20 October 2022
EMA/COMP/646322/2022 Corr.1[1]
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 12-14 July 2022

Chair: Violeta Stoyanova-Beninska – Vice-Chair: Armando Magrelli

Disclaimers

Some of the information contained in this set of minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review. Additional details on some of these procedures will be published in the COMP meeting reports once the procedures are finalised.

Of note, this set of minutes is a working document primarily designed for COMP members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

[1] Correction in section 2.2.27.

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

The Chair opened the meeting by welcoming all participants. Due to the coronavirus (COVID-19) pandemic, and the associated EMA Business Continuity Plan (BCP), the meeting was held remotely.

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some Committee members and experts for concerned agenda topics.

Participants were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion. No new or additional interests or restrictions were declared.

Restrictions applicable to this meeting are captured in the List of participants included in the minutes.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure. All decisions taken at this meeting were made in the presence of a quorum of members. All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

The agenda for 12-14 July 2022 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 14-16 June 2022 were adopted with amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. mazindol - EMA/OD/0000085890

Propharma Group The Netherlands B.V.; Treatment of idiopathic hypersomnia (IH)

COMP Rapporteur: Eva Malikova

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Number of people affected

The sponsor provided a prevalence estimate based on non-European sources. The sponsor was requested to re-calculate the prevalence estimate based on relevant epidemiological

source and registers for the proposed orphan condition. For the estimation and presentation of the prevalence estimate the sponsor is advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

In the written response, the sponsor provided a revision based on an assumption of a ratio between idiopathic hypersomnia and narcolepsy. A review article submitted reported that the ratio of IH to narcolepsy ranged from 10.6% (Billiard, 1996; France) to 76.9% (Roth, 1996; Czech Republic). The Anderson et al. (2007) article reported that within their cohort, the prevalence of IH was 60% of the prevalence of narcolepsy (77 vs. 126 patients), within the range of the ratios reported in the Billiard review article (10.6%-76.9%). A survey of 18,980 general-population European subjects from the UK, Germany, Italy, Portugal, and Spain reported that the diagnosis of narcolepsy (using International Classification of Sleep Disorders criteria) was found in 0.047% of the sample (4.7 per 10,000; Ohayon 2002). Applying the reported prevalence ratios of IH to narcolepsy, the prevalence of IH in the EU-27 in 2021 would thus be estimated at a range of 0.50 per 10,000 (4.7 narcolepsy patients per 10,000*10.6%) to 3.6 per 10,000 (4.7 narcolepsy patients per 10,000*76.9%).

The COMP accepted the more conservative estimate of 3.6 in 10,000 and recommended granting the orphan designation.

The Committee agreed that the condition, idiopathic hypersomnia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing mazindol was considered justified based on preliminary clinical data showing a mean Epworth Sleepiness Scale reduction score with 84% of patients being responders.

The condition is chronically debilitating due to episodes of excessive daytime sleepiness.

The condition was estimated to be affecting approximately 3.6 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for mazindol, for treatment of idiopathic hypersomnia, was adopted by consensus.

2.1.2. - EMA/OD/0000085805

Treatment of mastocytosis

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 29 June 2022, prior to responding to the list of issues.

2.1.3. allogeneic placenta-derived decidual stromal cells - EMA/OD/0000086580

MDC RegAffairs GmbH; Treatment of graft-versus-host-disease (GvHD)

COMP Rapporteur: Frauke Naumann-Winter

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

The arguments on significant benefit were based on an alternative mechanism of action and the potential improved efficacy in the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from their clinical study to justify the assumption of significant benefit over authorised medicinal products and in particular ruxolitinib for the proposed orphan condition.

In the written response, the sponsor provided an indirect comparison to two published ruxolitinib studies in a GvHD, REACH1 (Jagasia et al. 2020) and REACH2 (Zeiser et al. 2020).

The product compared (numerically) favourably to the two ruxolitinib studies in terms of overall response rate (ORR) and overall short-term survival (OS). It was noted that when examining the comparability of study populations, only n=11 corticosteroid-refractory patients were included in the sponsor's trial. The COMP was, however, of the opinion that the favourable results in corticosteroid-refractory patients could be regarded as sufficient for the demonstration of significant benefit and agreed to recommend granting the orphan designation.

The Committee agreed that the condition, graft-versus-host-disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogeneic placenta-derived decidual stromal cells was considered justified based on preliminary clinical data showing better overall response at 1 year including patients with steroid-refractory disease compared to patients in the historical control group.

The condition is chronically debilitating and life-threatening in particular due to intestinal inflammation causing diarrhoea, abdominal pain, nausea and vomiting, as well as due to hepatotoxicity, skin and mucosal damage, sicca syndrome, cholestasis, arthritis, obliterative bronchiolitis and the need for immunosuppression that increases susceptibility to infections.

The condition was estimated to be affecting approximately 0.9 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing allogeneic placenta-derived decidual stromal cells will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate an improvement in overall response including patients refractory to corticosteroid treatment and a reduction in the need for corticosteroid therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic placenta-derived decidual stromal cells, for treatment of graft-versus-host-disease, was adopted by consensus.

2.1.4. melatonin - EMA/OD/0000077279

Industria Farmaceutica Galenica Senese S.r.l.; Treatment of retinopathy of prematurity (ROP)

COMP Rapporteur: Tim Leest

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Number of people affected

The sponsor was requested to revise their prevalence calculation, standardising data as much as possible on a single definition of 'pre-term' in terms of gestational age and birthweight and using robust data sources to estimate the number of pre-term births in the EU in a given year.

The sponsor was invited to consult the COMP Guideline "Points to consider on the estimation and reporting on the prevalence of a condition for the purpose of orphan designation".

- Significant benefit

The sponsor was requested to present a discussion of significant benefit of melatonin over the authorized medicinal product Lucentis (ranibizumab). The sponsor was asked to substantiate any claims in this regard with relevant scientific data.

In the written response, and during an oral explanation before the Committee on 12 July 2022, the sponsor proposed a new prevalence estimate 1.2 per 10,000 persons and was based on the following considerations:

- An average percentage of children diagnosed with ROP compared to the total number of preterm newborns of about 15.44% (average quadratic deviation of 0.196%). This average was based on international data reported between 2007 and 2022, including also three EU countries (Netherlands, Poland and Sweden).
- The estimation of the calculation of preterm births in Europe was based on the following considerations: the COMP previously stated in the Summer Report that the number of preterm births in the EU-28 in 2019 lies somewhere between 580.000 and 320.000 (this is based on the 2015 EURO-Peristat data and the 2019 EU-28 Eurostat figures). As this is a very large range the sponsor resorted to estimate the birth rate of preterm infants and its growth rate over time also based on published data by the Centers for Disease Control and Prevention (CDC), USA. Based on this, it could be estimated that premature births in the EU were about 365,000 (considering the largest estimation range of about 9%) and the number of 4,168,656 infants were born in Europe in 2019 (https://ec.europa.eu).
- Applying the average percentage of ROP diagnosis of 15.44% on 365,000 children the applicant determines about 56,347 babies with ROP [CI: 51,763; 60,930] in 2019, which in turn translates to a general prevalence estimate of the condition in the EU of 1.2 per 10,000 persons (i.e. population with ROP (56,347) /entire EU population (446,446,444)).

The revised prevalence calculation and final estimate of 1.2 per 10,000 persons was accepted by the COMP and considered more likely to reflect the estimated prevalence rate of ROP in the EU.

To further support significant benefit of melatonin over the currently authorized medicinal product Lucentis, the sponsor presented several arguments and analysis on the risks associated with Lucentis.

The sponsor also pointed out shortcomings in the efficacy of ranibizumab.

Furthermore, the sponsor claimed that their product melatonin may be used also in patients where the authorized product Lucentis is not indicated.

Improved safety of melatonin vs ranibizumab

The sponsor presented several lines of arguments of potential and identified risks for Lucentis or other vascular endothelial growth factor A (VEGF-A) inhibitors. These included ocular haemorrhage, increased intraocular pressure (IOP) and long-term limitations as described in Arima M. et al., 2021. Also, (potential) issues related to Lucentis' mechanism of action, route of administration (intravitreal injections) and excipients used in the Lucentis formulation were mentioned by the sponsor as sources of safety risks.

The COMP pointed out that the benefit/risk balance of Lucentis is positive in the EU, which implies that overall the benefits outweigh its risks in the indicated target patient population. This is also supported by several publications reporting up to 2-year safety and efficacy data with Lucentis (Marlow N, et al. Lancet Child Adolesc Health. 2021 Oct;5(10):698-707; Stahl et al., Lancet. 2019 Oct 26;394(10208):1551-1559). Lastly, no evidence was found that particular safety issues reported for Lucentis are due to excipients within the Lucentis formulation. Overall, in the absence of comparative safety data for melatonin in the target patient population, it is not possible to contextualize the clinical safety data of Lucentis vis-à-vis melatonin, and to conclude on the claim of improved safety of melatonin over Lucentis.

Shortcomings in the efficacy of Lucentis

The sponsor also pointed out that there are limitations with the efficacy of Lucentis in terms of not reducing the risk of retinal detachment or preventing the recurrence of ROP in newborns with type 1 ROP. As per the above, in the absence of comparative efficacy data for melatonin in the target patient population, it is not possible to contextualize the clinical efficacy data of Lucentis vis-à-vis melatonin, and to conclude on the claim of improved efficacy of melatonin over Lucentis.

Benefit of Melatonin in ROP patients for which Lucentis is not indicated

The sponsor claimed that their product melatonin may be used also in patients where the authorized product Lucentis may not be indicated, i.e*. at the preliminary stages of ROP, as soon as ROP is diagnosed*. While the COMP agreed that a benefit of melatonin in patients not covered by the indication of Lucentis would in principle be a clinically relevant advantage, it does need to be supported by efficacy data for melatonin on relevant outcome measures of ROP. However, no such data has been presented by the sponsor.

The COMP did not consider that such a claim could be established based on non-clinical data, as a direct extrapolation to specific clinical stages of ROP is not considered possible.

Conclusion

The data presented by the sponsor were not considered sufficient to establish significant benefit of melatonin over the currently authorized product Lucentis.

Reference is made to the European Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03):

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2016_424_R_0003&from=EN

The intention to treat the condition with the medicinal product containing melatonin was considered justified based on non-clinical data in a valid model of the condition which showed improvements in the prevention of pathologic neovascularization, protection of the neuroglial cells and anti-inflammatory effects.

The condition is chronically debilitating due to visual loss that may progress to blindness in the most severe cases.

The condition was estimated to be affecting approximately 1.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has not provided sufficient justification for the assumption that the medicinal product containing melatonin will be of significant benefit to those affected by the condition. Based on the data provided by the sponsor a significant benefit over the authorised satisfactory method of treatment could not be established.

A negative opinion for melatonin, for treatment of retinopathy of prematurity, was adopted by consensus. The sponsor will have 90 days to appeal from the COMP decision.

2.1.5. - EMA/OD/0000085640

Treatment of COVID-19 and Dengue co-infection

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 24 June 2022, prior to responding to the list of issues.

2.1.6. - EMA/OD/0000073417

Treatment of CTLA-4 haploinsufficiency with autoimmune infiltration disease

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

CTLA-4 haploinsufficiency with autoimmune infiltration (CHAI) disease should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

There is a large overlap of symptoms between LATAIE (LRBA deficiency with autoantibodies, regulatory T-cell defects, autoimmune infiltration, and enteropathy) and CHAI. The sponsor was requested to discuss whether an umbrella term such as congenital CTLA-4 checkpoint related immunodeficiencies would be a more appropriate condition for orphan designation.

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of CTLA-4 haploinsufficiency with autoimmune infiltration disease the sponsor was asked to elaborate on the below:

a) In the non-clinical studies, the study subjects received the study drug before administration of toxic agent DSS and anti-CTLA-4 mAb which is considered preventive approach. Translation to the treatment of colitis in active CHAI disease is yet unclear and needs to be clarified.

b) To discuss any non-clinical models that are available and could support the medical plausibility.

- Number of people affected

For the estimation and presentation of the prevalence estimate the sponsor is advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor was asked to re-calculate the prevalence in case a broader condition is reconsidered.

In the written response, and during an oral explanation before the Committee on 13 July 2022, the sponsor agreed to modify the condition into: "congenital CTLA-4 checkpoint related immunodeficiencies". The COMP made a minor comment on the wording on the condition and would accept: ''CTLA-4 checkpoint related primary immunodeficiencies''.

Regarding the medical plausibility the sponsor argued that is not entirely correct to state that the studies in non-clinical model were performed in a preventive setting. Based on the mechanism of action the proposed product activates the repairing mechanism for colitis which works not only in the acute phase but also in the chronic colitis. Furthermore, the sponsor re-iterated that the study drug has been shown to be effective in alternative models of immune-mediated colitis. These models are considered to best recapitulate pathomechanisms of the immune-dependent colitis such as that occurring in patients treated with checkpoint inhibitors (Westdorp et al, 2021). During the discussion the sponsor agreed that the proposed product works in other types of colitis. Finally, the sponsor mentioned that that there was data available in another model but this data was not presented to the COMP. The COMP concluded that the initial model which was the basis for this application was not suitable for the specific condition since could not justify the specific mechanism of action. Furthermore, the data presented was considered representative for the acute phase only and not the chronic condition. Finally, the data mentioned by the sponsor in the additional model was not submitted and the COMP could not assess and conclude based on the sponsor's assumptions. Therefore, the medical plausibility was not acceptable.

The prevalence has been revised to reflect the proposed condition "congenital CTLA-4 checkpoint related immunodeficiencies". The COMP agreed on the proposed prevalence 0.01 per 10,000 persons.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 13 July 2022, prior to final opinion.

2.1.7. - EMA/OD/0000086052

Treatment of Alström syndrome

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of Alström syndrome the sponsor was asked to further elaborate on the bibliographic clinical data to support the use of liraglutide. The COMP noted

that none of the studies were conducted in non-clinical models of the condition or in patients with the condition.

In the written response, and during an oral explanation before the Committee on 13 July 2022, the sponsor indicated that there are no non-clinical in vivo or preliminary clinical data studying the effects of liraglutide in Alström syndrome. They do however note that non-clinical in vivo data exist with exenatide which is a different product with a similar mode of action. A new model of Alström syndrome is caused by a spontaneous mutation in the Alms1 gene (Arsov et al, 2006). These study subjects are of normal weight when young but, by 120 days of age, they become obese and hyperinsulinemic. Diabetes develops in these study subjects accompanied by pancreatic islet hyperplasia and islet cysts (Arsov et al, 2006). Kinetics of insulin-initiated intracellular (initial) Ca++ release from endoplasmic reticulum is significantly impaired in steatotic hepatocytes from obese Alström syndrome study subjects (Ali et al, 2021).

Recently, Ali et al (2021) showed that exenatide, reversed lipid-induced inhibition of intracellular Ca++ release kinetics in steatotic hepatocytes, without affecting the total content of intracellular Ca++ released. Exenatide reversed the lipid-induced inhibition of intracellular Ca++ release, at least partially, via lipid reduction in hepatocytes, which then restored hormone-regulated cytoplasmic Ca++ signalling and insulin sensitivity. These data provide additional evidence for the important role of Ca++ signalling pathways in obesity-associated impaired hepatic lipid homeostasis and insulin signalling. It also highlights a potential advantage of GLP-1 analogues when used to treat type 2 diabetes associated with hepatic steatosis (Ali et al, 2021).

The COMP acknowledged the non-clinical in vivo data submitted, in a model of the condition with exenatide, however, the data was derived with another product (exenatide) and not the one for designation. The extrapolation from exenatide to the proposed product was not considered acceptable. As a result, the Committee did not feel it could recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 July 2022, prior to final opinion.

2.1.8. - EMA/OD/0000086055

Treatment of Bardet-Biedl syndrome

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of Bardet-Biedl syndrome the sponsor should further elaborate on the bibliographic clinical data to support the use of liraglutide. The COMP noted that none of the studies were conducted in non-clinical models of the condition or in patients with the condition.

In the written response, and during an oral explanation before the Committee on 13 July 2022, the sponsor did not provide any additional new data to support the effects of liraglutide in the treatment of Bardet-Biedl syndrome. They attempted to bridge data as they did in the initial submission to the effects of the proposed product in the patients with

diabetes and obesity. The COMP did not accept this approach and informed the sponsor that they could not recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 July 2022, prior to final opinion.

2.1.9. - EMA/OD/0000076480

Treatment of myasthenia gravis

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 28 June 2022, prior to responding to the list of issues.

2.1.10. calmangafodipir - EMA/OD/0000086562

Egetis Therapeutics AB; Prevention of acute liver failure (ALF)

COMP Rapporteur: Robert Nistico

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Number of people affected

The reporting rates proposed by the sponsor appeared to be mainly driven by a paracetamol post-dose prophylaxis population rather than a primary prevention population. Therefore, this was considered to be an under-estimate of the potential patient population at risk. The sponsor was asked to recalculate the prevalence estimate for a relevant "at risk" patient population.

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

In the written response, the sponsor proposed a revised prevalence estimate of 3 per 10,000 persons.

The sponsor presented revised prevalence estimates, now also including patients with an underlying condition associated with a risk of acute liver failure who are hospitalized (as a reasonable surrogate for disease severity and patients who would be considered for preventive treatment). The inclusion of conditions potentially leading to ALF is based on the EASL Clinical Practice Guidelines 2017.

In the sponsor's view, the minimal requirements for a patient to be considered a candidate for being administered the product are: having an underlying condition associated with a risk of ALF and, being hospitalised.

ALF is a life-threatening condition managed in hospital critical care settings. The development of liver injury is associated with illness and will eventually require hospitalisation. Hospitalization is proposed as a reasonable surrogate for disease severity and a clinical assessment of the need to initiate preventative treatment, though it will include some patients in whom treatment is not determined to be clinically appropriate.

This includes patients with any suspicion of liver injury and is therefore a substantial broadening of the population compared to the initial ODD application, which included only those patients with (confirmed) acute liver injury (ALI).

Of note, chronic conditions (e.g. autoimmune hepatitis) are now included in the sponsors prevalence calculation, even if the definition of ALF assumes no pre-existing liver disease. The majority of patients with liver injury (for other reasons than paracetamol overdose) present at hospital with ALF i.e. they have not been detected at the ALI stage or earlier (Ganger, 2018; Wong et al. 2020). Thus, the inclusion of all patients hospitalized due to a condition is likely a severe over-estimate of patients eligible for prevention of ALF.

The sponsor did not consider it meaningful to define a "primary prevention population" beyond patients who have an underlying condition associated with a risk of ALF as such persons are by definition not "at risk" for ALF. The sponsor has complemented the systematic search performed in MEDLINE (MEDLINE, 2021) for the orphan designation application with additional searches to establish the prevalence for the broadened prevention population considered as potential candidates for being administered a preventive treatment. Basing the estimate on the observed best available country data resulted in an estimate of 81,150 (0.018%) hospitalisations due to paracetamol per year in EU.

Based on the revised criteria for the prevalence calculation, the estimated number of patients that could potentially be candidates to be administered the product was 134401, corresponding to a prevalence of 3.0 per 10,000, which is well below the orphan designation criterion of 5 per 10,000. Several reasons why this prevalence estimate is an over-estimate of the number of persons that are candidates for being administered the product were presented.

In conclusion, the revised prevalence estimate comprises a wider population compared to previous calculation, including also patients with an underlying condition associated with a risk of ALF and that are hospitalized. The sponsor did not consider it meaningful to define a "primary prevention population" beyond patients who have an underlying condition associated with a risk of ALF as such persons are by definition not "at risk" for ALF. Taking the hospitalisation as a proxy for disease severity/definition of a population amenable to prevention of ALF was considered acceptable. The inclusion of conditions potentially leading to ALF was based on the EASL Clinical Practice Guidelines, which was also considered to be an acceptable data source.

Overall, the methodology used for the revised prevalence calculation was adequate and the revised prevalence estimate of 3.0 per 10,000 deemed acceptable by the COMP. The oral explanation was therefore cancelled.

The Committee agreed that the condition, acute liver failure, is a distinct medical entity and meets the criteria for orphan designation.

The intention to prevent the condition with the medicinal product containing calmangafodipir was considered justified based on non-clinical and preliminary clinical data showing reduced paracetamol-induced liver failure.

The condition is life-threatening, with acute and rapid deterioration of liver function leading to encephalopathy with intracranial hypertension, and to the development of multi-organ failure and sepsis. Acute liver failure is associated with high mortality.

The population of patients eligible for prevention of the condition was estimated to be approximately 3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of prevention of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing calmangafodipir will be of significant benefit to the population at risk of developing the condition. The sponsor has provided preliminary clinical data with calmangafodipir as adjunct treatment to current standard of care, that demonstrate improved reduction in paracetamol-induced liver failure as compared to standard of care alone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for calmangafodipir, for prevention of acute liver failure, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. autologous CD34+ haematopoietic stem and progenitor cells genetically modified with a lentiviral vector encoding for the N-acetylgalactosamine 6-sulfatase cDNA - EMA/OD/0000072597

Fondazione Telethon; Treatment of mucopolysaccharidosis type IV A (Morquio A syndrome)

COMP Rapporteur: Armando Magrelli

The Committee agreed that the condition, mucopolysaccharidosis type IV A (Morquio A syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing autologous CD34+ haematopoietic stem and progenitor cells genetically modified with a lentiviral vector encoding for the N-acetylgalactosamine 6-sulfatase cDNA was considered justified based on non-clinical evidence demonstrating that the proposed product can restore N-acetylgalactosamine-6-sulfatase activity.

The condition is chronically debilitating and life-threatening due to short stature, severe skeletal dysplasia, cervical instability and cardiorespiratory failure.

The condition was estimated to be affecting approximately 0.02 per 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous CD34+ haematopoietic stem and progenitor cells genetically modified with a lentiviral vector encoding for the N-acetylgalactosamine 6-sulfatase cDNA will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical evidence demonstrating that one single administration can restore N-acetylgalactosamine-6-sulfatase activity. The proposed product could therefore reduce the need for regular treatment with the currently authorised therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous CD34+ haematopoietic stem and progenitor cells genetically modified with a lentiviral vector encoding for the N-acetylgalactosamine 6-sulfatase cDNA, for treatment of mucopolysaccharidosis type IV A, (Morquio A syndrome), was adopted by consensus.

2.2.2. toll-like receptor 4 agonist - EMA/OD/0000076094

Hephaistos-Pharma; Treatment of osteosarcoma

COMP Rapporteur: Jana Mazelova

The Committee agreed that the condition, osteosarcoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing toll-like receptor 4 agonist was considered justified based on non-clinical in vivo data in models of the condition showing a reduction in tumour size as well as improved survival.

The condition is chronically debilitating in particular due to the potential of limb amputation and life-threatening with a less than a 20% long-term survival rate following recurrence.

The condition was estimated to be affecting approximately 2.9 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing toll-like receptor 4 agonist will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate a reduction in metastases as well as relapses where current authorised treatments are not effective. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for toll-like receptor 4 agonist, for treatment of osteosarcoma, was adopted by consensus.

2.2.3. nanatinostat, valganciclovir - EMA/OD/0000081808

Pharma Gateway AB; Treatment of peripheral T-cell lymphoma

COMP Rapporteur: Frauke Naumann-Winter

The Committee agreed that the condition, peripheral T-cell lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing nanatinostat, valganciclovir was considered justified based on preliminary clinical data in relapsed/refractory patients who responded to treatment with the proposed combination.

The condition is life-threatening and chronically debilitating due to poor response to therapy and high rate of relapses. Clinical presentation and course vary from an indolent clinical behaviour for years in milder subtypes, to fulminant disease in aggressive subtypes.

The condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing nanatinostat, valganciclovir will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing anti-tumour activity in a heavily pretreated population that has relapsed or was refractory to existing treatments which is not covered by the only authorised treatment for a specific

subtype of peripheral T-cell lymphoma. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for nanatinostat, valganciclovir, for treatment of peripheral T-cell lymphoma, was adopted by consensus.

2.2.4. - EMA/OD/0000083190

Treatment of type 1 diabetes with residual β-cell function defined by stimulated C-peptide levels ranging between 0.2 and 0.6 nmol/L

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September 2022 meeting.

2.2.5. - EMA/OD/0000083743

Treatment of focal cortical dysplasia

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September 2022 meeting.

2.2.6. - EMA/OD/0000083978

Treatment of type 1 diabetes mellitus in individuals positive for GAD65 antibody and carrying the genetic human leukocyte antigen (HLA) DR3-DQ2 haplotype

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September 2022 meeting.

2.2.7. lithium carbonate - EMA/OD/0000084294

Amsterdam UMC; Treatment of familial adenomatous polyposis

COMP Rapporteur: Bozenna Dembowska-Baginska

The Committee agreed that the condition, familial adenomatous polyposis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing lithium carbonate was considered justified based on non-clinical in vivo data showing reduced polyp counts.

The condition is chronically debilitating and life threatening due to the high risk of developing colorectal cancer as well as extra colonic manifestations which include polyps of the gastric fundus and duodenum, desmoids, gastric and duodenal carcinoma, follicular or papillary thyroid cancer, and central nervous system tumours.

The condition was estimated to be occurring in approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for lithium carbonate, for treatment of familial adenomatous polyposis, was adopted by consensus.

2.2.8. - EMA/OD/0000084535

Treatment of Duchenne muscular dystrophy

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September 2022 meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 16 August 2022.]

2.2.9. bezafibrate - EMA/OD/0000085853

Amsterdam UMC; Treatment of primary sclerosing cholangitis

COMP Rapporteur: Joao Rocha

The Committee agreed that the condition, primary sclerosing cholangitis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing bezafibrate was considered justified based on published clinical data which showed a reduction of serum liver enzymes and bilirubin that are biomarkers of cholestasis and liver damage.

The condition is chronically debilitating and life-threatening due to progressive cholestasis and hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular cancer and bleeding of esophageal varices. Common findings include pruritus, hyperlipidaemia, fatigue, deficiency of fat-soluble vitamins and osteopenia.

The condition was estimated to be affecting less than 3.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing bezafibrate will be of significant benefit to those affected by the condition. The sponsor has provided clinical data which showed a reduction of serum liver enzymes and bilirubin when bezafibrate was used as add-on to standard of care, in patients with incomplete response to standard of care. Furthermore, bezafibrate has been demonstrated to improve symptoms of cholestatic pruritus, an effect not observed with the authorized medicinal product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for bezafibrate, for treatment of primary sclerosing cholangitis, was adopted by consensus.

2.2.10. - EMA/OD/0000085970

Treatment of microvillous inclusion disease

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September 2022 meeting.

2.2.11. H-Lys-Lys-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Lys-Lys-OH - EMA/OD/0000086532

S-Cubed Pharmaceutical Services ApS; Treatment of haemophilia A

COMP Rapporteur: Karri Penttila

The Committee agreed that the condition, haemophilia A, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing H-Lys-Lys-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Lys-Lys-OH was considered justified based on reduced level of FVIII inhibitor titres in non-clinical models of the proposed condition.

The condition is chronically debilitating due to recurrent bleeding in joints, gastrointestinal tract or in surgery, which may also be life-threatening.

The condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing H-Lys-Lys-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Lys-Lys-OH will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical data that demonstrate suppression of inhibitor antibody formation to FVIII which may reduce the need for immune tolerance induction. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for H-Lys-Lys-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Lys-Lys-OH, for treatment of haemophilia A, was adopted by consensus.

2.2.12. - EMA/OD/0000086550

Treatment of neuroblastoma

The sponsor withdrew the application for orphan designation on 5 July 2022 prior to the COMP discussion.

2.2.13. epetraborole - EMA/OD/0000089012

Dlrc Pharma Services Limited; Treatment of nontuberculous mycobacterial lung disease

COMP Rapporteur: Eva Malikova

The Committee agreed that the condition, nontuberculous mycobacterial lung disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing epetraborole was considered justified based on non-clinical data in a valid model of the condition, showing reduction of nontuberculous mycobacteria load.

The condition is life-threatening and chronically debilitating due to progressive lung damage in severe forms that respond poorly to treatment. Five-year mortality rates have been reported up to 40%.

The condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing epetraborole will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate a reduced nontuberculous mycobacteria load when epetraborole was added to standard of care first-line therapy. This indicates that epetraborole can be used in an earlier line of treatment as compared to the approved product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for epetraborole, for treatment of nontuberculous mycobacterial lung disease, was adopted by consensus.

2.2.14. - EMA/OD/0000090156

Treatment of apolipoprotein L1-mediated kidney disease (AMKD)

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September 2022 meeting.

2.2.15. - EMA/OD/0000090261

Treatment of Duchenne muscular dystrophy

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September 2022 meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 1 August 2022.]

2.2.16. autologous human bone marrow-derived hematopoietic and mesenchymal stem cells depleted of erythrocytes, monocytes and lymphocytes - EMA/OD/0000090545

Neuroplast B.V.; Treatment of frontotemporal dementia

COMP Rapporteur: Robert Nistico

The Committee agreed that the condition, frontotemporal dementia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing autologous human bone marrow-derived haematopoietic and mesenchymal stem cells depleted of erythrocytes, monocytes and lymphocytes was considered justified based on non-clinical data in a model of the condition showing a decrease in markers of neuroinflammation, and the rescue of the cognitive and social behavioural deficits.

The condition is chronically debilitating due to neurological and cognitive impairment and life-threatening with a limited life-expectancy.

The condition was estimated to be affecting approximately 3.8 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for autologous human bone marrow-derived hematopoietic and mesenchymal stem cells depleted of erythrocytes, monocytes and lymphocytes, for treatment of frontotemporal dementia, was adopted by consensus.

2.2.17. vutrisiran - EMA/OD/0000091543

Alnylam Netherlands B.V.; Treatment of Stargardt's disease

COMP Rapporteur: Tim Leest

The Committee agreed that the condition, Stargardt's disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing vutrisiran was considered justified based on non-clinical in vivo data in a model of the condition which showed reductions in TTR/RBP4 and retinol led to significantly decreased accumulation of toxic fluorescent retinoids in the eye.

The condition is chronically debilitating, in particular due to loss of visual acuity and central vision, which may progress to complete blindness.

The condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for vutrisiran, for treatment of Stargardt's disease, was adopted by consensus.

2.2.18. sotuletinib - EMA/OD/0000091771

Novartis Europharm Limited; Treatment of amyotrophic lateral sclerosis

COMP Rapporteur: Robert Nistico

The Committee agreed that the condition, amyotrophic lateral sclerosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sotuletinib was considered justified based on non-clinical in vivo data in a valid model of the condition showing a reduction in progressive weight loss as well as a reduced decline in motor function.

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure. The survival of the patients is usually limited.

The condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the

medicinal product containing sotuletinib will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that shows reduced decline in motor function and delay of disease progression which is not noted with the current authorised medicine. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sotuletinib, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.19. batoclimab - EMA/OD/0000091878

Pharma Gateway AB; Treatment of myasthenia gravis

COMP Rapporteur: Darius Matusevicius

The Committee agreed that the condition, myasthenia gravis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing batoclimab was considered justified based on clinical data showing positive responses on myasthenia gravis specific outcome measures in patients affected by the condition.

The condition is chronically debilitating due to muscle weakness affecting in particular muscles that control eye and eyelid movement, facial expressions, chewing, talking, and swallowing and life-threatening due to respiratory impairment.

The condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing batoclimab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate positive responses of batoclimab, when used as add-on treatment to standard of care, on myasthenia gravis specific outcome measures in patients affected by the condition in a population which is not covered by the currently authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for batoclimab, for treatment of myasthenia gravis, was adopted by consensus.

2.2.20. allogeneic adult liver-derived stem cells - EMA/OD/0000091899

Unicyte S.r.l.; Treatment of urea cycle disorders

COMP Rapporteur: Geraldine O'Dea

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of urea cycle disorders.

The Committee agreed that the condition, urea cycle disorders, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogeneic adult liver-derived stem cells was considered justified based on preliminary clinical data in

patients with argininosuccinic aciduria (one of the urea cycle disorders) showing that ammonia concentration in blood could be stabilised within normal limit.

The condition is chronically debilitating due to consequences of metabolic disturbance leading to developmental delay, intellectual disability and other types of neurological symptoms, and life threatening due to organ failure.

The condition was estimated to be affecting approximately 0.12 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing allogeneic adult liver-derived stem cells will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the product could be given as a bridging therapy for patients awaiting orthotic liver transplantation, for which limited treatment options are available. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic adult liver-derived stem cells, for treatment of urea cycle disorders, was adopted by consensus.

2.2.21. gold - EMA/OD/0000092111

Clene Netherlands B.V.; Treatment of amyotrophic lateral sclerosis (ALS)

COMP Rapporteur: Robert Nistico

The Committee agreed that the condition, amyotrophic lateral sclerosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing gold was considered justified based on clinical data suggesting improvement in clinically relevant indicators of amyotrophic lateral sclerosis disease progression.

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure. The survival of the patients is usually limited.

The condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing gold will be of significant benefit to those affected by the condition. The sponsor has provided clinical data suggesting improvement in clinically relevant indicators of ALS disease progression when the product is used as add-on to standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for gold, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.22. - EMA/OD/0000092197

Treatment of pneumonia due to *Pseudomonas aeruginosa*

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September 2022 meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 18 August 2022.]

2.2.23. - EMA/OD/0000092484

Treatment of congenital ichthyosis

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September 2022 meeting.

2.2.24. - EMA/OD/0000092639

Treatment of linear IgA bullous dermatosis

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September 2022 meeting.

2.2.25. clarithromycin, clofazimine, rifabutin - EMA/OD/0000093202

Regintel Limited; Treatment of nontuberculous mycobacterial lung disease

COMP Rapporteur: Armando Magrelli

The Committee agreed that the condition, nontuberculous mycobacterial lung disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing clarithromycin, clofazimine, rifabutin was considered justified based on non-clinical data in a valid model of the condition, showing reduction of nontuberculosis mycobacteria load.

The condition is life-threatening and chronically debilitating due to progressive lung damage in severe forms that respond poorly to treatment. Five-year mortality rates have been reported up to 40%.

the condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing clarithromycin, clofazimine, rifabutin will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that indicate a reduced nontuberculous mycobacteria load when the fixed dose combination was compared to the mono-components of the product. This indicates that the fixed dose combination of clarithromycin, clofazimine and rifabutin can be used in an earlier line of treatment as compared to the approved product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for clarithromycin, clofazimine, rifabutin, for treatment of nontuberculous mycobacterial lung disease, was adopted by consensus.

2.2.26. tamibarotene - EMA/OD/0000093305

Syros Pharmaceuticals (Ireland) Limited; Treatment of myelodysplastic syndrome (MDS)

COMP Rapporteur: Karri Penttila

The Committee agreed that the condition, myelodysplastic syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing tamibarotene was considered justified based on preliminary clinical data demonstrating response in patients with high risk, RARA-positive myelodysplastic syndrome who had failed prior treatment with hypomethylating agents.

The condition is life-threatening and chronically debilitating in particular due to anaemia, thrombocytopenia, and neutropenia, as well as transformation into acute myeloid leukaemia.

The condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tamibarotene will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that patients with high risk, RARA-positive myelodysplastic syndrome who had failed prior treatment with hypomethylating agents responded to the treatment with tamibarotene as single agent. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tamibarotene, for treatment of myelodysplastic syndrome, was adopted by consensus.

2.2.27. (7S)-8,8-dimethyl-7-{[(2E)-3-phenyl-2-propen-1-yl]oxy}-7,8-dihydro-2H,6H-pyrano[3,2-g]chromen-2-one - EMA/OD/0000093471

Global Medical Services Sp. z o.o.; Treatment of Hutchinson-Gilford progeria syndrome

COMP Rapporteur: Ingeborg Barisic

The Committee agreed that the condition, Hutchinson-Gilford progeria syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (7S)-8,8-dimethyl-7-{[(2E)-3-phenyl-2-propen-1-yl]oxy}-7,8-dihydro-2H,6H-pyrano[3,2-g]chromen-2-on was considered justified based on non-clinical data showing improved survival and phenotypic amelioration after treatment with the proposed product.

The condition is life-threatening due to atherosclerotic cardiovascular disease and strokes, with death generally occurring in early teenage years, and chronically debilitating with typical lipoatrophy, facial dysmorphia, premature aging, short stature, delayed dentition, and thin skin with sclerodermatous areas.

The condition was estimated to be affecting approximately 0.003 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for (7S)-8,8-dimethyl-7-{[(2E)-3-phenyl-2-propen-1-yl]oxy}-7,8-dihydro-2H,6H-pyrano[3,2-g]chromen-2-on, for treatment of Hutchinson-Gilford progeria syndrome, was adopted by consensus.

2.2.28. - EMA/OD/0000093474

Treatment of Werner's syndrome

The COMP adopted a list of issues that will be sent to the sponsor. The Committee will discuss the submitted answers to the list of issues at the September 2022 meeting.

2.2.29. humanised IgG1 tetravalent monoclonal antibody against death receptor 5 - EMA/OD/0000093683

TMC Pharma (EU) Limited; Treatment of chondrosarcoma

COMP Rapporteur: Jana Mazelova

The Committee agreed that the condition, chondrosarcoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing humanised IgG1 tetravalent monoclonal antibody against death receptor 5 was considered justified based on preliminary clinical data which showed antitumour activity in patients with the condition.

The condition is chronically debilitating due to surgery needed including amputations, and life-threatening, in particular for patients with metastatic disease.

The condition was estimated to be affecting approximately 1.2 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for humanised IgG1 tetravalent monoclonal antibody against death receptor 5, for treatment of chondrosarcoma, was adopted by consensus.

2.2.30. amphotericin B - EMA/OD/0000093873

Insight Drug Regulatory; Treatment of cryptococcosis

COMP Rapporteur: Eva Malikova

The Committee agreed that the condition, cryptococcosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing amphotericin B was considered justified based on non-clinical in vivo and preliminary clinical data showing reduction in infection.

The condition is life-threatening and chronically debilitating in particular due to the development of pulmonary cryptococcosis that leads to cryptococcal meningitis or meningoencephalitis, and rarely other forms such as cutaneous infection and peritonitis.

The condition was estimated to be affecting approximately 0.03 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing amphotericin B will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate an improvement in meningeal cryptococcal sterilisation in comparison to intravenous amphotericin due to better blood brain barrier crossing of the proposed oral formulation. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for amphotericin B, for treatment of cryptococcosis, was adopted by consensus.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

2.6.1. New applications for orphan medicinal product designation - Appointment of COMP rapporteurs

COMP rapporteurs were appointed for 23 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 0 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

None

3.2. Finalised letters

3.2.1. -

Treatment of pancreatic cancer

The finalised letter was circulated for information.

3.2.2. -

Treatment of mucopolysaccharidosis II (Hunter's syndrome)

The finalised letter was circulated for information.

3.2.3. -

Treatment of acute myeloid leukaemia

The finalised letter was circulated for information.

3.2.4. -

Treatment of myelofibrosis

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of congenital alpha-1 antitrypsin deficiency

The new request was noted.

4. Review of orphan designation for orphan medicinal products at time of initial marketing authorisation

4.1. Orphan designated products for which CHMP opinions have been adopted

4.1.1. Roctavian - valoctocogene roxaparvovec - EMEA/H/C/005830/0000, EU/3/16/1622, EMA/OD/0000067127

Biomarin International Limited; Treatment of haemophilia A

COMP Rapporteurs: Armando Magrelli; Karri Penttila

A list of issues was adopted on 16 June 2022.

An oral explanation was held on 13 July 2022.

An opinion recommending not to remove Roctavian, valoctocogene roxaparvovec (EU/3/16/1622) from the EC Register of Orphan Medicinal Products was adopted by majority (24 out of 28 votes). The Norwegian COMP member agreed with the above-mentioned recommendation of the COMP.

The divergent positions (Karri Penttila, Vasileios Papadopoulos, Enrico Costa, Brigitte Schwarzer-Daum*)* were appended to this opinion.

The orphan maintenance assessment report will be publicly available on the EMA website.

4.1.2. Scemblix - asciminib - EMEA/H/C/005605/0000, EU/3/20/2261, EMA/OD/0000068920

Novartis Europharm Limited; Treatment of chronic myeloid leukaemia

COMP Rapporteurs: Karri Penttila; Bozenna Dembowska-Baginska

A list of issues was adopted on 16 June 2022. The oral explanation scheduled on 13 July 2022, was cancelled.

An opinion recommending not to remove Scemblix, asciminib, EU/3/20/2261 from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

4.2. Orphan designated products for discussion prior to adoption of CHMP opinion

4.2.1. Amvuttra - vutrisiran - EMEA/H/C/005852/0000, EU/3/18/2026, EMA/OD/0000085855

Alnylam Netherlands B.V.; Treatment of transthyretin-mediated amyloidosis

COMP Rapporteurs: Armando Magrelli; Elisabeth Johanne Rook

A list of issues was adopted on 16 June 2022. The oral explanation scheduled on 12 July 2022, was cancelled.

An opinion recommending not to remove Amvuttra, vutrisiran, EU/3/18/2026 from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its July 2022 meeting.]

4.2.2. Tecvayli - teclistamab - EMEA/H/C/005865/0000, EU/3/20/2331, EMA/OD/0000083072

Accelerated assessment

Janssen-Cilag International; Treatment of multiple myeloma

A list of issues was adopted on 16 June 2022. An oral explanation was held on 12 July 2022.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 July 2022, prior to final opinion.

The orphan designation withdrawal assessment report will be publicly available on the EMA website.

4.2.3. Nulibry – fosdenopterin - EMEA/H/C/005378/0000, EU/3/10/777, EMA/OD/0000074822

Comharsa Life Sciences Ltd; Treatment of molybdenum cofactor deficiency type A

COMP Rapporteurs: Olimpia Neagu, Elisabeth Penninga

An opinion recommending not to remove Nulibry, fosdenopterin (EU/3/10/777) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its July 2022 meeting.]

4.2.4. Imcivree - setmelanotide - EMEA/H/C/005089/II/0002/G, EU/3/19/2192, EMA/OD/0000074865

Rhythm Pharmaceuticals Netherlands B.V.; Treatment of Bardet Biedl syndrome

COMP Rapporteurs: Joao Rocha; Vallo Tillmann; CHMP Rapporteur: Karin Janssen van Doorn

An opinion recommending not to remove Imcivree, setmelanotide (EU/3/19/2192) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its July 2022 meeting.]

4.2.5. - mitapivat sulfate - EMEA/H/C/005540/0000, EU/3/20/2270, EMA/OD/0000068458

Agios Netherlands B.V.; Treatment of pyruvate kinase deficiency

The status of the procedure at CHMP was noted.

4.2.6. Tecartus - brexucabtagene autoleucel - EMEA/H/C/005102/II/0008/G, EU/3/20/2344, EMA/OD/0000063560

Kite Pharma EU B.V.; Treatment of acute lymphoblastic leukaemia

COMP Rapporteurs: Maria Elisabeth Kalland

An opinion recommending not to remove tecartus, brexucabtagene autoleucel - EU/3/20/2344 from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its July 2022 meeting.]

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 2 applications.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

5. Review of orphan designation for authorised orphan medicinal products at time marketing authorisation extension

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Yescarta - axicabtagene ciloleucel - EMEA/H/C/004480/II/0046, EU/3/14/1393, EMA/OD/0000076832

Kite Pharma EU B.V.; Treatment of diffuse large B cell lymphoma

The COMP adopted a list of issues that will be sent to the sponsor.

5.2.2. Epidyolex – cannabidiol - EMEA/H/C/004675/II/0020

GW Pharma (International) B.V.

a) Treatment of Dravet syndrome, EMA/OD/0000097923, EU/3/14/1339

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is not needed.

b) Treatment of Lennox-Gastaut syndrome, EMA/OD/0000098337, EU/3/17/1855

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is not needed.

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for 1 application.

6. Application of Article 8(2) of the Orphan Regulation

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP membership

The Chair welcomed Joao Rocha, as the new member for Portugal.

The Chair thanked Dinah Duarte for her contribution as a member for Portugal.

7.1.2. Vote by proxy

None

7.1.3. Strategic Review & Learning meetings

Draft agenda of the COMP SRLM under the Czech Presidency of the Council of the EU to be held F-2-F on 21-23 September 2022 in Bonn, Germany

The COMP noted the topics and draft agenda for the meeting to be held F-2-F on 21-23 September 2022 in Bonn, Germany.

7.1.4. Protocol Assistance Working Group (PAWG)

None

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report

Documents were tabled for information.

7.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

7.3.1. Working Party with Patients' and Consumers' Organisations (PCWP) and Working Party with Healthcare Professionals' Organisations (HCPWP)

Documents were tabled for information.

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

7.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee

None

7.7. COMP work plan

None

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2022

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2022 were circulated.

7.8.2. Overview of orphan marketing authorisations/applications

An updated overview of orphan applications for Marketing Authorisation was circulated.

8. Any other business

8.1. Real World Evidence update, including DARWIN EU®

The COMP noted the update on Real World Evidence (RWE).

Regarding the DARWIN EU®, it was noted that the Phase I is currently half-way through and first benefits will be delivered with pilot studies performed in 2022. Starting in 2024, RWE will be available for the majority of committees. The DARWIN EU® should be fully operational in 2025/2026.

There is currently selection of data partners ongoing. Ten partners will be selected to onboard this year. Primary criteria for prioritisation was presented. The secondary criteria includes non-EU data sources, database which provides linkage and continuous follow up between primary and secondary care. Around 26 million EU patients are covered via this selection.

The second part of the presentation described, which analyses and studies will DARWIN EU® deliver.

The third part gave an update on the use of RWE studies for COMP. The status of studies requested by or offered to COMP was presented.

Finally, as a reminder it was explained how to request RWE – email should be sent with a specific template.

A call for volunteers was made to be the liaison with the RWE team and work more closely with the project team on RWE studies.

9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 12-14 July 2022 meeting.

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Chair	Netherlands	No interests declared	
Armando Magrelli	Member (Vice-Chair)	Expert recommended by EMA	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No restrictions applicable to this meeting	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Elli Loizidou	Member	Cyprus	No interests declared	
Jana Mazelova	Member	Czechia	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Cecile Dop	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Vasileios Papadopoulos	Member	Greece	No interests declared	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Enrico Costa	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No restrictions applicable to this meeting	
Aušra Matulevičienė	Member	Lithuania	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No restrictions applicable to this meeting	
Elisabeth Johanne Rook	Member	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Joao Rocha	Member	Portugal	No restrictions applicable to this meeting	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Pauline Evers	Member	Patients' organisation representative	No interests declared	
Julian Isla	Member	Patients' organisation representative	No interests declared	
Ines Alves	Member	Patients' organisation representative	No participation in final deliberations and voting on:	4.1.1. Roctavian - valoctocogene roxaparvovec - EMEA/H/C/005830/0000, EU/3/16/1622, EMA/OD/0000067127 Biomarin International Limited; Treatment of haemophilia A

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Maria Cavaller Bellaubi	Expert	Patients' organisation representative	No restrictions applicable to this meeting	
Susanne Brendler-Schwaab	Observer	Germany	No interests declared	
Jeanette McCallion	Observer	Ireland	No interests declared	
	Patient expert	European Union - EMA	No interests declared	
Meeting run with support from relevant EMA staff				

* Experts were evaluated against the agenda topics or activities they participated in.

10. Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission

OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

Orphan Designation *(section 2 Applications for orphan medicinal product designation)*

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures

(including protocol assistance), national incentives for research and development, 10-year market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.

Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

Protocol Assistance *(section 3 Requests for protocol assistance with significant benefit question)*

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Maintenance of Orphan Designation *(section 4 Review of orphan designation for orphan medicinal products for marketing authorisation).*

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/