpA, Leadiant Biosciences Ltd., Leadiant GmbH and Sigma-Tau Arzneimittel GmbH in liquidation, and of Altroconsumo, on February 14, 2022;

HAVING REGARD to the proceedings and the documentation acquired during the investigation;

CONSIDERING the following;

I. THE PARTIES

I.1 The reported company

1. Essetifin SpA (formerly Sigma Tau Finanziaria SpA), *holding* of the Leadiant group, is a company that deals with the management of shareholdings and which controls 100% Leadiant Biosciences Ltd., a British company, and Leadiant Biosciences Inc., a company of US law 1 .

[1] The preliminary investigation was also initiated against Leadiant Biosciences SpA, a group company established on January 30, 2017 by Essetifin SpA, which controlled it 100%. Leadiant Biosciences SpA in turn fully controlled Leadiant Biosciences Ltd. and Leadiant Biosciences Inc .. However, on 22 July 2021 Leadiant Biosciences SpA merged by incorporation into Essetifin SpA. As a result of this operation, therefore, Essetifin SpA directly controls, and no longer indirectly, the two English and US companies.

2. Leadiant Biosciences Ltd. is a company active in the market for the production and sale of orphan drugs. Leadiant Biosciences Ltd. is the new company name assumed in December 2016 by Sigma Tau Rare Disease Ltd., a company to which in May 2015, as a result of a more complex sale of the companies and *assets* of the group2, the branches related to the orphan drug business of Sigma Tau Pharmaceuticals Ltd., belonging to the former Sigma Tau3 Group.

3. Leadiant GmbH is a company under German law active in the market for the production and sale of pharmaceuticals, 100% controlled by Leadiant Biosciences Ltd. 4.

4. Sigma Tau Arzneimittel GmbH in liquidation is a company under law German wholly owned subsidiary of Essetifin SpA [5], previously active in market for the production and sale of pharmaceuticals.

5. Essetifin SpA, Leadiant Biosciences Ltd., Leadiant GmbH and Sigma Tau Arzneimittel GmbH in liquidation are therefore part of the same corporate group6 and will later be jointly referred to as "Leadiant" or the "Party" if necessary, except where the specific corporate identity of each of them, or of the companies of the *former* Sigma Tau group of which they are successors, is necessary for the understanding of the facts being ascertained.

The turnover of the Leadiant group in 2021 was equal to *[100-200] ÿ* million EUR.

I.2 The complainant

6. Altroconsumo is a consumer association registered in the list of the most representative associations on the national territory held by the Ministry of Economic Development.

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[2] See the provision of the Authority of 25 March 2015 on case C11988 - Marino Golinelli & c./Sigma tau Financial and other enterprises and parts of enterprises.

[3] See doc. 78,388. Previously, in turn, Sigma Tau Pharmaceutical Ltd. in December 2013 had acquired the business unit relating to orphan drugs as a result of a merger by incorporation of Sigma Tau Rare Disease SA, a company incorporated under Portuguese law, established in 2011 and belonging to the former Sigma Tau group.

[4] See doc. 110.4B.

[5] See doc. 110.4B.

[6] V. Corte Giust., 24 October 1996, in case C-73/95, *Viho v.* European *Commission ;* Court of First Degree, 12 December 2007, in case T-112/05, *Akzo Nobel NV et al. c.* European *Commission .*

[ÿ] In this version, some data are omitted, as elements of confidentiality or secrecy of the information have been deemed to exist.

II. THE INSTRUCTORY PROCEDURE

II.1 The official opening of the investigation file and the subsequent complaint

7. Between the end of August 2018 and the beginning of September 2018, news relating to some events concerning the production and sale of the orphan drug called *Chenodeoxycholic acid Leadiant*® for the treatment were disseminated in the press, both nationally and internationally. of an ultra-rare disease called cerebrotendinous xanthomatosis (CTX) in the Dutch and Italian markets7.

8. As of August 2018 the *Dutch Pharmaceutical Accountability Foundation* (Dutch agency for the surveillance of drug prices) sent a report to the Dutch *antitrust* authority concerning the request by Leadiant Biosciences Ltd. to health insurance companies for payment of a price for the sale of this product equal to approximately 15,300 euros for a pack of 100 capsules of 250 mg. This price was considered absolutely unjustified, especially due to the fact that until then Dutch patients with CTX had been treated in the Netherlands with a drug from Leadiant Biosciences Ltd. containing the same active ingredient, authorized for the treatment of gallstones. and used *off label* for the treatment of rare diseases, sold at a price of about 30 euros per pack, but then withdrawn from the market.

Leadiant® Chenodeoxycholic Acid was introduced to the market

9. Italian in June 2017. However, in the absence of an agreement on the price between the company and the Italian Medicines Agency (AIFA), it was marketed according to the rules of the so-called "C non-negotiated" (Cnn) class, or at a price freely set by the company, which in the aforementioned article was indicated as equal to 169,000 euros per year, to be paid by the patients8 .

10. Before the marketing authorization *of Leadiant® Chenodeoxycholic Acid,* the Italian patients affected by CTX were also treated with the drug owned by Leadiant Biosciences Ltd. based

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[7] V. *Appeal against the former Sigma Tau,* in *Milano Finanza,* 4 September 2018. See also *Dutch doctors fight pharma company's 500-fold drug price rise,* in *Financial Times,* 2 September 2018; *Dutch doctors resist pharma firms' 500-fold price hike,* in *www.pharmafile.com,* September 3, 2018; *New Dutch Foundation to Address High Medicines Pricing Announces Plan to File Complaint with Competition Authority,* in *www.medicineslawandpolicy.org dated* 25 August 2018. See doc. 1.

[8] See doc. 1.

of chenodeoxycholic acid registered for the treatment of gallstones but administered *off label* for the treatment of rare disease9 · And before that, the Oncological and Clinical Pharmacy (hereinafter, the "Pharmacy") of the Sienese University Hospital of Santa Maria alle Scotte (hereinafter, "AOU Senese") had produced the drug in galenic form, with the aim of administering it free of charge to all CTX10 patients .

11. Based on this information, on 25 September 2018, it was opened the preliminary investigation file A524 ex officio.

12. Subsequently, on 31 July 2019, a report was received from Altroconsumo, with which the association denounced the unlawfulness of the conduct of Leadiant Biosciences Ltd. from an *antitrust point of view,* as capable of integrating an abuse of exploitation *sub* specie of unjustly burdensome prices pursuant to article 102, lett. a), TFEU.

II.2 The preliminary and preliminary investigation activities

13. In order to acquire useful elements to understand the market context in which the orphan drug under investigation was inserted and to know the status and / or the outcome of the negotiation of the price *of Chenodeoxycholic Acid Leadiant®,* on 26 September 2018 A request for information was sent to AIFA, to which the Agency replied on 22 October 201811.

14. Starting from September 2018, moreover, they have been heard several times, within the ECN network established with the EC Regulation no. 1/2003, the competent investigation departments of the other national competition authorities, such as the *Authority for Consumers & Markets* (ACM) of the Netherlands, which had an investigation procedure has already begun on the case in relation to the Dutch market, and the *Comisión Nacional de los Mercados y la Competencia* (CNMC) of Spain, which was assessing the existence of the requirements to be able to initiate it in relation to the Spanish market12.

15. In particular, following the numerous contacts with ACM, pursuant to art. 12 of the EC Regulation n. 1/2003, on 9 May 2019 a copy of the exclusive chenodeoxycholic acid supply contract stipulated on 16 November 2016 by Sigma Tau Rare Disease Ltd. was acquired (now

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[9] See doc. 10, annex 2.
[10] See doc. 6.
[11] See docs. 2 and 3.
[12] See *https://www.acm.nl/en/publications/acm-extends-its-investigation-orphan-drug-cdca-leadiant* and *https://www.cnmc.es/prensa/inocacion-leadiant-20201222.*

Leadiant Biosciences Ltd.) with the Italian chemical company, Prodotti Chimici e Alimentari SpA 13, and then, on 5 June 2019, a copy of some documents relating to the proceedings initiated by the same ACM14.

16. Furthermore, in order to deepen the various phases that have characterized the decades-long clinical experience developed by the AOU Senese in relation to the treatment of rare disease, between March and May 2019, a specialist doctor of the AOU Senese and some pharmacists were contacted several times. of the Pharmacy of the same AOU15. On 10 May 2019, representatives of the Pharmacy16 were heard.

17. Subsequently, as anticipated, on 31 July 2019, the report was received by Altroconsumo17.

18. Finally, on 7 September 2019, in order to obtain more up-to-date information on the developments of the orphan drug price negotiation procedure, a second request for information was sent to AIFA, to which the Agency replied on 4 October 201918 .

19. On 8 October 2019, the Authority initiated, pursuant to article 102 of the TFEU and article 14 of law no. 287/1990, an investigation procedure against the companies of Essetifin SpA, Leadiant Biosciences SpA, Leadiant Biosciences Ltd., Leadiant GmbH and Sigma Tau Arzneimittel GmbH in liquidation, in order to verify the existence of any conduct contrary to competition law be from the aforementioned companies.

20. On 15 October 2019, inspections were carried out at the Rome offices of Essetifin SpA and Leadiant Biosciences SpA 19, at the offices of Industria Chimica Emiliana SpA (in Reggio Emilia) 20 and of its subsidiary Prodotti Chimici e Alimentari SpA (in Basaluzzo) 21, as well as at the offices of Leadiant GmbH and Sigma Tau Arzneimittel GmbH in liquidation in Munich22. Finally, on the dates of 15-17 October 2019, inspections were carried out at the Leadiant Biosciences headquarters

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[13] See docs. 5, 5.1 and 5.2.

[14] See docs. 7, and 7.1.

[15] See doc. 6.13.

[16] See docs. 4 and 6.

[17] See doc. 8.

[18] See docs. 9 and 11. This update followed a series of informal contacts with the competent AIFA Departments between February and June 2019.

[19] See doc. 18, 21 and 22.

[20] See docs. 24 and 25.

[21] See docs. 27 and 28.

[22] See docs. 83.1 and 83.2.

Ltd. of Windsor. The inspections at the premises of the foreign companies Leadiant Biosciences Ltd., Leadiant GmbH and Sigma Tau Arzneimittel GmbH in liquidation were carried out by the British *Competition Authority (Competition and Markets Authority)* and by the German Competition Authority *(Bundeskartellamt)* respectively. , in execution of two requests for cooperation *ex* art. 22 of the EC Regulation n. 1/200323.

21. The documents collected during the inspection by the *Competition and Markets Authority* were sent to the Authority on 4 December 2019 pursuant to art. 12 of the EC Regulation n. 1/2003 and on the same date were acquired in the investigation file24. The documents acquired during the inspection by the *Bundeskartellamt* were sent to the Authority on 30 June 2020 pursuant to art. 12 of the EC Regulation n. 1/2003 and on the same date were acquired in the preliminary file 25.

22. On 8 July 2020, following the extension of the deadline for the submission of commitments requested by the Party26 and the automatic suspension of the terms of the administrative proceedings established by art. 103 of Legislative Decree no. 18/2020, first, and of the art. 37 of Legislative Decree no. 23/2020, then27, a form for the presentation of commitments pursuant to art. *14-ter* of Law 287/1990 relating to the proceeding in question28. The Authority rejected the commitments with a resolution of 6 August 2020, deeming the Authority's interest in proceeding with the assessment of the infringement to exist29.

23. During the procedure, the Management formulated requests for information from the company in relation, among other things, to the costs incurred by the latter for the launch *of Chenodeoxycholic acid Leadiant*® on the European market30. **24.** Furthermore, in order to obtain relevant information for the purposes of the procedure, AIFA and the companies Industria Chimica Emiliana SpA (hereinafter, "ICE") and Prodotti Chimici Alimentari SpA (hereinafter, "PCA") were heard twice at the hearing.) 31.

25. During the investigation the Leadiant group companies have several times

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[23] See docs. 81 and 82.

[24] See doc. 42 and annexes.

[25] See doc. 83.

[26] See docs. 52, 60, 62 and 63.

[27] See doc. 76.

[28] See doc. 84.1 and 87.1.

[29] See docs. 88 and 89.

[30] See doc. 99, 105, 107 and 110.

[31] See doc. 72 and 108 and 69 and 120.1.

having accessed the documents32, they filed two briefs33 and were heard at a hearing on 7 May 202134.

26. The preliminary investigation procedure was extended four times, first on 13 October 202035, on 8 June 202136, then on 19 October 202137 and, finally, on 8 February 202238.

27. On 22 September 2021, the Parties were notified of the Communication of the Preliminary Results39.

28. The Parties presented their final briefs on January 28, 202240 and were heard in the final hearing before the Board on February 14, 202241.

III. THE INSTRUCTORY RESULTS

III.1 The reference regulatory framework

29. *Leadiant® Chenodeoxycholic Acid* is the so-called hybrid version of a pre-existing drug, called *Xenbilox®, which was* also owned by Leadiant until it was on the market. Therefore, in the first place, the set of European rules relating to the marketing authorization (AIC) of so-called hybrid medicines is highlighted42.

Furthermore, since it is a so-called "orphan" drug, the case must also be examined in the light of the provisions of EC Regulation no. 141/2000 and the subsequent acts issued by the European Commission on the subject.
Finally, in the light of the decades-long experience of Italian hospitals in the galenic production of chenodeoxycholic acid-based drugs, the rules governing the so-called "galenic preparations (or preparations) (i)" will be illustrated.

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[32] See docs. 66, 67, 78, 79, 96, 98, 100, 101 and 116, 168-bis, 168-ter, 168-quater, 170, 180, 188 and 189.
[33] See docs. 84 and 140.
[34] See doc. 122.
[35] See docs. 90, 91 and 93.
[36] See docs. 134-137.
[37] See docs. 171-173.
[38] See docs. 199-200.
[39] See docs. 159-160.
[40] See docs. 185, 186 and 187.
[41] See docs. 201, 201-bis, 202 and 202-bis.
[42] See Directive 83/2001 / EC, as amended by Directive 2004/27 / EC.

III.1.1 The European regulations governing the marketing authorization of so-called hybrid drugs

30. The request for the AIC for drugs other than the so-called *originators* is governed by art. 10 of Directive 83/2001 / EC, which provides for more streamlined procedures than those with full knowledge (governed by art.8, par.3, lett.i) of the same Directive) applicable to applications for marketing authorization for originating drugs, and therefore called "abbreviated".

31. The greater simplicity and speed of the "abbreviated" authorization procedures lies in the possibility for instant companies not to repeat the clinical *trials* already carried out to prove the safety, efficacy and quality of the originator drug, but to limit themselves to testing the bioequivalence43 between the drug for which the MA is requested and the originating drug, which thus acts as a so-called "reference" drug.

32. As part of the "abbreviated" procedures, the European Legislator has provided for a "simple" procedure (art. 10, par. 1 of Directive 83/2001 / EC) and a "hybrid" (art. 10, par. 3, of the same Directive). The first is used by drugs that fall within the legal definition of "generic medicine" pursuant to art. 10, paragraph 2, lett. *b),* or that they satisfy *"the criteria of the identity of the qualitative and quantitative composition in active ingredients, of the identity of the pharmaceutical form and of the bioequivalence" 44* with respect to the "reference" drug, while the latter are used by drugs that have some differences from the 'reference' medicine 45.

33. These differences between the two may reside *a)* in the different therapeutic indication or *b)* in the different route of administration or in the different dosage.

34. In both cases, the "hybrid procedure" of authorization pursuant to art. 10, par. 3 of the Directive makes it possible to refer to the clinical data of the "reference" medicine, without prejudice to their necessary integration to cope with the differences present. In particular, in the case *under a) ,* the

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[43] Two drugs are considered bioequivalent when, with the same dose, they have the same bioavailability, i.e. when the amount of active ingredient made available in the systemic circulation and the time it takes to reach its maximum concentration in the blood after administration of the drug, are so similar that there are no significant differences in terms of efficacy and safety. It is assumed that there is bioequivalence between two drugs when they are pharmaceutical equivalents, i.e. they contain the same active ingredient, in the same dosage, and have the same pharmaceutical form. See EMA, *Guidelines on the Investigation of Bioequivalence,* 2010, *https:// www.ema.europa.eu/ en/ documents/ scientific-guideline/ guideline-investigation-bioequivalence rev1_en.pdf.* available on

[44] Cf. CJEU, 3 December 1998, in case C-368/96, *Generics (medicines Captopril, Aciclovir and Ranitidine),* in *Collection* 1988, pI-7967, point 36, confirmed by CJEU, 29 April 2004, in case C-106 / 01, *SangStat v. Novartis Pharmaceuticals (Sandimmun medicine),* unpublished but available on the Court's website, paragraph 33.

[45] See CJEU, *SangStat,* cit., Paragraphs 52 and 55.

presentation of clinical documentation certifying the safety and efficacy of the drug for the different therapeutic use.

35. The present case falls under the hypothesis *under a): Chenodeoxycholic acid Leadiant*® is, in fact, as anticipated *above,* a so-called hybrid drug of the "reference" medicine *Xenbilox®,* to which it is identical from a chemical and pharmaceutical point of view, but from which it differs for the different therapeutic indication. For the purposes of the request for the marketing authorization of the orphan drug, therefore, Sigma Tau used part of the *dossier* of the latter drug, supplementing it with additional documentation (on which see better *below* par. 144).

36. The requirement of presenting additional clinical documentation can be waived, as happened in the present case, in exceptional circumstances, pursuant to art. 14, paragraph 8, of EC Regulation no. 726/2004: in the event that it is impossible to provide comprehensive information on the efficacy and safety of the medicinal product under normal conditions of use, the granting of the MA is subject to the fulfillment of certain requirements, including more stringent pharmacovigilance and completion of missing clinical studies within a given time limit.

37. The additional documentation produced by Sigma Tau as part of the AIC application procedure for *Chenodeoxycholic Acid Leadiant® did* not contain the clinical documentation necessary for the test
complete the efficacy and safety of the new therapeutic indication and the orphan drug was therefore authorized "in exceptional circumstances" (see par. 155 *below).*

III.1.2 The European regulation on orphan drugs

38. Medicines used for the treatment of rare diseases, designated as such when they integrate the requirements established by art. 3, paragraph 1, of EC Regulation no. 141/2000, i.e. when *a)* they are intended to treat a pathology involving a life-threatening or chronic debilitation affecting no more than 5 in 10,000 individuals in the European Union
(prevalence criterion), *or* a disease that is life threatening or chronic debilitation and it is unlikely that, in the absence of incentives, the marketing of this medicine within the European Union will be profitable enough to justify the necessary investment (return on investment criterion); *and* when *b)* there are no satisfactory treatments authorized in the European Union or, if they exist, the medicinal product in question will have "significant beneficial effects" for those affected by such

pathology (criterion of significant beneficial effects) 46.

39. The European Commission can therefore attribute the orphan designation to a drug - on the favorable opinion of the *Committee for Orphan Medicinal Products* (COMP) of the EMA - where the applicant company is able to prove one of the two requirements indicated *under a)* and the requirement *under b),* provided for by the aforementioned regulatory provision. **40.**

Subsequently, if the conditions are met, the European Commission can assign the MA to the orphan drug, on the favorable opinion of the EMA's *Committee for Medicinal Products for Human Use* (CHMP). At the same time, the EMA COMP verifies the permanence of the requirements for orphan designation, through a comparative examination with any therapies already authorized for the treatment of rare pathology47. **41.**

Only following the positive outcome of this scrutiny, in accordance with the provisions of art. 8, par. 1, of the EC Regulation n. 141/2000, the companies holding the marketing authorization of an orphan drug enjoy a commercial exclusivity of ten years (starting from the moment in which the marketing authorization is granted), by virtue of a ban on the European Union and the member states to grant other marketing authorizations for “similar” medicines 48 with the same therapeutic indications. According to the provisions of art. 8, paragraph 3, lett. *c),* of EC Regulation no. 141/2000, this market exclusivity is subject to exceptions and does not prevent the marketing authorization of a similar drug with the same therapeutic indications as the orphan drug already authorized, *inter alia,* when

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[46] The art. 3, par. 2, of Regulation (EC) no. 847/2000 of the Commission of 27 April 2000 provides that: *“For the purposes of implementing Article 3 of Regulation (EC) no. 141/2000 concerning orphan drugs, the following definition applies: - "significant benefit" means a substantial improvement in the patient's condition from the clinical point of view or from the point of view of general care ".* The Communication on the application of articles 3, 5 and 7 of Regulation (EC) no. 141/2000 concerning orphan drugs of 18 November 2016 at point B.5 establishes that a significant beneficial effect consists in the *"substantial improvement of the patient's condition from a clinical point of view",* or in an improved efficacy, in a better profile of safety or better tolerability of the drug; while, *“a substantial improvement in the patient's condition from the point of view of general care”* may be based on the ease of self-administration, or on better adherence to therapy thanks to a change in the pharmaceutical form.

[47] V. Court of the EU, 9 September 2010, in case T ÿ 74/08, *Now Pharm v. European Commission,* para. 43; Corte Giust., 3 March 2016, in case C-138/15, *Teva Pharma and Teva Pharmaceuticals Europe v. EMA,* par. 64; Court of the EU, 22 March 2018, in case T-80/16 *Shire Pharmaceuticals Ireland Ltsd. c. EMA,* par. 68. See also the Communication on the application of articles 3, 5 and 7 of Regulation (EC) no. 141/2000 concerning orphan medicinal products of 18 November 2016 in point B.5.

[48] The art. 3, par. 3, letter *b),* of EC Regulation no. 847/2000 of the Commission, of April 27, 2000, establishes that *"similar medicinal product" means a medicinal product containing one or more active principles similar to those contained in an orphan medicinal product already authorized, with the same therapeutic indication; […] "Similar active principle" means an identical active principle or an active principle with the same main characteristics of molecular structure (but not necessarily all the molecular structural characteristics) and which acts through the same mechanism ".*

the applicant company demonstrates that its medicinal product is safer, more effective or otherwise clinically superior49. Furthermore, the commercial exclusivity does not operate when the AIC request concerns drugs "not similar" to the orphan drug already authorized (even if they have the same therapeutic indications).

III.1.3 The national legislation on galenic preparations

42. Based on art. 3, paragraph 1, lett. *a)* and *b)* of Legislative Decree no. 219/2006, are galenic drugs:
a) medicines prepared in pharmacies on the basis of a medical prescription intended for a specific patient, called *"magistral formulas",* more fully regulated by art. 5 of the DL February 17, 1998, n. 23, converted, with modifications, by law n. 94/98;

b) medicines prepared in pharmacies on the basis of the indications of the European Pharmacopoeia or the national Pharmacopoeias in force in the Member States of the European Union, called *"medicinal formulas",* and intended to be supplied directly to undifferentiated patients, customers of that pharmacy.

43. Based on art. 5, paragraph 2, of Legislative Decree February 17, 1998, n. 23, converted, with modifications, by law n. 94/98, if on the market there is a medicinal product based on a specific active ingredient authorized for the treatment of a specific pathology, the doctor is not allowed to prescribe a patient a formula (or "preparation" or "preparation") masterful to base of the same active ingredient, unless the recipe, precisely for the purpose of customizing the therapy, does not provide for a different dosage or different excipients50.

III.2 Chenodeoxycholic acid (CDCA)

44. Chenodeoxycholic acid *(chenodeoxycholic acid* or CDCA) is a cd

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[49] The art. 3, par. 3, of the aforementioned EC Regulation no. 847/2000 establishes that a "clinically superior" medicinal product means a medicinal product that provides a significant therapeutic or diagnostic benefit compared to an authorized orphan medicinal product, as a result of one or more of the following effects: 1) greater efficacy, 2) greater safety, or 3) in exceptional cases, a significant contribution, by other means, to the diagnosis or treatment of the patient.

[50] In fact, the patient could be allergic to the excipients of the medicinal product on the market or present a better response to therapy when it is administered with a dosage other than that available on the market. These therapeutic needs, therefore, justify the exception to the prohibition of producing magisterial preparations based on certain active ingredients if medicinal specialties containing them are authorized.

primary bile acid, produced by the liver and derived from cholesterol. Together with cholic acid, CDCA is the main constituent of bile and plays a leading role in the processes of digestion and absorption of lipids.

45. CDCA was first isolated in 1924, first from domestic goose bile and then from human bile, and its chemical configuration was precisely defined in the 1930s. The process of synthesizing the active ingredient is currently not covered by industrial rights.

III.2.1 The manufacturing process of CDCA as an active pharmaceutical grade

46. CDCA as a pharmaceutical grade active ingredient is a naturally derived substance, which cannot be produced in the laboratory from synthetic material52. The main raw material from which this active principle is obtained is bovine bile, but it can also be obtained from the bile of poultry or pigs53.

47. The production of CDCA that makes use of bovine bile is structured as follows: cholic acid, or the other primary bile acid, is extracted from animal bile, which is then purified in order to obtain, through various steps of chemical synthesis , ursodeoxycholic acid, a secondary bile acid54; CDCA is an intermediate product in the synthesis process of ursodeoxycholic acid starting from cholic acid55.

48. For production purposes, a continuous availability of raw materials in sufficient quantities is necessary; therefore, especially as regards bovine bile, the companies that produce CDCA must have stable commercial relationships with the operators of the raw material extraction and collection market (or with the livestock slaughtering plants) such as to allow them to obtain a satisfactory supply of the same56.

49. The production of the CDCA must also undergo rigorous processes

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[51] V. MAXWELL, ECKHARDT, *Drug Discovery: A Casebook and Analysis,* Springer Science and Business Media, 1990, p. 383; SNEADER, *Drug Discovery: A History,* John Wiley & Sons, 2005, p. 273.

[52] See doc. 78.416: "[…] *the product cannot be synthesized in a laboratory [...]".*

[53] See doc. 25.3.8, 28.2.182, 78.303 and 120.1.

[54] See doc. 28.2.33, annex *"Documentation for pre-NDA meeting 15 07 2014.pdf".*

[55] See doc. 120.1.

[56] See doc. 78.416: "[…] *the product [...] is beholden to the API producers being able to contract with enough global meat producers to ensure that a sufficient level of bile is available for the bile acid products they produce".* Whether it is bovine bile emerges from the fact that the animals from which the bile is extracted the active principle are referred to as *"cattle",* ie cattle.

manufacturing in order to reach the purity standards required by the industry (the so-called pharmaceutical grade). In particular, in the European Union (but also in the United States) the sector is subject to the regulatory standards established by *Good Manufacturing Practices* (GMP), or Good Manufacturing Standards57, which require manufacturing companies to comply, also for the purpose of guaranteeing traceability. , with certain quality and safety requirements among the highest in the chemical industry, starting from raw materials up to the finished product58. These *standards* are more stringent than those imposed in other countries, such as, for example, India and China.

50. The CDCA production process is not complex in itself59. And
even after the purity *standard* required in the European Union for the synthesis of the CDCA from the raw material was made more stringent with the definition in 2019 of a new test, as a result of a review procedure of the Pharmacopoeia monograph European Commission carried out by the European Directorate for the Quality of Medicines and Health of the Council of Europe *(European Directorate for the Quality of Medicines,* hereinafter, "EDQM") 60 (on which see better *below* par. 53).

III.2.2 Companies active in the supply of CDCAs

51. Considering the prevalent method of extraction of CDCA (i.e. from bovine bile), taking into account the stringent production *standards* required in the European Union for the production of active pharmaceutical ingredients and the small size of the market (on which see par. 63 *below) ,* only a small number of companies have been, and still are, active in the supply of CDCAs for pharmaceutical use.

52. The aforementioned documentation indeed accounts for the fact that, in Sigma Tau's opinion, there were only two operators capable of

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[57] See for example, art. 46, lett. F) of Directive 2001/83 / EC of the European Parliament and of the Council of 6 November 2001 as amended by Directive 2004/27 / EC of the European Parliament and of the Council of 31 March 2004.

[58] See doc. 28.2.33, annex *"Documentation for pre-NDA meeting 15 07 2014",* from which it emerges that the quality standards imposed by the European regulation for the production of CDCA deriving from bovine bile require, *inter alia,* that slaughterhouses are certified and located in countries where there is no 'is the risk of cattle contracting TSE / BSE. The fact that PCA possesses this certification emerges from doc. 25.3.12.

[59] See doc. 120.1.

[60] See doc. 78.320: *"The active principle use [d] to manufacture CDCA Leadiant undergoes extensive testing, including determination of the correct form of CDCA in pharmaceutical grade and production according to the latest GMP and Quality control. This is relevant due to the fact that CDCA is a polymorph and testing ensures usage of the active molecule in industrial product, whilst not testing the active principle might result in usage of a form of the molecule that could be inactive ".* See also docs. 78.194 and 78.195.

procure adequate quantities of raw materials61. One of these was, and is, the Italian company PCA, which, in addition to being the world *leader* in the production of ursodeoxycholic acid62, has also been the main producer of CDCA in Europe for many years. The chemical company, in fact, has been part of a corporate group since 2008, at the top of which there is ICE (with which PCA has also recently merged63), which controls a series of companies active in the extraction, collection and processing of bovine bile in the areas of greatest production, namely Mexico, Costa Rica, Colombia, Brazil, Argentina, Uruguay, Paraguay, South Africa, India, Australia and the USA64.

53. The documentation acquired in the records shows that PCA has long been recognized as an operator with significant *know-how ,* a high level of regulatory *compliance ,* which is expressed in the ability to adhere to GMPs and to obtain and maintain a regulatory *dossier* (i.e. the so-called *Drug Master File* or *DMF),* and which enjoys an excellent commercial reputation, in general in the production of pharmaceutical grade active ingredients deriving from bile acids, as well as in the production of this specific molecule65. And indeed, at the end of 2011, the EDQM turned to PCA as the only producer of the active ingredient in the territory of the European Union to which reference should be made in order to improve the synthesization process of the CDCA in terms of the level of admitted impurities66. Since then and until 2019, the chemical company, involving Sigma Tau (which later became Leadiant), which in the meantime had developed a new purity test of the CDCA67, then transferred to PCA and implemented by the latter68 (see par. 127 *infra),* closely collaborated with the EDQM and the Body, for the purpose of elaborating the new *te*

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[61] See doc. 78.416: "[…] *there are two global API providers relevant for this product"* and doc. 78.133, annex "REPORT MEETING AIFA Sigma Tau June 24" ("[...] *Product of bovine derivation. 2-3 producers in the world").*

[62] See docs. 25.3.12 and 28.2.181.

[63] See doc. 120.1.

[64] See docs. 25.3.2 and 28.2.181.

[65] From doc. 28.2.16, annex, it emerges that PCA has produced CDCA since at least 1998, supplying Dr. Falk Pharma GmbH. V also docs. 28.2.54 and 78.102 *("CDCA Sigma-Tau is obtained through a complex extraction procedure and its production undergoes the most current GMP standards (reference). The production process of the CDCA has been standardized and optimized during the 30 years of production ...").* Finally, see Doc. 120.1.

[66] See doc. 78.6 ("[…] *I could not identify another manufacturer and I have therefore only information from your part").* See doc. 28.2.31 *("[…] they are waiting for our data and support. The finalization is depending on* us").

[67] See doc. 28.2.32, 28.2.34, 28.2.39, 28.2.47, 28.2.53, 28.2.73, 28.2.84, 78.54.

[68] See docs. 28.2.77.

largely on the contribution of PCA69.

54. The other company with similar characteristics is explicitly mentioned in a document of February 2016 and implicitly in other documents of 201770: this is the New Zealand company New Zealand Pharmaceuticals Ltd. (hereinafter, "NZP"), later acquired by ICE in August 202071.

55. This company was taken into consideration by Sigma Tau when, in 2016, it carried out a search to identify any other sources of supply of CDCAs other than PCA (with which it had an exclusive supply contract since June 2008, on which see better *infra* par.
96). However, as far as Sigma Tau is aware, NZP was at that time commercially engaged with another pharmaceutical company, the American company Retrophin Inc. [now Travere Therapeutics Inc. Ed.] 72. Furthermore, from the research carried out in July 2016, there were, at least abstractly, 13 suppliers of CDCAs, located inside and outside the European Union, including PCA and ICE, two German companies, one US, one Mexican and several companies Chinese. However, the quality of the raw material (apart from that produced by PCA and ICE) was not known73. For these reasons, in August 2016 Sigma Tau believed that it had no alternative sources of supply to PCA74.

56. The documentation acquired in the documents actually gives account of the sporadic existence of non-EU sources of CDCA production, in particular Chinese75, which, however, for a long time were not able to comply with the specific regulations required by the regulation European Union and to pass the quality controls required by GMPs to access European markets.

57. In fact, some documents indicate that in 2017 the PCA itself believed that non-EU CDCA suppliers and in particular the Chinese ones would not represent *"a problem"* for Sigma Tau76.

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[69] See docs. 28.2.31, 78.6, 78.15, 78.21-78.25, 78.189, 78.194, 78.195.

[70] See docs. 78.323, 78.416 and 78.133, annex "REPORT AIFA SIGMA TAU MEETING 24 June".

[71] See the press release available at *https:// www.iceitaly.com/ news/ ICE-acquires-New-Zealand Pharmaceuticals.*

[72] See docs. 78.323 and 22.7.114.

[73] See doc. 78.7. See also doc. 84, 185 and 187 which contain a historical extract from the Thomson Reuters Newport Global *database* , which according to Leadiant highlighted, as early as 2015, the presence on the market of (at least)
15 alternative API providers for CDCA. The suppliers indicated coincide minimally with those indicated in the list contained in doc. 78.7.

[74] See doc. 78.5.

[75] See docs. 25.3.5, 78.190, 78.303.

[76] See doc. 78.262: *"Compounding and foreign / exotic API supply of CDCA will not represent a problem".* V.
also showers. 28.2.132 ("[…] *a Chinese source will not represent an issue for* you").

58. The lower quality of the raw material coming from non-EU markets, in particular the Asian ones, is in fact proven by various inspection documents that give an account of the unsuccessful attempt of some Spanish pharmacies77, of the hospital in Amsterdam78, as well as of that of Antwerp79, to produce the CDCA in a galenic version between the end of 2017 and during 2018 on the basis of raw material imported from China by a wholesaler of pharmaceutical grade active ingredients80. In particular, the checks carried out by the competent Dutch authorities in August 2018, at Leadiant's request, highlighted the presence in the magisterial preparations produced by the Amsterdam hospital of excessive levels of impurities compared to those required by the monograph of the European Pharmacopoeia, with consequent interruption of the exhibition 81. Which indicates that, as PCA also confirmed at the hearing, the only alternative source of CDCA production of which there is evidence in those years *"turned out to be unable to produce an active ingredient compliant with purity standards. required by the European Pharmacopoeia "82.*

59. As a result of this, the same wholesaler, in October 2018, returned after two years to turn to PCA, as a certified manufacturer in Europe83, the only one with this characteristic according to what Leadiant herself stated in an internal document of the company in April 201884.

60. The quality level of the raw material from Asian producers has only recently improved. Some documents on file, including the PCA hearing report, indicate, in fact, that in February 2020 the Amsterdam hospital resumed the galenic production of CDCA thanks to the use of raw material from another source of origin. asian

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[77] See docs. 22.7.40 and 78.257 *("We have just received confirmation that the pharmacy was closed and forced to withdraw all compounded CDCA from the hospitals. The inspectors have collected samples of the product that is being tested and the pharmacy will receive a fine and likely lose the license to operate ").*

[78] See doc. 78.93.

[79] See doc. 78,297, where it is reported that the Antwerp hospital in December 2017 *"bought their CDCA raw material at Eurochemicals in the Netherlands and compound capsules themselves […] The raw material has been produced in China and took them quite a while before it arrived. They have re-analyzed it in order to assure that it is pharmaceutical grade ".* Following the withdrawal of the galenic products from the Dutch market, they were also withdrawn from the Belgian market.

[80] See docs. 22.7.64, annex "Theophylline - CDCA", 78.297 and 138.4.9, which indicate that this intermediary, Eurochemicals BV, in October 2017, had managed to enter into a contract with a CDCA producer other than PCA and to import the raw material into the European Union by supplying several hospitals in some Member States.

[81] See docs. 22.5.8, 78.93 and 78.326.

[82] See doc. 120.1.

[83] See doc. 28.2.183 and cfr. with doc. 22.7.64.

[84] See doc. 138.4.9 *("Furthermore, there is only one approved EU certified supplier of pharmaceutical grade CDCA ...").*

which up to now has proved to be compliant with European regulatory specifications, also in the new version deriving from the modification of the European Pharmacopoeia85. This supplier company is, therefore, currently to be counted among the production sources of CDCA capable of supplying the European Union markets86, exclusively to support production of a masterful nature.

III.3 The pharmaceutical uses of the CDCA: the treatment of CTX

61. Since their introduction on the market in the early 1970s, chenodeoxycholic acid-based drugs have been authorized for sale by individual national regulatory authorities of the European Union only for the treatment of gallstones87. However, since the beginning of the 90s (and in the literature even in the 80s) the CDCA was no longer considered adequate to the international standards in force for the dissolution of gallstones and was surpassed by other treatments that proved to be more effective for this. therapeutic indication 88.

62. As documented by numerous scientific studies published at the beginning of the 1980s , the medical-scientific community has however discovered that the active principle has a therapeutic utility in another medical field: in fact, it has proved effective right from the start in treatment of cerebrotendinous xanthomatosis (or CTX).

63. CTX is a disease generated by a congenital defect of primary bile acid synthesis. Patients suffering from this pathology are unable

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[85] See docs. 75, 75.1 and 120.1. In particular, from this last document it emerges that in PCA's opinion *"[the] need for the Amsterdam hospital to set up a galenic production [...] could have stimulated the investment necessary for this production of CDCA to be able to pass the controls of the European regulatory authorities ".*

[86] According to the chemical company, therefore, the *"Chinese source of CDCA would seem today to be able to comply with the purification standards required in Europe and to recently reach the high quality standards that PCA has always respected" (see* doc. 120.1) .

[87] V. DANZIGER, HOFMANN, SCHOENFIELD, THISTLE, *Dissolution of cholesterol gallstones by chenodeoxycholic acid,* in *N. Eng. J. Med.,* 1972, no. 286, pp. 1-8; CAREY, *Editorial: Cheno and urso: what the goose and the bear have in common,* in *N. Engl. J. Med.,* 1975, no. 293 (24), pp. 1255–7. *https:// www.farmaterverantwoording.nl/ wp-content/ uploads/ 2021/04/2018.09.07-Handhavingsverzoek-CDCA_English-unofficial-translation.pdf.*

[88] See In the medical literature v. *ex multis* RUPPIN, DOWLING, *Is recurrence inevitable after gallstone dissolution by bile acidtreatment ? ,* in *Lancet,* 1982, n. I, pp. 181 *et seq .;* PODDA, ZUIN, BATTEZZATI, GHEZZI, FAZIO, DIOGUARDI, *Efficacy and safety of a combination of chenodeoxycholic acid and ursodeoxycholic acid for gallstones dissolution: a comparison with ursodeoxycholic acid alone,* in *Gastroenterology,* 1989, n. 96, pp. 222 *et seq.*

[89] V., *ex multis,* BERGINER , SALEN , SHEFER , *Long-Term Treatment of Cerebrotendinous Xanthomatosis with Chenodeoxycholic Acid,* in *N. Engl. J. Med.,* 1984, no. 311, pp. 1649-1652. Even in the EMA / 650359/2016 *Assessment report. Chenodeoxycholic acid Sigma Tau* of 15 September 2016, p. 33, it is stated that there are at least 70 scientific studies that testify to the oral administration of the CDCA on at least 200 patients as early as 1975.

to produce chenodeoxycholic acid in sufficient quantities due to mutations in the CYP27A1 gene, which cause a lack of the hepatic enzyme sterol 27-hydroxylase. The enzymatic defect causes the accumulation of cholestanol and cholesterol in many tissues, including the tendons and the central nervous system, generating the so-called tendon and / or cerebral xanthomas, which cause neurological, cognitive and systemic dysfunctions90. It is therefore a very serious disease with a progressive course, impeding the normal development of the person, which generally leads to the loss of autonomy and early death. It affects a very small portion of the population in Europe (25091 patients diagnosed in Europe), and is therefore an ultra-rare disease. The countries in which it is most widespread are Italy, Holland, Belgium, Spain, France, the United Kingdom and, to a lesser extent, Germany. The number of patients diagnosed with CTX is not known precisely as there are several conflicting sources for this.

From the information acquired and the inspection evidence it emerges that the patients present in Italy are about 45 (41 in 2020) 92, in Spain 5093, in the Netherlands about 6094 and in the United Kingdom about 2495. It is therefore a very large market. reduced 96.

64. Since the discovery of this new therapeutic use, CDCA-based drugs have been used for the treatment of CTX and, until the introduction of Leadiant's orphan drug, they have been prescribed *off-label.*

65. It appears that Sigma Tau had commissioned market research in September 2014, which showed that the CDCA, from the point of view of prescription *patterns ,* had long been the *"standard of care"* for CTX in most Member States. European Union (France, United Kingdom, Italy, Germany, Spain, Sweden, Netherlands and Austria) 97.

66. One of the world's leading experts on CTX, defined as *“world key*

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[90] See doc. 133.

[91] See doc. 187.

[92] See doc. 122.

[93] See doc. 138.4.1.

[94] See the report of the *Dutch Pharmaceutical Accountability Foundation,* cit. See also *https:// www.biocentury.com/ bc-week-review/ company-news/ deals/ 2009-02-09/ sigma-tau-spa-solvay-deal.*
See also doc. 122.

[95] V. NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE), *Clinical evidence review of chenodeoxycholic acid for treating cerebrotendinous xanthomatosis,* 2018, p. 11.

[96] See doc. 22.7.17 *("I don't see any new drug arising in the treatment of CTX and I think that it will be very difficult to see somebody investing resources in this sector in the coming years …… it's a too small pathology… it's an orphan who nobody wants to adopt! ").*

[97] See doc. 22.7.17.

opinion leader " by Sigma Tau98 itself - a specialist doctor of the Sienese AOU who, with his *team,* carried out a retrospective study for Sigma Tau to support the request for AIC for the orphan drug (on which see better paragraph 145- 147 *below)* - as part of the procedure for approving the framework agreement concerning the carrying out of said study, the Ethics Committee of the Tuscany Region, in October 2014, stated that *"[…] its use* [of the CDCA. Ed] *in the therapy of cerebrotendinous xanthomatosis (rare disease) has been consolidated and scientifically recognized for many years. The prescription of the drug under examination is part of normal clinical practice "99.*

67. This assessment is also confirmed by documents relating to subsequent years. In fact, from further market researches commissioned between the end of 2015 and the first months of 2016, it emerged that for the specialist doctors interviewed, the CDCA was the chosen therapy in the majority of cases (15 out of 16 doctors) in France, Spain, Germany, Italy, the Netherlands, Belgium and the United Kingdom 100. Documents from 2016 also highlight that another European renowned pathology expert, who carried out a second retrospective study for Sigma Tau in support of the MA request for the orphan drug (on which see better paragraph 149 *below),* believed that the CDCA was a *"worldwide accepted (literature), applied (treating physicians), and effective (open-label, single arm study)" therapy 101.*

68. The same scientific literature collated by the same company and presented in support of its request for orphan designation and AIC
for CDCA as a treatment for CTX indicates that the active ingredient is the

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98 See docs. 95 and 138.4.7.

99 See doc. 6.4. 100

See doc. 78.105, annex "Market Research_clinican-FINAL" ("All *respondents in all countries, except for one respondent in the UK, stated they use CDCA to treat CTX"; "Xenbilox is the only CDCA treatment right now.*
And the key opinion leader on biliary acid diseases, Professor Peter Clayton in the UK, thinks it's the best option "; "We have demonstrated that CDCA improves not only biochemical, but also clinical and instrumental parameters in our patients, and also other colleagues have proven it, but in these years I have published many data on CDCA treatment, and we for example, have shown that CDCA intake improves conduction of myelinated fibers of both central and nervous system, and peripheral nervous system. Also it increases mineral density -it stabilizes the brain magnetic resonance imaging patterns, and in our experience we have never had side effects, neither in children nor adults with this drug "; "CDCA is the standard of care, and the neurological symptoms are the most difficult to live with, so we chose to use the product that offers the best results at the neurological level, to prevent neurological issues"; "Due to the biochemical pathway, there is really only one effective treatment, that is with chenodeoxycholic acid").

101 See doc. 78.417, of March 2016. See also doc. 78.17, annex *"ST-CDCA_Slidesmeeting 12092016.pptx"* of September 2016, which shows that in France the CDCA was considered the therapy of choice for the treatment of CTX at the time.

Treatment of choice 102 and that its efficacy in the treatment of rare disease has been specifically found with the administration to patients of 250 mg of CDCA three times a day103.

69. Some recent qualified institutional sources also indicate that, despite the absence of prospective clinical trials, the *first-line treatment* for CTX is CDCA104. This is especially true in Italy, where this active ingredient has always been the drug of choice for the treatment of rare disease because, when taken regularly in the dose indicated above, it slows down the spontaneous evolution of the disease in most of the patients, stabilizing neurological and psychiatric manifestations and slowing the increase in size of tendon xanthomas105.

70. Finally, the aforementioned specialist doctor of the Sienese AOU, during the hearing, stated that, on the basis of its forty years of experience, the CDCA is *"to be privileged in the treatment of the rare pathology in question"* and that *"there is a clear consensus in the medical community-international scientific opinion on whether the CDCA is the therapy of choice for* CTX"106.

71. The doctor also stated that at present there is no therapy other than CDCA, not even in the experimental phase. The only lines of research currently existing - which point to the future development of gene therapy - they are in an embryonic stage. Furthermore, given the scarcity of funding, research on this therapy continues very slowly and even if it proves effective, it would not be introduced to the market for ten years from now107.

III.3.1 CDCA-based drugs

72. From the information acquired in the files it emerged that, since the 1970s, CDCA-based drugs were sold in some European countries under different trade names *(Quenobilan*® and *Quenocol*® in Spain, *Chenodex*® in

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[102] See docs. 22.7.8, all., 22.5.17 *("CDCA is unanimously recognized as the therapy of choice for* CTX"), 78.30, all. "Annex 1 - Overview of product development", 78.385.

[103] See docs. 78.237, 78.385.

[104] See *https:// www.orpha.net/ consor/ cgi bin / Disease_Search.php? lng = EN & data_id = 605 & Disease_Disease_Search_diseaseType = ORPHA & Diseas e_Disease_Search_diseaseGroup = 909 & Ziekte (n) / ziektegroep = CTX & title = CTX & search = Disease_Search_ Simple* and NICE, *Clinical evidence review of cholic acid for treating inborn errors of primary bile acid synthesis,* cit., P. 12.

[105] See doc. 133. See also https://malattierare.toscana.it/percorso/scheda/xantomatosi-cerebrotendinea.

[106] See doc. 133.

[107] See doc. 133.

France, *Xebyl*® in Portugal, *Chenofalk*® in Holland, Belgium and Germany108). In Italy there were the following four CDCA-based products: *Chenossil®, Chenofalk®, Fluibil® and Chenocol®109.* Quenobilan® , Quenocol® and *Chenofalk*® were *produced* using the raw material supplied by PCA and ICE110. Among the various products mentioned, in particular *Chenofalk*® was administered *off label* by Italian doctors to treat patients suffering from CTX.

73. Chenofalk® *became* unavailable on the Italian market as early as 1996 and the other chenodeoxycholic acid-based drugs then present on the domestic market were less and less available over time and then definitively no longer marketed between the end of the 1990s and the 1990s. early 2000s 111.

74. Faced with the difficulty of supplying CDCA-based drugs, already in the second half of the 90s, at the request of doctors
specialists of the AOU Senese who were treating several patients affected by CTX112, the same decided to guarantee therapeutic continuity for these patients by producing the drug in a galenic form113.

75. The galenic production of CDCA began in 1997. Since then the Pharmacy has always purchased the active ingredient from ICE through an intermediary114 and with this production it has also supplied the pharmacies of other
Italian hospitals / ASL / e115.

76. The cost of the raw material was 0.083 euros per capsule, to which were added the professional fees applied according to the rates in force at the time, with a total production cost of 0.67 euros per capsule.
The price per 100 capsules of 250 mg was thus equal to 67 euros, which led to an annual price of therapy for a single patient of 733.65 euros116.

77. However, ICE in 2005 communicated to the Pharmacy that it did not intend

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[108] Chenofalk was first approved in Germany in 1976 and the holder of the AIC was *Dr.* Falk GmbH. See doc. 96.75.

[109] See docs. 3 and 8.1.

[110] See docs. 138.1 and 138.2.

[111] See docs. 3.3 and 6.13. The scarcity of the active ingredient has also been documented in the scientific literature. VA FEDERICO, MT DOTTI, *Cerebrotendinous xanthomatosis,* in *Neurology,* 2001, 57 (9), p. 1743; P. SAMENUK, BMKOFFMAN, *Chenodeoxycholic treatment of cerebrotendinous xanthomatosis,* 2001, 56 (5), p. 695.

[112] See doc. 133.

[113] See doc. 6.13.

[114] See doc. 25.1 and docs. 25.3.17-25.3.31 and 120.1.

[115] See doc. 6, 6.13, 10 and 120.1. These are, for example, the principals of the R. Margherita and Obstetric Children's Hospital Gynecological S. Anna of Turin.

[116] See docs. 6 and 22.7.17. See doc. 10, annex 1.

plus produce the active ingredient in question. In 2007, the Pharmacy therefore purchased the last 75 kg of *stocks* of the active ingredient from PCA, which was used for galenic production until November 2015, when the stocks of raw material ran out117.

78. In the other national markets of the European Union, doctors continued to administer *(off label)* the aforementioned CDCA-based drugs to patients affected by *Chenofalk*® became unavailable on the Belgian market starting from 2005 and from that moment the drug was imported from Germany where it had been marketed since the mid- 1970s118, first under the same trade name119 and then under the trade name of *Xenbilox*® *;* in the Netherlands the drug was marketed under the name of *Chenofalk*® until the end of 2009 (from mid-2008 upon import from Germany) and then of

Xenbilox® (see paragraphs 97 and 106 below) 120. Likewise, *Quenobilan*® and *Quenocol*® definitively left the Spanish market between the second half of 2008 and the beginning of 2009 and *Xenbilox*® has been imported since then . from Germany121. Chenodex® *has* not been sold on the French market since 1999 and its MA was withdrawn in early 2005. In its place in the French market was *Xenbilox®122.* Xebyl® *has* not been marketed in the Portuguese market since 2011123.

79. The documentation acquired in the proceedings indicates, therefore, that starting from 2011 (and from the beginning of 2016 for what concerns Italy) and until the introduction on the market of Leadiant's orphan drug, the only drug based of CDCA actually available in Europe was *Xenbilox*® owned by Sigma Tau124.

80. Likewise, starting from June 2017, patients taking *Xenbilox*® were given *Chenodeoxycholic acid Leadiant,* the only CDCA-based product, registered for the treatment of CTX, currently

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117 See doc. 6.9.

118 See docs. 96.75 and 96.165.

119 V. *Réponse de la ministre des Affaires sociales et de la Santé publique du 14 December 2015, à la question n. 554 de monsieur le député Olivier Chaster du November 2015,* p. 054, available at *https:// www.dekamer.be/ QRVA/ pdf/ 54/54K0054.pdf.* See also *https: // geneesmiddelendatabank.fagg afmps.be/ #/ query/ human/.*

120 See docs. 8 and 138.4.1.

121 See docs. 138.1 and 138.2.

122 See *https:// www.has-sante.fr/ upload/ docs/ application/ pdf/ 2014-07/ orphacol_ct13339.pdf.*

123 See *https:// app.infarmed.pt/ sgrt/ detalherstock.aspx?id=2503.*

124 See doc. 8.

available on the domestic market125, as well as on the other national markets of the European Union126.

81. The aforementioned specialist doctor of the AOU Senese at the hearing stated that, in his opinion, on the therapeutic level there is no difference between the masterful preparations based on CDCA from the Pharmacy, *Xenbilox*® and *Chenodeoxycholic acid Leadiant*® (hereinafter , also *"CDCA Leadiant®"),* which he has administered over time to his patients127.

III.4 Other drugs used to treat CTX

82. Although CDCA-based drugs are the predominantly chosen therapy by doctors for the treatment of CTX, the inspection documentation shows that there are also other therapies that have sometimes been used by doctors to treat this disease: cholic acid , ursodeoxycholic acid and statins (in particular, simvastatin, lovastatin and pravastatin).

83. Ursodeoxycholic acid and statins have, however, been the subject of an extremely limited clinical practice which has revealed immediately the production of scarcely appreciable effects in the correction of metabolic alterations associated with CTX and which has therefore led medical specialists, especially in Italia128, not to consider them effective on the rare disease and therefore substitutable for the CDCA129.

84. As regards cholic acid, the aforementioned market research, commissioned by Sigma Tau in September 2014, showed that this principle was only in some sporadic cases used as a therapy for the treatment of rare disease130 and that, according to most clinical studies

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125 See doc. 3.

126 See docs. 78.249 (where in a presentation in November 2015 there is explicit mention of *"switch"* and *"plan of transitioning"* from *Xenbilox*® to *CDCA Leadiant®),* 78.12, 78.225 *("Move all patients currently on compounding and Xenbilox to CDCA Leadiant") .*

127 See doc. 133.

128 See *https:// malattierare.toscana.it// percorso/ scheda/ xantomatosi-cerebrotendinea.*

129 See docs. 22.7.17, 78.59, annex "CDCA Launch Plan", 78.348, 78.369 and 96.23. As regards bile acids specifically, some inspection documents indicate a precise hierarchy based on efficacy in the treatment of rare disease: within this classification ursodeoxycholic acid is in last place, preceded by cholic acid and CDCA, which ranks first. See docs. 96.5, 96.12, 96.17, 96.23 and 96.189.

130 See doc. 22.7.17 *("used infrequently and most consensus is [that] it is inferior to CDCA"; "Little or no use* now"). In France, the United Kingdom and Spain this active substance had been used, albeit to a limited extent. In particular, cholic acid was seen by some French doctors as a potential alternative to CDCA, but, in the knowledge of less efficacy, they felt it was preferable not to replace CDCA.

and medical specialists, in *non-naïve* patients CDCA should not have been replaced with cholic acid for the treatment of CTX131.

85. One explanation for this, according to these researches, was that in several Member States of the European Union, cholic acid was considered by doctors to be less effective than CDCA in treating CTX132. This was true, and still holds true, for Italy where the leading experts present on the national territory showed a strong skepticism about the use of cholic acid for the treatment of rare disease133, possibly usable in pediatric patients134, and the subjects interviewed (defined therein as a *"payer")* believed that an increase in the price of the CDCA-based drug would not lead to the replacement of this active ingredient with cholic acid, precisely because of the lower efficacy of this active ingredient on CTX135.

86. Not even the authorization of *Kolbam®,* based on cholic acid, by the European Commission as an *on-label* drug for the treatment of CTX in 2014136 and its introduction into the French market, which in principle could have constituted a factor capable of overturning this therapeutic hierarchy137, significantly changed the choices of doctors.

The documentation acquired indicates, in fact, that even before obtaining these administrative qualifications, the CDCA, despite being an *off-label medicine,* continued to remain, even in France, the therapy of choice for the

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with cholic acid *("Should not be used in CTX if the patient can receive CDCA")* and prescribe the latter only in case of liver toxicity found in the patient following the administration of the CDCA ("2 *of 3 doctors prefer not to use it, 1 suggested could be used where liver problems ").* This means that, as the consultants themselves stated, also in France *"[i] t is now well accepted in the physician community that CDCA is the SoC* [Standard of Care. Ed] ".

[131] See doc. 22.7.17 *("many physicians thought it would be damaging to patients to replace CDCA with* CA!").

[132] See doc. 22.7.17: "[…] *considered less effective in CTX than CDCA and is not supported by very strong data in CTX. NOT interchangeable " (France); "I would not consider both (CDCA and CA) as equal. I have not experience with cholic acid but I know some studies comparing both and they do not consider them equal.*
Cholic acid has not demonstrated to be effective in these studies " (Spain).

[133] See doc. 22.7.17: *"We don't believe in the effectiveness of Cholic acid (in CTX) and it's not true that it has a better safety profile. […] We don't believe in the specificity of the cholic acid, the scientific literature doesn't confirm it and at the mean time we don't believe in the asserted safety of this molecule […] I know that the expectations about the use of cholic acid in the treatment of CTX have been disappointing ".* See *https:// malattierare.toscana.it// percorso/ scheda/ xantomatosi-cerebrotendinea.*

[134] See doc. 96.23.

[135] See doc. 22.7.17: *"[…] the cholic acid doesn't have any scientific credibility in the cure of CTX and also the declared greater safety is considered as a "bluff" not adequately supported by clinical evidences ".*

[136] The drug *Kolbam®,* owned by Retrophin Inc., classified as an orphan drug on 29 October 2009, after a long dispute, on 24 November 2015 (the MA was initially issued on 4 April 2014) was authorized by the European Commission for three therapeutic indications: in addition to two congenital defects of primary bile acid synthesis, also the treatment of CTX.

[137] See doc. 22.7.17.

treatment of CTX138.

87. The obtaining of the orphan designation and the AIC (see para. 152-154 *below)* definitively decreed the therapeutic superiority of the CDCA also at the regulatory level, and reduced the competition of cholic acid to a marginal issue, such as the company it had already predicted in November 2016 *("[m] arginal competition by Cholic Acid in Europe") 139* and as other more recent documents, dating back to 2019, confirm 140.

88. Lastly, the specialist doctor of the Sienese AOU heard in the hearing (see par. 70 *above),* in this regard stated that the *"level of cholic acid in bile has a lesser role in the development of rare disease than in CDCA. […] There are only two publications describing the results of the administration of cholic acid on patients suffering from the rare disease […]. On the basis of these two studies, it can be stated that cholic acid has a certain efficacy on the disease, but this remains much less documented than the efficacy of* CDCA ”141.

89. As regards the presence and / or use of cholic acid-based drugs in the Italian market, it is noted that *Kolbam®,* although available on some national markets of the European Union, has never been authorized in Italy 142. Moreover, at present, the drug is no longer marketed in any Member State, given that the relative MA was revoked by the European Commission on 13 July 2020 at the request of the manufacturer143.

90. There is also another cholic acid-based drug, *Orphacol®,* authorized in 2013 for the treatment of congenital defects in primary bile acid synthesis other than those that cause CTX144. *The Orphacol®* is

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[138] See doc. 78,343 which highlights that in 2015 French neurologists were trying to convince the competent national authorities that it would be better to continue prescribing CDCA to patients with CTX, and not redirect them to cholic acid. See doc. 78.105. annex "Market Research_clinician-FINAL" from which it emerges that the French doctor interviewed during a market research commissioned by Sigma Tau between the end of 2015 and the beginning of 2016 stated: "... *wants to use CDCA instead [and] so was happy to hear that Kolbam's MA had been canceled… ".*

[139] See doc. 78,236.

[140] See docs. 22.5.17 and 78.165.

[141] See doc. 133.

[142] See doc 3.

[143] See *https:// www.ema.europa.eu/ en/ documents/ public-statement/ public-statement-kolbam-withdrawal marketing-authorization-european-union_en.pdf.*

[144] The drug was classified as an orphan on December 18, 2002. After an equally long litigation, the European Commission issued the AIC for the drug with a decision of September 12, 2013. On the different therapeutic indication for which *Orphacol* was authorized, see . also doc. 3.2.

registered and is marketed in Italy145, but from the information acquired there is no evidence that the practice of *off-label* use of this drug for the treatment of the rare disease covered by this provision has prevailed in the national market, since, also from what the specialist doctor of the AOU Senese declared during the hearing, it appears that the CDCA is the only therapy ever used in Italy for the treatment of CTX146. On the other hand, the *off-label* use of cholic acid after the registration of the orphan drug was considered unlikely by the same company147.

III.5 The facts under investigation

III.5.1 The conception of the registration project for an orphan drug for the treatment of CTX (years 2007-2014)

91. Sigma Tau began undertaking the CDCA orphan drug registration project for CTX treatment in 2006 in the United States148. In that year, the US branch of the *former* Sigma Tau group requested the orphan designation of the CDCA, obtaining it in February 2007149. **92.**

Immediately after, and in particular in April 2007, Sigma Tau began to evaluate, through a consultancy company, the possibility of registering the CDCA as an orphan drug for the treatment of CTX also in Europe and already at the time prefigured to sell the future orphan drug at a higher price than the one at which a CDCA-based drug, registered for the treatment of gallstones but administered *off-label* for the treatment of CTX, was being sold at the time, which the company was preparing to acquire. To achieve this goal, the company planned to gradually increase the price of this product *("step price increase" 150).*

93. The company has identified the *Chenofalk®, which* is owned by the company

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[145] *Orphacol*® has been authorized for sale in Italy since January 20, 2017 and is classified as a group H medicine.

[146] See doc. 133.

[147] See doc. 78.104 where Leadiant herself states that *"it will be likely that once registered, an off-label use will be more difficult ".*

[148] See docs. 22.7.156, annex "CTX FDA meeting 08-31-2007, all. "CTX February 2008", 28.2.3 and 28.2.4.

[149] See docs. 22.7.156, annex "CTX FDA meeting 08-31-2007, 78.31, all. *"ODD Sigma Tau Section A to E. 10Sep2014_Final ".*

[150] See doc. 96.213 and 22.7.3 annex "121 06 Report Draft 250307" ("step *price increase should be possible. Step price increase could be achieved by 'withdrawal and reintroduction' or simple price increase on current pack (to evaluate best option requires further analysis). Precedent in Germany for novelty being recognized of old product in new indication. Clear rationale and KOL* [Key Opinion Leader. Ed] *support will be needed to facilitate reimbursement of CDC after a step price increase ").*

Pharmaceutical Dr. Falk Pharma GmbH151, as a drug to be acquired in order to obtain the availability of the *dossier* and the administrative rights relating to the CDCA to request the registration of the drug for the treatment of CTX152.

94. In May 2007 the company contacted the EMA to explain and prepare its application for the orphan designation. However, following discussions with the Agency, it realized that it was unable to provide all the clinical information requested by the Authority, and therefore temporarily put aside the registration project153.

95. Nonetheless, the company decided to carry out at least the initial part of the project and on 19 June 2008 Sigma Tau Pharmaceuticals Inc. purchased the entire Chenofalk® dossier from Dr. Falk Pharma GmbH , *including the* AIC of the drug. valid for the German market154,
taking over the product distribution business155.

96. Following the purchase of the distribution rights of *Chenofalk®,* in order to guarantee a safe source of raw material for the future production of the drug, Sigma Tau Pharmaceuticals Inc. and PCA, after the first contacts between the second half of 2007 and the first half of 2008156, entered into an exclusive supply agreement on June 24, 2008157.

97. The marketing authorization for *Chenofalk*® valid on the German market was then attributed to Sigma Tau Arzneimittel GmbH on 14 October 2008158. From that moment on, the German branch distributed the drug in Germany at the *ex factory* price of 37.75 euros (Excluding VAT) and at the retail price of € 58.69 (VAT included) for a pack of 100 capsules of 250 mg159. The medicine was also exported from Germany to various Member States, including the Netherlands160, the

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[151] See docs. 96.223, 96.213, 22.7.3, annex "121 06 Report Draft 250307", 22.7.156, annex "CTX Decision Analysis v3 ","CTX FDA meeting 08-31-2007 "and" CTX February 2008 ", 28.2.3 and 28.2.4.

[152] See doc. 96.54.

[153] See docs. 138.4.1 and 138.4.6.

[154] The *dossier* included all rights relating to *Chenofalk,* including the AIC for Germany, *know-how,* technology, production data, registration *dossiers ,* clinical and preclinical data and any industrial secrets relating to production, drug development, registration, marketing and exploitation.
The AIC for the German market was issued by the *Bundesinstitut für Arzneimittel und Medizinprodukte* (BfArM) to Dr. Falk Pharma GmbH on 13 September 1999. See docc. 28.2.19 and 127. See *https: // www.pharmaceutical-business review.com/ news/ 16498sigmatau_acquires_chenofalk_from_dr_falk_p/.*

[155] See doc. 78,300.

[156] See docs. 28.2.3, 28.2.4-11, 28.2.13-16, 28.2.28-28.2.30.

[157] See docs. 28.2.27 (containing the text of the agreement) and 28.2.25.

[158] See docs. 78.300, 96.165 and 127.

[159] See doc. 96.75.

[160] See doc. 96.75.

France and Belgium 161.

98. Various documents dating back to a period between mid-2008 and mid-2009 confirm that Sigma Tau intended to pursue its commercial strategy through a gradual increase in the price of the product sold in Germany162, to be applied even before the registration of the orphan drug, in in such a way as to prepare not only the German market, but also the other European markets for the higher price of the orphan drug163. **99.**

In particular, the company was aware that only if it had been a monopolist in the sale of CDCA-based drugs across Europe164
it could have applied a *"premium price"* already for the drug sold *off-label* for the treatment of CTX pending obtaining the orphan designation165. Some consulting firms, in the first half of 2007 and then in early 2008, had therefore suggested to the company to check how to prevent others from producing drugs based on CDCA166. Sigma Tau

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[161] See doc. 96.99.

[162] See docs. 22.7.3, annex *"006060_2 Report",* 96.165, 96.99 and 96.75, which reproduce exactly the formulation already used by the consulting firm in 2007: "[...] *step price increase should be possible" (see* doc. 96.213 and doc. 22.7.3, all . "121 06 Report Draft 250307").

[163] See doc. 22.7.3, annex "006060_2 Report": "[...] *therefore getting an increase in the German price is necessary (or removing this product as a price benchmark) if a higher level of price is the ambition for Chenorm* [commercial name that the company initially intended to give to the orphan drug. Ed] *across Europe. […] Options are a step price increase or product withdrawal, if the German price is not to limit the price achievable for Chenorm elsewhere "* and 22.7.3 all. "121 06 Report Draft 250307" ("Price *should ideally be at level desired post-approval. Desired step price increase can happen pre-or post CTX MA approval").*

[164] See doc. 96.99 which states: *"Acquisition of competing MAs:*
Estedi (Quenobilan) -Spain
Zambon (Quenocol) - Spain
Basi (Xebyl) - Portugal
[…] Acquisitions would give us market exclusivity in the EU (based on current regulatory and sales data ").

[165] See doc. 96.99 *("Sell product on a named patient basis as an unlicensed medicine at premium price [...]*
CDCA currently worth $ 160,000 in Germany (based on approximately 3,000 units sold per year)
If product can be sold as a premium priced unlicensed medicine in Germany, market could be worth between $ 3-4 million ").

[166] See doc. 96.213, 22.7.3, annex "121 06 Report Draft 250307" ("Current *and future suppliers / manufacturers of CDC*

Ease of manufacture?
Can pharmacists compound it?
Can ST stop others from making it?
Can ST stop others from supplying it to pharmacists?
Can ST prevent rival suppliers' CDC from being used in CTX?
If so, for how long and in which territories? "); doc. 22.7.3, annex "006060_2 Report" ("Check *availability of other supplies of CDC*
eg Estedi and Zambon product in Iberia
Other products / brands / generics?
Other countries?
Scale of operation, commercial / regulatory status?
Prices levels? Are they official, published prices?
Interchangeability with Chenorm for use in CDX?
Main current uses? ").

has therefore identified some *"competing MAs" 167,* namely those of the only CDCA-based medicines other than *Chenofalk*® by Sigma Tau still existing in the European Union, *Quenobilan®, Quenocol*® in Spain and *Xebyl*® in Portugal (see par. 78 *above),* which it planned to purchase, as well as the AIC of *Chenofalk*® valid for the Netherlands owned by another company and in relation to which Sigma Tau wondered *"how to proceed" 168.*

100. A document in the file shows that, after the spontaneous exit from the market of *Quenobilan®,* of *Quenocol®,* the German branch of the *former* Sigma Tau group acquired the ownership of the AIC of *Chenofalk*® valid for the Netherlands in September 2009169. However, the firm never used it, while considering it strategic to maintain its formal validity170. The request for revocation was finally presented on 9 September 2015171.

101. The company expected a substantial increase in turnover generated by the application throughout Europe of a price which, thanks to the application of the prefigured *premium price,* could extend from a minimum of € 1,327 to a maximum of € 3,318 per package, with an annual cost of therapy for each patient ranging from € 14,600 to € 36,500172.

102. These price assessments reflected the indications already expressed in April 2007 by the aforementioned consultancy company, which, on the basis of market research, indicated that demand was willing to accept an annual price corridor per patient between 10,000 and 40,000 euros and, in particular, he considered, within this corridor, an annual price of 14,600 euros (and therefore a price of 1,327 euros per package) as *"reasonable" .* The consultancy firm also believed that in some markets the higher price envisaged could also be obtained but that this eventuality might not be in line with the ethics of the company173.

103. In order to justify the application of this price even before the registration of the orphan drug, Sigma Tau (as suggested by the consulting company) intended to leverage the de facto *status* of the product as an orphan drug (subject to a specific awareness campaign among all

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[167] See doc. 96.99 *("competing* Mas").

[168] See doc. 96.99 *("Valid MA in Netherlands (TRAMEDICO) -How to proceed?").*

[169] See doc. 78,300. 170

See doc. 22.7.17 *("If the current license is withdrawn in NL, off-label use for CTX would no longer be possible which would be disastrous. However when the CTX EMA approval is imminent, it may make sense to withdraw the old indication in NL as this may create an opportunity to rebrand the product (and price it differently and higher compared to the old product) ").*

[171] See doc. 96.151.

[172] See doc. 96.99.

[173] See doc. 96.213.

relevant *stakeholders)* and carry out “personalized” sales of the drug administered (initially) *off label174.* In any case, it was essential to obtain the orphan designation for the drug and the AIC for the new indication and the related ten-year exclusive that would have ensured the company a significant expected profitability.

104. Two of the aforementioned documents in particular highlight the company's awareness of the complexity of implementing a strategy aimed at applying the predicted *premium price* in Germany, where the reimbursement price of the future orphan drug to be administered for the treatment of CTX (whether this was administered *off-label* or registered for this therapeutic indication) could have been anchored by the pharmaceutical regulation at the reimbursement price then in force for *Chenofalk®175.*

105. In order to minimize this circumstance, the company envisaged two hypotheses: the simple increase in the price of *Chenofalk*® or its withdrawal from the market and its subsequent reintroduction at a higher price176.

106. Not having acquired the "Falk" brand together with the regulatory *dossier ,* on 15 December 2009 Sigma Tau changed the trade name of *Chenofalk*® to *Xenbilox®177* and from February 2010178 increased the *ex factory* price of the drug to 660 euros per package (which then also reverberated on the sales made in the other member states of the European Union) 179. S commercial operation was not welcomed by the competent German authorities, which however could not prevent it180.

III.5.2 The 2014 Xenbilox® price increase

107. The second part of the project, consisting in the market launch of the CDCA-based orphan drug registered for the treatment of CTX at a long-planned high price, only really took off in 2014 (for

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[174] See doc. 96.213 *("CTX patients will be managed through named patient supplies up until CDC indication is licensed"),* docc. 96.75, 96.99 and 96.165, 22.7.3 (both annexes).

[175] See docs. 96.213 and 96.99.

[176] See docs. 22.7.3, annex "006060_2 Report", 96.99 and 96.165.

[177] See doc. 127. 178
See doc. 127.

[179] See docs. 96.141 and 96.143.

[180] V.doc. 22.7.17: *“Regarding price the history of CDCA, price activity may be very controversial. It was sold as Chenofalk by Dr Falk Pharma at € 58.69 for 100 capsules of 250 mg. Chenofalk went off the market and Xenbilox was introduced by Sigma Tau at € 861.14 for 100 capsules of 250 mg. Since it was a new product, no rebate was applicable. The system could not do anything against this price increase, but it was commented on negatively ".*

the reasons which will be explained *below* par. 145 et seq.) 181.

108. Between March and April 2014 the company therefore began to plan how to implement a new price increase for *Xenbilox®,* not only for the German market but for all of Europe182. It was aware of the fact that an increase in the *ex factory* price of the product in Germany to 860 euros per pack - the first hypothesis of a price increase found in the documents acquired - would have been nullified by the so-called price moratorium introduced in the German law a few years earlier183, which in any case would have imposed the maintenance of the redemption price at 660 euros.

However, given the failure to increase profits in Germany, the firm would have seen its profits grow abroad, where sales were not subject to the redemption price constraint. For foreign sales, the company planned to use a German wholesaler, Juers Pharma Import Export GmbH (hereinafter, "Juers Pharma"), at which to charge a selling price very close to 860 euros per pack, *[omissis].* The wholesaler would have taken over the commercial relations with distributors in the importing countries, thus assuming responsibility for the price increase184, from

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[181] See doc. 96.83 dating back to April 2014 *("For Xenbilox we have no intention to touch the current MA. The plan is to submit an ODD and later a CTX file in ST UK name. After approval we withdraw German product MA. Still this is not yet a plan just an intention chart (before implementation we need to check a few things namely if there are other active MAs in EU that could easily jeopardize our future pricing) ").*

[182] See doc. 96.141 *("You remember that we spoke about a price increase for Xenbilox. Last week I have met [...] the Managing Director of" Juers Imports / Exports "and we have developed an idea how we can keep the price in Germany but increase it for foreign markets (by rationing German wholesalers and have Juers as our wholesaler and point of sale for Xenbilox - who would sell the product to (foreign) customers at a higher* price "). See docs. 22.7.32 and 78.49 *(" we are planning to implement a significant price increase for international shipments outside Germany (where no price increase is possible due to local MA and price reimbursement). We aim to a max price equal to 4,000 euro x unit outside Germany, with and weighted average selling price of 3,500 euro x unit including Germany ").*

[183] The so -called *price moratorium* was introduced for the first time in 2010 in German law and was reformed in May 2017 through the law on strengthening the pharmaceutical offer *("Gesetz zur Stärkung der Arzneimittelversorgung"* or AMVSG for short). The *price moratorium* prevents increases in the reimbursement price of drugs already placed on the market, by requiring manufacturers to grant health insurance companies a discount equal to any price increase compared to the prices of 1 August 2009.
The 2017 novel extended the validity of the *preismoratorium* until 31 December 2022, after updating the redemption prices based on the inflation of 2018.

[184] The company was informed since the beginning of 2008 of the price freedom enjoyed by a pharmaceutical distributor in most European countries in a system in which medicines, especially those not provided with an MA for a given therapeutic indication, are imported and administered *off-label* to individual patients at the specific request of the doctor *("Named Patient Supplies"* mentioned in docs. 96.99 and 96.213). See in particular doc. 22.7.3, annex "006060_2 Report" ("[...] *In most cases, distributors are free to set the price they want. Exceptions are Spain (a state pricing committee evaluates) and France (where a formal national process is adhered to, though there is pricing flexibility). [...] In terms of price-setting, this will mostly be at the distributor's discretion, though in some countries price will be negotiated with the state authorities (eg Spain) ").*

to settle precisely in an amount equal to 860 euros plus transport costs185.
109. In April 2014 the company evaluated a second hypothesis of an increase in the *ex factory* price of *Xenbilox®,* equal to 950 euros per pack186. Subsequently, a third hypothesis of price increase was assessed: in the minutes of the meeting of the *Operational Team Rare Diseases* of Sigma Tau, held in Monaco on May 6, 2014, the *"short term"* and *"medium / long* " objectives were indicated *term "* of the *Xenbilox®* project , defined in the same minutes as *" 2014 Very Important Project ".* The short-term goal was a

"Price increase (in 2 steps)
=> 1st step 1 st of July 2014: 2400 € /
pack => 2nd step Jan, 1st 2014 [2015, ed]: *4000 € /* pack" 187.
The medium-long term objective was the *"registration process… to get the ODD [Orphan Drug Designation,* ed]" for the therapeutic indications of CTX188. The submission to the EMA was scheduled for the following September.

110. This significant increase in the price of *Xenbilox®* was therefore identified by the company as the first operational step in the project to obtain the orphan designation and to register the CDCA with the new therapeutic indication. Similar indications also emerge from the presentation relating to the *Strategic Plan* of the *Global Rare Disease Business Unit,* dated August 2014, where the possible increases in turnover deriving from the *"Xenbilox price increase and global*

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185 See doc. 96.141 ("[…] *how we can increase our profit without being stuck by the price moratorium. Here is the idea: Xenbilox units sold in 2013: 3.125 units (all sold at 660 Euro per unit = 2.06m Euro)*

Units sold to German wholesaler: 614 (we have to assume these packs stay in the German market, however I strongly believe that ca. 300 packs are still being sold to foreign markets)
Units sold to distributors with high likelihood of being send to a foreign market: 1.627
Units sold directly to a foreign market: 884
Idea to discuss: increase the price to 860 Euros per unit to ALL customers (incl. German market). Everything that ends up in Germany will be reimbursed with 660 Euros and we have to refund the German sick funds with the price difference of 200 Euros.
All units that are being sold to foreign markets will not have to be refunded -> 2.511 packs x 200 Euro = ca. 500.000 Euro increase in sales (+ ca. 300 units x 200 Euros = 60.000 Euros) -> all additional sales are profit.

We will only supply the German wholesalers. All other customers will be referred to JUERS who manage the distributors for us. Our price to JUERS will be similar to the 860 [omissis]. *We will have to agree that JUERS will only charge the 860 Euros plus a little surcharge for delivery ").*
186 See doc. 96.45.
187 See doc. 96,228.
188 See doc. 96,228.

registration "189.

111. The documentation on file indicates that from 1 July 2014 Sigma Tau finally increased, as a short-term objective, the *ex factory* price of *Xenbilox®,* sold in Germany to 2,900 euros per package190.

112. Starting from 2 July 2014 and until October 2016, sales of *Xenbilox*® in the EEA and non-EEA countries were mainly made by Juers Pharma, which purchased the medicine from Sigma Tau Arzneimittel GmbH, and, except in some Countries, including Italy, to a lesser extent also from the latter191.

113. In response to the protests of some patients who complained that it was impossible for them or their insurance companies to pay this price, the company, in a letter dated July 2014, justified this increase with the need to finance the development of the orphan drug indication *("In order to be able to maintain and further develop CDCA for this rare disease indication, Sigma Tau has to revise the price in accordance to an orphan indication* (CTX)") 192.

114. An internal document of the company dated September 2015 shows how the price increase implemented in July 2014 allowed Sigma Tau to enormously increase the turnover related to *Xenbilox®,* which has grown by about 2 million euros since 2013193 to over 7 million euros in 2015194.

115. This price increase did not immediately affect Italy as well, where patients were treated until November 2015 through the administration of CDCA-based magisterial preparations produced by the AOU Senese Pharmacy.

116. With the end of the galenic preparation of the Pharmacy and until the introduction in Italy *of the Chenodeoxycholic Acid Leadiant*® in June 2017, the Italian ASL, including the AOU Senese, were no longer able to resort to the galenic production of the Pharmacy and they had to import it

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[189] See doc. 95.5.

[190] See doc. 96.39, 96.43, 96.143 and 96.157. The company has decided not to make a second price increase, initially scheduled for January 2015, given the negative reactions of demand to the first increase in July 2014 (see doc. 96.175).

[191] See docs. 84, 105, 110.1, 138.4.1 and 147.

[192] See doc. 96.43 and 96.217. This document was a response to the negative reaction with which this price increase had been welcomed by patients and doctors in various EU countries, and in particular in France, Belgium, Portugal and the Netherlands, where patients taking Xenbilox® were in a position where they could no longer buy the drug, which had become too expensive . See docs. 96.87, 96.139, 96.147, 96.175 and 96.177.

[193] See doc. 96.155.

[194] See docs. 96.149 and 78.27.

Xenbilox® from Germany pursuant to Ministerial Decree 11 February 1997 and smi195 in order to guarantee therapeutic continuity for their patients (see paragraphs 130, 133 and 134 *below).* For example, in 2016 the ASL of Oristano purchased *Xenbilox*® at a final price, including the margin of the wholesaler and the other intermediaries involved in the distribution, which ranged between 3,400 and 3,600 euros per package196.

III.5.3 Obtaining preliminary orphan designation in 2014

117. On August 28, 2014 Sigma Tau Pharmaceuticals Ltd. requested the recognition *of Chenodeoxycholic acid Sigma Tau* as an orphan drug for the treatment of CTX based on the criteria of prevalence and significant beneficial effects (see para. 38 above) 197.

118. The orphan designation was preliminarily obtained from Sigma Tau Pharmaceuticals Ltd. on December 16, 2014198 (and was then transferred to Sigma Tau Arzneimittel GmbH on May 7, 2015199). In particular, the *Committee for Orphan Medicinal Products* (COMP) of the EMA conferred the orphan designation on the basis of the examination of the scientific literature which highlighted the effectiveness of the CDCA on the main symptoms of CTX, produced by the same Sigma Tau and used by the company to invoke the existence of "significant beneficial effects" of the CDCA with respect to already existing therapies (ie in particular with respect to the cholic acid contained in *Kolbam*® and *Orphacol®) 200.*

119. The importance that the orphan designation played in the project emerges from the documents on file, which show that it was the intention

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195 The decree, published in the Official Gazette n. 72, contains the measures for the methods of importing medicinal specialties registered abroad.

196 See docs. 10, annex 2, 22.7.25 and 28.2.100. See also doc. 78.124 *("All CTX patients were treated in Siena until 2015 - Since 2016 they were sent back to the hospital of the place they live for treatment. This is when only Xenbilox at about 3,7 € k / pack became available. Until then they were treated at € 4 / pack ").*

197 See the decision of the European Commission (2014) 10054 of 16 December 2014. See the preparatory documents for the application for orphan designation at doc. 78.32 and 78.398.

198 See European Commission decision (2014) 10054 of 16 December 2014 available at *http:// ec.europa.eu/ health/ documents/ community-register/ html/ o1406.htm.*

199 See European Commission decision (2015) 3246 of 7 May 2015 available at *http:// ec.europa.eu/ health/ documents/ community-register/ html/ o1406.htm.* also EMA / COMP / 744266/2014 Rev.1 Committee for Orphan Medicinal Products *summary of opinion on orphan designation Chenodeoxycholic acid for the treatment of inborn errors in primary bile acid synthesis,* May 2015, *https: // www.ema.europa .eu / documents / orphan designation / eu / 3/14/1406-public-summary-opinion-orphan-designation-chenodeoxycholic-acid-treatment-inborn-errors-primary_en.pdf.* available on

200 V. EMA, *Public summary of opinion,* cit ..

of the company to continue the request for the AIC for the new therapeutic indication only in the case of definitive obtainment of this administrative title, the possession of which alone would have allowed it to request higher reimbursement prices201.

III.5.4 The price assumptions of the orphan drug

120. Once the *ex factory* price of *Xenbilox® had been increased* to 2,900 euros per pack in the German market (on 1 July 2014), Sigma Tau began planning the next price increase, to be applied as soon as the drug had obtained the designation. definitive orphan. A document dated July 2014 contains the assessments carried out by Sigma Tau with regard to the European market, in the hypothesis of confirmation of the orphan designation for the end of 2015 and the consequent launch of the orphan drug for the first quarter of 2016; on this occasion, estimates of the Net Present Value (so -called *NPV analysis)* of the CDCA registration and marketing project as an orphan drug for the treatment of CTX were developed, elaborating two possible scenarios, a *"base case"* and a *"best case"* scenario (see section III.6.2.i *below).* These estimates made use of a hypothetical price per pack of the future drug of 5,000 euros (ie a hypothetical price of 55,000 per patient per year), which showed extremely high profitability202.

121. These price assumptions stood well above the values that would have emerged as a result of the aforementioned market research commissioned in September 2014 by Sigma Tau to acquire the evaluation of doctors and subjects expressing the demand for the drug about the level of price of a registered CDCA drug for CTX. From these it emerged that in France, for example, the price considered reasonable for the therapy was around 25-35,000 euros a year, in Italy around 15-20,000 euros a year.
[203] and in Spain it was around 20-30,000 euros per year, while in the Kingdom

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[201] See docs. 22.7.105, all., 22.7.129 *("in case of negative response, STRD will definitively withdraw the EMA authorization filing and will continue to sell Xenbilox under current procedures without any room for sales expansion"; "In case of negative response to the appeal to COMP opinion: - With no ODD, request for approval withdrawn; - Xenbilox sold off-label; - No price increase vs current; - No volume increase "),* 22.7.49, 78.8, 78.236, 78.239, 96.104.

[202] See doc. 95.6.

[203] See doc. 22.7.17 *("Given the current very-low price that CDCA is available for, it was unsurprising that when pricing was discussed, responses were constrained by the peculiarity of the situation in Italy "The actual cost of the CDCA internally produced is very cheap, maybe too cheap! I am not sure but I think that the cost of a capsule is lower than € 1 "*

Combined this rose to £ 50,000 a year, although some respondents had indicated that for an effective but old drug, the annual price of therapy would have to settle at 4-6,000 pounds204.

122. A document dated December 2014 also highlights Sigma Tau's awareness of the possibility that the application of a high price for the orphan drug would be negatively received by the medical community: *"Sigma Tau want to increase the monthly treatment cost of Xenbilox® and have already introduced some price increases but there are some concerns regarding a potential back-lash from treating clinicians "205.*

123. From a document dated October 2015, it appears that new market research commissioned by Sigma Tau indicated the existence of four risk factors, of a competitive nature, which could have compromised the application of the pricing policy envisaged by the company. These factors were identified in the presence of *Xenbilox*® in some national markets, in the production of magisterial preparations in Italy, in the need to justify this price request in light of the investments made, and finally in the price of medicines registered for other ultra-rare diseases, including which *Orphacol®206.* In particular, the research carried out highlighted the extreme reluctance of the interviewees *(health economists,* doctors and pharmacists consultants of the national regulatory authorities) to make a price comparison between the CDCA and these other drugs recently mentioned207.

124. A presentation containing the guidelines of the *Long Range Plan* 2016-2020 of the Sigma Tau *Global Rare Disease business unit* is attached to a subsequent internal *e-mail* dated January 2016208 . In the face of a

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"If the cost of an industrially-manufactured CDCA will be too far from the actual cost calculated through the value based system (14 € for a capsule) probably the National and the Regional Health Authorities will consider it too expensive"

If CDCA were supplied conventionally, annual costs of € 15-20,000 were considered appropriate, but we also heard;

"A very old molecule very easy to be manufactured is never too cheap!" ").

[204] See doc. 22.7.17.

[205] See doc. 78.71.

[206] See doc. 78.80 *("Based on discussions with Sigma Tau there were 4 price" points "that could be relevant to the project. Price of compounded CDCA (Italy). Price of off-label Xenbilox (Netherlands and Spain but price may not be visible). Premium price required by Sigma Tau to justify the investment. Prices of other ultra-orphan products that have a similar clinical impact. […] Expectation that prices 2-3x the Xenbilox price was feasible with an ideal upper limit of approx. € 100,000 / annum. Key risk were seen as follows: Presence of compounded CDCA: Lower threat. Withdrawal of Xenbilox: Needs to be well managed. Potential indication restriction: Probably only an issue if CDCA perceived to be "very" high price ").*

[207] See doc. 78.80 *("None of the respondents wanted to use benchmark or analogue products produced for the pricing exercise. [...] In some cases respondents were slightly confronted that and attempt was being made to make pricing decisions by this approach").*

[208] See doc. 95.4.

revised internal planning, which foreshadowed the approval of the orphan drug designation by the EMA for the month of August 2016 and the consequent launch of the product for the following month of October, three new price hypotheses were developed for the drug orphan: 1) the first, defined as “realistic”, amounted to 6,000 euros per package; 2) the second amounted to 7,500 euros per package *(“higher price”);* 3) the third, the most optimistic, was € 10,000 per pack *(“significantly higher price”).*
The presentation concluded by stating that *“Xenbilox / CDCA approval and launch in Europe and possibly in US represents a unique and exciting opportunity to grow and further develop the business”.* These three price assumptions were used in the subsequent documents found referring to the period prior to the market launch of the orphan drug. In no case was a price higher than 10,000 euros per package hypothesised209.

III.5.5 The signing of a new CDCA supply agreement exclusively with PCA in 2016

125. From some documents acquired in the file, it appears that already in 2008 the pharmaceutical company became aware of the fact that if it had charged particularly high prices for the orphan drug, pharmacists could have resorted to setting up a galenic production210.
However, as anticipated, in June 2008 Sigma Tau guaranteed the exclusivity in the procurement of the raw material from the only existing supplier in Europe (see paragraphs 52, 53, 59 and 96 *above).* As a result, several Italian ASLs that intended to set up their own galenic production were unable to have access to the PCA raw material, to which they had turned211. In two cases at least the requesting doctors were re-directed towards the purchase of *Chenofalk®212.* But this demand for CDCA was finally satisfied by the Pharmacy of the AOU Senese, which supplied its CDCA-based galenic drugs also to the other Italian hospitals thanks

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209 In particular, doc. 78.27 (e-mail entitled "Xenbilox 5 years plan + PY sales") of September 2016 - the one closest to the launch of the *CDCA Leadiant*® on the market - refers to the base scenario, ie 6,000 EUR.

210 See doc. 22.7.3, annex "006060_2 Report" ("If *ST charges prices significantly higher than currently available product, pharmacists will seek to supply using this lower-priced product instead of branded Chenorm if the two are interchangeable").*

211 See docs. 25.3.10, 25.3.32, 28.2.17, 28.2.18, 28.2.21, 28.2.26, 28.2.168, 28.2.169, 28.2.170, 28.2.171.

212 See docs. 28.2.17, 28.2.18, 28.2.26, 28.2.173.

to the *stock* of raw materials accumulated in 2007 (see par. 75 *above).*

126. Subsequently, in September 2014, the company was reiterated by a consultancy company that, especially for an *"old drug",* the production of masterful preparations, as in fact occurred in Italy, could have represented a risk for the success of the pricing strategy that Sigma Tau intended to apply213. Hence the need for the pharmaceutical company, suggested in 2015, to have the exclusivity of the raw material214 and, specifically for Italy, to try to put a *"stop"* on the galenic production of the Siena hospital and replace it with *Xenbilox®215.*

127. In order to confirm its exclusivity on the procurement of the raw material, at the beginning of 2015 Sigma Tau Pharmaceuticals Inc. therefore contacted PCA with the proposal to enter into a new exclusive supply agreement for the active ingredient216. In view of this, the pharmaceutical company first of all asked PCA to carry out activities aimed at preparing the *DMF,* improving the production of the active ingredient, through the implementation of the new purity test developed by Sigma Tau itself (see par. 53 above) 217. These activities were actually carried out by the chemical company for a total fee of *[300,000-*

400,000] euro 218.

128. The signing of the new exclusive supply agreement was preceded by a long negotiation219, which saw the parties oppose each other on various issues, including, in particular, the extent and reciprocity of the exclusivity220.

129. In relation to this clause, some documents of March 2016 show that during the negotiations the parties considered it necessary to find a legal justification for this clause, which made reference

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213 See doc. 22.7.17: *"Strategies to get around paying very high prices for old drugs include import from other countries and suggesting small batch manufacturing by pharmacies. CDCA seems to be available to be bought for compounding so this will remain a risk in Germany (as it is already done in Italy) ".*

214 See doc. 78.34: *"How can ST minimize the risk from compounded product availability in each country? How are compounding companies obtaining the API for CDCA? (High minimum order quantities and low prescribed volumes mean that API likely to be out of date). ST should have exclusive use for all API destined for use in CTX patients ".*

215 See doc. 22.7.17: "[…] *need to establish if will help Xenbilox supply* […] *Discussions in Italy to understand if any possibility to replace self-compounded CDCA with Xenbilox"; "Understand what, if anything, it would take to stop the hospital making its own CDCA and instead purchase imported CDCA",* doc. 78.44 *("The idea of buying their product was just to eliminate it"),* doc. 78.52 *("stop them selling CDCA").*

216 See doc. 78.203.

217 See docs. 28.2.32-28.2.42, 28.2.67 and 78.203.

218 See docs. 28.2.79, 28.2.81, 28.2.92, 28.2.102, 28.2.128, 28.2.134, 78.13, 78.199, 110.4B.

219 See docs. 22.7.43, 28.2.31, 28.2.32, 28.2.55, 28.2.66, 78.192, 78.198, 78.202, 78.220, 78.228 and 78.230.

220 See docs. 22.7.92, 22.7.113, 22.7.116, 28.2.68, 70.31, 70.33, 70.35, 70.39, 78.4, 78.209.

to the market exclusivity deriving from the orphan designation221. Some subsequent documents, dated October 2016, however, confirm that the concern of the pharmaceutical company was actually precisely that of preventing pharmacies from setting up a galenic production using the raw material of PCA *("the concern is that a compounding pharmacy could look to buy API from you on the grounds that it was to be used for a bile acid disorder other than CTX and then use some it for CTX patients ") 222.*

130. Pending the signing of the new agreement, in November 2015 the Pharmacy of the AOU Senese stopped producing galenic drugs based on CDCA because it had run out of stocks of raw materials (see paragraph 77 *above).* In January 2016, the Pharmacy communicated the shortage of raw material to Sigma Tau, which, during a meeting, however, declared itself not available to supply it with other raw materials, but proposed that the patients of the Sienese University Hospital be directly supplied the orphan drug produced by the company223. On the other hand, the possibility arose that the Sienese AOU would make use of the so-called early access pursuant to law no. 648/1996 for drugs not registered in Italy and still in the trial phase224 225.

131. The AIFA authorization request was carefully monitored and guided by Sigma Tau, who considered the issue to be *"sensitive",* as it could have significant implications, not only in Europe, but also outside, on the strategy of price that the company intended to implement226, especially if this request, not being able to relate to the orphan drug,

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[221] See doc. 28.2.66 *("ST for the reasons widely explained during our last meeting on November, 11th at PCA and in our e-mail exchanges, ST requires PCA to grant exclusivity on CDCA supply (at least 10 years) for the production of any FF use to treat any biliary acid disorders. PCA-ST will work together with their legal advisors in order to find a way to legally justify exclusivity, eg by linking to EU and US orphan drug designation of CDCA ").*

[222] See doc. 78.9.

[223] See docs. 6.10, 6.11 and 6.13.

[224] Law no. 648/1996 allows the dispensing of a drug at the expense of the NHS, subject to the opinion of the Technical-Scientific Commission (CTS) of AIFA, when there is no valid therapeutic alternative: for innovative medicines authorized in other States, but not in Italy, for medicines not yet authorized, but in clinical trials, for medicinal products to be used for a therapeutic indication other than that authorized. In the presence of a valid therapeutic alternative, this is allowed for medicinal products to be used for a therapeutic indication other than that authorized.

[225] See doc. 78,251.

[226] See docs. 78.270 and 78.290 *"The 648 application for Siena is very a" delicate "issue and I want to be sure to move properly. […] We agree this is a "delicate", but crucial topic that needs to handled carefully.*
Especially given the potential implications this might have across EU and beyond, under the International Reference Pricing Scheme ".

at the time still not in production, had concerned *Xenbilox®227, a* circumstance that the company absolutely intended to avoid228. The company therefore took time, even though it was aware of the potential negative consequences that this would have on patients229, and in the meantime decided to redirect the AOU Senese towards the purchase of *Xenbilox*® from Juers Pharma230.

132. In mid-February 2016, however, the AOU Senese urged the company to provide what was necessary to start the AIFA request procedure for early access pursuant to law no. 648/1996231 as the *stock* of magisterial preparations already prepared would have allowed it to supply the medicine only to three patients and only for the following two or three months232. The serious supply problem and the difficulty in guaranteeing the continuity of therapy to their patients, however, still persisted in mid-March, generating the strong concern and disappointment of the Sienese doctors *("Unfortunately, the information we received, not from AIFA but by dr.* [N.] *that as you will recall he should have sent us all the documents to forward the procedure to AIFA, were that we would have had to wait until April, the time necessary for the completion of I no longer remember what on their part ... contrary, therefore to all the statements of principle made and reiterated that patients should not have had any*

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[227] See doc. 78.154 and 78.288 ("[...] *we are waiting for a pending decision from the NRG committee to have a commercial brand name. Until we do have one, 648 is on hold. [...] What I meant is that, in the current circumstances , given that we still have Xenbilox on the market, if any of the stakeholders you listed requests for a 648, it will be under the commercial brand name of Xenbilox. Please take into account that part of the procedure to request for a 648 is to mention commercial brand name and active principle ".*

[228] 78.110 *("My current understanding is that a 648 submission for the new product can't be done under the price of Xenbilox. That would mean this 648 is for Xenbilox, and not for the new product. [...] Agree. 648 has to be for CDCA and not for Xenbilox. ").* See doc. 78.270 *("Please note that the document (which Sue has already seen even though in a previous version) deals with CDCA, as that being the object of the request (and not Xenbilox)").* See doc. 78.287 *("The request and the report is based on CDCA (no mention of Xenbilox whatsoever). At some point, when we address the therapeutic plan, the name of the drug and the producer / supplier must be indicated. At that point the new brand name and the MAH or MA applicant, that I understand at the moment is still ST GmbH, will have to be included ".).*

[229] See doc. 78.270: *"An ethical issue. There are patients that sooner or later will need the drug that Siena cannot provide. I know they can get it from Germany but it may not be so easy. […] Understand the ethical concern, but quite honestly from ST-RD perspective the patients in Italy are in the exact same conditions of all other patients across the world, with the exception of Germany and the US. […] I'm not worried about haggling and managing Siena. However, I hope this will happen in due time. The March meeting of the CTS could be a target. The reference to the ethical aspect of Italian patients was a way to raise awareness of the times ".*

[230] See doc. 78.145 and 78.154.

[231] See doc. 78.154 *("Dear Dr.* [N.], *having not yet received the necessary documentation to start the process of supplying CDCA to CTX patients, I would like to ask you in consideration of the practical difficulties associated with the unavailability of the drug, which unfortunately we will have soon").*

[232] See docs. 6.10 and 6.11.

discomfort resulting from the "industrial process", they will have it and how [and how. ed] *and us with them ... ") 233.*

133. From the documentation acquired it emerges that at the end of March 2016 the request had not yet been finalized, because, contrary to the initial forecasts (which contemplated the start of production in April 2016) the product was not yet in production and did not have a commercial name234 . Patients with CTX followed by the Sienese AOU were therefore treated with the administration of *Xenbilox*® imported from Germany235.

134. With the end of the galenic preparation by the Pharmacy of the AOU Senese, the other Italian public structures also encountered great difficulties in supplying the drug to continue the therapy hitherto administered to their patients. Therefore they again turned to PCA (or Sigma Tau itself) to obtain the active ingredient and thus proceed with the galenic preparation, however without success, given the exclusivity that had bound the chemical company since 2008236.

135. In June 2016, the PCA, concerned about the growing and pressing demand for CDCA from Italian hospitals, which complained about the serious lack of the active ingredient and the risk for their patients, reported the problem to the pharmaceutical company, fearing an exception to the exclusivity clause contained in the supply contract stipulated with Sigma Tau. The latter considered these requests as potential threats for the introduction of the orphan drug at the desired price in the Italian market, and above all for its future reimbursement by the NHS, and therefore countered them by spreading the message in the market that the only source that the hospitals would have had to use was Sigma Tau itself (with the purchase of *Xenbilox®)* 237.

136. CDCA's new exclusive supply agreement was entered into between Sigma Tau Rare Disease Ltd. and PCA on 11 November 2016 and replaced

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[233] See docs. 6.9, 6.10, 6.11, 22.7.146.
[234] See docs. 78.287 and 78.288.
[235] See docs. 6 and 78.124 *("All CTX patients were treated in Siena until 2015 - Since 2016 they were sent back to the hospital of the place they live for treatment. This is when only Xenbilox at about 3,7 € k / pack became available") .*

[236] See docs. 28.2.58-28.2.61, 28.2.86, 78.197, 78.243. From doc. 22.7.64, annex “Theophylline - CDCA” also shows that in October 2016 hospitals in other Member States were also trying to find the active ingredient on the market. Given the exclusivity of the CDCA, the pharmaceutical company was also aware of the unavailability of the CDCA on the market (see Doc. 78.104: *“Differently from us, CA API can be acquired”).*
[237] See docs. 78.19 and 78.241 *("They perfectly know how and where to buy. They are trying to get it from PCA at a cheap price to create a precedent that will kill our future reimbursability and price. ").*

the agreement between Sigma Tau Pharmaceuticals Inc. and the same PCA dated June 24, 2008, resolved by mutual consent238.

137. The new agreement has a duration of 7 years, automatically renewable for another two, and is valid globally. *Inter alia,* it provides that the pharmaceutical company can purchase CDCA exclusively from PCA and use this active ingredient only for the production and marketing *of Chenodeoxycholic acid Sigma Tau*® for the treatment of CTX (Article 2.2); similarly, binding the chemical company even more than in the past, the agreement establishes that PCA sells the CDCA exclusively to the pharmaceutical company for the production and marketing of the aforementioned product (Article 2.3) 239. The exclusivity that binds the chemical company does not prevent it from supplying the raw material to third parties if the CDCA is used to produce other drugs for different treatments. The art. 5.1 of the agreement also provides for a fee for PCA equal to *[1,000-5,000]* euro / kg - where in the context of the 2008 agreement, PCA initially received a fee equal to *[1-500]* euro / kg for the years 2008 and 2009, subsequently increased to *[500-1,000]* euro / kg240 -, and the payment to PCA of two *royalties,* each equal to *[200,000-300,000]* euro, upon the achievement by Sigma Tau of the AIC at the EMA and the FDA (art. 7.2) 241.

138. Various pieces of evidence acquired in the documents show that, in compliance with the exclusivity clause contained in the agreement of November 2016, PCA has refused over the years multiple requests for supply of CDCA, aimed at fueling the production of galenic medicines .

139. Between 2017 and 2019, PCA was, in fact, contacted by various suppliers of pharmaceutical grade active ingredients to hospital pharmacies in some European countries - including Italy according to the assessments of the pharmaceutical company itself - who intended to proceed with the galenic preparation242, as well as once again, again in this period of time, by two Italian doctors who were treating patients with CTX and who, in at least one case considering the price at which the orphan drug was sold *" extremely onerous "* and *" inadmissible ",* likewise

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238 See docs. 28.2.99 (bearing the text of the agreement), 28.3B, 78.191 and 78.192, 78.198, 78.231.

239 See for this purpose clause 2.1 of the 2008 agreement with clause 2.3. of the 2016 agreement.

240 See docs. 28.2.27, 28.2.68 and 22.7.92.

241 See doc. 25.3.9, 28.2.99, 28.2.111, 28.2.112, 28.2.115.

242 See docs. 28.2.117, 28.2.119, 28.2.123, 28.2.131, 28.2.132, 28.2.156-28.2.159, 28.2.161-28.2.165, 28.2.183, 28.2.184, 78.201, 78.204-78.208 and 78.210.

they required the active ingredient in order to prepare the drug themselves243. Similar disappointment was shown by another Italian doctor, who, aware of the previously existing galenic production and considering the price of *Xenbilox® already high,* assessed the price at which Leadiant intended to introduce (and then introduced) the *CDCA Leadiant* very negatively. ® on the Italian market and underlined its unfairness with respect to the investments made244. Moreover, the company was aware of the fact that this position would be shared not only by the medical-scientific community, but also by AIFA245.

140. In response to these requests, PCA has always refused the supply of CDCA (sometimes citing the end of stocks246) and promptly reported all requests received to Leadiant. For its part, Leadiant has always carefully monitored the behavior of PCA, verifying, especially in the first six months of 2017, that it had not supplied the active ingredient to companies that could serve hospital pharmacies, including the Italian ones247.

III.5.6 Obtaining the definitive orphan designation and the AIC in 2017

141. After Sigma Tau Arzneimittel GmbH transferred the German marketing authorization for *Xenbilox®* to Sigma Tau Rare Disease Ltd. 248 in August 2015, on 29 October 2015 the German branch of the group submitted an application for marketing authorization for *Chenodeoxycholic acid Sigma Tau,* through the aforementioned procedur

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243 See docs. 22.7.68, 22.7.69, 28.2.121, 28.2.136, 28.2.140, 28.2.141, 28.2.189, 28.2.191, 78.89, 78.98, 78.122, 78.158, 78.213, 78.286, 78.347, 78.350, 78.367.

244 See doc. 78.124 ("- *All CTX patients were treated in Siena until 2015 - Since 2016 they were sent back to the hospital of the place they live for treatment. This is when only Xenbilox at about 3,7 € k / pack became available. Until then they were treated at 4 € / pack -Given that all companies need to make money (no doubt on that), the x 1k increment is not perceived as "fair" toward the investments (retrospective study in Siena and production upgrade, that he wasn 't even aware of) - A second increment with change to Leadiant will sound even more inappropriate ").* See doc. 78.159, where in the internal correspondence of the company the article *Appeals against the former Sigma Tau is commented,* in *Milano Finanza,* 4 September 2018, cit., And with concern it is highlighted that a doctor affirmed that the price of the drug orphan should have been 10 times lower.

245 See doc. 78.124 *("His position will probably be common in Italy, both among clinicians and AIFA commission members (especially now that EPAR is clear on the hybrid medicine of Xenbilox) ").*

246 See docs. 28.2.158 and 28.2.162. 247

See docs. 22.7.104, 78.206, 78.207 *("We continue with our investigation and I am confident that any threat to our commercial position will be quashed. I would ask that you continue to be vigilant and let me know if you see anything else suspicious coming to you from the Netherlands ")* and docs. 28.2.149, 78.219, 78.312,78.313 *("Anyway it would really help if PCA would close the tap on all of this for the coming months.*
I am sure it is also not in their best interest to have compounding around. They have a nice contract ") and 78.314.

248 See docs. 96.151, 96.83 and 138.4.1.

authorization in the so-called “hybrid” abbreviated form (see paragraphs 32-35 above) 249.

142. The *dossier* presented by Sigma Tau Arzneimittel GmbH for the marketing authorization request for the orphan drug drew part of the data from the *Xenbilox® dossier* (which, as anticipated *above* in paragraph 35, is the so-called reference drug of the orphan drug250), and in particular Module 4 relating to pre-clinical pharmacological, pharmacokinetic and toxicological studies of the drug251. The other parts of the *dossier* - the product quality profiles (Module 3) and the clinical trial of the drug (Module 5) - were developed by the company.

143. In Module 3 the company presented the results of the tests carried out to improve the quality of the product. The acquired documentation highlights that Sigma Tau did not carry out bioequivalence studies, given that the two molecules were identical from a pharmaceutical point of view, in terms of composition (active ingredient and excipients) and dosage, as well as being produced on the basis of the raw material from the same chemical company, or PCA252.

144. In Module 5, which concerns the "additional documentation" required by the applicable discipline for the proof of the efficacy and safety of "hybrid" drugs in the new therapeutic indication (see paragraph 34 *above),* the company presented two retrospective studies based on the administration of two similar CDCA-based drugs (Xenbilox, in one case, and

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[249] See doc. 78.68. See the European Commission decision of 10 April 2017 C (2017) 2488 (final), available *https:// ec.europa.eu/ health/ documents/ community register / 2017/20170410136235 / dec_136235_it.pdf.*

[250] See EMA, *Assessment report,* cit., P.

[251] 5.g The content of the *dossier* is specified in Annex I of Directive 2001/83 / EC, which contains "analytical, toxic-pharmacological and clinical standards and protocols in the field of tests carried out on medicinal products". The first of the four parts into which Annex I is divided (entitled "requirements relating to the standardized dossier for marketing authorization") contains 5 modules, of which, as far as is noted here, one dedicated to chemical information , pharmaceutical and biological for medicines containing chemical and / or biological active substances ("Module 3"), one dedicated to non-clinical reports ("Module 4"), in which it is required to produce evidence of pharmacological, pharmacokinetic and toxicological studies conducted on the medicinal product under application, and one on clinical studies ("Module 5"). See doc. 138.4.13.

[252] See doc. 95.5, 95.6, 78.30, annex "Annex 1", p. 28 *("This product does not meet the definition of a generic, nor are there changes to the bioavailability as the reference and proposed product are the same"),* 78.60, 78.211, 78.352, all. "Chenodeoxycholic acid - 2nd LoOI", 78.357 ("[...] *the retrospective data that will be collected have been obtained with a galenic formulation of chenodeoxycholic acid and the retrospective protocol is purposely focused on chenodeoxycholic acid and not Xenbilox. The Univ of Siena will prepare a technical report that will in some way "validate" it and will highlight overlapping features with Xenbilox indicating the same API.* [...] *the galenic formulation manufactured in house at the pharmacy can be considered pharmaceutically equivalent and this means at least in the EU no bioequivalence studies are required. The API comes from the same manufacturer and the excipients and composition are according to the Ph.Eur monograph for CDCA ").* See EMA, *Assessment report,* cit., P. 8.

galenic preparations from the Pharmacy of the AUO Senese, in the other case253) to patients with CTX followed by the two main treatment centers for rare disease existing in Europe254, replacing prospective placebo-controlled studies *(clinical trials),* the main method of clinical trial.
In fact, the company decided not to carry out prospective clinical studies, in consideration of the fact that their completion, which involves the creation of a control group, or a group of patients to whom the drug is not administered, would have raised ethical problems, given that patients included in this group are effectively denied access to therapy, and from since in any case the low spread of the disease would not have allowed the creation of a statistically significant sample of patients on which to carry out *clinical trials255.*

145. Towards the middle of 2014 Sigma Tau Pharmaceuticals Inc. had, in fact, begun to collaborate directly with the specialist doctor of the AOU Senese to verify his willingness to carry out a retrospective study on 25 patients affected by the rare disease and treated for decades with the CDCA in galenic form at the AOU Senese256.

146. Sigma Tau was not the only company to contact the University of Siena to carry out such a study. Indeed, even Retrophin Inc. (hereinafter, also "Retrophin"), owner since 2014 of a CDCA-based orphan drug authorized for the treatment of gallstones in the United States but administered for the treatment of CTX, *Chenodal257,* had

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253 To support the consistency between the two retrospective studies (carried out on the basis of the administration of the galenic drug and *Xenbilox®)* presented in support of its MA application, Sigma Tau has it carried out a comparison activity between the capsules produced by the Pharmacy of 'AOU Senese and *Xenbilox®.* See doc. 78.44. See also EMA, *Assessment Report,* cit, p. 35: *"Results of studies of dissolution comparing the two products demonstrated that, despite minor differences in excipients contained in the compounded and reference formulations, both products can be considered similar".*

254 See doc. 72.1, p. 18.

255 See docs. 78.30, annex "Annex 1 - Overview of product development", 78.45, 78.60, 78.66, 78.68, 78.69, 78.70, 78.346, 78.351, annex "CDCA reg strategy EU_21.01.16.pptx", 78.405.

256 That is the collection and organization of material relating to the clinical observation of patients treated with a given drug. See docs. 6.1, 22.7.56, 22.7.62, 22.7.67, 22.7.71, 22.7.119, 22.7.121, 78.36, 78.37, 78.41, 78.55.

257 *Chenodal* has the 2013 United States orphan designation (cf. *https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=300510 (https://www.sec.gov/Archives/edgar/data/1438533/000162828016011857/rtrx-201510k.htm).* Retrophin Inc. obtained ownership of *Chenodal* with the acquisition of Manchester Pharm Inc. in early 2014 (see https://www.thepharmaletter.com/article/retrophin-to-acquire-manchester-pharma-in-62 -5-

million-deal). Chenodal *is* in phase 3 of *clinical trials* to study the efficacy of CDCA for the treatment of CTX (see *https://clinicaltrials.gov/ct2/show/NCT04270682* and *https://www.globenewswire.com/en/news release/2020/02/24/1989511/0/en/Retrophin-Reports-Fourth-Quarter-and-Full-Year-2019-Financial Results.html).*

made a similar attempt, which however proved unsuccessful258. The exclusive collaboration of the University of Siena with Sigma Tau began at least in May 2014 and continued in the months prior to the presentation of the request for orphan designation for the CDCA259.

147. The collaboration established was then formalized. In fact, in October 2014, Sigma Tau Research Switzerland SA and the AOU Senese entered into an agreement concerning one of the two aforementioned retrospective studies260, which was merged in December 2014 into a framework agreement between Sigma Tau Pharmaceuticals Inc. and the company that it disciplines, in addition to the execution of the study, also the transfer of all data, knowledge and results obtained there261. In particular, art. 7 of the convention provides that the scientific results achieved are owned by Sigma Tau (now Leadiant). Similarly, the lett. *c)* the framework agreement provides for the obligation for the Sienese University Hospital to transfer to Sigma Tau all data, knowledge and results achieved / obtained in the course of the retrospective study and the prohibition to transfer, sell or license or otherwise assign the data and / or the rights connected to them to third parties. Furthermore, Sigma Tau Research Switzerland SA has entered into a protocol with the hospital which, *inter alia,* provides for art. 12.4 the mandatory transfer of the data obtained in the retrospective studies to Sigma Tau262.

148. All this, namely the exclusivity in favor of the company on the data and results of the study stipulated at the end of 2014 as well as the simultaneous obtaining by Sigma Tau of the preliminary orphan designation263, was considered by the company itself sufficient for the US company to have no access to the European market264.

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[258] See docs. 95, 133 and 138.4.7.

[259] See docs. 6.1, 6.2, 22.7.71, 95 and 138.4.7 *("We need to take this relation with Prof* [F.] *directly on board (STRD), get the clinical data on the CTX study asap and eventually involve him in a new study. We need to engage him and soon ").*

[260] See docs. 6.6 and 6.7.

[261] See docs. 6.3 and 6.8. This agreement is attached to Resolution no. 84 of 20 February 2015 of the Company University Hospital of Siena which approved the framework agreement. See also doc. 22.7.141.

[262] See doc. 78.41.

[263] See doc. 95.15, from which it emerges that the company at the end of 2014 considered that *"ODD protects against other CDCA products".* This circumstance then evidently convinced Sigma Tau of the fact that Retrophin Inc. would not have entered the European market, so much so that it assumed that it owned 100% of the market. See docs. 22.7.129 and 95.15 *("Retrophin will not enter RoW market").* See also doc. 78.249 from which it emerges that Sigma Tau in July 2015 stated that the US competitor *"is thought to have pulled out of Europe (in terms of plans to launch there) since ST obtained the Orphan designation for CDCA so Retrophin's CDCA is not expected to be a competitor in Europe ".*

[264] In fact, in July 2015, the company itself discussed internally the potential effects that the registration of *Chenodal* would have on the European market, concluding that if Retrophin Inc. had wanted to request the orphan designation also in Europe, it would not have been able to use the data of the Italian center nor of

149. In addition, in early 2015, Sigma Tau Pharmaceuticals Ltd. entered into a similar agreement with the Dutch Casinius Wilhelmina hospital in Nijmegen for the conduct of another retrospective study based on the *off-label* administration of *Xenbilox*® to 35 patients since 1981. Similar contractual obligations regarding the exclusive ownership of Sigma Tau of the data underlying the retrospective study and the relative results are contained in art. 4 of the agreement and in art. 12.4 of a second protocol also entered into with Sigma Tau Pharmaceuticals Ltd. 265.

150. According to the information that the same company has included in its regulatory *dossier* submitted to AIFA for the purposes of the request for reimbursement *of the Chenodeoxycholic acid Leadiant®,* information confirmed in a hearing by the specialist doctor of the AOU Senese266, the two retrospective studies are the largest ever carried out globally, not only in terms of the sample of patients involved, but above all in terms of the length of the observation period of the results of administering CDCA to said patients267.

151. The retrospective study of the Sienese University Hospital and the retrospective study of the Dutch Casinius Wilhelmina hospital in Nijmegen cost Sigma Tau, respectively, *[100,000-200,000]* euro268 and *[100,000-200,000]* euro269, for a total of *[300,000-400,000]* euro, to which *[200,000-300,000]* euro could be added corresponding to the *royalty* provided for in the contract stipulated between Sigma Tau Research Switzerland SA and AOU Senese270.

152. The company submitted the marketing authorization application on 14 September 2015271. From the inspection documentation it emerges that in the context of the procedure for the assignment of the MA, in September 2016 the *Committee for Medicinal Products for Human Use* (CHMP) of the EMA, in giving a positive opinion to the AIC request, considered that the *CDCA Sigma Tau* were not "similar", to

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the Dutch one, due to the exclusivity enjoyed by Sigma Tau on these data *("Require EU case studies to support EU filing and ST has exclusive agreement with* [F.] *and potentially* [V.] to *have access to their case studies so Retrophin could not use these major centers " (see* doc. 78.249).

265 See doc. 22.7.117, 78.41, 78.224, 78.227 and 78.237.

266 See doc. 133.

267 See doc. 72.1, from which it emerges that in terms of patient sample, the two retrospective studies are the largest; the reimbursement *dossier* also cites a Spanish study with a sample of patients comparable to those of the two Dutch and Italian studies, but still lower (23 patients). The samples from the other studies are significantly lower. See also doc. 140.3.

268 See doc. 6.8.

269 See docs. 78.222, 78.223, 78.237 and 78.387.

270 See doc. 141.

271 See EMA, *Assessment Report,* cit .

pursuant to art. 8, par. 1, of the EC Regulation n. 141/2000272, neither to *Kolbam*® nor to Orphacol®273 , given the structural difference between CDCA and cholic acid, their different mode of action and their consequent different biochemical action, highlighted by Sigma Tau during the procedure274 . The judgment of non-similarity therefore allowed the company not to suffer the foreclosure effects linked to the *market exclusivity* already enjoyed by *Kolbam*® and *Orphacol*® (see paragraph 41 *above).*

153. Furthermore, after an initial negative opinion in October 2016275, following the appeal lodged by Sigma Tau (already Leadiant), in February 2017 the *Committee for Orphan Medicinal Products* (COMP) of the EMA finally considered that the for the orphan designation continued and confirmed the orphan drug *status* for the CDCA276, basing this decision on the clinical evidence adduced by the same company regarding the possession by the CDCA of "significant beneficial effects", especially on the neurological level, with respect to acid colic, contained in *Kolbam*® and *Orphacol®277.*

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[272] For the notion of similarity see par. 41 *below* in the text and relative footnote on the page.

[273] See EMA, *Assessment Report,* cit .

[274] See docs. 78.176 *("structurally they differ in terms of the number of hydroxyl group substituents of the nuclear steroid backbone. CA is a trihydroxylated while CDCA is dihydroxylated. It is indeed known that even small structural differences in structural features, such as is the case between can chenodeoxycholic acid and cholic acid can lead to major differences in biochemical activity "),* 78.352, 78.53 and 78.351. It should be noted that in April 2016 the EMA's CHMP was moving, conversely, towards a judgment of similarity between CDCA and cholic acid (see doc. 78.176), overturned thanks to the arguments put forward by Sigma Tau based on the differences between the two. molecules indicated in the text.

[275] In the *meeting* of 4-6 October 2016, the COMP of the EMA had issued a negative opinion on the maintenance of the orphan designation, believing that the superiority of the CDCA over cholic acid had not been sufficiently demonstrated by Sigma Tau. In particular, according to the EMA, Sigma Tau would not have demonstrated through comparative scientific studies that the CDCA actually had a *"significant benefit"* compared to colic acid. In January 2017 Sigma Tau appealed against this opinion, citing the superiority of the CDCA versus cholic acid through a qualitative comparative analysis of the effects of the two molecules. See doc. 22.7.8, 22.7.49, 22.7.105, 78.235, 78.366, 78.391, 78.392, 78.405, 78.407. See also *www.ema.europa.eu/ documents/ minutes/ minutes-comp-meeting-4-6-october-2016 _en.pdfe www.ema.europa.eu/ documents/ minutes/ minutes-comp-meeting-17 -19-january-2017_en.pdf.*

[276] See *https:// www.ema.europa.eu/ en/ documents/ orphan-review/ recommendation-maintenance-orphan designation-time-marketing-authorization-chenodeoxycholic-acid_en.pdf* and doc. *Timelines for publishing of EPAR for CDCA.*

[277] See docs. 78.405 and 78.373 and 22.7.105. See the decision of COMP EMA / 39662/2017 Rev. 1 of 22 June 2017, available at *https://www.ema.europa.eu/en/documents/orphan-review/recommendation-maintenance-orphan designation-time-marketing-authorization-chenodeoxycholic-acid_en.pdf*, to maintain the status of orphan where, in fact, it is stated: *"that the claim of a significant benefit of Chenodeoxycholic acid sigma-tau in inborn errors in primary bile acid synthesis is justified because data show that patients with a type of inborn error in primary bile acid synthesis called cerebrotendinous xanthomatosis (CTX) show neurological improvements when treated with this medicine which have not been seen with cholic acid in the treatment of this disease. […] Therefore, although other methods for the treatment of this condition have been authorized in the EU, the COMP concluded that Chenodeoxycholic acid sigma tau is of significant benefit to patients affected by inborn errors in primary bile acid synthesis ".*

154. The marketing authorization *for Chenodeoxycholic acid Sigma Tau*® was issued to Sigma Tau Arzneimittel GmbH on 10 April 2017. Therefore, according to what is reported in the Community register, the 10 years of *market exclusivity* expire on 12 April 2027.

155. Given the difficulty of fully demonstrating the safety and efficacy profile of the drug278 for the above reasons, the AIC for the orphan drug was awarded by the European Commission "in exceptional circumstances" 279, that is to say subject to the imposition to the company with the obligation to collect data on the safety and efficacy of long-term treatment of patients with CTX and to send the results by 2022 (and then every 5 years). This conditional release compensates for the lack of complete clinical data to support the application for marketing authorization by the applicant company.

156. On 12 May 2017, the orphan drug was renamed *Chenodeoxycholic acid Leadiant®.* On May 31, 2017, the relevant AIC was transferred from Sigma Tau Arzneimittel GmbH to Leadiant GmbH, a newly established company of the *former* Sigma Tau group (on which see section III.5.7.ii below) 280.

157. On 12 June 2017, the definitive orphan designation *of Chenodeoxycholic acid Leadiant*® was also transferred from Sigma Tau Arzneimittel GmbH to Leadiant GmbH281.

III.5.7 The differentiation strategy of CDCA Leadiant® *from* Xenbilox®

158. The documentation acquired in the file shows that in order to launch the new orphan drug on the market and support the prefigured pricing policy (see section III.5.4 *above),* Sigma Tau has put in place a strategy to differentiate it from *Xenbilox®282* which unfolded through two closely related courses of action: the withdrawal of *Xenbilox*® from the German market prior to the launch of the *CDCA Leadiant®,* and the

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[278] As confirmed by the expert consulted by Leadiant herself, whose opinion is contained in doc. 138.4.13.

[279] Pursuant to art. 14, paragraph 8, of EC Regulation no. 726/2004. See EMA, *Assessment report,* cit. pp. 35 and 39. See European Commission Decision C (2017) 2488 (final) of 10 April 2017.

[280] See European Commission decision C (2017) 3894 of 31 May 2017.

[281] See European Commission decision C (2017) 4087 (final) of 8 June 2017 available at *https://ec.europa.eu/health/documents/community-register/html/o1406.htm.*

[282] See doc. 78.57, dating back to 2015, where reference is made to the commercial differentiation of the two products *("Brand differentiation").*

creation of a new company, other than Sigma Tau Arzneimittel GmbH, or Leadiant GmbH, to which to attribute the marketing authorization of the orphan drug.

the) *The withdrawal of Xenbilox® from the German and other national markets*

159. The decision to proceed with the withdrawal of *Xenbilox*® from the German market was assessed in early 2014283, and then considered with greater determination in September 2014, immediately after the company had applied for preliminary orphan designation for the CDCA (cf. . para. 117 *above),* since the consultations commissioned clearly indicated that the desired price increase would not have been possible without the withdrawal of *Xenbilox*® from the market284. Also in this case, the identity between the active ingredient of the orphan drug and that of the *off-label drug,* in fact, would have triggered the price moratorium and would have forced the company to refund the difference between the reimbursement price currently to German health insurers. approved for *Xenbilox*® and the price of the future orphan drug
(in the form of a discount on the price), hindering the objective of maximizing revenues that the company had set itself to achieve285. A price increase, and more generally the freedom to fix it, would have been feasible in Germany only if the orphan drug had been qualified as a product that, from a commercial and regulatory point of view, could be considered as new compared to *Xenbilox®286 .*

160. Given the multiple implications of this strategy, the firm carried out the withdrawal operation and managed it carefully287. On one side,

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283 See doc. 96.83 *("For Xenbilox we have no intention to touch the current MA. The plan is to submit an ODD and later a CTX file in ST UK name. After approval we withdraw German product MA. Still this is not yet a plan just an intention chart (before implementation we need to check a few things namely if there are other active MAs in EU that could easily jeopardize our future pricing) ").*

284 See doc. 22.7.17 (: *"[…] In some countries a further price increase may only be possible with combination of current license withdrawal, approval in CTX and rebranding ").*

285 See doc. 22.7.17 *("[…] Xenbilox currently costs 36 € per tablet, 3 capsules per day would cost less than treatment with cholic acid. In Germany there is a de facto price freeze. The statutory sickness funds will charge the net price increase back from the manufacturer, Sigma Tau GmbH in Germany (the PZN of the drug is 5484764). Thus Sigma Tau will not benefit from any price increase (including the last one) to Xenbilox ").*

286 See doc. 22.7.17 ("An *(effective) price rise may be possible as follows. With a new approval for a new indication, a new brand name and a new PZN . Since the drug substance / active pharmaceutical ingredient is not new, there would not be an automatic mandatory requirement to submit a benefit dossier and have it evaluated (AMNOG) ").*

287 See docs. 78.80, 78.92 and 78.244, annex "AP1122 CDCA Pricing Study Results 22nd oct 2015 V3F updated 27 November 2015" ("Withdrawal *of Xenbilox: Needs to be well managed").*

in fact, the withdrawal of *Xenbilox*® from the market seemed useful to suggest that the orphan drug was considered as new and therefore to avoid anchoring its reimbursement price to that of the *off-label drug288;* on the other hand, however, if the orphan drug were found to be new, it would have been subjected to the assessment procedure289 by the German regulatory authorities of the added therapeutic value290, which the company initially wanted to avoid291.

161. Subsequently, the company evaluated the hypothesis of subjecting the orphan drug to this procedure for assessing the added therapeutic value, as it had realized that even in the event that *Xenbilox*® had been withdrawn from the market, the on the price of newly introduced drugs on the market and owned by companies that have previously marketed drugs with the same active substance and with a comparable pharmaceutical form292 would in any case have linked the reimbursement price of the orphan drug to that of the old *off-label drug293.* If, on the other hand, it had succeeded in demonstrating that the orphan drug had an added therapeutic value compared to *Xenbilox®,* it could have disengaged from the reimbursement price of the latter drug and not have to grant the discount to health insurance companies294.

162. Nonetheless, the outcome of that procedure, according to an external consultant, remained uncertain, *inter alia* given the absence of prospective studies to support it. In particular, the consultant suggested to the company to request the activation of the evaluation procedure only if it was actually convinced that it could demonstrate a significant therapeutic added value that justified the prefigured price increase that the company

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[288] See doc. 96.171.

[289] See docs. 78.379 and 96.171.

[290] Pursuant to the Law for the Reform of the Drug Market *("Arzneimittelmarkt-Neuordnungsgesetz",* or AMNOG), in force since January 1, 2011, retail prices for drugs are freely defined by companies at the time of launch. However, for the purpose of defining the reimbursement price, which is negotiated on the other hand, the Federal Committee *("Gemeinsamer Bundesausschus"* or G-BA) and the Institute for Quality and Efficiency in Health Care *("Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen "* or IQWiG) have the task of assessing the additional therapeutic value of all newly authorized medicines, ie those introduced on the German market since 2011. If there is evidence of added value, the Central Federal Association of Health insurance funds and the pharmaceutical company negotiate the reimbursement price of the new drug that will be paid by the health insurance funds. This takes the form of a discount on the retail price originally set by the firm. See docs. 96.41 and 96.167.

[291] See docs. 96.41 and 96.167.

[292] See § 130a (1a) SGB V.

[293] See doc. 78.80 ("[...] *central negotiation with insurers not required, although individual insurers may request separate negotiations. Anti-Avoidance Regulation will tie price to latest Xenbilox price, and possibly to that prior to thelatest price freeze (effective date 1 August 2009)").*

[294] See docs. 78.379, 96.171 and 96.183.

intended to apply for the orphan drug (at the time € 10,000 per pack) 295. If not, he suggested asking the competent authority for formal confirmation that the assessment procedure was not applicable to the orphan drug296.

163. The non-obligatory procedure for assessing the added therapeutic value of the orphan drug was communicated in December 2015 by the German authority in charge, to which Sigma Tau had addressed with a request for clarification sent at the end of October 2015297. This precisely in when the drug was not new and contained the same active ingredient as an existing drug. As a result, despite the planned withdrawal of *Xenbilox®,* the orphan drug would fall back into the bed of the price moratorium and would force Sigma Tau to return the difference between the introductory price of the orphan drug and the reimbursement price to health insurance funds. of *Xenbilox®298.*

164. However, the price moratorium would not have been applicable if, at the time of the launch of the orphan drug on the German market, in addition to the unavailability of *Xenbilox*® in the official price list, the MA holder of the new orphan drug had been a company other than the owner of the distribution rights of *Xenbilox®299* (on which see the following section).

165. Therefore, the planning of the withdrawal of *Xenbilox*® from the German market continued also in the following months300 and in May 2016 the company decided that the *Xenbilox*® would be withdrawn when the launch of the new product was finalized, which in turn it depended on when the company would obtain the marketing authorization on the orphan drug301.

166. In September 2016, after obtaining the positive opinion of the EMA COMP on the AIC request for the orphan drug, Sigma Tau began to define the withdrawal strategy in a more concrete way, identifying for the first time a precise timing, albeit not final: the company has decided to start the *Xenbilox*® withdrawal procedure at the end of September 2016, fulfilling the last orders in October 2016, and to conclude it between April and May 2017, withdrawing any packages still

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295 See doc. 78,379.

296 See docs. 78,379.

297 See docs. 78.379, 96.171 and 96.183.

298 See docs. 96.187 and 78.379.

299 See doc. 96.187.

300 See doc. 96.73 and 96.107.

301 See docs. 78.374 and 96.131.

on the market302. In mid-October 2016 Sigma Tau sold the existing *stock* of *Xenbilox*® to the wholesaler Juers Pharma who continued to sell the product to end customers until the drug was finally withdrawn from the market303.

167. In the documentation already cited, reference is also made to the reasons, already identified on other occasions, which should have supported the decision to withdraw *Xenbilox*® from the German market304. These reasons emerge from a more dating document, dated September 2015, in which it is established that the withdrawal was justified by the fact that the original therapeutic indication, the treatment of gallstones, no longer had a market, as therapies were now much more widespread. effective305. However, from the internal correspondence of the company in the second half of May 2017, it emerges that the real reason for the withdrawal of *Xenbilox*® from the market was strategic ("I *confirm that Xenbilox is only recalled locally in Germany. It is recalled only for strategic reasons, not for a quality or a safety* reason "306), or functional to avoid that at the time of negotiating the price of the orphan drug the competent authorities could refer to *Xenbilox®,* as had been feared several times in the aforementioned documentation.

168. Between March and April 2017 the company also decided to request the cancellation of *Xenbilox*® from the official list after the conclusion of the procedure for withdrawing *Xenbilox*® from the market, i.e. in the first half of May 2017, to obtain it between the end of May and early June 2017 307. Immediately afterwards, the inclusion of the orphan drug in the official list was requested308. This prevented the two products, *Xenbilox*® and the orphan drug, from formally coexisting on the market309.

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302 See docs. 78.10, 78.12, annex, 78.161, 96.185, 96.49 and 96.227.

303 See docs. 105 and 138.4.1.

304 See doc. 96.49 and 96.227.

305 V, doc. 96.145, 96.41, 96.167 and 96.85 *("It would be important to had that the number of CTX patients in Germany is very low - estimated to be less than 20 patients, currently. Therefore, it is no longer viable to have Xenbilox commercially available for such a small patients population. Basically, making the case that we are operating at a financial loss and we cannot continue to supply the drug, hence the need for a centralized procedure and launching a new product. ")*

306 See doc. 96.57.

307 See docs. 78.81 and 78.161.

308 See docs. 96.49 and 96.227. 309

See docs. 78.244, annex *"Pricing Strategy for CDCA_15FEB2017"* and all. *"AP1122 CDCA Pricing Study Results 22nd Oct V3F updated 27 November 2015.pdf",* 78.249 from which it emerges that the consultancy firm the company had contacted suggested leaving *Xenbilox*® on the market until the introduction of the orphan drug; however, the firm did not agree *("Xenbilox could remain on the market until a number of EU launches in order to maintain patient supply However, ST does not want Xenbilox to co-exist on the market with CDCA and intends to remove Xenbilox from the German market prior to first CDCA launch "),* 78.262 *(" Xenbilox and the new CDCA Leadiant will not co-exist in the market ")* and 96.185.

169. Sigma Tau (now Leadiant) did not, on the other hand, also request the revocation of the marketing authorization of *Xenbilox®310.* The definitive revocation of the marketing authorization for *Xenbilox*® was requested from the German regulatory authorities only in June 2019311.

170. The inspection documentation indicates that the strategy aimed at avoiding the co-presence on the market of *Xenbilox*® and *CDCA Leadiant*® played a role in the negotiation procedures initiated before the other national regulatory authorities312, including AIFA (see par. 197, 199 and 203 below) 313.

ii) *The creation of a new company under German law that would take ownership of the MA on the orphan drug*

171. Documents from early 2016 show that the company had decided to create a new company in Germany (Leadiant GmbH). In a presentation of the time, the company carried out an evaluation of the advantages and disadvantages of this choice, coming to the conclusion that there were several positive aspects that derived from it: among these, the possibility of obtaining the desired price for the future drug orphan314.

172. The document of March 2016, already cited, makes explicit the link between the creation of the new company and the repercussions of this decision on the price of the future orphan drug: according to the company, neither Sigma Tau Rare Disease Ltd., holder of the MA on *Xenbilox*® at that time, neither Sigma Tau Arzneimittel GmbH, former MA holder of *Xenbilox®,* could have been MA holders of the new orphan drug, without the competent authorities referring to the reimbursement price of the first drug

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310 See docs. 96.49, 96.227 and 138.4.1. The company has in fact decided to wait until, based on the so-called *sunset clause,* the AIC of *Xenbilox* automatically expires at the end of three years from the cessation of the sale of the medicine (October 2019). The *cdsunset clause,* or forfeiture clause, is defined in art. 14 of Regulation (EC) no. 726/2004 and art. 24 of Directive 2001/83 / EC. It provides that the marketing authorization for a centrally authorized medicinal product ceases to be valid if: *i)* the medicinal product is not placed on the market within three years from the date of the authorization granted or, *ii)* if a medicine previously placed on the market is no longer effectively on the market for three consecutive years. The equivalent statutory provision applicable in German law is § 31 (1) No. 1 AMG.

311 See doc. 138.4.1.

312 See doc. 78.329 *("If a rebranding process is implemented in Germany, and the manufacturer of both drugs remains the same (Sigma Tau), Spanish authorities will try to use the previous price of Xenbilox as an external reference price instead of the new branded product's price. However, Xenbilox has not received a formal price from the Spanish authorities, thereby avoiding a formal ability to act as a reference. Sigma Tau can argue the product is different because it has a new indication unrelated to the previous one, and that research activities have been conducted to prove the efficacy and safety of this new orphan indication ").*

313 See doc. 108.

314 See docs. 22.7.50.

in the allocation of the redemption price of the second. Hence the need to create a new entity, controlled by Sigma Tau Rare Disease Ltd. *("As we discussed before we will need a newco in Germany because neither ST GmbH nor STRDL can be MA holders and / or distributors of the new CDCA without an immediate reference to the old Xenbilox® price. A name change is not enough. This must be a new pharmaceutical entrepreneur (new numbers, register, etc). However the newco can be fully owned by* STRDL "315).

173. In November 2016, when Sigma Tau Rare Disease Ltd. was about to change its name to Leadiant Biosciences Ltd. (in December 2016) 316, doubts arose within the company in relation to whether *Xenbilox*® was also suitable for owned by a company of the Leadiant group, albeit different from the German branch itself. In other words, it was feared that notifying the British regulatory authorities of the change of the name of the MA holder on *Xenbilox*® from Sigma Tau Rare Disease Ltd. to Leadiant Biosciences Ltd. would lead back to the two products, *Xenbilox*® and the orphan drug, within the same corporate group and would have led the German regulatory authorities to associate them as part of the procedure for assigning the reimbursement price to the orphan drug. In this way, the efforts linked to the creation of a new company under German law, functional to realize the profits deriving from the introduction in Germany of the orphan drug at a higher price than that charged for *Xenbilox®317, would have been thwarted.*

174. However, the internal discussion ended in March 2017 in the sense that the existence of a controlling relationship between Leadiant Biosciences Ltd. and Leadiant GmbH would not have called into question the latter's autonomy under German law318.

175. In August 2017, the German health insurance association sent a communication to Leadiant GmbH stating that the provisions of the price moratorium for newly introduced drugs owned by businesses that

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[315] See doc. 96.79.

[316] See doc. 28.2.96.

[317] See doc. 96.153 *("I'm not quite sure whether it is a good idea to transfer Xenbilox to Leadiant. As far as I did understand the situation around the pricing issue with CDCA we should not mix up the MAH for Xenbilox with the MAH of CDCA. As the German Leadiant and the UK Leadiant are a so called group of companies I assume if we transfer the Xenbilox license to a Leadiant company that we then jeopardize all our effort to set up a new company to get a high price for CDCA ").*

[318] V doc. 96.117 *("And remember in the UK we are not creating a new company but simply changing the name of the current one so there is no transfer but a change in name of the* MAH"). See also docs. 96.49, 96.153 and 96.185.

have previously marketed drugs with the same active substance and with a comparable pharmaceutical form, and asked for a discount on the price equal to the difference between this price and the reimbursement price of the previously marketed drug, *Xenbilox®,* equal to 660 euros per pack319.

176. Between August and September 2017 Sigma Tau and the association had some correspondence exchanges in which the company pointed out that Leadiant GmbH was a new company and not a *spin off* or the successor of Sigma Tau Arzneimittel GmbH, from which it did not had acquired any *assets,* rights or obligations. Therefore, the two companies should have been considered different and independent. Likewise, it stated that the orphan drug was a new drug and not *Xenbilox®* with a new trade name320.

177. The documentation on file shows that the company has managed to convince the health insurance association of the correctness of the its thesis and to avoid that it asks for a discount, when defining the reimbursement price of the orphan drug, referring to the lowest price of *Xenbilox®321.*

III.5.8 Market reactions to orphan drug prices in Germany and other European countries

178. From some internal documents of the company Leadiant is aware of the opposition of the German regulator to the price with which the orphan drug was launched on the market322, equal to approximately *[20,000-30,000]* euro per package323, especially against the perception of the commercial operation as a mere *"repurposing" activity 324.*

179. The negative reaction that greeted the price with which the orphan drug was launched in Germany also manifested itself in the press, to whose requests for explanation Sigma Tau responded by leveraging the difference between the *CDCA Leadiant®* and *Xenbilox® ,* registered for the treatment of a

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319 See doc. 96.65.

320 See doc. 96.65, 96.196, 96.113 and 96.169. Similar arguments were prepared by the company in a document of September 2017, containing the answers to be provided to potential questions from the German press about the reasons for the high price with which the orphan drug was introduced in Germany. See doc. 22.7.16, annex "170908_EN_QA Leadiant V5".

321 See docs. 22.7.63 and 78.144.

322 See doc. 96.19.

323 See docs. 78.244, annex "Pricing Strategy for CDCA_15FEB2017", 78.91 and 96.121.

324 See doc. 78.225 *("Stakeholder perception of transition from Xenbilox to CDCA Leadiant. [...] Payers might take CDCA Leadiant as an example of repurposing not being acceptable, even under* ODD ").

different pathology, from which many more patients were affected, and on the fact that Leadiant had had to bear significant costs of research and development and of registration of the orphan drug325.

180. Despite this complicated institutional context, the company considered it useful to keep the orphan drug on the German market at a high price, as this price, at least for the first year in which the company was free to choose the level, would have constituted a reference for trading in other European countries326.

181. Other documents acquired in the proceedings give account of the equally negative reaction of some *stakeholders,* expression of the demand for the drug, to the prices proposed by Leadiant in various countries of the European Union for the launch of the *CDCA Leadiant®.*

182. A document dated October 2017, in particular, gives evidence of the negative reaction of Austrian doctors to the price of the orphan drug327.

183. Also, a letter dated April 2018 sent by the Dutch Ministry of Health to the President of the House of Representatives of the States General contains a negative assessment of the price of the orphan drug, in light of the related investment in innovation made. In particular, the Minister believed that the annual price of 160,000-220,000 euros proposed by Leadiant to Dutch insurance companies was inappropriate with respect to the activity carried out by the company for the purpose of obtaining the orphan designation, based on the mere recognition of the scientific literature and on the having commissioned two retrospective studies that showed the effect of the drug on disease, activities considered useful but not "revolutionary" and such as to deserve the economic remuneration requested by the company328.

III.5.9 The introduction of Chenodeoxycholic acid Leadiant in Italy and the price negotiation with AIFA

184. In relation to the introduction of the orphan drug in the Italian market, the documentation on file shows that in the first half of 2016 the company was preparing for a preliminary meeting with AIFA to be held in June 2016, in view of the of the price negotiation procedure in Italy.

From a document in particular it emerges that the company has given instructions to

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[325] See docs. 96.31 and 22.7.16, annex "170908_EN_QA Leadiant V5".
[326] See doc. 96.19.
[327] See doc. 96.24.
[328] See doc. 96.77.

a consulting company, which assisted her during the negotiation, about the information to be indicated in the reimbursement *dossier* of the orphan drug: this had to be described, not as a drug based on a known active ingredient with a new therapeutic indication, but as a completely new drug for the Italian market329. Likewise, another document from the same period (June 2016) indicates that the company intended to move *"in Italy, carefully avoiding creating [...] links with the name Sigma-Tau" 330.*

185. For this reason, the company was concerned, for example, to avoid that, close to the start of the negotiation procedure for the price of the orphan drug with AIFA, the hospitals did not ask the Agency for access to the so-called AIFA National Fund 5% 331 for the purchase of *Xenbilox®,* but instead requested it for the new orphan drug soon to be introduced on the market332.

186. In March 2017, the company began to collect the information necessary to include in the reimbursement *dossier* to be submitted to AIFA not only the data relating to the investments in research and development made in Italy in the three-year period 2014-2016, but also those relating to other medicines, other than and unrelated to CDCA333. The research led to the identification, within these overall investments, of an amount of costs related to the orphan drug registration project in Italy which - with the exclusion of the

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[329] See docs. 78.172 and 78.291 *("new indication of a known compound. OK? No, not ok. I understand your comment about this being strange, but in fact this is a 1st registration of a new pharmaceutical product in Italy. Let us keep it like that , because this is something we can argue from a Legal standpoint. We should state it as is and not mention the compounding if we do not have* to ").

[330] See doc. 78.95.

[331] The law establishing AIFA establishes a national fund for the use of orphan drugs for rare diseases and medicines that represent a hope of cure, pending commercialization, for particular and serious diseases (Article 48, paragraph 19, letter a, of Legislative Decree no. 269 of 30 September 2003 converted by law no. 326 of 24 November 2003). This fund is fed by 5% of the annual expenses for the promotion activities of pharmaceutical companies. Applications for access to the fund are forwarded to AIFA, through the Regions, by the reference centers that treat the sick, or by specialist structures identified by the Regions, with the definition of the diagnosis and the therapeutic plan.

[332] See doc. 22.7.150, from which it emerges that an Italian hospital, BESTA, which in March 2017 intended to purchase *Xenbilox*® and request access to the AIFA 5% National Fund: the company therefore hypothesized to provide the orphan drug free of charge to hospital to avoid asking for access to the Fund for *Xenbilox*® and to prepare the reports that would have allowed the sale of the *CDCA Leadiant*® in the future or in any case to request access to the Fund for the price proposed to AIFA, and doc. 78.90. Similarly, the Sienese University Hospital intended to submit the same application (see doc. 78.86).

[333] See docs. 78.420 *("The P&R dossier that Dario and Lucia are assembling for AIFA must include the R&D investments that the" Company or Group "has sustained in the last three years in Italy and asked me some support on this. R&D costs independently of the specific product (CDCA in this case) and of the Applicant (eg Germany) can be indicated. They refer generically to the Leadiant Group and to R&D projects and for this reason we can also include costs sustained in Italy for example on Heparanase (which I have) or other projects ")* and 78,168.

price paid to the University of Siena for carrying out the retrospective study - was equal to approximately *[100,000-200,000]* euro334.

187. At the end of May 2017, the company's *Chief Financial Officer* (CFO) also indicated that the overall investments in research and development made in Italy by Sigma Tau / Leadiant between 2014 and 2017, also relating to products other than the CDCA, they amounted to approximately *[2-3]* million euros (of which *[100,000-200,000]* euros related to the CDCA) 335.

188. In the meantime, the company, expecting difficult discussions with the national authorities in relation to the price it intended to ask for the orphan drug with respect to the investments made for its development336, in view of the negotiation procedure to be started at AIFA, also verified the amount of external costs sustained up to then for the CDCA project at a global level, thus establishing in detail (item by item) that these, for the years 2014-2017, were equal to approximately *[10- 20]*
million euros337. Of these, only a small part can actually be classified as investments in research and development338. Other documents on file, internal to the company, and dating back to the years 2014-2017, give account of the estimates of the costs in research and development, not particularly significant, that the company had incurred or expected to incur for the launch of the orphan drug on the European market 339.

189. The request for reimbursement and classification of the *Leadiant*® *Chenodeoxycholic Acid* was presented to AIFA by Leadiant on 15 June 2017. With this request, the company proposed a retail price equal to 25,592.64 euros (and a *ex factory* of € 15,506.93) for a pack of 100 capsules of 250 mg340; assuming that patients take three 250 mg capsules per day, or 1095 capsules per year, the annual cost

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334 See docs. 78.420 and 78.421.

335 See docs. 78.449, 78.463, 78.172, 78.173.

336 See doc. 78.438 *("In the spirit of expecting very difficult discussions concerning our proposed price vs R&D investment ...").* The awareness of this had matured, however, even in March 2016: "[...] *it would seem inevitable that at some point we will have to offer to 'open our books' in order to assist with the justification of price for CDCA* [...] "(See doc. 78.441).

337 See docs. 78.419, 78.433, 78.438, 78.439, 78.443, 78.149, 78.458, 78.442, 78.459, 22.7.5, 78.460.

338 See docs. 22.7.5, 78.459, annex "STRD CDCA RD cost final v2 with only external costs" and all. "LB Inc 2014-Feb ytd 2017 CDCA Expenses ". It should be noted that in the documents cited the company has classified as research and development costs cost items that are not attributable to this category (see for example, the cost items called *"fee for service", "promo trade show exhibits" , "Promo sales material development", "advertising"* contained in the sheet "Raw Data Bdg 17" of the attachment "STRD CDCA RD cost final v2 with only external costs").

339 See doc. 78.62, annex "GRD Strategic Plan 2015-2019 (FINAl selection) 20OCT2014", 95.4, 95.5, 78.434, 78.447.

340 See docs. 3.2, 72.1, 78.72.

of the therapy per patient would therefore have been equal to 280,239.41 euros (to which apply the legal reductions 5% + 5%).

190. The request was examined by the Technical Scientific Commission (CTS) of AIFA341. With a resolution dated August 4, 2017, AIFA entered the drug in the Cnn class (i.e. the class in which the drugs for which the price negotiation procedure is still in progress, pursuant to art. paragraph 5 of Law 189/2012) at a price equal to that proposed by the company in the request for reimbursement342.

191. Therefore, pending the reaching of an agreement on the price, the *CDCA Leadiant*® was sold at a free price to the Italian ASLs, which purchased it using the import procedure referred to in the aforementioned Ministerial Decree of 11 February 1997343 at the *ex factory* price of € 15,506.93 per pack of 100 capsules of 250 mg344.

192. In December 2017 Leadiant received the request from a hospital for the free supply of the orphan drug based on the so-called compassionate use, but decided to refuse this request because this would have implied the absence of profits in Italy until the end of the negotiation procedure with AIFA345.

193. In the following months, the *Health Technology Assessment* (HTA) Sector and the AIFA CTS carried out their investigation on the drug, noting that the evidence supporting the effectiveness of the treatment was obtained mainly in the academic field, in one case using the active ingredient of the drug in galenic form, which during the registration process of the orphan drug was no longer available, effectively causing the interruption of treatment for a number of patients346.

194. As a result of this investigation, the AIFA Prices and Refunds Committee (CPR), in the meeting of 19 March 2018, found that the *ex factory* price of € 15,506.93 per package requested by the company, equal to five times the price of the product previously used, *Xenbilox®,* for the activities carried out for the purpose of introducing the drug on the market (the

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341 See docs. 78.72, 78.78, 78.83 and 78.84 for submitting the application.

342 See doc. 78.152. The determination was published in the Official Gazette no. 203 of 31 August 2017.

343 This channel is managed by the Ministry of Health through the border offices (USMAF). annex also 8.2, 8.4

344 V. 8.3, And 10, 3. V. showers *https:// www.aslroma1.it/ uploads/ files/ 32_56_2357_del_16.08.2017.pdf.*

345 See doc. 78.157 *("This is a can of worms we really do not want to open if we can avoid. You agree to one you agree to all and then no sales in Italy until reimbursement which will happen god knows when ").*

346 See doc. 3.1.

presentation of retrospective studies and literature review), could not be accepted without additional elements that could justify it. Therefore, the Committee requested the company in writing to present a *cost-based justification347.* Likewise, the CPR believed that the number of CTX patients in Italy in three years thereafter would be higher (90) than that estimated by the company (49) 348.

195. Some documents acquired in the file indicate that, between March and April 2018, the company discussed internally on how to respond to the Agency and prepared a draft letter in which it indicated the number of patients served until then (37) and the amount of investments in research and development made in Italy (see paragraph 187 *above).* At the same time, it decided to avoid as much as possible any reference to *Xenbilox*® in order to exclude the existence of any commercial link with said drug349.

196. This reply to AIFA was received on 10 April 2018. With it, the company also asked to be called for a new meeting, informing the Agency that it was available to reach an agreement that provided for the return to the ASL of any difference between the negotiated price and the price paid by them for the purchase of the orphan drug350.

197. In the session of 29 May 2018, the AIFA CPR noted the unavailability in the Italian market of the only drug that had been used for the treatment of CTX in Italy following importation from abroad, *Xenbilox®351.* In this regard, at the hearing, AIFA stated that it perceived the withdrawal of this drug from the Italian market as a major obstacle in the negotiation procedure for the price of the *CDCA Leadiant*® and as one of the tools, together with the change of ownership of the new orphan drug, of artificial differentiation of the two products352.

198. On 14 June 2018, AIFA's CPR sent a communication calling the company for 26 June 2018 and, in reply to

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[347] See docs. 3.2 and 11.1.

[348] See docs. 3.2., 11.1. 78.113, 22.7.142, 22.7.148, 78.85, 78.114, 78.132, 78.136-78.140, 78.142, 78.170, 78.171, 78.178, 78.179 and 78.441.

[349] See docs. 78.99, 22.7.143 ("I *would prefer to avoid discussing direct relations with Xenbilox. Especially because Leadiant Biosciences or the ST companies never sold Xenbilox in Italy, the commercialization of Xenbilox in Italy was always done by a 3rd party and hence outside our control")* and 78.111, annex *"CPR letter"* and *"CPR letter eng".*

[350] See doc. 3.2 and 11.1.

[351] See doc. 3.2 and 11.1.

[352] See doc. 108.

counter-arguments, stated what had already been expressed in the sessions of March 19 and May 29 2018: *"in consideration of the fact that the authorization procedure was based exclusively on retrospective studies and literature data, reiterates that it cannot accept a price five times higher than the product previously authorized XENBILOX* (...) "353.

199. The company wanted to reply that the only existing correlation with *Xenbilox*® stemmed from the fact that this last drug is the so-called *CDCA Leadiant*® reference . Otherwise there was no correlation, since Leadiant had never marketed any drugs a CDCA based on the Italian territory nor had it ever had to do with the price with which *Xenbilox*® had been marketed in Italy. In doing so, the company believed it would avoid entering into the merits of any discussion relating to *Xenbilox®354.* This line of argument was not, however, unanimously shared neither within the company nor by external consultants, because it is considered risky and ineffective355. The company then considered to state at least that the *off-label* drug was authorized only in Germany and that in Italy it was imported by third parties356. However, since this route was also considered dangerous, the company finally decided to limit itself to stating that *Xenbilox®,* approved in Germany for the treatment of gallstones and used as a reference drug in the so-called hybrid authorization procedure of orphan drug, was a distinct product357.

200. In the days preceding the meeting with AIFA, Leadiant also has

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353 See docs. 78.77, annex and 78.79, annex

354 See docs. 78.141 *("1. There is no" previously authorized product "in Italy not for CTX not for any other indication in what concerns Leadiant products; 2. Leadiant has never commercialised / sold any other Chenodeoxycholic acid in Italy. 3.The only relation between the products is that Xenbilox was referenced in the CMC part since CDCA is an Hybrid drug; 4. For the above reasons we reject the notion of "5 fold price increase"; 5. The company is willing to negotiate a sustainable solution based on CDCA Leadiant added value for patients but cannot and will not be referred to a drug it never commercialised in Italy for a completely different indication; 6.The framing should be other EU countries price. Price for drugs with similar epidemiology etc .; 7. XENBILOX discussion is a lost one. Will not enter lost d [i] scussions "),* 78.77, all. *(slide* 5): *"Xenbilox was a drug approved exclusively in Germany for Gallstone dissolution. It was to the best of our knowledge imported into Italy through wholesalers, international pharmacies and other similar distributors as an unlicensed medicine and used off-label in CTX patients. Leadiant has never engaged the Italian authorities for funding or for price negotiations regarding Xenbilox as an unlicensed off-label medicine […] The reference medicine for CDCA Leadiant was Xenbilox. However CDCA Leadiant is not the same medicine as Xenbilox "),* 22.7.149. all., 78.79, all., 78.116 *("The point is that we had nothing to do with the selling of this drug in Italy. This is not a price increase in any way sort or form"; "I want to avoid a discussion and price comparison with Xenbilox as center of the conversation. I do not believe we can get out with the best outcome if we do not avoid it at all cost ").*

355 See docs. 78.112 *("we must be very careful in saying that LB has never sold Xenbilox etc etc.")* and 78.116.

356 See doc. 78.77.

357 See docs. 78.118 and 78.119.

elaborated some hypotheses of price / volume agreement to be proposed to the Agency, prefiguring to obtain a compromise price which, in the worst case scenario (which had expressly decided to reserve itself for the subsequent negotiation *rounds),* could have been equal to approximately 9,000 euros358 .

201. During the meeting of 26 June 2018 it emerged first of all that, as already noted by the HTA Sector in September 2017, there was no on- *label medicine on* the domestic market that could be considered a therapeutic alternative, as *Kolbam*® does not was authorized in Italy and *Orphacol*® was registered for other therapeutic uses359.

202. At the same meeting, the company illustrated the characteristics of the product, the authorization process, the sales data and the prices applied in other EU countries. For its part, the CPR renewed its perplexities to the company about the requested price level, referring once again to the fact that the molecule at the base of the orphan drug was dating back to

and had been present on the Italian market at a price five times lower than that requested by the company360. In response, Leadiant illustrated the cost items that made up the financial investment made by the company to keep the orphan drug on the market. However, this was not considered sufficient by the CPR, which requested the presentation of documentation proving these costs.

203. Furthermore, the CPR requested clarifications regarding the unavailability of the molecule, not only in the Italian market, but also in the other national EU markets, also for other therapeutic indications, after the approval of the orphan drug by the EMA. To this last question, Leadiant replied that there was a market exclusivity linked to obtaining the orphan designation361.

204. Leadiant also stated that it was unable to document in detail the costs of producing the drug and proposed two different price / volume agreements (quantity discounts) with three price brackets to the Agency362. For its part, the AIFA CPR replied to both proposals that the starting price requested by the company was too high,

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358 See doc. 22.7.136 and 78.75.

359 See docs. 3.2 and 11.1. 360
See docs. 3.2 and 11.1.

361 See docs. 3.2 and 11.1.

362 See doc. 3.2. At first the company proposed a 15% discount on the price for packs sold from 0 to 37 patients, a 30% discount from 38 to 47 patients and a 60% discount over the 47th patient. Following the refusal of the CPR, it then proposed a 20% discount on the price from 0 to 37 patients, 30% from 38 to 47 patients and 80% over the 47th patient. See docs. 22.7.136 (78.75), 22.7.137 (78.76) and 78.113. for further offer hypotheses.

asking to formulate a new proposal that would align the price with that of *Xenbilox*® and thus make the cost of the therapy sustainable for the NHS. At Leadiant's request, the negotiation was therefore suspended pending the sending of a new proposal by the company within 15 days363.

205. Subsequently, in July 2018, the company deemed it preferable, despite AIFA's request, not to continue the quantification of research and development costs364.

206. In the absence of any reply from Leadiant, on 9 November 2018 the competent AIFA HTA Sector sent a reminder to the company. Leadiant did not reply to this communication. On 15 February 2019, the AIFA CPR then sent a second reminder, giving the company a deadline of thirty days for the transmission of the reply365.

207. Following these reminders, on 11 March 2019 the company sent a new reimbursement *dossier ,* announcing a new price proposal366, which was effectively detailed on 1 April 2019. It provided for a new price / volume agreement with three new brackets based on three different discounts, again on the *ex factory* price initially proposed of € 15,506.93 per pack367. On 15 April 2019, the CPR decided not to accept the proposal and in turn re-launched with a counter-proposal368. After several exchanges of correspondence aimed at finding an agreement369, the parties met again on 22-25 July 2019. However, even on that occasion they were not able to reach a compromise. The negotiating table was therefore once again interrupted and the procedure was suspended again until a date to be defined. The CPR also announced that precise data on the production costs of the drug and in particular on investments were awaited.

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[363] See docs. 3.2 and 11.1.

[364] See doc. 78.150 *("Pierre in fact pulled the number together for me a while ago and after seeing it I thought it best not to take it any further").* From doc. 78.113 in fact, it emerges that the company had decided to move the bargaining to another level *("We should set the turnover that we want to secure and move from there").*

[365] See doc. 11.

[366] See docs. 11 and 72.1. The new proposal was based on the handling of annual packages: the first group concerned the packages from 0 to 370, the second from 371 to 490 and the third from 490 onwards. The latter group would have been *"free of charge".*

[367] See docs. 11.1 and 78.121, where it is indicated that the discounts applied to the three brackets indicated in the footnote previous page were 25%, 50% and 100%.

[368] See doc. 11.1, which shows that the CPR had proposed a discount of 50% on the price from 0 to 370 packs, 80% from 371 to 490 packs and from the four hundred and ninetieth packs the spending ceiling of 2.9 million euros would have been applied.

[369] See doc. 70.6. First on May 13, 2019, the company sent a communication proposing a 30% discount on the first bracket, then on the occasion of the July 2019 session a discount of 36% on the first bracket and a spending ceiling of 3.3 million euros. In the session of 21 May 2019, the CPR expressed an opinion in which it was decided to convene the company and to reiterate the request for a 50% discount for the first bracket. See doc. 72.1.

in research and development carried out by Leadiant, as well as information on the reimbursement prices charged in the other Member States mentioned by the company at the meeting370.

208. In September 2019, AIFA again asked Leadiant to send information about the cost data, together with the indication of the reimbursement price applied in the other Member States of the European Union371. The information requested by the Agency was sent by Leadiant with two communications, respectively, of 11 October 2019372 and of 26 November 2019373. In particular, in the first communication, the company provided information relating to the prices charged for the *Leadiant® CDCA* in Germany (as mentioned, equal to approximately *[20,000-30,000]* euros) and in the United Kingdom (equal to approximately *[10,000-20,000]* pounds) 374; in the second communication (sent, therefore, after the notification of the Authority's initiation measure) it provided information about the costs incurred for the launch of the orphan drug.

209. More precisely, in the second communication, Leadiant, based on the study carried out by the consulting firm *Copenhagen Economics* following the start of the preliminary investigation procedure pursuant to art. 102, lett. *a),* TFEU by the Dutch ACM375, stated that it had spent almost *[30-40]* million euros between 2014 and 2017 - a figure that represents the total costs, direct and indirect, incurred to bring the CDCA product to the market, including the development of the new test for the production of the updated active ingredient, the pharmaceutical product and the development of the *dossier* for the European AIC - and to expect to spend *[100-200]* million euros from 2017 to 2023 (for a total of approximately *[100-200]* million euros), due to the activities imposed by the EMA for the maintenance of the AIC (patient register and compliance with the requirements imposed by national laws to be able to place the product on the respective markets).

210. The figures contained in the consulting firm's study were revised downwards by Leadiant itself in February 2020, during discussions with the Netherlands Competition Authority376. In in particular, it appears that the costs initially supplied by Leadiant contained significant intragroup items that should not have been calculated.

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370 See docs. 11, annex 1 and 70.6.

371 See doc. 78.127, 78.128 and 78.156.

372 See docs. 49.3 and 72.2.

373 See doc. 72.1.

374 See docs. 49.1 and 72.4.

375 See doc. 70.7, 70.9 and 70.11.

376 See docs. 95, 95.16 and 95.17.

The costs thus adjusted (which in principle correspond to the costs communicated by the company during the procedure, on which see section III.6.2.ii *infra)* amounted, for the period 2014-2023, to approximately *[70-80]* million euro, ie less than half of the costs provided in the dialogue with AIFA. However, according to the information acquired during the investigation, Leadiant did not provide AIFA with any additional and different information on costs compared to those offered in November 2019377.

III.5.10 The final outcome of the negotiation of the CDCA Leadiant® price with AIFA

211. Following AIFA's receipt of the aforementioned information in October and November 2019, on 18 December 2019 a new meeting was held between Leadiant and the CPR, during which the parties reached an agreement on the *CDCA Leadiant*® price , valid from March 2020 for a period of 24 months378.

212. From the information acquired during the investigation it emerged that, for the purposes of reaching the agreement, the cost data provided by the company did not play an effective role, as they did not possess the degree of detail required by the CPR nor were sufficiently documented. Therefore, the CPR of AIFA, in accepting the new Leadiant agreement proposal, adopted an approach mainly based on the therapeutic value of the drug379.

213. In relation to the content of the agreement, AIFA stated that this provides for the application on the price requested by the company of a confidential discount equal to *[50-60%],* the definition of a maximum expenditure ceiling equal to 2.8 million euros per year and the use of *payback* in the event of exceeding this ceiling. These parameters were set taking into account a number of patients equal to *[40-50],* therefore closer to the firm's estimates (see par. 196 *above),* and the expected purchase of approximately *[400-500]* packages in one year. Under these conditions, the NHS pays the *CDCA Leadiant*® *[5,000-7,000]* euros per package380. Currently, the spending ceiling has never been exceeded and the number of packages necessary to achieve it is higher than the sales forecasts in Italy formulated by Leadiant itself up to 2023381.

214. Furthermore, the *payback* clause contained in the agreement provides that

377 See doc. 108, 378

See doc. 72 and 72.1.

379 See doc. 72 and 72.1.

380 See doc. 72 and 72.1.

381 See doc. 110.1.

Leadiant returns the difference between the price negotiated with AIFA and the price previously charged to the ASL and the Regions by Leadiant for the sale of the orphan drug, when the drug was in class Cnn (i.e. when it had not yet been classified and could be purchased only at a price freely defined by the company). According to the company's estimates, included in the negotiation agreement signed with the Agency, this difference was quantified in the total amount of *[6-7]* million euro382.

215. On the occasion of the two hearings, the representatives of the Agency stated that the agreement stipulated, albeit sufficiently satisfactory, considering the starting negotiating positions - the price initially proposed by Leadiant by the company, equal to 5 times that of *Xenbilox*® , and the discount requested by AIFA equal to 80% of the price proposed by the -, it goes Leadiant383 assessed in the light of the context in which the negotiation took place.

216. In particular, according to AIFA, it is necessary to consider some elements that negatively influenced the negotiation of the price of the *CDCA Leadiant*® and the outcome of the same: the drug had, in fact, been on the market for about two years and mezzo and the ASLs, sustaining a significant outlay, had been using the orphan drug classified in CNN for some time as a therapy for patients affected by CTX, who, moreover, had to be guaranteed therapeutic continuity; the negotiations, which had been interrupted several times due to lack of agreement on the price, had been going on for a long time and this denoted a substantial lack of interest on the part of the company to reach a compromise and made the scenario in which the negotiation procedure would have ended more likely with no agreement and the *CDCA Leadiant*® would have been permanently included in class C384; finally, the Agency had no therapeutic alternatives. Therefore, in light of the difficult context in which the negotiation took place, the Agency considered that the *ex factory* price of the orphan drug of *[5,000-7,000]* euros per pack was the best result it could have reached at that moment. to avoid the hypothesis that the drug was permanently included in class C at the *ex factory* price of € 15,506.93 per pack.

217. Absent these contextual elements, the Agency would have considered it appropriate to grant the company a price increase equal to a few points

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382 See doc. 72 and 72.1.

383 See doc. 72 and 72.1.

384 That this was a hypothesis concretely contemplated by Leadiant in September 2018 not only for Italy, but more generally for all the countries where the company was conducting price negotiations, emerges from doc. 22.7.12.

percentage (less than 10%) compared to the price paid by the ASLs for the import of *Xenbilox*® between 2016 and 2017. This is because, compared to *Xenbilox®,* the orphan drug has a single added value, given by being registered for the treatment of rare disease which until then had been treated with *off-label drugs385.*

III.6 Analysis of the prices charged by Leadiant in Italy

III.6.1 Introduction

218. In this section we will proceed to identify the elements necessary for the analysis of the prices applied by Leadiant to the drug *CDCA Leadiant*® in Italy starting from June 2017. In particular, on the basis of the evidence in the files, Leadiant has applied the following prices : the *ex factory* price

- per pack of € 15,506.93, applied from the start of marketing of the drug in Italy (June 2017) until the agreement reached with AIFA which became operational in March 2020, following the start of the preliminary investigation;
- the *ex factory* price per pack of *[5,000-7,000]* euros (net of legal reductions), the subject of the agreement with AIFA, applied starting from March 2020 and still in force. In order to give the negotiated price retroactive application to all purchases made by the NHS starting from the placing on the market of the *CDCA Leadiant®,* Leadiant has undertaken, as already illustrated, to return to hospitals *[6-7]* million euros of turnover achieved thanks to the sales of the orphan drug carried out in the validity of its classification in the class Cnn386. This amount was, as of May 7, 2021, not fully repaid, with approximately *[300,000-400,000]* euro remaining in the process of being paid to the SSN387.

219. These prices will be compared with the costs incurred by Leadiant for the activities necessary for the registration of the CDCA as an orphan drug and for the subsequent production, placing and maintenance on the market.

220. In order to evaluate the profitability of the *CDCA Leadiant*® and, therefore, if there is a disproportion between the price and the costs incurred, in the case under consideration, two different methods of analysis will be used: the first consists in measuring the internal rate of performance (IRR or IRR, *Internal Rate of Return)* of the registration and marketing project of the orphan drug for use for the treatment of CTX (hereinafter, also the "project

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385 See doc. 108.
386 See doc. 72.1.
387 See doc. 122.

CDCA "); the second measures the difference between the revenues deriving from the sales of the *CDCA Leadiant*® and the so-called *cost plus,* ie the costs incurred for the realization of the product plus a reasonable profit for the business activity.

221. Note that the first of the two methodologies described above is the same one adopted by Sigma Tau, in July 2014, to evaluate the profitability of the CDCA388 project.

222. In the rest of this section the two methodologies will be illustrated and first of all the analysis of the profitability of the *CDCA Leadiant*® carried out by the company itself in the project start-up phases will be presented, as mentioned, on the basis of the first of the two methodologies. This assessment was carried out on a global level, separately for the United States and the Rest of the World389, which also includes Europe.

223. On the basis of the same methodology and with the final and forecast data provided by the company during the procedure, the excess price of the *CDCA Leadiant*® for Italy will be analyzed.

Subsequently, we will proceed to the analysis of the price applied by Leadiant on the basis of the second method, that is the *cost plus.*

III.6.2 The analysis of the IRR

224. The first methodology for the analysis of price excessiveness used here makes use of one of the tools used in corporate finance to support business investment decisions, namely the internal rate of return (IRR) 390.

225. In corporate finance, the analysis of investment projects (so-called *capital budgeting analysis)* is aimed at identifying which projects to undertake with a view to maximizing value for shareholders. To this end, with the methodology in question, the expected internal rate of return of the project is determined and compared with the cost of capital which

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388 In general, companies choose which projects to develop and which to abandon based on their prospective profitability, adjusted for the risk factor.

389 This formulation follows that used by the same company. See doc. 95.6, defined indifferently *"Rest of the World", "RoW"* or *"EU & Other Markets",* as opposed to *"US Market".*

390 The IRR (or IRR) of an investment project is the discount rate that equates to zero the sum of the present value of the cash flows (negative and positive) generated by the project. The formula for calculating the IRR (indicated by *i* in the formula) is the following:

$$\sum_{t=0}^{n} \frac{CF_t}{(1+i)^t} = 0$$ where is it:

t = deadlines;

CFt = cash flow (positive or negative) at time t.

A methodology for analyzing investment projects substantially equivalent to the IRR is that of the Net Present Value (NPV, *Net Present Value),* calculated as the sum of the present value of the cash flows generated by the project net of the initial outlay: if the NPV is positive, the project is profitable. The IRR represents the discount rate that equals the NPV value to zero.

the firm must support to carry out the project. If the expected rate of return exceeds the cost of capital, the project is profitable and the company therefore has an incentive to undertake the project. Otherwise (or if the cost of capital is higher than the expected rate of return), the company will not be profitable at the start of the project.

226. It should be noted that the use of the cost of capital (ie the *Weighted Average Cost of Capital,* WACC), as a discounting factor, makes it possible to evaluate the profitability of the investment, also taking into account its specific degree of risk. The more risky the project, the greater the cost of capital required to finance the project and, consequently, the higher the rate of return necessary to remunerate the risk borne. Furthermore, the methodology in question, based on the discounting of cash flows, takes into consideration the time factor: the cash flows closest in time (normally negative as they reflect the initial outlays of the project) have a greater weight than the flows cash farther away (normally positive as after a certain period the project begins to generate revenue).

227. IRR analysis is usually used *ex ante* when a company has to decide whether to undertake a project or not. As will be seen, Sigma Tau itself, in the start-up phase of the CDCA project, carried out a financial analysis of its net present value at European level. In an *ex ante analysis,* by definition, the cash flows considered are based on the firm's expectations with regard to costs and revenues (ie, expected costs and revenues). However, the same methodology can also be applied *ex post*
to evaluate the actual profitability of the project, using the final data relating to costs and revenues actually realized.

the. *The analysis carried out by Leadiant*

228. In July 2014, in an internal document called *"Xenbilox - Deciding the strategic path ... ",* Sigma Tau evaluated the different options available in relation to the commercialization of the future orphan drug - that the same company continued to call *Xenbilox*® - in the USA and in the aggregate “Rest of the World”, substantially coinciding with Europe391. At the time, the company had already obtained orphan designation in the US and was in the process of applying for it for Europe.

229. With regard to the Rest of the World aggregate - and therefore to Europe - the economic analysis carried out by Sigma Tau shows a very strong

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[391] See doc. 95.6 ("A *top level assessment has been carried out to understand the value associated with different future options").*

incentive to proceed with the request for orphan designation by the CDCA and AIC of the future orphan drug for the new therapeutic indication. This is mainly due to the high profitability expected from the production and sales activities of the orphan drug, which according to Sigma Tau's calculations had a gross operating margin of 99%. This level of operating margin resulted from the large difference in production costs (4 euros per package, as indicated under the item *"COGS euro / unit"* in Figure 1 and Figure 2) and the price at which the drug was supposed to be sold. In particular, as can be seen in the *"Assumptions"* section of the document, a first increase in the *ex factory* price was expected to € 2,900 in mid-2014 (which actually took place), a second increase to € 4,100 at the beginning of 2015 and a final increase to € 5,000 per package in the second half of 2015 in conjunction with obtaining the orphan designation; such increases would have been effective in all the countries of the "Rest of the World" aggregate with the exception of Germany (whose sales were estimated at 10% of the total), where, in consideration of the price moratorium (see par. 108 *above) ,* it was assumed that the price would not increase until 2017, when it would reach the level of 5,000 euros already practiced in other European countries392. It should be noted that in the assumptions present in the document the assumption of a monopoly position of Sigma Tau in Europe always occurs *("market share 100%"* in Figure 1

230. In particular, in applying the NPV model, the company (which assumed the marketing of the orphan drug starting from 2016) considered two scenarios. A more conservative basic scenario, in which, in the absence of changes to the company's operating model, it assumed a modest growth (from 1.7% to 2.5%) in the rate of diagnosis of the disease in the affected population (Figure 1), and a more optimistic scenario, in which, in the face of higher costs incurred by the company aimed at improving the diagnosis of the disease, it would have been diagnosed in 10% of cases (Figure 2).

231. In the first scenario *("base case"),* discounting the expected cash flows in the period 2015-2024393 through a project WACC of 12%, Sigma Tau obtained a NPV of over € 58 million. In the second scenario *("best case") ,* the NPV exceeded 107 million euros, while discounting the expected cash flows through a project WACC of 15%, therefore higher than in the previous scenario, in order to take into account the additional risk resulting from the higher costs to be incurred to improve the diagnosis of the disease (and so on

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[392] The *"Average Selling Prices"* shown in the two Figures and relating to the years 2014-2016 represent weighted averages of the subsequent price increases applied in fractions of the year and take into account the hypothesis that sales in Germany have not undergone such increases.

[393] This is evident from the analysis of the document, where the cash flows taken into account in the calculation of the NPV are those indicated with numbers from 1 to 9.

achieve higher sales volumes). The IRR calculated on the basis of these data is of infinite value in both scenarios, as Sigma Tau expected to generate positive cash flows in each year of the project and, mathematically, the only value of the IRR that can reset the NPV takes on value infinite.

232. These results derive from the fact that Sigma Tau planned to increase the *ex factory* price of *Xenbilox*® from 660 to 2,900 euros per package - as in fact happened in July 2014 - already at the beginning of the project, before the start of the request for registration of the orphan drug, as already illustrated, to finance its costs (essentially the estimated registration costs for the years 2014, 2015 and 2016). The revenues of the project considered by Sigma Tau in the estimate of the cash flows take into account the sales of *Xenbilox*® at the increased price, as well as the sales of the orphan drug, once confirmation of the orphan designation has been obtained, at the hypothesized price of 5,000 euros per pack.

Figure 1 - Base case scenario 394

XENBILOX

EU & Other Markets

currency: euro		2012	2013	2014	2015	EMA approval (Q1) 2016	2017	2018	2019	2020	2021	2022	2023	2024	
Potential n. of patients based on extrapolated prevalen				10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	
% of patients dignose				1.7%	1.7%	2.2%	2.3%	2.4%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	
market share				100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	
n. of patients treate		211	279	171	171	222	232	242	242	252	252	252	252	252	
growth vs. P			*33%*	*-39%*	*0%*	*29%*	*5%*	*4%*	*0%*	*4%*	*0%*	*0%*	*0%*	*0%*	
Units (bottles of 100 tab		2,316	3,071	1,885	1,885	2,439	2,550	2,661	2,661	2,772	2,772	2,772	2,772	2,772	
growth vs. P			*33%*	*-39%*	*0%*	*29%*	*5%*	*4%*	*0%*	*4%*	*0%*	*0%*	*0%*	*0%*	
Average Selling Price (euro/unit		641.1	649.2	1,663	4,160	4,783	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	
growth vs. P			*1%*	*156%*	*150%*	*15%*	*5%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	
Annual Treatment cost x patient (euro'00(		7	7	18	46	53	55	55	55	55	55	55	55	55	
Net Sales (euro'000		**1,485**	**1,994**	**3,134**	**7,841**	**11,666**	**12,751**	**13,306**	**13,306**	**13,860**	**13,860**	**13,860**	**13,860**	**13,860**	
growth vs. P			*34%*	*57%*	*150%*	*49%*	*9%*	*4%*	*0%*	*4%*	*0%*	*0%*	*0%*	*0%*	
COGS (euro/unit)	4.0														
COGS (euro'000)		9	12	8	8	10	10	11	11	11	11	11	11	11	
% on sale		*0.6%*	*0.6%*	*0.2%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	
Gross Margi		**1,476**	**1,981**	**3,126**	**7,834**	**11,656**	**12,741**	**13,295**	**13,295**	**13,849**	**13,849**	**13,849**	**13,849**	**13,849**	
% on sale		*99.4%*	*99.4%*	*99.8%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	
Distributior	0.3%	4	6	9	24	35	38	40	40	42	42	42	42	42	
Registration exp				100	300	200									
Other OPEX	3.5%						446	466	466	485	485	485	485	485	
Total OPE)		**4**	**6**	**109**	**324**	**235**	**485**	**506**	**506**	**527**	**527**	**527**	**527**	**527**	
				3%	*4%*	*2%*	*4%*	*4%*	*4%*	*4%*	*4%*	*4%*	*4%*	*4%*	
EBIT		**1,471**	**1,975**	**3,017**	**7,510**	**11,421**	**12,256**	**12,789**	**12,789**	**13,322**	**13,322**	**13,322**	**13,322**	**13,322**	
Tax	20.0%	294	395	603	1,502	2,284	2,451	2,558	2,558	2,664	2,664	2,664	2,664	2,664	
Net Income		**1,177**	**1,580**	**2,413**	**6,008**	**9,137**	**9,805**	**10,231**	**10,231**	**10,658**	**10,658**	**10,658**	**10,658**	**10,658**	
	days														
A/R	60	247	332	522	1,307	1,944	2,125	2,218	2,218	2,310	2,310	2,310	2,310	2,310	
Inventory	360	9	12	8	8	10	10	11	11	11	11	11	11	11	
A/P	30	1	2	10	28	20	41	43	43	45	45	45	45	45	
NWC (euro'000		**256**	**343**	**520**	**1,287**	**1,934**	**2,094**	**2,185**	**2,185**	**2,276**	**2,276**	**2,276**	**2,276**	**2,276**	
NWC change (euro'000			**-87**	**-177**	**-767**	**-647**	**-160**	**-91**	**0**	**-91**	**0**	**0**	**0**	**0**	
Free Cash Flov		**1,177**	**1,493**	**2,236**	**5,242**	**8,490**	**9,645**	**10,140**	**10,231**	**10,567**	**10,658**	**10,658**	**10,658**	**10,658**	**59,558**
					0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**9**
					5,242	**7,581**	**7,689**	**7,218**	**6,502**	**5,996**	**5,400**	**4,821**	**4,305**	**3,843**	**21,477**
WACC	12%														
NPV Auto	58,595														
NPV Manua	58,595														
TV	21,477														

[394] See doc. 95.6 p. 19.

Figure 2 - Best case scenario 395

XENBILOX

EU & Other Markets

Best Case Scenario

EMA approval (Q1)

currency: euro		2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	
Potential n. of patients based on extrapolated prevalen				10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	
% of patients dignose				1.7%	1.7%	2.2%	2.5%	4.0%	6.5%	8.0%	10.0%	10.0%	10.0%	10.0%	
market share				100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	
n. of patients treatec		211	279	171	171	222	252	403	655	806	1,008	1,008	1,008	1,008	
growth vs. P			*33%*	*-39%*	*0%*	*29%*	*14%*	*60%*	*63%*	*23%*	*25%*	*0%*	*0%*	*0%*	
Units (bottles of 100 tab:		2,316	3,071	1,885	1,885	2,439	2,772	4,435	7,207	8,870	11,088	11,088	11,088	11,088	
growth vs. P			*33%*	*-39%*	*0%*	*29%*	*14%*	*60%*	*63%*	*23%*	*25%*	*0%*	*0%*	*0%*	
Average Selling Price (euro/unit		641.1	649.2	1,663	4,160	4,783	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	
growth vs. P			*1%*	*156%*	*150%*	*15%*	*5%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	
Annual Treatment cost x patient (euro'00(		7	7	18	46	53	55	55	55	55	55	55	55	55	
Net Sales (euro'000		**1,485**	**1,994**	**3,134**	**7,841**	**11,666**	**13,860**	**22,176**	**36,036**	**44,352**	**55,440**	**55,440**	**55,440**	**55,440**	
growth vs. P			*34%*	*57%*	*150%*	*49%*	*19%*	*60%*	*63%*	*23%*	*25%*	*0%*	*0%*	*0%*	
COGS (euro/unit)	4.0														
COGS (euro'000)		9	12	8	8	10	11	18	29	35	44	44	44	44	
% on sale		*0.6%*	*0.6%*	*0.2%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	
Gross Margi		**1,476**	**1,981**	**3,126**	**7,834**	**11,656**	**13,849**	**22,158**	**36,007**	**44,317**	**55,396**	**55,396**	**55,396**	**55,396**	
% on sale		*99.4%*	*99.4%*	*99.8%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	
Distributior	0.3%	4	6	9	24	35	42	67	108	133	166	166	166	166	
Registration exp:				100	300	200									
Other OPEX	15.0%					875	2,079	3,326	5,405	6,653	8,316	8,316	8,316	8,316	
Total OPE)		**4**	**6**	**109**	**324**	**1,110**	**2,121**	**3,393**	**5,514**	**6,786**	**8,482**	**8,482**	**8,482**	**8,482**	
				3%	4%	10%	15%	15%	15%	15%	15%	15%	15%	15%	
EBIT		**1,471**	**1,975**	**3,017**	**7,510**	**10,547**	**11,728**	**18,765**	**30,494**	**37,531**	**46,913**	**46,913**	**46,913**	**46,913**	
Tax	20.0%	294	395	603	1,502	2,109	2,346	3,753	6,099	7,506	9,383	9,383	9,383	9,383	
Net Income		**1,177**	**1,580**	**2,413**	**6,008**	**8,437**	**9,383**	**15,012**	**24,395**	**30,025**	**37,531**	**37,531**	**37,531**	**37,531**	
	days														
A/R	60	247	332	522	1,307	1,944	2,310	3,696	6,006	7,392	9,240	9,240	9,240	9,240	
Inventory	360	9	12	8	8	10	11	18	29	35	44	44	44	44	
A/P	30	1	2	10	28	93	178	284	462	568	711	711	711	711	
NWC (euro'000		**256**	**343**	**520**	**1,287**	**1,861**	**2,143**	**3,430**	**5,573**	**6,859**	**8,574**	**8,574**	**8,574**	**8,574**	
NWC change (euro'000			**-87**	**-177**	**-767**	**-574**	**-283**	**-1,286**	**-2,143**	**-1,286**	**-1,715**	**0**	**0**	**0**	
Free Cash Flov				**2,236**	**5,242**	**7,863**	**9,100**	**13,726**	**22,251**	**28,738**	**35,816**	**37,531**	**37,531**	**37,531**	209,099
					0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	9
					5,242	**6,838**	**6,881**	**9,025**	**12,722**	**14,288**	**15,484**	**14,109**	**12,269**	**10,669**	59,439
WACC	15%														
NPV Auto	107,526														
NPV Manua	107,526														
TV	59,439														

233. It should be noted that the profitability of the project in question was considerably high for Sigma Tau already considering a sale price for the drug not exceeding 5,000 euros per package, such as to make it decide to proceed with the request for orphan designation and marketing authorization for the marketing of the orphan drug in Europe. This implies that the setting of a sale price at a higher level, as actually happened, could only have had the effect of causing a further widening of the difference between prices and costs.

ii. *The economic analysis carried out during the procedure*

234. Starting from the analysis described above, which Sigma Tau carried out prospectively with regard to the Rest of the World aggregate, an analysis of the excessive price of the *CDCA Leadiant*® practiced in Italy was carried out

[395] See doc. 95.6 p. 22.

using the same methodology adopted by the company. For this purpose, it was calculated the profitability of the orphan drug registration and marketing project on the basis of the final data (2014-2020) and the forecast data provided by the same company in relation to the Italian market.
As will be better specified from time to time, the assumptions adopted in carrying out the analysis are all in favor of the Party.

235. According to financial theory, the costs and revenues to be considered in the calculation of cash flows for the analysis of the IRR are "incremental", i.e. those that derive from the comparison of the situation that takes into account the project with the one that would have occurred in the absence of the project. However, Leadiant, in its *ex ante analysis,* seems to consider overall cash flows and not just incremental ones. Therefore, in the following calculations, the analysis was carried out both taking into account the overall cash flows and only the incremental flows.

236. With regard to Italy, in the years 2014-2015 there were no sales of *Xenbilox®.* In 2016 and in the first months of 2017, *Xenbilox*® was imported into Italy, through the wholesaler Juers Pharma, to whom Sigma Tau sold the product at the *ex factory* price of 2,900 euros per pack. Finally, from June 2017, once *Xenbilox*® was withdrawn from the market (see section III.5.7.i *above),* the company started marketing the *CDCA Leadiant*® in Italy which, in the absence of a negotiated price, is it was sold to the ASLs at the *ex factory* price of € 15,506.93 per pack, a price that was still applied at the time of the procedure. Starting from March 2020, the date of entry into force of the negotiation agreement entered into with AIFA on December 19, 2019, the product was sold at the negotiated *ex factory* price of *[5,000-7,000]* euros, net of legal reductions, and the difference between the price paid and the negotiated one, as anticipated, was returned by the company to the ASLs after the agreement entered into force. In the following it has been assumed, in a favorable manner to the Party, that the *ex factory* price of *[5,000-7,000]* euros has been applied to all sales in Italy since the beginning of 2020 and that the *[6-7]* million euros are were returned by the company to the NHS for the most part *([6-7]* million euros) in 2020 and that the remainder *([300,000-400,000]* euros) was fully paid in 2021396.

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[396] More in detail, it is assumed: *i)* that the agreement was implemented from 1 January 2020 instead of the day following its publication in the Official Gazette (3 March 2020), applying the negotiated price to all sales in 2020; *ii)* that the *[6-7]* million euros that had already been reimbursed to the SSN on 7 May 2021 (see doc. 122) have been fully paid during the year of entry into force of the agreement (2020) and that the remaining *[300,000-400,000]* euros are fully paid in 2021.

237. Using actual and forecast sales data for *Xenbilox*® and *CDCA Leadiant*® provided by the Party for the years 2014-2023397 and assuming, again in favor of the Party, that sales of the *CDCA Leadiant*® for the years between 2024 and 2027398 do not increase compared to those of 2023, the revenues relating to the sales in Italy of *Xenbilox*® and *CDCA* were calculated *Leadiant*®*,* shown in Table 1.

Table 1 - Revenues from the CDCA project in Italy (values in euros)

Year	Quantity Xenbilox® (QX)	Price Xenbilox® (PX)	Quantity CDCA Leadiant® (QCDCA)	CDCA price Leadiant® (PCDCA)	Revenues from the CDCA Italy project * (RP Italy = QX * PX + QCDCA * PCDCA)
2016	*[100-200]*	*2,900*			*[300,000-400,000]*
2017	*[50-100]*	*2,900*	*[100-200]*	*15.506.93*	*[2-3 million]*
2018			*[300-400]*	*15.506.93*	*[5-6 million]*
2019			*[300-400]*	*15.506.93*	*[5-6 million]*
2020			*[300-400]*	*[5,000-7,000]*	*[2-3 million]*
2021			*[300-400]*	*[5,000-7,000]*	*[2-3 million]*
2022			*[400-500]*	*[5,000-7,000]*	*[2-3 million]*
2023			*[400-500]*	*[5,000-7,000]*	*[2-3 million]*
2024			*[400-500]*	*[5,000-7,000]*	*[2-3 million]*
2025			*[400-500]*	*[5,000-7,000]*	*[2-3 million]*
2026			*[400-500]*	*[5,000-7,000]*	*[2-3 million]*
2027			*[100-200]*	*[5,000-7,000]*	*[800,000-900,000]*

* Gross of refunds to the NHS.

238. With regard to the costs of the project, made available by Leadiant aggregated at European level399, it is noted that they are composed of the direct costs of production and distribution of *Xenbilox*® for the years 2014-2017, as well as the direct and common costs (final balance and forecast) incurred for the registration, placing and maintenance on the market of the *CDCA Leadiant*® from 2014 to 2027400. These, net of intragroup items (including *inter-company royalties401)* and financial charges, are shown

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397 See doc. 110.1.

398 For the year 2027, only one third of annual sales was considered, considering the exclusivity of market ends in April.

399 The Party reported that its accounting system is not structured in such a way as to be able to differentiate costs by individual country or by only the countries belonging to the EEA. The costs provided therefore refer to all the countries (with the exception of the USA) in which *CDCA Leadiant® is marketed,* although almost all of the activities and related costs were incurred for the EEA countries. See docs. 105 and 110.3.

400 Also with regard to costs, given the fact that the market exclusivity expires in April, for 2027 was considered a value equal to one third of annual costs.

401 It is believed that the *intercompany royalties* paid in 2016 by Leadiant UK to Leadiant US under a license agreement for the marketing of *Xenbilox*® outside the United States should not, like the other intragroup items already excluded by the Party in the calculation of the costs, be considered in this analysis. In fact, these are sums paid by a group company to another group company, which do not constitute significant costs for the purposes of this analysis and have therefore been excluded.

239. With regard to these costs, it is noted, with regard to the entire period 2014-2027, that only *[40-50%]* of the same is attributable to costs directly attributable to the product, while the remaining *[50-60%]* is the result of the allocation made by the Party to the *CDCA Leadiant*® of the common costs incurred by the company for the generality of the products in the portfolio. Furthermore, of *[40-50%]* of direct costs, approximately *[10-20%]* is related to the costs of production and distribution of the product and *[30-40%]* to regulatory, market access402, marketing *costs ,* legal and, to an extent less than 1%, research and development403 (also including the costs incurred for improving the quality of the API, recorded by Leadiant itself within a different cost category).

240. With regard to the legal costs included in the direct costs of the *CDCA Leadiant®,* they also include significant costs incurred by the company in the years 2019 and 2020 for consultancy in the context of *antitrust* proceedings opened by several national competition authorities in Europe, pursuant to of article 102, lett. *a)* of the TFEU in relation to the pricing policy applied by the company for the marketing of the orphan drug. Costs of this type, albeit to a lesser extent, are also foreseen for each year from 2021 to 2027. In principle, these costs should not be considered in the context of the price abuse assessment under consideration, as they have been incurred precisely because of the contested conduct. In the analysis carried out here, however, in a conservative and favorable view of the Party, these costs have been taken into consideration.

241. With reference, moreover, to the criterion for attributing the costs common to the *CDCA Leadiant*® used by the company, i.e. the estimate of the working time employed by its employees on the various products in the portfolio (on the basis of an *ex post* estimate made by Party itself), which leads to attributing to the orphan drug as much as *[30-40%]* of the total common costs incurred by the company over the period 2014-2027 (and over 60% looking at the period 2016-2020), it is noted that this criterion may also be vitiated by the fact that the time spent on this product was so high precisely because it required a significant amount of work for regulatory, medical and market access activities aimed at supporting the demand for a price. potentially excessive. With the criterion used

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[402] Among these, the costs attributable to scientific information *(disease awareness)* amount to approximately *[100,000-200,000]* euros. See doc. 110.3.

[403] Of these, approximately *[100,000-200,000]* euros are attributable to the development of the so-called *"easy to swallow" formulation ".* v. doc. 110.3.

by the Party, the indirect costs allocated to the *CDCA Leadiant*® constitute more than 50% of the total costs of the product that the Party declared for the period 2014-2027. However, even in this case, with an extremely concessive approach, no corrections were made to the common cost allocation criterion identified by the Party.

242. The costs of the project referable to Italy were obtained on the basis of the share of sales in Italy compared to the total 404 (for the years 2014-2016, taking an approach favorable to the Party, for the sole purpose of attributing the costs of the CDCA project to Italy, the average share of sales volumes in Italy for the years 2017-2027 equal to *[10-15%],* being the sales volumes of *Xenbilox*® in Italy equal to zero for the years 2014-2015 and low for the year 2016405).

Table 2 - Costs of the CDCA project for Italy (values in euros)

Year	Costs Xenbilox® (CX)	CDCA costs Leadiant® (CCDCA)	Project costs CDCA on volumes (CP = CX + CCDCA)	Volumes Italy total (%)	Project costs CDCA Italy (CP Italy = CP *% volumes Italy)
2014	*[200,000-300,000]*	*[1-2 million]*	*[2-3 million]*	*[10-15]*	*[200,000-300,000]*
2015	*[300,000-400,000]*	*[6-7 million]*	*[7-8 million]*	*[10-15]*	*[800,000-900,000]*
2016	*[50,000-100,000]*	*[7-8 million]*	*[7-8 million]*	*[10-15]*	*[900,000-1 million]*
2017	*[1-50,000]*	*[7-8 million]*	*[7-8 million]*	*[10-15]*	*[900,000-1 million]*
2018		*[7-8 million]*	*[7-8 million]*	*[10-15]*	*[900,000-1 million]*
2019		*[10-20 million]*	*[10-20 million]*	*[10-15]*	*[1-2 million]*
2020		*[10-20 million]*	*[10-20 million]*	*[5-10]*	*[1-2 million]*
2021		*[9-10 million]*	*[9-10 million]*	*[10-15]*	*[1-2 million]*
2022		*[7-8 million]*	*[7-8 million]*	*[10-15]*	*[900,000-1 million]*
2023		*[6-7 million]*	*[6-7 million]*	*[10-15]*	*[800,000-900,000]*
2024		*[6-7 million]*	*[6-7 million]*	*[10-15]*	*[800,000-900,000]*
2025		*[6-7 million]*	*[6-7 million]*	*[10-15]*	*[800,000-900,000]*
2026		*[6-7 million]*	*[6-7 million]*	*[10-15]*	*[800,000-900,000]*
2027		*[1-2 million]*	*[1-2 million]*	*[10-15]*	*[200,000 - 300,000]*

243. To calculate the IRR of the CDCA project it is necessary to determine, starting from the costs and revenues represented above, the cash flows (i.e. the difference

[404] Starting from the year 2021, sales of *CDCA Leadiant*® in the Netherlands were considered to be zero , in consideration of the regulatory change that has allowed the setting up of galenic productions since 2019
even in the presence of an orphan drug. For the details of the calculations carried out, see the Economic Appendix.

[405] This cost allocation criterion is favorable to the Party because it allows to take into account part of the costs incurred for *Xenbilox*® and *CDCA Leadiant*® even in the absence of sales (years 2014-2015) or low sales (year 2016) in Italy.

between monetary inflows and outflows that occurred over a period) actually achieved for the 2014-2020 period and the expected cash flows for the 2021-2027 period, i.e. until the end of the exclusive ten-year market.

244. To this end, in Table 3 the annual profits relating to Italy relating to the CDCA project have been calculated as the difference between the revenues and costs of the project; the reimbursements to the SSN made by the Party in execution of the agreement with AIFA and relating to the difference between the price paid and the negotiated price were subtracted from the profit for the years 2020 and 2021. The average tax rate incurred by Sigma Tau / Leadiant in the period 2014-2019 was also applied to the profits thus calculated as resulting from the financial statements filed by Leadiant Biosciences Ltd. and its assignors406. In particular, it is equal to 21% 407. It should be noted that the rate used here is the highest (and therefore more favorable to the Party) both with respect to that used by Sigma Tau itself in the *ex ante* analysis described above (equal to 20%) 408 and the average tax rate recorded in Europe in the pharmaceutical sector in the same period (equal to 19%) 409. The change in net working capital (NWC) compared to the previous period was also subtracted for each year410. The change in the CCN was calculated using the methods adopted by Sigma Tau in its *ex* ante evaluation mo

Table 3 - Cash flows of the CDCA Leadiant® project for Italy (values in euros)

Year	CDCA project profit Italy - CP Italy)	Project profit Change in NWC CDCA Italia at CDCA Italia after taxes	Cash flow for Italy project (UP Italy = RP	
2014	*- [200,000-300,000]*	*- [200,000-300,000]*	*0*	*- [200,000-300,000]*

406 See docs. 129 and 131 and related annexes.

407 In calculating the tax effect, a fiscal loss carryover mechanism was assumed, ie that any tax losses incurred in one year can be deducted from the income of subsequent years. For the details of the calculations carried out, see the Economic Appendix.

408 See doc. 95.6.

409 *Dataset Damodaran online, Effective tax rate by industry - Europe* - 2014-2019 average of the *"Average across only money-making companies"* data relating to the "Drugs (Pharmaceutical)" sector *(http:// people.stern.nyu.edu/ adamodar / New_Home_Page / dataarchived.html).*

410 A firm's net working capital (NWC) is the difference between its short-term assets (trade receivables, inventory, other short-term assets) and its short-term liabilities (trade payables, other short-term liabilities). A reduction in the NWC generates a positive cash flow, on the contrary an increase generates a negative cash flow. Given the small value of the relative value, depreciation was not considered, which in principle should also have been added to the profit to obtain the cash flow. Since they would have increased, albeit marginally, the value of the cash flows, this choice is in any case favorable to the Party. Given the small value of the relative value, depreciation was not considered, which in principle should also have been added to the profit to obtain the cash flow. Since they would have increased, albeit marginally, the value of the cash flows, this choice is in any case favorable to the Party

411 See doc. 95.6. For the details of the calculations carried out, see the Economic Appendix.

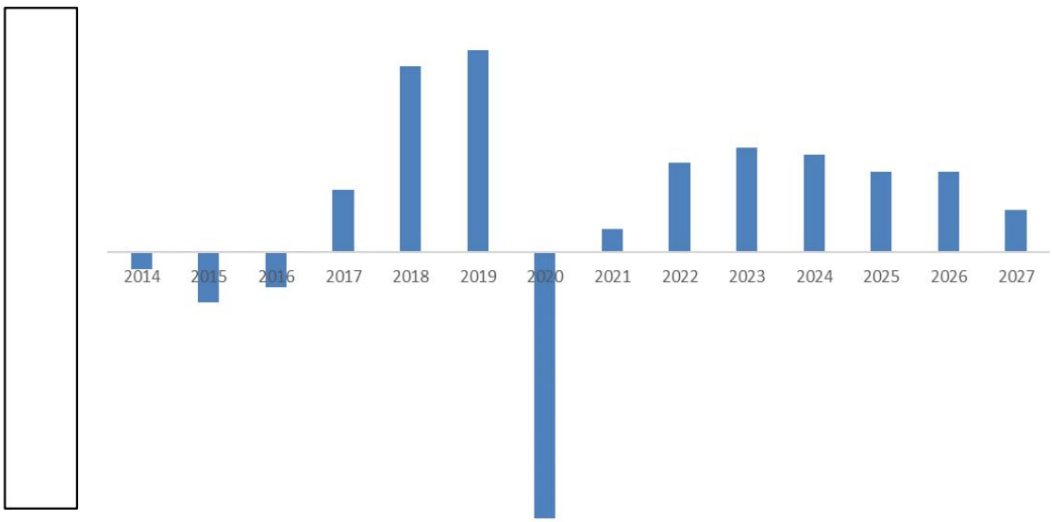
Profit Year	CDCA Italy project (UP Italy = RP Italy - CP Italy)	Useful project CDCA Italy net of taxes	Change in NWC Cash flow project CDCA Italy
2015	- [800,000-900,000]	- [800,000-900,000]	- [1-50,000] - [500,000-600,000]
2016	- [500,000-600,000]	[1-50,000]	[1-2 million] [1-2 million] [300,000-400,000]
2017	[1-2 million]	[1-2 million]	[4-5 million] [3-4 million] [500,000-600,000]
2018	[3-4 million]	[1-2 million]	[50,000-100,000] [4-5 million] [3-4 million]
2019	[3-4 million]	[1-2 million]	[1-2 million] [1-2 million] [1-2 million] [600,000-700,000]
2020	- [4-5 million]	[400,000-500,000]	- [200,000-300,000]
2021	[300,000-400,000]		
2022	[1-2 million]		
2023	[1-2 million]		
2024	[1-2 million]		
2025	[1-2 million]		
2026	[1-2 million]		
2027	[700,000-800,000]		

* On the basis of the hypothesis of refunds to the NHS of the difference between the negotiated price and the price paid, in 2020 *[6-7]* million euros were returned to hospitals .

** It is assumed that the remaining *[300,000-400,000]* euros will be fully repaid in 2021.

245. Figure 3 shows the trend of project cash flows referable to Italy for the period 2014-2027. The negative flows for the years 2014-2016 reflect the costs associated with the preparatory activities for obtaining the orphan designation for the CDCA and for registering the *CDCA Leadiant®* as an orphan drug for the treatment of CTX and are only partially compensated, in Italy, by the sales of *Xenbilox®* at the increased price. Since 2017, the project has begun to produce largely positive cash flows, with the exception of 2020, the year in which almost all of the sum agreed in the agreement with AIFA was returned.

Figure 3 - Cash flows of the CDCA Leadiant® project for Italy (thousands of euros)



246. The calculation of the internal rate of return for the period 2014-2027, ie the entire time frame of the project, provides a value of *[50-60%].*
This value must be compared with the cost of capital (the WACC) to determine the profitability of the project.
247. In the present case, it is considered appropriate to use the WACC value used by Sigma Tau itself in its *ex ante analysis.* Once again in a perspective favorable to the Party, the highest value will be considered, that associated with the *"best case scenario"* - which therefore incorporates a higher risk component - equal to 15%. This value is considered to be significantly concessive, considering that the average WACC observed for pharmaceutical companies in Western Europe in 2014 amounted to 10% 412.
248. Therefore, on the basis of the above analysis, the sales price of the *Leadiant® CDCA* in Italy generates a project return rate equal to *[three-four]* times the cost of capital.
249. Again as a precautionary measure for the Party, the IRR analysis was carried out also taking as reference only the cash flows incremental, i.e. those attributable to the project and which, in the absence of the same, would not have occurred. In the present case, since the project being assessed consists in the launch of a new product *(CDCA Leadiant®)* which replaces an existing product *(Xenbilox®),* only the relevant cash flows were taken into account incremental revenues and costs, i.e. the difference between the revenues (costs) attributable to the new product and the revenues (costs) relating to the replaced product, which would have been realized (incurred) in the absence of the project.
250. In addition to the aforementioned documents, which show that the increase in the *ex factory* price of *Xenbilox®* from 660 to 2,900 in mid-2014 was an integral part of the CDCA project (see paragraphs 109 and 113 *above),* are highlighted other documents on file showing that if the registration of the orphan drug had not been successful, Sigma Tau would have continued to sell *Xenbilox®* administered *off label* for the treatment of CTX413 and that, in the absence of the project, no increases in price for it

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[412] See Dataset Damodaran online, *Cost of Capital by industry - Europe* - year 2014, *"Cost of Capital"* data relating to *(Pharmaceutical) ", http:// www.stern.nyu.edu/ adamodar/ pc/ archives/ waccEurope14 .xls* available on *Drugs*

[413] See, *inter alia,* doc. 22.7.129.

Xenbilox®414 for years to come. In particular, in a document dated August 2014, we read that, in the absence of the project in question, the revenues of *Xenbilox®* would have remained in line with those of previous years *("Base case 2015-19 forecast is conservative and includes 2 Mln € flat sales in EU only, consistent with historical* trend ") 415. In the same document, the incremental revenues deriving from the CDCA project are indicated and quantified separately *("What-if: Xenbilox price increase and global registration ...*
Based on a preliminary analysis driven by assumptions on price increase, prevalence and diagnosis rate, Xenbilox shows a great potential. A global registration (EMA + FDA) with a significant price increase (€ 110k annual treatment per patient in EU and about € 140k in US) may lead up to 29 Mln sales increase in 2019 (best case + 80Mln) and 31 Mln in EBITDA (best case +69 million) "). Assuming a package price of around 10,000 euros, Leadiant therefore believed it could increase its turnover by 29 million euros per year, indicated in the document as *"Xenbilox Incremental sales" 416* compared to the scenario in the absence of a project, in which revenues are quantified in 2 million euros, in line with the revenues of previous years when *Xenbilox®* was sold at a price of 660 euros per pack.

251. Therefore, the incremental cash flows attributable to the CDCA project to be considered are the differential ones compared to the scenario in the absence of the project itself, i.e. the continuation of the sale of *Xenbilox® off label* at the price of 660 euros per package in effect before the project417. Consequently, the incremental revenues were calculated by subtracting, from the revenues realized or expected by the Party, the revenues that would have been realized in any case by selling *Xenbilox®* for 660 euros.

252. With regard to the incremental costs, i.e. the costs that would not have been incurred in the absence of the CDCA project (but continuing with the sale of *Xenbilox®* administered *off label),* the Party has provided an estimate of the same which does not appear realistic for the following reasons. Firstly, in the incremental cost estimate provided418, the Party considered all direct costs of the *CDCA Leadiant®* as incremental: this cannot be likely, expected

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414 Doc. 95.5, p. 41.
415 Doc. 95.5.
416 Incremental sales of *Xenbilox®* are even quantified at 80 million in the *"best case" scenario,* in which a significant increase in the rate of diagnosis of the disease is assumed and, therefore, in the quantities sold.

417 Again with a view to favoring the Party, it was not taken into account that, in the absence of the CDCA project and the related activities aimed at encouraging the diagnosis of the disease, the *off-label* sales of *Xenbilox®* starting from 2017 could have been lower than those occurred or expected for the *CDCA Leadiant®.*
418 See docs. 110, 110.5 and 127.

that the *CDCA Leadiant*® production process does not differ significantly from that of *Xenbilox*® and therefore a large part of these costs would have been incurred in the absence of the project.

253. Secondly, it is noted that the Party has provided the value of the incremental common costs not - as would be expected - by separating from the common costs attributed to the *CDCA Leadiant*® those that would have been incurred in the absence of the project; otherwise, the company has made this estimate starting from the total common costs, that is, incurred by the company for the production and marketing of all the products in the portfolio. This method of identifying incremental costs leads to the paradox that for some years - and in particular the initial and final ones of the project - the incremental costs of the *CDCA Leadiant*® would be higher than the total costs reported by Leadiant itself to the same product, while, in the entire period of the project, the incremental costs and the total costs of the *CDCA Leadiant*®

substantially they would coincide. In other words, according to the Party, all the common costs attributed to the *CDCA Leadiant®,* which as already noted (see par. 239 *above),* represent more than half of the total costs of the product over the time span of the project, would have an incremental nature.

254. Furthermore, according to the Party, for the first 8 years of the project (2014-2021) over 50% of the total common costs, ie those incurred for all the products in the portfolio, would be incremental to the *CDCA Leadiant®.* This is because, if the CDCA had not obtained the designation as an orphan drug, the company, while continuing to market the other products in the portfolio (including *Xenbilox*® administered *off label)* would have significantly reduced its structure in Europe, *[omissis] .*

255. On this point, it should be noted that the scenario of drastic reduction of Leadiant's European structure in the event of a negative outcome of the CDCA project does not appear to be supported by any concrete evidence. The documentation filed shows, however, how the company planned, in this case, to continue in any case in the sale of *Xenbilox*® *off* label without being able to expand its sales, but never assuming a drastic restructuring of its European presence419.

256. It should also be considered that the same Party has provided an estimate of the multiannual incremental costs *([50-60%]* of the total common costs for the years 2014-2021 and *[20-30%]* for the years 2022-2027), representing that *"the year-by-year estimate of the incremental common costs would not·provide a value*

[419] See doc. 22.7.129.

additional information "420 and that the more granular allocation of common costs year by year has been carried out (in defining the data relating to the total costs of the *CDCA Leadiant®),* using the allocation key of the time worked.

257. All this considered, it is considered more precautionary in the continuation of the analysis of the incremental cash flows to consider the total costs of the *CDCA Leadiant*® supplied by the Party. Note that this choice is extremely favorable to the Party, since incremental costs are by definition a subset of total costs.

258. Table 4 shows the incremental profits relating to the CDCA project, obtained considering the incremental revenues (i.e. net of the revenues deriving from the sales of *Xenbilox*® that would have occurred anyway) minus the incremental costs (which in this case, with a extremely favorable approach to the Party, are considered to coincide with total costs for the reasons illustrated above). The calculation of the profit after taxes and the change in CNN in order to determine the incremental cash flows was carried out in accordance with what has already been done for the calculation of the total cash flows421.

Table 4 - Incremental cash flows of the CDCA Leadiant® project for Italy (values in euros)

Year	Incremental profit from CDCA Italy project (Incremental **RP** Italy **- Incremental CPs Italy)**	Incremental profit CDCA project Italy net of taxes	Change in CCN	Incremental cash flow CDCA project Italy
2014	*- [200,000-300,000]*	*- [200,000-300,000]*	*- [200,000-300,000]*	*0*	
2015	*- [800,000-900,000]*	*- [800,000-900,000]*	*- [800,000-900,000]*	*- [1-50,000]*	
2016	*- [600,000-700,000]*	*- [600,000-700,000]*	*- [600,000-700,000]*	*[1-50,000]*	
2017	*[1-2 million]*	*[1-2 million]*	*[800,000-900,000]*	*[300,000-400,000]*	
2018	*[4-5 million]*	*[3-4 million]*	*[2-3 million]*	*[500,000-600,000]*	
2019	*[4-5 million]*	*[3-4 million]*	*[3-4 million]*	*[1-50,000] - [1-2*	
2020	*- [5-6 million] * - [5-6 million] - [4-5 million]*			*million]*	
2021	*[600,000-700,000] ** [600,000-700,000] [100,000-200,000] [500,000-600,000]*				
2022	*[1-2 million]*	*[1-2 million]*	*[1-2 million]*	*[50,000-100,000]*	
2023	*[1-2 million]*	*[1-2 million]*	*[1-2 million]*	*[1-50,000] [1*	
2024	*[1-2 million]*	*[1-2 million]*	*[1-2 million]*	*-50,000] [1-50,000]*	
2025	*[1-2 million]*	*[1-2 million]*	*[1-2 million]*	*[1-50,000] -*	
2026	*[1-2 million]*	*[1-2 million]*	*[1-2 million]*	*[200,000-300,000]*	
2027	*[300,000-400,000] [200,000-300,000] [400,000-500,000]*				

* On the basis of the hypothesis of refunds to the NHS of the difference between the negotiated price and the price paid, in 2020 *[6-7]* million euros were returned to hospitals .

** It is assumed that the remaining *[300,000-400,000]* euros will be fully repaid in 2021.

420 See doc. 127.

421 For the detailed calculation, see the Economic Appendix.

259. Figure 4 shows the incremental cash flows of the CDCA project, obtained as described above, compared with the overall cash flows (already reported in Figure 3). Incremental flows are more contained than non-incremental flows, as the latter were not subtracted from the sales of *Xenbilox*® (which would have taken place in the absence of the project).
The use of incremental cash flows is therefore favorable to the Party.

Figure 4 - Incremental and overall cash flows of the CDCA project for Italy (thousands of euros)

260. The result of the calculation of the internal rate of return on cash flows incremental for the period 2014-2027, corresponding to the entire time frame of the project, provides a value of *[40-50%].* Also in this case, always considering a cost of capital equal to 15% in a perspective favorable to the Party, the prices applied by Leadiant generate a profitability of the project that is three times the cost of capital.

III.6.3 Analysis of the cost plus

261. The second methodology of price excess analysis used consists in examining the disproportion between the prices applied and the costs incurred by Leadiant for the *CDCA Leadiant®,* according to the following relationship: PQ - (C + ROS) = EXC.

262. The value in brackets represents the so-called *cost plus* (C +) and is given by the sum of the costs (indicated with C and made up of both the costs directly attributable to the product and the share of indirect costs attributed to it) and a measure of the reasonable profitability business *(Return on Sales* or ROS).

263. The difference between the revenues (PQ) and the *cost plus* represents the excess (EXC) of which the possible disproportion must be evaluated. The measure of the excess thus obtained will be related to the *cost plus* to obtain a percentage value (EXC%), invariant with respect to the sales volumes and comparable with the results achieved in other cases of unjustifiably burdensome prices.

264. In the present case, the excess was calculated starting from June 2017, the year in which the *CDCA Leadiant*® was marketed in Italy, and considered both up to 2020, the last full year for which sales of the *CDCA* actually took place. *Leadiant®,* and until the end of the market exclusivity, i.e. April 2027, based on the data relating to costs and revenues provided by the Party.

265. For the purpose of calculating revenues, the quantities sold in Italy starting from June 2017 (effective until 2020 and estimated from 2021 onwards) have been multiplied for each year by the unit price of *[5,000-7,000]* euros . This is because the price negotiated in the agreement with AIFA, net of legal reductions, was applied retroactively to sales made to hospitals in the CNN class through a refund mechanism for the difference between the price paid and the negotiated one. In the following analysis, since the monetary manifestation of revenues is not relevant but the relative economic competence, it will be considered as if the negotiated price was applied *aborigine422.*

266. As regards all costs, direct and indirect, the data already considered in the TIR methodology were taken into consideration (cf. Table 2).

267. With regard to the measure of the profitability of the company, which ensures it an adequate remuneration for its activity, it was chosen, in continuity with the previous cases of unjustifiably burdensome prices in the pharmaceutical sector423, to use a balance sheet index that measures the

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[422] From the information provided by the company, the difference between the amount paid by the ASL in the years 2017-2019 and the amount due if it had been applied *aborigine,* the negotiated price is higher than the [6-7] million agreed in the agreement with AIFA. From this it would follow that the actual revenues were higher than those which would have occurred in application of the negotiated price to all sales. However, with a view to the Party's favor, the negotiated price will be applied to all sales of *CDCA Leadiant® for the calculation of revenues.*

[423] See the provision AGCM n. 26185 of 29 September 2016, *A480 - Aspen drug price increase.*

profitability of sales, the ROS (given by the ratio between operating profit and sales). The choice of this indicator appears appropriate as the CDCA project essentially consists in a *repurposing* of *Xenbilox®,* a product already present in the company's portfolio, and is not characterized by high levels of investments or risk. In order to identify an appropriate ROS value that can represent a reasonable profit margin for the business activity, the average data relating to the ROS of the pharmaceutical sector companies in Western Europe in the period 2014- was considered.

2019, which amounts to 20.54% 424 (approximated to 21% in the rest of the analysis). It should be noted that this profitability *benchmark* is significantly higher than that used in the Authority's precedents425.

Considering that the investigation is aimed at verifying the possible imposition of excessive prices, it is considered inappropriate to calculate the ROS starting from the turnover achieved by applying these prices. Consequently, the reasonable return for the company will be calculated by applying an adequate *mark up* on costs *(cost uplift)* based on the ROS identified above426.

Table 5 - Calculation of cost plus and excess in percentage (values in euros)

Year	CDCA Leadiant® quantity (QCDCA)	CDCA price Leadiant® (PCDCA)	CDCA revenues costs (RCDCA = PCDCA * QCDCA)	CDCA Leadiant® (CCDCA)	C + (CCDCA / (1-ROS))	EXC% ((RCDCA - C +) / C +)
Jun-Dec 2017	*[100-200]*	*[5,000-7,000]*	*[800,000-900,000]*	*[500,000-600,000] **	*[600,000-700,000]*	*[20-30%]*
2018	*[300-400]*	*[5,000-7,000]*	*[2-3 million]*	*[900,000-1 million]*	*[1-2 million]*	*[80-90%]*
2019	*[300-400]*	*[5,000-7,000]*	*[300-400]*	*[2-3 million]*	*[1-2 million]*	*[1-2 million]*	*[60-70%]*
2020	*[5,000-7,000]*	*[300-400]*	*[2-3 million]*	*[1-2 million]*	*[1-2 million]*	*[60-70%]*
2021	*[5,000-7,000]*	*[400-500]*	*[2-3 million]*	*[1-2 million]*	*[1-2 million]*	*[50-60%]*
2022	*[5,000-7,000]*		*[2-3 million]*	*[900,000-1 million]*	*[1-2 million]*	*[100-150%]*
2023	*[400-500]*	*[5,000-7,000]*	*[2-3 million]*	*[800,000-900,000]*	*[1-2 million]*	*[100-150%]*
2024	*[400-500]*	*[5,000-7,000]*	*[2-3 million]*	*[800,000-900,000]*	*[1-2 million]*	*[100-150%]*
2025	*[400-500]*	*[5,000-7,000]*	*[2-3 million]*	*[800,000-900,000]*	*[1-2 million]*	*[100-150%]*

[424] See Dataset Damodaran online, *Operating and Net Margins by Industry - Europe* - 2014-2019 average of the *"Pre-tax Unadjusted Operating Margin"* data relating to the *"Drugs (Pharmaceutical)" sector,* available on *http: // people.stern. nyu.edu/ adamodar/ New_Home_Page/ dataarchived.html.*

[425] See *A480 - Price increase for Aspen drugs,* cit., Para. 174, 182, 319, where a ROS of 13% was used.

[426] See *CMA Pfizer / Flynn Decision,* point III.C.5.56. The coefficient to be applied to the costs to obtain the *cost plus* is equal to 1 / (1-ROS).

Year	CDCA Leadiant® quantity (QCDCA)	CDCA price Leadiant® (PCDCA)	CDCA revenues Leadiant® (RCDCA = PCDCA * QCDCA)	CDCA costs Leadiant® (CCDCA)	C + (CCDCA / (1-ROS))	EXC% ((RCDCA - C +) / C +)
2026	*[400-500]*	*[5,000-7,000]*	*[2-3 million]*	*[800,000-900,000]*	*[1-2 million]*	*[100-150%]*
2027	*[100-200]*	*[5,000-7,000]*	*[800,000-900,000]*	*[200,000-300,000]*	*[300,000-400,000]*	*[150-200%]*
Jun 2017-Dec 2020	*[1,000-2,000]*	*[5,000-7,000]*	*[7-8 million]*	*[3-4 million]*	*[4-5 million]*	***[60-70%]***
Jun 2017-Apr 2027	*[3,000-4,000]*	*[5,000-7,000]*	*[20-30 million]*	*[10-20 million]*	*[10-20 million]*	***[90-100%]***

* Considering that sales of *CDCA Leadiant*® in Italy began in June 2017, the costs incurred in 2017 by the company were re-proportioned to an equivalent period of the year.

268. Starting from June 2017, as shown in Table 5, the Party reported revenues in excess of costs (including an appropriate remuneration margin); this excess, as a percentage of the *cost plus,* in the period 2017-2020 assumes values between *[20-30%]* and *[80-90%],* with an excess for the whole period equal to *[60-70%].* Considering the entire period of market exclusivity, ie until April 2027, the percentage excess amounts to *[90-100%].*

IV. THE ARGUMENTS OF THE PARTIES

IV.1 Procedural Exceptions

269. Preliminarily, Leadiant complained that the principle of equality of arms between prosecution and defense had been violated as a result of the postponement of the date of the hearing after it had already filed its briefs. In fact, the company believes that the fairness of the dispute between the Party and the Offices before the Board at the final hearing was altered by the fact that, due to the postponement of the final hearing, the Offices were able to benefit from a period of more than three times the time (17 days) of that foreseen by the aforementioned Presidential Decree (5 days) for the analysis of the party's b
Therefore, in consideration of the postponement of the final hearing, it would have been appropriate for the Authority to identify specific methods to ensure equality of arms also in this case.

IV.2 The existence of a dominant position in Leadiant

270. With regard to the attribution of a dominant position to Leadiant in the national market of CDCA-based drugs for the treatment of CTX - the definition of which has not been the subject of counter-arguments by the Party - from January 2016, the company believes that this position of pre-eminence did not exist before the achievement of the AIC for the orphan drug. Since *Xenbilox®,* authorized in Germany for the treatment of gallstones, but without AIC in Italy, was imported on the domestic market by independent wholesalers (in a totally independent way and moreover in very limited quantities and only for a few months between the 2016 and 2017427), Leadiant was not directly active in the national market. Therefore, it would not be possible to attribute to it a real market position in Italy428.

271. In any event, according to the Party, Leadiant's market position was contestable by various parties capable of placing CDCA-based products on the market, both of a galenic and industrial nature.

272. As regards the former, Leadiant believes that PCA was not, and is not, the only credible operator on the market for CDCA as a pharmaceutical grade active ingredient capable of supplying CDCA to hospital pharmacies wishing to produce the drug in galenic form. This would be demonstrated by *i)* a historical extract from the *Thomson Reuters Newport Global database ,* which would highlight the presence on the market of (at least) 15 alternative CDCA suppliers as early as 2015, *ii)* the offer to supply CDCA to PCA by a wholesaler of pharmaceutical grade active ingredients, which in all likelihood was sourcing itself from a Chinese manufacturer in 2017,
iii) the CDCA offer presented by Pierre Fabre directly to Leadiant in 2019 *iv)* the ascertained existence, from the beginning of 2020, of a Chinese source of CDCA which was operational in Europe through the sale of the active ingredient to the hospital of Amsterdam, which since February 2020 has set up a galenic production capable of adhering to the specifications of the European Pharmacopoeia, and, finally, *v)* the existence of at least two operators who have the MA relating to pharmaceutical products based on CDCA *(Chenodal,* marketed in the United States by Retrophin and *Chino,* marketed in Japan by Fujimoto Pharmaceutical Corporation) and which would purchase the active substance from suppliers other than PCA429. It should also be considered, according to Leadiant, that the production of CDCA is not a complex activity and that there are also other subjects able to enter any

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427 See doc. 84.
428 See docs. 185 and 187.
429 See docs. 84, 126, 185 and 187.

moment in the market, especially the companies that, as emerged during the procedure, produce ursodeoxycholic acid and could also produce CDCA, as an intermediate product of the former.

273. On the basis of these factual elements, Leadiant believes that, after the end of the stocks of CDCA by the University Hospital of Siena, the Italian hospitals could easily have procured from these alternative sources to PCA and that, therefore, the failure access to the active ingredient would not be attributable to the exclusive CDCA supply contract, also considering that as early as 2005 PCA had stopped supplying CDCA to the AOU Senese[430] Pharmacy, and that this contract had the sole purpose of protecting the investments made on both sides.

274. In relation to the competitive threats posed by other industrial-type CDCA-based drugs capable of competing for the market with Leadiant prior to obtaining the MA for the orphan drug, the company generally observes that *Xenbilox*® did not enjoy no protection of a regulatory nature, since the *dossier protection has expired,* nor patent, since the drug is *off patent,* so that any other company could have entered the market with a drug based on CDCA. Furthermore, it identifies in particular two drugs allegedly potential competitors of the CDCA: the aforementioned *Chenodal* of which Retrophin was, and is the owner, and *Kolbam®*[431]*.*

275. As regards the market position held by the company after obtaining the orphan designation and the MA of the orphan drug, the company merely states that Leadiant's ability to exercise market power could be limited in the future by the dynamics competition in other EU member states that can influence the Italian market and the sustainability of Leadiant's presence on this market, given the extremely small patient base at EU level.

276. Finally, the company believes that the significant negotiating power held by AIFA, the manifestation of which can be found in the fact that the agreement entered into by the company with the Agency in December 2019 led to the application of a negotiated price that it appears to be the lowest in Europe, does not allow Leadiant to be given a dominant position on the relevant market.

IV.3 The increase in the price of Xenbilox®

277. The company believes that its conduct, as it emerged in the

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[430] See doc. showers 185 and 187.

[431] See doc. showers 185 and 187.

preliminary findings, are normal, physiological and merely aimed at the development of the CDCA project.

278. Preliminarily, the Party disputes the relevance of events dating back to 2007 for the purposes of ascertaining the infringement, which would possibly have started only from 15 June 2017[432].

279. In any case, Leadiant states that all the documents that refer to an increase in the price of the product, the so-called *"step price increase"* and more generally to the future sale price of the medicine, would be nothing more than mere assessments of a which reflected the drastic drop in sales deriving from the contraction in demand, in turn linked to the obsolescence of the CDCA for the treatment of CTX, the instability of the market at that historical moment and the profitability of the project, especially in light of the achievement of the orphan designation.

IV.4 The artificial differentiation between Xenbilox® *and the orphan drug*

280. Leadiant first of all disputes the Authority's own competence to hear about the events relating to the withdrawal of *Xenbilox*® from the German market and the establishment of Leadiant GmbH, under penalty of formulating assessments on facts that from a geographical point of view would not fall within the scope of the Proceedings.

281. Furthermore, in particular, the withdrawal of *Xenbilox*® was not dictated by the intention to influence neither the German regulator nor those of other Member States, but would merely be the result of the fact that the original therapeutic indication, the treatment of stones biliary, no longer had a market.

It would therefore have been financially unsustainable to keep both drugs on the market in the face of the small number of rare disease patients in Germany. In this sense, the document should be understood in which it is stated that the reasons for the withdrawal of the *off-label* drug are "strategic", to be interpreted as a synonym for "commercial".

282. Similarly, the establishment of Leadiant GmbH would not have had any anti-competitive purpose, since this would not have prevented health insurance companies from referring to the reimbursement price of *Xenbilox®,* but at the most from benefiting from an automatic discount on the price of the *CDCA Leadiant*® equal to the difference between the price of that drug and the

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[432] In this regard, the Party quotes the Lazio Tar, sent. n. 8239/2021 which considered a series of investigative documents unusable, as they were outside the time perimeter of the alleged anti-competitive practice, or referred to events prior to the period of explication of the alleged agreement.

redemption price of *Xenbilox*® in Germany, a circumstance which would be irrelevant to the present case.

IV.5 The procedure for negotiating the price of the orphan drug before AIFA

283. Leadiant also denies having obstructed conduct towards AIFA. From this point of view, in fact, the case would differ significantly from the previous one of the *Aspen Authority.* Leadiant did not, in fact, exert any negotiating pressure on the Agency either through the reiteration of the request to move the drug into class C, nor threatened the withdrawal of the drug from the domestic market, nor finally exploited the unavailability of the product on the national territory. On the contrary, the company would always have adopted a cooperative attitude towards AIFA, so much so that in April 2018 the company told the Agency that the difference between the purchase price at the time and the price negotiated with AIFA would have been returned to health facilities. Secondly, the Company would never have intended to cause or has caused any harm to the NHS or to patients, both in light of the negligible size of the drug *budget* and the absence of evidence on cases of interruption of treatment attributable to Leadiant.

284. Furthermore, the company claims that the duration of the negotiation procedure relating to the price of the orphan drug, albeit articulated and complex, *inter alia* due to the uncertainties on the pathology's incidence, was not particularly long compared to the average. The average time between the EMA authorization and AIFA's determination of admission to reimbursement in the period 2017-2020 would in fact be 24 months, with maximum values of 89 months. In the case of the *CDCA Leadiant®,* between the authorization of the EMA (April 2017) and the resolution approving the price agreement (December 2019) approximately 32 months have elapsed, of which 2 were used to submit the reimbursement *dossier* and 12 passed pending the call of the company by the AIFA CPR (which took place in June 2018), so the effective negotiation on the price (also taking into account the periods of consensual suspension of the procedure) took place in a total of 18 months. It would therefore not be possible to attribute to Leadiant a delaying and obstructive conduc

285. The firm also denies having delayed the cost data requested by the Agency during the negotiation procedure. Instead, it promptly presented, or at the time of preparing the reimbursement *dossier ,* the information required by CIPE Resolution no. 3/2001 and

from the attached *dossier* scheme , which require the indication of the total amount of investments in research and development and production investments made by the proposing company in Italy in the last three years. The request by AIFA to know the amount of the production costs of the orphan drug would therefore be irrelevant because it does not correspond to the criterion adopted by the CIPE Resolution itself, which would be totally and exclusively focused on the cost-effectiveness attributable to a drug, i.e. on a *value based* and not *cost based approach.*

286. AIFA would also have disregarded the indications of the applicable regulatory framework to the extent that it claimed to align the price of *CDCA Leadiant*® with that of *Xenbilox*®*,* whereas art. 48, paragraph 5, lett. d) of Legislative Decree 269/2003 binds AIFA to assume *"as terms of comparison the reference price for the related homogeneous therapeutic category and the comparative daily cost in the context of drugs with the same therapeutic indications".* From this it would also follow that AIFA would not have been able to use *Xenbilox*® as a comparator drug of reference for the purposes of negotiating the price of the *CDCA Leadiant*®*,* as it is legally forbidden to compare with drugs without AIC in Italy and authorized for different indications. For this reason, the artificial differentiation between *Xenbilox*® and *CDCA Leadiant*®*,* whose implementation is in any case denied by the company, would have had no effect on AIFA.

287. On the subject, Leadiant concludes by stating that the negotiation did not take place in unfavorable conditions for AIFA, so much so that it ended with an outcome much closer to the position of the Agency than to that of the company, so much so that the negotiated price is the lowest among those practiced in the other EU Member States, that the drug *budget* is absolutely negligible and that the Agency itself declared itself sufficiently satisfied with the negotiation outcome.

IV.6 The excessively priced CDCA Leadiant®

IV.6.1 The analysis of the IRR

288. According to the Party, the analysis of the IRR carried out during the procedure to demonstrate the excessive disproportion between the price of the *CDCA Leadiant*® and the costs incurred is based on an unsuitable model, which does not

it would properly take into account the risks faced by the firm in the project in question and / or be based on erroneous assumptions that would not reflect the facts.
289. From the point of view of the risks to which the company has gone, and will continue to face, Leadiant noted first of all that obtaining and maintaining the designation as an orphan drug was not a certain result, especially considering that the The European Commission had already authorized two other drugs indicated for the treatment of inborn errors of primary bile acid synthesis (which also includes CTX), *Kolbam*® and *Orphacol®433.*

290. Secondly, Leadiant recalled that the marketing authorization for the orphan drug was granted "in exceptional circumstances" and that the permanence of the conditions under which the marketing authorization was granted is examined annually. To this end, the company must collect data on the safety and long-term efficacy of the therapy in patients treated with the *CDCA Leadiant®,* through a register of patients affected by CTX, functional to the collection of such data and the presentation to the EMA. , on the basis of this register, the results and evidence of a study (involving children, adolescents and adults) 434.
291. In addition, Leadiant mentioned the risks associated with the negotiation of the reimbursement conditions: the determination of the market price, in fact, depends on the success of the negotiations to be conducted on the basis of the individual national reimbursement regimes with subjects with strong negotiating power.
292. Furthermore, it would be necessary to consider the risks associated with market / quantity coverage, particularly pronounced for drugs used for the treatment of extremely rare diseases such as CTX and further exacerbated by the fact that the market exclusivity deriving from the orphan designation, in addition to being shortened to six years, it is likely to be exceeded in the presence of “similar” drugs considered safer, more effective or in any case clinically superior435.

293. To better reflect risk information, Leadiant believes it would be more efficient to use a risk-adjusted NPV model.
This approach, unlike the model used during the procedure, where the risk component is incorporated in the WACC, uses several parameters to take into account the risk (probability of success and discount rate). These parameters are estimated not from the perspective of

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[433] See doc. 84 and 122.
[434] See docs. 84 and 122.
[435] See doc. 84.

Leadiant but in that of an *ex ante investor,* a circumstance that would guarantee an objective and not subjective assessment of the risk. In the model proposed by the Party, the choice of the probability of success in the different *steps* is based on a literature search relating to the average probability of success of the development projects of orphan drugs, adapted to the specificities of the case. The discount rate was instead estimated through a *survey* conducted in 2020 on over 400 evaluation experts in the pharmaceutical sector. Using this methodology, in the opinion of the Party, the price of the *CDCA Leadiant*® would not be excessive; the *Minimum Viable Price,* ie the minimum price that according to the Party an investor would have required to decide to invest in the project, would amount to approximately *[5,000-7,000]* euros per package.

294. With specific regard to the value of the WACC used in the investigation, Leadiant argues that it would not be appropriate, as it would have been obtained from a document internal to Leadiant, *[omissis],* and would therefore tend to underestimate this value. Furthermore, it would constitute a corporate WACC and would not be referable to the specific CDCA project, which would be characterized by a higher WACC value.

295. The Party also argues that the preliminary analysis is based on some erroneous assumptions. In particular, Leadiant argues that in the no project scenario, used in the procedure to conduct the IRR analysis on incremental cash flows, the fact that, even if the CDCA project had not been undertaken, the price of the *However, Xenbilox*® would have been increased. This is because the company would have had similar incentives to raise the price of *Xenbilox*®

in both scenarios (i.e. whether the project is implemented or not).
296. Lastly, the fact that the price of *CDCA Leadiant*® is destined to decrease progressively even during the period of exclusivity has not been taken into consideration, given that the supply conditions are subject to periodic renegotiation with the regulator.

IV.6.2 Analysis of the so-called cost plus method

297. Leadiant believes that it is not adequate to verify the unjust severity of the price of the orphan drug through the so-called *cost plus method,* as occurred in the precedent of the Authority, *Aspen436,* and in that of the supervisory authority

[436] See the provision AGCM n. 26185 of 29 September 2016, *A480 - Aspen drug price increase.*

British competition, *Pfizer / Flynn437.* These cases, in fact, unlike the one at *issue,* concerned already existing products, whose initial investments had been recovered and in relation to which no scientific contribution had been made. The present case, on the other hand, is characterized above all by the aforementioned significant regulatory and commercial risks at all stages of its development. On the other hand, Leadiant points out, even AIFA has decided not to apply a *'value-based'* approach to the drug instead of a *'cost-based'438* approach in determining the reimbursement price of the *CDCA Leadiant®439.*

298. In addition to the inadequacy linked to the nature of the product, for Leadiant the *cost plus* method would not take into consideration the time value of money and, therefore, the dynamic evolution of a project for the development of a new drug such as *CDCA Leadiant® .*

299. Furthermore, the calculation of the *cost plus* starting from 2017 would not take into account of the initial investment made by Leadiant in the years 2014-2016 to bring the product to the market.

300. Finally, the sector average ROS used as a *benchmark* to assess price excess would not be adequate, as it would not reflect the specific risk of the CDCA project.

IV.7 The unfair price of the CDCA Leadiant®

301. According to the Party, the second phase of the *United Brands* test developed by the Court of Justice, aimed at determining the unfairness of prices, in the present case should have enhanced the economic value of the drug (also including *non-cost related* factors , such as benefits for patients and society) and the price of the same drug in other European countries or the price of comparable pharmaceutical products440.

302. Leadiant criticizes, in fact, the choice to consider only the first of the two criteria indicated in the *United Brands text,* which looks at inequity in an absolute sense. In fact, according to the Party, this criterion would only apply to those cases in which the unfair nature of prices can be determined without the need for any comparison with similar or competing products.

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437 See the decision of the *Competition & Markets Authority* of 7 December 2016, *Unfair pricing in respect of the supply of phenytoin sodium capsules in the UK* (Case CE / 9742-13).

438 See doc. 72.

439 See doc. 105.

440 See docs. 185 and 187.

Such cases would only be identified in relation to the prices for which consumers do not receive any product in exchange441. Leadiant's abusive conduct would not be included in these cases442.

303. The correctly applied inequity test should, vice versa, verify the existence or not of a rational economic explanation to the price applied by the company443, to which a necessary and fundamental "security check" 444 should have been added to be carried out through a assessment of the unfairness of the price in comparison with the price of other comparable products, which do not necessarily belong to the same relevant market445.

304. Based on these observations, Leadiant claims that the unfairness assessment is incorrect and that a comparative assessment of the *CDCA* price
Conversely , *Leadiant*® would have indicated that this price is not unfair.

305. According to the Party, in fact, in the present case, various pharmaceutical products are found which, for the purposes of assessing unfairness, can be considered close comparators of the *CDCA Leadiant®.* One of these would be *Orphacol,* an orphan drug marketed in Italy absolutely comparable with the *CDCA Leadiant®,* as it too *repurposed,* authorized in exceptional circumstances, with a *patient population* and comparable cost levels for placing and maintaining on the market. , and with similar patient value to Leadiant's orphan drug. The Party underlines that the annual price of the *CDCA Leadiant*® (equal to *[60,000-70,000]* euros) would be lower than that of *Orphacol* (equal to *[100,000-200,000]* euros) by almost *[50-60%]* 446.

306. The company also claims that *CDCA Leadiant*® is less expensive than the average Italian price of orphan drugs contained in a sample of 75 drugs by approximately *[40-50%]* and less expensive than the average price of orphan drugs in therapeutic areas similar to that of CTX by approximately *[50-60%]* 447.

307. Furthermore, from the comparison with the data on actual expenditure on orphan drugs

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441 In support of these statements, the Party cites par. 122-123 of the opinion of Advocate General Wahl in Case C-177/16, *AKKA / LAA.*

442 See docs. 185 and 187.

443 In support of these statements, the Party cites par. 131 of the opinion of Advocate General Wahl in Case C-177/16, *AKKA / LAA.*

444 In this regard, the Party takes up an expression used in par. 124 of the opinion of Advocate General Wahl in Case C-177/16, *AKKA / LAA.*

445 The Party cites the European Commission, COMP / A.36568 / D3, *Port of Helsingborg,* par. 171 and Corte Giust., 4 May 1998, in case C-30/87 *Bodson v. Pompes funèbres libérées,* par. 31.

446 See docs. 185, 186 and 187.

447 See docs. 185, 186 and 187.

in Italy found in two *reports* from AIFA and the Orphan Drugs Observatory, it would appear that the total annual expenditure for the *CDCA Leadiant*® (equal to approximately *[2-3]* million euros) is *[80-90%]* lower than the cost total annual average for an orphan drug in Italy (equal to approximately € 14.98 million), and is essentially negligible in terms of both values and consumption, respectively equal to approximately *[0-1%]* and *[0- 1%]* of total orphan drugs448.

308. Finally, the company claims that the Italian price of the *CDCA Leadiant*® is lower than the French, British and German prices, respectively, by *[30-40%],* [40-50%] and *[70-80%].* Leadiant denies that these differences are due to the strategy that supported the abuse and argues that, conversely, these are the result of negotiation with national regulatory authorities. According to the company, the English and French prices are particularly relevant, since the former was considered by AIFA itself as a "valid reference" and the second reflects the competitive relationship existing between CDCA and cholic acid449.

309. In any case, the assessment of the inequality in itself of the price of the *CDCA Leadiant®,* according to the Party, would be incorrect: the qualitative factors used for the assessment would not take into account the added value that the orphan drug brings for patients and SSN, and the significant costs and risks incurred by Leadiant for its development450.

IV.7.1 The differences between Xenbilox® *and* CDCA Leadiant®

310. Leadiant argues that there are wide differences between *Xenbilox*® and *CDCA Leadiant®:* the latter is an orphan drug specifically developed for the treatment of an ultra-rare disease, while the former was merely used as a reference drug in the procedure. of the AIC request to the European Commission and was, according to the Party, only one of various CDCA-based products, authorized for a different therapeutic indication, the treatment of gallstones451.

311. Furthermore, with respect to *Xenbilox®,* but also with respect to the galenic formulations prepared by hospital pharmacies, the orphan drug developed by the company would present substantial differences, attributable to *i)* the

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448 See docs. 185, 186 and 187.
449 See docs. 185, 186 and 187.
450 See docs. 185 and 187.
451 See docs. 84, 122 and 140.3.

improvement of the production method of the drug, *ii)* the demonstration in a systematic manner and for the first time of the efficacy, safety and quality of the treatment, *iii)* the certainty of supply and access to the drug, thanks to obtaining an MA in Italy, as well as *iv)* guarantees and post-registration obligations, including those deriving from improved pharmacovigilance452.

312. In this regard, Altroconsumo underlines, conversely, the connections existing between *Xenbilox*® and *CDCA Leadiant®,* which prevent the belief that the latter is comparable to a newly introduced drug.
Moreover, Altroconsumo states that, in the present case, it could also be doubted that Leadiant has put in place a real *reporpusing activity,* since the molecule was already used exclusively for the treatment of rare disease, even if in *off label* regime .

IV.7.2 The costs and risks associated with the project

313. Leadiant stated that the project undertaken, despite being *repurposing,* involved, and does involve, very significant costs and risks, not being limited to research and development costs and the “out of pocket” costs of drug production.

314. The price of the *CDCA Leadiant*® therefore covers, *inter alia,* the implementation of a wide range of new synthesization and purification tests of the active ingredient at the basis of the production process of the orphan drug, the autonomous development of of the *DMF* and the *dossier*
CDCA Leadiant® regulatory activity, distribution and logistics activities and the fulfillment of stringent regulatory obligations related to obtaining the orphan designation, AIC (and its maintenance), *marketing,* scientific information453.

315. In addition, according to the company, it is important to recognize the value that the CDCA Project has brought to patients and the NHS, since, in general, this represents an incentive for further investments. This would be in line with the evaluation activity of the EMA, which recognized the importance of the investments of the company and of the project by positively evaluating both the application for orphan designation and that of AIC.

316. Finally, the company believes that the appropriate consideration of the non-economic advantages that the *CDCA Leadiant*® brings to the NHS and to the application - the

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[452] See docs. 84, 122, 126, 185 and 187.
[453] See docs. 84 and 122 and 140.3.

which would not have suffered any inconvenience or harm in terms of supply shortages and / or health risks - alone would be sufficient to conclude that the price of the orphan drug is not unfair.

317. On the other hand, Altroconsumo believes that, given that the price of a drug must reflect its social and therapeutic value (and therefore also the activity carried out by the pharmaceutical company in relation to the drug) and that the latter must not be measured absolutely, but incrementally, in this case the price requested by Leadiant for the orphan drug is disproportionate to the social value created by the company.

V. EVALUATIONS

V.1 Introduction

V.1.1 Procedural Exceptions

318. In relation to the alleged infringement of the equality of arms, it should be noted that Leadiant had a very broad deadline available to produce its defense writings in response to the Communication of the Investigation Results: the latter was, in fact, notified on 22 September 2021 and, following the extension of the deadline for the acquisition of evidence, resolved by the Board of Statutory Auditors on 22 October 2021 at the request of these same companies, the deadline for filing the briefs was set at 19 January 2022. This deadline was further deferred to January 28, 2022, following a first postponement of the final hearing to February 2, 2022, communicated to this Company on December 29, 2021.

319. The Party has, therefore, had a total of 128 days at its disposal, or a term more than four times that of 30 days provided for by art. 14, paragraph 2, of Presidential Decree no. 217, to produce their own defensive memoirs. This deadline was further extended by 9 days with the communication of January 31, 2022, which provided for a second postponement of the deadline for obtaining evidence and the date of the final hearing to February 14, 2022 and a new deadline for the production of further defensive documentation by this Company, set for February 9, 2022.

320. In the light of the *above,* it is believed that the deferral of the

deadline for the acquisition of the evidence and the date of the final hearing on February 14, 2022 did not involve any infringement of the principle of equality of arms between prosecution and defense.

V.1.2 The abuse and the strategy that allowed it

321. The investigation conducted first of all made it possible to ascertain that in the Italian market of CDCA-based drugs used for the treatment of a rare disease, called CTX, Leadiant has a dominant position *(rectius,* monopoly) acquired from the beginning of 2016.

322. Furthermore, the elements acquired clearly indicate that Leadiant has abused this market position since June 2017 through a negotiating conduct adopted towards AIFA which allowed it to impose unjustifiably heavy prices on the Italian SSN for the sale of the *Leadiant® CDCA. .* This abuse is the result of a very complex strategy, conceived long ago and intentionally cultivated for several years by the dominant company, with the aim of creating the appropriate context to allow it to effectively apply its abusive pricing policy.

323. In the following we will proceed to summarize what will then be fully illustrated in the following sections: the constitutive elements of the strategy that allowed Leadiant to acquire a dominant position and to prepare the context in which the price abuse took place, first outside Italy and then on the domestic market, the application of the *CDCA Leadiant®* price obtained thanks to the negotiation levers adopted during the procedure before AIFA, and the economic analysis that led to ascertaining the illegality of this price pursuant to art. 102, lett. *a),* TFEU.

324. The dominant company, in mid-2008, purchased a CDCA-based drug, registered for the treatment of gallstones but now used almost exclusively *off-label* for the treatment of CTX, thus becoming the only active operator at European level in the marketing of this drug. Leadiant's ultimate goal was to obtain his orphan designation and register him in the care of the CTX. Crucial to achieving this goal was the signing, again in mid-2008, of a supply agreement that allowed it to obtain exclusive control of the active ingredient underlying the drug, through the contracting of the only credible supplier of CDCA. existing in Europe, the Italian chemical company PCA.

325. Once a position of pre-eminence on the national markets (except in Italy) of the European Union has been obtained in the marketing of

CDCA-based drug used *off label* for the treatment of CTX, Leadiant prepared these markets for the future price with which it intended to sell the orphan drug, significantly increasing, in mid-2014, the price of *Xenbilox®,* as it was then called the aforementioned drug, from 660 euros to 2,900 euros per pack.

326. This price increase, which significantly increased the revenues of the dominant company, served to finance the concomitant regulatory activities aimed at obtaining the orphan designation (December 2014) and the AIC for the orphan drug (April 2017).

327. Xenbilox® *entered* the Italian market only starting from January 2016, immediately after the end of the galenic production that the AOU Senese Pharmacy had been carrying out since 1997. In particular, thanks to the aforementioned supply contract for CDCA exclusively stipulated with PCA, Leadiant prevented Italian hospitals from finding the active ingredient and continuing the galenic preparation previously managed by the Pharmacy, causing considerable inconvenience to patients suffering from the rare disease and forcing hospitals to import *Xenbilox®,* precisely the only medicinal product based on CDCA available, paying the highest price with which it was marketed since 2014. This allowed Leadiant to extend its dominant position to the domestic market of CDCA-based medicines , becoming the only operator also in Italy. With the signing of a new agreement with PCA, in November 2016, Leadiant also strengthened its position on the Italian market, ensuring that, through an even more stringent exclusivity clause, the production of CDCA-based galenic drugs was definitively prevented.

328. Furthermore, again near the completion of the orphan drug registration project, which was a prelude to a rapid introduction of the same on national markets, including the Italian one, between the end of 2016 and the beginning of 2017, Leadiant has implemented a of artificial differentiation of *CDCA Leadiant*® from *Xenbilox®.* This differentiation activity consisted in the withdrawal of *Xenbilox*® from the German market and in the *ad hoc* constitution of a company under German law, which would become

owner of the MA of the orphan drug. This is to ensure that the holder of the orphan drug was formally distinct from the holder of *Xenbilox*® and that the two drugs were not associated in the determination of the

reimbursement price by the competent authorities, not only the German ones but also those of the other Member States, including Italy.

329. Upon introduction of the *CDCA Leadiant*® on the market

domestic, in June 2017, the dominant company initiated the negotiation of the price of the orphan drug with AIFA, proposing a fee for the orphan drug equal to € 15,506.97 per pack. This price was considered by AIFA not justified either in light of the costs, which the company did not provide in any case in the detail requested by the Agency, nor in the light of the activities carried out to obtain the registration of the orphan drug or, finally, in the light of the therapeutic value of the medicinal product.

330. The Agency, on the other hand, considered that the adequate price of the orphan drug should not exceed that of *Xenbilox*® by more than 10%, the maximum value attributable to the benefit linked to the registration of the orphan therapeutic indication.

331. However, the dominant undertaking adopted a dilatory and obstructive attitude which greatly extended the length of the procedure, which lasted about two and a half years. This has placed the Agency in a position of weakness, which already exists due to the need for the NHS to provide patients with an essential, irreplaceable and life-saving drug in a reasonable time and at an economically sustainable price.

332. By intentionally exploiting this negotiating weakness, the dominant company was able to obtain an *ex-factory* price for the orphan drug equal to *[5,000-7,000]* euro per package, which, although much lower than the initially proposed one, resulted, on the basis of the analyzes carried out also during the procedure, in any case unjustifiably burdensome, as *a)* disproportionate to the overall costs incurred and *b)* unfair in light of the nature of the product, the investments in research and development made, the risk faced in the project registration and the added therapeutic value that AIFA, as well as the demand expressed by doctors, attributes to the *CDCA Leadiant®.* Moreover, it is believed that, in the absence of the Authority's intervention, this negotiated price would have been higher and, therefore, further disproportionate and even less justified in the light of the aforementioned parameters.

333. This conduct required the NHS to face a significantly higher expense for the purchase of the drug.

334. In summary, therefore, for the reasons that will be better and more fully discussed in the following sections, it is believed that Leadiant has put in place, starting from 15 June 2017, a conduct
illegitimate pursuant to article 102, lett. *a),* of the TFEU, as it has abusively exploited its dominant position to charge unjustifiably burdensome prices for the sale of the orphan drug called

CDCA Leadiant® to the NHS.

V.2 The relevant market

335. The consolidated practice of the European Commission and of the jurisprudence of the Court of Justice454, constantly applied also by the Authority455, indicates that the identification of the relevant product market in the pharmaceutical sector is based on the notion of therapeutic substitutability of medicines.

336. This relationship of interchangeability is based in the first instance on the therapeutic classes identified *by the Anatomical Therapeutic Chemical classification system* (ATC system), which divides drugs according to an alpha-numerical classification, divided into five hierarchical levels. The third level of this classification, ATC3, identifies a therapeutic-pharmacological subgroup to which medicines usually intended for the treatment of the same diseases belong and which are, in general, replaceable with each other but not with those belonging to other classes located in the first and on the second level. The ATC3 is, therefore, the level from which we start to identify pharmaceutical products that can be substituted for the purposes of defining the relevant market456.

337. Often, however, considerations linked to the prescribing trends of doctors, to the institutional organization of their supply and demand (determination of prices, reimbursement methods, existence of an insurance system, etc.) and to the greater or lesser effectiveness of a drug in the treatment of the disease, require a more specific substitutability analysis which can lead to the identification of interchangeability relationships between drugs at a different level of the ATC classification (ATC4 or ATC5457) or between drugs belonging to other classes.

338. With reference to the geographic market, the practice is to consider the scope

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[454] See the decision of the European Commission of 15 June 2005 COMP / A. 37.507 / F3 - *AstraZeneca,* para. 380 *et seq.* With reference to this case, it should be noted that both the EU Court (judgment of 1 July 2010, in case T321 / 05, par. 154-155) and the Court of Justice of the European Union (judgment of 6 December 2012, in case C457 / 10) confirmed the decision of the European Commission regarding the definition of the relevant market. See also the decision of the European Commission of 10 February 2021 AT.40394 - *Aspen,* para. 26 *et seq.*

455Cf. Provv. AGCM n. 15175 of February 8, 2006, on case A363 -Glaxo-Principi Attivi, in Bull. 6/2006; Provv. AGCM n. 16597 of 21 March 2007, on the A364-Merck-Principi Attivi case, in Bull. 11/2007.

[456] See European Commission, *AstraZeneca,* cit., Para. 371 *et seq.*

[457] The definition of the relevant product market was made to coincide with level 4 of the ATC classification both in the Community case AstraZeneca and in the national cases Merck and Glaxo, while the Commission went so far as to limit the relevant market to the single active substance in some cases of concentration.

competition on a national scale, due to the institutional differences that characterize the healthcare systems and pharmaceutical policies of the individual Member States (by which we mean the regulation of prices, reimbursement methods, classification of medicines, distribution channels), of the various regimes access (i.e. the patenting and marketing authorization regimes), as well as in consideration of the possible different epidemiological diffusion of a given pathology and the different economic availability of the Member States, although an accentuated process can currently be recognized harmonization that is taking place at Community level and which has introduced significant innovationsÿ
legislative, especially with regard to market access regimes458.

V.2.1 The market for drugs for the treatment of CTX

339. The market affected by this provision is the market for the production and sale of medicines for the treatment of an ultra-rare disease, CTX.

the) *The demand for drugs for the treatment of CTX*

340. The demand for drugs to be used for the treatment of CTX tends to be expressed by specialist doctors who treat patients in the hospitals where they operate and, therefore, by the ASLs who, at the request of said doctors, purchase these drugs, which are therefore marketed through the hospital channel.
341. The investigation carried out shows that different therapies are, or have been, used by doctors for the treatment of this disease: drugs based on CDCA, and in limited cases medicines based on cholic acid, ursodeoxycholic acid and statins (in particular, simvastatin, lovastatin and pravastatin), in combination with CDCA (see section III.4 *above).*
342. *Chenodeoxycholic acid Leadiant* is one of the drugs for the treatment of bile diseases (code ATC3, A05A) and in particular belongs to the class of bile acids and their derivatives (code ATC4, A05AA) since it contains one of the bile acids primary products, chenodeoxycholic acid (code ATC5, A05AA01).

343. In the therapeutic subgroup of bile acids and their derivatives, vi

458 See European Commission, *AstraZeneca,* cit .; the prov. AGCM n. 25186 of 19 November 2014, *A480 - Aspen drug price increase.*

are the other two active ingredients that in some cases have been administered, also *off label,* for the treatment of CTX. These are in particular cholic acid (code ATC5, A05AA03) and ursodeoxycholic acid (code ATC5, A05AA02).

344. Simvastatin (class ATC5, C10AA01), lovastatin (class ATC5, C10AA02) and pravastatin (class ATC5, C10AA03) belong to the therapeutic class of HMG-CoA reductase inhibitors (class ATC4, C10AA), which in turn part of the class of drugs acting on lipids (class ATC3, C10).

ii) The offer of drugs for the treatment of CTX

345. From the preliminary findings it emerges that in the Italian market for some time there have been no drugs based on CDCA on the market other than the orphan drug marketed by Leadiant.

346. The obsolescence of chenodeoxycholic acid in the treatment of gallstones and the reduced size of the market for the treatment of CTX, from the second half of the 1990s, led to the exit from the domestic market of the companies that marketed these drugs (cf. . paras. 61, 72, 73 and 78 *above).*

347. From 1997 to 2016, CDCA-based galenic drugs were present on the Italian market, produced to address the aforementioned shortage of industrially manufactured drugs containing this active ingredient and to ensure therapeutic continuity for patients with CTX. However, the galenic preparation ceased in November 2015 due to the lack of availability of raw material on the Italian market (see paragraphs 73-77 *above).*

348. From that moment, and until the introduction on the market of the orphan drug of *CDCA Leadiant®,* for the treatment of rare disease CTX in Italy *Xenbilox®,* the only drug based on CDCA at the time , was used *off label* available in Europe, owned by the company (see para. 79 *above).*

349. In June 2017 , *Chenodeoxycholic Acid Leadiant®* was introduced on the domestic market and has since been the only CDCA-based product for the treatment of CTX currently available (as well as on the other national markets of the European Union) (see paragraph 80 *above).*

350. During the proceedings it was also ascertained that *Kolbam®,* a drug based on cholic acid, was never authorized in Italy. And in any case, the AIC granted by the European Commission was revoked in July 2020 (see paragraphs 86 and 89 *above).* Therefore, it cannot be either

imported from abroad.

351. The other cholic acid-based drug, *Orphacol®,* has been authorized for the treatment of congenital defects in primary bile acid synthesis other than those that cause CTX and as such is also marketed in Italy (cf. para. 90 *above).*

352. There are no ursodeoxycholic acid-based drugs or statins marketed in Italy and used for the treatment of CTX.

iii) Conclusions on the relevant market

353. The documentation acquired during the investigation clearly indicates that there is no interchangeability from a therapeutic point of view between the aforementioned drugs. This emerges both from the trend in the prescribing choices of doctors made over a period of time that extends at least from 2014 to today, and from the evaluations expressed by the doctors themselves on the efficacy of the aforementioned drugs in the treatment of CTX.

354. From the point of view of the prescribing *pattern* adopted by doctors, the CDCA has always represented the therapy of choice for CTX in all the Member States of the European Union in which the disease is present (see paragraphs 65-70 *above).* The effectiveness of the CDCA in the treatment of rare pathology is, in fact, recognized *i)* at a scientific level, in the literature, *ii)* at an empirical level, in clinical practice *("worldwide accepted (literature), applied (treating physicians), and effective (open-label, single arm* study) ") 459, and *iii)* at institutional level *(" first-line treatment ") 460.*

355. In this regard, one of the world's leading CTX experts confirmed that the CDCA is *"to be privileged in the treatment of the rare pathology in question"* and that *"there is a clear* consensus *in the medical-scientific community at the international level on the fact that the CDCA is the therapy of choice for* CTX ”461.

356. The evidence gathered during the investigation indicates that this is particularly true for Italy, where the active principle has been used for about forty years essentially exclusively in the treatment of rare pathology (see paragraph 70 *above) .*

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[459] See doc. 78.417, of March 2016. See also doc. 78.17, annex *"ST-CDCA_Slidesmeeting 12092016.pptx"* of September 2016, which shows that in France the CDCA was considered the therapy of choice for the treatment of CTX at the time.

[460] See *https:// www.orpha.net/ consor/ cgi-bin/ OC_Exp.php?lng=en&Expert=909* and NICE, *Clinical evidence review of cholic acid for treating inborn errors of primary bile acid synthesis,* cit., p. 12.

[461] See doc. 133.

357. Numerous investigative elements also highlight that on the plan of efficacy in the treatment of CTX, CDCA is considered superior to cholic acid, which in turn is considered superior to ursodeoxycholic acid (see paragraphs 83-84 *above).*

358. Cholic acid is used only rarely, in the rare cases where CDCA gives side effects. In particular, doctors, especially Italian doctors462, do not prescribe cholic acid for the treatment of rare disease, nor do they replace CDCA with cholic acid in *non-naïve patients,* as the active ingredient, while lowering the levels of bile acids, does not appreciably affect the clinical picture of patients (see paragraphs 84, 85, 88 *above).*

359. This appears first of all confirmed by the absence of evidence in the records indicating that *Orphacol®,* although available on the market (including domestic) before *Chenodeoxycholic acid Leadiant®,* was never prescribed *(off label)* for the treatment of the disease rare object of this provision463. Doctors' preference for CDCA over cholic acid was even maintained in the time frame (about 3 years) in which *Kolbam®* was the only drug authorized for CTX. In other words, they preferred to prescribe an *off-label* drug instead of an *on-label one,* precisely because of the therapeutic superiority of the first, even though this was not formally recognized on a regulatory level (see paragraph 86 *above).*

360. The non-equivalence in therapeutic terms between CDCA and cholic acid was stated by the EMA itself, on the evidence produced by the same pharmaceutical company with the aim of demonstrating the existence of "significant beneficial effects" of the CDCA with respect to cholic acid (see paragraphs 87 and 153 above) 464, at the conclusion of the process that first led to the release of the orphan designation for the *CDCA Sigma Tau* in 2014 and then to the confirmation of the maintenance of the orphan *status* in 2017.

361. Ultimately, given the minimal therapeutic substitutability of the CDCA with

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462 See doc. 22.7.17 *("We don't believe in the effectiveness of Cholic acid (in CTX) and it's not true that it has a better safety profile. [...] We don't believe in the specificity of the cholic acid, the scientific literature doesn't confirm it and at the mean time we don't believe in the asserted safety of this molecule […] I know that the expectations about the use of cholic acid in the treatment of CTX have been disappointing " […] the cholic acid doesn't have any scientific credibility in the cure of CTX and also the declared greater safety is considered as a "bluff" not adequately supported by clinical evidences ").* See also doc. 96.23.

463 See doc. 133.

464 See the COMP's decision to maintain orphan *status* where, in fact, it states: *"Therefore, although other methods for the treatment of this condition have been authorized in the EU, the COMP concluded that Chenodeoxycholic acid sigma-tau is ofsignificant benefit to patients affected by inborn errors in primary bile acid synthesis ".*

cholic acid for the treatment of CTX, believes that the latter molecule is unable to exert a sufficient competitive constraint over the former to be able to consider both as belonging to the same relevant market465.

362. Therefore, *Orphacol*® cannot be considered as an effective and effective competitor *of the Chenodeoxycholic acid Leadiant®,* and
it cannot therefore be included in the same relevant market.
363. Similar considerations can be made for ursodeoxycholic acid and for statins, in relation to which there is a very limited clinical practice which in any case reveals, especially according to Italian doctors, the inexistence of an appreciable effect in the correction of the metabolic alterations present in the CTX (see par. 83 *above).*
364. Therefore, in the light of the consolidated jurisprudential principles regarding the definition of the relevant market in the pharmaceutical field, as most recently confirmed in the decision of the Council of State on the *Aspen466 case,* it is considered correct in the present case to limit the relevant market to the level of the individual active ingredient (ATC5 level) and to define it, from the point of view of the product, as inclusive only of drugs based on CDCA (code ATC5, A05AA01).
365. Furthermore, for the aforementioned reasons, relating to the specific features of the NHS, the level of epidemiological diffusion of the disease in the Italian territory and the different willingness to pay of Italy compared to the other Member States, it is believed that even in this case the market of the product identified above has a limited extension to the national territory.

V.3 Leadiant's dominant position

366. Several elements in the file contribute to identifying in the relevant market thus defined a dominant position for Leadiant, the only company active there since the beginning of 2016.
367. First of all, the exclusive CDCA supply agreement stipulated in 2008 between Sigma Tau and PCA, the only credible producer of this raw material in Europe (see section V.3.2.ia *below),* conferred on the pharmaceutical company control of the raw material, representing a contractual barrier that

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[465] This is also confirmed by a document which indicates that the same company had predicted that, once the marketing authorization for its CDCA-based orphan drug was obtained, cholic acid would have exerted a marginal competitive pressure. See doc. 78.236 *("[m] arginal competition by Cholic Acid in Europe").*
[466] V. Cons. State, sent. n. 1823 of March 13, 2020, para. 6.1 and 6.2.

made it possible to protect itself from competition from the producers of medicines based on CDCA, and in particular from the manufacturers of galenic medicines based on the same molecule. This closed the domestic market to masterful preparations starting from January 2016, when the galenic preparation of the Pharmacy of the AOU Senese ended, thus allowing the company to become from that moment the only operator present on the Italian market with the sale of *Xenbilox*® (position strengthened with the new exclusive supply agreement of November 2016).

368. Furthermore, starting from April 2017, i.e. after obtaining the AIC for the orphan drug, Leadiant was able to count not only on the aforementioned contractual barrier, but also on a double regulatory barrier, valid both towards competing medicines producers based on industrial CDCAs used for the treatment of CTX, and in relation to competing producers of masterful preparations based on the same molecule. In fact, the achievement of the AIC for the orphan drug allowed Leadiant, at first, to acquire a ten-year market exclusivity which, pursuant to art. 8, par. 3, of the EC Regulation n. 141/2000, prevents the registration of other products similar to the *CDCA Leadiant*® for the treatment of the rare disease in question (see par. 41 *above).* Secondly, art. 5 of the DL February 17, 1998, n. 23 prohibits, except in very limited cases, the production of galenic drugs when on the domestic market there is an industrial product registered for a specific therapeutic indication, or, in this case, since June 2017, when the orphan drug was introduced in Italy (see para. 189 *above).* This meant that, since then, patients with CTX present in Italy have been treated only with the orphan drug of Leadiant (see par. 80 *above).*

369. Several elements in the records, however, indicate that this will also happen in the next few years, reasonably at least until the expiry of the patent rights enjoyed by Leadiant, in April 2027.

370. Leadiant disputes this reconstruction, first of all because it believes that the exclusive agreements signed by Sigma Tau with PCA did not close the market to masterful preparations and in any case because the sales of *Xenbilox*® in Italy between 2016 and 2017 were managed by a third party, while Sigma Tau has never been directly operational on the domestic market.

371. Furthermore, the Party states that, even after obtaining the orphan designation and MA of the *CDCA Leadiant®,* its ability to exercise market power would have been limited, and could also be

in the future, from the competitive dynamics of other EU Member States, which can influence the Italian market and the very sustainability of Leadiant's presence on this market, given the extremely small patient base at EU level.

372. These statements cannot be shared: as will be illustrated in below, the investigation showed that, at the beginning of 2016, the company extended to Italy the dominant position it already enjoyed in the other national markets of the European Union, thanks to the sale of the only drug based of the existing CDCA, *Xenbilox®,* and which consolidated this market position by obtaining the AIC for the orphan drug also for the national territory.

V.3.1 The acquisition of a dominant position by Sigma Tau outside Italy

373. The documents acquired indicate that in June 2008 Sigma Tau Pharmaceuticals Inc. acquired the entire *dossier* of *Chenofalk®,* a drug based on CDCA, owned by Dr. Falk Pharma GmbH, used *off label* for the treatment of the disease rare and then, in October 2008, transferred the ownership of the marketing authorization for this medicinal product valid for Germany to Sigma Tau Arzneimittel GmbH (now in liquidation), which thus replaced Dr. Falk Pharma GmbH (see para. 91 -95 *above).*

374. At a time when in Europe there had long been no interest in the marketing of CDCA-based medicines for the treatment of gallstones, as the active ingredient had been supplanted by other treatments, and companies were gradually leaving the market (cf. par. 346 *above),* the only valid economic reason for entering it was to do
entry into another niche market, extremely small, but potentially very profitable thanks to the significantly high prices generally granted to orphan drugs: that of CTX, which for decades has now been treated with the CDCA. This was, in fact, the stated goal of Sigma Tau 467.

375. The objective pursued by the company presupposed, however, that there were no other companies on the European market that marketed medicines to

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467 See communicated following *https: // www.pharmaceutical-business review.com/ news/ 16498sigmatau_acquires_chenofalk_from_dr_falk_p/; https:// www.biocentury.com/ bc week-review / company-news / deals / 2009-02-09 / sigma-tau-spa-solvay-deal; https: // www.pharmaceutical business-review.com/ news/ 16498sigmatau_acquires_chenofalk_from_dr_falk_p/.*

CDCA basis, that is, that the company became a monopolist in the market for the sale of CDCA-based drugs in Europe (see paragraph 99 *above).*

376. Therefore, the company considered in mid-2008 to purchase the four MAs relating to the few CDCA-based medicines registered for the treatment of gallstones still present in the EU national markets. owned by other companies, *Quenobilan*® and *Quenocol*® in Spain, *Xebyl*® in Portugal, the AIC of *Chenofalk*® valid for the Netherlands (the *"competing MAs" 468),* to eliminate them from the market. However, at the time when Sigma Tau was making these assessments, the structure of the national markets for CDCA-based medicines naturally underwent further changes which made it impossible to such acquisitions are necessary (if not in one case, on which see better *below)* and which have facilitated Sigma Tau in achieving its objective. The aforementioned Spanish products in fact exited the market, with the consequent revocation of the relative MA, between the end of 2008 and the beginning of 20 There remained, therefore, only the "competing" AIC of *Chenofalk*® valid for the Netherlands, which Sigma Tau bought in September 2009 and which it strategically kept valid469 without ever using it470, until it expressly renounced it on 9 September 2015 Similarly, the MA of *Xebyl*® remained inactive after the drug was not marketed at the beginning of 2011 (see paragraphs 78 and 99 *above).*

377. In essence, therefore, the documentation clearly indicates that from the beginning of 2011 in Europe there was only one drug based on CDCA available on the market, *Xenbilox*® owned by Sigma Tau.

378. In this regard, it is noted that when the undertaking claims that its market position in Europe was at the time absolutely contestable, as *Xenbilox*® did not enjoy any regulatory protection, having expired the *dossier protection,* nor patent, being the drug *off patent,* the Party fails to consider that the stipulation, already in 2008, by Sigma Tau, the exclusive supply agreement of CDCA with PCA, as already mentioned, the only credible supplier of the raw material on the market

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[468] See doc. 96.99.

[469] See doc. 96.75, from which it emerges that the Netherlands was one of the markets to which from the second half of 2009 Sigma Tau Arzneimittel GmbH would have exported *Chenofalk®.* From this it follows that, even though it holds a marketing authorization valid for the Netherlands, which would have allowed it to distribute the drug directly on the Dutch market, but at the same time to be subject to national price regulation, the company was resorting to export. of the drug from Germany, which being based on the *"Named Patient Supplies" mechanism,* was not subject to price restrictions (see footnote 238).

[470] See doc. 22.7.17 *("If the current license is withdrawn in NL, off-label use for CTX would no longer be possible which would be disastrous. However when the CTX EMA approval is imminent, it may make sense to withdraw the old indication in NL as this may create an opportunity to rebrand the product (and price it differently and higher compared to the old product) ").*

European, as well as the only producer of the active ingredient in question with adequate access to raw materials, equipped with adequate technological capacity and the necessary administrative requirements, in terms of regulatory *compliance ,* existing at the European level at the time (see par. 52-53 *above),* constituted an important barrier to entry for any company wishing to enter the market. Indeed, any company wishing to produce a drug based on CDCA would have suffered the difficulty of finding a source of production of this raw material.

379. Also Leadiant deliberately does not give any relief to the element, indeed very important, due to the extremely small size of the market, which in any case would have discouraged the entry of new operators, even in the unlikely event that they were able to find another source of CDCA production (see also section . V.3.2.ia *infra).* This appears laconically confirmed by Leadiant's own statements, which can be found in the inspection documentation, where the company assessed the entry of new drugs on the market as highly unlikely due to its small size471. It should be noted that the document cited dates back to September 2014, or a moment after the price increase of *Xenbilox*® to 2,900 euros per pack in July 2014, which had made the drug very profitable for Sigma Tau (see par. 114 *above)* and, therefore, also for any other potential entrants. Therefore, if the incentive to enter the market by other operators was non-existent, in the opinion of the company itself, even after the market for CDCA-based medicines had become profitable, all the more reason there could be no potential competitive threat before that moment, when the market was much less profitable, given the much lower price at which the drug was previously sold (660 euros per pack). And this despite the absence of patent and regulatory protections.

380. The only company producing CDCA-based drugs that did not suffer from the obstacles posed by the small size of the market and the exclusivity agreement, was Retrophin Inc., which had access to the raw material through the only other supplier deemed credible outside Europe, the aforementioned NZP (see paragraph 54 *above),* already produced and marketed (in the United States) a drug based on CDCA and therefore did not need to make new investments in the production and

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[471] See doc. 22.7.17 *("I don't see any new drug arising in the treatment of CTX and I think that it will be very difficult to see somebody investing resources in this sector in the coming years …… it's a too small pathology… it's an orphan who nobody wants to adopt! ").*

marketing of the medicinal product.

381. However, the Party's assessments regarding Retrophin's ability to contest the market position of Sigma Tau cannot be shared because they completely fail to consider what emerged in the investigation regarding the real possibility for the US company to enter the European market. The documents on file show, in fact, unequivocally, that the two conditions that Retrophin already enjoyed were not at all sufficient to make a competitive entry into the market with a drug based on CDCA for the treatment of CTX. In fact, in order to represent a concrete competitive threat, Retrophin would have needed to obtain the orphan designation. And to this end it was also necessary to have supporting clinical studies472.

382. The way in which Sigma Tau has carried out its project is a clear confirmation of this: the first attempt to request an orphan designation, preliminarily presented by the company to the EMA in May 2007, was in fact shipwrecked, precisely because it was presented in the absence of any support of a clinical nature (see paragraph 94 *above).* Sigma Tau concretely resumed the project in mid-2014 when it began to collaborate directly with the specialist doctor of the Sienese AOU to begin collecting clinical data useful *primarily* for the request for orphan designation (see paragraph 145 *above).* This collaboration accelerated in May 2014 when Sigma Tau, as the Party itself declares, learned of the news that Retrophin intended to enter the European market *("We need to take this relation with Prof [F.] directly on board (STRD) , get the clinical data on the CTX study asap and eventually involve him in a new study. We need to engage him and* soon ") 473. The ongoing collaboration made Sigma Tau feel confident enough to submit the request for preliminary orphan designation in August 2014, which was then obtained in December of the same year (see paragraphs 117-118 *above).* The clinical support received by Sigma Tau was then further strengthened thanks to the scientific collaboration started at the beginning of 2015 with the other treatment center, the Dutch Casinius Wilhelmina hospital in Nijmegen (see paragraph 149 *above).*

383. The documentation on file, therefore, clearly shows the decisive role that these scientific collaborations have had in the concrete implementation of the second phase of the project and in the success of the same.

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[472] See doc. 78.249 *("Require EU case studies to support EU filing and ST has exclusive agreement with* [F.] *and potentially* [V.] *to have access to their case studies so Retrophin could not use these major centers ").* See doc. 133.

[473] See docs. 6.1, 6.2, 22.7.71 and 138.4.7.

(obtaining the AIC and definitive orphan designation). If Retrophin had wanted to apply for registration in the European Union of its own CDCA-based orphan drug for the treatment of CTX, it would have had to therefore submit their own equally valid studies to support the request, and should therefore have enjoyed clinical support similar to that received from Sigma Tau.

384. Retrophin actually attempted towards the middle of 2014 to establish a collaboration with the Sienese University-Hospital, without success (see par. 146 *above).* Moreover, the possibilities of collaborating both with this treatment center and with the Dutch Casinius Wilhelmina hospital in Nijmegen subsequently ceased completely, due to the exclusions stipulated by Sigma Tau with them (see paragraphs 147 and 149 *above).* This represented a significant obstacle to Retrophin's entry into the market European.

385. The Party's thesis according to which the US company could have found clinical support from other specialists, is denied by the investigation, which clearly highlighted that there were no other treatment centers and / or other specialists who could have offer similar clinical support. First of all, it is noted that, as stated by the same company, the specialist doctor of the Sienese AOU - one of the few experts in Europe with decades of experience in the treatment of rare disease with the CDCA - was at that time the *"world opinion leader" 474.* Furthermore, the two European centers with which Sigma Tau has entertained an exclusive collaboration are those that globally possessed, and still possess, the largest database ever collected, in terms of sample of patients involved, but above all in terms of length of the observation period of the results of administering the CDCA to said patients (see paragraph 150 *above).* The statements of the Party are not, therefore, able to revoke in doubt the fact that the impossibility of counting on the clinical experience gained by the most important expert in the world and by the doctors of the second most important treatment center in Europe has constituted a significant barrier to entry for Retrophin.

386. Confirmation of the existence and effect of the overall barrier built by Sigma Tau between 2014 and 2015, which prevented, and still prevents, even the sole attempt to enter the US company on the European market, comes from the evaluations expressed by the company itself in relation to the US competitor *("ODD protects against other*

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[474] See docs. 95 and 138.4.7.

CDCA products "; "Pulled out of Europe (in terms of plans to launch there) since ST obtained the Orphan designation for CDCA so Retrophin's CDCA is not expected to be a competitor in Europe") 475.

387. In conclusion, therefore, Retrophin has never been able, nor for the same reasons will it be, to represent a competitive threat to Sigma Tau before obtaining the MA of the orphan drug.

388. It follows from all of this that, contrary to what Leadiant claims, *Xenbilox*® was not just one of several licensed CDCA-based products for the treatment of gallstones, nor could any company have entered the market using *Xenbilox*® as a reference drug in a project similar to that carried out by Sigma Tau. On the contrary, since 2011 *Xenbilox*® was in fact *the only* drug based on CDCA in circulation in Europe and since 2014 the company has built special barriers to entry so that it will continue to remain so.

389. As for the competitive threat allegedly represented by *Kolbam,* existing on the market before the *CDCA Leadiant®,* the considerations expressed above regarding the therapeutic inadequacy of cholic acid for the treatment of CTX, deriving from the evaluations of the specialist doctors who had treats patients with rare disease (see para. 357-359 *above),* they preferred to treat them in any case with an *off-label* drug ,

because more effective.

390. In conclusion, therefore, already for several years before obtaining the AIC for the orphan drug Sigma Tau enjoyed an undisputed market position in almost all the national markets of the European Union.

This then extended, starting from January 2016, for the reasons that will be explained below, to the Italian market.

V.3.2 The extension of Leadiant's dominant position to the Italian market in 2016

the) *The closure of the market for galenic preparations based on CDCA*

391. The documentation acquired in the records indicates that since 2007 Leadiant felt the need to have control of the raw material and to avoid the possibility that other competitors could produce drugs based on CDCA476. In particular, it feared that the possible presence of

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475 See docs. 95.15 and 78.249.

476 See doc. 22.7.3, annex "121 06 Report Draft 250307" ("Current *and future suppliers / manufacturers of CDC*

galenic preparations on domestic markets could hinder the project CDCA. Since the molecule is very dated, it was also produced and / or producible by hospital pharmacies, as was the case especially in Italy, where the galenic set-up organized by the Pharmacy of the AOU Senese enjoyed a very old and consolidated operation over time (cf. para. 75 *above).*

392. In order to acquire control of the raw material, in June 2008 Leadiant entered into an exclusive CDCA supply contract with PCA on the several occasions mentioned (see paragraph 96 *above).* The exclusivity clause present in this contract, however, did not prevent, until January 2016, that on the Italian market there were galenic products based on CDCA used for the treatment of CTX. This is because in 2007 the Pharmacy of the AOU Senese purchased from PCA a *stock* of the active ingredient that was used to feed this preparation until November 2015, when the stocks of raw material ran out (see paragraph 77 *above .).*

393. The production activity of the Pharmacy, therefore, had hitherto prevented Leadiant from entering the Italian market, the only one of the European markets concerned in which it was not present with *Xenbilox®.*

This explains why the company between 2014 and 2015 tried to understand how to stop galenic production in Italy and replace it with *Xenbilox*® ("[...] *replace self-compounded CDCA with Xenbilox" 477;* "[...] *stop the hospital making its own CDCA and instead purchase imported* CDCA "478; *" stop them selling* CDCA "479).

394. However, the company did not succeed in its intent and had to wait for the end of the galenic production of the Pharmacy of the AOU Senese in November 2015. In January 2016, the same Pharmacy communicated the shortage of raw material to Sigma Tau and, not being able to find it on the market, precisely because of the aforementioned exclusive contract, it asked Sigma Tau directly to be able to have it, however receiving a clear refusal. Similarly, the other Italian hospitals that previously obtained their supplies from the Pharmacy, in the first half of 2016 tried unsuccessfully to obtain the active ingredient from PCA or Sigma Tau (see paragraphs 130 and 134 *above).*

Ease of manufacture?
Can pharmacists compound it?
Can ST stop others from making it?
Can ST stop others from supplyingit to pharmacists?
Can ST prevent rival suppliers' CDC from being used in CTX?
If so, for how long and in which territories? ");

[477] See doc. 22.7.17.

[478] See doc. 22.7.17.

[479] See doc. 78.52.

395. Not only that. Through a constant and intense monitoring activity towards PCA, Sigma Tau carefully verified that the chemical company actually respected its contractual obligations and did not transfer the active ingredient, especially to those who could use it to produce galenic drugs. Sigma Tau did not change its behavior even when PCA proposed to waive the exclusivity to meet the hospitals complaining of the serious situation of shortage of raw materials and the risk for their patients. Conversely, it took advantage of the situation of necessity to redirect hospitals towards the purchase of *Xenbilox*® in view of the introduction of the orphan drug on the Italian market480 (see paragraph 135 *above).*

396. Sigma Tau's strategy has achieved its goals: since the beginning of 2016, in fact, the masterful preparations have disappeared from the Italian market and the ASLs, forced to do so by the pharmaceutical company, have begun to import *Xenbilox* from Germany. ®*,* which has thus become the only product on the domestic market (see par. 116 *above).*

397. The position thus obtained by Sigma Tau in the Italian market was greatly strengthened with the signing of the second supply contract with PCA in November 2016, which contains an even more stringent exclusivity clause. The art. 2.3 of the exclusive contract of November 2016, in fact, places an additional obligation on PCA, which is bound to verify that any third party to which it sells the CDCA does not use it to produce drugs aimed at treating CTX (cf. . para. 137 above) 481. It is no coincidence, in fact, that this contract was signed in November 2016, or two months after Sigma Tau had received the positive opinion of the *Committee for Medicinal Products for Human Use* (CHMP) on its request for AIC for the orphan drug. In this crucial moment of the project482 it was, indeed, even more necessary to have absolute control of the raw material to eliminate any disturbing element, such as economic masterful preparations, to the market position that Leadiant had acquired in Italy.

398. The evidence acquired therefore contradicts what Leadiant stated about the uniqueness of the function of the agreement stipulated with PCA, to be found in the need to protect reciprocally investments

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[480] See docs. 78.19 and 78.241 *("They perfectly know how and where to buy. They are trying to get it from PCA at a cheap price to create a precedent that will kill our future reimbursability and price ").*

[481] See for this purpose clause 2.1 of the June 2008 agreement with clause 2.3. of the November 2016 agreement.

[482] Note that at the time Sigma Tau believed she would have the MA from the European Commission in November 2016.

indispensable carried out by both parties and to avoid *free riding* on these investments, elements that should bring the contract back into the framework of research and development agreements. The main purpose of the exclusivity clause contained in the agreement is, on the other hand, to give Sigma Tau control of the primary source of CDCA present in Europe in order to continue, and indeed, strengthen, the activity of hindering the entry of masterful preparations on national markets, and in particular on the Italian one, which had already had its effects since January 2016 *("the concern is that a compounding pharmacy could look to buy API from you on the grounds that it was to be used for a bile acid disorder other than CTX and then use some it for CTX patients*

399. In fact, the refusals of supply by PCA and the control activity carried out by Sigma Tau continued even after the signing of this second CDCA supply contract exclusively with PCA (see paragraphs 138-140 *above) . ,* and in particular in the first months of 2017, relating to an even more delicate phase of the orphan drug registration project, namely the one that led to the obtaining of the AIC by Sigma Tau and the confirmation of the CDCA's orphan *status ,* before the introduction of the *CDCA Leadiant*® on the market and the subsequent price negotiation with AIFA.

400. Ultimately, the evidence described above clearly shows that after the end of the set-up organized by the Pharmacy of the AOU Senese, therefore well before the regulatory barrier deriving from art. 5 of the DL February 17, 1998, n. 23 (more precisely, a year and a half earlier), the legitimate attempts made by Italian hospitals starting from the beginning of 2016 to find the raw material to feed a galenic production were deliberately prevented by the dominant company, asserting in relations with PCA the exclusivity clause contained first in the agreement signed with the chemical company in June 2008 and then in the subsequent agreement in November 2016. In this way, Leadiant from January 2016 and until the orphan drug has not received an MA, also valid nationally (in June 2017), it closed the Italian market to galenic productions and reserved it for itself.

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[483] See doc. 78.9. See also doc. 78.34 *("how can ST minimize the risk from compounded product availability in each country? How are compounding companies obtaining the API for CDCA? […] ST should have exclusive use for all API destined for use in CTX patients");* doc. 28.2.66 *("ST for the reasons widely explained during our last meeting on November, 11th at PCA and in our e-mail exchanges, ST requires PCA to grant exclusivity on CDCA supply (at least 10 years) for the production of any FF use to treat any biliary acid disorders. PCA-ST will work together with their legal advisors in order to find a way to legally justify exclusivity, eg by linking to EU and US orphan drug designation of CDCA ").*

to. The irreplaceable nature of PCA as a credible supplier of CDCA in Europe

401. The contractual barrier erected by Leadiant had its effects because both contracts entered into with PCA made it possible to commercially link the only credible supplier in Europe at the time to the pharmaceutical company.

402. The pre-eminence of PCA's position in the European market is attested by various documents in the file: first of all, those that show that in 2011 the EDQM turned to PCA as the only producer of the active ingredient in the territory of the European Union are highly indicative ("[...] *I could not identify another manufacturer" 484)* to which to refer to improve the purity *test* of the CDCA, and that for the purposes of the revision of the CDCA monograph the contribution of the chemical company, albeit supported by Sigma Tau, is was essential and that the Entity finally defined a *test* that is largely based on the one developed by Sigma Tau and owned by PCA485 (see par. 53 *above).*

403. The market position that PCA enjoyed, and still enjoys, was also recognized by Sigma Tau both in 2016 and 2017, in terms of privileged access to bovine bile, the main *input* from which the CDCA is drawn, and of compliance with GMP486, both in 2018, when it defined it as the only certified operator in Europe487.

404. However, Leadiant today denies that PCA enjoyed such a market position and disputes the existence of this contractual barrier on the basis of the alleged existence of multiple sources of CDCA production other than PCA which could have easily fed the galenic preparation between January 2016 and June 2017, if the hospitals had promptly taken action to search for them and establish commercial relationships with them, as for example the hospital in Amsterdam did between 2019 and 2020.

405. These statements cannot be shared because they are widely denied by the same evidence produced by the Party. Before reviewing them, however, it is necessary to premise that the time frame in which it is necessary to verify the existence of alternative sources to PCA is that of approximately 18 months.

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484 See docs. 28.2.53 and 78.6.

485 See doc. 28.2.31 *("[…] they are waiting for our data and support").*

486 See doc. 78.416 ("[…] *there are two global API providers relevant for this product"),* one being PCA and the other NZP, 78.133, all. "REPORT MEETING AIFA Sigma Tau June 24" ("[...] *Product of bovine derivation. 2-3 producers in the world")* and 78,323 ("[...] *there are truly only 2 GMP, FDA approved suppliers globally").*

487 See doc. 138.4.9 *("Furthermore, there is only one approved EU certified supplier of pharmaceutical grade CDCA ...").*

between the end of CDCA stocks by the AOU Senese Pharmacy (late 2015 / early 2016) and the introduction of the *CDCA Leadiant*® in the Italian market (June 2017), an event which, as already illustrated, determined the raising of a regulatory barrier that does not allow, except in exceptional cases, the production in the domestic market of CDCA-based magisterial preparations. The existence of any alternative sources of production of the active ingredient to PCA in a period subsequent to this last mentioned moment is, therefore, irrelevant since it could not in any case legitimately feed any galenic preparation capable of satisfying all the demand for drugs a base of CDCA in Italy.

406. From this point of view, therefore, the evidence produced by the Party regarding the offer of supply of CDCA to PCA by a wholesaler of pharmaceutical grade active ingredients, which in turn probably obtained from a Chinese manufacturer, as these date back
to October 2017, when it was already forbidden for Italian pharmacies to set up a galenic production of CDCA. The same applies to documents proving *i)* that *Pierre Fabre* offered the supply of CDCA directly to Leadiant in 2019, *ii)* that there is a Chinese source of CDCA capable of feeding the CDCA galenic production of the Amsterdam hospital
at least from February 2020 and *iii)* that there are other European companies which, as producers of ursodeoxycholic acid, could enter the market for the production and sale of CDCA as an active ingredient of pharmaceutical grade.

407. But even if we want to consider such evidence as an indication of the fact that alternative sources to PCA existed even before the temporal moments to which these documents date back, as the Party affirms, the following is observed. First of all, the document proving that a pharmaceutical grade active ingredient wholesaler offered CDCA to PCA in October 2017 contains another document, an *e-mail exchange,* dating back exactly one year earlier (October 2016 , therefore at a relevant moment for the purposes of this assessment) in which it was instead the wholesaler who asked PCA to supply CDCA on behalf of a hospital488. In 2016 the roles were, therefore, reversed. And they were again a year later (October 2018), when the same wholesaler again asked PCA to supply the CDCA.

408. These events are strongly indicative, not only of the fact that in 2016, or when the Italian hospitals asked PCA to supply

[488] See doc. 28.2.183 and cfr. with doc. 22.7.64.

CDCA, the source indicated by Leadiant as an alternative to PCA was not actually available, because it did not have access to the raw material (so much so that it itself turned to PCA), but they are also explanatory of other very important elements for the evaluation of the 'existence of a dominant position in the hands of Sigma Tau in the period prior to obtaining the marketing authorization for the orphan drug.

409. First of all, it clearly emerges that the source of CDCA production to which the wholesaler was addressing at least as of October 2017 was not a reliable and stable source. In this regard, it is noted that, given the severity of the disease and the life-saving nature of the drug, even a galenic preparation requires a stable and lasting source of supply that guarantees continuity of supplies. Evidently this source, such as the one identified by Leadiant in its defense (as well as *Pierre Fabre,* whose offer is completely sporadic), did not possess these characteristics and could therefore not be taken into consideration by Italian hospitals as a valid alternative to PCA, not even in the 2016.

410. Furthermore, the evidence relating to the relationship between PCA and the wholesaler of pharmaceutical grade active ingredients must be read together with the documents on the records concerning the unsuccessful attempt of various hospitals and pharmacies located in other Member States, and in particular of the Amsterdam hospital, to set up a galenic production between 2017 and 2018 thanks to the raw material coming from an Asian source through the importation of said wholesaler. These evidences show that in August 2018 it emerged that this galenic production did not comply with the technical specifications imposed by the European Pharmacopoeia as it contains too many impurities. It was immediately after this event that the aforementioned raw materials wholesaler approached again to PCA, stating that they only trust the quality of the CDCA produced by European operators489, and in particular in PCA. Which shows that the Asian sources, described by Leadiant in his defense as being available on the market for a long time, were not only not stable, but at the end of 2018 they were not yet adequate to support a galenic production of CDCA. Nor would they have been so in 2016, when the Italian hospitals had tried to resume setting up.

411. In particular, the document that would highlight the effective operation inside and outside the European Union of (at least) 15 alternative CDCA suppliers to PCA already in 2015 is largely devoid of value

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[489] See doc. 28.2.183.

evidence, not only from the events just mentioned, but also from a plethora of inspection documents that indicate that these production sources were not actually available on the market, neither before 2015 nor after.

412. It appears, indeed, that the sporadic sources of CDCA production from outside Europe, and in particular from China, have not been able to access the European market for a long time, precisely due to the inability to comply with the GMPs imposed. by European authorities, which require stricter *standards* than those imposed in other countries, such as India, China and other Asian countries490. This circumstance was recognized by the PCA itself, which in October 2016 - therefore in the relevant period for this assessment - stated that non-EU CDCA suppliers and in particular the Chinese ones would not have represented *"a problem"* for Sigma Tau, in the sense that these sources of production at that time could not generally be considered as valid alternatives by anyone who wanted to produce drugs based on CDCA491. And the aforementioned events that occurred in the years 2017-2018 proved her right.

413. Moreover, Sigma Tau itself clashed with this reality in 2016 when, before entering into a new exclusive supply contract with PCA, it sought out alternative producers, first obtaining a list of potential operators who, however, they did not prove capable of either replacing or supporting PCA, precisely because the quality of the raw material they produced was not certain, and then concluded, *at the outset* of the stipulation of the contract with PCA, that there were no valid alternatives to the company Italian chemistry (see par. 55 *above).* So much so that, at the end of this market research, in November 2016 Sigma Tau decided to choose PCA again as its exclusive CDCA supplier.

414. The only other operator seriously considered by Sigma Tau itself, because it is able to obtain sufficient quantities of bovine bile, the main *input* from which the raw material is drawn, and to adhere to GMPs in a similar way to PCA - the NZP being in 2016 deemed an effective alternative to PCA because at the time it was commercially engaged with Retrophin for the production of *Chenodal* marketed in the United States (see paragraphs 54-55 *above).* Moreover, the same documentary evidences are also valid to deprive the other arguments of the Party about the concrete availability of operators who

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490 See docs. 25.3.5, 78.190, 78.303.

491 See doc. 78.262: *"Compounding and foreign / exotic API supply of CDCA will not represent a problem".* See also docs. 28.2.132 ("[…] *a Chinese source will not represent an issue for* you").

they would supply other manufacturers of industrial-grade CDCA-based drugs (like *Chino).* Finally, the aforementioned documentation from which it is clear that the pharmaceutical company itself in 2018 believed that there was only a single certified operator in Europe, and that this was PCA, demonstrates that it has itself excluded other European companies, such as PharmaZell GmbH and Dipharma Francis Srl, today indicated, however without any evidence to deny the aforementioned inspection documentation, as subjects with the potential and skills to enter the market for the production and sale of CDCA as an active pharmaceutical grade, as producers of ursodeoxycholic acid from non-bovine bile, with respect to which chenodeoxycholic acid is an intermediate product.

415. All the considerations made up to now on the effective operation of alternative sources of CDCA to PCA also deny the arguments of the Party regarding the ease of supply of CDCA by a hospital. The aforementioned events of the Amsterdam hospital, which since 2018 attempted to set up a galenic production of CDCA by turning to non-EU sources, actually succeeding only in February 2020, demonstrate how it is far from easy for a hospital pharmacy.

find a reliable, stable source of raw material capable of adhering to the European Pharmacopoeia: it took the Amsterdam hospital 18 months to find a supplier with these characteristics, i.e. exactly the time lapse between the time the stocks of CDCA of the Pharmacy of the Sienese AOU and the introduction of the *CDCA Leadiant*® in the Italian market ended. In any case, it was not possible for a hospital to wait for this long period to elapse before resuming the administration of therapy to its patients, without causing serious damage to them. In the urgency of having to continuously administer the therapy to their patients, hospitals therefore had no alternative but to contact Sigma Tau for the purchase of *Xenbilox*®*.*

416. From all this it follows that, at least between January 2016 and June 2017, PCA was the only source of CDCA production from which hospital pharmacies could have obtained the raw material that would have fed a galenic preparation pending the entry of the orphan drug on the domestic market. This was not possible due to the commercial exclusivity that bound the chemical company to Sigma Tau and on which the latter leveraged to prevent the continuation of the production of magisterial preparations after January 2016.

ii) Entry into the Italian market with the sale of Xenbilox® starting from January 2016

417. The arguments of the company also appear to be worthless - used to argue the impossibility of attributing it a dominant position in the relevant market starting from January 2016 - according to which *Xenbilox*® did not have an MA in Italy nor was it marketed directly from Leadiant on the Italian market, but from a third-party wholesaler, Juers Pharma, who would have acted in total autonomy.

418. In this regard, it is noted first of all that Leadiant's alleged extraneousness with respect to the marketing of *Xenbilox*® in Italy is denied by the documents already referred to, which show that the company wanted to eliminate the production of the Pharmacy of the Sienese AOU to induce the The company itself, and consequently the other Italian hospitals, to purchase *Xenbilox*® (see paragraph 126 *above),* and that it was the company itself that redirected the AOU Senese, as well as all the Italian hospitals that requested the supply of raw material after the cessation of the pharmacy's galenic production, towards the purchase of *Xenbilox*® from Juers Pharma (see par. 135 *above).*

419. The evidence acquired in the documents also shows that, as already illustrated, a distribution system based on personalized sales carried out by a third party in markets other than the German one was the model specifically chosen by Leadiant (at the time Sigma Tau) precisely to invoke the formal extraneousness of the company with respect to the price charged in these markets: behind the commercial policy applied by independent distributors in Italy for the sale of *Xenbilox*® there was Juers Pharma, and therefore Leadiant[492]. In fact, Juers Pharma since mid-2014, when the company had implemented the *ex factory* price increase of *Xenbilox*® to 2,900 euros, implemented its commercial policy in national markets other than the German one, including the Italian one. , on the basis of precise indications by Leadiant (see par. 108 *above).*

420. The thesis according to which Leadiant would have been commercially unrelated to the sales of *Xenbilox*® is however denied by some documents in the file, which indicate that both some employees of the company and the

[492] The fact that Leadiant was perfectly aware of the economic and commercial conditions under which *Xenbilox*® was sold in Italy emerges from doc. 78.124 *("All CTX patients were treated in Siena until 2015 - Since 2016 they were sent back to the hospital of the place they live for treatment. This is when only Xenbilox at about 3,7 € k / pack became available").*

external consultants, as part of the negotiation procedure with AIFA, advised against its use *("we must be very careful in saying that LB has never sold Xenbilox etc* etc." 493).

421. This means that the sales of *Xenbilox*® in Italy, made since the beginning of 2016, when the drug began to be imported from the Italian ASLs from Germany, are obviously attributable to Leadiant, even in the absence of a valid MA for the drug in Italy.

422. It should also be noted that, contrary to what the Party affirms, the closure of the Italian market to CDCA-based galenic productions and the entry of Sigma Tau on the Italian market with the sale of *Xenbilox*® they did not occur without significant inconvenience for the Italian patients and for the centers that were treating them.

423. Some documents in the file, in particular, show that the lack of access to raw materials has created a situation of lack of supply and risk for patients, complained by several Italian hospitals. An example of the risk that patients took is given by the evidence showing that the *stock* of magisterial preparations already prepared at the end of 2015 would have allowed AOU Senese to supply the medicine only to three patients and only for the following two or three months. (see paragraph 132 *above).*

424. The enormous difficulty that all this caused to the patients and the structures that treated them is clearly exemplified by the complaints of a doctor, who complained that the procedure for request early access to the orphan drug pursuant to law no. 648/1996, proposed by the dominant company itself in place of the access to the PCA raw material required by the hospital to continue the galenic preparation: *"Unfortunately the information we have had, not from AIFA but from dr.* [N.] *that as you will recall he should have sent us all the documents to forward the procedure to AIFA, were that we would have had to wait until April, the time necessary for the completion of I no longer remember what on their part ... contrary, therefore to all the statements of principle made and reiterated that patients should not have had any discomfort resulting from the "industrial process", they will have it and how* [and how. ed] *and us with them ... "494.* This risk situation was only remedied by importing *Xenbilox*® from Germany.

425. The difficulties at least for the Sienese AOU are, however, made

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[493] See doc. 78.112.

evident from the same defenses of the Party, which states that early access to orphan drugs pursuant to law no. 648/1996, instead of the purchase of *Xenbilox®,* would in any case have only had a redistributive effect, in the sense that, pending the negotiation of the redemption price of the *CDCA Leadiant®,* the resources necessary for the purchase of therapy for patients affected by CTX would not have come from the NHS but would have remained at the expense of the Sienese University Hospital (with the purchase of *Xenbilox®).*

426. And in fact, more precisely, after the end of the stocks of CDCA by the Pharmacy of the AOU Senese, in the presence of the exclusivity clause contained in the contract with PCA, the problem of lack of supply could be solved with the use of the so-called early access pursuant to law no. 648/1996, as initially hypothesized, or with the importation of *Xenbilox®,* as it actually happened later.

However, from a financial point of view the two solutions were not equivalent, precisely because, as Leadiant herself states, in the first case the public structures could have continued to guarantee therapy without charges, while in the second case they had to incur significant outlays (a package of *Xenbilox®* of 100 capsules of 250 mg cost about 3,400 / 3,600 euros), much higher than what they had up to now had to support as long as the galenic preparation existed (a package of 100 master preparations in 250 mg capsules was equal to 67 euros). Therefore, in the impossibility of supplying the orphan drug in the early access regime, a derogation from the exclusivity clause contained in the supply contract stipulated with PCA could have represented a valid solution, which was later proposed by the same chemical company, but to which Leadiant nevertheless did not want to consent (cf. para. 135 *above).* All this has undoubtedly caused difficulties for the public health structures involved and confirms the successful acquisition by Sigma Tau of a position of absolute pre-eminence on the domestic market.

V.3.3 The stability of the dominant position acquired in Italy

427. The argument of the Party about the obstacles to the future maintenance of the dominant position acquired in Italy by obtaining the AIC for the marketing of the orphan drug in the national territory is evanescent, since it does not identify precisely what the competitive forces may be potentials capable of effectively regulating its market power.

428. In terms of potential competition, it is necessary, in fact, to reiterate once again that the Italian market (but also that of the other Member States of the European Union) for the production and sale of CDCA-based drugs used for the treatment of CTX has a extremely small size, linked to the rarity of the pathology in question (see par. 63 *above).* This means that the number of companies that can reasonably have an effective economic interest in entering this market is, as acknowledged by the company itself, extremely small495.

429. Furthermore, it must be considered that, within this restricted group of subjects, any company that intends to introduce a new pharmacological therapy for the treatment of CTX, at present, must first of all prove that pursuant to art. 3, paragraph 1, lett. *b)* of EC Regulation no. 141/2000, the orphan drug candidate has "significant beneficial effects" for people affected by this pathology, compared to existing therapies496. In addition, the applicant company must demonstrate that the orphan drug candidate is not "similar" to the one that already has an orphan designation or, if it is "similar", that it is "clinically superior" to the latter, as envisaged. from art. 8, para. 1 and 3, of the EC Regulation n. 141/2000 (see paragraph 41 *above).*

430. The aforementioned regulatory framework integrates an important barrier to entry for Leadiant's potential competitors on the market. Proof of "significant beneficial effects" and / or "clinical superiority", in fact, in the present case is not easy, given the presence on the market of the orphan drug owned by Leadiant, containing an active ingredient that is currently considered the *" first line treatment "* of CTX. In other words, the scientific, and therefore economic, effort required of any future competing company by the applicable regulation is much greater than that which Leadiant had to face. If, on the one hand, the latter, in fact, managed to enter the market even though *Kolbam® was already present,* on the other hand, however, the comparison activity carried out by Leadiant to demonstrate the existence of a beneficial effect significant of the CDCA with respect to cholic acid, aimed at maintaining the orphan designation, occurred against an active principle that in clinical practice had *already* been considered lower than the CDCA for some time. Otherwise said, the demonstration of a beneficial ef

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[495] See doc. 22.7.17 *("I don't see any new drug arising in the treatment of CTX and I think that it will be very difficult to see somebody investing resources in this sector in the coming years …… it's a too small pathology… it's an orphan who nobodywants to adopt! ").*

[496] And on this point, what has already been illustrated in parr. 383-387 *above* in relation to the clinical support necessary to give such evidence.

significant of a drug compared to existing therapies is certainly easier when, as in the present case, their therapeutic inferiority is already known in the medical-scientific community which has already experienced, with its consolidated prescribing choices, the superiority of the candidate orphan drug.
On the other hand, it is much more difficult to demonstrate the therapeutic superiority of an orphan drug with respect to what is, at that time, considered in the scientific field to be the *standard* therapy for the disease.
431. Moreover, it is noted that the preliminary analysis conducted clearly shows that at present there are no other therapies, not even in the experimental phase, for the treatment of the rare disease in question and that the only lines of research currently existing - which point to the future development of gene therapy - are at an embryonic stage. The elements in the file allow, therefore, to affirm with reasonable certainty that there are no other therapies for CTX that can be approved by the regulatory authorities in the near future (see par. 71 *above).*

432. It follows from all this that the legislative and regulatory context that characterizes the present case makes it completely remote the possibility that other companies obtain an orphan designation and an MA for a medicinal product with the same therapeutic indication for which the *CDCA* is registered *Leadiant*® and effectively enter the market within a reasonable time, or in any case before the expiry of the patent right enjoyed by the dominant company.

V.3.4 Conclusions on Leadiani's dominant position in Italy

433. In light of the foregoing , it is believed that from 2016 Leadiant unquestionably holds a dominant position on the national market for CDCA-based drugs used for the treatment of CTX.

V.4 The articulated preparatory strategy of the abuse planned by Leadiant

434. The investigation activity conducted has shown that Leadiant has leveraged a highly articulated and preordained strategy over time which subsequently allowed it to carry out the abusive behavior ascertained in this provision.

435. In this regard, the dominant undertaking takes the preliminary view that the evidence documents of this complex strategy are unusable since

prior to the conduct. In support of this thesis, it cites a ruling by the Lazio TAR of 2021 with which the administrative judges ruled the usability of investigative documents *"external [i] to the time perimeter of the alleged* [anti-competitive] practice", that is, *"referring to facts prior to the explication period of the alleged agreement "497.*

436. The ruling cited by the Party is, however, irrelevant with respect to the present case, since the documents deemed unusable at that time constituted, in the context of the provision, proof of the contested conduct, and specifically of the beginning of the same, and not , as in the case in question , elements that prepared and allowed the contested conduct, the consideration of which is necessary to understand how the dominant company was then able to carry it out.

437. These elements consist *of i) the* increase in the price of *Xenbilox*® even before obtaining the MA of the *CDCA Leadiant®,* as a tool to prepare the market for the future price of the orphan drug, and *ii)* in the artificial differentiation between *Xenbilox*® and *CDCA Leadiant*® obtained through the withdrawal of the first drug from the market upon the introduction of the second and the attribution of ownership of the orphan drug to a company other than the one that owned the *off-label drug.*

V.4.1 The increase in the price of Xenbilox® *in preparation for the price of the orphan drug*

438. The investigation carried out indicates that the objective pursued by the company since 2007 through the registration project of the orphan drug in Europe was to introduce it on the market at a particularly high price in order to increase its profits.

439. This aim was pursued through a *"step price increase" strategy 498* of the only CDCA-based drug remaining on the market and administered *off-label* for the treatment of CTX, of which the he became the owner in 2008, and which in the future would be replaced by the *on-label* orphan drug at an even higher price.

440. Specifically, the long-term price target for the drug

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[497] V. Tar Lazio, sent. n. 8239/2021

[498] See docs. 96.213, 22.7.3 annex *"121 06 Report Draft 250307" ("[...] step price increase should be possible; step price increase could be achieved by 'withdrawal and reintroduction' or simple price increase on current pack (to evaluate best option requires further analysis); precedent in Germany for novelty being recognized of old product in new indication; Clear rationale and KOL support will be needed to facilitate reimbursement of CDC after a step price increase "),* 22.7.3 all. *"006060_2 Report",* 96.75, 96.99 and 96.165.

orphan was achieved through the pursuit of medium-term goals consisting of two distinct increases in the price of the drug
administered *off label.* A first increase in the price of *Chenofalk®,* in the meantime renamed *Xenbilox®* starting from December 2009, took place in February 2010, when the company set the *ex factory* price for the sale of the drug on the German market at 660 euros per pack. 100 capsules of 250 mg, where previously the same pack of *Chenofalk®* was sold on that market at the *ex factory* price of 37.75 euros (see paragraph 97 *above).*

441. Subsequently, in the first months of 2014, when it was about to launch the CDCA project, it took up the idea of the progressive increase in the price of the *off-label drug.* Thus, after various hypotheses, in the end the company resolved to set the *ex factory* price for the sale of *Xenbilox®* in Germany at 2,900 euros per pack starting from 1 July 2014 (see paragraphs 120-123).

442. The application of a *"premium price"* for the *off-label* drug , conceived some time ago and justified on the basis of the rare therapeutic indication499, has therefore prepared the market - including the domestic one starting from 2016 when *Xenbilox®* entered in the Italian market - at the future price with which Sigma Tau wanted to launch the orphan drug *on label* in Europe500.

443. In the light of the numerous evidence gathered on this point (see paragraphs 92, 98, 99 and 122), the statements of the Party regarding the correlation between the increase in the price of *Xenbilox®* and the drastic reduction in demand, are without foundation . This is primarily because the demand for CDCA had been drastically reduced for a long time, well before the price increase of 2014 and even that of 2009; in particular, from the scientific literature it emerges that the prevalence of the rare therapeutic indication of CDCA dates back to at least 20/25 years earlier, because the CDCA was not used for the treatment of gallstones at least since the beginning of the 1990s (see par. 61
above). The significant temporal discrepancy, in particular, between the 2014 price increase and the commercial reason that Leadiant would like to attribute today, it also emerges from the same statements contained in the memorandum of Part501

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499 See doc. 96.213 ("[…] *step price increase should be possible, based on rationale of: - Ultra orphan status").*

500 See doc. 96.213 and 22.7.3 annex "121 06 Report Draft 250307" ([…] *"Price should ideally be at level desired post-approval. Desired step price increase can happen pre-or post CTX MA approval ").*

501 See par. 282 on p. 74 where we read: *"At this stage, the revenues from Chenofalk were essentially attributable exclusively to sales made by Dr. Falk to German wholesalers, who in turn resold the Chenofalk to pharmacies that imported CDCA-based products to to treat patients with CTX ".* The wording *"in this phase"* must be understood as the period prior to the purchase of *Chenofalk* by Sigma Tau, as can be deduced from the context in which the quoted period falls and from the title of the section in which it is contained: *"The context of market in 2006 ".*

which indicate that in 2006 the demand for CDCA had already greatly reduced due to the exclusive use of the principle for the treatment of CTX.
444. But the arguments of the Party are above all denied by the numerous documents on file that demonstrate the true intent of the company, namely that the increase in the *ex factory* price of *Xenbilox*® to 2,900 euros per package which took place in 2014 had no relationship with the reduced demand for CDCA and, on the other hand, had to do with the CDCA project that Sigma Tau had decided to relaunch exactly at that time. The fact that the company has implemented a new increase in the *ex factory* price of *Xenbilox*® precisely in the imminence of the request for the orphan designation of the CDCA or, therefore, when it was approaching the achievement of another important medium-long term objective for the completion of his project *("1 / short term goal: price increase (in 2 steps) [...] 2 / medium / long term goal: registration process Goal: to get the ODD in the wider indication as possible") 502,* and that it has itself linked this price increase to the development of the orphan indication of the drug *("In order to be able to maintain and further develop CDCA for this rare disease indication, Sigma Tau has to revise the price in accordance to an orphan indication* (CTX) ") 503, are in fact clear indications of the connection between the new price increase and the completion of the regulatory activities included in the CDCA project that would have allowed the launch of the orphan drug. With the concrete launch of the second phase of the project to introduce the orphan drug on the market, in fact, the objective of "preparation" of the market for the future price has again acquired relevance and required the implementation of the new price increase of the drug *off label* already pr
445. The price evaluations found in the inspection documentation, moreover, cannot be considered as mere *market access evaluations,* as claimed by the Party, since the preparatory value of the 2014 *Xenbilox*® price increase is clearly evident from the documents already cited, in which the company itself has expressly linked the price increases with the price of the future orphan drug (" [...] *Impact of current price on future potential price [...] -step price increase should be possible - step price increase could be achieved by 'withdrawal and reintroduction' or simple price increase on current* pack "504).

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[502] See doc. 96,228.
[503] See doc. 96.43 and 96.217.
[504] See doc. 22.7.3, annex "121 06 *Report draft 250307 (PA again again)".*

446. The existence of a functional relationship between the 2014 price increase and the future price of the orphan drug, finally, cannot be disputed by the fact that, as the company states, the sales made outside the of the German market were managed by Juers Pharma in total autonomy and independence (see paragraph 108 *above).* In fact, from the documentation on file it clearly emerges that the involvement of the German wholesaler in the *Xenbilox*® distribution chain was planned *ad hoc* by the company so that in markets other than Germany the price increase, decided by Sigma Tau, was formally referable to a third party. The interposition of this operator in the distribution chain had the sole purpose of avoiding the pharmaceutical company having to justify and / or negotiate the new price increase with the patients and with the hospitals that treated them. This distribution strategy not only allowed the company to overcome the constraint on profits deriving from the German regulation - where the reimbursement price was set at 660 euros per pack and therefore the difference compared to the new *ex factory* price had to be returned to health insurance companies. of *Xenbilox*® set at 2,900 euros per pack -, raising the price to the desired level in the national markets of the European Union (where it was not subject to regulation), which at the time imported *Xenbilox*® from Germany505, but also allowed it to prepare those markets at the price that would be charged in the future.

447. Finally, the connection between the price increase implemented by Leadiant in 2014 and the price policy that the company intended to practice for the orphan drug emerges clearly from a document dated December 2014, which commented on the *former post* what had already been done in the past by the company and could be repeated in the future *("Sigma Tau want to increase the monthly treatment cost of Xenbilox® and have already introduced some price increases") 506.*

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[505] See doc. 96.141 ("[…] *we have developed an idea how we can keep the price in Germany but increase it for foreign markets (by rationing German wholesalers and have Juers as our wholesaler and point of sale for Xenbilox - who would sell the product to (foreign) customers at a higher price.* […] *we can increase our profit without being stuck by the price moratorium.* […] *increase the price to 860 Euros per unit to ALL customers (incl. German market). Everything that ends up in Germany will be reimbursed with 660 Euros and we have to refund the German sick funds with the price difference of 200 Euros.*

All units that are being sold to foreign markets will not have to be refunded -> 2.511 packs x 200 Euro = ca. 500.000 Euro increase in sales (+ ca. 300 units x 200 Euros = 60.000 Euros) -> all additional sales are profit.

We will only supply the German wholesalers. All other customers will be referred to JUERS who manage he distributors for us ").

[506] See doc. 78.71.

V.4.2 The artificial differentiation of the orphan drug from Xenbilox®

448. The investigation also indicates that Sigma Tau has pursued its objective by implementing a strategy of artificial differentiation of the *CDCA Leadiant*® from the *off-label* drug *("brand differentiation" 507),* the foundations of which were initially laid in Germany between 2014 and 2017 and whose effects then reverberated in other European countries, including Italy. This strategy, which included the withdrawal of *Xenbilox*® from the market and the attribution of ownership of the *CDCA Leadiant*® to a company other than the one that was the holder of the marketing authorization for the *off-label drug,* was intended to avoid the difficulties that would inevitably be arose where the regulatory authorities had asked, as it later happened, to justify the high price that Sigma Tau intended to ask for the orphan drug in the face of the fact that the project carried out by the dominant company consisted in the reuse of an old drug, *Xenbilox®,* for a new therapeutic indication (so -called *“repurposing”)* which was already treated with the c

449. The fact that this strategy concerned Germany in the first instance does not make it irrelevant to the object of this provision, as stated by the Party, which qualifies these events as pertaining to a different geographic market and suggestive of the alleged violation of a national legislation other than the Italian one, in relation to which the Authority has no competence. Indeed, the inspection evidence substantially refutes these claims, insofar as they clearly demonstrate that the success of the envisaged commercial strategy in Germany would have had positive repercussions also on the prices of the other Member States *("getting an increase in the German price is necessary (or removing this product as a price benchmark) if a higher level of price is the ambition for Chenorm across Europe* […] ”) 509. In other words, the investigation showed that it was particularly important for Sigma Tau to obtain a high price in Germany, the national market of choice from which the dominant company operated throughout Europe, since this would have represented a point of reference also for price negotiations in other Member States, including Italy.

450. Leadiant's arguments, in particular, about rationality

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[507] See doc. 78.57.

[508] See doc. 78.225 *("Stakeholder perception of transition from Xenbilox to CDCA Leadiant. [...] Payers might take CDCA Leadiant as an example of repurposing not being acceptable, even under* ODD ").

[509] See doc. 22.7.3, annex "006060_2 Report".

economic aspects of the withdrawal of *Xenbilox®,* responding to considerations of a commercial nature about the cost of maintaining on the market a drug whose therapeutic indication was now obsolete, appear to be largely contradicted by the documentation acquired.

451. Sigma Tau itself had included among the risk factors, of a competitive nature, which could have hindered the pricing policy it had decided to apply for the orphan drug, *Xenbilox*® (see par. 123 *above).*

452. Xenbilox® *represented* a threat *primarily* in Germany, since the moratorium on drug prices existing in the German law until 2022 for products marketed starting from 2010, also applying to the orphan drug, as it contains a principle asset already marketed in the German market, would have generated an automatic compulsory discount equal to the difference between the price of the *CDCA Leadiant*® and that of reimbursement of *Xenbilox*® to be paid to German health insurances (see par. 159 *above).* This would have prevented the planned pricing policy for the launch of the orphan drug.

453. In order to overcome the regulatory obstacle posed to Sigma Tau's price targets it was necessary that the *CDCA Leadiant*® be perceived as a new and different product compared to *Xenbilox®.* This goal was pursued and achieved first of all with the withdrawal of *Xenbilox®, which* began in October 2016 (with the formal cessation of sales by Sigma Tau and the continuation of the same while stocks last by Juers Pharma) and concluded between April and May 2017. Once the *off-label* withdrawal procedure has been completed from the German market, in May 2017 Sigma Tau requested the cancellation of *Xenbilox*® from the official price list, exactly simultaneously with the request for registration of the *CDCA Leadiant*® in the same price list. This meant that the two products were never on the market at the same time *("Xenbilox and the new CDCA Leadiant will not co-exist in the market" 510)* (see paragraphs 166 and 168 *above).*

454. The link between the withdrawal of *Xenbilox*® from the market and Leadiant's profit objective also emerges with all its evidence in particular from a document, referred to several times, of September 2014, where the company itself identify the withdrawal of *Xenbilox*® from the market as a necessary tool to increase the price of the drug to be administered for the

[510] See docs. 78.262 and 78.249.

CTX511 .

455. The other element on which Sigma Tau built the differentiation between *Xenbilox*® and *CDCA Leadiant*®, consisted in the establishment of a new company under German law, holder of the MA of the orphan drug. This is because Sigma Tau had realized that, although necessary, the withdrawal of *Xenbilox*® from the market would not have been sufficient to exclude the anchoring of the reimbursement price of the orphan drug to that of the *off-label drug,* because according to the *CDCA Leadiant*®, despite having a new therapeutic indication, contains a molecule that had already existed on the market, regardless of whether this was still marketed or not (see par. 164 *above).* It therefore set up a company under German law that was formally different from the former owner of *Xenbilox*®, to which it attributed the ownership of the orphan drug.

456. The Party's arguments according to this decision would in no way prevent German insurers from referring to the reimbursement price of *Xenbilox*® in negotiating the reimbursement price of the orphan drug, but at most it would not have allowed them to obtain the discount automatic mandatory equal to the difference between the *CDCA Leadiant*® price and the Xenbilox® reimbursement *price,* do not hit the mark.

457. Indeed, apart from the fact that substantially the two effects of the establishment of the new company under German law to which Leadiant refers are identical (take the price of *Xenbilox*® as a reference in the negotiation of the redemption price of the *CDCA Leadiant*®, indeed,
was used precisely to obtain the discount to which the Party refers), it is noted in any case that these statements are contradicted by the words of the same dominant company contained in the inspection documentation, which gives a precise account of the fact that the project for the establishment of the new company holding the MA of the orphan drug, Leadiant GmbH, was outlined in early 2016 and continued until the launch of the orphan drug with the primary and exclusive purpose of not allowing German health insurers to refer to the price of *Xenbilox*® when defining the reimbursement price of the orphan drug *("[…] we will need a*

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[511] See doc. 22.7.17 *("[…] In some countries a further price increase may only be possible with combination of current license withdrawal, approval in CTX and rebranding").* Since the *ex factory* price increase of *Xenbilox*® to 2,900 euros per package has already taken place, the planned *"further price increase"* by the company necessarily refers to the price at which the orphan drug would have been launched on the market, after the registration of the new therapeutic indication.

newco in Germany because neither ST GmbH nor STRDL can be MA holders and / or distributors of the new CDCA without an immediate reference to the old Xenbilox price. A name change is not enough. This must be a new pharmaceutical entrepreneur (new numbers, register, etc) " 512) and to obtain the desired price for the future orphan drug (see paragraphs 171-174 *above).*

458. The constitution of the new German company was also part of a broader strategy implemented at European level aimed at excluding the possibility of establishing links between the ownership of *Xenbilox*® and that of the *CDCA Leadiant®,* so that these appeared as two completely distinct assets513 . As early as mid-2015, the ownership of *Xenbilox*® was formally entrusted to the British branch of the group, while that of the orphan drug, under construction, was formally managed by the German branch. The establishment of a new German branch with a new company name different from that of the previous distributor of *Xenbilox*® on the German market and by the owner of this *off-label* drug , had, therefore, the sole purpose of further separating the two *businesses* under a formal profile.

459. This strategy allowed the dominant firm to argue before the competent authorities that Leadiant GmbH had no connection with Sigma Tau Arzneimittel GmbH and that the orphan drug was not related in any way to *Xenbilox*® (see para. 176 *above) .*

460. All this completed the work of differentiating the two products and allowed the dominant company *to first* present to the German market a drug which, at least on a formal level, was different from the one that had been present on the market until then. market, and to definitively overcome the constraint placed by the price moratorium on the profit objectives pursued by the dominant firm.

461. In other words, thanks to this composite strategy Leadiant has created a formal distinction between *Xenbilox*® and *CDCA Leadiant®,*

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512 See doc. 96.79.

513 Indicative in this sense are the numerous transfers of ownership of the administrative rights insistent on *Xenbilox*® and on the orphan drug that have occurred over time between the companies of the group. Since October 2008 Sigma Tau Arzneimittel GmbH was, in fact, the holder of the marketing authorization relating to *Xenbilox*® in Germany (see para. 97 *above).* In August 2015, this administrative title was transferred from Sigma Tau Arzneimittel GmbH to Sigma Tau Rare Disease Ltd., which later became Leadiant Biosciences Ltd in December 2016 (see paragraph 141 *above).* The request for the preliminary orphan designation of the CDCA was submitted by Sigma Tau Rare Disease Ltd. on August 28, 2014 and obtained by the same company on December 16, 2014. This administrative title was transferred on May 7, 2015 to Sigma Tau Arzneimittel GmbH (cf. para. 117-118). The application for the MA on the orphan drug was submitted by Sigma Tau Arzneimittel GmbH on 29 October 2015 and obtained by the same on 10 April 2017. The title was then transferred to Leadiant GmbH on 31 May 2017 (see paragraphs 141 and 156 *above).*

which was purposely built to artificially differentiate the two products also on a substantial level.

462. Several documents in the file indicate that this differentiation had the effects sought: the thesis of the German health insurance association regarding the identity between the two molecules was, in fact, successfully contested by Leadiant. Consequently, the association could not refer to the redemption price of *Xenbilox*® to obtain the mandatory automatic discount on the price of the *CDCA Leadiant*® (see par. 177 *above).*

463. This strategy, which started in Germany, was then extended to the other Member States interested in purchasing the orphan drug, including Italy. More specifically, the formal and substantial difference between *Xenbilox*® and *CDCA Leadiant*® was re-proposed to AIFA when the Agency asked for explanations about the price difference between the orphan drug and *Xenbilox®,* in order to obtain in this way the high price that the dominant firm had set itself (see section V.5.1.iii *below).*

V.5 Leadiant's Abusive Behavior

V.5.1 The negotiating levers adopted in the procedure for defining the redemption price of the CDCA Leadiant®

464. The evidence acquired in the records indicates that during the negotiation procedure of the reimbursement price of the orphan drug Leadiant intentionally maintained a dilatory and obstructive attitude towards AIFA: indeed, for a year and a half, despite the repeated requests of the 'Agency, the dominant firm did not provide any information and documentation on investments in research and development that could adequately support its initial and / or subsequent price proposals, and thus justify the price difference between the *CDCA Leadiant*® and the *Xenbilox®,* and has strategically extended the timing of the negotiation procedure with the late submission of corrective economic offers for the initial one.

the) *The delay in providing cost data*

465. In relation to the cost data incurred to carry out the orphan drug registration project, it is noted that from the beginning of the negotiation of the price of the orphan drug, and in particular following the

session of the CPR of 19 March 2018, AIFA formally asked the dominant company to justify its initial request of € 15,506.93 per package by providing the appropriate detailed information on the costs incurred for the registration project of the orphan drug, with particular with regard to investments in research and development (see paragraph 194 *above).* This request was also reiterated a second time in the meeting in July 2019 and a third time, again in writing, in September 2019 (see par.
208 *above).* It originated from the finding that this price was too high and unjustified with respect to the presumed financial effort sustained and the activities carried out for the purpose of introducing the drug on the market, given that for the Agency *"the authorization procedure was based exclusively on retrospective studies and literature data "514.*

466. This information was transmitted, however only in aggregate form and without the support of specific documentation, with great delay, only on 26 November 2019 (see paragraphs 208-209 *above),* or more than a year and a half after the first formal request sent by the Agency, thus hindering AIFA's evaluation activity.

467. The arguments of the Party, which objects to this reconstruction in many respects since it maintains that AIFA was not legitimized by CIPE Resolution no. 3/2001 to ask the dominant company for information about the investments made for the development of the orphan drug but should only look at the therapeutic value of the drug on the basis of the cost-effectiveness criterion, appear, however, to be based on a partial and reductive reading of the applicable regulation. *First of all ,* it is noted that the CIPE Resolution no. 3/2001 assumes, yes, as the main criterion in art. 3.1 that of cost-effectiveness515, but does not exclude the Agency from asking the instant company for information on the investments made for the development of a given drug.
On the contrary, art. 6 establishes that the parties, therefore also the dominant company, *"for the purpose of defining the price,* [must] *accompany their proposals with adequate economic evaluations of the product and the industrial context (with reference to investments in production, research and development and at*

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[514] See doc. 78.77 and 78.79, annex
[515] See art. 3.1 of the CIPE Resolution no. 3/2001 which states: *"3. Criteria for the contract request. The Company must support its price request with documentation showing:*
3.1. A favorable cost-effectiveness in any of the following situations:
3.1.1 the new drug proves useful for the prevention or treatment of diseases or relevant symptoms for which there is no effective therapy;
3.1.2 the new medicine proves useful for the prevention or treatment of diseases or relevant symptoms to which the medicines already available provide an inadequate response;
3.1.3 the new drug has a more favorable risk / benefit ratio than drugs already available in the prescription-only for the same indication ".

exports), of the market and competition in which the same product is placed ". Furthermore, art. 3.3.5 the CIPE Resolution no. 3/2001 clearly states that *"In any case, other elements relating [...] to any other information that may be useful to the parties must be provided".* This closing clause, by clarifying that the *"other elements that may be useful"* must be provided *"in any case",* confers the power on AIFA to always ask the applicant company for any information it deems useful for its own evaluation.

468. Furthermore, as regards the usefulness for AIFA of the information relating to the investments in research and development carried out for the development of the orphan drug, it is noted that these were of particular importance in the present case. It should in fact be considered that in relation to the *CDCA Leadiant*® it was not It is possible to apply the cost-effectiveness criterion within the terms required by art. 48 of d. lgs. n. 326/2003 or *"assuming as terms of comparison the reference price for the related homogeneous therapeutic category and the comparative daily cost in the context of drugs with the same therapeutic indications",* because, as AIFA noted during the investigation, this comparator - an *on-label* drug with the same therapeutic indication -
did not exist. Hence the importance of having a reference point for bargaining which, in the present case, could only be given by the level of investment in research and development sustained by the dominant company for the registration of the orphan therapeutic indication, and explains why the Agency has requested to know this pivotal element three times.

469. From this point of view, the delay in the transmission of information relating to the cost of production of the *CDCA Leadiant®,* therefore, undoubtedly had a negative impact on the ability of the Agency to adequately assess the value of the drug and on the activity carried out by the company. dominant for registration purposes. Therefore, it is useless to state, as Leadiant does, to have promptly provided information on the overall costs incurred in Italy in the last three years and then to have worked to quantify the data expressly requested by AIFA by contacting a consultancy company, whose determination took some time. These statements are, in fact, denied by the documents in the files which clearly demonstrate that the dominant company was aware of the difference between the data provided and that requested by the Agency and that it had internally proceeded well a year before the request for a quantification of costs. previously supported specifically for the development of the orphan drug (whereas, on the other hand, the quantification activity required of *Copenhagen Economics* consultants was

subsequently commissioned in the context of the Dutch ACM investigation procedure).

470. Already in March 2017, in fact, the dominant company knew that the costs related to the CDCA project that could be qualified as research and development in Italy amounted to *[100,000-200,000]* euros (excluding the cost of the retrospective study commissioned to the University of Siena of *[100,000-200,000]* euros) (see par. 186 *above).* Furthermore, the dominant company was already aware from May 2017 of the amount of all costs up to then (2007-2017) incurred for the orphan drug registration project globally, amounting to approximately *[10-20]* million euro (see par. 188 *above).* Furthermore, Leadiant had a detailed understanding of the composition of these costs, their nature and the weight that each of them had covered in the overall investment made516.

471. Despite having them in its possession, the dominant company did not provide these data nor when AIFA, in March 2018, formally requested for the first time a *"cost-based"* justification of the price proposal nor since then. Neither the mere illustration by Leadiant of the cost items that made up the financial investment made to keep the orphan drug on the market, which took place in June 2018 on the occasion of a meeting with AIFA, can indeed be used as an element which demonstrates that the dominant company at that time responded to the requests of the Agency, given that, as pointed out by AIFA itself, Leadiant did not present any documentation proving them at that time (see paragraph 202 *above).*

472. The reasons for this reticence can be found in the inspection evidence already illustrated which indicates that the costs associated with the drug registration project sustained up to then, especially those that could be considered as investments in research and development (equal to at most *[200,000-300,000]* euros, precisely) as part of the overall investments made in Italy in the three-year period 2014-2016 *([2-3]* million euros) (see paragraphs 186-187 *above),* were, indeed, modest entity and could never have justified the request for a price made by AIFA.

473. Not even the level of investments of about *[10-20]* million euro that emerged as a result of the quantification of all costs up to then supported for the orphan drug registration project globally - moreover, it was carried out precisely because of the awareness that it would have been

[516] See in particular doc. 22.7.5.

it was difficult for Leadiant to justify the price it intended to ask for the orphan drug517 - it was evidently considered by the dominant firm to be sufficient to justify the price request. This emerges from the documents acquired in the records that show very clearly how in July 2018, four months after the first AIFA request, after having ascertained the amount of costs requested, Leadiant decided that it was better not to continue the investigations. he had carried out the previous year on the costs of the orphan drug registration project518.

474. After the third request by the AIFA CPR in the meeting of July 2019, Leadiant finally resolved to communicate the data requested by AIFA in November 2019, after the data relating to the total amount of costs incurred at global was updated by the consultants of *Copenhagen Economics* to *[100-200]* million euro in the period 2014-2023 (see par. 209 *above).*

475. However, not even on this occasion did the dominant company provide *"detailed"* or adequately *"documented" information,* as requested by AIFA, but limited itself to providing aggregate data, without supporting documentation, which were for this reason they proved to be of little use to the Agency (see par. 212 above). Leader therefore only formally fulfilled AIFA's request but in essence it did not allow the Agency to be able to effectively evaluate the information provided.

476. On the other hand, the dominant company, in the following months, did not bother to provide the Agency with the updated value of the total amount of costs incurred globally, which was much lower than the one communicated, *[70-80]* million euros instead of the initials *[100-200]* million euros (see paragraph 210 *above).*

477. From all this it follows that the Party intentionally exploited an obvious information asymmetry and engaged in behavior that was anything but cooperative and inspired by good faith.

ii) The lengthening of the negotiation procedure times

478. The evidence acquired in the proceedings indicates that Leadiant has further exploited AIFA's negotiating weakness - already inherent in the fact that the negotiation concerned the price of a life-saving orphan drug -,

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[517] See doc. 78,438.

[518] See doc. 78.150 *("Pierre in fact pulled the number together for me a while ago and after seeing it I thought it best not to take it any further ").*

letting time go by without the negotiation progressing in any sense.

479. On this point, the arguments of the Party that are based on the comparison between the duration of the negotiation of the *CDCA Leadiant*® price (equal to 18 months) with the average time that a drug takes to obtain reimbursement by AIFA are not convincing. from the moment of its approval by the EMA (equal to 24 months). In this regard, it is noted, first of all, that neither the type of drugs nor the scientific context and the reference market that characterized these negotiations, nor their possible assimilation to the present case is known. The finding of their longer or shorter duration with respect to the negotiation procedure in question *does* not therefore allow to reach any meaningful conclusion in this regard. Secondly, what matters is not only and exclusively the duration of the negotiation procedure itself but rather the ways in which it was conducted by the parties and, in particular, as regards this provision, by the dominant company. .

480. In this regard, the evidence acquired during the investigation shows that the parties met three times, in June 2018, in July and in December 2019, and between March 2018 and November 2019 they had a substantial exchange of correspondence which involved various economic proposals and counter-proposals (see paragraphs 194-209 *above).*

481. What emerges *ictu oculi* is the significant temporal distance - a good thirteen months - between the first and second meeting between the parties. After in the first meeting the CPR reiterated its dissatisfaction with the first two price-volume agreement proposals presented by Leadiant (corrective of the initial price proposal) and that the procedure was consequently suspended, the dominant company resolved to submit a third corrective offer only in March 2019 (actually detailed only in April 2019), or with seven months delay (almost eight if we consider when the detailed proposal arrived) compared to the 15-day deadline set by AIFA for the sending it, and after two reminders from the Agency (in November 2018 and February 2019) (see paragraphs 201-207 *above).* This constitutes a first element which in itself allows to affirm that the negotiation procedure of the orphan drug has undergone a lengthening as a consequence of the negotiating attitude adopted by Leadiant.

482. As proof, it is sufficient to consider that since the second meeting between the parties (July 2019), still other months have passed, especially five, before

Leadiant, however, after a further reminder in September 2019, decided to submit a fifth corrective proposal to AIFA which then led to the agreement of December 2019 (see paragraphs 207-208 *above).*

483. As regards the argument of the Party according to which the length of the negotiation procedure in question *was* caused rather by the particular complexity of the reference context, given in particular by the uncertainties about the actual number of patients affected by CTX, it is observed that the documents on file show that the conflict between the parties in relation to this element only occurred on the occasion of the first meeting, in March 2018. Starting from April 2018, the issue of the number of patients, moreover defined in a way closer to the initial estimates of the company in the agreement of December 2019 (see paragraph 213 *above),* was no longer the subject of discussion and the bargaining was largely redirected to another level, i.e. on the economic impact that a possible price lower than the one initially requested would have had on the *budget* of the NHS and, therefore, on the turnover targets of the dominant company *("We should set the turnover that we want to secure and move from* there "519). The subsequent proposals were presented to AIFA with this aim in mind only and not, as the Parties maintain, on the basis of epidemiological data520, on the peculiarity of the drug and its effectiveness in treating the disease.

484. In summary, therefore, taking into account *i)* the long timescales with which Leadiant presented its financial offers, *ii)* the negligence shown in relation to the response terms established by the Agency, and, finally, *iii)* the fact that the Agency sent three reminders in the space of almost a year, in order to obtain these offers (November 2018-September 2019), it seems reasonable to believe that the dominant company has caused the lengthening of the price negotiation procedure of the orphan drug for the sole purpose of maximizing one's profit.

485. This was not a problem for Leadiant, since it was already on the market with its own product, a factor which contributed to

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519 See doc. 78.113.

520 A series of documents acquired in the records indicate that the company itself harbored uncertainties regarding the actual spread of the disease in the national territory, even though it was aware of the fact that Italy was one of the countries with the highest prevalence. This circumstance was perceived as a critical issue with respect to the need to justify the request for a high price for the orphan drug, more justifiable in other countries with a lower prevalence of the disease (see Docs. 78.113, 78.170 and 78.441 *([...]) Given that in some countries we have a very large number of pts and a negligible OEPX it seems that we must do this on a EU basis with an ability to then drill down to a country specific level if needed. By example - in the UK and Germany we could quite easily justify a high price based on pts numbers, OPEX requirement and subsequent product profit contribution, in Italy, Spain, Netherlands however we will have to adopt a different approach given pts numbers are so high and OPEX requirement is so low [...]).*

making demand *captive,* and it was under the extremely favorable commercial conditions granted by the Cnn class discipline.
Conversely, these delays led the Agency to fear that the negotiation would end with a failed agreement and with the definitive inclusion of the *CDCA Leadiant*® in class C (see par. 216 *above).* This outcome was seen by AIFA as extremely negative, since a drug for which there are no therapeutic alternatives, and which is therefore essential, as in the present case, should not be included in this class.

486. And in fact, AIFA declared during the investigation that it considered it appropriate to avoid the classification scenario of the *CDCA Leadiant*® in class C, renouncing to obtain the 80% discount on the initially requested price and accepting a much higher price (see para. 215-216 *above).* This negotiation outcome appears very far from the maximum deviation that AIFA, considering the added value of the *CDCA Leadiant*® compared to *Xenbilox*®*,* and in the absence of the aforementioned unfavorable context elements in the context of the negotiation, would have accepted with respect to its own negotiating position. of departure. According to AIFA's declarations, in fact, this maximum deviation would have led at the most to accept a price 10% higher than that at which *Xenbilox*® had been marketed on the Italian market between 2016 and mid-2017 (see par. 217 *above).*

487. As for the statements by the Party according to which the negotiation of the *CDCA Leadiant*® price would have ended with a more favorable outcome for AIFA than for the company, it is important to underline that the agreement of December 2019 was reached after the initiation of the preliminary investigation procedure by the Authority in October 2019. This allows us to reasonably presume that in the absence of the preliminary investigation procedure, due to the aforementioned unfavorable negotiating conditions, AIFA would not have been able to obtain the he current *ex factory* price of *[5,000-7,000]* euros per pack, but he probably would have had to accept an even higher price. This conclusion is not, as the Party believes, a mere unfounded assumption, but is based on precise investigative documents, which indicate that Leadiant, in June 2018, a few days before the meeting with AIFA, intended to obtain an compromise price that , in the worst case scenario (which, moreover, he had expressly decided to reserve for subsequent *rounds* of negotiation), it was equal to approximately 9,000 euros (see par

488. For the same reasons, the assertion of the Party according to which the circumstance that AIFA has expressed satisfaction

on the conclusion of the negotiation procedure the price of the *CDCA Leadiant*® would demonstrate the correctness of its behavior in the negotiation, as well as the legitimacy of the negotiated price. On this point, it is noted that the Agency's declaration on the fact that the price agreement was *"sufficiently satisfactory",* in consideration of the starting negotiating positions and the difficult context described above, only confirms that, in circumstances more favorable to it , the negotiation outcome would certainly have been different. The economic and commercial terms of the price agreement reached represent, in other words, the best of the sub-optimal results achievable under the conditions described.

489. In conclusion, therefore, Leadiant leveraged a negotiating context that was already unfavorable for AIFA, exacerbating it through a delaying strategy that did not allow the Agency to conduct a serene negotiation of the price of the orphan drug based on elements evaluation objectives.

iii) The impact of the artificial differentiation between Xenbilox® *and* CDCA Leadiant® *on the negotiation with AIFA*

490. A third factor that negatively influenced the price negotiation procedure of the *CDCA Leadiant*® resides in the series of initiatives and precautions taken by the dominant firm to exclude any kind of link between *Xenbilox*® and the orphan drug, and thus avoid having to justify the difference between the price of the latter medicinal product and that requested for the former, despite being identical in chemical and pharmacological terms and both used for the same therapeutic indication.

491. From this point of view, the evidence acquired during the investigation must be read, which shows how, close to the start of the negotiation procedure for the price of the orphan drug with AIFA, the dominant company has managed to avoid hospitals required early access for *Xenbilox*® pursuant to law no. 648/1996 or access to the cd
AIFA National Fund 5%. This is in order to divert the request towards the new orphan drug soon to be introduced on the market and thus avoid that AIFA could then associate the two products during the negotiation (see paragraph 185 *above).*

492. With the same purpose, on the recommendation of the dominant company, the reimbursement *dossier* to be submitted to AIFA to request the opening of the negotiation of the price of the *CDCA Leadiant*® was drawn up with the indication that the medicine was not a medicine based on a principle

active known with a new therapeutic indication, but a completely new drug for the Italian market that had nothing to do with *Xenbilox*® or with the masterful preparations produced by the Pharmacy of the AOU Senese 521 (see par. 184 *above).*

493. Subsequently, as part of the negotiation of the price of the *CDCA Leadiant®,* after AIFA in its communications of March and June 2018 had tried to highlight the disproportion of the requested price for the *CDCA Leadiant*® compared to the price with which *Xenbilox*® had been marketed in Italy up until then (see paragraphs 194, 201 and 202 *above),* the dominant company decided to act by eluding as much as possible any discussion of merit on *Xenbilox*® ("[...] *I want to avoid a discussion and price comparison with Xenbilox "* 522) (see paragraph 199 *above).*

494. In fact, at the meeting in June 2018 in which the CPR asked for information on *Xenbilox® for the third time,* and in particular on its unavailability on the market, Leadiant avoided providing the requested information on the *off-label* drug by using arguments of a legal-formal nature, which relied on the lack of authorization of *Xenbilox*® in Italy and on its different therapeutic indication, which made it a distinct product, or on the existence of a market exclusivity for Leadiant linked to obtaining the orphan designation (see para. 203 *above).*

495. From this point of view, the objections of the Party regarding the illegitimacy of the reference to *Xenbilox*® by AIFA during the negotiation procedure do not appear to be fitting. Apart from the fact that the information about the unavailability of *Xenbilox*® in the Italian market and the relationship between the *off-label* drug and the orphan drug, both from a therapeutic and commercial point of view, are among the *"other elements that may result profits ",* which must be provided *" in any case "* and that AIFA is therefore, pursuant to CIPA Resolution no. 3/2001, entitled to ask, however it is noted that the Agency did not hire *Xenbilox*® following a formal comparator for the definition of the price. But, given that the molecule

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[521] See docs. 78.172 and 78.291 *("[…] new indication of a known compound. OK? No, not ok. I understand your comment about this being strange, but in fact this is a 1st registration of a new pharmaceutical product in Italy. Let us keep it like that, because this is something we can argue from a Legal standpoint. We should state it as is and not mention the compounding if we do not have* to ").

[522] See docs. 78.116. See also doc. 22.7.143 ("I *would prefer to avoid discussing direct relations with Xenbilox. Especially because Leadiant Biosciences or the ST companies never sold Xenbilox in Italy, the commercialization of Xenbilox in Italy was always done by a 3rd party and hence outside our control ")* and doc. 78.141 *("[…] 7. XENBILOX discussion is a lost one. Will not enter lost d [i] scussions")* and docc. 78.118 and 78.119.

contained in the *CDCA Leadiant*® is identical to that of *Xenbilox*®*,* until then used *off label* for the treatment of rare disease, and that the records showed that the dominant company had based the registration of the new therapeutic indication of this molecule on retrospective studies and on the literature review, AIFA asked Leadiant to justify from an economic point of view its price request for the orphan drug, the level of which was significantly far from that of *Xenbilox*®*.* In other words, since the *CDCA* Project consists in the transition from an *off-label* drug to an *on-label drug,* the Agency asked to quantify the economic effort required for the completion of the Project to understand if this justified the requested price.

496. The fact that during the negotiation procedure Leadiant never raised the illegality of AIFA's references to *Xenbilox*® *is also significantly indicative of the specious nature of the Party's argument.*
On the other hand, the documents on file already cited (see paragraph 493 *above),* as well as numerous other documents where the dominant company itself often identifies the orphan drug with the name of the *off-label* drug *("Xenbilox / CDCA"; "Xenbilox in CTX - EMA; Xenbilox [...] Filing for CTX indication in EU in 2015 (approval 2016) "; " Xenbilox 2014 very important project "* 523), highlight Leadiant's full awareness of the fact that *Xenbilox*® was inevitably part of “History” of the *CDCA Leadiant*®*.*

497. Not only that. The preliminary documentation also highlights the attempt by the dominant company to prevent the part of the *CDCA Leadiant*® development project linked to *Xenbilox*® from playing a role in the negotiation. It is not otherwise explained why in the context of the procedure before AIFA Leadiant intended to avoid *“carefully creating […] links with the name Sigma-Tau” 524,* or with *Xenbilox*®*.* All this finds a precise confirmation in the statements of AIFA, which argued that the choice to launch the orphan drug when *Xenbilox*® was now unavailable in Italy, and to attribute the ownership of the new orphan drug to another company, has had the main purpose of not providing the Agency with opportunities to verify the reasons for the enormous price difference between the orphan drug and *Xenbilox*® (see paragraph 197 *above).*
498. In conclusion, it is believed that the set of initiatives adopted by the dominant company to ensure that AIFA did not have adequate

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[523] See docs. 95.4, 95.5, 95.6 and 96.228.
[524] See doc. 78.95.

information, albeit explicitly and repeatedly requested, with respect to the therapeutic and market context relating to CTX prior to the introduction of the orphan drug, represented a highly impeding behavior of the negotiation procedure and certainly not responding, as Leadiant claims, in good faith.

V.5.2 The imposition of unjustifiably burdensome prices for the sale of the orphan drug in Italy by Leadiant

the) *The jurisprudential principles to be applied to the present case*

499. Article 102, lett. *a),* of the TFEU prohibits an undertaking in a dominant position from directly or indirectly imposing purchase or sale prices or other unfair commercial conditions and, in particular, prohibits the application of excessively expensive prices that are not justified by any legitimate reason .

500. The Court of Justice of the European Union has ruled in the *United Brands* ruling that a price is unlawful within the meaning of that provision when the undertaking, making use of its dominant position, has gained commercial advantages that it would not have obtained had it been normal and sufficiently effective competition in the relevant market525. For this reason, the price charged does not appear to have a reasonable relationship with the economic value of the service provided526.

501. It is well known that there is no single method, prescribed by *law* or resulting from the case law of the Court of Justice, for assessing this relationship between the economic value of a product or service and its price. On the contrary, the Court itself has pointed out that different methods can be used to determine whether a price charged by a dominant firm is excessive and unfair and, therefore, abusive527.

502. One of these modalities is based on the *"comparison between the selling price of the product in question and its cost of production […] which would give rise to the size of the profit margin" 528.* This analysis of comparison between price and costs, in the methodology indicated by the European judges, is developed in two phases: the first

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525 See Corte Giust. EU, February 14, 1978, in case 27/76 *United Brands Company and United Brands Continentaal BV c. Commission of the European Communities. Chiquita bananas,* par. 249.
526 See Corte Giust. EU, *United Brands,* cit., Par. 250.
527 See Corte Giust. EU, *United Brands,* cit., Par. 253.
528 See Corte Giust. EU, *United Brands,* cit., Par. 251.

is aimed at verifying *"whether there is an excessive disproportion between the cost actually incurred and the price actually requested"* and the second to ascertain whether the excessive price compared to the costs is also *"unfair, in absolute terms or compared to competing products" 529 It should* be noted that the examination aimed at identifying possible justifications for the disproportion between prices and costs must be particularly stringent when it concerns goods on which consumers are completely dependent530, as in the present case.

503. The two criteria for measuring the unfairness of an excessive price are alternatives. Therefore, to establish that a price is unlawful pursuant to Article 102, lett. *a),* of the TFEU, it is sufficient that even only one of the two alternatives envisaged in the second phase of the test is satisfied531.

504. Having said all this, from the application of these principles to the present case it emerges that Leadiant, exploiting its dominant position, has charged excessively onerous prices, devoid of any reasonable relationship with the economic value of the service provided, for the sole purpose of take advantage of it economically. In other words, the prices applied by the dominant company for the sale of the orphan drug in Italy are excessive and unfair and therefore violate Article 102, lett. *a),* of the TFEU.

ii) The excessive prices charged by Leadiant for the sale of the orphan drug in Italy

505. With regard to the determination of the economic value of the service provided, necessary for the first part of the *United Brands* test , it is believed, on the basis of the aforementioned consolidated practice and jurisprudence532, that this value must at least reflect a measure of the costs incurred by the dominant firm to carry out the good or service.

506. Preliminarily, it should be noted that the numerous documents on file clearly show that, from the early stages of the project, the price level of the *CDCA Leadiant*® was never defined by the dominant company on the basis of the costs incurred. The different price assumptions formulated by

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[529] See Corte Giust. EU, *United Brands,* cit., Par. 252. See also Cf. Corte Giust. EU, *OSA,* C-351/12, par. 88; C-52/07, *Kanal 5 and TV* 4; C-226/84, *British Leyland v. Commission;* C-26/75, *General Motors v Commission;* C-30/87, *Corinne Bodson v. SA Pompes funèbres des régions libérées;* C-323/93, *Crepes;* European Commission, COMP / C-1 / 36.915 - *Deutsche Post AG - Interception of cross-border mail;* European Commission, COMP / A.36.568 / D3, *Scandlines Sverige AB v. Port of Helsinborg.*

[530] See the opinion of Advocate General Jacobs of 26 May 1989 in case C-395/87 *Ministère public v. Jean-Louis Tournier,* para. 43, 65 and 66.

[531] See also Corte Giust. EU, order of 25 March 2009, in case C-159/08 P, *Isabella Scippacercola and Ioannis Terezakis v. Commission,* para. 47

[532] See Corte Giust. EU, *United Brands,* cit., Par. 251.

Leadiant (see section III.5.4 *above)* rather refer to its expectations of the maximum price that demand was willing to pay for the drug in question, also taking into account the rigidity of the demand for the price for a good such as a drug for the treatment of an ultra-rare disease, regardless of any measure of costs incurred.

507. In particular, the quantification of the global costs incurred for the registration of the *CDCA Leadiant*® that the dominant company had carried out internally to support the requested price, in fact, show a level of costs far from what would have justified such a high price. (see par. 188 *above),* so much so that this data was not produced in the negotiation with the Regulatory Authority. A different and broader reconstruction of the costs was elaborated only *a posteriori,* in the study commissioned to the consultancy firm *Copenaghen Economics,* in the context of the *antitrust* proceeding initiated by the Dutch competition authority pursuant to article 102, lett. *a),* of the TFEU. The costs declared by the Party during the investigation constitute an updated version of this study.

508. Having said this, and also taking into account the costs declared by the Party on the basis of this *ex post reconstruction,* the investigation activity highlighted a very high disproportion between the prices applied in Italy for the sale of the *CDCA Leadiant*® to the SSN and the value of that drug which must reflect the costs for its production, marketing and maintenance on the Italian market.

509. Although not necessarily required by the jurisprudence of the Court of Justice of the EU533, two different methodologies were used to assess the excess of the price: one of a financial nature and the other of an accounting nature, which allows for a control of robustness of the analysis carried out, thus placing itself in the wake of that part of legal and economic doctrine that encourages the parallel application of several methods534.

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[533] As already stated, the Court of Justice of the European Union has pointed out that different methods can be used to determine whether a price charged by a dominant firm is excessive and unfair and, therefore, abusive. See *United Brands,* cit., Par. 253. The Court also recognized that it is up to the competition authority to select the appropriate method and "define the framework" in a specific case. In particular, "it should be kept in mind that *" [... an authority has a certain margin of maneuver and that there is no single adequate method ".* With respect to the chosen method, what matters is that the method itself is “considered valid”. See Corte Giust. EU, 14 September 2017, in case C-177/16 *Autortiesÿbu un komunicÿšanÿs konsultÿciju aÿentÿra / Latvijas Autoru apvienÿba v. Konkurences padome, para .* 38 and 49.

[534] In this regard, see M. Motta and A. de Steel (2017), *Excessive Pricing in Competition Law; Never say Never ?.* Furthermore, v. the Opinion of Advocate General Nils Wahl presented on 6 April 2017, Case C ÿ *177/16 Biedrÿba «Autortiesÿbu un komunicÿšanÿs konsultÿciju aÿentÿra - Latvijas Autoru apvienÿba» c. Konkurences padome;* request for a preliminary ruling from the Augstÿkÿ tiesa (Supreme Court, Latvia).

to. *The financial methodology*

510. The first methodology applied took into consideration the internal rate of return (IRR) of the CDCA project, launched in 2014 with the increase in the price of *Xenbilox*® and the request for orphan designation for the CDCA with the new therapeutic indication, and which will end in 2027 upon the expiry of the market exclusivity for the *CDCA Leadiant*® (section III.6.2.ii).

511. The IRR of the project was calculated on the basis of the cash flows deriving from the project in question, taking into account the *ex factory* price applied by Leadiant to the sales of *Xenbilox*® *which* took place in Italy in the period January 2016 - May 2017 (equal to 2,900 euros), as well as to the *ex factory* price of the *CDCA Leadiant*® in the years 2017-2019, in accordance with the classification of the drug in the Cnn class (equal to € 15,506.93) and starting from 2020, following the agreement with AIFA (equal to € *[5,000-7,000]).*

512. The IRR was calculated both taking into consideration all the cash flows deriving from the revenues realized minus the costs incurred for the project in question and only the incremental flows compared to those that would have been achieved in any case with the continuation of the sales of *Xenbilox*® *off label.* The value of the IRR is, in the two hypotheses, respectively equal to *[50-60%]* and *[40-50%].*

513. In order to evaluate the profitability of the project, the two values of the IRR were compared with the value of the cost of capital of the project in question (WACC) as quantified by the same Leadiant in the start-up phases of the project: 12% in *the base case* and 15% in *the best case, the* latter identified as riskier535. The comparison between the project IRR and the WACC has led to ascertain not only that the project is profitable for the dominant firm, but also that the first value is significantly higher than the second.

514. On the basis of the analysis carried out, in fact, the IRR is equal to at least *[250-350%]* of the cost of capital. This means that, even considering all the assumptions in favor of the Party, the sales of the *CDCA Leadiant*® generated extremely high and therefore excessive returns for the dominant company.

515. In relation to the arguments of the Party, which criticizes this

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[535] See doc. 95.6.

conclusion as it is based on an allegedly underestimated WACC, the following is observed. The value of the cost of capital reflects a premium for the specific riskiness of the project, as estimated by the dominant firm itself in the initial phase of the project. Leadiant itself in 2014 had in fact identified a WACC of more than 15% as a cost of capital adequate to take into account all the risk factors that the dominant company mentioned in its arguments aimed at justifying the prices charged for the *CDCA Leadiant*® in Italy.

516. In this regard, the defensive arguments of the Party do not hit the mark, aimed at diminishing the value of the internal document of the company containing the aforementioned value of the WACC, which moreover - according to Leadiant - it would be related to the whole company and not to the specific project. In fact, the document in question was developed internally by Leadiant's management at the time of deciding whether to undertake the project to assess its profitability and constitutes the most reliable information on the company's expectations *ex ante* regarding the risks, costs and expected revenues of the CDCA project. The fact that the WACC identified therein is different for the two scenarios of the project *(base case* and *best case) completely* denies the argument of the Party according to which it refers to the cost of capital of the company and not to that of the specific project. .

517. Moreover, it should be noted that using the cost of capital identified by the dominant company for the riskiest scenario constitutes a choice of extreme *favor* towards it, considering various elements that characterize the present case.

518. In this regard, it is first noted that the turnover achieved between 2014 and 2016 thanks to the increase in the *ex factory* price of *Xenbilox*® to 2,900 euros per package, has largely contributed to financing the cost of the regulatory activities undertaken by the dominant company for obtain the orphan designation and the MA of the orphan drug (see paragraphs 113-114 *above).* Therefore, Sigma Tau was not in danger of suffering irreparable economic damage in the event of failure of the project.

519. Furthermore, during the course of the Sigma Tau project, it predicted that if the project was not successful, in the worst case scenario, it would continue the *business* with the sale of *Xenbilox*® as an *off-label* drug for the treatment of CTX *("With no ODD, request for approval withdrawn; - Xenbilox sold off-label; - No price increase vs current; - No volume increase "536).* That is

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[536] See doc. 22.7.129.

means that Sigma Tau, despite the failure of the CDCA project, could still have remained on the market and achieved turnover targets that already benefited significantly from the *Xenbilox*® price increase in mid-2014. two years, from 2013 to 2015, the turnover of *Xenbilox*® had increased from 2 to 7 million euros (see paragraph 114 above) 537. It should also be noted that Leadiant, having maintained the marketing authorization for *Xenbilox*® in Germany without requesting its revocation until June 2019, has for a long time reserved the possibility of resuming the marketing of the drug *off-label* even after its withdrawal from the market: this it also protected it from the risks that the company today fears, linked to the maintenance of the AIC of the *CDCA Leadiant*® (see par. 169 *above).*

520. With regard to the Party's criticism of the valuation model used, which would not take due account of the riskiness of the project, and the need to carry out this valuation on the basis of a different model (risk-adjusted NPV) from the perspective of an investor *ex ante,* the following is noted. Firstly, Leadiant itself carried out its own profitability assessment of the CDCA project in 2014, i.e. when deciding whether *[omitted]* and investing in the project in question to market the product, based on real expectations on risks, revenues and costs. available at that time, using the methodology that it itself considered most suitable (see section III.6.2.i *above).* This assessment, as already highlighted above, duly took into account the risk through the project-specific WACC. The claim of the Party to carry out today an assessment of the profitability of the project from the perspective of an *ex ante investor,* but using success probabilities and discount rates constructed retrospectively on the basis of the literature or a *survey* of experts in the sector, is a sterile and not very reliable, since a more realistic *ex ante* evaluation was actually carried out in 2014

by the dominant firm itself. In other words, when Leadiant analyzed the profitability of the project in 2014, it was exactly in the position of the *ex ante* investor that the Party today would like to reconstruct *ex post.*

521. Furthermore, the assessment of the profitability of the project carried out by the Party in its defense shows significant inconsistencies. On the one hand, the estimate of the

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[537] It should be noted that the dominant company in October 2016 limited itself to withdrawing the drug *off-label* from the German market, without however requesting the revocation of the relevant marketing authorization immediately. In this way it was able to benefit from the period of time (equal to three years) provided for by the *sunset clause,* which would have allowed it to "reactivate" its AIC at any time simply by resuming sales of *Xenbilox*® before the expiry of the aforementioned term.

risk and sales volumes was calculated on the basis of what the Party believes were the expectations of an *ex ante* investor (probability of being able to bring *CDCA* Leadiant® to the market estimated at only *[30-40%]* and expected volumes lower both than those expected by Leadiant itself in its *ex ante* evaluation and to those actually carried out). On the other hand, for the estimate of the expected costs, the Party used the costs charged by it *ex post* to the *CDCA Leadiant*® for the period 2014-2020 and expected in 2020 for the period 2021-2027 (over 100 million euros). As already noted several times, these costs appear to overestimate the project costs expected by a hypothetical investor in 2014. Suffice it to say that these expected costs also include the huge legal costs *([5-10]* million euros) incurred by Leadiant for *antitrust* proceedings before numerous competition authorities in Europe (see para. 239-240 *above).* In this regard, one cannot fail to note that, in its 2014 assessment, Leadiant had estimated the total expected costs of the project at approximately 5 million euros538.

522. Furthermore, the analysis with which the Party estimated, on the basis of the assumptions described above, the *Minimum Viable Price* of the *CDCA Leadiant*® *(with* which the negotiated price whose excessiveness is assessed is compared) is vitiated by a further incorrect assumption. In fact, in identifying this *Minimum Viable Price,* the Party assumes that this price applies to all sales of *CDCA Leadiant®,* ignoring the fact that from June 2017 until the entry into force of the agreement with AIFA (March 2020) the orphan drug was purchased by the ASLs at a much higher price than that of the agreement and that the *payback* mechanism , which took place in the years 2020-21, only partially offset this difference if we consider the time value of money. In other words, the Party's analysis does not take into account the actual timing of cash flows, an essential factor in a financial analysis. This leads to a significant underestimation of the *Minimum Viable Price.*

523. The two further criticisms of the Party to the assessment of excessiveness deriving from the TIR methodology are not convincing either. As regards the price level of *Xenbilox®,* which in Leadiant's opinion would have been increased in any case even in the absence of the CDCA project, thus reducing the rate of return attributable to the project itself, it is observed that, in an analysis of cash flows incremental, the inertial scenario (ie the one “in the absence of a project”, against which to evaluate the cash flows

538 See doc. 95.6, p. 19.

deriving from the project under evaluation) is the one existing at the time of the investment decision. Numerous evidences in the records, referred to several times, certify that the price increase of *Xenbilox®,* which took place on 1 July 2014, was made to finance the costs of obtaining orphan *status* designation and to prepare the market for a much higher price, a registration has been obtained (see par. 113 *surpa).*

In other words, this increase is part of the CDCA project and would not have occurred in the absence of it, contrary to what the Party claims. In this sense, an internal Leadiant document provides in which, in the absence of a project, the forecasts of revenues deriving from the sale of *Xenbilox*® for the period 2015-2019 were constant and estimated at 2 million euros, in line with the revenues achieved in the previous years when *Xenbilox*® was sold at a price of 660 euros per pack539. It is Leadiant itself, therefore, in its internal documents, to qualify as incremental revenues attributable to the CDCA project all those deriving from the increase in the price of *Xenbilox*®
compared to the price charged until June 2014.

524. With regard to the negotiated price of the *CDCA Leadiant®,* which according to the Party could be reduced even before the end of the exclusivity period due to the periodic renegotiations with AIFA, it should be noted that there is no element in the documents that proves this sense. On the contrary, in its model for evaluating the investment made in 2014, the dominant firm assumed a constant price for the entire period. Leadiant confirmed the validity of this assumption in its economic memo: *"once a redemption price agreement is in effect, a hypothetical investor in 2014 would have expected this agreement to persist under the same conditions with a probability of* 100%" 540 . The literature cited by Leadiant on the alleged price reductions during the period of legal exclusivity refers, on the other hand, to the generality of the drugs covered by a patent; The situation of the *CDCA Leadiant® is quite different,* for which the renegotiation levers of the regulatory authorities are substantially zeroed, since there are no therapeutic alternatives for patients affected by the rare disease.

525. In conclusion, contrary to what the Party maintains, the analysis carried out with the TIR methodology made it possible to correctly ascertain the existence of an excessive disproportion between the price charged in Italy by the dominant company for the *CDCA Leadiant*® and the costs incurred by the same.

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[539] See doc. 95.4, p. 41.
[540] See doc. 186.

b. *The accounting methodology*

526. The second methodology used in the analysis of excess is that which is based on the comparison between the sales revenues realized in Italy by applying the price whose excess is assessed (in this case the negotiated price of *[5,000-7,000]* euro) and the so-called *cost plus,* corresponding to the costs, direct and indirect, incurred by the dominant company for Italy in relation to the *CDCA Leadiant®,* including a reasonable profit margin for the same.
In the present case, this measure of profitability was concessively quantified as a return on sales rate of 21%. The percentage excess of revenues from sales of the *CDCA Leadiant®* at the price of *[5,000-7,000]* euros compared to the *cost plus* was equal to *[60-70%]* for the period from the start of marketing of the *CDCA Leadiant®* in Italy until the end of 2020 and by *[90-100%]* considering the expiry of the market exclusivity, set in April 2027 as the term of the period (see section III.6.3 *above).*

527. With regard to the criticisms made by the Party on the *cost plus* methodology and its method of application, it is noted in the first place that this valuation criterion is of an accounting-income type and therefore, by its nature, both a static and non-static model. takes into account the time value of money, unlike the criteria for evaluating investments of a financial nature, such as the IRR. Precisely for this reason the *cost plus* methodology
in the analysis of the disproportion between prices and costs, it was accompanied by a financial methodology, which the Party considers more appropriate for the evaluation of this type of project, in order to corroborate the results and provide greater robustness of the evaluation. Moreover, the circumstance that the *cost plus* methodology does not consider the time value of money is not in itself unfavorable to the Party: precisely by virtue of this specificity, in fact, in the evaluation of the *cost plus* - in an advantageous way for the Party - it is assuming that the negotiated price had been applied aborigine , right from the first sales of the *CDCA Leadiant®* in Italy in 2017, while as known, this price entered into force only from March 2020 and was then applied retroactively to previous sales (see par. . 265 *above).* This considerably reduced the revenues attributed to the Party for sales of the *CDCA Leadiant®*

in the years 2017-2020 and, consequently, the value of their excess compared to the *cost plus,* which however remains extremely high.
528. Regarding Leadiant's criticism of the year from which the *cost plus* was applied (2017), it is observed that the average profitability of a product can only be measured starting from when it is

marketed, that is, in the present case, from June 2017. It is noted, however, that the expenses incurred in the years prior to the marketing of the orphan drug were adequately considered in the IRR methodology, which is by its nature aimed at determining the profitability of the project throughout its life cycle.

529. Finally, the use of the average ROS for the sector, which in the Party's opinion would not constitute an adequate *benchmark* to reflect the specific risks of the CDCA project, on the other hand appears extremely favorable to the Party, considering that the project in question consists in the *repurposing* of a product already present in the portfolio of the dominant company, an activity that presents characteristics of risk and investment well below those of the *ex novo* development of a pharmaceutical product. The measure of the reasonable rate of profit adopted in the analysis in question is, moreover, much higher than that used in the previous cases of excessive prices in the pharmaceutical sector541.

530. Both methodologies applied therefore converge on the same conclusion regarding the existence of a very strong disproportion between the prices applied by the dominant undertaking and the costs incurred by it. This excess is well above the levels of disproportion that were considered abusive in the main decisions ascertaining the violation of Article 102, lett. *a),* of the TFEU542.

531. It seems appropriate to reiterate that the analyzes described above were carried out using a series of extremely precautionary hypotheses in favor of the Party, in the absence of which the excessiveness of the prices charged by Leadiant would have been much greater. It is considered useful to summarize them below:

- the costs provided by the Party were used with regard to both *Xenbilox®543* and *CDCA Leadiant®.* For the latter product, the Party allocated the common costs incurred on the basis of its own estimate, which was made *ex post,* of the time worked by employees on the *CDCA Leadiant*® compared to all the other products in the portfolio. This criterion leads to allocate *[30-40%]* of all common costs incurred to the *CDCA Leadiant*®

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[541] See *A480 - Price increase for Aspen drugs,* cit., Para. 174, 182, 319, where a ROS of 13% was used.

[542] See the decision of the European Commission of 25 July 2001, COMP / C-1 / 36.915 - *Deutsche Post AG - Interception of cross-border mail,* para. 156, 162, 166 and 167; UK Competition Appeal Tribunal, judgment of 7 November 2008, *Albion Water Ltd, Albion Water Group Limited v Water Services Regulatory Authority and Dwr Cymru Cyfyngedig, United Utilities Water PLC intervening,* Case Number 1046/2/4/04 [2008] CAT 31, par. 265.

[543] The only cost item provided by the Party and not considered in the analysis concerns *intercompany royalties* paid by the English company to the US company of the group for the marketing license of *Xenbilox*® in Europe (see paragraph 238 *above* and the related footnote).

by the dominant company for the entire 2014-2027 period and over 60% for the 2016-2020 period, i.e. the period that also includes the complex strategy implemented by Leadiant described above, aimed at obtaining extremely high prices for the orphan drug. In other words, the common costs were attributed to the *CDCA Leadiant*® based on the time spent by the employees of the dominant firm in carrying out numerous and complex activities of a regulatory and market access nature (such as planning the withdrawal of *Xenbilox*® or establishment of a new company that owns the orphan drug) which, as the investigation has shown, were not (only) necessary to launch the *CDCA Leadiant*® on the market, but also to obtain a particularly high price. The criterion used by the Party therefore appears to overestimate the common costs attributable to the product and to be vitiated by circularity, as it claims to justify the level of prices charged on the basis of costs deriving from activities that constitute the instrument of the abuse. Finally, it should be noted that the common costs that the Party has allocated to the *CDCA Leadiant*® in the manner mentioned above have a considerable weight on the total costs of the product (over 50%). In conclusion, therefore, the fact that the cost data provided by the Party were in any case used in the analyzes in question is particularly concise (see par. 241

above);

among the direct costs provided, the Party also reported the significant legal costs it has incurred and plans to incur in the years to come in the various proceedings in which it has been involved before the national competition authorities in application of Article 102 of the TFEU, precisely because of the allegedly excessive and unfair prices of the *CDCA Leadiant®.* Since these costs are directly attributable to the conduct in question here, they should not be taken into consideration in the analysis of price excess.

Nevertheless, the analysis was carried out considering all the costs declared by the Party and therefore also these (see paragraph 240 *above);*

the figure relating to the incremental costs of the *CDCA Leadiant*® was not considered usable in identifying the incremental cash flows useful for calculating the IRR. In the absence of this information, the data relating to the total costs of the orphan drug, which by definition are higher than the incremental costs (as they also include non-incremental ones), was used in a very favorable perspective (see paragraph 257). *above);*

it was assumed that the negotiated price of *CDCA Leadiant® would be applied* to all sales made in Italy in 2020 (despite the fact that the agreement entered into force in March) and the reimbursement of almost all

of the amount of the *payback544* in the same year *([6-7]* out of *[6-7]* million euros). This hypothesis anticipates the negative financial flows borne by the Party due to the *payback,* reducing the value of the closest cash flows in time and, therefore, the overall IRR of the project. In the absence of this assumption, the IRR of the project would therefore have been even higher (see paragraph 236 *above);*

- the cost of capital (WACC) used by the dominant company in its internal calculations to evaluate the project in question was considered as the cost of capital (WACC) with which to compare the IRR , equal to 15%. This is an extremely concessive hypothesis, considering that in the start-up year of the project (2014) the average WACC for the pharmaceutical sector in Europe was significantly lower and equal to 10%, due to the specific risk of the project (see par. . 247 *above);*

- the average tax rate incurred by Leadiant in the 2014-2019 period (21%) was used, which is higher - and therefore more favorable to the Party - both the average rate incurred in Europe in the pharmaceutical sector in the same period and the rate used by the Party in its *ex ante* analysis (see paragraph 244 *above);*

- finally, as mentioned above, an extremely concessive profitability *benchmark* was used in the *cost plus* analysis , considering the type of project in question, characterized by lower levels of risk and investment than the average of projects in the pharmaceutical sector, and previous cases of excessive prices in the sector in question
(see para. 267 *above).*

532. In conclusion, for the reasons set out above, it is considered that the arguments put forward by the Party are not likely to revoke the conclusions reached regarding the existence of a high disproportion between the prices applied and the costs incurred by the dominant company for the *CDCA Leadiant®,* and therefore such prices are to be considered excessive.

iii) The unfairness of the prices charged by Leadiant for the sale of the orphan drug in Italy

533. This section is dedicated to verifying the existence of so-called *non-cost related* factors that may justify this disproportion. In fact, where these elements are not deemed to exist, the prices charged by Leadiant

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[544] That is, the return, provided for by the agreement of December 2019, of the difference between the price paid by the ASL before the agreement for the *CDCA Leadiant* and the negotiated price.

they would be *"devoid of any reasonable relationship"* with respect to the economic value of the service rendered and would therefore be unfair.

534. Preliminarily, it should be specified that the inequity analysis suggested by the Party, which believes that in the present case it is necessary to look at both the unfairness of the price in an absolute sense, based on the economic value of the drug and the benefits for patients and for the company, whether in comparison with the price of the same drug in other European countries or of comparable pharmaceutical products, it does not find any confirmation in the jurisprudence of the Court of Justice of the EU, which on this point did not follow the indications of the Advocate General Wahl in his opinion on the *AKKA / LAA case,* cited by Leadiant. Indeed, as anticipated, this jurisprudence rather states that the national competition authorities enjoy a margin of discretion both in the choice of the test for determining the legitimacy of a company's commercial policy.

dominant pursuant to art. 102, lett. *a),* TFEU, and in the choice, in the context of the *United Brands test,* between the two criteria identified for the purposes of the analysis of unfairness (see paragraphs 501 and 503 *above).*

535. Equally unsupported by the rulings of the Court of Justice is the assertion of the Party regarding the possibility of applying the criterion of unfairness in an absolute sense, without the comparison of the comparative analysis, only to cases in which consumers do not receive any product in exchange for the price paid. It is known, in fact, that the Court did not follow the approach adopted by Advocate General Wahl in his opinion on the *AKKA / LAA* case even in relation to this interpretation of the *United Brands test*[545]. Furthermore, this interpretation does not find the support even of the practice of the Authority, which has applied the criterion of unfairness in itself to cases that do not integrate the requirements of those identified by Leadiant[546], receiving the recent endorsement of the administrative judges[547].

536. Having said this, for the reasons set out below, it is considered more correct to opt, in the present case, for an assessment of the unfairness in itself of the pricing policy applied by Leadiant, and not for an assessment based on comparative criteria. .

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[545] Indeed, it cannot be said that the Court endorsed Advocate General Wahl's opinion solely because in that case it considered the method based on the comparison between the prices applied in the Member State concerned and those applied in other Member States to be applicable (see paragraph 38 of the decision). This method was, in fact, chosen in place of the *United Brands test,* which was thus replaced in its entirety because it was deemed inappropriate in the case of intangible assets whose cost cannot be easily determined.

[546] V. prov. 26185 of 29 September 2016, *A480 - Aspen drug price increase,* para. 329-351.

[547] V. Cons. Status, March 13, 2020, sent. n. 1832/2020, para. 12.116 and 12.7.

to. The inapplicability of comparative criteria for the analysis of unfairness in the present case

537. The second option provided by the Court of Justice of the European Union to the competition authorities for the purpose of assessing the unfairness of the price charged by a dominant firm refers to the comparison of this price with those of *"competing products".* The European Commission in the previous *Port of Helsinborg* considered it possible *in the abstract* to apply the formulation adopted by the Court also by comparing it with the price of the same product by the same company in other markets or with the price of "similar products" sold in other markets,
as two *second best* options in the event that "competing products" or belonging to the same relevant market in which the product under examination is not identifiable548.
538. Given that, for the reasons set out in sect. V.2.iii *above,* the *CDCA Leadiant*® in the present case there are no "competing products" to be considered in the context of a potential comparison of the price of the *CDCA Leadiant*® with that of other drugs, and wanting to enhance the practice of the European Commission and the jurisprudence of the Court of Justice, thus looking at the price of orphan drugs indicated as comparable to the *CDCA Leadiant*® by the Party, the following is observed.

a.1 Comparison with similar products

539. First of all, it must be considered that precisely in order to avoid inappropriate comparisons, both the European Commission and the Court of Justice have established that the comparison between similar products must take place in conditions of homogeneity. In other words, it is necessary that the products considered similar are actually comparable, so that the comparison is valid and that the results of this comparison are meaningful. For this reason, the conditions under which the comparison takes place are of fundamental importance549.

540. However, it is believed that the comparison proposed by the Party does not pass this scrutiny since it is methodologically incorrect in many respects.

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548 See European Commission, COMP / A.36568 / D3, *Port of Helsingborg,* para. 170-171.
549 See European Commission, COMP / A.36568 / D3, *Port of Helsingborg,* para. 169 and Corte Giust. EU, 14 September 2017, in case C-177/16, *AKKA / LAA, para .* 38 and 44 .; v. also Cons. State, sent. n. 1823 of March 13, 2020, par. 12.8.

541. First, it is noted that Leadiant assumes as a term of comparison the average price of an unidentified group of 75 orphan drugs marketed in Italy and, again, the average price of a group of 14 orphan drugs, equally not precisely identified, but indicated as
belonging to similar therapeutic areas.
542. Given that the Party does not provide information on the matter, it appears It is first of all reasonable to assume, given the large size of the sample, that the 75 orphan drugs included in the first group indicated have completely different therapeutic indications. This in itself contributes to making them non-comparable from a product point of view, and therefore not "similar", to the *CDCA Leadiant®,* with which they have in common only the fact that they are orphan drugs. Furthermore, the Party makes the comparison on the basis of an average price, which in itself says nothing about the comparability of the price of the orphan drug owned by Leadiant with the prices of the 75 orphan drugs considered.
543. As regards the 14 drugs included in the second group, considerations similar to those already expressed *above are valid.* They are medicinal
belonging to the following therapeutic classes of the ATC classification: A16AA, which includes medicines used to treat various metabolic deficits, and A16AB, which includes medicines that contain enzymes used to treat metabolic disorders, and A16AX, which includes products used to treat metabolism and the alimentary tract, and N07XX, which includes drugs used to treat diseases affecting the nervous system. These therapeutic indications, however, do not in themselves make these drugs comparable, and therefore similar, to the *CDCA Leadiant®.* In fact, it is not enough that two or more drugs treat any metabolic *deficit* or any disease of the nervous system for them to be considered similar.

from the therapeutic point of view to the *CDCA Leadiant®,* for the sole fact that the CTX consists of a metabolic dysfunction that generates, *inter alia,* disturbances to the nervous system.

544. It should also be considered that, for the Part itself, the comparative analyzes carried out do not take into account the number of patients taking the drugs included in the two groups considered. In other words, the prices of these products are determined by unknown epidemiological data which are presumed to be distinct. Yet, it is known that the definition of the price level of a given drug is necessarily influenced by the magnitude of the demand, since the volumes, together with the price, determine the overall impact on the NHS *budget ,* as indeed the facts also demonstrate. which characterized the negotiation of the *CDCA Leadiant® price.* This means

that, in the absence of information demonstrating that the prices of drugs included in the two groups considered by the Party refer to drugs that treat pathologies with epidemiological characteristics similar to those of the orphan drug in *question,* also from this point of view it does not appear correct to carry out any type of significant comparison between them and the *CDCA Leadiant®.*

545. Finally, it is believed that the comparison proposed by the Party does not take into due consideration the innovative character of some orphan drugs included in the largest sample. The distinction between medicines which, like the orphan drug *de quo,* are so -called *repurposed* and medicines based on unknown and *newly* developed active ingredients is not irrelevant. Indeed, the two categories of drugs are distinguished by the amount of resources invested in their development. Indeed, as recognized by the European Commission, the investments in research and development made for repurposed orphan drugs are much lower than those made for completely new orphan drugs550 . This explains why they are on average (or at least should be) marketed at lower prices, as is evident from the data that Leadiant itself has produced in its memoirs551. Not considering the category of innovative drugs separately from non-innovative ones therefore leads to taking, as the Party does, an overestimated and therefore inappropriate term of comparison for evaluating the unfairness of the *CDCA Leadiant® price.*

546. Finally, it should be considered that the unsuitability, for the purposes of assessing the unfairness of Leadiant's pricing policy, of the comparative analysis proposed by the Party also arises from some documents to

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[550] See Technopolis, Ecorys, *Study to support the evaluation of the EU Orphan Regulation,* July 2019, study carried out for the European Commission as part of the revision of the Regulation on Orphan Drugs, which states: "[...] *the costs a sponsor has had to make to repurpose or reposition a product may be substantially smaller than in cases where a sponsor has developed a wholly new medicinal product through all phases of the R&D pipeline, including the conduct of clinical trials " (p.* 232); *"In case of an" average "orphan medicine there is a risk over overcompensation if turnover levels are high (in our analysis 14% of orphan medicines showed an annual turnover of € 100m or more). […] In case of repurposed products (including well-established use products and known active substances), overcompensation may occur because the R&D costs may be "below average"* "(p. 271); *"Price increases such as these appear to be unrelated to actual costs of R&D as the development had already been completed many years before and the products were previously sold at a much lower price. Here, it is likely that the market exclusivity that the marketing authorization holders gained from the orphan designation was the main factor that enabled them to engage in monopolistic price setting " (p.* 260-261). It should be noted that this last passage of the study refers to some specific cases of price increases of so-called repurposed drugs , among which the *CDCA Leadiant® is explicitly included.* See also European Commission, *Commission Staff Working Document Evaluation,* SWD (2020) 163 final, of 11 November 2020, pp. 60 and 103-104.

[551] See Figure 13 on p. 98 of the Economic Memorandum (doc. 186). It should be noted, however, that the same Figure also indicates that drugs made up of synthetic molecules, such as *CDCA Leadiant®,* have average prices lower than that of the orphan drug in question .

acts. For example, the research commissioned by the dominant company in October 2015 showed that the *stakeholders* interviewed *(health economists,* doctors, and pharmacists consultants of the national regulatory authorities) were extremely reluctant, if not even *"offended",* by the attempt of Sigma Tau consultants to induce them to make a comparison between the price of the future orphan drug and the medicines registered for other ultra-rare diseases *("None of the respondents wanted to use benchmark or analogue products produced for the pricing exercise. [...] In some cases respondents were slightly confronted that and attempt was being*

made to make pricing decisions by this approach "552). It should be noted, however, that among the drugs proposed as a comparator, and rejected by the *stakeholders,* there was also *Orphacol* (see par. 123 *above* and on which see the following section better *below).*

a.2 Comparison with Orphacol

547. In relation to the comparison proposed by the Party between the drug most recently cited and the *CDCA Leadiant®,* it is important to underline first of all that this does not represent a correct application of the judgment of the Court of Justice of the EU, *Bodson v Pompes Funèbres,* cited by the same Leadiant . In such
in fact, the Court abstractly hypothesized the possibility of comparing two identical services rendered in two different markets, where the difference was due to the fact that one was in concession and the other was in competition. The Court therefore hypothesized that the unfairness of the price at which the concession service was rendered could be assessed by comparing it with a competitive *benchmark .* In the present case, however, the Party actually suggests making a comparison between products which are both

with a market exclusivity (the *market exclusivity* connected to the orphan designation), which by definition allows them to benefit from a significant *mark up .* In other words, *Orphacol* cannot be considered as a competitive *benchmark* capable of providing adequate indications about the unfair price of the *CDCA Leadiant®.*

548. Apart from this, albeit decisive, finding, it is noted in any case that the Party comes to the conclusion that *Orphacol* is *[50-60%]* more expensive than the *CDCA Leadiant®* on the basis of incorrect or unverified assumptions. The conclusion about the comparability between the two drugs, in fact, starts first from the assumption that, being *Orphacol* a repurposed drug , the costs of

[552] See doc. 78.80.

registration are similar, if not even lower since it is a procedure based on the so-called *well established use,* that is mainly based on scientific literature. However, this remains an unproven assumption and not substantiated by Leadiant in any way. Any conclusion about the similarity between the two drugs on the basis of this criterion would therefore discount the risk of being a "false positive".

549. Secondly, it is based on the consideration of erroneous epidemiological data. The Party, in fact, states that *Orphacol* is aimed at a *patient population* in Europe of approximately 2,300 individuals, while the number of patients affected by CTX is approximately 250, defining them as "comparable". Notwithstanding the fact that these data certainly cannot be defined as "comparable", since one is ten times the other, it is noted in any case that the comparison made by Leadiant suffers from some important errors.

550. First of all, it is incorrect to assess the price level of two products applied at *national* level by referring to *European epidemiological data.* It is hardly necessary to recall, in fact, that in the context of the current architecture of the Treaty, the competence to define the prices (even if only for reimbursement) of drugs remains the exclusive prerogative of the governments of the Member States553, which for this purpose consider the number of patients who take it, exclusively nationally. Likewise, even in health systems where the definition of the price of drugs is not provided for through the administration, but is based on mechanisms that exploit the forces of the free market or replicate its attitude (on which see better paragraph 554 *below),* the strategies price discrimination implemented by firms is based, *inter alia ,* on the size of each national market, as the assessments of the dominant firm itself show.

551. Secondly, while the number of CTX patients in Europe is an actual figure based on the diagnosis, that relating to the two congenital defects treated with *Orphacol,* in addition to being obsolete554, is a statistical figure based on the prevalence disease theory555. Furthermore, the careful analysis of public sources should have led the Party to realize that the data of 2300 patients refers to *all congenital errors in the synthesis.*

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[553] See art. 167 TFEU.

[554] The data is, in fact, taken from *https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu302127* and dates back to 2002.

[555] The prevalence figure for this type of disease is much higher than that of patients to whom they were actually diagnosed, due to significant underdiagnosis.

of primary bile acids556, of which the two congenital defects treated with *Orphacol* represent only a small part. The specific prevalence of the two congenital defects that *Orphacol* intends to treat is, in fact, 3-5 patients out of 10 million (i.e. 0.003-0.005 patients out of 10,000), for one defect, and 0.3-0.5 out of 10 million patients (i.e. 0.0003-0.0005 out of 10,000 patients), for the other defect557. Applying the prevalence percentage of the rare disease to the Italian population, the patients affected in the domestic market by the two congenital defects mentioned above would be about 12-20 patients, while the patients affected by CTX, according to what Leadiant herself states, are *[40-50],* a number more than double, if not triple, which easily explains the price differential of about *[50-60%]* existing between the two drugs.

a.3 The comparison with the price of CDCA Leadiant® *in the other Member States*

552. It is also not considered appropriate to evaluate the unfairness of the price of *CDCA Leadiant*® in Italy by comparing the prices charged for the same drug in the other European countries identified by the Party (United Kingdom, France and Germany). The investigation conducted, in fact, clearly indicates that Sigma Tau / Leadiant has put in place a pan-European commercial strategy, which is subject to *antitrust* scrutiny by various national competition authorities. The foreign prices of the *CDCA Leadiant*® could therefore be the result of the strategy put in place by the dominant company, as much as the price charged in Italy558. Indeed, the documentation acquired in the records is eloquent in this regard, highlighting the opposition with which demand also in other Member States accepted the sales prices with which the orphan drug was launched there (see section
III.5.8 *above).*

553. But the *across-the-border* comparisons in the pharmaceutical market more generally run the risk of not respecting the homogeneity criterion required by the European Union jurisprudence, because they take place in a context of strong economic, institutional and epidemiological heterogeneity that still characterizes the national pharmaceutical markets of the 'European Union. The market

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[556] See *https:// www.ema.europa.eu/ en/ medicines/ human/ orphan-designations/ eu302127.*

[557] V. *information https://www.ema.europa.eu/ en/ documents/ product-information/ orphacol-epar-product*

[558] See the provision on this point AGCM n. 26185 of 29 September 2016, *A480 - Aspen drug price increase,* par. 330.

European pharmaceutical industry is characterized, indeed, by the persistence of price differentials from one Member State to another, linked, not only to the price differentiation strategies implemented by pharmaceutical companies, which should reflect the price elasticity of demand (based on willingness to pay and the size of the market), but also, and above all, the institutional and economic differences that inform the various national pharmaceutical policies559. In this context, it is clear that the comparison between prices of the same product in the various Member States of the European Union does not give any meaningful result or indicative of the fairness or unfairness of the price of that product in one of those Member States.

554. The three Member States taken as a reference by the Party to carry out the comparison exercise between the prices of the *CDCA Leadiant®,* Germany, France and the United Kingdom, have *pricing and reimbursement* systems that are very different from the Italian one. Unlike Italy, Germany and the United Kingdom admit free prices at launch, a circumstance that the domestic legal system does not allow560. In turn, the two countries are distinguished because in Germany the reimbursement price is negotiated in the form of a discount on the retail price originally set by the dominant firm, and paid for by health insurance funds561; vice versa, in the United Kingdom there is no direct regulation of prices, indirectly governed through a *profit cap* established by the PPRS *(Pharmaceutical Price Regulation Scheme)* which determines a continuous modulation of product prices562. In France, where the introductory price is regulated as in Italy, the

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[559] See the provision on this point AGCM n. 26185 of 29 September 2016, *A480 - Aspen drug price increase,* par. 330. These differences have also been recognized by v. Cons. State, no. 1823 of March 13, 2020, par. 12.8.In literature v. WHO, *Medicines Reimbursement Policies in Europe,* 2018; C. JOMMI, *Pharmaceutical regulation in 15 European countries review,* in *Health Systems In Transition - European Observatory on Health Systems and Policies,* 2016, vol. 18, no. 5, pp.1-122; C. JOMMI, *Innovation and drugs price and reimbursement: a comparison between Italy and the other major EU countries,* in *Grhta,* 2015, vol. 2, no. 3, pp. 117-162; Hai Europe, *Variations in Prices and Reimbursement of medicines in the European Union,* 2014; M. Garau, J. Mestre-Ferrandiz, *Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries,* in *OHE Briefing,* n. 52, October 2009; OECD, *Pharmaceutical Pricing Policies in a Global Market,* 2008; E. MOSSIALOS, M. MRAZEK, T. WALLEY, *Regulating Pharmaceuticals in Europe: Striving for efficiency, equity and quality,* Oxford University Press, 2004; P. KANAVOS, *Pharmaceutical regulation in Europe,* in *Institute for Research on Public Policy Conference - Toward a National Strategy on Drug Insurance: Challenges and Priorities,* 2002.

[560] VC JOMMI, *Innovation and drugs price and reimbursement;* cit., p. 119-121.

[561] See footnote 290 *above.*

[562] Under section 261 of the NHS Act, the NHS *Pharmaceutical Price Regulation Scheme* (PPRS), agreed every five years between the *Department of Health* (DH) and *the Association of the British Pharmaceutical Industry* (ABPI), regulates the profits that manufacturers can realize from their sales to the NHS of *branded* medicines (under patent and off-patent). Pharmaceutical companies can freely set the price of new drugs, but any future increases must be offset by reductions in the price of other drugs so that the total overall expenditure for the NHS respects the *profit cap* established by the PRS.

technical evaluation of a drug and price negotiation are carried out by two different authorities, competences that in the domestic system, vice versa, are both concentrated on AIFA563. Finally, the valuation process set up in France and Germany to define reimbursement prices gives rise to a sort of sharing of private demand in pharmaceutical expenditure, which goes hand in hand with the financing provided by public demand, which is in no way comparable to mild forms of *cost-sharing* established by various Italian Regions (the so-called ticket). 564 All this in itself makes the four price and reimbursement systems not comparable and potentially inappropriate any comparison between the prices charged in these markets, even if relative to the same product.

555. All this is also reflected in the price of the *CDCA Leadiant®,* for which already in 2014 it emerged - from the same market researches commissioned by Sigma Tau - a structural difference in the prices that would have been applicable in the various Member States (in France, 25 -35,000 euros a year, in Italy around 15-20,000 euros a year, in Spain around 20-30,000 euros a year, while in the United Kingdom around 50,000 pounds a year) (see par. 121 *above).* These structural differences, also linked to the number of patients, emerge from the same assessments of the dominant firm565 and are also observed in relation to the prices currently applied for the orphan drug, for the reasons set out below.

556. For example, the price of the *Leadiant® CDCA* in the UK was negotiated by Leadiant with the NHS for a number of CTX patients equal to about 24, that is almost half of the Italian patients. Which, coupled with a very different willingness to pay by the UK NHS, explains why

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563 In France, the price of drugs is first negotiated by *the Comité économique des produits de santé* (CEPS), generally on the basis of its therapeutic utility, but also in relation to other factors, such as the price of the drug in other countries. Subsequently, the *Commission de la transparence of the Haute Autorité de Santé* assesses *i)* its therapeutic value *(soin médical rendu* or SMR) to verify that the drug is sufficiently effective from a therapeutic point of view to deserve to be paid partially or totally by the system social security, and *ii)* the added therapeutic value *(amélioration du soin médical renduo* ASMR) to check whether the medicine can be considered an improvement over the other medicines available, and thus to fix the amount reimbursed by the social security system. See also C. Jommi, *Innovation and drugs price and reimbursement;* cit., p. 119-121.

564 The *co-payment* in fixed form (such as that provided by the so-called *ticket)* is very different from the *co-payment* in percentage form, especially when this percentage is significant, in terms of incentive to choose more or less expensive therapies.

565 See doc. 78.441 *([…] Given that in some countries we have a very large number of pts and a negligible OEPX it seems that we must do this on a EU basis with an ability to then drill down to a country specific level if needed. By example - in the UK and Germany we could quite easily justify a high price based on pts numbers, OPEX requirement and subsequent product profit contribution, in Italy, Spain, Netherlands however we will have to adopt a different approach given pts numbers are so high and OPEX requirement is so low [...]).*

the price of *CDCA Leadiant*® in the United Kingdom is almost double that of the Italian one (equal to GBP *[10,000-20,000]* per pack of 100 250 mg capsules).

557. In France, *CDCA Leadiant*® is sold at a negotiated price of EUR *[10,000-20,000]* per pack of 100 capsules of 250 mg566, which is reimbursed at 30% 567. Therefore, the price negotiated in France for the *CDCA Leadiant*® in reality cannot represent a good term of comparison because it has been defined with institutional mechanisms completely different from those envisaged in our legal system and provides for a wide sharing of private demand which, on the other hand , is not contemplated in Italy.

558. In the light of all these considerations, it is considered that, in the present case, the circumstances of homogeneity required by the practice of the European Commission and by the jurisprudence of the Court of Justice of the European Union to carry out a comparative assessment of the inequity of the price charged by Leadiant for the orphan drug.

b. *The inequity in itself of the price of the* CDCA Leadiant®

559. Having said all this, it is believed that there are numerous evidences in the files that allow it to be affirmed that the prices charged by the dominant company for the *CDCA Leadiant*® in Italy are in themselves unfair. These are qualitative factors, relating to the nature of the product, the investments in research and development made by the Party, the added therapeutic value of the orphan drug compared to pre-existing therapies - not measurable through the consumer's willingness to pay, given that the *willingness to pay* for life-saving drugs with no therapeutic alternative tends to infinity, making any price level plausible568 -, and to the effects of the conduct on the NHS.

b.1 The nature of the product

560. First, *CDCA Leadiant®,* being a repurposed drug ,

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566 See *https:// www.legifrance.gouv.fr/ jorf/ id/ JORFTEXT000041497659.*

567 *https:// www.has-sante.fr/ upload/ docs/ application/ pdf/ 2019-03 / chenodeoxycholic_acid_leadiant_11072018_ct16384_transcription.pdf; https: // www.has sante.fr/ jcms/ c_2865403/ fr/ chenodeoxycholic-acid-leadiant-acide-chenodesoxycholique-medicament-a base-d-acides-biliaires; http:// www.codage.ext.cnamts.fr/ codif/ bdm_it/ fiche/ index_fic_ucd.php?p_code_cip=9426887&p_site=AME*

THERE.

568 See on this point the provision AGCM n. 26185 of 29 September 2016, *A480 - Aspen drug price increase,* para. 137 and 346; indirectly Cons Stato, 13 March 2020, sent. n. 1832/2020, par. 12.6, lett. d) and e), where reference is made to the fact that the elasticity of the demand for life-saving drugs is substantially equal to zero.

or a drug whose molecule was already on the market with a specific therapeutic indication, and reintroduced on the market with a new therapeutic indication, cannot be considered as a newly introduced medicinal product on the market. This is by no means intended to connote *repurposed* drugs in a negative sense, but merely to state that, even if the *CDCA Leadiant*® is a drug that, compared to the previous therapeutic alternatives, has a specific registration for the treatment of CTX and an orphan designation, it cannot be regarded as a completely new drug.

561. This is true above all on the chemical-pharmaceutical level. The improvement of the drug production method resulting from the implementation of a new purity test (see par. 127 *above),* although it made it possible to reduce the level of impurities, did not in fact alter the essential characteristics of the active principle.

562. In this regard, we cannot fail to observe that, even after these changes to the production process, *CDCA Leadiant*® remains equivalent to *Xenbilox®,* and even to the magisterial preparations of the AOU Senese Pharmacy, from a chemical and pharmaceutical point of view: the three drugs have, indeed, the same active principle, have the same dosage, are produced on the basis of the same raw material produced by the same chemical company and are bioequivalent.

563. This appears to be highlighted by the documents acquired in the proceedings which indicate that, although there are some differences in the excipients between the capsules produced by the Pharmacy and *Xenbilox® ,* the two drugs are substantially similar, as recognized by the EMA569 on the basis of the studies of comparability carried out by the same dominant firm (see paragraph 144 *above).* Also, others documents collected during the investigation indicate that between *Xenbilox*® and *CDCA Leadiant®570* there is a relationship of equivalence, or rather identity, chemical-pharmaceutical, demonstrated *i)* by the statements contained in the documentation submitted to the EMA by the dominant company *("[...] the reference and proposed product are the same" 571, ii)* by the fact that the latter, for the purpose of applying for the marketing authorization for the orphan drug, did not have

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[569] As regards in particular CDCA-based galenic products, in the EMA Assessment *Report* of September 2016 it is stated: *"Results of studies of dissolution comparing the two products demonstrated that, despite minor differences in excipients contained in the compounded and reference formulations, both products can be considered similar ".*

[570] See EMA, *Assessment Report,* cit., P. 8: *"The application for Chenodeoxycholic acid sigma tau only referred in certain areas to Xenbilox and in all these areas there was no need for bioequivalence or comparable bioavailability studies to the reference medicinal product".*

[571] See doc. 78.30, annex "Annex 1 - Overview of product development", p. 33.

need to carry out bioequivalence studies, as well as *iii)* the circumstance that the AIC of the orphan drug was requested using the so-called hybrid abbreviated procedure (see paragraphs 141 and 143 *above),* made possible thanks to the fact that the *CDCA Leadiant*® despite having a distinct therapeutic indication, it is pharmaceutical equivalent *to Xenbilox*® . It was therefore sufficient for the dominant company to refer to the relevant part of the *Xenbilox*® *dossier* to prove its pharmaceutical equivalence.

b.2 The low investment in research and development

564. The documentation acquired during the investigation also clearly shows that the Party within the CDCA project did not incur significant research and development costs that could justify the price initially requested from AIFA or the price subsequently negotiated with the Agency .

565. In fact, although the two retrospective studies commissioned two retrospective studies carried out by the AOU Senese and by the Dutch hospital Casinius Wilhelmina in Nijmegen still constitute a very important medical-clinical activity for the knowledge of the rare pathology, especially given the their (hitherto unsurpassed) breadth and duration, it should in any case be noted that this activity was carried out by public structures that have developed and consolidated extensive clinical experience in the administration of CDCA to patients with CTX over a period of over forty years (see paragraphs 147, 149 and 150 *above)* and that the financial effort made by Leadiant to remunerate this activity and this experience has been decidedly negligible, being figures equal to *[300,000-400,000]* euros and, at the most, in the future to *[500,000-600,000]* euro (see paragraph 151 *above).*

566. The aforementioned activities carried out by PCA on behalf of Sigma Tau for the implementation of the purity test developed by the dominant firm for the improvement of CDCA production also required a minimum outlay: according to what was declared by the dominant firm itself, in fact, it paid PCA an amount equal to *[300,000-400,000]* euro (see par. 127 *above).* Therefore, also in this case, these are extremely limited investments, which, although capable of bringing a benefit to patients, do not represent a "significant innovation", given that, as the PCA itself states, even with the new purity the production process of CDCA as a pharmaceutical grade active ingredient remains rather simple (see par. 50 *above).* Therefore, they certainly cannot

to help justify the price requested by AIFA for the purchase of the orphan drug.

567. Beyond these specific expense items, various documents in the file also prove the extreme limitation of investments in "research and development" in general planned over time by Leadiant as the CDCA project has been brought forward: the planned investments have always resulted, in fact, very contained, not only if considered in their absolute value, but also in comparison with most of the investments relating to the other drugs present in the portfolio of the dominant company and with the total investments in research and development that it envisaged supporting (see par. 188 *above).* And also referring to the economic study carried out by *Copenhagen Economics ,* a completely similar result emerges: the costs classified therein as research and development, incurred by the dominant company in the context of the CDCA project, are less than 1% of the total cost of it claimed (cf. par. 239 *above).*

568. Then in relation to the argument of the Party according to which Leadiant would have made substantial and important investments, even if not strictly classified as research and development, such as the drafting of an *ad hoc DMF* for the orphan drug and the repeatedly mentioned improvement of the drug production methods, and having to support as many, linked to the regulatory obligations in terms of pharmacovigilance and scientific information and maintenance of the AIC, wider and more stringent than those to which it previously subjected with *Xenbilox®,* the following is observed .

569. As clearly emerges from the investigation carried out, most of the activities mentioned by Leadiant have a marginal weight on the costs that the dominant company has declared to have incurred and to have to bear. The direct costs linked to the production of the orphan drug, in fact, are not significant *([10-20%]* of the total), despite the increase in compensation due to PCA for the purchase of the raw material, with respect to the previous supply agreement (see paragraphs 137 and 239 *above).* Furthermore, the costs associated with scientific information are practically negligible572. Nor is it believed that the pharmacovigilance activity of the orphan drug, which is also required for *Xenbilox®,* is particularly expensive as it pertains to a function that the dominant company already performed for the other products in its portfolio.

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[572] See doc. 110.3.

570. As regards, on the other hand, the direct costs associated with regulatory activities (market access, *marketing* and legal fees), which account for *[30-40%]* of the total, it is noted that, as clearly emerged in section V.4.1 *above,* they derive from activities that largely made up the strategy put in place by Leadiant to pursue its pricing policy and / or are linked precisely to the legal costs incurred in the various *antitrust* proceedings concerning this commercial policy. This means that a large part of the costs on the basis of which the dominant company believes it can justify the prices charged in Italy for the orphan drug relate to activities that represent the tools of the abuse currently challenged by Leadiant. Finally, indirect costs which account for more than 50% of the total cost (see paragraph 239 *above)* (administrative costs, overheads, personnel costs),
they represent charges that, at least in part, the dominant company would have incurred in any case.

571. Finally, it should be considered that the costs and risk that Leadiant claims to have faced in the context of the CDCA project were not considered by the EMA for the purpose of assigning the orphan designation. This is because the dominant company has presented its application on the basis of the criterion of prevalence (and of the significant beneficial effects), and not of the criterion of the return on investments (see paragraph 38 *above),* also because, as already stated, the quantification of the investments incurred was carried out *ex post* by the dominant undertaking in the context of the ACM's *antitrust* proceedings (see paragraph 209 *above).* There is, therefore, no element in the file that allows us to affirm that the prices requested by the dominant firm are necessary to remunerate the investments made and compensate for the risk faced, and that lower prices would decrease the incentive for innovation and the value of the orphan designation conferred by the EMA.

572. On the contrary, the documentation on file shows that, in the same analysis conducted by Leadiant in 2014, the incentive to undertake the investment was very significant even with a price lower than that actually applied. In the above analysis, in fact, Leadiant estimated a particularly high NPV even with a price of 5,000 euros per package. This means that Leadiant would have had the incentive to undertake the project even at a much lower price, which in any case would have allowed it to remunerate the costs and ensure the dominant company a profit margin, and to compensate for the risk incurred. In other words, Leadiant's excessive pricing cannot be justified by the need to stimulate the incentive to

undertake the registration project, offsetting the risk associated with this project, since, as Leadiant itself had estimated, even at a price of 5,000 euros, the project was already extremely profitable, i.e. the risk was, with this price, already largely plywood.

b.3 The added therapeutic value of the orphan drug

573. These investments, however, did not lead to the achievement of an added value from the therapeutic point of view compared to the therapies already existing on the Italian market (Xenbilox® and the magisterial preparations produced by the Pharmacy of the AOU Senese). This emerges clearly from several elements in the file.

574. There is indeed an identity relationship between the three drugs mentioned from a therapeutic point of view. This was first of all incisively confirmed by the hearing specialist, who stated that in his clinical experience, based on the administration in the last forty years before the masterful preparation produced by the Pharmacy of the AOU Senese, then of *Xenbilox*® and finally of the *CDCA Leadiant®,* there is no therapeutic difference between them (see par. 81 *above).*

575. Some documents in the file prove, moreover, that the dominant company itself was aware of the fact that the orphan drug did not have an added therapeutic value compared to *Xenbilox®:* in fact, Sigma Tau did not want to subject the orphan drug to the evaluation procedure of the added therapeutic value carried out by the competent German authorities in relation to newly introduced drugs on the market. And when the dominant firm explored the hypothesis of requesting the evaluation procedure, it was advised against doing so: according to the consultants the outcome of the evaluation procedure of the added therapeutic value was uncertain, given the absence of clinical studies. in support. Particularly indicative in this context is the fact that the consultants suggested to the dominant company to request the activation of the evaluation procedure only if it was convinced that it could demonstrate a significant added value that justified the prefigured price increase that it intended to apply for the orphan drug (see paragraphs 161-162 *above).*

576. In essence, therefore, the only difference between the orphan drug and pre-existing therapies is that the former is formally registered for the treatment of CTX. The added value deriving from the activity carried out by Leadiant consists, therefore, in having formalized the therapeutic indication with

which the drug had already been administered to patients with CTX for decades. In other words, this activity allowed the transition from an *off label* to an *on label treatment.*

577. In relation to the argument of the Party that considers it necessary to attribute adequate recognition of the value that the CDCA Project has brought to patients and to the NHS, thanks to the registration of the rare therapeutic indication, the following is observed.

578. According to AIFA, the registration of the orphan drug achieved through the CDCA Project was in itself socially useful, but it is not sufficient, neither in terms of the resources used nor the actual result achieved, to justify the prices requested by the dominant company for the sale of the orphan drug in Italy (see paragraph 198 *above),* since the registration of the orphan drug was based *"exclusively on retrospective studies and literature data" 573.*

579. In addition to the fact that the activity carried out by Leadiant was based in a significantly preponderant manner on activities other than innovation, it is also important to underline that the registration of the therapeutic indication, while entailing in itself undoubted benefits for patients, cannot in any case lead to the affirmation, as the Party does, that Leadiant would first formally demonstrate the efficacy and safety of the drug and its risk / benefit profile. On the contrary, given that, albeit for understandable reasons, it did not carry out prospective placebo-controlled studies, the efficacy and safety and risk / benefit profile of CDCA in the treatment of CTX is still scientifically not fully known. This is also what the expert consulted by the dominant company affirms, who stated
in his opinion that *"In fact, comprehensive evidence […] was not even established at the time the MA was granted" 574.* On the other hand, it would not be explained otherwise why the European Commission granted the marketing authorization for the orphan drug "in exceptional circumstances" (see par. 155 *above),* whereas most of the orphan drugs are authorized with a "full marketing authorization" " 575. The conditional release of the administrative title, in fact, is aimed precisely at monitoring the efficacy and safety of the drug over time, given that at the time of the granting of the AIC this had not been proven.

580. The evaluations of the Dutch Ministry of Health go in this same direction, which considered that the annual price of 160,000-220,000

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[573] See docs. 78.77 and 78.79, annex
[574] See doc. 138.4.13.
[575] See doc. 138.4.13.

euro, equal to 14,000-20,000 per package, proposed by Leadiant to health insurance companies in 2017 for the purchase of the orphan drug was disproportionate to the actual investment in innovation made in this case. The activities carried out by the dominant company for the purposes of registering the orphan drug were considered useful but not "revolutionary" from a therapeutic point of view (see paragraph 183 *above).*

581. This circumstance was expressed even more clearly by *the Commission de la transparence* of the *Haute Autorité de Santé,* which for the purpose of identifying the added therapeutic value of the *CDCA Leadiant®,* found that the data on efficacy efficacy presented by 'dominant company were very limited and not very robust, since they were based on the retrospective analysis of the medical records of some groups of patients treated with CDCA drugs with discordant results on the symptomatic clinical criteria, and that the data on the criteria of clinical morbidity and mortality and as well as comparative data were absent576. So much so that, as already illustrated, the *Commission* has established that the orphan drug has a low therapeutic value added and has not brought about any improvement or has brought about an insignificant improvement from the therapeutic point of view compared to the past, deserving of a price of reimbursement equal to 30% of the negotiated price, or *[4,000-5,000]* euro per package577.

582. It should be noted that the reimbursed price established by the French authorities has an order of magnitude similar to that which AIFA declared during the investigation to be the price that can be granted to the dominant company for the sale of the *CDCA Leadiant*® in the Italian market (or higher than the price of 3,400 / 3,600 euros per package paid by the ASL for the import of *Xenbilox*® between 2016 and 2017 by a maximum of 10%) (see paragraphs 116 and 217 *above).*

583. It should also be emphasized that the price levels identified by the two national regulators are also higher than those identified on the basis of the assessment expressed by the demand in 2008 and 2014 regarding the adequate remuneration to be attributed to the orphan drug. Market research conducted in 2008 indicated, in fact, that the price of the orphan drug was deemed

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576 See *https:// www.has-sante.fr/ jcms/ c_2865403/ fr/ chenodeoxycholic-acid-leadiant-acide chenodesoxycholique-medicament-a-base-d-acides-biliaires.*

577 V. *https:// www.has-sante.fr/ upload/ docs/ application/ pdf/ 2019-03 / chenodeoxycholic_acid_leadiant_11072018_ct16384_transcription.pdf; https: // www.has sante.fr/ jcms/ c_2865403/ fr/ chenodeoxycholic-acid-leadiant-acide-chenodesoxycholique-medicament-a base-d-acides-biliaires; http:// www.codage.ext.cnamts.fr/ codif/ bdm_it/ fiche/ index_fic_ucd.php? p_code_cip=9426887&p_site=AME*

THERE.

"Reasonable" was equal to 1,327 euros per package (see par. 102 *above).* Even market research commissioned by Leadiant in 2014 indicated, indeed, that in Italy the medical community and demand believed that the *"reasonable"* price for a registered CDCA-based drug for the treatment of CTX could be around 1,300-1,800. euro per package, or therefore a price in line with that already identified in 2008. Both the introduction price of the *CDCA Leadiant*® on the Italian market and the price subsequently negotiated with AIFA, therefore, are placed at levels significantly distant from the assessment that the demand of the drug had carried out.

584. Moreover, Leadiant was aware that the asking price went well beyond what could be considered an adequate economic remuneration for the activity carried out *("Sigma Tau want to increase the monthly treatment cost of Xenbilox® and have already introduced some price increases but there are some concerns regarding a potential back-lash from treating clinicians "578),* and his fears materialized in all their evidence when the drug was introduced on the domestic market at the *ex factory* price of € 15,506.93 per pack . The reaction of the treating doctors was, in fact, extremely negative, since the price of *Xenbilox*® had already been deemed inappropriate579. They have, indeed, defined the price as *"extremely onerous"* and *"inadmissible" 580* (cf. par. 139 *above).*

iv) The qualification of Leadiant's behavior as an abuse of a dominant position

585. In light of the foregoing, it is believed that Leadiant, by exploiting its dominant position in the domestic market for the production and sale of CDCA-based drugs for the treatment of CTX, has violated Article 102, lett. *a),* of the TFEU, through the imposition of unfair prices for the sale to the NHS of the orphan drug called *CDCA Leadiant®.*

586. This unlawful conduct was implemented through a complex and articulated strategy, of a commercial and regulatory nature, which also includes dilatory and obstructive behavior adopted towards AIFA when negotiating the price of the orphan drug.

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[578] See doc. 78.71.

[579] See doc. 78.124 *(("Given that all companies need t / o make money (no doubt on that), the x 1k increment is not perceived as" fair "toward the investments (retrospective study in Siena and production upgrade, that he wasn't even aware of) -A second increment with change to Leadiant will sound even more inappropriate ").*

[580] See docs. 22.7.68, 22.7.69, 28.2.121, 28.2.136, 28.2.140, 28.2.141, 28.2.189, 28.2.191, 78.89, 78.98, 78.122, 78.158, 78.213, 78.286, 78.347, 78.350, 78.367.

587. This abuse directly caused economic damage to the SSN, generated by the purchase of a drug at an unjustifiably heavy price. Leadiant defended itself on this point, stating that the drug *budget* is absolutely negligible and that, during the negotiation procedure, it committed itself with AIFA and with the ASLs to return any difference between the price charged pending the achievement of a agreement and the price that would subsequently be negotiated with the Agency. However, in this regard it is noted that this commitment is usual in the negotiations between pharmaceutical companies and AIFA and nothing says in relation to Leadiant's unwillingness to cause damage to the SSN, since the amount of the price differential to be repaid would depend on the level of the negotiated price.

588. It is noted, on the other hand, that the high excess obtained by Leadiant with respect to the economic value of the orphan drug, regardless of the limited *budget* of the same, had a direct effect on the limited resources of the NHS earmarked for pharmaceutical expenditure.

v) The imputability of the conduct to the companies of the Leadiant group

589. The documentation on the file gives an account of the existence of a complex strategy that has seen the involvement, in the various phases and in the various elements that compose it, of the companies belonging to the Leadiant group: Leadiant Biosciences Ltd., Leadiant GmbH, Sigma tau Arzneimittle GmbH in liquidation, Leadiant Biosciences SpA and the current parent company Essetifin SpA, and which allowed the carrying out of the abusive conduct under examination. For the purposes of assessing the subjective element of the offense, it is necessary to verify its attributability to the aforementioned companies.

590. In the first place, it emerges that the abusive conduct, consisting in the imposition of unjustifiably burdensome prices for the sale of the *CDCA Leadiant*® to the SSN, as part of the procedure for negotiating the price of this drug with AIFA, was placed in place by Leadiant Biosciences Ltd ..

591. The abusive conduct also appears attributable to the parent company Essetifin SpA, by virtue of the fact that the latter fully controls Leadiant Biosciences Ltd .. On the basis of a now constant jurisprudence, it is believed that *"the behavior of a subsidiary can be attributed to parent company if, despite having a distinct legal personality, this subsidiary does not independently determine its line of conduct on the market, but essentially complies with the instructions given to it*

by the parent company, in particular in consideration of the economic, organizational and legal constraints existing between the two legal entities "581. On this point, the jurisprudence has also established that *"the parent company and its subsidiary are part of the same economic unit and constitute a single company, and therefore fines may well be imposed on the parent company even without the need to demonstrate the personal involvement of the latter in the infringement "582.*

592. More specifically, *"in the particular case in which a parent company holds all or almost all of the capital of its subsidiary that has committed an infringement of the Union competition rules, there is a relative presumption according to which such the parent company actually exercises decisive influence over its subsidiary.* [...] *This presumption implies, except for its inversion, that the effective exercise of decisive influence by the parent company over its subsidiary is considered to be established and authorizes the Commission to hold the former responsible for the behavior of the latter, without having to provide additional tests "583.*

593. Ultimately, in application of the aforementioned principles regarding the attributability of anti-competitive conduct - with particular reference to the relative presumption of effective exercise of a decisive influence of the parent company over its subsidiary, deriving from the holding of the entire share capital - as well as in light of the factual evidence referred to, it is believed that the conduct described above must be attributed to Leadiant Biosciences Ltd. and the parent company Essetifin SpA.

YOU. INJURY TO INTRA-COMMUNITY TRADE

594. The contested conduct falls within the scope of EU competition law and, in particular, within the scope

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[581] See Corte Giust. EU, July 14, 1972, in case 48/69, *Imperial Chemical Industries v. Commission;* 16 November 2000, in case C-294/98 P, *Metsä-Serla and ac Commission;* 29 March 2011, in cases C 201/09 P and C-216/09 P, *ArcelorMittal Luxembourg v. Commission and Commission c. ArcelorMittal Luxembourg and others ;* November 26, 2013, in case C-50/12 P, *Kendrion v. Commission;* April 10, 2014, in the joined cases from C-231 / 11P to C-233/11 P, *Commission and ac Siemens Österreich and others;* 8 May 2014, in case C-414/12 P, *Bolloré v. Commission;* June 24, 2015, in cases C-293/13 P and C-294/13 P, *Fresh Del Monte Produce Inc. v. Commission;* April 27, 2017, in case C-516/15 P, *Akzo Nobel NV, Akzo Nobel Chemicals GmbH, Akzo Nobel Chemicals BV v. Commission.*

[582] V. TAR Lazio, 10 March 2016, sent. n. 3077, in case *I759 - Trenitalia supplies (Firema Trasporti SpA).*

[583] In particular, v. Court of Justice UE, *Akzo Nobel,* cit.

of article 102 of the TFEU, relating to the prohibition of abuse of a dominant position, being potentially capable of affecting intra-Community trade. Pursuant to the *Communication from the European Commission laying down the Guidelines the notion of effect on trade between Member States referred to in Articles 81 and 82 of the Treaty584,* the concept of effect on trade between Member States must be interpreted taking into account the direct or indirect, actual or potential, on trade flows between Member States.

595. Thus considered, the abuse in question concerns drugs distributed throughout the territory of the Italian Republic and, therefore, corresponding to a significant part of the European market. The abuse carried out by Leadiant is therefore suitable by its very nature to hinder the economic integration pursued by the European Union.

596. Therefore, on the basis of the foregoing, it is considered that this abuse is to be considered likely to affect trade between Member States and that the conduct attributable to the Party assumes relevance pursuant to Article 102 of the TFEU.

VII. SERIOUSNESS AND DURATION OF THE INFRINGEMENT

597. Article 15, paragraph 1, of law no. 287/90, provides that the Authority, in cases of serious infringements, taking into account their gravity and duration, shall order the application of a pecuniary administrative sanction of up to ten percent of the turnover achieved by the dominant company responsible for the infringement in the last year, considering the gravity and duration of the infringement itself.

598. According to consolidated European and national jurisprudence585, in order to assess the gravity of an infringement, various factors must be taken into account, the character and importance of which vary according to the type of infringement and its particular circumstances. Among these factors, the nature of the contested conduct is mainly relevant, as well as the context in which the infringements were carried out.

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584 Published in OJ C 101, 27.4.2004, p. 81–96.

585 *See, ex multis,* Council of State, judgments nos. 896 of 9 February 2011 and 5171 and 5172 of 16 September 2011, in relation to case I694 - *Price list of pasta;* Court of Justice, judgment of 15 July 1970, C-45/69, *Boehringer Mannheim GmbH v. Commission,* in Collection 1970, p. 769, paragraph 53. This last sentence was resumed and clarified by the Court of Justice in the judgment of 7 June 1983, joined cases C 100-103 / 80, *Musique Diffusion Francaise,* in Collected 1983, p. 1825, as well as in the judgment of 9 November 1983, C-322/81, *Michelin,* in Collezione 1983, p. 3461.

599. As for the nature of the conduct in question, it is noted that Leadiant has engaged in an abuse of exploitation of the limited resources of the National Health Service, consisting in the imposition of unjustifiably burdensome prices for the sale of *CDCA Leadiant*® to the SSN.

600. In relation to the context, it is noted that the imposition of an excessive price was achieved through an articulated strategy, knowingly planned and stubbornly pursued for a long time, which Leadiant used in negotiations to weaken AIFA, thus managing to obtain an extremely high and disproportionate reimbursement price compared to the costs incurred.

601. Leadiant Biosciences Ltd. is, moreover, an operator that has the legal and economic knowledge necessary to know the illegitimate nature of its conduct and the consequences that derive from it from the point of view of competition. In fact, it must be considered that, according to constant jurisprudence, for a conduct to be considered intentional, it is not necessary that the company carrying it out has been aware of transgressing these rules, but it is sufficient that it could not ignore the purpose of its own behavior586.

602. In the present case, not only Leadiant Biosciences Ltd. could not ignore the illegitimate nature of their conduct and the consequences deriving from it, but the investigation has shown that it has intentionally carried out its behavior.

603. In the present case, the fact that the imposition of unjustifiably burdensome prices concerned a drug with no therapeutic alternatives, intended for the treatment of an ultra-rare pathology and which leads to death, is also relevant.

604. The objective pursued by the dominant company was however fully achieved, given that Leadiant Bioscences Ltd., following the negotiation with AIFA, obtained and effectively applied a price that the analyzes carried out proved to be unjustifiably onerous. The conduct therefore produced concrete effects.

605. Considering the aforementioned circumstances, the abuse of a dominant position carried out by Leadiant Biosciences Ltd. must be considered very serious and the arguments put forward by the Party to demonstrate the non-seriousness of the conduct, which re-propose the defenses advanced to invoke

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[586] See Court of Justice of the EU 8 November 1983, IAZ point 35; EC Court 6 April 1995 case T-141/89, Trefileurope, paragraph 176 and 14 May 1998, case T310 / 94 Gruber Weber, paragraph 259; 12 July 2001, British Sugar, paragraph 127.

the fairness of the *CDCA Leadiant® price,* are not likely to revoke these conclusions.

606. With regard to the duration of the contested conduct - and in particular, the beginning of the latter - it can be traced back to June 15, 2017, or when Leadiant, with the presentation to AIFA of the request for reimbursement and classification of the *CDCA Leadiant*® at *ex factory* price of € 15,506.93 per pack, thanks to a preparatory strategy for abuse conceived long before and stubbornly pursued, it was able to negotiate and apply an unjustifiably heavy price.

607. The infringement is still ongoing. In fact, the *ex factory* price negotiated with AIFA in December 2019, retroactively applied from 15 June 2017 to date, for the reimbursement of the *CDCA Leadiant*® by the SSN, equal to *[5,000-7,000]* euros per package, is unjustifiably burdensome on the basis of the preliminary investigation carried out.

VIII. QUANTIFICATION OF THE SANCTION

608. Once the seriousness and duration of the infringements committed by Leadiant Biosciences Ltd. have been ascertained, for the purposes of identifying the quantification criteria, it is necessary to keep in mind the provisions of article 11 of law no. 689/1981, as referred to in article 31 of law no. 287/90, as well as the interpretative criteria set out in the *"Guidelines on the methods of application of the criteria for quantifying administrative pecuniary sanctions imposed by the Authority in application of article 15, paragraph 1, of law no. 287/90 " (hereinafter,* the" Guidelines "), approved by the Authority on 22 October 2014.

609. As regards the relevant turnover for the purposes of the sanction, the Authority's Guidelines on sanctions provide that the sanctions *"must be calculated starting from the value of the sales of goods or services that are the object, directly or indirectly, of the infringement, by the company in the relevant market (s) in the last full year of participation in the same infringement (hereinafter, value of sales) " (points* 8 and 9). In the present case, this value consists of the value of sales made by Leadiant in Italy for the drug *CDCA Leadiant*® in the year 2021, equal to *[2-3 million]* euros.

610. For the purposes of determining the basic amount of the penalty, a percentage determined on the basis of the seriousness of the infringement is applied to the value of sales as determined above, for which reference is made in full to what is represented in section VII. According to the Guidelines, in particular,

this percentage must be set at a level that can reach 30% of the value of the sales, *"according to the degree of seriousness of the violation" (point* 11).

611. Pursuant to point 14 of the Guidelines and the criteria set out therein, and on the basis of what is stated in par. 599-605 *above* about the seriousness of the case, the percentage of the sanctioning base amount must be placed at *[20-25%]* of the value of sales made by Leadiant in Italy for the drug *CDCA Leadiant*® in the year 2021. The result is a amount equal to *[500,000-600,000]* EUR.

612. The amount thus obtained must be multiplied by the duration of the infringement. In the present case, on the basis of what is stated *above* in par. 606-607, this turns out to be equal to 4 years, 11 months and 2 days. Therefore, the basic amount was calculated using “4.922222” as a multiplying factor of the amount referred to in par. 611 *above,* resulting in an amount of *EUR [2-3 million] .*

613. In order to give the Authority the necessary character of effective deterrence to the sanctioning power of Guide, insert an additional amount of *[20-25%]* into the basic amount

the value of the sales of the goods or services subject to the infringement (so-called *entry fee),* or equal to *[600,000-700,000]* euros. Specifically, it is believed that this additional amount is justified precisely in consideration of the particular gravity of the infringement committed by Leadiant, given the ascertained pre-ordination of the conduct (see sections V.4 and V.5.1. Above) and the nature life of the drug (see par. 478 *above).*

614. In the present case, the amount of the sanction, as determined up to now, should be increased pursuant to point 25 of the Guidelines, in consideration of the fact that the company responsible for the infringement carried out in the last financial year previously closed upon notification of the formal notice, a particularly high total worldwide turnover compared to the value of the sales of the goods or services subject to the infringement.

615. However, in consideration of the fact that the actual specific deterrence is, in the present case, also guaranteed by the procedural initiatives taken by the other national competition authorities pursuant to art. 102, lett. *a),* TFEU against Leadiant (see paragraph 14 *above),* and the opportunity for coordination on the sanctioning level between the prosecuting authorities which ensures that the set of sanctions imposed is

proportional to the seriousness of the offenses committed, it is deemed not to apply the aforementioned increase in the sanction, even if the case in question falls among those worthy of such increase.

616. In light of all this, the final amount of the fine is set at 3,501,020 euros, which, thus determined, does not exceed the maximum edictal, referred to in article 15, paragraph 1, of ln 287/1990.

617. Lastly, it is believed that, pursuant to point 32 of the Guidelines, which provides that "[n] in the *event that more than one company belonging to the same group took part in the infringement, the Authority may impose the sanction in solidarity with these companies ",* and given the attribution of the violation committed by Leadiant Biosciences Ltd. also to Essetifin SpA, by virtue of the control relationship between them, these companies are jointly and severally liable for the payment of the fine as calculated above.

All this having been stated and considered;

RESOLVES

a) that Leadiant Biosciences Ltd. and Essetifin SpA have imposed unjustifiably heavy prices for the sale to the NHS *of Leadiant® Chenodeoxycholic acid,* used for the treatment of the rare disease called cerebrotendinous xanthomatosis, in violation of article 102 of the Treaty on Operation of European Union;

b) that the companies Leadiant Biosciences Ltd. and Essetifin SpA put in place all obligations aimed at defining prices that are not unjustifiably burdensome with reference *to the Chenodeoxycholic acid Leadiant®* and refrain in the future from engaging in conduct similar to those covered by the infringement ascertained in point a);

c) that Leadiant Biosciences Ltd. and Essetifin SpA within sixty days from the notification of this provision notify the Authority of the initiatives taken to comply with the requirements of the previous letter b), by sending a specific written report;

d) to impose, jointly and severally, the companies Leadiant Biosciences Ltd. and Essetifin SpA a total administrative fine equal to 3,501,020.13 (three million five hundred one million / 13).

For professionals having their registered office in Italy, the administrative sanction imposed must be paid within ninety days from the notification of this provision, using the tax codes indicated in the attachment model F24 with identification elements, as per Legislative Decree no. 241/1997. Payment must be made electronically by debiting your bank or postal current account, through the *home-banking and* CBI services made available by banks or Poste Italiane SpA, or by using the electronic services of the Revenue Agency, available on the website . *www.agenziaentrate.gov.it.*

Pursuant to article 37, paragraph 49, of decree-law no. 223/2006, subjects with a VAT number are obliged to submit the F24 form electronically.

For professionals having their registered office in a foreign country, the administrative sanction imposed must be paid within ninety days, by bank transfer (in euros) in favor of the State Budget, using the IBAN code IT04A0100003245348018359214 (BIC code: BITAITRRENT), which corresponds to the accounting triad 18/3592/14.

After the aforementioned deadline, for the delay period of less than one semester, interest on arrears must be paid at the legal rate starting from the day following the expiry of the payment deadline and up to the date of payment. In case of further delay in compliance, pursuant to article 27, paragraph 6, of law no. 689/81, the sum due for the sanction imposed is increased by one tenth for each semester starting from the day following the expiry of the payment deadline and up to the day in which the role is transmitted to the concessionaire for collection; in this case the increase absorbs the default interest accrued in the same period.
The Authority must be immediately notified of the payments made by sending a copy of the form certifying the payment made.

Pursuant to article 26 of the same law, companies that find themselves in difficult economic conditions can request payment in installments of the sanction.

This provision will be notified to the interested parties and published in the Bulletin of the Antitrust Authority.

An appeal may be filed against this provision to the Lazio Regional Administrative Court, pursuant to Article 135, paragraph 1, letter b), of the Administrative Process Code (Legislative Decree No. 104 of 2 July 2010), within sixty days from the date of notification of the provision itself, without prejudice to the greater terms referred to in article 41, paragraph 5, of the Code of the administrative process, or an extraordinary appeal may be lodged with the President of the Republic, pursuant to article 8 of the Decree of the President of the Republic 24 November 1971, n. 1199, within the term of one hundred and twenty days from the date of notification of the provision itself.

THE SECRETARY GENERAL
Guido Stazi

THE PRESIDENT *acting*
Michele Ainis