19 February 2025
EMA/COMP/48379/2025
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 21-23 January 2025

Chair: Tim Leest – Vice-Chair: Frauke Naumann-Winter

Health and safety information

In accordance with the Agency's health and safety policy, delegates were briefed on health, safety and emergency information and procedures prior to the start of the meeting.

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 agenda 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).

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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. The meeting was held in-person.

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 meeting, the Committee Secretariat announced the restricted involvement of some Committee members 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.

The Chair thanked the departing member for his contributions to the Committee.

The EMA Secretariat announced the names of the Committee members who delegated their vote via proxy and the Committee members who received such proxy.

The Chair announced the start of the Polish presidency of the Council of the European Union (EU).

1.2. Adoption of agenda

The agenda for 21-23 January 2025 was adopted with no amendment.

1.3. Adoption of the minutes

The minutes for 03-05 December 2024 were adopted with no amendments and will be published on EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. adeno-associated virus sector serotype rh74 containing the human *SGCG* gene - EMA/OD/0000230201

Sarepta Therapeutics Ireland Limited; Treatment of limb-girdle muscular dystrophy

COMP Rapporteur: Gloria Maria Palomo Carrasco

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:

- Prevalence

The sponsor has based the prevalence estimate in a single publication (Witting et al., 2013). However, this paper only considered recessive forms of limb-girdle muscular dystrophy (LGMD), rendering an incomplete result. Other publications have not been included in the prevalence estimation.

In the written response, the sponsor acknowledged that the calculation provided in the initial application referred only to recessive forms of LGMD. The sponsor provided an updated literature review from several European countries which included all forms of LGMD. Based on data from LGMD studies conducted in Europe (Hughes et al., 1996; Urtasun et al., 1998; van der Kooi et al., 1996), the estimated prevalence of overall LGMD (dominant and recessive) was confirmed to range from 8.1 to 69 cases per million (0.081-0.69 cases per 10,000) (Deenen et al., 2015; Mah et al., 2016; Pegoraro and Hoffman, 2012). The sponsor proposed the most conservative estimate of 69 per million (0.69 per 10,000) derived from their literature review, for the purposes of establishing the overall LGMD prevalence in the European Union.

The sponsor also discussed a reported prevalence estimate from Norway of 1.28 per 10,000 which was higher than all other reported values throughout Europe (Müller et al., 2021). The publication by Müller and colleagues acknowledged that their results showed higher values than previously reported and in comparison with other Norwegian regions, without further exploration of the causes. Therefore, this value may rather be an unusually high reported prevalence in one particular region in Norway, rather than being representative of a higher prevalence throughout the whole of the EU/EEA.

Taken all together, the proposed value of 0.69 (the most conservative approach, the upper limit of the range) can be accepted, but given the uncertainties (higher values reported in one region of Norway) and the limited available data, the COMP can use the figure "approximately 1 in 10,000 persons" for the initial designation, as in previous applications.

The Committee agreed that the condition, limb-girdle muscular dystrophy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated virus sector serotype rh74 containing the human *SGCG* gene was considered justified based on non-clinical data in a valid in vivo model demonstrating improved muscle function.

The condition is chronically debilitating due to muscle wasting causing reduced mobility and fatigue and potentially life-threatening due to respiratory complications.

The condition was estimated to be affecting approximately 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 adeno-associated virus sector serotype rh74 containing the human *SGCG* gene, for treatment of limb-girdle muscular dystrophy, was adopted by consensus.

2.1.2. epertinib - EMA/OD/0000228469

3R Pharma Consulting GmbH; Treatment of amyotrophic lateral sclerosis

COMP Rapporteur: Darius Matusevicius

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 are 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 non-clinical in vivo study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. The argumentation provided for riluzole was limited and should be further elaborated.

In the written response, the sponsor provided a response to the question on significant benefit. Arguments were presented as to why the selected model is relevant for the evaluation of epertinib effects on functional endpoints and survival of animals. Arguments stating that riluzole did not have any effect on functional measures of muscles strength in clinical trials were noted and acknowledged. The COMP noted that no data on clinical effects of epertinib were available, hence a clinical comparison between riluzole and epertinib was not possible.

A comparison of four experiments assessing riluzole effects vs epertinib effects in a non-clinical model of amyotrophic lateral sclerosis was submitted.

The COMP considered this data could be considered as sufficient at stage of designation of orphan drug status to support the assumption of significant benefit and the oral explanation was cancelled.

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 epertinib was considered justified based on non-clinical in vivo data in a model of the condition showing an improvement in survival and hind limb motor function.

The condition is chronically debilitating and life-threatening due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure with shortened life expectancy.

The condition was estimated to be affecting approximately 1.3 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 epertinib will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate an improvement in survival and hind limb motor function when compared indirectly to the currently authorised medicine. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.3. hydroxocobalamin acetate - EMA/OD/0000230149

Day Zero ehf.; Treatment of homocystinuria and/or methylmalonic acidaemia due to genetic defects of intracellular cobalamin processing

COMP Rapporteur: Cécile Dop

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:

- Condition

The COMP did not support the proposed condition wording and asked the sponsor to justify their proposed condition as a distinct medical entity or a valid subset.

Alternatively, consideration was given to the following condition wordings: "Treatment of homocystinuria with or without methylmalonic acidaemia due to genetic defects of intracellular cobalamin processing" or "Treatment of homocystinuria with or without methylmalonic acidaemia due to cobalamin C disorder".

Note that this is for the purposes of orphan medicinal product designation. The sponsor's attention was drawn to the orphan regulations and relevant guidelines (especially section A of 2022/C 440/02).

- Medical plausibility

In support of medical plausibility, only data in patients with cobalamin C disorder was submitted. The sponsor was asked to discuss the potential benefit of ultra-high doses of parenteral hydroxycobalamin also in other forms of intracellular cobalamin processing disorders and support this by available scientific data.

- Number of people affected

The sponsor was asked to revise their prevalence calculation and final estimate according to the revised condition.

As a general comment, it was noted that the sponsor only provided birth incidence values but not prevalence information as per the total EU population. This was not acceptable. The sponsor was expected to present prevalence information and final estimate, as per the general EU population, i.e. X per 10,000 persons in the EU.

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".

- Significant benefit

The COMP considered that authorised lower strengths preparations of parenteral hydroxycobalamin are satisfactory methods, for the purpose of this procedure.

In view of this, the sponsor was asked to clarify the exact significant benefit claim over these authorised parenteral hydroxycobalamin preparations and support their claim(s) with available data/information. Of note, significant benefit is defined either as a clinically

relevant advantage (i.e. improved efficacy or improved safety) or a major contribution to patient care (Article 3(2) of Commission Regulation (EC) No 847/2000).

The sponsor was invited to further elaborate and show if there are current difficulties with available formulations to treat the proposed target patient population and explain how their proposed formulation is expected to overcome these difficulties.

In the written response, and during an oral explanation before the Committee on 22 January 2025, the sponsor changed the condition wording to "Treatment of homocystinuria and/or methylmalonic acidaemia due to genetic defects of intracellular cobalamin processing", which was considered acceptable by the COMP. The sponsor explained that ultra-high doses of parenteral hydroxycobalamin are likely to also benefit patients with other forms of intracellular cobalamin processing disorders, besides cobalamin C (CblC). In fact, current guidelines recommend early treatment with parenteral hydroxocobalamin injections for all types of defects of intracellular cobalamin processing (Huemer et al., 2017).

The COMP accepted the sponsors proposed prevalence estimate of less than 0.6 in 10,000 persons. This value was mainly based on birth incidence data from Portugal and Italy, (Nogueira et al., 2017; Ruoppolo et al., 2022) multiplied by life expectancy of the general population. The COMP acknowledged that this is likely a very conservative estimate and uncertainty over the actual prevalence of these conditions in the EU remains, due to the limited epidemiologic data.

The sponsor was of the opinion that the higher strength parenteral preparation presents a significant benefit as a major contribution to patient care. The currently authorised lower strength parenteral preparations require high volumes of injections that are painful to the patient and jeopardize adherence to treatment. This was confirmed by a clinical expert consulted by the sponsor. Case reports have shown a dose-dependent response to hydroxocobalamin, suggesting that the lower estimate of 0.3 mg/kg bw per day might not be sufficient (Carrillo-Carrasco et al., 2009; Kacpura et al., 2022; Scalais et al., 2023, 2019). The COMP agreed that a formulation that reduces the volume required for daily parenteral administration of the treatment is expected to reduce patient discomfort, including in children, and may allow treatment at an optimal dose, therefore constituting a major contribution to patient care.

In conclusion, following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of homocystinuria and/or methylmalonic acidaemia due to genetic defects of intracellular cobalamin processing.

The intention to treat the condition with the medicinal product containing hydroxocobalamin acetate was considered justified based on bibliographic clinical data in children with early-onset severe cobalamin type C (CblC) disease showing a reduction of serum methylmalonic acid and homocysteine levels and suggestive of improved neurodevelopment.

The condition is life-threatening due to severe complications such as thrombotic microangiopathy and encephalopathy, and chronically debilitating due to the progressive nature of symptoms associated with neurodevelopmental delay including cognitive impairment, retinopathy, and haematological issues.

The condition was estimated to be affecting not more than 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 hydroxocobalamin acetate will be of significant benefit to those affected by the condition. The proposed medicinal product is expected to reduce patient burden due to reduced injection volumes. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for hydroxocobalamin acetate, for treatment of homocystinuria and/or methylmalonic acidaemia due to genetic defects of intracellular cobalamin processing, was adopted by consensus.

2.1.4. volixibat potassium - EMA/OD/0000228739

Mirum Pharmaceuticals International B.V.; Treatment of primary sclerosing cholangitis

COMP Rapporteur: Joao Rocha

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 supporting the claim of significant benefit are based on the novel mechanism of action and the potential for improved efficacy in the condition.

The sponsor was requested to provide a more detailed discussion of the arguments presented for significant benefit, specifically elaborating on the results of both non-clinical and clinical studies to substantiate the assumption of significant benefit, with a particular emphasis on efficacy compared to authorised medicinal products for the proposed orphan condition. Additionally, the sponsor was invited to further clarify which specific clinical outcomes the proposed product would address that are not adequately managed by existing treatments, such as any preliminary effects observed in pruritus or fibrosis.

In the written response, the sponsor addressed the concerns raised, suggesting that volixibat may provide a meaningful therapeutic advantage over ursodeoxycholic acid (UDCA) in the treatment of primary sclerosing cholangitis (PSC). This conclusion is based on a preliminary analysis of safety and efficacy data.

While UDCA is authorised for PSC treatment in some EU Member States, its clinical benefit remains a subject of debate. Evidence supporting its effectiveness in alleviating symptoms or improving quality of life is limited, and its impact on pruritus, a debilitating symptom of PSC, has not been consistently demonstrated. In contrast, volixibat, a minimally absorbed ileal bile acid transporter (IBAT) inhibitor, has shown pharmacodynamic effects in healthy volunteers, reinforcing its mechanistic potential to address PSC-related symptoms.

Furthermore, the sponsor provided details on the ongoing VLX-301 study, which is investigating volixibat for the treatment of cholestatic pruritus in PSC. Although the study remains blinded, an interim analysis conducted in June 2024 met predefined safety and efficacy criteria. The selected dose was to be retained only if the confidence interval for a statistically significant effect met the predefined threshold for pruritus effect, suggesting the potential for a relevant therapeutic benefit. Given the limited treatment options and the significant burden of pruritus on quality of life, these findings could support the argument for a significant benefit.

Based on the available evidence, the COMP concluded that, at this stage, the arguments for a significant benefit were sufficiently substantiated, leading to the cancellation of the oral explanation and adoption of a positive opinion.

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 volixibat potassium was considered justified based on non-clinical data in models which showed a reduction in biochemical markers of cholestasis and liver injury, and clinical data in patients with the condition which showed preliminary efficacy results meeting the criteria for non-futility.

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 volixibat potassium will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients with the condition which showed a potential effect in symptoms of cholestatic pruritus, an effect not observed with the authorised medicinal product. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.5. - EMA/OD/0000231115

Treatment of Duchenne muscular dystrophy

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 16 December 2024, prior to responding to the list of issues.

2.1.6. - EMA/OD/0000225792

Treatment of mucosal melanoma

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 16 December 2024, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1. adeno-associated virus vector serotype SNY001 containing the human *PAH* gene - EMA/OD/0000223873

Sanofi B.V.; Treatment of hyperphenylalaninemia

COMP Rapporteur: Elisabeth Johanne Rook

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

The intention to treat the condition with the medicinal product containing adeno-associated virus vector serotype SNY001 containing the human *PAH* gene was considered justified based on non-clinical in vivo and preliminary clinical data showing a reduction in phenylalanine serum levels as well as non-clinical in vivo data showing an increment in neurotransmitter levels in the central nervous system and an improvement in behaviour.

The condition is chronically debilitating due to high blood phenylalanine levels which cause cognitive developmental delay, attention deficit and irritability, seizures and skin rash.

The condition was estimated to be affecting approximately less than 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 adeno-associated virus vector serotype SNY001 containing the human *PAH* gene will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the product could offer benefits in a broader patient population than currently authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus vector serotype SNY001 containing the human *PAH* gene, for treatment of hyperphenylalaninemia, was adopted by consensus.

2.2.2. tafasitamab - EMA/OD/0000226861

Incyte Biosciences Distribution B.V.; Treatment of follicular lymphoma

COMP Rapporteur: Jana Mazelova

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

The intention to treat the condition with the medicinal product containing tafasitamab was considered justified based on preliminary clinical data which showed increased progression free survival, and improved overall response rate in patients with previously treated Grade 1 – 3a follicular lymphoma.

The condition is life threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction and the potential of transformation to aggressive lymphoma.

The condition was estimated to be affecting approximately 4.9 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 tafasitamab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that tafasitamab in combination with lenalidomide and rituximab showed increased progression free survival and improved overall response rate in adult patients with previously treated Grade 1 – 3a follicular lymphoma compared to the authorised medicinal products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tafasitamab, for treatment of follicular lymphoma, was adopted by consensus.

2.2.3. - EMA/OD/0000230735

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 February meeting.

2.2.4. (R)-(3-(2'-cyclopropyl-3-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)pyrrolidin-1-yl)(5-hydroxy-6-methylpyridin-2-yl)methanone - EMA/OD/0000231617

Granzer Regulatory Consulting & Services GmbH; Treatment of Olmsted syndrome

COMP Rapporteur: Joao Rocha

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

The intention to treat the condition with the medicinal product containing (R)-(3-(2'-cyclopropyl-3-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)pyrrolidin-1-yl)(5-hydroxy-6-methylpyridin-2-yl)methanone was considered justified on non-clinical data in a model of the condition which showed a reduction in keratoderma severity and an anti-pruritic effect.

The condition is chronically debilitating in particular due to progressive keratoderma in the palms and soles, periorificial keratotic plaques, erythromelalgia, pruritus and pain, which may lead to impairment of mobility and limb amputation.

The condition was estimated to be affecting less than 0.01 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 (R)-(3-(2'-cyclopropyl-3-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)pyrrolidin-1-yl)(5-hydroxy-6-methylpyridin-2-yl)methanone, for treatment of Olmsted syndrome, was adopted by consensus.

2.2.5. - EMA/OD/0000232365

Treatment of bradykinin-mediated angioedema

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 February meeting.

2.2.6. adeno-associated virus serotype rh.10 containing the human *PKP2* gene - EMA/OD/0000233191

Scendea (NL) B.V.; Treatment of arrhythmogenic cardiomyopathy caused by pathogenic mutations in the *PKP2* gene

COMP Rapporteur: Gloria Maria Palomo Carrasco

The Committee agreed that the condition, arrhythmogenic cardiomyopathy caused by pathogenic mutations in the *PKP2* gene, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated virus serotype rh.10 containing the human *PKP2* gene was considered justified based on non-clinical in vivo data showing an improvement in cardiac function, a reduction in arrythmia and improvement in survival.

The condition is chronically debilitating and life-threatening due to ventricular instability which may lead to arrhythmic sudden cardiac death, or progression of ventricular muscle disease resulting in right ventricular systolic dysfunction.

The condition was estimated to be affecting approximately 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 adeno-associated virus serotype rh.10 containing the human *PKP2* gene, for treatment of arrhythmogenic cardiomyopathy caused by pathogenic mutations in the *PKP2* gene, was adopted by consensus.

2.2.7. autologous CD34+ cell enriched population containing haematopoietic stem and progenitor cells transduced ex vivo with a lentiviral vector encoding the human *ADA2* gene - EMA/OD/0000233467

ESPL Regulatory Consulting Limited; Treatment of adenosine deaminase 2 deficiency (DADA2)

COMP Rapporteur: Evangelia Giannaki

The Committee agreed that the condition, adenosine deaminase 2 deficiency (DADA2), 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+ cell enriched population containing haematopoietic stem and progenitor cells transduced ex vivo with a lentiviral vector encoding the human *ADA2* gene was considered justified based on non-clinical data showing the correction of the pro-inflammatory phenotype and the re-establishment of intracellular *ADA2* expression in relevant non-clinical models.

The condition is life-threatening and chronically debilitating due to vasculopathy and life-threatening ischemic and/or haemorrhagic stroke at young age. Case mortality for DADA2 is estimated at about 8% related to vasculopathy-associated complications and infections.

The condition was estimated to be affecting less than 0.1 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 autologous CD34+ cell enriched population containing haematopoietic stem and progenitor cells transduced ex vivo with a lentiviral vector encoding the human *ADA2* gene, for treatment of adenosine deaminase 2 deficiency (DADA2), was adopted by consensus.

2.2.8. - EMA/OD/0000233979

Treatment of Rett syndrome

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 February meeting.

2.2.9. paltusotine - EMA/OD/0000234998

Voisin Consulting Life Sciences; Treatment of acromegaly

COMP Rapporteur: Vallo Tillmann

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

The intention to treat the condition with the medicinal product containing paltusotine was considered justified based on preliminary assessment of clinical data showing normalisation of growth hormone and IGH-1 serum levels.

The condition is life-threatening and chronically debilitating due to disproportionate skeletal, tissue, and organ growth, leading to multisystem morbidities and terminal cardiovascular, cerebrovascular, and respiratory disease.

The condition was estimated to be affecting approximately 1.1 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 paltusotine will be of significant benefit to those affected by the condition. Preliminary assessment of the clinical data provided by the sponsor has indicated improved efficacy to current authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for paltusotine, for treatment of acromegaly, 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

None

2.7. Evaluation on-going

None

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of nephrotic syndrome

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

3.1.2. -

Treatment of Gaucher disease

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

3.1.3. -

Treatment of Berardinelli-Seip syndrome (congenital generalised lipodystrophy)

The Committee was briefed on the significant benefit issues in preparation of the February 2025 meeting.

3.1.4. -

Treatment of pancreatic cancer

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

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. Rytelo - imetelstat - EMEA/H/C/006105, EU/3/20/2305, EMA/OD/0000225798

Geron Netherlands B.V.; Treatment of myelodysplastic syndromes

COMP Rapporteur: Darius Matusevicius; COMP Co-rapporteur: Karri Penttila

A list of issues was adopted on 06 November 2024.

An oral explanation was held on 21 January 2025.

An opinion recommending not to remove Rytelo, imetelstat, EU/3/20/2305 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. - vorasidenib hemicitrate hemihydrate - EMEA/H/C/006284, EU/3/22/2737, EMA/OD/0000159477

Les Laboratoires Servier; Treatment of glioma

The status of the procedure at CHMP was noted.

4.2.2. Fabhalta - iptacopan hydrochloride - EMEA/H/C/005764/II/0001, EU/3/18/2104, EMA/OD/0000224423

Novartis Europharm Limited; Treatment of C3 glomerulopathy

CHMP Rapporteur: Janet Koenig

The status of the procedure at CHMP was noted.

4.2.3. Vyvgart - efgartigimod alfa - EMEA/H/C/005849/II/0020, EU/3/21/2555, EMA/OD/0000222245

Argenx; Treatment of chronic inflammatory demyelinating polyneuropathy

CHMP Rapporteur: Thalia Marie Estrup Blicher; CHMP Co-Rapporteur: Alexandre Moreau

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 5 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

None

5.3. Appeal

None

5.4. On-going procedures

None

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 thanked Dinko Vitezic for his contribution as the member for Croatia.

7.1.2. Vote by proxy

None

7.1.3. Strategic Review & Learning meetings

The COMP noted the preliminary information for the meeting to be held face-to-face on 29-30 April 2025 in Warsaw, Poland.

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 17 January 2025.

7.1.5. COMP Decisions Database

The COMP acknowledged the importance of adding further topics to the database.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report

None

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)

None

7.3.2. Innovation Task Force (ITF) meetings

Documents were tabled for information.

7.3.3. Methodology Working Party

Scope: Call for volunteers - Q&A on indirect comparisons

A call for volunteers was done and members were invited to express interest by end of January 2025.

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

Scope: Exchange of views with European Commission on Pharmaceutical Legislation Reform

The COMP members received an update on the reform of the pharmaceutical legislation, in particular on the proposed reform of the EMA committees and exchanged views with the EC Representatives.

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

Scope: EMA / FDA collaboration and introduction to Liaison program

The topic was cancelled.

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

7.7.1. COMP Work Plan for 2025

COMP Chair: Tim Leest

The COMP work plan for 2025 was adopted by COMP and has been published.

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2025

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2025 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. Patient engagement methodologies

An overview of the various methodologies available to capture patient (and healthcare professional) input into COMP activities was presented.

8.2. EMA business Pipeline activity

The business pipeline report for Q4/2024 was presented for information.

8.3. Aspects of the orphan regulation Article 8(2)

The COMP discussed the applicable principles and relevant procedure envisaged under Article 8(2) of Regulation (EC) No 141/2000.

9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 21-23 January 2025 COMP meeting, which was held in-person.

An asterisk (*) after the role, in the second column, signals that the member attended remotely. Additional experts participated in (part of) the meeting, either in person or remotely.

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Tim Leest	Chair	Belgium	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No restrictions applicable to this meeting	
Ioannis Kkolos	Member	Cyprus	No interests declared	
Jana Mazelova	Member	Czechia	No interests declared	
Sine Buhl Naess-Schmidt	Member	Denmark	No restrictions applicable to this meeting	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttila	Member	Finland	No interests declared	
Cecile Dop	Member	France	No interests declared	
Frauke Naumann-Winter	Member (Vice-Chair)	Germany	No interests declared	
Evangelia Giannaki	Member	Greece	No restrictions applicable to this meeting	
Zsofia Gyulai	Member	Hungary	No interests declared	
Enrico Costa	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No restrictions applicable to this meeting	
Ruta Mameniskiene	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Luana Mifsud Buhagiar	Member	Malta	No interests declared	
Elisabeth Johanne Rook	Member	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Bożenna Dembowska-Baginska	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	
Jana Schweigertova	Member	Slovak Republic	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Ines Alves	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Mariette Driessens	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Fernando Mendez Hermida	Member	Expert recommended by EMA	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No interests declared	
Maria Judit Molnar	Member	Expert recommended by EMA	No participation in discussion, final deliberations and voting on:	2.1.5.-EMA/OD/0000231115 2.2.3.-EMA/OD/0000230735 4.2.3. Vyvgart - efgartigimod alfa -

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				EMEA/H/C/005849/II/0020, EU/3/21/2555, EMA/OD/0000222245
Maria Cavaller Bellaubi	Expert	Patients' Organisation Representative	No restrictions applicable to this meeting	
Alexandru-Mihail Simion	Expert	Belgium	No restrictions applicable to this meeting	
Representatives from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

Experts' declared interests 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.

For a list of acronyms and abbreviations, see:

Abbreviations used in EMA scientific committees & CMD documents and in relation to EMA's regulatory activities

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