16 February 2023
EMA/COMP/49263/2023
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 17-19 January 2023

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

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 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).

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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 in-person with some members connected remotely (hybrid setting).

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 that no restriction in the involvement of meeting participants in upcoming discussions was identified.

Participants were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions 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 and as included in the list of participants. 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 17-19 January 2023 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 6-8 December 2022 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. (3beta,24S)-25,25,25-trifluoro-3-methyl-26,27-dinorergost-5-ene-3,24-diol - EMA/OD/0000111992

Raremoon Consulting Esp S.L.; Treatment of Huntington's disease (HD)

COMP Rapporteurs: Enrico Costa, Michel Hoffmann

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 Huntington's disease, the sponsor was invited to elaborate on the available clinical data. In particular, the sponsor was invited to elaborate on the baseline characteristics of the Huntington's disease patients (such as the severity of the disease stage), and the relevance of the neurological cognition results observed. Possible confounding elements, such as a learning curve component, should be discussed as well as any mitigation actions if applicable.

In the written response, the sponsor further elaborated on the methodology (in particular the use of Cogstate Brief Battery of tests to assess cognition), the population and results of the clinical study presented in the application.

The possibility of learning effects in the executed tests was in particular considered. The sponsor noted that the tests were specifically designed to minimize learning effects and that test familiarisation was also conducted. Moreover, no noticeable learning effects were observed in the healthy volunteers in the relevant part of the clinical study. The COMP considered the written answer sufficient and the oral explanation was therefore cancelled.

The Committee agreed that the condition, Huntington'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 (3beta,24S)-25,25,25-trifluoro-3-methyl-26,27-dinorergost-5-ene-3,24-diol was considered justified based on preliminary clinical observations supporting improvement of cognitive function in affected patients.

The condition is life-threatening and chronically debilitating due to severe behavioural and cognitive disturbances and progressive motor dysfunction.

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 the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (3beta,24S)-25,25,25-trifluoro-3-methyl-26,27-dinorergost-5-ene-3,24-diol will be of significant benefit to those affected by the condition. While authorised treatments only treat the chorea-related symptoms of the disease, the sponsor has provided preliminarily clinical observations supporting beneficial effects in the cognitive function of affected patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (3beta,24S)-25,25,25-trifluoro-3-methyl-26,27-dinorergost-5-ene-3,24-diol, for treatment of Huntington's disease, was adopted by consensus.

2.1.2. - EMA/OD/0000105270

Diagnosis of glioma

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 sponsor was asked to elaborate on the arguments of the significant benefit of the proposed product versus all the authorised treatments.

In the written response, and during an oral explanation before the Committee on 17 January 2023, the sponsor presented bibliographical data and positioned the proposed product in the diagnosis of glioma by PET imaging. Improved standard uptake values and tumour-to-background ratio versus other available diagnostic agents was argued in that regard. A discussion also ensued versus an existing authorised product that contained the same active substance. This product is authorised in limited European countries and the sponsor intends to extend the commercialisation by making the product available in more European countries. It was envisioned to reduce the potential harm for glioma patients by providing the best diagnosis tool for the characterization of the tumour after MRI detection, especially in the population of patients where it has been shown superior to other PET markers and/or in combination with other treatment. However, no data have been provided to support these theoretical arguments and the COMP considered that the significant benefit had not been justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 January 2023, prior to final opinion.

2.1.3. - EMA/OD/0000104730

Treatment of congenital alpha-1 antitrypsin deficiency (AATD)

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 sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. In particular, the sponsor was asked to elaborate on the biomarker endpoints and their correlation with the clinical outcome in comparison with alpha-1 antitrypsin deficiency augmentation therapy. Additional data on the baseline characteristics of the patient population included in the indirect comparison should also be submitted.

In the written response, and during an oral explanation before the Committee on 17 January 2023, the sponsor elaborated on the relevance of Saint George's Respiratory Questionnaire (SGRQ)-Activity domain in AATD lung disease, noting alignments with relevant symptoms (decreased exercise tolerance, shortness of breath and not feeling fit or having strength to do daily activities) and correlation with functional parameters of maximal oxygen uptake, shuttle tests and gas transfer. There is a progressive worsening in SGRQ-Activity score in longitudinal follow-up of patients with AATD.

The choice of elastase-related biomarkers was based on the pathogenic pathway of the disease, and their association with measures of lung structure and function and clinical measures of disease severity. In a post-hoc analysis a possible association between biomarkers and SGRQ (in particular, the Activity domain) was observed.

The comparability of the juxtaposed studies for the purpose of justifying significant benefit was also further elaborated with regards to baseline demographics, medical history and elastase-related biomarkers. The COMP did not consider the comparability of the populations justified. For example, the duration of the disease was not discussed and baseline lower forced expiratory volume per second (FEV1) was not comparable. Overall, it was considered that the sponsor advanced its position with regards to the relevance of the

studied endpoints, but it was considered that any comparisons vis-a-vis the authorised counterparts remained inconclusive. Therefore, the significant benefit could not be considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 January 2023, prior to final opinion.

2.1.4. - EMA/OD/0000070986

Treatment of megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS)

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

The data presented by the sponsor was considered preliminary. The sponsor was therefore requested to further elaborate on how the current in vitro data can be translated into a clinical potential.

In addition, the sponsor was asked to discuss the possibility of using patient derived cells to demonstrate proof of concept.

In the written response, and during an oral explanation before the Committee on 17 January 2023, the sponsor did not present any relevant new data to support medical plausibility.

In the sponsor's view, the data from the in vitro model using the HEK293 cell line was considered sufficient, by making reference to a siRNA developed for another condition which had been generated via the same bioinformatics approach. Parallels were drawn to a similar siRNA therapeutic approach that was used to treat CLCN7-dependent Autosomal Dominant Osteopetrosis Type 2 (ADO2). In that case, HEK293 cells were also used in vitro and the effects of the siRNA translated to positive effects in a non-clinical in-vivo model for ADO2, i.e. overall improvement of the osteopetrotic bone phenotype. The principle of achieving a condition of haplo-sufficiency is the same in ADO2 and the applied for condition.

The sponsor plans to establish the proof of concept of the proposed product and the proposed condition by additional in vitro studies using two different models, i.e. primary cell culture from patient derived fibroblasts from the urine and induced pluripotent stem cells engineered with the CRISPR/Cas9 system to express the mutation(s) that trigger MMIHS disease. These studies are currently ongoing and (interim) data is not yet available.

The COMP concluded that the currently available in vitro data is not sufficient to establish medical plausibility for the purpose of orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 January 2023, prior to final opinion.

2.1.5. humanised IgG1 monoclonal antibody against annexin-A1 - EMA/OD/0000105836

Rapport Global Strategic Services Ireland Limited; Treatment of pancreatic cancer

COMP Rapporteur: Brigitte Schwarzer-Daum

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

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to consider on the calculation and reporting of a prevalence of a condition for orphan designation".

The sponsor was asked to describe and justify the methodology used for the prevalence calculation. The sponsor was asked to rely on EU epidemiological studies and registers (e.g., ECIS).

In the written response, the sponsor further elaborated on the basis of the calculation (yearly incidence rate times duration) and consulted further literature and registry (ECIS) data.

The COMP considered the impact of age-standardization on the old European standard population and noted that it is the crude incidence rate (approximately 2.12 /10,000 per ECIS in 2020 for both sexes in EU27+EFTA) that should be taken into consideration when calculating prevalence from incidence. By further assuming an approximately 1-year duration, the prevalence was estimated at approximately 1 /10,000 at the time of designation.

The Committee agreed that the condition, pancreatic cancer, 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 monoclonal antibody against annexin-A1 was considered justified based on inhibition of tumour growth and improvement in survival in non-clinical in-vivo models of the condition.

The condition is chronically debilitating due to pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression and life-threatening with a markedly reduced life expectancy.

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 humanised IgG1 monoclonal antibody against annexin-A1 will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a model of the condition that report additive effects when the product is combined with existing treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised IgG1 monoclonal antibody against annexin-A1, for treatment of pancreatic cancer, was adopted by consensus.

2.1.6. - EMA/OD/0000108995

Treatment of autosomal dominant polycystic kidney disease (ADPKD)

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 data presented by the sponsor was considered insufficient to support a claim of improved safety of the proposed product compared to tolvaptan. While the contraindication for tolvaptan in ADPKD patients with elevated liver enzymes and/or signs or symptoms of liver injury is acknowledged, no data in the target population has been presented for the proposed product.

The sponsor also claimed improved efficacy of their product with regards to controlling liver cyst progression / liver growth. The sponsor was asked to further substantiate this claim with relevant data in the applied condition.

In the written response, and during an oral explanation before the Committee on 18 January 2023, the sponsor further elaborated on their position but did not present any new relevant data to further substantiate the claim for improved safety. The clinical development of the proposed product is still ongoing and no clinical data in ADPKD patients is available to date. Therefore, safety can only be assessed based on the current preclinical data and clinical data available in another condition, i.e. Non-Alcoholic Fatty Liver Disease.

The sponsor pointed out a potential improvement in tolerability profile and patient adherence of the proposed product vs tolvaptan, linked to the aquaretic related symptoms of tolvaptan (polyuria, pollakiuria, nocturia and thirst with secondary polydipsia). However, no data to substantiate such a comparative improvement with the proposed product in the proposed target population of ADPKD patients has been provided.

Moreover, no new relevant data was presented to further substantiate the claim for improved efficacy of the proposed product vs tolvaptan in the applied for condition. The claim was based on the potential of the proposed product to improve aspects of the proposed condition, which tolvaptan is not expected to cover, i.e. hepatic and renal efficacy. The sponsor pointed out the existing pre-clinical and clinical data in other conditions, i.e. Non-Alcoholic Fatty Liver Disease / Non-Alcoholic Steatohepatitis, which suggests that the proposed product ameliorates liver disease. In addition, the sponsor was of the opinion that the proposed product has the potential to provide renal protective efficacy for patients that are not eligible to receive or not optimally responsive to tolvaptan. The sponsor intends to include also this specific patient population in future ADPKD clinical trials with the proposed product. The sponsor also envisages a potential use of the proposed product as an adjunct therapy, in patients not sufficiently controlled with tolvaptan (i.e. patients with continuing and substantial residual rate of eGFR decline).

While the COMP acknowledged the additional arguments by the sponsor, the committee pointed out that the presented indirect evidence is not regarded as sufficient to support the claims of significant benefit of the proposed product over tolvaptan, for the purpose of this procedure.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 January 2023, prior to final opinion.

2.1.7. - EMA/OD/0000102985

Treatment of hereditary cerebral amyloid angiopathies

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 hereditary cerebral amyloid angiopathies the sponsor was asked to further elaborate on the preliminary clinical data presented with particular focus on data generated with the metabolite of the proposed product, while the sponsor is applying for the proposed product. In addition, the COMP noted that there were limitations regarding the clinical data where there were no details regarding concomitant diseases or treatments, and the validity of the biomarkers used should be further elaborated.

In the written response, and during an oral explanation before the Committee on 18 January 2023, the sponsor presented further information regarding the concomitant diseases and treatment of the studied patients. The relevance of the biomarkers used was also discussed. The sponsor presented results from the longitudinal sampling and monitoring of human Cystatin C aggregation in skin biopsies from the Phase II study, and the decrease in the intensity of staining in patients who were treatment-naïve at study entry was also discussed.

The sponsor additionally highlighted several characteristics of the proposed product over its metabolite, in an attempt to bridge with the available data for the latter. Several points were highlighted such as the higher potency over the metabolite in preventing/dispersing human cystatin C in in vitro cellular modelling studies, the higher bioavailability and the proposed product's ability to cross the blood-brain barrier after oral administration in study subjects. The sponsor, however, brought no new pre-clinical or clinical data with the proposed product in the condition.

In their follow-up discussions the COMP considered that the sponsor had not adequately addressed the question and data with the proposed product in the condition was considered essential to support the medical plausibility. Consequently, it was concluded 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 18 January 2023, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000083629

Treatment of scedosporiosis

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.

2.2.2. fosmanogepix - EMA/OD/0000083630

Pfizer Europe MA EEIG; Treatment of fusariosis

COMP Rapporteur: Olimpia Neagu

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

The intention to treat the condition with the medicinal product containing fosmanogepix was considered justified based on improved survival in non-clinical models of the condition as well as preliminary clinical observations supporting responses in affected patients.

The condition is life-threatening with 90 day mortality rates up to 60% for disseminated cases and chronically debilitating in particular due to ocular and dermal complications.

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.

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 fosmanogepix will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that support improved survival when the product is combined with available treatments. The sponsor has also provided preliminary clinical observations supporting responses in patients who had failed or were not eligible for available treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for fosmanogepix, for treatment of fusariosis, was adopted by consensus.

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

2.2.3. fosmanogepix - EMA/OD/0000083631

Pfizer Europe MA EEIG; Treatment of mucormycosis

COMP Rapporteur: Olimpia Neagu

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

The intention to treat the condition with the medicinal product containing fosmanogepix was considered justified based on non-clinical studies reporting improvement in survival and fungal burden, as well as preliminary reports of clinical and mycological improvements in affected patients.

The condition is life-threatening due to possible fungal invasion of the vascular network which results in thrombosis and death of surrounding tissue in different organs.

The condition was estimated to be affecting approximately 0.06 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 fosmanogepix will be of significant benefit to those affected by the condition. The sponsor has provided data in a non-clinical model showing add-on effects to amphotericin, and reported clinical responses in affected patients, who had previously failed or were not eligible for treatment with the existing products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for fosmanogepix, for treatment of mucormycosis, was adopted by consensus.

2.2.4. fosmanogepix - EMA/OD/0000083632

Pfizer Europe MA EEIG; Treatment of lomentosporiosis

COMP Rapporteur: Olimpia Neagu

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

The intention to treat the condition with the medicinal product containing fosmanogepix was considered justified based on improvement of survival in a non-clinical in vivo model of disseminated lomentosporiosis.

The condition is chronically debilitating in particular due to airway colonization which is a risk factor for disseminated infection and associated with chronic inflammation, and life-threatening with high mortality rates for disseminated disease up to 90% that have been reported in the literature.

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.

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 fosmanogepix will be of significant benefit to those affected by the condition. The sponsor has provided in vivo data in a model of disseminated lomentosporiosis which is resistant to available treatments, showing improved survival after treatment with the product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for fosmanogepix, for treatment of lomentosporiosis, was adopted by consensus.

2.2.5. autologous CD34+ cells transduced with a lentiviral vector containing the human *GAA* gene - EMA/OD/0000100299

Erasmus Universitair Medisch Centrum Rotterdam (Erasmus MC); Treatment of glycogen storage disease type II (Pompe disease)

COMP Rapporteur: Lyubina Racheva Todorova

The Committee agreed that the condition, glycogen storage disease type II (Pompe'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 autologous CD34+ cells transduced with a lentiviral vector containing the human GAA gene was considered justified based on non-clinical in vivo data in a model of the condition showing improvement in motor function and a reduction of glycogen storage and neuroinflammation in the central nervous system.

The condition is life-threatening and chronically debilitating due to accumulation of glycogen in muscle and nerve cells resulting in progressive skeletal myopathy, cardiomyopathy, and respiratory insufficiency. This leads to death within the first two years of life in the infantile forms, and in the fourth decade of life in forms with later onset.

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 autologous CD34+ cells transduced with a lentiviral vector containing the human *GAA* gene 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 glycogen storage and neuroinflammation markers in the central nervous system which is not achieved with authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous CD34+ cells transduced with a lentiviral vector containing the human *GAA* gene, for treatment of glycogen storage disease type II (Pompe's disease), was adopted by consensus.

2.2.6. - EMA/OD/0000105112

Treatment of osteogenesis imperfecta

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.

[Post-meeting note: The sponsor withdrew the application for orphan designation on 31 January 2023].

2.2.7. patidistrogene bexoparvovec - EMA/OD/0000111986

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

COMP Rapporteur: Michel Hoffmann

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

The intention to treat the condition with the medicinal product containing patidistrogene bexoparvovec was considered justified based on non-clinical in vivo data showing an improvement in muscle strength.

The condition is chronically debilitating due to muscle wasting, 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/for the population at risk of developing the condition.

A positive opinion for patidistrogene bexoparvovec, for treatment of limb-girdle muscular dystrophy (LGMD), was adopted by consensus.

2.2.8. - EMA/OD/0000112018

Treatment of spinal muscular atrophy

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.

[Post-meeting note: The sponsor withdrew the application for orphan designation on 30 January 2023].

2.2.9. adeno-associated viral vector serotype 9 expressing fukutin-related protein - EMA/OD/0000113368

Brainvectis; Treatment of limb-girdle muscular dystrophy

COMP Rapporteur: Zsofia Gyulai

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 viral vector serotype 9 expressing fukutin-related protein was considered justified based on improvement in muscle endurance shown in a non-clinical in vivo model of the proposed condition.

The condition is chronically debilitating due to muscle wasting, 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.

A positive opinion for adeno-associated viral vector serotype 9 expressing fukutin-related protein, for treatment of limb-girdle muscular dystrophy, was adopted by consensus.

2.2.10. humanised IgG1 monoclonal antibody against TfR1 conjugated to double stranded siRNA oligonucleotide against DUX4 mRNA via a non-cleavable linker - EMA/OD/0000113568

MWB Consulting S.A.R.L.; Treatment of facioscapulohumeral muscular dystrophy

COMP Rapporteur: Elisabeth Penninga

The Committee agreed that the condition, facioscapulohumeral 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 humanised IgG1 monoclonal antibody against TfR1 conjugated to double stranded siRNA oligonucleotide against DUX4 mRNA via a non-cleavable linker was considered justified based on non-clinical in vivo data showing an improvement in muscle force and treadmill running.

The condition is chronically debilitating due to progressive severe weakness of facial and skeletal muscles, leading to impaired mobility, chronic fatigue and pain. Patients may also develop visual and hearing impairment and decreased lung function. Patients with infantile onset disease may have a reduced life-expectancy.

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 monoclonal antibody against TfR1 conjugated to double stranded siRNA oligonucleotide against DUX4 mRNA via a non-cleavable linker, for treatment of facioscapulohumeral muscular dystrophy, was adopted by consensus.

2.2.11. melatonin - EMA/OD/0000114101

ESPL Regulatory Consulting Limited; Treatment of perinatal asphyxia

COMP Rapporteur: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing Melatonin was considered justified based on non-clinical in vivo data showing improvement in neuroprotection as measured through the survival of oligodendrocytes, in electroencephalographic recovery and delayed onset of seizures.

The condition is chronically debilitating due to the long lasting neurological and developmental sequelae. The condition is also life threatening, with high mortality associated with the most severe cases.

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 melatonin, for treatment of perinatal asphyxia, was adopted by consensus.

2.2.12. - EMA/OD/0000114282

Treatment of *RPE65* retinopathies

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.

2.2.13. - EMA/OD/0000114439

Treatment of primary sclerosing cholangitis

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.

2.2.14. - EMA/OD/0000114452

Treatment of GM1 gangliosidosis

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.

2.2.15. - EMA/OD/0000114581

Treatment of galactosialidosis

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.

2.2.16. - EMA/OD/0000114584

Treatment of sialidosis

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.

2.2.17. H-L-tryphophanyl-L-seryl-glycyl-L-tryptophanyl-L-seryl-L-seryl-L-cysteinyl-L-seryl-L-arginyl-L-seryl-L-cysteinyl-glycyl-OH (disulfide bond), acetate salt - EMA/OD/0000115114

Axoltis Pharma; Treatment of spinal cord injury

COMP Rapporteur: Robert Nistico

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

The intention to treat the condition with the medicinal product containing H-L-tryphophanyl-L-seryl-glycyl-L-tryptophanyl-L-seryl-L-seryl-L-cysteinyl-L-seryl-L-arginyl-L-seryl-L-cysteinyl-glycyl-OH (disulfide bond), acetate salt was considered justified based on non-clinical data which showed improved functional outcomes compared to controls.

The condition is chronically debilitating and life-threatening due to sensory and motor loss of function in the limbs and reduced life expectancy.

The condition was estimated to be affecting approximately 4.3 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 H-L-tryphophanyl-L-seryl-glycyl-L-tryptophanyl-L-seryl-L-seryl-L-cysteinyl-L-seryl-L-arginyl-L-seryl-L-cysteinyl-glycyl-OH (disulfide bond), acetate salt will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data showing improved functional outcomes in the treated groups when the product was given in the sub-acute injury setting for which there are no authorised medicinal products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for H-L-tryphophanyl-L-seryl-glycyl-L-tryptophanyl-L-seryl-L-seryl-L-cysteinyl-L-seryl-L-arginyl-L-seryl-L-cysteinyl-glycyl-OH (disulfide bond), acetate salt, for treatment of spinal cord injury, was adopted by consensus.

2.2.18. crisdesalazine - EMA/OD/0000115116

MDC RegAffairs GmbH; Treatment of amyotrophic lateral sclerosis

COMP Rapporteur: Darius Matusevicius

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 crisdesalazine was considered justified based on non-clinical in vivo data in a model of a condition, where treatment with the product delays the onset of neurological symptoms and improves motor function, strength and survival.

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

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing crisdesalazine will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in-vivo data in a model of the condition, with the product comparing favourably to riluzole with respect to its effects on motor function and survival. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.19. isotretinoin - EMA/OD/0000115356

Granzer Regulatory Consulting & Services GmbH; Treatment of recessive X-linked ichthyosis

COMP Rapporteur: Elisabeth Johanne Rook

The Committee agreed that the condition, recessive X-linked ichthyosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing isotretinoin was considered justified based on preliminary data which showed improvement on the clinical severity of the disease in patients with recessive X-linked ichthyosis.

The condition is chronically debilitating due to the appearance of major symptoms which include widespread dryness and scaling of the skin, which could lead to painful fissures and infections, and functional impairment of joints, impaired tactile sensitivity and disturbance of sweating and body heat control. Other common symptoms are corneal opacities, neurodevelopmental disorders (autism and attention deficit hyperactivity disorder), cryptochidism and testicular cancer.

The condition was estimated to be affecting approximately 2.5 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 isotretinoin will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that showed that patients, for which authorised treatments are not an option, improved when treated with the

proposed product in a topical formulation. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for isotretinoin, for treatment of recessive X-linked ichthyosis, was adopted by consensus.

2.2.20. bitopertin - EMA/OD/0000115370

Disc Medicine B.V.; Treatment of erythropoietic protoporphyria (EPP)

COMP Rapporteur: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing bitopertin was considered justified based on in vivo non-clinical data in animal models which showed reduction in protoporphyrin IX levels and improvement in liver fibrosis score and bile duct proliferation.

The condition is chronically debilitating due to skin photosensitivity, anaemia and liver complications and life-threatening as patients may die from liver failure.

The condition was estimated to be affecting approximately 0.2 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 bitopertin will be of significant benefit to those affected by the condition. The sponsor has provided in vivo non-clinical data that demonstrate therapeutic effects in patients with erythropoietic protoporphyria which have not been observed with the current authorised product such as reduction in protoporphyrin IX levels and improvement in liver fibrosis score. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for bitopertin, for treatment of erythropoietic protoporphyria, was adopted by consensus.

2.2.21. (2S,3R,4R,5S)-1-[5-(2-fluoro-biphenyl-4-ylmethoxy)-pentyl]-2-hydroxymethyl-piperidine-3,4,5-triol - EMA/OD/0000116088

Azafaros B.V.; Treatment of GM2 gangliosidosis

COMP Rapporteur: Enrico Costa

The Committee agreed that the condition, GM2 gangliosidosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (2S,3R,4R,5S)-1-[5-(2-fluoro-biphenyl-4-ylmethoxy)-pentyl]-2-hydroxymethyl-piperidine-3,4,5-triol was considered justified based on non-clinical data in a valid model of the condition showing longer survival and improved motor function.

The condition is life-threatening with a reduced life expectancy and chronically debilitating due to ataxia, muscle weakness, loss of motor function, sight and hearing, and development of seizures and cognitive impairment.

The condition was estimated to be affecting approximately 0.4 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 (2S,3R,4R,5S)-1-[5-(2-fluoro-biphenyl-4-ylmethoxy)-pentyl]-2-hydroxymethyl-piperidine-3,4,5-triol, for treatment of GM2 gangliosidosis, was adopted by consensus.

2.2.22. - EMA/OD/0000116158

Treatment of Niemann-Pick disease type C (NP-C)

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.

2.3. 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 10 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 14 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of short bowel syndrome

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues via written procedure following its January 2023 meeting.

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. Pombiliti – cipaglucosidase alfa - EMEA/H/C/005703, EU/3/18/2000, EMA/OD/0000098435

Amicus Therapeutics Europe Limited; Treatment of glycogen storage disease type II (Pompe's disease)

COMP Rapporteur: Cécile Dop; COMP Co-Rapporteur: Elisabeth Johanne Rook

A list of issues was adopted on 8 December 2023.

An opinion recommending the removal of pombiliti, cipaglucosidase alfa, EU/3/18/2000 from the EC Register of Orphan Medicinal Products was adopted by consensus.

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. – artesunate - EMEA/H/C/005718/0000, EMA/OD/043/15, EU/3/15/1521, EMA/OD/0000063220

B And O Pharm; Treatment of malaria

The discussion was cancelled as the Marketing Authorisation Application had been withdrawn after the CHMP December meeting.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 4 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. Reblozyl – luspatercept - EMEA/H/C/004444/II/0009, EU/3/14/1300, EMA/OD/0000072540

Bristol-Myers Squibb Pharma EEIG; Treatment of beta-thalassaemia intermedia and major

CHMP Rapporteur: Daniela Philadelphy; CHMP Co-Rapporteur: Ewa Balkowiec Iskra

An opinion recommending not to remove Reblozyl, luspatercept, EU/3/14/1300

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 January 2023 meeting.]

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 welcomed Ruta Mameniskiene, as the new member for Lithuania.

7.1.2. Vote by proxy

Elisabeth Johanne Rook gave a proxy to Pauline Evers to vote on behalf of Elisabeth Johanne Rook during the entire meeting.

Dinko Vitezic gave a proxy to Ingeborg Barisic to vote on behalf of Dinko Vitezic during part of the meeting.

7.1.3. Strategic Review & Learning meetings

The COMP noted the upcoming SRLM in Uppsala, Sweden to be held in May 2023.

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 13 January 2023.

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

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)

None

7.3.2. Upcoming ITF meetings

The COMP noted the upcoming ITF meetings.

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

The COMP adopted the work plan.

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2022/2023

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2023 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. Revision of the PAWG COMP answer template

The PAWG COMP answer template was discussed and it was agreed that further discussions will be held at the next COMP plenary.

8.2. Committee representatives at SAWP: call for re-nomination

The COMP noted the presentation and call for re-nomination. In accordance with the SAWP mandate, the SAWP composition will be reviewed and the members/alternates as well as the Committee representatives re-nominated for an adoption of the new composition at the CHMP plenary in March 2023. The criteria for the re-nomination was presented and the call for expression of interests among the committees was launched.

8.3. Regulatory and scientific virtual conference on RNA-based medicines

Document(s) tabled: Agenda

The COMP noted the agenda of the conference.

8.4. Feedback from the ENCePP Plenary

Frauke Naumann-Winter presented the feedback from ENCePP Plenary and COMP noted the update.

8.5. Call for COMP member for the appointment of EC on EMA's recommendation.

The COMP noted the call.

9. List of participants

including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 17-19 January 2023 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	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	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Cecile Dop	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
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	
Robert Nistico	Member	Malta	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	
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 restrictions applicable to this meeting	

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 - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
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/