

JUDGMENT OF THE GENERAL COURT (Fifth Chamber)

23 September 2026 [\(*\)](#)(1)

(Public health – Medicinal products for human use – Orphan medicinal product for human use Ocaliva – obeticholic acid – Revocation of the conditional marketing authorisation – Procedure for review – Procedure initiated without awaiting the outcome of the renewal procedure – Consultation of an ad-hoc expert group by the EMA's Committee for Medicinal Products for Human Use – Impartiality of the experts consulted – Declaration of a conflict of interest – Procedural defect – Principle of sound administration – Article 116 of Directive 2001/83/EC, as amended by Directive 2004/27/EC – Manifest errors of assessment – Legitimate expectations – Proportionality – Article 57 of Regulation (EC) No 726/2004 as amended by Regulation (EU) 2019/5)

In Case T-455/24,

Advanz Pharma Ltd, established in Dublin (Ireland), represented by M. Meulenbelt, B. Baum, A. Vermulst and A. Robert, lawyers,

applicant,

supported by

CBP Portugal, established in Pousos Leiria (Portugal), represented by A. Souto Moura, P. Marques Bom, M. Maló Hipólito, M. Fernandes Cerejo and J. Silveira Botelho, lawyers,

intervener,

v

European Commission, represented by R. Lindenthal, E. Mathieu and A. Spina, acting as Agents,

defendant,

supported by

European Medicines Agency (EMA), represented by G. Gavriilidou, H. Kerr, M. van Egmond and G. Ramo, acting as Agents,

intervener,

THE GENERAL COURT (Fifth Chamber),

composed of M. Sampol Pucurull, President, J. Laitenberger (Rapporteur) and W. Valasidis, Judges,

Registrar: A. Marghelis, Administrator,

having regard to the order of 26 November 2024, *Advanz Pharma v Commission* (T-455/24 R, not published, EU:T:2024:863),

having regard to the written part of the procedure, in particular:

- the orders of 14 March 2025 granting CBP Portugal and the EMA leave to intervene in support of the applicant and the Commission, respectively;
- the request for the adoption of a measure of inquiry, submitted by the applicant on 3 March 2025 and amended in the context of its observations on the statement in intervention submitted by the EMA, seeking an order from the General Court for the production of two documents,
- the request for examination of a witness, submitted by the applicant on 3 July 2025,
- the measure of organisation of procedure of 12 November 2025 and the replies of the Commission, the EMA and CBP Portugal, lodged at the Court Registry on 27 and 28 November 2025, respectively,

further to the hearing on 15 January 2026,

gives the following

Judgment

- 1 By its action under Article 263 TFEU, the applicant, Advanz Pharma Ltd, seeks the annulment of Commission Implementing Decision C(2024) 6281 final of 30 August 2024 ('the contested decision') revoking, under Article 20 of Regulation (EC) No 726/2004 of the European Parliament and of the Council, the conditional marketing authorisation granted by Decision C(2016) 8685 final for 'Ocaliva – obeticholic acid', an orphan medicinal product for human use.

Legal framework

- 2 Point 28 of Article 1 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ 2001 L 311, p. 67), as amended by Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 (OJ 2004 L 136, p. 34), defines 'risks related to use of the medicinal product' as 'any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health' and 'any risk of undesirable effects on the environment.'
- 3 Point 28a of Article 1 of Directive 2001/83, as amended by Directive 2004/27, defines the concept of a 'risk-benefit balance' as 'an evaluation of the positive therapeutic effects of

the medicinal product in relation to the risks as defined in point 28, first indent.'

- 4 The first paragraph of Article 116 of Directive 2001/83, as amended by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (OJ 2010 L 348, p. 74), provides:

'The competent authorities shall suspend, revoke or vary a marketing authorisation if the view is taken that the medicinal product is harmful or that it lacks therapeutic efficacy, or that the risk-benefit balance is not favourable, or that its qualitative and quantitative composition is not as declared. Therapeutic efficacy is lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.'

- 5 The first paragraph of Article 2 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ 2004 L 136, p. 1), as amended by Regulation (EU) 2019/5 of the European Parliament and of the Council of 11 December 2018 (OJ 2019 L 4, p. 24), provides:

'The definitions laid down in Article 1 of Directive [2001/83] shall apply for the purposes of this Regulation. ... '

- 6 Article 14-a of Regulation No 726/2004, as amended by Regulation No 2019/5, provides:

'1. In duly justified cases, to meet unmet medical needs of patients, a marketing authorisation may, for medicinal products intended for the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, be granted prior to the submission of comprehensive clinical data provided that the benefit of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. ...

...

3. Marketing authorisations may be granted pursuant to this Article only if the risk-benefit balance of the medicinal product is favourable and the applicant is likely to be able to provide comprehensive data.

4. Marketing authorisations granted pursuant to this Article shall be subject to specific obligations. Those specific obligations and, where appropriate, the time limit for compliance shall be specified in the conditions to the marketing authorisation. Those specific obligations shall be reviewed annually by the [European Medicines] Agency.

5. As part of the specific obligations referred to in paragraph 4, the holder of a marketing authorisation granted pursuant to this Article shall be required to complete ongoing studies, or to conduct new studies, with a view to confirming that the risk-benefit balance is favourable.

...'

- 7 Article 20 of Regulation No 726/2004, as amended by Regulation 2019/5, states:

'1. Where the supervisory authorities or the competent authorities of any other Member State are of the opinion that the manufacturer or importer established within the Union territory is no longer fulfilling the obligations laid down in Title IV of [Directive 2001/83], they shall forthwith inform the Committee for Medicinal Products for Human Use and the Commission, stating their reasons in detail and indicating the course of action proposed.

The same shall apply where a Member State or the Commission considers that one of the measures envisaged in Titles IX and XI of Directive [2001/83] should be applied in respect of the medicinal product concerned or where the said Committee has delivered an opinion to that effect in accordance with Article 5 of this Regulation.

2. The Commission shall request the opinion of the [European Medicines] Agency within a time limit which it shall determine in the light of the urgency of the matter, in order to examine the reasons advanced. Whenever practicable, the holder of the authorisation for placing the medicinal product for human use on the market shall be invited to provide oral or written explanations.

...'

- 8 The first subparagraph of Article 57(1) of Regulation No 726/2004, as amended by Regulation No 2019/5, is worded as follows:

'The [European Medicines] Agency shall provide the Member States and the institutions of the Union with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human use or veterinary medicinal products which is referred to it in accordance with the Union legislation relating to medicinal products for human use or veterinary medicinal products.'

- 9 Article 63(2) of Regulation No 726/2004 provides:

'Members of the Management Board, members of the committees, rapporteurs and experts shall not have financial or other interests in the pharmaceutical industry which could affect their impartiality. They shall undertake to act in the public interest and in an independent manner, and shall make an annual declaration of their financial interests. All indirect interests which could relate to this industry shall be entered in a register held by the [European Medicines] Agency which is accessible to the public, on request, at the [European Medicines] Agency's offices.

The [European Medicines] Agency's code of conduct shall provide for the implementation of this Article with particular reference to the acceptance of gifts.

Members of the Management Board, members of the committees, rapporteurs and experts who participate in meetings or working groups of the [European Medicines] Agency shall declare, at each meeting, any specific interests which could be considered to be prejudicial to their independence with respect to the items on the agenda. These declarations shall be made available to the public.'

10 The recitals of Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation No 726/2004 of the European Parliament and of the Council (OJ 2006 L 92, p. 6) state:

- '(1) Before a medicinal product for human use is authorised for placing on the market of one or more Member States, it generally has to undergo extensive studies to ensure that it is safe, of high quality and effective for use in the target population. ...
- (2) In the case of certain categories of medicinal products, however, in order to meet unmet medical needs of patients and in the interests of public health, it may be necessary to grant marketing authorisations on the basis of less complete data than is normally the case and subject to specific obligations, hereinafter "conditional marketing authorisations". ...
- (3) Although the data upon which an opinion on a conditional marketing authorisation [are] based may be less complete, the risk-benefit balance, as defined in Article 1(28a) of Directive [2001/83] should be positive. Furthermore, the benefits to public health of making the medicinal product concerned immediately available on the market should outweigh the risk inherent in the fact that additional data are still required.

...

- (5) In order to ensure that the right balance is struck between facilitating access to medicines for patients with unmet medical needs and preventing the authorisation of medicines with an unfavourable risk-benefit profile, it is necessary to make those marketing authorisations subject to specific obligations. The holder should be required to complete or initiate certain studies with a view to confirming that the risk-benefit balance is positive and resolving any questions relating to the quality, safety and efficacy of the product.
- (6) Conditional marketing authorisations are distinct from marketing authorisations granted in exceptional circumstances in accordance with Article 14(8) of Regulation [No 726/2004]. In the case of the conditional marketing authorisation, authorisation is granted before all data are available. The authorisation is not intended, however, to remain conditional indefinitely. Rather, once the missing data are provided, it should be possible to replace it with a marketing authorisation which is not conditional, that is to say, which is not subject to specific obligations. In contrast, it

will normally never be possible to assemble a full dossier in respect of a marketing authorisation granted in exceptional circumstances.

...

(8) Since the provisions of Regulation [No 726/2004] apply to conditional marketing authorisations unless otherwise provided for in this Regulation, the procedure for evaluating a conditional marketing authorisation is the normal procedure laid down in Regulation [No 726/2004].

(9) In accordance with Regulation [No 726/2004], conditional marketing authorisations will be valid for one year on a renewable basis. The deadline for submission of a renewal application should be six months prior to the expiry of the marketing authorisation, and the opinion of the [European Medicines Agency] on the application should be adopted within 90 days of its receipt. To ensure that medicinal products are not removed from the market except for reasons related to public health, the conditional marketing authorisation should, as long as a renewal application is submitted within the deadline, remain valid until the Commission reaches a decision based on the renewal assessment procedure.

...

(11) Enhanced pharmacovigilance for medicinal products granted a conditional marketing authorisation is important and is already adequately provided for in Directive [2001/83] and Regulation [No 726/2004]. However, the time schedule for submitting periodic safety update reports should be adapted to accommodate the annual renewal of conditional marketing authorisations.'

11 Article 1 of Regulation No 507/2006 provides:

'This Regulation lays down rules on the granting of a marketing authorisation subject to specific obligations in accordance with Article 14(7) of Regulation [No 726/2004], hereinafter "conditional marketing authorisation".'

12 Article 2 of Regulation No 507/2006 states:

'This Regulation shall apply to medicinal products for human use that fall under Article 3(1) and (2) of Regulation [No 726/2004] and belong to one of the following categories: ...

13 Article 4 of Regulation No 507/2006, entitled 'Requirements', provides in paragraph 1:

'A conditional marketing authorisation may be granted where the Committee finds that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all the following requirements are met:

- (a) the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive [2001/83], is positive; ...'

14 Article 5(1) of Regulation No 507/2006 is worded as follows:

'By way of specific obligations, the holder of a conditional marketing authorisation shall be required to complete ongoing studies, or to conduct new studies, with a view to confirming that the risk-benefit balance is positive and providing the additional data referred to in Article 4(1).

In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.'

15 Under Article 6 of Regulation No 507/2006:

'1. After its period of validity of one year the conditional marketing authorisation may be renewed annually.

2. The application for renewal shall be submitted to the [European Medicines Agency] at least six months before the expiry of the conditional marketing authorisation, together with an interim report on the fulfilment of the specific obligations to which it is subject.

3. The Committee [for Medicinal Products for Human Use] shall assess the application for a renewal, on the basis that the risk-benefit balance is to be confirmed, taking into account the specific obligations contained in the authorisation and the timeframe for their fulfilment, and shall formulate an opinion as to whether the specific obligations or their timeframes need to be retained or modified. ...

4. Once a renewal application has been submitted in accordance with paragraph 2, the conditional marketing authorisation shall remain valid until a decision is adopted by the Commission in accordance with Article 10 of Regulation [No 726/2004].'

16 Under section 2.3.2 of the Code of Conduct of the European Medicines Agency (EMA) in its version of 16 June 2016 (EMA/385894/2012 rev. 1) ('the EMA Code of Conduct'), referred to in the third subparagraph of Article 63(2) of Regulation No 726/2004:

'The definition of what is an interest is set out in the specific EMA policies ...'

17 Under section 2.3.3 of the EMA Code of Conduct:

'For members of the Management Board or Scientific Committees, rapporteurs and experts as well as EMA staff involvement in the [EMA]'s activities is subject to the availability of a signed declaration of interests form and an assessment of the declared interests.

The restrictions that will apply in terms of the individual's activities in the context of the EMA's role and responsibilities will depend on the specific individual's competing interest

and their particular role. The details of the relevant restrictions are set out in the EMA policy documents.’

18 Section 2.4.4 of the EMA Code of Conduct provides:

‘The EMA Secretariat, under the direct responsibility of the Head of Division concerned, undertakes the following:

- Remind all parties concerned of their obligation to declare their interests;
- Assess and monitor regularly declarations and make preliminary appraisal of compatibility of interests declared with general or specific office or duties of the individuals concerned ...’

19 Under Section 2.4.5 of the EMA Code of Conduct:

‘Members of the Management Board and Scientific Committees, rapporteurs and experts ... and [EMA] staff members ... have a primary obligation to disclose at any time the existence of possible competing interests that may place the impartiality of EMA at risk. The individual should state, in particular, the type and nature of interests, specifying whether they are general or relate to a specific activity, e.g. a product, tender, recruitment etc. Failure to fill in the declaration of interests in a complete and/or correct manner may be considered as a prima facie breach of trust towards the EMA. In the case of Scientific Committee members, rapporteurs and experts, it may lead to the exclusion of the concerned person from EMA activities and to the initiation of the Breach of Trust procedure.

...’

20 Section 2.4.6 of the EMA Code of Conduct provides:

‘... On the basis of the type and nature of interests noted, chairpersons and EMA secretariat shall apply the EMA policies in place.’

21 Point 3.2.2.1 of the document entitled ‘EMA policy on the handling of competing interests of scientific committees’ members and experts’ in its version of 1 January 2023 (‘the policy on competing interests’) defines the concept of ‘strategic advisory role for a pharmaceutical company’ as ‘any activity where the expert is participating (with a right to vote/influence the outputs) in a(n) (scientific) advisory board, steering committee or executive committee with the role of providing advice/expressing opinions on the (future) strategy, direction and development activities of a pharmaceutical company ..., either in terms of general strategy or product related strategy, regardless of contractual arrangements or any form of remuneration.’

22 Point 3.2.3 of the policy on competing interests defines the concept of ‘rival product for a medicinal product’ as a ‘medicinal product that targets a similar patient population with

the same clinical objective (i.e. to treat, prevent or diagnose a particular condition), and constituting a potential commercial competition.'

23 Point 4.2.2 of the policy on competing interests states:

'The following should enable the establishment of an efficient process:

- as regards the handling of competing interests a [two-step] procedure applies: following receipt of the [declaration of interests,] an interest level is automatically assigned according to the aforementioned interest levels. Subsequently the level of participation in the [EMA]'s activities is determined by the [EMA] secretariat taking into account the assigned interest level and the restrictions which apply to participation in the various activities of the [EMA].
- For scientific committees' and the [EMA]'s other bodies' members a proactive approach is applied as regards the possible identification of the need for restrictions in involvement in the [EMA]'s activities through mandatory pre-screening by the [EMA] of the declared interests prior to any formal nomination by the Nominating Authority ...'

24 Point 4.3.2 of the policy on competing interests provides:

'All scientific committees' and the [EMA]'s other bodies' members and experts must be included in the [EMA]'s Experts Management tool prior to the first appointment resulting in involvement in activities at the level of the [EMA] (meeting attendance, scientific evaluation, inspections, guidance development, etc.) ...'

The Nominating Authority has to ensure, in close collaboration with the nominated member/expert, that all relevant information necessary for the [EMA]'s review has been made available prior to the member's/expert's involvement in any activity of the [EMA].

The [EMA] undertakes the inclusion in the [Experts Management] tool for individual patients and healthcare professionals, for patients and healthcare professionals organisations' representatives and for other experts not covered by nominations by the Member States but identified by the [EMA].

...'

25 Annex I to the policy on competing interests contains a table which specifies, for each type of involvement in the evaluation of pharmaceutical products in the context of procedures before the EMA, the restrictions that apply depending on the nature of the declared interest and the period during which that interest existed.

26 As regards experts who have declared a current interest as a strategic adviser for a pharmaceutical company, the table in Annex I to the policy on competing interests draws a distinction between, on the one hand, the situation where that interest consists of providing strategic advice which is general or covers several medicinal products and, on

the other hand, the situation where that interest consists of providing strategic advice concerning an individual medicinal product. In the first case, any involvement in an ad hoc expert group ('AHEG') is prohibited, whereas, in the second case, the possibility of being a member of an AHEG is prohibited only in relation to procedures concerning that specific medicinal product.

- 27 As regards experts who have declared a past interest as a strategic adviser for a pharmaceutical company in the preceding zero to three years, the table in Annex I to the policy on competing interests draws a distinction between, on the one hand, the situation where that interest consists of providing strategic advice which is general or covers several medicinal products and, on the other hand, the situation where that interest consists of providing strategic advice concerning an individual medicinal product. In the first case, involvement in an AHEG is restricted, as regards the relevant medicinal products of the undertaking, to involvement in discussions, whereas involvement in deliberations and votes is prohibited. In the second case, the possibility of being a member of an AHEG is restricted, as regards that individual medicinal product, to involvement in discussions, whereas involvement in deliberations and votes in procedures relating to that medicinal product is prohibited.

Background to the dispute

- 28 The applicant is a pharmaceutical company established in Ireland.
- 29 On 16 December 2022, the applicant was transferred ownership of a conditional marketing authorisation ('MA') for the orphan medicinal product for human use Ocaliva – obeticholic acid ('Ocaliva'), initially granted by Commission Implementing Decision C(2016) 8685 final of 12 December 2016 granting a conditional MA under Regulation No 726/2004 for Ocaliva. That conditional MA was renewed annually from 2016 to 2023.
- 30 Ocaliva, the active substance of which is obeticholic acid, is a medicinal product indicated for the treatment of patients with a liver disease, primary biliary cholangitis ('PBC'), who do not tolerate or respond well to ursodeoxycholic acid ('UDCA').
- 31 According to Section E of Annex II to Implementing Decision C(2016) 8685 final, the holder of the conditional MA had to complete two clinical studies as a specific obligation, in accordance with Article 14(7) of Regulation No 726/2004 in the version applicable at that time. The first study, namely study 747-302, aimed to analyse the clinical benefit associated with Ocaliva treatment for PBC patients who are either unresponsive or intolerant to UDCA treatment based on clinical endpoints. The second study, namely study 747-401, had as its objective an analysis of the efficacy, safety and pharmacokinetics of that medicinal product in PBC patients with moderate to severe hepatic impairment, which was intended to address the uncertainties relating to the lack of data in a population with a more advanced stage of the disease. The final reports on those studies were due to be submitted by 2023 at the latest.

- 32 In December 2022, the applicant submitted an application to convert the conditional MA for Ocaliva into a standard MA, in accordance with the rules of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ 2008 L 334, p. 7).
- 33 In the course of that procedure, the EMA's Committee for Medicinal Products for Human Use ('the CHMP') concluded that study 747-302 had failed to demonstrate the clinical benefit of Ocaliva and, therefore, it issued an opinion on 12 October 2023 recommending the refusal of the variation.
- 34 On the same day, the European Commission initiated a procedure for review of the conditional MA for Ocaliva, by submitting an application to the CHMP, inter alia, to assess the impact of that information on the risk-benefit balance of that medicinal product and to 'give its opinion by June 2024 on whether the [conditional MA] for [that medicinal product] should be maintained, varied, suspended or revoked'.
- 35 On 21 May 2024, the applicant submitted an application for renewal of the conditional MA for Ocaliva, in accordance with Article 6 of Regulation No 507/2006 ('the renewal procedure').
- 36 In the course of the procedure for review of the conditional MA for Ocaliva, the CHMP consulted, on various points, an AHEG composed of gastroenterologists and hepatologists, including patient representatives, which convened on 12 June 2024.
- 37 Following the assessment conducted under the procedure for review of the conditional MA for Ocaliva, the CHMP concluded, in its opinion of 27 June 2024, that the therapeutic efficacy of the orphan medicinal product had not been established and that the risk-benefit balance was not favourable. Consequently, it was of the opinion, by consensus, that that conditional MA should be revoked. The revised and final versions of that opinion and of the assessment report of that committee, which contains a scientific discussion and a section on the risk-benefit balance of that medicinal product and the reasoned recommendation for that revocation, were adopted on 29 July 2024.
- 38 A few days earlier, by email of 23 July 2024, the EMA had confirmed to the applicant that the renewal procedure had been initiated following its valid application and communicated a timetable for that procedure resulting in an opinion of the CHMP on the renewal by 19 September 2024.
- 39 By letter of 7 August 2024, the Commission informed the applicant that, in view of the developments in the procedure for review of the conditional MA for Ocaliva, the procedure for renewal of that conditional MA had become devoid of purpose and would not be resumed.
- 40 On 20 and 22 August 2024, the EMA responded to the applicant's request for access to the file.

- 41 On 30 August 2024, the Commission adopted the contested decision, relying on the conclusions and recommendation of the CHMP in its opinion of 29 July 2024, which was issued in the procedure for review of the conditional MA for Ocaliva.

Events subsequent to the bringing of the action

- 42 From 30 September 2024, the applicant submitted three further requests to the EMA for access to various documents. The EMA responded to those requests.
- 43 On 12 December 2024, the EMA adopted a new version of its policy on the handling of competing interests of scientific committees' members and experts (EMA/54457/2024).

Forms of order sought

- 44 The applicant, supported by CBP Portugal, claims that the Court should:
- annul the contested decision;
 - order the Commission to pay the costs.
- 45 The Commission contends that the Court should:
- dismiss the action;
 - order the applicant to bear its own costs and pay those incurred by the Commission;
 - order CBP Portugal to pay the costs relating to its intervention.
- 46 The EMA contends that the Court should:
- dismiss the action;
 - order the applicant to pay the costs.

Law

- 47 In its application, the applicant puts forward five pleas in law alleging, first, infringement of the right to an effective remedy guaranteed by Article 47 of the Charter of Fundamental Rights of the European Union ('the Charter') and an infringement of Article 6(4) of Regulation No 507/2006, second, infringement of the right to sound administration under Article 41 of the Charter, third, infringement of the last sentence of the first paragraph of Article 116 of Directive 2001/83, as amended, and, in essence, a manifest error of assessment, fourth, in essence, a manifest error of assessment and, fifth, a breach of the principles of proportionality and the protection of legitimate expectations, and of Article 57 of Regulation No 726/2004, as amended by Regulation 2019/5.

48 As a preliminary point, it should be noted that, in its reply, the applicant withdrew the first part of the first plea raised in the application, in which it claimed that the contested decision had infringed its right to an effective remedy, as guaranteed by Article 47 of the Charter. Therefore, it is no longer necessary to rule on the first part of the first plea.

49 In addition, the Court considers it appropriate to examine first of all the second plea and then the first, third, fourth and fifth pleas.

The second plea, alleging infringement of the right to sound administration under Article 41 of the Charter

50 The present plea, alleging infringement of the right to sound administration under Article 41 of the Charter, which should be examined first, concerns the composition and procedure of the AHEG created by the EMA in the procedure for review of the conditional MA for Ocaliva. The plea is divided into three parts.

51 The first part alleges irregularities relating to the involvement of Expert A in the AHEG under Article 63(2) of Regulation No 726/2004 and the EMA rules implementing it. The applicant, supported by CBP Portugal, raises, in essence, four complaints, relating, first, to a lack of expertise on the part of that expert, secondly, to a situation in which the expert finds himself in a conflict of interest, thirdly, to a breach of that expert's obligations in the light of section 2.4.5 of the EMA Code of Conduct and, fourthly, to omissions on the part of the EMA.

52 The second part alleges irregularities relating to the involvement of Expert B in the AHEG under Article 63(2) of Regulation No 726/2004 and the EMA rules implementing it.

53 The third part alleges a lack of expertise and preparation time for AHEG members.

54 In its observations on the EMA's statement in intervention, the applicant suggests that some of the irregularities on which it relies in the present plea also constitute an infringement of Article 57(1) of Regulation No 507/2006.

55 The Commission, supported by the EMA, disputes the applicant's line of argument.

The second complaint in the first part and the second part

56 In the second complaint in the first part of the second plea, the applicant claims that Expert A had a current interest when he attended the AHEG meeting of 12 June 2024 relating to elafibranor, a medicinal product produced by the 'Institut Produit Synthèse (IPSEN) AB' ('IPSEN').

57 According to the applicant, in accordance with the policy on competing interests and the right to sound administration, provided for in Article 41 of the Charter, the current interest which Expert A had when he participated in the AHEG meeting of 12 June 2024 should have led to his exclusion, as an expert, from the AHEG in order to exclude any legitimate doubt as to his impartiality, for two reasons. First, elafibranor is a rival

medicinal product to Ocaliva with the same clinical objective, namely the treatment of PBC. Secondly, that meeting also covered elafibranor and another rival product, as is apparent from a slide in the presentation of the CHMP rapporteur provided as Annex A.24 to the application.

58 It follows from Expert A's declaration of a conflict of interest ('eDoI') that he participated as a strategic adviser in a meeting organised by IPSEN on 7 and 8 December 2023, which concerned the 'treatment of patients with [PBC]'. In view of the fact that, on the first day of that meeting, IPSEN issued a press release on elafibranor, which is the only medicinal product produced by IPSEN for the treatment of PBC and in the light of the subject of that meeting, there is no reasonable doubt that the meeting in question could not qualify as 'cross product related/general (non-product related)' as indicated in that eDoI, but concerned 'one or more products within one or more therapeutic areas', including elafibranor and 'likely' Ocaliva. The only plausible reason to organise such a meeting was to prepare for the marketing of elafibranor.

59 The applicant submits that Expert A's interest at the time of his participation in the AHEG meeting of 12 June 2024 was not a past interest, but a current one, and that the Commission has failed, in particular, to provide any evidence in support of the assumption that that expert, following the meeting organised by IPSEN on 7 and 8 December 2023, no longer had any professional relationship with IPSEN.

60 The applicant adds, in its observations on the statement in intervention submitted by the EMA, that, even if the interest which Expert A had when he participated in the AHEG meeting of 12 June 2024 was a past interest and was non-product related within the meaning of the policy on competing interests, that interest should nevertheless have resulted in the exclusion of that expert in accordance with a new, stricter EMA policy on the matter, adopted on 12 December 2024.

61 In the second part of the second plea, the applicant argues that Expert B had demonstrated prejudice, and thus subjective bias, against Ocaliva. More specifically, the applicant states that, on 27 June 2024, that expert, as coordinator of the European Reference Network on rare hepatological diseases, submitted a draft communication to the EMA, which was due to be published immediately after the publication of the EMA recommendation in the context of the review procedure relating to that medicinal product, representing the views of that network on that subject. The EMA considered that that draft communication was too negative with regard to that medicinal product and, for that reason, asked that expert to 'remove ... any action linked to safety (such as stopping treatment) from [his] communication.'

62 The applicant submits that, in the statement that was eventually published, Ocaliva continued to be disparaged, and that that statement contained recommendations which raised issues of medical-professional ethics due to the promotion of unauthorised medicinal products to the general public, such as the recommendation of 'stopping treatment' with that medicinal product immediately and the recommendation to

consider the use of then-unauthorised medicinal products, in particular elafibranor and seladelpar, described as 'better' products.

63 Moreover, the applicant submits that the publication at issue required a certain amount of preparation time and that that publication therefore reflects Expert B's state of mind during the AHEG's work.

64 The EMA failed to fulfil its obligation to take remedial action with regard to Expert B, who demonstrated subjective bias.

65 In its observations on the statement in intervention submitted by the EMA, the applicant also alleges a lack of objective impartiality on the part of Expert B. In its view, the selection of that expert was not consistent with the policy on competing interests, since he had advised IPSEN less than three years before on the competing medicinal product elafibranor.

66 The Commission, supported by the EMA, disputes the applicant's arguments.

– *Preliminary observations*

67 The fundamental right to sound administration, enshrined in Article 41 of the Charter, includes, under paragraph 1 of that provision, the right to have one's affairs handled impartially by the institutions, bodies, offices and agencies of the European Union.

68 It is incumbent upon the institutions, bodies, offices and agencies of the European Union to comply with the requirement of impartiality in its two components, which are, on the one hand, subjective impartiality, whereby no member of the institution concerned may show personal bias or prejudice, and, on the other hand, objective impartiality, according to which that institution must offer sufficient guarantees to exclude any legitimate doubt as to possible bias on the part of the institution concerned (see judgment of 27 March 2019, *August Wolff and Remedia v Commission*, C-680/16 P, EU:C:2019:257, paragraph 27 and the case-law cited). The Court of Justice has clarified in that respect that, in order to show that the organisation of an administrative procedure does not ensure sufficient guarantees to exclude any legitimate doubt as to possible bias, it is not necessary to prove lack of impartiality. It is sufficient for a legitimate doubt to arise which cannot be dispelled (judgments of 27 March 2019, *August Wolff and Remedia v Commission*, C-680/16 P, EU:C:2019:257, paragraph 37, and of 21 October 2021, *Parliament v UZ*, C-894/19 P, EU:C:2021:863, paragraph 54).

69 The Court has found, in particular, that the objective impartiality of the CHMP, and therefore of the EMA, is compromised where a conflict of interest on the part of one of the members of that committee is likely to result from an overlap of functions. That finding is valid irrespective of the personal conduct of that member. The resulting failure to fulfil obligations is liable to render unlawful the decision adopted by the Commission at the end of the procedure (see, to that effect, judgment of 14 March 2024, *D & A*

Pharma v Commission and EMA, C-291/22 P, EU:C:2024:228, paragraph 74 and the case-law cited).

- 70 The objective impartiality of the CHMP is also compromised where an expert who is in a situation of conflict of interest is part of the expert group which is consulted by that committee in the review leading to the opinion of the EMA and the Commission's decision on the revocation of an MA (judgment of 14 March 2024, *D & A Pharma v Commission and EMA*, C-291/22 P, EU:C:2024:228, paragraph 75).
- 71 It must be observed, in that regard, that the opinion expressed by the expert group convened by the CHMP has a potentially decisive influence on the EMA's opinion and, through that opinion, on the Commission's decision. Each member of that group may, in some circumstances, have a considerable influence on the discussions and deliberations that take place, on a confidential basis, within that group. Accordingly, involvement in the group in question of a person who is in a situation of conflict of interest gives rise to a situation that does not offer sufficient guarantees to exclude any legitimate doubt as to possible bias (judgment of 14 March 2024, *D & A Pharma v Commission and EMA*, C-291/22 P, EU:C:2024:228, paragraph 76).
- 72 The fact that a member of the expert group whose involvement is challenged in the light of the requirement of objective impartiality does not exercise a management or coordination function in that group is irrelevant, since it cannot be accepted that only members exercising such a role may have a significant influence on the conduct or outcome of the procedure (see, to that effect, judgment of 14 March 2024, *D & A Pharma v Commission and EMA*, C-291/22 P, EU:C:2024:228, paragraph 79).
- 73 Moreover, persons whose affairs are handled by an EU institution, body, office or agency cannot be required to provide, in support of their argument that the requirement of objective impartiality was not complied with during an EU administrative procedure, proof of specific indications of bias, such as statements or positions taken by the expert concerned within the expert group of which he or she is a member. Objective impartiality is to be assessed independently of the specific conduct of the person concerned. In any event, since the statements and positions taken in the context of that group's work are confidential, it is impossible to determine the influence exercised by the experts concerned (see, to that effect, judgment of 14 March 2024, *D & A Pharma v Commission and EMA*, C-291/22 P, EU:C:2024:228, paragraph 80).
- 74 The EU legislature chose, as regards the requirement of impartiality of the EMA's experts, to lay down essential criteria in Regulation No 726/2004 and then to entrust that agency with the task of implementing them (see judgment of 14 March 2024, *D & A Pharma v Commission and EMA*, C-291/22 P, EU:C:2024:228, paragraph 84 and the case-law cited).
- 75 In that regard, it is for the EMA to reconcile, on the one hand, the twofold requirement of impartiality and independence of its experts, as laid down in Article 63(2) of Regulation

No 726/2004, and, on the other hand, the public interest, referred to in Article 57(1) of that regulation, as amended by Regulation 2019/5, relating to the need for the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use that is referred to it (see judgment of 14 March 2024, *D & A Pharma v Commission and EMA*, C-291/22 P, EU:C:2024:228, paragraph 85 and the case-law cited).

- 76 In order to enable the EMA to pursue effectively the objective thus assigned to it, and in view of the complex technical assessments which it must undertake, the broad discretion conferred on it manifests itself in particular in the definition of the criteria which must govern the impartiality and independence of the individuals contributing to the preparation of its scientific opinions (see judgment of 14 March 2024, *D & A Pharma v Commission and EMA*, C-291/22 P, EU:C:2024:228, paragraph 86 and the case-law cited).
- 77 However, notwithstanding the existence of that broad discretion and the importance of the public interest referred to above, the EMA is required, in the exercise of its powers, under Article 51(1) of the Charter, to respect the rights and principles mentioned therein (judgment of 14 March 2024, *D & A Pharma v Commission and EMA*, C-291/22 P, EU:C:2024:228, paragraph 87).
- 78 The EMA is, in particular, bound by the requirements of Article 52(1) of the Charter, according to which any limitation on the exercise of the rights and freedoms recognised by the Charter must be provided for by law and respect the essence of those rights and freedoms and the principle of proportionality, with the result that limitations may be made only if they are necessary and genuinely meet objectives of general interest recognised by the European Union or the need to protect the rights and freedoms of others (judgment of 14 March 2024, *D & A Pharma v Commission and EMA*, C-291/22 P, EU:C:2024:228, paragraph 88).
- 79 It follows that, while taking care to comply with the objective of general interest referred to in Article 57(1) of Regulation No 726/2004, as amended by Regulation 2019/5, which may justify, as is apparent from the case-law referred to in paragraph 75 above, a mitigation of the requirement of objective impartiality of the persons involved in the review of an MA application, a requirement which stems from the fundamental right to sound administration, the EMA must respect the essence of that fundamental right and the principle of proportionality. In particular, it cannot be accepted that that agency, on the pretext of wishing to maximise the number of experts available, should impose restrictions on the exercise of their mandate that appear insufficient to guarantee, in the context of that exercise, an impartial procedure. That would be the case, in particular, if experts whose activities revealed a current interest in relation to a rival product of the product that is the subject of an MA were allowed to be members, without restriction or mitigation, of the expert group convened by the CHMP for the purpose of reviewing that MA (see, to that effect and by analogy, judgment of 14 March 2024, *D & A Pharma v Commission and EMA*, C-291/22 P, EU:C:2024:228, paragraph 89).

80 Following the judgment of 14 March 2024, *D & A Pharma v Commission and EMA* (C-291/22 P, EU:C:2024:228), the EMA introduced, pending the adoption of a new policy on competing interests, a number of interim measures. Those measures include exclusion criteria for experts with a current interest in a medicinal product that could be considered as a rival to the product under examination by the CHMP, in order to prevent their involvement in a scientific advisory group or an AHEG meeting. According to the EMA, however, those exclusion criteria were not extended to past interests in the pharmaceutical industry, that is to say, activities that had been concluded at the time of an expert meeting.

81 As regards the criticism raised by the applicant in its observations on the statement in intervention submitted by the EMA, according to which that agency should have complied with the new policy on competing interests adopted on 12 December 2024, in addition to the interim measures, it is sufficient to note that that policy was introduced six months after the AHEG meeting on 12 June 2024. Accordingly, it was not applicable to the facts giving rise to the present case. In so far as the applicant submits that the 2024 policy on competing interests reflects the EMA's final position on conflict of interest requirements following the judgment of 14 March 2024, *D & A Pharma v Commission and EMA* (C-291/22 P, EU:C:2024:228), and that compliance with that policy in its entirety is required either by the case-law of the Court of Justice in that judgment or by Article 41 of the Charter as interpreted by the Court of Justice in that judgment, the applicant does not explain why the policy on competing interests in force at the time of that meeting, including the interim measures, applied in the present case, runs contrary thereto. The judgment in question concerns the current interest of an expert in relation to a rival product who carried out a relevant activity within the meaning of a previous version of the policy on competing interests, namely that of 6 October 2016, which means that that activity continued during the AHEG's work on the MA application (see, to that effect, judgment of 14 March 2024, *D & A Pharma v Commission and EMA*, C-291/22 P, EU:C:2024:228, paragraph 92).

82 The mere fact that the EMA adopts, at a later point in time, a policy which is allegedly stricter does not, as such, mean that the previous policy was unlawful.

83 It is therefore necessary to assess the present case in the light of the right to sound administration, enshrined in Article 41 of the Charter, and the policy on competing interests, including interim measures, in force at the time of the AHEG meeting of 12 June 2024, by which the EMA applied that right.

– *The subject of the AHEG meeting of 12 June 2024*

84 As regards, first of all, the applicant's argument, raised only in its observations on the statement in intervention submitted by the EMA – that both Expert A and Expert B had a current or past interest in relation to a rival product, namely elafibranor, which had been the subject of the AHEG meeting of 12 June 2024 – it must be noted that it is not apparent from the file that elafibranor was also the subject of that meeting.

85 According to the minutes of the AHEG meeting of 12 June 2024, that meeting concerned Ocaliva.

86 The minutes of the AHEG meeting of 12 June 2024 do not therefore support the conclusion that another medicinal product, such as elafibranor, was discussed at that meeting.

87 In support of its argument, the applicant relies exclusively on a slide in the presentation of the CHMP rapporteur, provided as Annex A.24 to the application, on which it is stated, under the heading 'Background of the disease [and] treatment options', inter alia, that two medicinal products, including elafibranor, were at that time under examination by that committee for the treatment of PBC. However, it does not follow from that brief and contextual reference, at the start of the AHEG meeting of 12 June 2024, that elafibranor had been discussed by the AHEG in the course of the procedure leading to the adoption of the contested decision, which was a procedure for review of the conditional MA relating to another medicinal product, namely Ocaliva. In those circumstances, that argument must be rejected as having no factual basis, without there being any need to assess its admissibility.

– *The second complaint in the first part of the second plea*

88 The applicant claims that Expert A had a current interest when he attended the AHEG meeting of 12 June 2024, relating to elafibranor.

89 In the present case, in order to determine whether Expert A should have been excluded from the AHEG, it is therefore necessary, first, to examine whether, during the AHEG's work, he had a current interest linked to a specific product.

90 In that regard, it is common ground that the AHEG's work in the context of the procedure for review of the conditional MA for Ocaliva began at the earliest on Monday 3 June 2024, namely the day on which he was invited to the AHEG meeting of 12 June 2024. At no point did the applicant claim that the work was already ongoing at the time when Expert A was pursuing an activity for IPSEN, at the meeting which the latter organised on 7 and 8 December 2023. Nor has it submitted any evidence to substantiate its claim that that expert had continued that activity, and therefore had an interest resulting from that activity, after that meeting, in particular during that work.

91 Consequently, any interest which Expert A had during his involvement in the AHEG meeting of 12 June 2024, resulting from his involvement in the meeting organised by IPSEN on 7 and 8 December 2023, must be regarded as being a past interest.

92 Next, it is necessary to examine the nature of the alleged interest and, more specifically, whether it was linked to a specific product. In that regard, it must be stated that the applicant has also failed to provide sufficient evidence in support of its assumption that such an interest was not of a general nature, as stated in Expert A's eDoI, but was related

to a specific product. It merely asserts that, in its view, the meeting organised by IPSEN on 7 and 8 December 2023 concerned elafibranor and 'likely' Ocaliva.

- 93 The words 'treatment of patients with [PBC]' used in Expert A's eDol in order to describe his activity for IPSEN do not necessarily imply that his advice related to one or more specific medicinal products, such as elafibranor or Ocaliva.
- 94 First, the concept of 'treatment' is not limited to the prescription of medicinal products. Accordingly, as the Commission notes, the activity at issue may have covered a wide range of topics unrelated to any specific medicinal product, such as a discussion on clinical experience, treatment strategies, the future therapeutic landscape, and new strategies to facilitate patient access to clinical trial sites. In accordance with those considerations and given the wide-ranging medical implications of treating a disease, there were other reasonably plausible topics for the meeting organised by IPSEN on 7 and 8 December 2023 apart from the sole issue of marketing elafibranor.
- 95 The mere fact, as the applicant claims, that the first day of the meeting organised by IPSEN on 7 and 8 December 2023 coincided with the day on which a press release on elafibranor was published is not capable of demonstrating that that meeting specifically related to that medicinal product to the exclusion of any other more general subject matter, with the result that the involvement of Expert A was necessarily linked to a particular product.
- 96 On the contrary, if the meeting organised by IPSEN on 7 and 8 December 2023 and the press release on elafibranor had been linked in that way, the publication of that press release would more logically have taken place at the end of that meeting and would have reported on some of the findings in that regard.
- 97 Furthermore, an assessment of all the evidence put forward by the applicant, as a whole, does not support the conclusion that the activity carried out by Expert A for IPSEN was not general in nature.
- 98 Consequently, where there is no other evidence pointing to a specific interest linked to a particular product, it follows from the past and general nature of Expert A's interest that the latter was not likely to justify restrictions under the policy on competing interests.
- 99 It should be recalled that, when exercising its powers, the EMA is bound by the Charter and must therefore, in any event, interpret and apply the policy on competing interests in a manner consistent with the Charter.
- 100 The application of the policy on competing interests must therefore not constitute a disproportionate limitation on the protection of objective impartiality (see, to that effect, judgment of 14 March 2024, *D & A Pharma v Commission and EMA*, C-291/22 P, EU:C:2024:228, paragraphs 112 and 113).

- 101 In the present case, however, the involvement in the AHEG of an expert with a brief, past and general interest, as set out in paragraphs 90 to 98 above, cannot constitute a disproportionate limitation on the protection of objective impartiality.
- 102 On the contrary, if that were the case, the EMA would be required to exclude a very large number of experts, which would be at the expense of the need to have the best possible scientific advice, enshrined in Article 57(1) of Regulation No 726/2004, as amended by Regulation 2019/5.
- 103 That conclusion is not called into question, in the present case, by the applicant's argument, raised in its observations on the statement in intervention submitted by the EMA, that Expert A had been recommended to the EMA by email by an unidentified member of the CHMP who was informed of his involvement in the meeting organised by IPSEN on 7 and 8 December 2023.
- 104 Neither the fact that Expert A was recommended by a CHMP member who was aware of his involvement in the meeting organised by IPSEN on 7 and 8 December 2023, nor the fact that the EMA did not provide the email at issue to the applicant, is capable of constituting evidence calling into question the impartiality of that expert.
- 105 As regards the applicant's request for the production of the email at issue, raised in its observations on the statement in intervention submitted by the EMA, it should be noted that the Court is the sole judge of any need to supplement the information available to it concerning the cases before it (see judgment of 22 November 2007, *Sniace v Commission*, C-260/05 P, EU:C:2007:700, paragraph 77 and the case-law cited). Any party requesting the adoption of a measure of organisation of procedure or inquiry must provide the Court with at least a minimum of information indicating the utility of the measure for the purposes of the proceedings (see, to that effect, judgment of 23 May 2014, *European Dynamics Luxembourg v ECB*, T-553/11, not published, EU:T:2014:275, paragraph 318 and the case-law cited).
- 106 In the present case, none of the arguments put forward by the applicant are capable of explaining how disclosure of the email at issue could demonstrate Expert A's bias.
- 107 The applicant merely claims that disclosure of the email at issue is the only means of verifying whether, as the EMA maintains, the email does not contain any details relating to the meeting organised by IPSEN on 7 and 8 December 2023 and more specifically whether the identity of the CHMP member who recommended Expert A is significant.
- 108 The applicant does not in any way explain to what extent the identity of the CHMP member who recommended Expert A could be relevant in order to demonstrate an infringement of the right to sound administration. Furthermore, it does not cite any factual element capable of calling into question the veracity of the EMA's assertion and which would be proven by producing the email at issue. The applicant must specify which factual evidence it wants to support by requesting access to that email.

- 109 Accordingly, the applicant's request for production of the email at issue must be refused.
- 110 Lastly, the conclusion that Expert A's involvement in the AHEG cannot constitute a disproportionate limitation on the protection of objective impartiality also cannot be called into question by the applicant's argument, raised in its observations on the statement in intervention submitted by the EMA, that the involvement of that expert should also be assessed taking into account the fact that, in its view, Expert B should also have been excluded from the AHEG, without it being necessary to assess the admissibility of that argument.
- 111 The arguments based on Expert B's alleged bias are ineffective in so far as they are put forward in support of the present part of the plea, since the situation of each expert must be examined in relation to his or her specific situation and not in relation to that of another member of the AHEG.
- 112 The second complaint in the first part of the second plea must therefore be rejected.
- *The second part of the second plea in law*
- 113 The applicant alleges a lack of subjective impartiality on the part of Expert B during the AHEG's work. In that regard, as recalled in paragraph 68 above, it is incumbent upon the institutions, bodies and agencies of the European Union to comply with the requirement of impartiality in its two components, which are, on the one hand, subjective impartiality, whereby no member of the institution concerned may show personal bias or prejudice, and, on the other hand, objective impartiality, according to which that institution must offer sufficient guarantees to exclude any legitimate doubt as to possible bias on the part of the institution concerned (see judgment of 27 March 2019, *August Wolff and Remedia v Commission*, C-680/16 P, EU:C:2019:257, paragraph 27 and the case-law cited).
- 114 According to the case-law, subjective impartiality is presumed where there is no evidence to the contrary (see judgment of 20 October 2021, *Kerstens v Commission*, T-220/20, EU:T:2021:716, paragraph 35 and the case-law cited).
- 115 As regards the rules relating to the burden of proof and the taking of evidence, it should be pointed out that, as a general rule, in order to satisfy the Court as to a party's claims or, at the very least, as to the need for the Court itself to take evidence, it is not sufficient merely to refer to certain facts in support of the claim. There must also be adduced sufficiently precise, objective and consistent indicia of their truth or probability (judgment of 6 March 2001, *Connolly v Commission*, C-274/99 P, EU:C:2001:127, paragraph 113).
- 116 In the present case, the applicant has not provided sufficiently precise, objective and consistent indicia to support the truth or probability of its claims that Expert B was not impartial.
- 117 In the first place, the applicant misinterpreted the press release co-drafted by Expert B.

- 118 Neither the press release at issue, nor the reactions that followed its publication, nor the exchange of emails between Expert B and the EMA secretariat suggest that any assessment of Ocaliva failed to comply with scientific standards, let alone that Ocaliva was disparaged.
- 119 First, it is not apparent from the press release at issue that Expert B considered other unauthorised medicinal products, in particular elafibranor or seladelpar, to be 'better'. That press release describes the results of two studies relating to those medicinal products as being 'very encouraging' and expresses the hope that the scientific community will continue its efforts to develop better medicinal products.
- 120 Secondly, Expert B did not advise that all Ocaliva treatment be stopped immediately. In the press release at issue, patients are simply advised to consult their doctors in order to determine whether it would be reasonable to stop treatment.
- 121 Thirdly, it is apparent from the exchange of emails between Expert B and the EMA secretariat that the EMA asked that expert to delete from the press release at issue, which he had co-drafted, any information or action relating to safety solely on the ground that the CHMP's final considerations were not supposed to include such information.
- 122 Fourthly, it is true that the PBC Working Group of the European Reference Network on rare hepatological diseases and the 'PBC Foundation' expressed, in their respective communications of 3 July and 29 June 2024, provided as Annexes A.37 and A.38 to the application, concerns and critical comments regarding the process by which the press release at issue was published and the EMA's assessment of the medicinal product at issue, but those documents do not contain any evidence to support the assumption that Expert B was subjectively biased during the AHEG's work.
- 123 In the second place, the publication of a press release co-drafted by Expert B and based on the results of the EMA's work cannot, as such, form the basis for the assumption of subjective bias on the part of that expert during the AHEG's work. It is particularly common in the field of science – and more specifically in the field of medicine – for newly acquired knowledge to be published as quickly as possible.
- 124 In the third place, the fact that the applicant does not appear to agree with Expert B's scientific opinion is not sufficient to assume that Expert B lacked impartiality in that regard, since that expert's opinion reveals only scientific beliefs.
- 125 In the fourth place, in view of the fact that scientific issues often generate disagreement among specialists in the field, the fact that a scientific opinion is, as the case may be, disputed, held by a majority or even unanimous cannot constitute a factor in assessing the impartiality of an expert who defends it.
- 126 Since the applicant has not demonstrated that Expert B lacked subjective impartiality during the AHEG's work, the EMA was not required to take remedial steps in that regard.

127 Consequently, the second part of the second plea must be rejected.

The third complaint in the first part of the plea

128 The applicant submits that Expert A should have been excluded from the AHEG, since he failed to fulfil his obligation, under section 2.4.5 of the EMA Code of Conduct, to fill in his eDol in a complete and correct manner.

129 In the first place, the name of the pharmaceutical company organising the meeting of 7 and 8 December 2023 representing the declared interest, as indicated in Expert A's eDol, is not complete. It therefore did not allow that interest to be identified precisely. The term 'IPSEN' is not an acronym for the name of the pharmaceutical company 'Institut Produits Synthèse', but is part of its full name. Accordingly, that expert's explicit oral reference to the expression 'IPSEN', at the beginning of the AHEG meeting of 12 June 2024, did not constitute a 'repetition' of that eDol, but in fact a new statement in order to remedy previous omissions, since that statement was made after a request to declare any 'changes, omissions or errors' in the eDol of the participants to that meeting.

130 In the second place, in the reply, the applicant submits that section 2.4.5 of the EMA Code of Conduct requires the expert concerned to fill in the statement personally. Expert A did not complete the statement himself. The EMA secretariat completed it on his behalf. The applicant infers from this that the expert concerned did not familiarise himself with the content of the declaration, including the explanatory notes, and, therefore, the extent of his obligations. In addition, the applicant submits that the expert did not familiarise himself with the completed declaration and did not sign it. In its observations on the statement in intervention submitted by the EMA, it asks the Court to order the EMA to produce the criteria relating to conflicts of interest which were communicated to that expert, in order to dispel doubts as to whether that expert had been duly informed before signing the eDol.

131 The Commission, supported by the EMA, disputes the applicant's arguments.

132 Pursuant to section 2.4.5 of the EMA Code of Conduct, it is for the expert to fill in the declaration of interests in a complete and correct manner.

133 As regards the applicant's claim that Expert A did not fill in his eDol in a complete and correct manner within the meaning of section 2.4.5 of the EMA Code of Conduct, it must be held that, in the light of the objective pursued by that code, that provision requires the experts in question to declare their interests in such a way as to enable the EMA to examine them and, where appropriate, to restrict their involvement in its procedures. It is common ground that that expert, by mentioning 'Institut Produits Synthèse' in that eDol, did not submit the full company name of the undertaking in question, namely 'Institut Produit Synthèse (IPSEN) AB'. However, the indication 'Institut Produits Synthèse', as used in that eDol, did not prevent the EMA from examining it and, in the event of doubt, even if only by means of a quick internet search, from identifying the full company name and therefore the undertaking in question.

- 134 Accordingly, the indication provided in Expert A's eDoI cannot be interpreted as being incorrect or as constituting an attempt to conceal the name of the undertaking in question, which could, as such, call into question the impartiality of that expert.
- 135 Consequently, it must be held that Expert A's eDoI was filled in in a complete and correct manner within the meaning of section 2.4.5 of the EMA Code of Conduct.
- 136 That finding is not called into question by the oral statement made by Expert A at the beginning of the AHEG meeting of 12 June 2024. The minutes of that meeting highlight the fact that the expert concerned did not intend to amend his previous statement or to declare a new interest. This cannot be interpreted as casting doubt on his written statement.
- 137 As regards whether, as an expert, he can be assisted in filling in the eDoI, it should be noted that, first, it is not expressly stated in section 2.4.5 of the EMA Code of Conduct that the statement must be filled in by the expert himself, without the assistance of a third party.
- 138 Secondly, the EMA secretariat filled in Expert A's eDoI after an exchange with that expert and in accordance with the information given by the latter during that exchange.
- 139 Thirdly, Expert A confirmed, in an email of 12 June 2024 provided as Annex E.13 to the applicant's observations on the statement in intervention submitted by the EMA, that his eDoI, as completed, could be processed by the EMA secretariat for the purposes of registration, thus endorsing the information included in that statement.
- 140 Fourthly and finally, the eDoI of Expert A, provided as Annex A.32 to the application, contains explicit references to the policy on competing interests.
- 141 It follows from all of the above that Expert A was in a position to read his eDoI and familiarise himself with its content and the scope of his obligations.
- 142 In those circumstances, it is not necessary to answer the question raised by the applicant as to whether the blank version of the eDoI containing an active hyperlink to the policy on competing interests, provided as Annex D.2 to the rejoinder, was in fact attached to the email sent by the EMA secretariat to Expert A on 11 June 2024 at 13:01, forming part of an exchange of emails provided as Annex B.8 to the defence, as one of the emails exchanged expressly states.
- 143 Consequently, and in the light of the case-law cited in paragraph 105 above, there is no need to order the EMA to produce the criteria relating to conflicts of interest which were communicated to Expert A.
- 144 The argument alleging infringement of section 2.4.5 of the EMA Code of Conduct must therefore be rejected and, accordingly, the third complaint in the first part of the second plea.

The fourth complaint in the first part of the second plea

- 145 The applicant claims that the EMA failed to fulfil its obligations under its code of conduct, as well as the policy on competing interests, in several respects.
- 146 In the first place, in view of the sensitive nature of the situation at the time when the AHEG meeting of 12 June 2024 took place, and in particular in the light of the two parallel procedures which were ongoing concerning, on the one hand, elafibranor and, on the other hand, Ocaliva, the EMA did not take sufficient precautions during the pre-selection of experts for that meeting.
- 147 In the second place, the applicant submits that the EMA also failed to carry out a sufficiently diligent examination of Expert A's declaration of interests in good time before the AHEG meeting of 12 June 2024. That is evidenced by the email sent by the secretariat to that expert on 12 June 2024, which is the same day as that meeting. In the light of that situation, the EMA failed to fulfil its obligation to postpone that meeting and to initiate a breach of trust procedure against the expert in question.
- 148 In its observations on the statement in intervention submitted by the EMA and on the basis of the documents received from it after the reply was lodged, the applicant submits more specifically, in essence, that the EMA did not correctly carry out any of the steps required by Article 41(2) of the Charter and Article 63(2) of Regulation No 726/2004 and which are set out in its code of conduct, in its procedural guidelines for experts on filling in declarations of interests, and in its standard operating procedure for the assessment of declarations of interests, all of which are necessary to rule out any legitimate doubt as to experts' impartiality.
- 149 First, there is no evidence that Expert A received an explanation of the policy on competing interests.
- 150 Secondly, Expert A did not make any solemn declaration that his eDoI had been filled in fully and correctly, nor did he complete that form himself, nor did he fill it in correctly and in full.
- 151 Thirdly, Expert A's eDoI was not included in the experts management tool.
- 152 Fourthly, the EMA did not spend enough time verifying the expert's eDoI assessment form correctly. The file shows that the procedure was chaotic and conducted in haste. For example, that assessment form, provided as Annex E.22 to the applicant's observations on the statement in intervention submitted by the EMA, contains the words 'past advisory for rival product, no restrictions', whereas, in that eDoI, that expert declared a 'cross product related/general (non-product related)' activity. The EMA secretariat expressed its surprise upon discovering, at the beginning of the AHEG meeting of 12 June 2024, that the expert in question had advised IPSEN. The EMA therefore failed to fulfil its obligation to verify that unclear assessment form.

- 153 Fifthly, the EMA did not raise any questions regarding the unusual situation referred to in paragraph 152 above.
- 154 Sixthly, the EMA did not await the completion of the steps referred to in paragraph 148 above before sending confidential documents to the AHEG experts in order for them to begin their discussions.
- 155 The Commission, supported by the EMA, disputes the applicant's arguments.
- 156 It should be borne in mind that, under Article 41(1) of the Charter, in accordance with the case-law cited in paragraph 113 above, it is incumbent on the institutions of the Union to provide sufficient guarantees to exclude any legitimate doubt as to possible bias on their part.
- 157 It is apparent from the second indent of section 2.4.4 of the EMA Code of Conduct and point 4.2.2 of the policy on competing interests that it is the responsibility of the EMA secretariat to assess and monitor carefully the eDoI submitted by the expert in question in order to determine whether the declared interests are compatible with the functions of that expert and, where appropriate, the restrictions to be applied to his or her involvement.
- 158 Furthermore, according to section 2.4.6 of the EMA Code of Conduct, the chairpersons and the EMA secretariat are to apply EMA policies, including the policy on competing interests, on the basis of the type and nature of interests noted.
- 159 According to point 4.3.2 of the policy on competing interests, all members and experts of the scientific committees and other bodies of the EMA must be included in the EMA's experts management tool prior to the first appointment resulting in involvement in activities at the EMA.
- 160 In the present case, it should be recalled, first of all, that the applicant's arguments that Expert A did not fill in his eDoI personally and in a complete and correct manner were rejected in the examination of the third complaint in the first part of the second plea in paragraphs 133 to 144 above.
- 161 Next, it was also concluded in the examination of the second complaint in the first part of the second plea that Expert A did not have a conflict of interest when he attended the AHEG meeting on 12 June 2024 (see paragraphs 88 to 112 above).
- 162 In those circumstances, none of the other factors raised by the applicant are capable of giving rise to a legitimate doubt as to any possible bias on the part of one or more AHEG experts.
- 163 First, the fact that the procedure surrounding the AHEG meeting of 12 June 2024 was conducted, at least in part, in a swift manner is irrelevant, since the speed of an administrative procedure does not in itself indicate the existence of a defect vitiating that procedure.

- 164 Secondly, the fact that an EMA official used the words 'past advisory for rival product, no restrictions' in the eDol assessment form of Expert A does not demonstrate that the EMA's final conclusion that no restriction applied is incorrect. On the contrary, that final conclusion is consistent with the fact that that expert did not state in the eDol that he held an interest in relation to a rival product. Accordingly, the EMA's explanation that the remark 'past advisory for rival product, no restrictions' was the result of a clerical error is plausible and not contradicted by the facts.
- 165 Thirdly, the fact that a member of the EMA secretariat asked Expert A, immediately after that expert's oral statement, at the beginning of the AHEG meeting of 12 June 2024, whether he had understood that statement correctly, also has no impact on the earlier characterisation of the interest declared by that expert, as analysed by the EMA. As is apparent from the examination of the second and third complaints of the first part of the second plea, that classification is not vitiated by error. The fact that an EMA official asked such a question for the purposes of clarification does not indicate that the EMA had not previously carefully assessed the eDol of the expert in question.
- 166 Fourthly, in those circumstances, the EMA was not required to ask more questions about the allegedly unusual situation.
- 167 Fifthly, it is true that it is apparent from an email from the EMA secretariat dated 12 June 2024 at 11:38 and provided as Annex E.12 to the applicant's observations on the statement in intervention submitted by the EMA that Expert A's eDol was evaluated outside the experts management tool.
- 168 However, in point 4.3.2 of the policy on competing interests, it is only stated that experts should be included in the experts management tool. That provision does not state that the evaluation itself of an expert's eDol must be carried out in that tool. The applicant has not disputed the EMA's response to a question from the Court, put by way of a measure of organisation of procedure, according to which all experts, including Expert A, were included in the tool at issue.
- 169 In any event, even if the failure to evaluate Expert A's eDol in the experts management tool constitutes a procedural irregularity, it should be recalled that, according to settled case-law, a procedural irregularity can justify the annulment of a measure only if, had it not been for such an irregularity, the outcome of the procedure might have been different (see judgment of 20 October 2021, *Kerstens v Commission*, T-220/20, EU:T:2021:716, paragraph 44 and the case-law cited).
- 170 In the present case, first of all, the EMA's failure to evaluate Expert A's eDol in the experts management tool concerns a past interest which was not product-related. Next, that expert correctly declared that past interest. Lastly, as is apparent from the examination of the second complaint in the first part of the second plea, that past interest was not such as to call into question the involvement of that expert in the AHEG,

either according to the policy on competing interests or according to the principle of proportionality (see paragraphs 88 to 112 above).

171 It follows that any evaluation of Expert A's eDol in the experts management tool before the start of the AHEG meeting of 12 June 2024 could not have resulted in the exclusion of that expert from the AHEG's work.

172 Accordingly, the fourth complaint in the first part of the second plea must be rejected.

The first complaint in the first part and the third part

173 In the third part of the second plea, the applicant, supported by CBP Portugal, raises, in essence, two complaints relating, first, to a lack of expertise on the part of AHEG members, which it also raises in the first complaint in the first part and, secondly, to a lack of preparation time before the AHEG meeting of 12 June 2024.

– *The first complaint in the first part and the first complaint in the third part*

174 The applicant, supported by CBP Portugal, submits that Expert A had no practical experience with regard to Ocaliva treatment. In particular, he had never prescribed that medicinal product. For a product which was on the market for many years, doctors accustomed to prescribing that treatment would have been the true experts.

175 By its arguments raised in the first complaint in the third part of the second plea, the applicant claims that only two members of the AHEG regularly treated PBC patients. Expert B and Expert C – the latter of whom served as chair of the AHEG – were not among them. As regards Expert C, the applicant contends that his expertise in the field of gastroenterology did not justify his appointment as chair of the AHEG, since an expert in gastroenterology would not automatically possess the necessary expertise in hepatology, given that the latter is a sub-speciality of gastroenterology.

176 In its observations on the EMA's statement in intervention, the applicant submits that Article 57 of Regulation No 726/2004, as amended by Regulation 2019/5, was infringed since Expert A was not in a position to provide the 'best possible scientific advice' on PBC on the sole basis that he was an expert in the vast field of hepatology.

177 The Commission, supported by the EMA, disputes the applicant's arguments.

178 In the first place, it should be noted that an expert group cannot properly carry out its task unless it is composed of persons possessing the necessary scientific knowledge in the various fields concerned or its members are advised by experts having that knowledge (see, to that effect and by analogy, judgments of 21 November 1991, *Technische Universität München*, C-269/90, EU:C:1991:438, paragraph 22, and of 9 September 2010, *Now Pharm v Commission*, T-74/08, EU:T:2010:376, paragraph 76).

179 In the second place, it should be observed that the procedure for review of the MA for an orphan medicinal product is an administrative procedure involving complex scientific

assessments in respect of which the Commission has broad discretion (see, by analogy, judgment of 9 September 2010, *Now Pharm v Commission*, T-74/08, EU:T:2010:376, paragraph 77).

- 180 Consequently, the applicant's argument concerning the alleged lack of qualification on the part of the experts would be well founded only if their appointment to the AHEG constituted a manifest error of assessment (see, to that effect and by analogy, judgment of 9 September 2010, *Now Pharm v Commission*, T-74/08, EU:T:2010:376, paragraph 79).
- 181 As a preliminary point, it should be noted that there is no rule according to which, where a medicinal product has been granted an MA, only the appointment to the AHEG of doctors prescribing that medicinal product may be regarded as legitimate in the context of the procedure for review of that MA. Moreover, there is no equivalent rule for procedures for the assessment of applications for MAs for medicinal products which have not yet been placed on the market, for which it would be difficult, if not impossible, to appoint experts who have already administered them. Therefore, the mere fact that an expert has not yet prescribed the medicinal product in question is not sufficient to rule out his or her expertise in the field concerned.
- 182 First, as regards Expert B, although the applicant submits that that expert is not among the doctors regularly treating PBC patients, that does not demonstrate a manifest error of assessment concerning the appointment of that expert to the AHEG.
- 183 Secondly, as regards Expert A, although the applicant submits that he had no practical experience with regard to Ocaliva treatment and that the mere fact that he was an expert in the vast field of hepatology was not sufficient to conclude that he was able to give the 'best possible scientific advice' on PBC, that does not demonstrate a manifest error of assessment concerning the appointment of that expert to the AHEG. The evidence put forward by the applicant does not rule out the possibility that such an expert with undisputed medical and scientific expertise in internal medicine and hepatology has the skills required to evaluate a medicinal product treating a liver disease.
- 184 Thirdly, as regards Expert C, although the applicant submits that that expert is not among the doctors dealing regularly with PBC patients and that his expertise in the field of gastroenterology did not justify his appointment as chair of the AHEG – since an expert in gastroenterology would not automatically possess the necessary expertise in hepatology, given that the latter constitutes a sub-speciality of gastroenterology – that does not demonstrate a manifest error of assessment concerning the appointment of that expert to the AHEG. The evidence put forward by the applicant does not rule out the possibility that the expert in question, having undisputed medical and scientific knowledge and specialisation in gastroenterology, of which hepatology is a sub-speciality, has the skills required to evaluate a medicinal product treating a liver disease. Contrary to what the applicant suggests, there is no basis for assuming that experts specialised in a specific field do not possess the necessary expertise in a sub-speciality of that field.

- 185 Consequently, the applicant has failed to demonstrate that there was a manifest error of assessment committed, in the present case, when experts A, B and C were appointed to the AHEG.
- 186 It is therefore necessary to reject the first complaint in the first part of the second plea and the first complaint in the third part of that plea, without there being any need to answer the question whether the applicant's argument raised in its observations on the EMA's statement in intervention – according to which Article 57 of Regulation No 726/2004, as amended by Regulation 2019/5, was infringed because of Expert A's alleged lack of expertise – is admissible in the light of Article 84 of the Rules of Procedure of the General Court.
- *The second complaint in the third part of the second plea*
- 187 The applicant, supported by CBP Portugal, claims that the AHEG members were not given adequate time to study the relevant scientific data. The invitation to attend the AHEG meeting of 12 June 2024, which included a large volume of documents representing the views of the CHMP, was reportedly only sent to the experts at 17:00 on 3 June 2024, that is to say six working days before that meeting. In addition, the applicant claims that it submitted to the EMA, on Wednesday 5 June 2024, its own briefing book addressed to the AHEG. The EMA, in turn, did not send it to those members until Friday 7 June 2024, at 17:00. In the reply, the applicant claims that at least one of the experts in the AHEG only became aware of the document on 11 June 2024.
- 188 The Commission, supported by the EMA, disputes the applicant's arguments.
- 189 According to the settled case-law, where the EU institutions have a wide power of appraisal, respect for the rights guaranteed by the EU legal order in administrative procedures is of even more fundamental importance. Those guarantees include, in particular, the duty of the competent institution to examine carefully all the relevant aspects of the individual case (see, to that effect, judgments of 21 November 1991, *Technische Universität München*, C-269/90, EU:C:1991:438, paragraph 14, and of 9 September 2010, *Now Pharm v Commission*, T-74/08, EU:T:2010:376, paragraph 87).
- 190 Furthermore, in order to fulfil their functions, scientific advice on matters relating to human health must, in the interests of those persons and industry, be based on the principles of excellence, independence and transparency (see, to that effect and by analogy, judgment of 11 September 2002, *Alpharma v Council*, T-70/99, EU:T:2002:210, paragraph 172).
- 191 Accordingly, the AHEG experts consulted by the CHMP must have sufficient time to examine carefully the documents submitted before discussing, in full consideration of the best available scientific data and the most recent results of international research, the scientific opinion to be issued during a key AHEG meeting.

- 192 In the present case, the documents relating to the AHEG meeting of 12 June 2024 were communicated as follows.
- 193 On Monday 3 June 2024, the draft agenda of the AHEG meeting of 12 June 2024, the rapporteur's draft assessment report and the briefing note to the experts concerning Ocaliva, which contained the CHMP's questions, were communicated to AHEG members.
- 194 On Friday 7 June 2024, at 17:12, the applicant's briefing book, including detailed explanations of the disease in question, the clinical development programme of Ocaliva and a demonstration of the clinical benefits, together with their annexes and references, were communicated to AHEG members.
- 195 On Tuesday 11 June 2024, further documents, such as the definitive list of participants in the AHEG meeting of 12 June 2024 and the interventions of third parties, neither of which were previously included in the briefing note to the experts, were communicated to AHEG members.
- 196 As regards, first of all, the documents sent to AHEG members on 3 June 2024, the evidence provided by the applicant does not demonstrate that the period of six working days remaining up to the day of the AHEG meeting of 12 June 2024 proved to be too short for a meticulous examination of those documents. The applicant merely claims that the time available to the AHEG experts to study the relevant scientific data was not sufficient, without mentioning specific and concrete evidence in support of that claim, such as the number of pages, the amount of information included or a demonstration of the allegedly high complexity of the information contained in those documents. Nevertheless, any failure on the part of the experts to grasp lengthy and complex documents within a timeframe of several working days necessitates a more thorough demonstration.
- 197 As regards, next, the documents sent to AHEG members on 7 June 2024, the same conclusion must be reached, even though they had only a period of two working days remaining until the day of the AHEG meeting of 12 June 2024 for a meticulous examination of those documents which were not provided by the applicant until 5 June 2024.
- 198 Although, in the email which an AHEG expert sent to the EMA secretariat during the evaluation procedure following the AHEG meeting of 12 June 2024 in order to point out, *inter alia*, several aspects which could have made that meeting 'more efficient and effective' that expert states that certain documents were not 'received' until one day before that meeting, the only document to which that expert explicitly refers is a presentation provided by the applicant; that does not call into question the fact that that document forms part of the documents which were communicated to AHEG members earlier, namely on 3 and 7 June 2024.
- 199 It is apparent from an extract from the information exchange platform used by the EMA, provided by the Commission as Annex D.4 to the rejoinder, that the expert in question,

who alleged that certain documents were 'received' only one day before the AHEG meeting of 12 June 2024, did not exhaust the time limit which had been proposed to that expert for the study of the only document to which he referred in the email which he sent to the EMA secretariat during the evaluation procedure subsequent to that meeting. That expert downloaded and consulted the documents sent to him as early as 7 June 2024 only one day before that meeting, namely 11 June 2024, meaning that the lack of time he essentially complained about in that email was largely due to his own conduct.

200 Moreover, none of the experts criticised the date on which those documents had been communicated during the procedure in question. In particular, if one of the experts had considered that such communication was likely to affect the experts' ability to examine the distributed documents with due care, it is reasonable to assume that he or she would have already reported such an obstacle during the AHEG's work.

201 Consequently, the second complaint in the third part of the second plea must be rejected and, therefore, that plea in its entirety.

Second part of the first plea, alleging infringement of Article 6(4) of Regulation No 507/2006

202 In the second part of the first plea, the applicant, supported by CBP Portugal, submits that, by rendering the procedure for renewal of the conditional MA for Ocaliva devoid of purpose, the Commission, in the contested decision, infringed Article 6(4) of Regulation No 507/2006, in that it deprived it of the specific renewal assessment provided for in Article 6(3) of that regulation.

203 According to the applicant and CBP Portugal, the risk-benefit balance assessed in a procedure for renewal of a conditional MA for a medicinal product is a highly specific one since it is the 'conditional' risk-benefit balance for the purposes of Article 14-a of Regulation No 726/2004, as amended by Regulation 2019/5, and of Article 4 of Regulation No 507/2006.

204 The applicant submits that it follows from the relevant provisions that the criteria to be applied and the burden of proof differ between, on the one hand, the procedure for review of the conditional MA for Ocaliva and, on the other hand, the procedure for renewal of that MA.

205 By initiating the procedure for review of the conditional MA for Ocaliva, the Commission chose not to await the outcome of the procedure for renewal of that MA, whereas, in the latter procedure, in accordance with Article 6(3) of Regulation No 507/2006, the CHMP, the EMA and the Commission also examine whether the specific obligations need to be retained or modified.

206 In addition, the applicant states that the procedure for renewal of the conditional MA for Ocaliva involved the assessment of the various analyses of study 747-302, in accordance with Article 6(3) of Regulation No 507/2006.

- 207 In the context of the procedure for review of the conditional MA for Ocaliva, the CHMP was not asked to assess, and did not reassess, the 'conditional' risk-benefit balance within the specific context and meaning of a renewal assessment. It never sought to determine whether the conditions for that conditional MA were still satisfied. Nor did it assess the need to amend the specific obligations necessary to maintain that conditional MA, but considered only the possibility of converting the conditional MA into a standard MA or of revoking it entirely.
- 208 The applicant, supported by CBP Portugal, submits that the requirements laid down in Article 14-a of Regulation No 726/2004, as amended by Regulation 2019/5, and in Article 4 of Regulation No 507/2006 were still met at the time of publication of the CHMP opinion and the contested decision and continue to be met.
- 209 The applicant submits that the initiation of the procedure for review of the conditional MA for Ocaliva cannot be justified by urgency. The procedure for renewal of that conditional MA would have resulted in a final opinion of the CHMP by 19 September 2024 at the latest. By contrast, the duration of that procedure for review was more than eight months and the opinion of that committee and the termination of the procedure were planned for June 2024.
- 210 The Commission, supported by the EMA, disputes the applicant's arguments.
- 211 In order to determine whether the Commission infringed Article 6(4) of Regulation No 507/2006 by initiating the procedure for review of the conditional MA for Ocaliva while the procedure for renewal of that conditional MA was ongoing, it is necessary to interpret the relevant provisions, in particular, first, Article 20(1) of Regulation No 726/2004, as amended by Regulation 2019/5, and secondly, Article 6(4) of Regulation No 507/2006.
- 212 As a general rule and as follows from settled case-law, in interpreting a provision of EU law, it is necessary to consider not only its wording but also the context in which it occurs and the objectives pursued by the rules of which it is part, bearing in mind, however, that no interpretation may exceed the limits of clear and precise wording. The legislative history of a provision of EU law may also reveal elements that are relevant to its interpretation (see judgment of 15 May 2024, *Fresenius Kabi Austria and Others v Commission*, T-416/22, EU:T:2024:316, paragraph 78 and the case-law cited).
- 213 As regards, first of all, the wording of Article 20 of Regulation No 726/2004, as amended by Regulation 2019/5, it should be noted that that provision provides that the Commission is to act 'immediately' where it considers that one of the measures provided for in Titles IX and XI of Directive 2001/83, including those provided for in Article 116 of that directive, as amended, should be applied in respect of the medicinal product concerned or where the CHMP has delivered an opinion to that effect in accordance with Article 5 of that regulation.

- 214 It follows that the procedure for review provided for in Article 20 of Regulation No 726/2004, as amended by Regulation 2019/5, is characterised by the urgent need to act as soon as the conditions in that article have been met.
- 215 Moreover, neither that provision nor any other provision of Regulation No 726/2004 lays down a minimum period for initiating a procedure for review of a conditional MA for an orphan medicinal product.
- 216 Similarly, there is no indication in Regulation No 726/2004, as amended by Regulation 2019/5, that Article 20 thereof does not apply in situations where a procedure for renewal of a conditional MA for an orphan medicinal product is ongoing in respect of the same medicinal product.
- 217 Next, Article 6(4) of Regulation No 507/2006 provides that the conditional MA '[is to] remain valid until a decision is adopted by the Commission in accordance with Article 10 of Regulation ... No 726/2004', once the application for renewal has been submitted, in accordance with Article 6(2) of Regulation No 507/2006.
- 218 It is apparent from the wording of Article 6(4) of Regulation No 507/2006 that the conditional MA for a medicinal product remains valid until the Commission has taken a decision on that application.
- 219 Article 6(4) of Regulation No 507/2006 makes no express reference to the procedure for review, to measures taken in accordance with the first paragraph of Article 116 of Directive 2001/83, as amended, or to other reasons as to why the conditional MA for a medicinal product could be varied or cease to be valid, such as, for example, annulment by the EU judicature or waiver of the conditional MA by the holder.
- 220 Consequently, the wording of Article 6(4) of Regulation No 507/2006 neither excludes nor expressly allows the Commission to initiate and complete a procedure for review of a conditional MA for a medicinal product while a procedure for renewal of that conditional MA is ongoing.
- 221 As regards the context of the two provisions referred to in paragraph 211 above, first, it must be stated that, according to Article 1 of Regulation No 507/2006, that regulation lays down the rules on the granting of a conditional MA, which is subject to specific obligations, and that, according to Article 2, that regulation is to apply only to medicinal products for human use which also fall under Regulation No 726/2004.
- 222 Accordingly, as is confirmed by recital 8 of Regulation No 507/2006, the provisions of Regulation No 726/2004 apply to conditional MAs, unless Regulation No 507/2006 provides otherwise.
- 223 Secondly, it is apparent from the context of Article 6(4) of Regulation No 507/2006 that that provision provides for the validity of the conditional MA in the context of the renewal procedure.

- 224 Accordingly, given the context of Article 6(4) of Regulation No 507/2006, that provision does not lay down any absolute rule of validity for the conditional MA of a medicinal product, which precludes the possibility of the conditional MA being revoked or varied for other reasons, such as, for example, the outcome of a re-examination procedure relating to that conditional MA.
- 225 It follows from the foregoing that the context of the two provisions referred to in paragraph 211 above supports an interpretation according to which, in the absence of a provision to the contrary in Regulation No 507/2006, Article 20 of Regulation No 726/2004, as amended by Regulation 2019/5, remains applicable, even in a situation such as that in the present case in which a procedure for renewal of the conditional MA is ongoing.
- 226 As regards the objective of the two provisions referred to in paragraph 211 above, it should first of all be recalled that, as is apparent from the preamble to Regulation No 726/2004, in particular recital 19 of that regulation, the centralised procedure for the authorisation of medicinal products provided for in that regulation is based on a scientific evaluation procedure being conducted by the EMA to address the quality, safety and efficacy of medicinal products. One of the main objectives of the authorisation regime provided for in that legislation is to ensure that patients are not administered medicinal products with a negative risk-benefit balance (judgment of 19 December 2019, *Vanda Pharmaceuticals v Commission*, T-211/18, EU:T:2019:892, paragraph 42).
- 227 The objective of ensuring that patients are not administered medicinal products with a negative risk-benefit balance is also pursued by Regulation No 507/2006, as is apparent from recital 5 of that regulation.
- 228 As regards, more specifically, the objective of Article 6(4) of Regulation No 507/2006, that provision seeks to ensure that medicinal products are not removed from the market except for reasons related to public health. As is apparent from recital 9 of that regulation, it is for that reason that that provision provides that conditional MAs are to remain valid until the Commission reaches a decision based on the application for renewal, as long as it is submitted within the deadline.
- 229 By contrast, the objective of Article 6(4) of Regulation No 507/2006 was not to prevent a conditional MA from being revoked on public health grounds. On the contrary, the legislature considered that the application of pharmacovigilance measures, as provided for in Directive 2001/83 and Regulation No 726/2004, is particularly important for medicinal products which have been granted a conditional MA, as is apparent from recital 11 of Regulation No 507/2006.
- 230 It follows from the foregoing that both Article 20 of Regulation No 726/2004, as amended by Regulation 2019/5, and Article 6(4) of Regulation No 507/2006 must be interpreted as meaning that the fact that a procedure for renewal of a conditional MA for a medicinal product is ongoing does not prevent the Commission from initiating a

procedure for review of that conditional MA, in the circumstances provided for in paragraph 1 of that article, and from completing it before the closure of that renewal procedure.

231 The possibility for the Commission to act effectively against a potential risk to public health associated with a medicinal product for human use would be unduly limited if it were required to await the CHMP opinion in the context of a procedure for renewal of the conditional MA for that medicinal product.

232 Nor was the Commission required to await the CHMP opinion in the course of the procedure for renewal of the conditional MA for a medicinal product in the light of the specific temporal circumstances of the present case, within which the time limit for issuing that opinion was set at 19 September 2024, that is to say, three months after the date laid down for the opinion of that committee in the context of the procedure for review and the closure of that procedure. In order to be able to pursue its objective effectively, that is to say, to protect public health, the possibility of triggering a procedure for review cannot depend on the stage of a potential renewal procedure, in a situation in which the risk-benefit balance of a medicinal product concerned is not favourable.

233 Consequently, in the present case, the Commission did not infringe Article 6(4) of Regulation No 507/2006 by triggering the procedure for review of the conditional MA for Ocaliva.

234 That conclusion is not called into question by the other arguments raised by the applicant.

235 In the first place, even assuming that there are relevant differences between the procedure for review of a conditional MA for Ocaliva and the procedure for renewal of that conditional MA which are capable of affecting the applicant's rights, such differences would result from the fact that the two procedures may apply in overlapping situations, but for which the legislature has established different rules.

236 In the second place and in any event, the applicant has not demonstrated the existence of relevant differences between the procedure for review of a conditional MA for Ocaliva and the procedure for renewal of that conditional MA which would have had an actual impact on its rights.

237 First, the applicant's argument that the risk-benefit balance assessment in a procedure for the renewal of a conditional MA for a medicinal product is a highly specific one since it is the 'conditional' risk-benefit balance for the purposes of Article 14-a of Regulation No 726/2004, as amended by Regulation 2019/5, and of Article 4 of Regulation No 507/2006 is unconvincing.

238 In that regard, it must be borne in mind that Article 4 of Regulation No 507/2006, which lays down the requirements for a conditional MA for a medicinal product, refers to the definition of the 'risk-benefit balance' provided for in Article 1(28a) of Directive 2001/83.

Similarly, Article 2 of Regulation No 726/2004, as amended by Regulation 2019/5, refers to that definition.

239 It is apparent from the definitions of 'risk-benefit balance' and 'risks related to use of the medicinal product' in Directive 2001/83 that the establishment of a positive risk-benefit balance is based, first, on an assessment of the positive therapeutic effects and, secondly, on an assessment of the risks to patient health or public health relating to the quality, safety or efficacy of the medicinal product.

240 It follows that there is no difference between the definition of the concept of a 'risk-benefit balance' which applies in the context of the renewal procedure provided for in Article 6(3) of Regulation No 507/2006 and that which applies in the context of the procedure for review provided for in Article 20 of Regulation No 726/2004, as amended by Regulation 2019/5.

241 In addition, it is apparent from recitals 1 to 3 of Regulation No 507/2006 that the risk-benefit balance of a medicinal product which is the subject of a conditional MA must be positive and that the public health benefits arising from the immediate availability of the medicinal product concerned on the market must outweigh the risk inherent in the fact that additional data are still required.

242 In addition and in any event, given that the applicant had already completed the studies provided for as specific obligations, a procedure for renewal of the conditional MA for Ocaliva would have involved an assessment of the risk-benefit balance on the basis of the data obtained in the context of those specific obligations, even where there is no procedure for review of that conditional MA. Consequently, the applicant's argument that an assessment of the risk-benefit balance in the context of that renewal procedure could have had a more positive result than an assessment in the context of that procedure for review cannot succeed.

243 Secondly, the difference which, according to the applicant, exists between, on the one hand, the assessment of the risk-benefit balance in the context of a procedure for renewal of the conditional MA for a medicinal product and, on the other, such an assessment in the context of a procedure for review of that conditional MA does not follow from any difference between the criteria to be applied in those two procedures either.

244 Article 6(3) of Regulation No 507/2006 provides as a requirement for a renewal of a conditional MA for a medicinal product that the 'risk-benefit balance is to be confirmed' by the CHMP, taking into account the specific obligations and the timeframe for their fulfilment. Neither that provision nor any other provision which applies to the renewal procedure refers to Article 4(1) of Regulation No 507/2006, which lays down the requirements for the first grant of a conditional MA to a medicinal product.

245 It follows that, in the context of a procedure for renewal of a conditional MA for a medicinal product, the CHMP is not required to determine whether the conditions for the

grant of that conditional MA are still met.

- 246 Thirdly, assuming that, in the context of the procedure for review of the conditional MA for Ocaliva, it was for the Commission to demonstrate that the conditions laid down in the first paragraph of Article 116 of Directive 2001/83, as amended, were met, whereas, in the context of a procedure for renewal of that conditional MA, the burden of proof relating to the efficacy and safety of the medicinal product would have been borne by the applicant, as the applicant submits, the latter does not explain how that difference in the burden of proof and the fact that it falls on the Commission in the context of that procedure for review would have placed it at a disadvantage.
- 247 The questions as to who bears the burden of proof and, assuming that the burden of proof lies with the Commission, whether the Commission has demonstrated that the conditions of the first paragraph of Article 116 of Directive 2001/83, as amended, were met, will be addressed in the examination of the third plea.
- 248 Fourthly, the applicant's argument concerning a reduction in its rights to specific obligations cannot be accepted.
- 249 In the course of the procedure for review of the conditional MA for Ocaliva, the Commission requested an opinion from the CHMP on whether that conditional MA should be 'maintained, varied, suspended or revoked'. In the light of the results of study 747-302, the CHMP concluded, in its opinion of 29 July 2024, that 'the totality of data available from randomised clinical trials and real-world data [did] not confirm the clinical benefit of [that medicinal product]' and that, as a consequence, 'the efficacy of [that medicinal product was] not established and [that,] therefore ... the [risk-benefit] balance of [that medicinal product was] not favourable.'
- 250 In the light of that evidence, there is nothing to indicate that the CHMP was unaware of the possibility, in principle, of proposing a variation of the conditional MA for Ocaliva, including specific obligations. The applicant's assertion to the contrary is unsubstantiated. On the contrary, it follows from the opinion of that committee of 29 July 2024 that it considered that no clinical benefit of that medicinal product had been confirmed. In those circumstances, its decision not to propose an amendment of that conditional MA is consistent.
- 251 The question as to whether the CHMP, and subsequently the Commission, took into account all the available evidence, including the data to which the applicant refers, namely the numerous studies favouring Ocaliva and the additional risk minimisation measures and the study programme proposed by the applicant which, according to the applicant, could have been regarded as the basis for amended specific obligations, will be addressed in the examination of the fourth and fifth pleas.
- 252 Fifthly, the applicant's argument that no new or serious safety concerns were raised for Ocaliva in the recent renewal assessments or the recommendations from EMA's Pharmacovigilance Risk Assessment Committee ('PRAC') is ineffective in the present part

of the plea. The fact that the PRAC, in those recent renewal assessments or recommendations, did not raise the existence of a new or serious safety concern for that medicinal product, even if it were established, has no impact on the question whether the Commission infringed Article 6(4) of Regulation No 507/2006 by initiating the procedure for review of the conditional MA for that medicinal product.

253 Sixthly, the applicant has not raised, in the present part of the plea, any argument demonstrating a difference between the procedure for reviewing the conditional MA for a medicinal product and the procedure for renewal of that conditional MA as regards the application of general procedural rights, such as the right to be heard or the right to an effective remedy.

254 It must be concluded that the applicant has not demonstrated that the Commission infringed Article 6(4) of Regulation No 507/2006 by initiating and completing the procedure for review of the conditional MA for Ocaliva, while the procedure for renewal of that conditional MA was ongoing, or that it had infringed one of its rights resulting from that procedure.

255 Consequently, the second part of the first plea must be rejected.

The third plea, alleging infringement of the first paragraph of Article 116 of Directive 2001/83, as amended, and a manifest error of assessment

256 As a preliminary point, the applicant, supported by CBP Portugal, submits that, in the present case, it was for the Commission to establish that the conditions relating to the revocation of an MA, set out in Article 116 of Directive 2001/83, as amended, were met.

257 In the first place, the applicant submits that the Commission has not demonstrated that Ocaliva lacked therapeutic efficacy, within the meaning of Article 116 of Directive 2001/83, as amended, according to which the medicinal product in question does not enable therapeutic results to be obtained.

258 The applicant submits that, during the procedure leading to the adoption of the contested decision, neither the Commission nor the EMA assessed whether therapeutic results could be obtained from Ocaliva.

259 The applicant adds that although the CHMP found in its opinion that ‘no clinical benefit [had been] observed from treatment with Ocaliva’ and ‘concluded that the efficacy [of that medicinal product was] not established’, that conclusion, even if it were based on the intention-to-treat analysis (‘the ITT analysis’), is not based on any evidence, reason or finding capable of substantiating the assertion that ‘therapeutic results [could not] be obtained with [that] medicinal product’.

260 In the second place, the applicant, supported by CBP Portugal, submits that all the evidence, with the exception of the ITT analysis, which is at issue in the fourth plea, indicates that therapeutic results can be obtained with Ocaliva.

261 The Commission, supported by the EMA, disputes the applicant's arguments.

Preliminary observations

262 As a preliminary point, it should be noted that the present plea consists, in essence, of two parts.

263 In the first part, the applicant alleges, in essence, that there was an error of law in that neither the CHMP nor the Commission examined or established whether it was possible to obtain therapeutic results with Ocaliva.

264 In the second part, the applicant submits, in essence, that the CHMP and the Commission made a manifest error of assessment in concluding that the efficacy of Ocaliva was not established and that the risk-benefit balance of that medicinal product was unfavourable.

265 Under the first paragraph of Article 116 of Directive 2001/83, as amended, the competent authorities are to suspend, revoke or vary an MA if the view is taken that the medicinal product is harmful, that it lacks therapeutic efficacy, that the risk-benefit balance is not favourable or that the medicinal product's qualitative and quantitative composition is not as declared.

266 The conditions of variation, suspension or revocation of an MA are alternative and not cumulative (judgments of 11 December 2014, *PP Nature-Balance Lizenz v Commission*, T-189/13, not published, EU:T:2014:1056, paragraph 41, and of 19 September 2019, *GE Healthcare v Commission*, T-783/17, EU:T:2019:624, paragraph 44).

267 The conditions of variation, suspension or revocation of an MA must, moreover, be interpreted in accordance with the general principle, set out in the case-law, that the protection of public health must unquestionably take precedence over economic considerations (judgments of 19 April 2012, *Artegoda v Commission*, C-221/10 P, EU:C:2012:216, paragraph 99, and of 19 September 2019, *GE Healthcare v Commission*, T-783/17, EU:T:2019:624, paragraph 44).

The Commission's argument that the third plea is ineffective

268 It is appropriate, first of all, to examine the Commission's argument that the third plea is ineffective.

269 According to the Commission, the arguments put forward by the applicant in support of the third plea seek only to prove that it has not demonstrated that Ocaliva lacked therapeutic efficacy, without challenging the unfavourable risk-benefit balance of that medicinal product, which is the other ground on which the contested decision is based.

270 In that regard, it must be stated that the CHMP maintained, in its scientific conclusions annexed to the contested decision, that the efficacy of Ocaliva could not be established

and that, consequently, the risk-benefit balance of that medicinal product was unfavourable.

271 As the Commission rightly points out, the concept of a 'risk-benefit balance' is defined in Article 1(28a) of Directive 2001/83, as amended, as 'an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks as defined in point 28, first indent'.

272 In so far as the unfavourable risk-benefit balance of Ocaliva results, in particular, according to those scientific conclusions, from that medicinal product's lack of efficacy, the applicant's arguments that the lack of therapeutic efficacy has not been established also indirectly concern the establishment of the unfavourable risk-benefit balance of that medicinal product.

273 Consequently, the Commission's argument that the third plea is ineffective must be rejected.

The first part

274 As regards the applicant's argument that neither the CHMP nor the Commission examined or established whether it was possible to obtain therapeutic results with Ocaliva, it must be stated that such an argument has no factual basis. It is apparent from the scientific conclusions set out in the annex to the contested decision that the efficacy of that medicinal product could not be established and that, consequently, the risk-benefit balance was unfavourable. Furthermore, it is apparent from those conclusions that, according to that committee, in study 747-302, treatment with that medicinal product had no clinical benefit, whatever the stage of the disease.

275 The mere fact that neither the CHMP, in its opinion and its revised assessment report for the Article 20 referral procedure for Ocaliva of 29 July 2024, nor the Commission, in the contested decision, used the concept of 'therapeutic results' does not mean that those authorities did not examine or establish that the medicinal product in question lacked therapeutic efficacy. Moreover, the applicant has not explained to what extent the finding that 'no clinical benefit [had been] observed' or the finding that the 'efficacy of [that medicinal product was] not established' are in any way different from a finding that 'therapeutic results cannot be obtained from [that medicinal product]'. In response to a question to be answered in that regard by the Court at the hearing, it merely stated that each concept used by the legislature was important.

276 However, the applicant's argument that the concept of 'therapeutic results' is not covered by the finding that 'no clinical benefit was observed' or that 'the efficacy of Ocaliva could not be established', results in a restrictive interpretation of the terms used by the competent authorities to the detriment of their identical assessment, namely the lack of positive therapeutic effects of that medicinal product, rather than any omission on the part of those authorities, which constitutes an error of law. The first part of the third plea must therefore be rejected.

277 The question whether the CHMP, and subsequently the Commission, made a manifest error of assessment in concluding that Ocaliva was not effective and, consequently, its unfavourable risk-benefit balance will be examined in the second part of the third plea and in the fourth plea.

The second part

278 As regards the alleged manifest error of assessment committed by the CHMP and the Commission in concluding that the efficacy of Ocaliva had not been established and that the risk-benefit balance of Ocaliva was unfavourable, it should be recalled that the first paragraph of Article 116 of Directive 2001/83 confers rights on undertakings holding MAs, since it guarantees them the maintenance of the MAs as long as the existence of one of the conditions to vary, suspend or revoke them has not been established (see, to that effect, judgment of 19 April 2012, *Artegodan v Commission*, C-221/10 P, EU:C:2012:216, paragraph 96).

279 It follows that, as regards the burden of proof, it is for the competent authority, in the present case the Commission, to establish that the conditions relating to the revocation, suspension or variation of an MA, set out in Article 116 of Directive 2001/83, are met (see, to that effect, judgment of 7 March 2013, *Acino v Commission*, T-539/10, not published, EU:T:2013:110, paragraph 79, and of 19 September 2019, *GE Healthcare v Commission*, T-783/17, EU:T:2019:624, paragraph 47).

280 In view of the precautionary principle, the Commission may nevertheless merely provide serious and conclusive evidence which, without ruling out scientific uncertainty, gives reasonable grounds for doubting the harmlessness of the medicinal product concerned, its therapeutic effect, the existence of a favourable risk-benefit balance or the qualitative and quantitative composition declared (judgments of 3 December 2015, *PP Nature-Balance Lizenz v Commission*, C-82/15 P, not published, EU:C:2015:796, paragraph 23, and of 19 September 2019, *GE Healthcare v Commission*, T-783/17, EU:T:2019:624, paragraph 48).

281 That principle, which is a general principle of EU law, authorises the competent authorities, where there is uncertainty, to take appropriate measures in order to prevent certain potential risks for public health, safety and the environment without having to wait until the reality and seriousness of those risks become fully apparent (see judgment of 19 September 2019, *GE Healthcare v Commission*, T-783/17, EU:T:2019:624, paragraph 45 and the case-law cited; see, also, to that effect, judgment of 3 December 2015, *PP Nature-Balance Lizenz v Commission*, C-82/15 P, not published, EU:C:2015:796, paragraph 21).

282 Consequently, in accordance with the precautionary principle, the health risks which the grounds set out in the first paragraph of Article 116 of Directive 2001/83 aim to prevent need not be specific, but only potential (see judgment of 19 September 2019, *GE Healthcare v Commission*, T-783/17, EU:T:2019:624, paragraph 46; see, also, to that effect,

judgments of 10 April 2014, *Acino v Commission*, C-269/13 P, EU:C:2014:255, paragraph 59, and of 3 December 2015, *PP Nature-Balance Lizenz v Commission*, C-82/15 P, not published, EU:C:2015:796, paragraph 23).

283 However, the decision to vary, suspend or revoke an MA for a medicinal product is justified only where that decision is substantiated by new, objective, scientific or medical data (see judgment of 19 September 2019, *GE Healthcare v Commission*, T-783/17, EU:T:2019:624, paragraph 49 and the case-law cited).

284 In that respect, the competent authority is obliged to refer to the main reports and scientific expert opinions on which it relies and to explain, in the event of a significant discrepancy, the reasons why it has departed from the conclusions of the reports or expert opinions supplied by the undertakings concerned. That obligation is particularly strict in cases of scientific uncertainty. The consultation is to be *inter partes* and transparent in order to ensure that the substance considered has undergone an in-depth and objective scientific assessment, based on using the most representative scientific theories and scientific positions put forward by the relevant pharmaceutical laboratories (judgment of 19 September 2019, *GE Healthcare v Commission*, T-783/17, EU:T:2019:624, paragraph 50 and the case-law cited).

285 According to the case-law, when the Commission is called upon to carry out complex technical or scientific assessments, it has a broad discretion. In the context of its judicial review, the EU judicature must verify compliance with the procedural rules, the substantive accuracy of the facts adopted by the Commission, the absence of a manifest error in the assessment of those facts or the absence of misuse of powers (see judgment of 9 September 2010, *Novo Pharm v Commission*, T-74/08, EU:T:2010:376, paragraph 111 and the case-law cited).

286 As regards the scope of the review of the scientific assessments, it should be borne in mind that the Court cannot substitute its own assessment for that of the CHMP. Its power of judicial review is exercised only over the lawfulness of its operation, and over the internal consistency and reasoning of that committee. With regard to the latter element, the EU judicature may only examine whether the opinion contains a statement of reasons from which it is possible to ascertain the considerations on which the opinion is based, and whether it establishes a comprehensible link between the medical or scientific findings and their conclusions (see, to that effect, judgments of 11 December 2014, *PP Nature-Balance Lizenz v Commission*, T-189/13, not published, EU:T:2014:1056, paragraph 52, and of 19 September 2019, *GE Healthcare v Commission*, T-783/17, EU:T:2019:624, paragraph 51).

287 In the present case, as is apparent from Article 1 of the contested decision, the Commission, after consulting the CHMP (recitals 2 and 3 of that decision), based that decision on the scientific conclusions of that committee. Those conclusions are set out in the annex to that decision and thus form an integral part of that decision. Therefore, it must be held that the judicial review incumbent on the Court, in particular the

examination as to whether there has been a manifest error of assessment, must be exercised over those scientific conclusions as a whole (see, to that effect, judgment of 15 May 2024, *Fresenius Kabi Austria and Others v Commission*, T-416/22, EU:T:2024:316, paragraph 119 and the case-law cited).

288 In its opinion of 29 July 2024, the CHMP concluded that ‘the totality of data available from randomised clinical trials and real-world data [did] not confirm the clinical benefit of Ocaliva’ and that, as a consequence, ‘the efficacy of [that medicinal product was] not established and [that,] therefore ... the [risk-benefit] balance of [that medicinal product was] not favourable.’

289 None of the arguments raised by the applicant in the second part of the third plea is capable of demonstrating that the contested decision is vitiated by a manifest error of assessment in that regard.

290 In the first place, as regards the arguments of the applicant and CBP Portugal alleging that Ocaliva reduces biomarkers, first, it is stated in the ‘EMA Reflection Paper on regulatory requirements for the development of medicinal products for PBC and PSC’ (‘the EMA reflection paper’) that the goals for PBC treatment and management are the prevention of end-stage liver disease and the amelioration of associated symptoms.

291 Consequently, it is necessary to reject as factually incorrect the applicant’s argument that the reduction in biomarkers is, according to the EMA reflection paper, one of the key treatment goals for PBC.

292 Secondly, although it is true that the EMA reflection paper confirms that the reduction in biomarkers holds a degree of relevance, it also states that it could be difficult to confirm any resulting clinical benefit.

293 It follows that the Commission’s approach is consistent with the EMA reflection paper, in that the conditional MA for Ocaliva was granted in view of the observed reduction in biomarkers, but with the specific obligation that the efficacy of that medicinal product be confirmed by study 747-302, in accordance with Article 5(1) of Regulation No 507/2006.

294 In addition, it is expressly stated in the EMA reflection paper that the existence of a relationship between a reduction in biomarkers and clinically meaningful liver-related endpoints had been demonstrated only for the natural history of the disease and UDCA.

295 It follows that the existence of a relationship between a reduction in biomarkers and clinically meaningful liver-related endpoints had not yet been demonstrated for Ocaliva.

296 Thirdly, the applicant’s argument that the PRAC acknowledges, in its last assessment report, the direct correlation between biomarkers and the clinical efficacy of a medicinal product must be rejected as factually incorrect. The applicant cites in that regard the annex to the document entitled ‘PRAC rapporteur assessment comments on [the safety update report]’, which contains only the safety update report submitted by the MA

holder and the comments of the PRAC rapporteur, but does not reflect the opinion of the PRAC itself.

297 Fourthly, it is irrelevant that the Commission granted conditional MAs for two other medicinal products, namely Iqirvo – elafibranor and Seladelpar Gilead – seladelpar, on the basis of a reduction in the rates of ALP (alkaline phosphatase) and bilirubin biomarkers. That fact is irrelevant to the question whether the Commission made a manifest error of assessment when adopting the contested decision which concerns a different medicinal product, namely Ocaliva. In any event, those conditional MAs had also been granted subject to the specific obligation to confirm the efficacy of the medicinal products concerned. Accordingly, the approach followed by the Commission and the EMA for those medicinal products is consistent with that adopted for Ocaliva.

298 In the second place, the applicant refers to clinical guidelines and real-world evidence studies and to the fact that 7 000 patients are reported to be stabilised on Ocaliva, all of which demonstrate that therapeutic results can be obtained with that medicinal product.

299 First, the applicant's argument based on real-world evidence studies is not substantiated in the third plea.

300 Secondly, as regards the clinical guidelines, the applicant merely claims that those guidelines recognise the use of Ocaliva to achieve the therapeutic objectives of PBC patients. However, it does not dispute the Commission's argument that those guidelines do not constitute scientific evidence demonstrating the clinical benefit of that medicinal product. Consequently, the applicant's argument must be rejected as ineffective.

301 Thirdly, the applicant's argument that 7 000 patients are stabilised on Ocaliva is unsubstantiated and must, therefore, be rejected. The applicant does not provide any scientific evidence in support of that mere assertion. The mere fact that stabilised patients have used that medicine, even if assumed to be established, would at most demonstrate a correlation, but not a causal link capable of substantiating a finding of efficacy for that medicine.

302 In the third place, the applicant's argument that the PRAC reached a conclusion contrary to that of the CHMP is factually incorrect. In support of that argument, the applicant cites the annex to the document entitled 'PRAC rapporteur assessment comments on [the safety update report]'. As stated in paragraph 296 above, that document contains the safety update report submitted by the MA holder and the comments of the PRAC rapporteur, but does not reflect the opinion of the PRAC itself. In addition, certain quotations referred to by the applicant, namely those recognising a 'trend for positive effect of [Ocaliva] on the clinical outcomes' which, 'taken together, ... reinforce the antifibrotic benefit of [that medicinal product] beyond the treatment effect on the primary endpoint', concern study 747-303, which relates to a disease other than PBC, namely non-alcoholic steatohepatitis. Consequently, those quotations are not relevant to the answer to the question whether that medicinal product has clinical effects

corresponding to its indication, namely the treatment of patients with PBC who do not tolerate or respond well to UDCA (see paragraph 30 above).

303 It follows from the foregoing that the second part of the third plea must be rejected and, consequently, that plea must be rejected in its entirety.

The fourth plea, alleging a manifest error of assessment

304 The applicant, supported by CBP Portugal, raises the fourth plea, which is divided into three parts. In the first part, the applicant submits that the CHMP failed to provide evidence and plausible reasoning that the ITT analysis of study 747-302 was capable of providing the sole basis for a risk-benefit assessment of Ocaliva. By the second part, it claims that the CHMP did not carry out an analysis of the real risks of residual confounding in the other studies before concluding that they were objectively invalid. In the third part, it claims that that committee did not conduct a comparative analysis of the risks of bias and confounding in the ITT analysis of that study or in the other analyses. Furthermore, it failed to assess the remarkable consistency between the other studies before reaching a finding of relative invalidity. The second and third parts will be examined together.

305 The Commission, supported by the EMA, disputes the applicant's arguments.

The first part

306 The present part of the plea consists of three complaints.

– *The first complaint*

307 The applicant claims, in essence, that the CHMP committed a manifest error of assessment by accepting on several occasions that the results of study 747-302 could be interpreted by means of a comparison with the historical control group ('study 302-CE'). Accordingly, the CHMP also acknowledged that the ITT analysis of study 747-302 was never intended as the sole basis for interpreting that study.

308 The applicant infers from this that the results of study 747-302 and the risk-benefit assessment of Ocaliva should at least have been interpreted by including study 302-CE.

309 The Commission, supported by the EMA, disputes the applicant's arguments.

310 In the first place, it is apparent from the CHMP's revised assessment report for the Article 20 referral procedure for Ocaliva of 29 July 2024 that that committee took into account all the available data, including not only study 747-302, but also several other studies. In particular, it took into account study 302-EC. In that regard, it concluded that the results obtained from external control studies and analyses, including those resulting from study 747-302, based on real-world data, were not robust evidence sufficient to overcome the negative results of a double-blind, randomised, placebo-controlled trial.

Consequently, it took into account those other studies and the available real-world evidence, including study 302-EC, only as supporting exploratory information.

- 311 Accordingly, the applicant's claim that the CHMP merely took into account the ITT analysis of study 747-302 must be rejected.
- 312 The question whether the CHMP's conclusion that the results of studies and external control analyses based on real-world data were not robust evidence sufficient to overcome the negative results of a double-blind, randomised, placebo-controlled trial is vitiated by a manifest error of assessment will be examined in the third complaint in the first part of the fourth plea.
- 313 In the second place, it is apparent from the annex to Implementing Decision C(2016) 8685 final that the conditional MA for Ocaliva was granted with the specific obligation that the efficacy of that medicinal product be confirmed by study 747-302 (see paragraph 31 above).
- 314 In the third place, it is not apparent from the documents cited by the applicant that the CHMP agreed to replace the ITT analysis of study 747-302 with other studies or to attach greater weight to other studies.
- 315 First, it is true that the CHMP stated, in the document of 22 January 2015 provided as Annex A.44 to the application, that multiple historical controls could be used and that an alternative analysis could be useful, acknowledging that a randomised per-placebo analysis may lack power due to an insufficient sample size. However, it also stated in that document that the only analysis that is able unequivocally to determine a causal relationship and to ensure an unbiased analysis was the comparison between the two randomly selected treatment arms. Consequently, irrespective of any difficulties in subject enrolment and retention or if randomisation is ceased, the primary efficacy analysis which was initially planned – that is, that of comparing the randomly selected arm treated with Ocaliva ('the Ocaliva arm') with the arm that received a placebo ('the placebo arm'), also selected at random – should, according to that committee, nonetheless be performed.
- 316 Secondly, it is true that it is stated in the EMA's email of 12 October 2016, provided as Annex A.45 to the application, that 'with reference to the historical controls the protocol [could] be accepted'. However, it is also stated therein that the historical comparison and its conditions first had to be discussed with the EMA. Accordingly, it is in no way apparent from that email that the CHMP agreed to attach greater weight to historical comparisons than to the randomised, placebo-controlled trial. On the contrary, it is apparent from the remainder of the communication concerning the negotiation of the protocol, dated 11 October 2016 and provided as Annex B.17 to the defence, that the EMA had conveyed the CHMP's concerns as regards the historical comparison and the alternative primary analysis based on historical controls. According to that communication, the primary analysis was intended to be based on a comparison of the two randomly selected arms.

Accordingly, the holder of the conditional MA had to remove from the study protocol the possibility of an alternative analysis. In response, the former holder of the conditional MA stated that it understood the abovementioned concerns, specifying that it undertook to continue the study with the primary analysis by comparison with the placebo, that it did not wish to carry out an alternative analysis without having first discussed it and without having obtained approval from the regulatory bodies, and that it undertook to carry out a placebo-controlled study and that implementation of that study was a condition for a positive opinion and the grant of an MA.

317 Thirdly, it is true that it is apparent from the conditional MA renewal assessment report, drawn up by the CHMP on 11 November 2021, that that committee supported the approach of the conditional MA holder to conduct real-world studies. However, that committee also stated in that report that the data obtained from those studies were intended to supplement the confirmatory results of study 747-302. According to that report, the weight to be given to such data in the context of the assessment of the results of that study – that is to say, pending the final decision on the risk-benefit balance of Ocaliva for the indication that was subsequently approved – would be decided at the time of the full assessment of the data provided. That committee stated that those data would normally be regarded only as supporting or supplementary data, but not as essential data.

318 Fourthly, as the applicant itself submits, the CHMP stated, in the document dated 22 April 2021 and provided as Annex A.47 to the application, that it was not clear whether any further collection of data from open-label treatment and comparison to external controls could fill a gap in the comprehensiveness of the study 747-302 results. Accordingly, there is nothing in that document to indicate that that committee agreed to replace that study with other studies or to attach greater weight to other studies.

319 Consequently, no manifest error of assessment has been demonstrated in taking into account all the available data and the first complaint in the first part of the fourth plea must therefore be rejected.

– *The second complaint*

320 The applicant, supported by CBP Portugal, claims that study 747-302 is vitiated by shortcomings.

321 According to the applicant, study 747-302 suffered from functional unblinding and from the fact that almost 50% of patients who were initially randomly assigned to receive a placebo had switched to commercially available Ocaliva. Consequently, that study was ‘insufficiently “powered” to draw conclusions about the comparison between the placebo arm and the [Ocaliva] arm.’ The CHMP did not assess the impact of those factors on the suitability of the ITT analysis as the sole basis for the interpretation of that study and the risk-benefit assessment of that medicinal product. According to the applicant, the CHMP made a manifest error in considering that the analysis for the placebo arm of that study

had not been distorted by patients who had switched to that medicinal product, on the basis that that had occurred in the two randomly selected treatment arms and not only in the placebo arm. In reality, the switch from a placebo to Ocaliva did not occur solely in the placebo arm and a greater number of patients left the placebo arm rather than the Ocaliva arm.

322 The Commission, supported by the EMA, disputes the applicant's arguments.

323 In the first place, it is apparent from the CHMP's revised assessment report for the Article 20 referral procedure for Ocaliva of 29 July 2024 that that committee took into account the premature termination of study 747-302. That committee also responded to the applicant's argument that that study was insufficiently 'powered' to detect the effect of the proposed treatment. In that regard, the CHMP noted that, in view of the results of the study, it was highly unlikely that the observed lack of effect – with nearly 70% of the planned number of events – could have been reversed had the study not been terminated prematurely. In its view, a consistent trend in the main clinically meaningful endpoints would have been expected had there been a genuine clinical benefit. However, according to that committee, no such trend has been observed.

324 The applicant does not put forward any argument capable of demonstrating that that assessment is manifestly incorrect. It merely claims, in the reply, that the question whether a trend observed in a halted trial might be reversed in a hypothetical continuation of the study in question has no impact on the 'statistical power' of the data already gathered. However, that argument ignores the fact that the CHMP plausibly concluded that no consistent trend in the main clinically meaningful endpoints had been observed, whereas such a trend could have been expected had there been a genuine clinical benefit.

325 In the second place, the CHMP examined the applicant's argument alleging dropouts and taking of commercially available treatments allegedly caused by unblinding. In this regard, it considered that there may have been some differences in the timing of treatment discontinuation, but that observed rates in the premature discontinuation of treatment were similar in both treatment groups, namely 81.9% for the placebo arm and 72% for the Ocaliva arm. It is true that the rate of discontinuation was higher in the placebo arm than in the Ocaliva arm. However, the CHMP's conclusion that those rates were 'similar' is not manifestly incorrect.

326 The CHMP also considered that the percentage of subjects in the study who had started a commercially available treatment with a potential effect on ALP levels had been low and that the percentage was similar in the two treatment arms of study 747-302.

327 It is clear that there was no switch from placebo to Ocaliva in the Ocaliva arm, as argued by the applicant, but it follows from the CHMP's revised assessment report for the Article 20 referral procedure for that medicinal product of 29 July 2024 that a comparable

number of subjects in the Ocaliva arm had started treatment with that medicinal product or with bezafibrate, both of which are commercially available.

328 In the third place, in so far as the CHMP thus considered that neither the premature termination of the trial nor the adoption of commercially available treatments had had any impact on the conclusion that that trial had not demonstrated any clinical benefit from Ocaliva treatment, that committee was not required to reassess the impact of those circumstances in the context of the risk-benefit assessment or in its weighting, as the applicant appears to suggest.

329 It follows from the foregoing that the second complaint in the first part of the fourth plea must be rejected.

– *The third complaint*

330 The applicant submits that the other analyses carried out on the same dataset as that of study 747-302, such as an ‘as-treated’ analysis of that study, adjusted by means of the ‘inverse probability of censoring weighting’, and that an analysis ‘focused on the patient population matching the summary of product characteristics as requested from the CHMP’, favour Ocaliva. The CHMP acknowledged that the results of those analyses pointed in the right direction. However, it discarded them from the risk-benefit balance of that medicinal product without examining whether they could call into question the assumption that the ITT analysis was a suitable sole basis for assessing that balance.

331 The Commission, supported by the EMA, disputes the applicant’s arguments.

332 It should be noted that, in the context of the present complaint, the applicant refers to two analyses which had not been pre-specified – unlike the ITT analysis of study 747-302 – but which are post hoc analyses.

333 In that regard, the CHMP considered, in its revised assessment report for the Article 20 referral procedure for Ocaliva of 29 July 2024, that the post-hoc analyses could merely be considered as complementary and exploratory, since they presented a much lower level of evidence than the results of the randomised, placebo-controlled trial.

334 In so far as the applicant does not put forward any argument capable of demonstrating that that conclusion is vitiated by errors, the third complaint in the first part of the fourth plea and, consequently, that first part in its entirety must be rejected.

The second and third parts

335 In the second part of the fourth plea, first, the applicant claims that the CHMP infringed the principle of scientific excellence by discarding study 302-CE, study 301-LSTE-CE, study 405 (HEROES) and the study RECAPITULATE (together, ‘the four real-world studies’) from the risk-benefit assessment without assessing the measures taken in the context of those studies. As regards study 302-CE, the Commission also failed to take account of the

'Kowdley article', which reported in detail on the measures taken to address residual confounding in that study.

336 Secondly, the applicant submits that the CHMP neither assessed the 'remarkable' consistency between the four real-world studies nor responded to the arguments which it raised in that regard.

337 In the third part of the fourth plea, the applicant submits that the CHMP did not establish the risk of residual confounding in any of the real-world studies, as is apparent from the second part of the fourth plea. Nor did it assess the risk of bias and confounding in the ITT analysis of study 747-302. Nor did it compare the degree of bias and confusion between the real-world studies and that analysis.

338 The applicant further submits that the CHMP did not take into account the interventions of third parties submitted during the procedure. Moreover, after the adoption of the contested decision, several groups and associations criticised that decision on the ground that it was based on an inconclusive analysis which diverges from all other available evidence.

339 The Commission, supported by the EMA, disputes the applicant's arguments.

340 In the first place, it should be recalled that, first, according to the CHMP's revised assessment report for the Article 20 referral procedure for Ocaliva of 29 July 2024, that committee took into account all the available data, including the four real-world studies.

341 Consequently, the applicant's argument that the CHMP discarded the four real-world studies must be rejected as factually incorrect.

342 Secondly, it is apparent from the CHMP's revised assessment report for the Article 20 referral procedure for Ocaliva of 29 July 2024 that that committee took into account all the data submitted to it, including those received from 14 third parties, in particular patient associations, health professionals and academics. According to that report, those parties shared their experiences and advocated for the continued availability of that medicinal product and for the views of patients and healthcare professionals to be taken into account.

343 Consequently, the applicant's argument that the CHMP did not take into account arguments based on third party interventions during the procedure must also be rejected as factually lacking.

344 Thirdly, the applicant's argument based on the statements of the groups and associations made after the adoption of the contested decision must be rejected as ineffective. It is settled case-law that the legality of an EU measure must be assessed on the basis of the facts and the law as they stood at the time when the measure was adopted (see judgment of 28 July 2011, *Agrana Zucker*, C-309/10, EU:C:2011:531,

paragraphs 31 and 45 and the case-law cited; judgment of 17 October 2013, *Schaible*, C-101/12, EU:C:2013:661, paragraph 50).

345 In the second place, the CHMP considered that, during the studies, risk rates in favour of Ocaliva had been observed, although they were characterised by significant confidence intervals. It found that a divergence between the real-world data and the results observed during the controlled trial had been observed and considered that it was due to the lack of a randomised comparison with a very high risk of residual confounding in the baseline balance and during follow-up. Consequently, it concluded that the results obtained from those studies and analyses, based on real-world data, were not robust evidence sufficient to overcome the negative results of a double-blind, randomised, placebo-controlled trial. Accordingly, in its view, those other studies had to be regarded only as complementary and exploratory, but were not sufficient to demonstrate the clinical efficacy of that medicinal product.

346 Therefore, the applicant's argument that the CHMP failed to examine the reasons for the divergence between real-world data and the results observed during the controlled trial is factually incorrect and must be rejected.

347 In the third place, the applicant criticises, in essence, the fact that the CHMP concluded that the other data were not sufficient to overcome the negative results of a double-blind, randomised, placebo-controlled trial. In its view, that approach is dogmatic and all of the evidence should have been weighed up.

348 The following should be noted in that regard.

349 First, it is true that the CHMP's conclusion is based on the consideration that the double-blind, randomised, placebo-controlled trial had greater probative value than the other evidence provided by the applicant.

350 As the Commission and the EMA explain, the hierarchy of evidence used in the present case, which is referred to in paragraph 349 above, is explained in particular by the specific characteristics of a randomised and controlled trial, such as the choice of a control group, randomisation and often blinding. That approach is in line with the EMA Directive entitled 'ICH Topic E9 Statistical Principles for Clinical Trials', according to which a confirmatory trial is an adequately controlled trial in which the hypotheses are stated in advance and evaluated. According to that directive, as a general rule, confirmatory trials are necessary to provide solid evidence of efficacy or safety. It is also stated in that directive that the ideal is to include all subjects selected at random following the ITT analysis, in order to preserve the initial randomisation in the analysis, which is important in preventing bias and in providing a secure foundation for statistical tests.

351 By contrast, according to the Commission and the EMA, real-world studies do not have the same design features intended to minimise the risk of bias, in particular randomisation.

- 352 This is confirmed by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology. According to that guide, unmeasured confounding can be adjusted for only through randomisation.
- 353 Therefore, according to the EMA reflection paper, the use of real-world evidence is generally not recommended but would be acceptable as an explorative approach.
- 354 Secondly, the applicant has not raised any argument calling into question the principles set out in paragraphs 350 and 353 above relating to the hierarchy of evidence as such. The CHMP and the Commission complied with those principles.
- 355 However, the applicant submits that the CHMP should have taken into account the steps taken in the four real-world studies to address residual confounding, which are also described in the 'Kowdley article'. In that context, it refers in particular to propensity scores.
- 356 In that regard, it should be noted that the CHMP considered, in its revised assessment report for the Article 20 referral procedure for Ocaliva of 29 July 2024, that methods based on propensity scores are useful tools for balancing prognostic factors, but that, unlike randomisation, they only allow adjustment for known and measured factors, so that they will never overcome the effect of randomisation.
- 357 That is consistent with the principles set out in paragraphs 350 and 352 above.
- 358 Furthermore, the EMA's argument that it is, by definition, impossible to resolve an unknown bias completely must be accepted. It is logical to assume that such a bias cannot be directly measured or corrected.
- 359 Conversely, the applicant's assertion that, in sensitivity analyses, the effect of unknown sources of bias could be estimated, modelled and addressed is unsubstantiated. The mere fact that sensitivity analyses are recognised in EMA guidelines does not demonstrate that those analyses are recognised in order to estimate and model the occurrence of unknown bias.
- 360 Consequently, the applicant has not demonstrated that the CHMP made a manifest error of assessment in concluding that, despite certain measures taken in the context of the real-world studies, the results of those studies did not make it possible to overcome the negative results of a double-blind, randomised, placebo-controlled trial.
- 361 Thirdly, as regards the applicant's argument that the CHMP did not assess the risk of confounding and bias of the ITT analysis of study 747-302, as is apparent from the first part of the fourth plea, it is sufficient to note that the applicant's arguments alleging deficiencies in that analysis were rejected in the examination of the second complaint in the first part of the fourth plea.
- 362 It follows that that argument must also be rejected in the third part of the fourth plea.

363 Fourthly, in so far as the CHMP concluded, without committing a manifest error of assessment, that the ITT analysis of study 747-302 was reliable, it was not required, in accordance with the principles relating to the hierarchy of evidence described in paragraphs 350 to 353 above, to carry out an 'impartial and systematic ... weighing of the evidence' or a 'comparison between the degree [of] bias and confounding between the [real-world studies], on the one hand, and [that analysis], on the other hand', as the applicant understands them, as the applicant understands them. In that regard, the EMA's argument that the difference in probative value between the types of evidence stems from a difference in their quality – namely on the one hand, the double-blind, randomised, placebo-controlled trial and, on the other hand, the real-world studies – is the very reason for that hierarchy. Accordingly, that difference in value cannot be called into question by a greater amount of evidence with less probative value, such as evidence taken from real-world studies.

364 Consequently, the applicant's argument that the CHMP dogmatically discarded the real-world studies on the grounds that, irrespective of the number of studies, they could never outweigh the negative results of a double-blind, randomised, placebo-controlled trial, must be rejected.

365 For that reason, the applicant's argument that the CHMP neither assessed the 'remarkable' consistency between the four real-world studies or responded to the arguments which it raised in that regard should also be rejected.

366 It follows from all of the foregoing that the applicant has not shown that the CHMP committed a manifest error of assessment in the assessment of the available data and demonstrated bias in that regard.

367 Consequently, the second and third parts of the fourth plea must be rejected and, therefore, the fourth plea in its entirety must be dismissed.

The fifth plea, alleging infringement of the principles of proportionality and the protection of legitimate expectations and infringement of Article 57 of Regulation No 726/2004, as amended by Regulation 2019/5

368 The applicant, supported by CBP Portugal, submits that the CHMP did not conclude that there were comprehensive data. By contrast, it concluded that there was no conclusive evidence that Ocaliva prolonged the time to relevant clinical events. That conclusion does not amount to conclusive evidence that that medicinal product lacks efficacy.

369 The CHMP should have assessed whether the studies proposed by the applicant were capable of supplementing the available data, thus allowing the conditional MA to be maintained, if necessary, with a modification of the specific obligations. In that regard, the applicant submits that the legislature did not set a time limit for the adoption of a final decision on a conditional MA.

- 370 First, the applicant submits that, consequently, the Commission acted in breach of the principle of the protection of legitimate expectations, since, in the 2021 scientific advice and in the 2021 renewal assessment report, the CHMP specifically informed the conditional MA holder that it would carry out an assessment of the clinical study programme and of its ability to provide comprehensive data.
- 371 Secondly, the applicant, supported by CBP Portugal, claims that the Commission infringed the principle of proportionality, in that the CHMP, the EMA and the Commission directly adopted the most onerous measure, namely the revocation of the conditional MA for Ocaliva, without assessing the possibility of imposing other specific obligations, even in the absence of safety concerns.
- 372 Thirdly, the Commission infringed Article 57(1) of Regulation No 726/2004, as amended by Regulation 2019/5, by failing to evaluate the proposed study programme.
- 373 The Commission, supported by the EMA, disputes the applicant's arguments.
- 374 As a preliminary point, it should be noted that the fifth plea is based on the premiss that a conditional MA must be renewed as long as the data are not 'comprehensive'. The applicant relies on Article 14-a(1) of Regulation No 726/2004, as amended by Regulation 2019/5, according to which a conditional MA may be granted prior to the submission of comprehensive clinical data. In the context of the CHMP's previous practice regarding other medicinal products, the CHMP explicitly found the data to be comprehensive, leading the applicant to conclude that, in the absence of such an explicit finding in the present case, the EMA and the Commission were under an obligation to supplement the file before they could revoke the conditional MA for Ocaliva.
- 375 However, the applicant's line of argument cannot succeed.
- 376 The fact that a conditional MA is granted only where the data are not yet comprehensive does not mean that such an authorisation can be revoked only once the data are comprehensive.
- 377 More specifically, Article 20 of Regulation No 726/2004, as amended by Regulation 2019/5, does not set out any requirement that the data must be comprehensive in order for the Member States or the Commission to be able to initiate a procedure for review of the conditional MA for a medicinal product. On the contrary, as is apparent from that provision, as interpreted in the examination of the first plea (see paragraphs 213 to 255 above), it applies regardless of the stage of the procedure for renewal of the conditional MA concerned and takes effect 'immediately' once one of those actors considers that it is appropriate to apply, inter alia, one of the measures provided for in the first paragraph of Article 116 of Directive 2001/83, as amended.
- 378 As regards the first paragraph of Article 116 of Directive 2001/83, as amended, it is settled case-law that, in view of the precautionary principle, the Commission may nevertheless merely provide serious and conclusive evidence which, without ruling out

scientific uncertainty, gives reasonable grounds for doubting the harmlessness of the medicinal product concerned, its therapeutic effect, the existence of a favourable risk-benefit balance or the qualitative and quantitative composition declared (judgments of 3 December 2015, *PP Nature-Balance Lizenz v Commission*, C-82/15 P, not published, EU:C:2015:796, paragraph 23, and of 19 September 2019, *GE Healthcare v Commission*, T-783/17, EU:T:2019:624, paragraph 48).

379 Similarly, the decision to vary, suspend or revoke an MA for a medicinal product is justified only where that decision is substantiated by new, objective, scientific or medical data (see judgment of 19 September 2019, *GE Healthcare v Commission*, T-783/17, EU:T:2019:624, paragraph 49 and the case-law cited).

380 It follows from the foregoing that it is not necessary for the data to be comprehensive, as understood by the applicant, in order either for a procedure for review to be initiated under Article 20 of Regulation No 726/2004, as amended by Regulation 2019/5, or for one of the measures provided for in the first paragraph of Article 116 of Directive 2001/83, as amended, to be applied.

381 That is also the only interpretation that enables the competent authorities to achieve the objective pursued by Article 116 of Directive 2001/83, as amended, namely the protection of public health, as set out in recital 2 of that directive (see, to that effect, judgment of 15 May 2024, *Fresenius Kabi Austria and Others v Commission*, T-416/22, EU:T:2024:316, paragraphs 93 to 95 and the case-law cited).

382 The ability to pursue the objective of protecting public health would be considerably undermined if the competent authorities were required to wait until the holder of a conditional MA has completed the dossier before being able to adopt one of the measures provided for in the first paragraph of Article 116 of Directive 2001/83, as amended, where they already have new, objective, scientific or medical data (see, to that effect and by analogy, judgment of 16 December 2020, *PlasticsEurope v ECHA*, T-207/18, EU:T:2020:623, paragraph 52 and the case-law cited).

383 Furthermore, in so far as the applicant, in arguing that the data were not comprehensive, contends that those data were insufficient in the present case, it suffices to note that the CHMP concluded, without committing a manifest error of assessment, in its opinion of 29 July 2024, that ‘the totality of data available from randomised clinical trials and real-world data [did] not confirm the clinical benefit of Ocaliva’ and that, as a consequence, ‘the efficacy of [that medicinal product was] not established and [that,] therefore ... the [risk-benefit] balance of [that medicinal product was] not favourable’ (see paragraphs 288 to 303 above and the Court’s assessment in the context of the examination of the fourth plea).

384 In those circumstances, neither the CHMP nor the Commission, which endorsed the scientific conclusions of that committee, was obliged to assess whether it was appropriate to wait for the results of other studies. In that regard, that committee rightly

noted, in its revised opinion of 29 July 2024, that the possibility that the holder of the conditional MA for Ocaliva might carry out a study in the future, in order to provide more data on the efficacy and safety of that medicinal product, had no impact on the conclusion based on the data available when that opinion was adopted.

385 It follows that the fifth plea is based on an incorrect premiss.

386 Furthermore, first, as regards the alleged breach of the principle of protection of legitimate expectations, it must be noted that the documents provided by the applicant in support of its line of argument do not establish such a breach.

387 The CHMP stated, in its initial scientific advice of 2021, provided as Annex A.47 to the application, that it would be in a position to decide whether the data were comprehensive only when all the data obtained in studies 747-302 and 747-401 had been submitted and evaluated. Similarly, it noted that it was not certain, at that time, that other data would be able to fill the gap and that that would depend on the evaluation and conclusions to be drawn from the data obtained in those studies.

388 Furthermore, it is stated in the 2021 assessment report on the renewal of the conditional MA, provided as Annex A.28 to the application, that it is necessary first to submit and assess the results from studies 747-302 and 747-401 before deciding whether other data could fill a gap observed in those studies.

389 The assessment of the CHMP in its opinion and its revised report of 29 July 2024, followed by the Commission in the contested decision, is entirely consistent with the two documents cited by the applicant.

390 Consequently, the applicant's argument must be rejected as factually incorrect.

391 Secondly, as regards the principle of proportionality, it should be borne in mind that the acts adopted by EU institutions must not exceed the limits of what is appropriate and necessary in order to attain the objectives legitimately pursued by the legislation in question; when there is a choice between several appropriate measures recourse must be had to the least onerous, and the disadvantages caused must not be disproportionate to the aims (judgments of 13 November 1990, *Fedesa and Others*, C-331/88, EU:C:1990:391, paragraph 13; of 5 May 1998, *United Kingdom v Commission*, C-180/96, EU:C:1998:192, paragraph 96; and of 11 December 2014, *PP Nature-Balance Lizenz v Commission*, T-189/13, not published, EU:T:2014:1056, paragraph 111).

392 In an area such as that at issue in the present case, in which the public authority concerned is called upon to undertake complex assessments, the legality of a measure adopted in that area can be affected only if the measure is manifestly inappropriate having regard to the objective which the competent institutions are seeking to pursue (see judgment of 19 December 2019, *Vanda Pharmaceuticals v Commission*, T-211/18, EU:T:2019:892, paragraph 153 and the case-law cited).

- 393 In order to assess whether the principle of proportionality has been observed in the field of public health, account must be taken of the fact that human health and human life rank foremost among the assets and interests protected by the FEU Treaty (see judgment of 19 December 2019, *Vanda Pharmaceuticals v Commission*, T-211/18, EU:T:2019:892, paragraph 154 and the case-law cited).
- 394 The Court has also held that, given the exclusive nature of the criteria of safety, efficacy and quality enshrined in the EU system for harmonising the grant and management of MAs for medicinal products, it is solely in the light of those criteria that the proportionality of a measure suspending or revoking an MA must be assessed. It follows that the relevant interests in the context of the review of proportionality are the same as those related to the protection of public health, taken into consideration in the application of the relevant legislation (see judgment of 19 December 2019, *Vanda Pharmaceuticals v Commission*, T-211/18, EU:T:2019:892, paragraph 155 and the case-law cited).
- 395 The first paragraph of Article 116 of Directive 2001/83, as amended, provides for three possibilities for a competent authority when it finds that the risk-benefit balance of a medicinal product is not favourable. In such a situation, the competent authority may suspend, revoke or vary the MA in question. By providing for those three options of differing intensity, the EU legislature has taken account of the principle of proportionality.
- 396 In that regard, the competent authority must have recourse, as a first step, to variation of the MA, which is the least restrictive of the measures provided for in the first paragraph of Article 116 of Directive 2001/83, as amended, provided that such modification constitutes an appropriate measure.
- 397 It follows from the case-law that any measures which are less restrictive than the measure adopted may be taken into consideration in the context of the proportionality test only if they are equally suitable for achieving the objective pursued by the contested measure adopted by the EU institution (see, to that effect, judgments of 14 December 2004, *Arnold André*, C-434/02, EU:C:2004:800, paragraph 55; of 14 December 2004, *Swedish Match*, C-210/03, EU:C:2004:802, paragraph 56; and of 4 May 2016, *Philip Morris Brands and Others*, C-547/14, EU:C:2016:325, paragraph 180).
- 398 The Commission, in the contested decision, relies, according to Article 1 of that decision, on the CHMP's scientific conclusions, including the conclusion that 'the totality of data available from randomised clinical trials and real-world data [did] not confirm the clinical benefit of Ocaliva' and that, as a consequence, 'the efficacy of [that medicinal product was] not established and [that,] therefore ... the [risk-benefit] balance of [that medicinal product was] not favourable.' None of the measures proposed by the applicant, such as a variation of the conditional MA, for example through the adoption of additional risk minimisation measures and a study programme, were equally suitable for achieving the objective pursued by that decision, namely to ensure that patients are not administered

the same medicinal product with a negative risk-benefit balance due to lack of efficacy (see paragraphs 226 to 229 above as regards the objectives pursued by Regulations No 726/2004 and No 507/2006).

399 Consequently, the applicant's line of argument alleging breach of the principle of proportionality cannot succeed.

400 Thirdly and lastly, as regards the alleged infringement of Article 57(1) of Regulation No 726/2004, as amended by Regulation 2019/5, it is sufficient to note that the applicant has not demonstrated that the CHMP committed a manifest error by failing to take into account the available data, as is apparent in particular from the assessment carried out by the Court in the examination of the third and fourth pleas. As regards, more specifically, the study programme proposed by the applicant, it is sufficient to note that that paragraph stipulates that the EMA is to provide the Member States and the institutions of the Union with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human use or veterinary medicinal products which is referred to it in accordance with the Union legislation relating to medicinal products for human use or veterinary medicinal products. The fact that, in the future, more data relating to the safety and efficacy of a medicinal product for human use could be obtained, does not in any way prevent the CHMP from proposing – and the Commission from approving – the revocation of a conditional MA in a situation in which the CHMP concludes, on the basis of a reliable and conclusive study, that such a medicinal product lacks therapeutic efficacy.

401 Consequently, the applicant's complaint alleging infringement of Article 57(1) of Regulation No 726/2004, as amended by Regulation 2019/5, and, consequently, the fifth plea in its entirety, must be rejected.

The additional plea raised by CBP Portugal

402 In its statement in intervention, CBP Portugal raises an additional plea.

403 CBP Portugal submits that the contested decision was in breach of the right of access to health, as guaranteed by Articles 35 and 52 of the Charter.

404 CBP Portugal argues that the contested decision constitutes a limitation to the right of access to health of PBC patients who rely on Ocaliva to stabilise their condition and prevent further liver degradation, since they can no longer access the prescribed medical treatment as easily and rapidly as they could when Ocaliva had a valid conditional MA.

405 According to CBP Portugal, the revocation of the conditional MA for Ocaliva by the contested decision constitutes a limitation to the right of access to health which is neither necessary nor proportionate.

406 In the first place, the revocation of the conditional MA for Ocaliva was not the least intrusive measure, as provided for in Article 116 of Directive 2001/83, as amended.

According to CBP Portugal, that conditional MA could have been varied by imposing new specific obligations or restricted to patients already using Ocaliva.

407 In the second place, CBP Portugal submits that the negative impact of the contested decision on the lives of PBC patients who rely on Ocaliva to stabilise their disease is greater than any positive outcome related to the protection of public health that could result from the revocation of the conditional MA for Ocaliva.

408 First, CBP Portugal claims that most of the available data demonstrate that Ocaliva achieved favourable therapeutic results for more than 7 000 patients in the European Union. According to CBP Portugal, the EMA issued a favourable opinion and concluded that Ocaliva remained in compliance with the requirements of Article 14-a of Regulation No 726/2004, as amended by Regulation 2019/5, in the context of the procedure for renewal of its conditional MA of November 2023, which was the last such renewal before the entry into force of the contested decision.

409 Secondly, the ITT analysis of study 747-302, on which the decision to initiate the procedure for review of the conditional MA for Ocaliva was based, is neither conclusive nor reliable and stands in opposition to the opinions of international panels of experts.

410 In addition, according to CBP Portugal, the constant reduction in biomarkers confirmed by study 747-302 should have been a critical factor in the Commission's evaluation process concerning the conditional MA for Ocaliva instead of exclusively taking into account the inconclusive ITT analysis.

411 Thirdly, the application in the present case of the procedure for review of the conditional MA for Ocaliva was incorrect and resulted in the unjust revocation of that conditional MA. The previous renewals of that conditional MA underscored the ongoing compliance of Ocaliva with the necessary regulatory standards for quality, safety, and efficacy.

412 Fourthly, according to CBP Portugal, patients who took Ocaliva have no viable alternatives to stabilise their disease and prevent other pathologies.

413 The applicant considers that the present additional plea is admissible.

414 The applicant agrees with CBP Portugal that the contested decision infringes Articles 35 and 52 of the Charter.

415 The applicant submits that a direct consequence of the contested decision is that it is unable to supply patients who rely on Ocaliva in Portugal and other Member States, which has resulted in a denial of access to that therapy.

416 The Commission submits that the present additional plea is inadmissible and, in any event, unfounded.

417 In that regard, it must be borne in mind that, under Article 142(1) of the Rules of Procedure, intervention is to be limited to supporting, in whole or in part, the form of order sought by one of the main parties. In addition, as Article 142(3) of those rules provides, the intervener must accept the case as he or she finds it at the time of his or her intervention.

418 According to the case-law, Article 142(1) and (3) of the Rules of Procedure confer on the intervener the right to set out arguments as well as pleas independently, in so far as they support the form of order sought by one of the main parties and are not entirely unconnected with the issues underlying the dispute, as established by the applicant and defendant, as that would otherwise change the subject matter of the dispute (see, to that effect, judgment of 15 June 2005, *Regione autonoma della Sardegna v Commission*, T-171/02, EU:T:2005:219, paragraph 152 and the case-law cited).

419 In the present case, the dispute, as established by the applicant and the Commission, concerns the annulment of the contested decision. The parameters of that dispute are delimited by the five pleas put forward by the applicant: the first alleges in essence an infringement of Article 6(4) of Regulation No 507/2006; the second, an infringement of the right to sound administration under Article 41 of the Charter; the third, an infringement of the last sentence of the first paragraph of Article 116 of Directive 2001/83, as amended; the fourth, a manifest error of assessment; and the fifth, a breach of the principles of proportionality and the protection of legitimate expectations, as well as of Article 57 of Regulation No 726/2004, as amended by Regulation 2019/5.

420 In so far as the arguments raised by CBP Portugal under the heading 'First plea', alleging that the 'contested decision infringes Articles 35 and 52 of the Charter' in so far as the Commission, by revoking the conditional MA for Ocaliva, unlawfully limited the right of access to health must be understood as alleging infringement of those provisions, it must be stated that neither the application nor the defence contains any arguments concerning a possible breach of the rights of patients guaranteed by Articles 35 and 52 of the Charter. That allegation of infringement was raised for the first time in CBP Portugal's statement in intervention.

421 The present additional plea must therefore be rejected as inadmissible.

422 In any event, in so far as, irrespective of the provisions the infringement of which is alleged by CBP Portugal, the essence of the arguments which it raises under the heading 'First plea' may be linked to the pleas and arguments raised by the applicant and, more specifically, to the first, third, fourth and fifth pleas, it must be pointed out that those arguments have all already been rejected in the context of the examination of those pleas.

The request for examination of a witness

423 The applicant requests, by way of the measures of inquiry referred to in Article 91 of the Rules of Procedure, that Professor D. be heard as a witness. The witness is a PBC expert

who co-drafted the 'Kowdley article' which the EMA and the Commission failed to take into account. According to the applicant, that expert must be examined in order to understand what actually happened in study 747-302 from a medical and ethical point of view, taking into account the views of patients.

424 CBP Portugal supports the request for a witness to be heard. According to CBP Portugal, the expert in question can, inter alia, clarify the reasons why the ITT analysis of study 747-302 should not have been used as the sole basis for the contested decision. The expert in question can also explain the role of biomarkers in assessing the efficacy of Ocaliva. Lastly, according to CBP Portugal, the examination of that expert must allow for a comparison of that medicinal product and its functioning with other solutions available on the market.

425 The Commission and the EMA take the view that the request for a witness to be heard must be refused.

426 In that regard, the Court is the sole judge of any need to supplement the information available to it in respect of the cases before it (see judgment of 22 November 2007, *Sniace v Commission*, C-260/05 P, EU:C:2007:700, paragraph 77 and the case-law cited).

427 In that context, where a request for the examination of witnesses, made in the application, states precisely about what facts and for what reasons the witness or witnesses should be examined, it then falls to the Court to assess the relevance of that request to the subject matter of the dispute and the need to examine the witnesses (see judgment of 26 January 2017, *Duravit and Others v Commission*, C-609/13 P, EU:C:2017:46, paragraph 109 and the case-law cited).

428 In the present case, there is no need to proceed with the witness examination requested by the applicant.

429 First, the request for the examination of a witness was not submitted until after the closure of the written part of the procedure and the applicant has not provided any argument to justify that late request. In accordance with Article 88(2) of the Rules of Procedure, where a request for the adoption of a measure of inquiry is made after the first exchange of pleadings, the party submitting that request must state the reasons for which it was unable to submit it earlier.

430 Secondly, the applicant does not state with the necessary precision the facts on which the witness should be heard, but merely asserts in general terms that Professor D's witness statement would provide the Court with guidance on what actually happened in study 747-302.

431 Thirdly, it must be noted that the information in the file, supplemented by the explanations provided by the parties at the hearing, was sufficient to enable the Court to rule on the present action on the basis of the forms of order sought, the pleas in law and

the arguments put forward during the proceedings and in the light of the documents lodged by the parties.

Conclusion on the action

432 It follows from all of the foregoing that the action must be dismissed in its entirety, without there being any need to adopt the measure of inquiry requested by the applicant for the examination of a witness.

Costs

433 Under Article 134(1) of the Rules of Procedure, the unsuccessful party is to be ordered to pay the costs if they have been applied for in the successful party's pleadings. Since the applicant has been unsuccessful, it must be ordered to bear its own costs and to pay those incurred by the Commission, including the costs relating to the interlocutory proceedings, in accordance with the form of order sought by the Commission.

434 Under Article 138(1) of the Rules of Procedure, read in conjunction with Article 1(2)(f) thereof, the Member States, institutions, bodies, offices and agencies of the European Union which have intervened in the proceedings are to bear their own costs. Accordingly, the EMA must bear its own costs.

435 Under Article 138(3) of the Rules of Procedure, the General Court may order an intervener other than those referred to in paragraphs 1 and 2 to bear its own costs. In the circumstances of this case, CBP Portugal must be ordered to bear its own costs.

On those grounds,

THE GENERAL COURT (Fifth Chamber)

hereby:

- 1. Dismisses the action;**
- 2. Orders Advanz Pharma Ltd to bear its own costs and those incurred by the European Commission, including those relating to the proceedings for interim relief;**
- 3. Orders the European Medicines Agency (EMA) and CBP Portugal to bear their own costs.**

Sampol Pucurull

Laitenberger

Valasidis

Delivered in open court in Luxembourg on 23 September 2026.

Registrar

President

Table of contents

Legal framework

Background to the dispute

Events subsequent to the bringing of the action

Forms of order sought

Law

The second plea, alleging infringement of the right to sound administration under Article 41 of the Charter

The second complaint in the first part and the second part

- Preliminary observations
- The subject of the AHEG meeting of 12 June 2024
- The second complaint in the first part of the second plea
- The second part of the second plea in law

The third complaint in the first part of the plea

The fourth complaint in the first part of the second plea

The first complaint in the first part and the third part

- The first complaint in the first part and the first complaint in the third part
- The second complaint in the third part of the second plea

Second part of the first plea, alleging infringement of Article 6(4) of Regulation No 507/2006

The third plea, alleging infringement of the first paragraph of Article 116 of Directive 2001/83, as amended, and a manifest error of assessment

Preliminary observations

The Commission's argument that the third plea is ineffective

The first part

The second part

The fourth plea, alleging a manifest error of assessment

The first part

- The first complaint
- The second complaint
- The third complaint

The second and third parts

The fifth plea, alleging infringement of the principles of proportionality and the protection of legitimate expectations and infringement of Article 57 of Regulation

No 726/2004, as amended by Regulation 2019/5

The additional plea raised by CBP Portugal

The request for examination of a witness

Conclusion on the action

Costs

^{*} Language of the case: English.

¹ This judgment is published in extract form.