05 October 2023
EMA/COMP/422323/2023
Human Medicines Division

# Committee for Orphan Medicinal Products (COMP)

## Minutes for the meeting on 05-07 September 2023

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

**Disclaimers**

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

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

**Note on access to documents**

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

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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 remotely.

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced 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 concerning the matters for discussion. No new or additional interests or restrictions were declared.

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

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

## 1.2. Adoption of agenda

The agenda for 05-07 September 2023 was adopted with amendments.

Topic added:

7.2.2. COMP-CAT Working Group

## 1.3. Adoption of the minutes

The minutes for 11-13 July 2023 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. - EMA/OD/0000142116

Treatment of amyotrophic lateral sclerosis

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 21 July 2023, prior to responding to the list of issues.

### 2.1.2. humanised IgG1 monoclonal antibody against TfR1 conjugated to exon 44 specific phosphorodiamidate morpholino oligonucleotide via a non-cleavable linker - EMA/OD/0000140986

MWB Consulting; Treatment of Duchenne muscular dystrophy (DMD)

COMP Rapporteur: Elisabeth Penninga

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 Duchenne muscular dystrophy the sponsor was requested to provide further support from any additional non-clinical and/or clinical data.

- Significant benefit

The sponsor was asked to justify the significant benefit of the proposed product versus ataluren.

In the written response, and during an oral explanation before the Committee on 05 September 2023, the sponsor explained that for the in vitro data which showed increase in dystrophin protein production in human DMD patient myotubes, the patients had confirmed gene mutations amenable to exon-44 skipping. The extrapolation of the in vivo data from a non-clinical model with exon-23 skipping, to the target population of Duchenne muscular dystrophy patients with gene mutations amenable to exon-44 skipping was acceptable based on the updated information on the in vitro data. The COMP considered that the totality of the data would support the medical plausibility.

Regarding the significant benefit, the sponsor argued that ataluren (Translarna) is authorised for the treatment of DMD patients aged 2 years and older with the specific genetic defect of nonsense mutations in the dystrophin gene. Therefore, the proposed product, unlike ataluren, has the potential to be a disease modifying therapy in patients with mutations amenable to exon-44 skipping, and consequently provides a clinically relevant advantage for this different and distinct subpopulation of patients. Based on the non-clinical data provided, the COMP considered the product is expected to cover a different population compared to ataluren and accepted the justification for the significant benefit.

The Committee agreed that the condition, Duchenne 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 exon-44 specific phosphorodiamidate morpholino oligonucleotide via a non-cleavable linker was considered justified based on in vitro data which showed increase in dystrophin protein production in human DMD patient myotubes. Supportive evidence was also provided in a non-clinical surrogate model of the condition.

The condition is life-threatening and chronically debilitating due to progressive muscle weakness eventually affecting all voluntary muscles; this is followed by dilated cardiomyopathy and cardiac output decrease, leading to terminal respiratory or cardiac failure.

The condition was estimated to be affecting approximately 0.5 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 humanised IgG1 monoclonal antibody against TfR1 conjugated to exon-44 specific phosphorodiamidate morpholino oligonucleotide via a non-cleavable linker will be of significant benefit to those affected by the condition. The sponsor has provided data which showed increase in dystrophin protein production in human Duchenne muscular dystrophy myotubes from patients with genetic mutations amenable for exon-44 skipping. Based on this, compared to the authorised medicinal product, the product is expected to cover a different population. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised IgG1 monoclonal antibody against TfR1 conjugated to exon-44 specific phosphorodiamidate morpholino oligonucleotide via a non-cleavable linker, for treatment of Duchenne muscular dystrophy, was adopted by majority (22 out of 25 votes).

The COMP member of Norway agreed with the above-mentioned recommendation of the COMP.

The COMP Member of Liechtenstein did not participate in the meeting.

The COMP Member of Iceland was vacant.

The divergent positions (Tim Leest, Elisabeth Johanne Rook, Ines Alves) were appended to this opinion.

### 2.1.3. - EMA/OD/0000124476

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 04 August 2023, prior to responding to the list of issues.

### 2.1.4. eplontersen - EMA/OD/0000128649

Astrazeneca AB; Treatment of transthyretin-mediated amyloidosis (ATTR amyloidosis)

COMP Rapporteur: Eva Malikova

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

- Intention to diagnose, prevent or treat

Transthyretin-mediated amyloidosis should be changed to ATTR amyloidosis to be in line with previous designations.

- Significant benefit

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

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from their ongoing clinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. The indirect comparisons should be presented and discussed in more detail.

In the written response, the sponsor submitted data in comparison to tafamidis, which focused on a subgroup analysis of patients treated with eplontersen with Stage 2 showing a statistically significant difference versus placebo in Norfolk QoL Score. As tafamidis is not authorised for Stage 2 ATTR amyloidosis (only Stage 1) significant benefit versus tafamidis was thus accepted.

Indirect comparisons to patisiran and vutrisiran were considered impossible by the sponsor as the study designs differ. Nevertheless, eplontersen has achieved a steady improvement in the Norfolk QoL Score over 66 weeks (15.5 months) compared to studies with patisiran and vutrisiran where a decline was observed in this endpoint from month 9 to 18. Based on these data, the significant benefit over patisiran and vutrisiran can be acceptable at this stage of development. The COMP concluded that the data and arguments provided adequately addressed their concerns and thus agreed that an oral explanation was no longer needed.

The Committee agreed that the condition, transthyretin-mediated amyloidosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing eplontersen was considered justified based on preliminary clinical data showing a clinically meaningful and statistically significant reduction from baseline in serum transthyretin concentration as well as a halting or slowing of polyneuropathy, as assessed by modified Neuropathy Impairment Score +7 Composite Score.

The condition is life-threatening and chronically debilitating due to the development of polyneuropathy and cardiomyopathy.

The condition was estimated to be affecting not more 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 eplontersen will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that patients with Stage 2 transthyretin-mediated amyloidosis benefit from the eplontersen treatment. Specifically, an improvement in polyneuropathy as assessed by the modified Neuropathy Impairment Score +7 when compared to authorised medicinal products has been shown. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for eplontersen, for treatment of transthyretin-mediated amyloidosis, was adopted by consensus.

### 2.1.5. - EMA/OD/0000135016

Treatment of diffuse large B-cell lymphoma

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 01 August 2023, prior to responding to the list of issues.

### 2.1.6. mitapivat sulfate - EMA/OD/0000122901

Agios Netherlands B.V.; Treatment of thalassaemia intermedia and major

COMP Rapporteur: Enrico Costa

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 sponsor should consider separating the conditions into alpha-thalassaemia intermedia and major and beta-thalassaemia intermedia and major. Under the current procedure the COMP can only consider one of the two conditions. Note that this was 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).

- Number of people affected

The COMP considered that alpha-thalassaemia intermedia and major and beta-thalassaemia intermedia and major are different conditions. The sponsor was asked to re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan conditions and given the substantial uncertainty about many of the assumptions regarding the prevalence, they should perform a sensitivity analysis of the reported calculations.

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

The sponsor was requested to detail the results of any clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, and during an oral explanation before the Committee on 06 September 2023, the sponsor amended the condition to treatment of beta-thalassaemia intermedia and major which was accepted. A revised prevalence estimate was consequently submitted. The estimated prevalence of beta-thalassaemia intermedia and major was 0.46/10,000 (range of 0.42 to 1.1/10,000 based on sensitivity analyses). The COMP proposed a prevalence of less than 1 in 10,000 which the sponsor accepted. These topics were not further discussed at the oral explanation.

Concerning significant benefit, the COMP considered that further clarification was needed. During the oral explanation, the sponsor further elaborated on the patient population studied in their clinical trial. Patients had non-transfusion dependent beta-thalassaemia intermedia which have generally been considered milder than the severe forms. It was

highlighted that many of these patients have end organ damage due to iron overload. It is nowadays believed that morbidity can be as serious in intermedia patients as in severe patients resulting in the need of treatments to reduce the iron overload. Data from the non-clinical in vivo study was used to show the effect of reduction of organ iron overload and contextualised within the target patient population identified. The COMP accepted that target end organ iron overload was a serious source of morbidity and that reducing it in beta-thalassaemia intermedia patients would constitute a clinically relevant advantage.

The Committee agreed that the condition, beta-thalassaemia intermedia and major, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing mitapivat sulfate was considered justified based on preliminary clinical data showing a durable increase in haemoglobin levels over a period of 72 weeks.

The condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these, in particular in beta-thalassaemia major patients.

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 mitapivat sulfate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary non-clinical data that demonstrate a reduction in iron load in target end organs in a valid model of the condition supporting an important therapeutic effect which can translate into a reduced need for chelating agents. Furthermore, this effect provides a potential benefit over luspatercept as the latter did not show clinically meaningful reductions in iron deposition in target end organs, and on haemolysis. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for mitapivat sulfate, for treatment of beta-thalassaemia intermedia and major, was adopted by consensus.

### 2.1.7. adeno-associated virus vector serotype 9/rh74 containing the human *CAPN3* gene and a target sequence of cardiac-specific microRNA - EMA/OD/0000140879

Atamyo Therapeutics; Treatment of limb-girdle muscular dystrophy (LGMD)

COMP Rapporteur: Armando Magrelli

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 limb-girdle muscular dystrophy (LGMD) the sponsor should further elaborate on the results obtained in the in vitro pharmacology study and the translatability of this data to clinical outcomes. In addition, the sponsor, was requested to provide any additional in vivo non-clinical and or preliminary clinical data.

In the written response, the sponsor clarified that the functional test that was initially described as an in vitro assessment of muscular force included in fact, muscle samples

which were obtained from the animals of the in vivo study, therefore this test constitutes an ex vivo functional evaluation.

Based on the evidence of the correction of the histological signs and the force deficit of the skeletal muscles in the in vivo study, the COMP considered that the medical plausibility was considered justified and the oral explanation was cancelled.

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 vector serotype 9/rh74 containing the human *CAPN3* gene and a target sequence of cardiac-specific microRNA 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, consequent 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 vector serotype 9/rh74 containing the human *CAPN3* gene and a target sequence of cardiac-specific microRNA, for treatment of limb-girdle muscular dystrophy, was adopted by consensus.

### 2.1.8. - EMA/OD/0000140620

Treatment 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 arguments on significant benefit were based on the new 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 the non-clinicals studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. In particular, the sponsor was invited to elaborate on the methodology and measurement of the outcomes.

The sponsor was also asked to elaborate on the arguments of improved efficacy in temozolomide resistant tumour cells.

Furthermore, it would be useful to obtain more information on the ongoing study/planned development.

In the written response, and during an oral explanation before the Committee on 06 September 2023, the sponsor addressed the lack of data supporting a significant benefit comparison with available treatments. The sponsor emphasised the claims of better efficacy based on a O6-methylguanine-DNA methyl-transferase - independent mechanism of action,

which could offer an alternative to temozolomide resistant patients. For this purpose, data was provided in temozolomide resistant cell lines and in patient-derived glioblastoma neurospheres. However, these data were limited to the in vitro setting only, which hampers the interpretation.

During the oral explanation, further enquiries were posed by the Committee to elucidate the significant benefit potential, however, the responses produced by the sponsor did not dispel the existing doubts. Overall, it was the opinion of the COMP that the information provided by the sponsor was not sufficient to support the claim on significant benefit of the proposed product in the applied condition.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 06 September 2023, prior to final opinion.

### 2.1.9. - EMA/OD/0000133480

Treatment of Stargardt's disease

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

- Intention to diagnose, prevent or treat:

The sponsor was asked to consider changing the condition to 'treatment of inherited retinal dystrophies due to *ABCA4* gene deficiency' (please see COMP notification on inherited retinal dystrophies on EMA Website). Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (especially section A of 2022/C 440/02).

To establish correctly whether there exists a scientific rationale for the development of the proposed product for the target condition the sponsor should further elaborate on:

- the relevance of the mode of action of the product within the context of treating the condition and the interpretation of the results obtained in the experiments submitted.
- number of people affected.

The sponsor was requested to consider changing the condition to 'treatment of inherited retinal dystrophies due to *ABCA4* gene deficiency'. They should therefore provide a new prevalence estimate which covers this condition and justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. They were asked to describe and justify the methodology used for the prevalence calculation.

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

In the written response, and during an oral explanation before the Committee on 06 September 2023, the Committee initially discussed the condition and the prevalence with the sponsor. This was done within the context of the mode of action of the product and its applicability to other retinal conditions. The sponsor did not fully reply to the issues regarding the relevance of the mode of action. No clarification was made on whether the inserted gene was to replace/enhance/substitute existing RORA in the retinal tissues and no

real discussion was provided either on the breadth of potential application of this treatment outside of *ABCA4* deficiencies. The following statement was made in the response, paraphrased here: '*hRORA* gene is a transcription factor that is known to affect multiple genes/gene network in the cellular pathways of lipid metabolism, inflammation, oxidative stress and complement pathway'. It was acknowledged that the product had potential to be used in other similar conditions such as age-related macular degeneration. There was, however, no additional data in other conditions which would support the use of the product at this stage. The COMP informed the sponsor that the acceptable condition for the moment was therefore treatment of inherited retinal dystrophies due to *ABCA4* gene deficiency and the prevalence estimate should reflect this. The sponsor accepted this proposal from the Committee.

The discussion then focused on the medical plausibility. The sponsor was asked to further elaborate on the variability seen in the electroretinography (ERG) data that was submitted.

The sponsor accepted that the data in the single non-clinical in vivo study submitted was not conclusive enough to establish the efficacy of the product in restoring retinal function in a permanent manner. Doubts remained regarding the real efficacy of the product particularly due to the non-specificity of the mode of action. Although the sponsor indicated that they had more data they were not able to share it with the Committee during the oral explanation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 07 September 2023, prior to final opinion.

### 2.1.10. certepetide - EMA/OD/0000138974

Lisata Therapeutics 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:

- Significant benefit

The sponsor was asked to discuss the significant benefit of their proposed product vis a vis updated results of all standard of care treatment options in the target patient population, based on outcome measures including disease control rate (DCR), overall response rate (ORR) and overall survival (OS).

In the written response, and during an oral explanation before the Committee on 07 September 2023, the sponsor presented a more wholesome side by side efficacy comparison of the proposed product to standard of care (SoC) therapy in metastatic pancreatic ductal adenocarcinoma (mPDAC), including also FOLFIRINOX and more recent data sources from published literature.

The updated dataset confirmed a positive trend towards improved efficacy (ORR, mPFS and mOS) of the triple combination of the proposed product together with the SoC gemcitabine + nab-paclitaxel vs this SoC therapy alone. When comparing the efficacy of the triple combination of the proposed product + gemcitabine + nab-paclitaxel to the FOLFIRINOX SoC, the results show a more varied picture where a trend towards improved efficacy could not be concluded.

Apart from the efficacy aspects, the sponsor also emphasised that the FOLFIRINOX regimen is known to be associated with greater toxicity than gemcitabine/nab-paclitaxel. The safety results from the Dean et al., 2022 trial suggested that the observed improved efficacy of the proposed product when added to the combination with gemcitabine/nab-paclitaxel was not accompanied by a concomitant increase in adverse events as compared to gemcitabine/nab-paclitaxel alone. While COMP acknowledged this information, they concluded that the currently limited safety data with the proposed product vis a vis FOLFIRINOX does not allow a conclusion on improved safety.

Apart from the scientific aspects, the COMP also discussed the difficulty with defining FOLFIRINOX as a satisfactory method for mPDAC from a regulatory perspective as not all constituents are authorised in the EU for this specific indication.

Considering the above, the COMP concluded that the sponsors preliminary clinical efficacy data with the proposed product in pancreatic cancer patients with metastatic disease showed improvements in ORR, progression-free survival, and overall survival when the product was added to currently authorised standard of care therapy, as compared to standard of care therapy alone.

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 certepetide was considered justified based on preliminary clinical data in pancreatic cancer patients with metastatic disease which showed improvements in objective response rate, progression-free survival, and overall survival.

The condition is chronically debilitating due to pain, nausea, vomiting, weight loss, fatigue, 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 certepetide will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical efficacy data in pancreatic cancer patients with metastatic disease which showed improvements in objective response rate, progression-free survival, and overall survival when the product was added to currently authorised standard of care therapy, as compared to standard of care therapy alone (published data). The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for certepetide, for treatment of pancreatic cancer, was adopted by consensus.

### 2.1.11. humanised IgG4 monoclonal antibody against C1q - EMA/OD/0000139967

Kinesys Consulting NL B.V.; Treatment of Guillain-Barre syndrome

COMP Rapporteur: Elisabeth Johanne Rook

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

- Significant benefit

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

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. Particular attention should be made regarding the axonal forms versus the demyelinating forms.

The sponsor was asked to detail the results of any additional clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, the sponsor addressed significant benefit. In their response the COMP noted that an indirect comparison between the proposed product and intravenous immunoglobulin (IVIg) are challenging from a methodological perspective, since the number of patients included in the analyses were small. Nevertheless, a comparison of the clinical trial data with the proposed product (using 18 patients from the high dose group) to other studies with IVIg were presented in two tiers. The first was an indirect comparison versus Bangladesh registry data. After 1 week of treatment, the proposed product demonstrated superior efficacy vs IVIG regarding improvement of muscle strength, as measured by the Medical Research Council (MRC) sum score, to a statistically significant level (median change 6 vs 0 point on the MRC muscle strength score). The second was an indirect comparison versus the Dutch trial on second dosing of IVIg. In the 93 Dutch patients with a poor prognosis treated with IVIg in the first phase of the study, 85% of patients were still deteriorating at week 1 (showing a reduction in MRC sum score), with a mean decline in MRC sum score of approximately -16 (Walgaard et al., 2021). This is thus less favourable than observed for the proposed product, where 15% deteriorated after 1 week of treatment. The sponsor did not study patients refractory to IVIg as part of the proposed product's development programme, as treatment with IVIg is considered to be suboptimal. The sponsor did not perform direct comparisons versus plasma exchange, as this is hardly applied in modern practice.

Regarding the applicability of the acute motor axonal neuropathy (AMAN) subtype to the EU, the COMP acknowledged that although the axonal subtype (AMAN) is seen more often in Bangladesh, it was agreed that the data from Bangladeshi patients was still relevant for the EU target population with severe disease.

The COMP concluded that the sponsor had adequately answered in their written response and that the oral explanation could be cancelled. The Committee recommended granting the orphan designation.

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

The intention to treat the condition with the medicinal product containing humanised IgG4 monoclonal antibody against C1q was considered justified based on preliminary clinical data showing an improvement in the Guillain-Barré syndrome disability score.

The condition is chronically debilitating due to acute and potentially permanent nerve damage associated with progressive paralysis which can lead to life-threatening breathing difficulties.

The condition was estimated to be affecting approximately 0.3 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 humanised IgG4 monoclonal antibody against C1q will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate an improvement in muscle strength and reduction of the need of mechanical ventilation when compared indirectly to patients treated with the authorised treatment IVIg (intravenous immunoglobulin). The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised IgG4 monoclonal antibody against C1q, for treatment of Guillain-Barre syndrome, was adopted by consensus.

### 2.1.12. ulefnersen - EMA/OD/0000141035

Ionis Development (Ireland) Limited; Treatment of amyotrophic lateral sclerosis (ALS)

COMP Rapporteur: Robert Nistico

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

- 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 amyotrophic lateral sclerosis (ALS) the sponsor was asked to further elaborate on the results from the non-clinical and clinical studies. In particular, the sponsor should elaborate on the correlation between the levels of reduction in the FUS (Fused in Sarcoma) mRNA transcript, and disease progression, and the phenotype correlations of FUS-ALS phenotype.

In addition, should any additional clinical data be available from the individual expanded access application, the sponsor was invited to discuss this information.

- Significant benefit

The arguments on significant benefit were based on the new 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 the non-clinical and clinical studies 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 correlation between the levels of reduction in the FUS mRNA transcript, and disease progression and disease phenotype.

Furthermore, it would be useful to obtain more information on the ongoing study/planned development.

In the written response, the sponsor provided new information which strengthens the level of evidence for medical plausibility and significant benefit.

Compared to the original application in which the sponsor had provided evidence in favour of a reduction of mRNA levels following the product administration, the sponsor now provides a parallel reduction in the levels of FUS protein as part of the non-clinical studies.

Moreover, clinical data from an additional investigator initiated study has been included indicating a potential functional improvement in one patient. A comparison of the timing of changes in this patient's Neurofilament light chain (NfL) and ALS Functional Rating Scale-Revised (ALSFRS-R) was illustrated, suggesting a temporal relationship between change in NfL and clinical benefit. NfL has emerged as a leading candidate with potential to aid ALS therapy development, however a nuanced understanding of the temporal dynamics of NfL in ALS only partially supports the notion that NfL is a reasonably likely surrogate end-point — because the correlative clinical effects of lowering NfL depend on the timing of treatment.

Assumption of significant benefit is therefore supported since this medicinal product could exert a disease-modifying effect by specifically targeting the pathogenic mechanism in FUS ALS. This could be advantageous in a subpopulation of familial ALS presenting FUS mutation where authorised treatments would not be effective.

Overall, although preliminary, these data can be supportive of a positive opinion and the COMP decided to cancel the oral explanation.

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 ulefnersen was considered justified based on non-clinical data in a model of the condition showing improvement in biomarkers of the condition and motor function, and preliminary clinical data that could indicate an improvement in 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 ulefnersen will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that ulefnersen could bear disease-modifying effect by targeting the pathogenic mechanism in FUS amyotrophic lateral sclerosis possibly attenuating the decline in motor function. This would not be expected from the currently authorised treatment for the condition. The Committee considered that this constitutes a clinically relevant advantage.

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

### 2.1.13. setmelanotide - EMA/OD/0000138272

Rhythm Pharmaceuticals Netherlands B.V.; Treatment of hypothalamic obesity

COMP Rapporteur: Tim Leest

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

- Condition

The sponsor was asked to change the condition wording to "treatment of acquired hypothalamic obesity".

- Number of people affected

The sponsor appeared to limit their prevalence calculation to hypothalamic obesity (HO) due to brain tumours. The COMP therefore asked the sponsor to also consider other underlying causes for HO such as cranial radiation, surgery, infections, and head trauma in their prevalence calculation.

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 sponsor was requested to discuss the significant benefit of setmelanotide vis a vis currently authorised weight-loss products (e.g. semaglutide) and support their arguments with relevant data.

Furthermore, the sponsor was asked to clarify the previous treatment history of HO patients included the completed phase 2 study (Study RM-493-030) with regards to weight-loss therapies, if any, and whether patients continued their weight-loss therapy during the study.

The COMP discussed the written responses from the sponsor during their September 2023 plenary meeting.

The sponsor accepted the COMP's request and agreed to change the condition wording to "treatment of acquired hypothalamic obesity".

As regards the prevalence, the sponsor cites one new publication, i.e. Rose et al. (2018) which described 87 patients with HO in the International Registry of Hypothalamic Obesity Disorders (IRHOD). Non-tumour related causes such as traumatic brain injury, inflammatory conditions, and infections represent a relatively small proportion of the overall HO population likely occurring in significantly less than 10% of cases. With this addition (Rose et al., 2018), the prevalence estimates previously provided have increased slightly to 0.11 to 0.35 in 10,000 patients. The COMP concluded that the sponsors revised methodology with an up-rounded value of 0.4 per 10,000 persons is acceptable for orphan designation stage. However, for the purpose of the orphan maintenance review at time of marketing authorisation, the sponsor is strongly encouraged to also consider the population of patients who received cranial irradiation for conditions other than brain tumours, such as for example survivors of childhood acute lymphoblastic leukaemia (ALL). As reported in the literature, 40 % of ALL survivors who received cranial irradiation with 24 Gy to the brain were overweight (BMI > 85th centile) and 38% of those who received 18 Gy (Sklar et al., 2000, Med Pediatr Oncol. 2000 Aug;35(2):91-5. doi: 10.1002/1096-911x(200008)35:2<91::aid-mpo1>3.0.co;2-g. PMID: 10918229).

As regards the significant benefit and current satisfactory methods, the COMP emphasised again that the underlying mechanistic pathways leading to acquired HO are not well defined

and incompletely understood, which complicates the answer to the question of possible satisfactory methods for this condition. While the COMP acknowledged the fundamental role of the signalling pathway of melanocortin 4 receptor (MC4R) in energy homeostasis and appetite regulation, it is not fully clear to the Committee whether this specific pathway is always impaired in patients with HO and whether there is always a deficiency of the satiety hormone α-MSH in these patients. The COMP also emphasised that the pharmacological class of GLP-1 receptor agonists, i.e. semaglutide and liraglutide may also be efficacious in HO patients due to their central action on hindbrain and or hypothalamic signalling pathways (Roth et al., 2015; Shoemaker et al., 2023). The COMP acknowledged that the sponsor has provided at least some preliminary clinical data in two patients with the proposed condition who have been previously treated with liraglutide or semaglutide and who showed reductions in body weight, BMI and hunger scores while treated with setmelanotide. The Committee considered that at the stage of orphan designation this data is sufficient to support the assumption of clinically relevant advantage. However, the Committee considered that at the time of marketing authorisation further data are necessary to support the clinically relevant advantage over currently authorised weight loss drug. The sponsor is strongly recommended to seek EMA Protocol Assistance to discuss the data expected to support the significant benefit of setmelanotide vis a vis currently authorised weight loss drugs, at time of orphan maintenance review.

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of acquired hypothalamic obesity.

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

The intention to treat the condition with the medicinal product containing setmelanotide was considered justified based on clinical data in patients with the condition who showed reductions in body weight, BMI and hunger scores.

The condition is chronically debilitating due to severe obesity, hyperphagia, an increased risk to develop severe atherosclerotic disease and type 2 diabetes mellitus, and life-threatening due to an increased risk of fatal cardiovascular events.

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.

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 setmelanotide will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in two patients with the proposed condition who have been previously treated with currently authorised weight loss drugs and who showed reductions in body weight, BMI and hunger scores while treated with setmelanotide. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for setmelanotide, for treatment of acquired hypothalamic obesity, was adopted by consensus.

### 2.1.14. tasimelteon - EMA/OD/0000137651

Vanda Pharmaceuticals Netherlands B.V.; Treatment of Smith-Magenis syndrome

COMP Rapporteur: Zsofia Gyulai

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 claim for the significant benefit was based on the broader population covering patients above 18 years old. However the sponsor should further justify it based on subgroup analyses of the efficacy based on the age (above and under 18 years old).

In the written response, the sponsor provided additional subgroup analyses of the efficacy based on the age. Based on this data, tasimelteon has shown clinical improvements in sleep disturbances for both adult and paediatric patients with Smith-Magenis syndrome. The COMP considered that the significant benefit can be justified, since the efficacy was shown in patients affected by the condition for whom the authorised medicinal product is not approved. The COMP concluded that the additional data is sufficient to support the designation and cancelled the oral explanation.

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

The intention to treat the condition with the medicinal product containing tasimelteon was considered justified based on preliminary clinical data which showed improvement in sleep disturbances in patients affected by the condition.

The condition is chronically debilitating due to failure to thrive, mental retardation, sleep disturbance, craniofacial and skeletal anomalies, self-injurious and attention-seeking behaviours, and speech and motor delay.

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 tasimelteon will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that showed improvement in sleep disturbances in patients affected by the condition for whom the authorised medicinal product is not approved.

The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tasimelteon, for treatment of Smith-Magenis syndrome, was adopted by consensus.

## 2.2. For discussion / preparation for an opinion

### 2.2.1. - EMA/OD/0000128462

Treatment of Alport 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 October 2023 meeting.

### 2.2.2. sodium selenate - EMA/OD/0000128771

Monash University; Treatment of progressive supranuclear palsy

COMP Rapporteur: Michel Hoffmann

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

The intention to treat the condition with the medicinal product containing sodium selenate was considered justified based on non-clinical data in an in vivo model of tauopathy which showed reduced levels of phosphorylated tau protein in the hippocampus and improved cognition.

The condition is chronically debilitating due to progressive neurological impairment including development of parkinsonism, risk of falls, inability to walk, progressive paralysis and cognitive deterioration. The condition is also life-threatening due to pneumonia (due to aspiration) and other complications related to the progression of the disease.

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 sodium selenate, for treatment of progressive supranuclear palsy, was adopted by consensus.

### 2.2.3. 1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime - EMA/OD/0000131662

AC Biotech; Treatment of pancreatic cancer

COMP Rapporteur: Frauke Naumann-Winter

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 1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime was considered justified based on non-clinical data in several models of the condition showing an effect on tumour volume and tumour growth when used in combination with gemcitabine.

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 2.1 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 1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in models of the condition that showed increased antitumour activity in combination with gemcitabine, when compared to standard of care

treatment for the proposed patient population with previously untreated metastatic pancreatic ductal adenocarcinoma. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone oxime, for treatment of pancreatic cancer, was adopted by consensus.

### 2.2.4. sildenafil citrate - EMA/OD/0000135459

Charite Universitaetsmedizin Berlin KöR; Treatment of Leigh syndrome

COMP Rapporteur: Zsofia Gyulai

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

The intention to treat the condition with the medicinal product containing sildenafil citrate was considered justified based on few clinical cases which reported improvements such as exercise tolerance, reduction of hemiplegic episodes, general improvement of mobility and independence, improvement of muscle strength and reduction of epileptic seizures.

The condition is chronically debilitating due to neurological deficits, psychomotor delay, dysmorphic features, cardiac, renal and metabolic dysfunction, and life-threatening with most patients dying in early childhood.

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 sildenafil citrate, for treatment of Leigh syndrome, was adopted by consensus.

### 2.2.5. - EMA/OD/0000137539

Treatment of narcolepsy

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 October 2023 meeting.

### 2.2.6. - EMA/OD/0000139099

Treatment of pancreatic cancer

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 October 2023 meeting.

### 2.2.7. resminostat - EMA/OD/0000139511

4 SC AG; Treatment of cutaneous T-cell lymphoma

COMP Rapporteur: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing resminostat was considered justified based on clinical data in the maintenance therapy setting which demonstrated an increase in progression-free-survival as compared to the placebo group.

The condition is chronically debilitating due to the development of cutaneous lesions, generalised erythroderma, lymphadenopathy, pruritus and life-threatening due to disease progression or ulceration of tumours, with secondary bacterial infections.

The condition was estimated to be affecting approximately 2.4 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 resminostat will be of significant benefit to those affected by the condition. The sponsor has provided clinical data which demonstrated that maintenance therapy with resminostat increased progression-free-survival as compared to the placebo group, in patients with advanced stage disease who achieved disease control during their prior systemic therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for resminostat, for treatment of cutaneous T-cell lymphoma, was adopted by consensus.

### 2.2.8. - EMA/OD/0000140934

Treatment of pulmonary arterial hypertension

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 October 2023 meeting.

*[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 20 September 2023.]*

### 2.2.9. (R)-(3-(2'-cyclopropyl-3-(hydroxymethyl)-[1,1'-biphenyl]-4-yl) pyrrolidin-1-yl)(5-fluoropyridin-2-yl)methanone - EMA/OD/0000142438

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-fluoropyridin-2-yl)methanone was considered justified based on in vivo non-clinical data which showed improvement in skin hyperkeratosis and 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-fluoropyridin-2-yl)methanone, for treatment of Olmsted syndrome, was adopted by consensus.

### 2.2.10. alpelisib - EMA/OD/0000142531

Novartis Europharm Limited; Treatment of lymphatic malformations

COMP Rapporteur: Bozenna Dembowska-Baginska

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

The intention to treat the condition with the medicinal product containing alpelisib was considered justified based on non-clinical data in a model of the condition showing improvement in lymphatic malformations volume and survival.

The condition is chronically debilitating due to discomfort, pain, swelling, thrombosis and psychological distress and life threatening due to impairment of vital functions if left untreated.

The condition was estimated to be affecting approximately 3.3 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 alpelisib, for treatment of lymphatic malformations, was adopted by consensus.

### 2.2.11. glycerol phenylbutyrate - EMA/OD/0000143040

Immedica Pharma AB; Treatment of STXBP1 developmental and epileptic encephalopathy

COMP Rapporteur: Darius Matusevicius

The Committee agreed that the condition, STXBP1 developmental and epileptic encephalopathy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing glycerol phenylbutyrate was considered justified based on preliminary clinical data showing a 50% reduction in seizures and an improvement in communication as well as sleep.

The condition is chronically debilitating due to neurodevelopmental abnormalities, epilepsy, and motor and behavioural disturbances.

The condition was estimated to be affecting approximately 0.25 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 glycerol phenylbutyrate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate an additional reduction of 50% in seizures when the product is used on top of antiseizure medication. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for glycerol phenylbutyrate, for treatment of STXBP1 developmental and epileptic encephalopathy, was adopted by consensus.

### 2.2.12. - EMA/OD/0000143251

Treatment of Prader-Willi 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 October 2023 meeting.

### 2.2.13. adeno-associated viral vector serotype 9 containing the human *NPC1* gene - EMA/OD/0000143825

FGK Representative Service GmbH; Treatment of Niemann-Pick disease, type C

COMP Rapporteur: Joao Rocha

The Committee agreed that the condition, Niemann-Pick disease, type C, 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 containing the human *NPC1* gene was considered justified based on non-clinical efficacy data in a valid in vivo disease model showing improved survival and motor function as well as reduced tremor and maintenance of body weight.

The condition is chronically debilitating due to neurological decline with ataxia, dysphagia, dysarthria, seizures, cognitive decline, hepatosplenomegaly, and life-threatening due to progressive neurological deterioration and bronchopneumonia.

The condition was estimated to be affecting approximately 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 adeno-associated viral vector serotype 9 containing the human *NPC1* gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical efficacy data in a valid in vivo disease model showing that the proposed product, which aims at modifying the course of the disease, leads to improved survival and bodyweight when compared to the current standard of care therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 9 containing the human *NPC1* gene, for treatment of Niemann-Pick disease, type C, was adopted by consensus.

### 2.2.14. - EMA/OD/0000143999

Treatment of ovarian cancer

The COMP adopted a list of issues that will be sent to the sponsor. The Committee will discuss the submitted answers to the list of issues at the October 2023 meeting.

### 2.2.15. 2-(3-(3,5-dimethyltriazol-4-yl)-5-((S)-oxan-4-yl(phenyl)methyl)pyrido(3,2-b)indol-7-yl)propan-2-ol - EMA/OD/0000144104

Bristol-Myers Squibb Pharma EEIG; Treatment of myelofibrosis

COMP Rapporteur: Karri Penttila

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

The intention to treat the condition with the medicinal product containing 2-(3-(3,5-dimethyltriazol-4-yl)-5-((S)-oxan-4-yl(phenyl)methyl)pyrido(3,2-b)indol-7-yl)propan-2-ol was considered justified based on preliminary clinical data which showed responses as measured by spleen volume reduction in patients with myelofibrosis.

The condition is chronically debilitating and life-threatening due to anaemia, splenomegaly, extramedullary haematopoiesis, constitutional symptoms such as fatigue, night sweats and fever, cachexia and leukaemic progression.

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 2-(3-(3,5-dimethyltriazol-4-yl)-5-((S)-oxan-4-yl(phenyl)methyl)pyrido(3,2-b)indol-7-yl)propan-2-ol will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data which showed activity and preliminary clinical data suggesting responses as measured by spleen volume reduction and possible disease modification effects when the product is used as add-on to the authorised medicinal products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-(3-(3,5-dimethyltriazol-4-yl)-5-((S)-oxan-4-yl(phenyl)methyl)pyrido(3,2-b)indol-7-yl)propan-2-ol, for treatment of myelofibrosis, was adopted by consensus.

### 2.2.16. adeno-associated viral vector serotype 9 containing the human *PLA2G6* gene - EMA/OD/0000144182

FGK Representative Service GmbH; Treatment of infantile neuroaxonal dystrophy

COMP Rapporteur: Maria Judit Molnar

The Committee agreed that the condition, infantile neuroaxonal 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 containing the human *PLA2G6* gene was considered justified based on in vivo non-clinical data which showed increased survival, improvements in weight and motor coordination, and reduction in neurodegeneration in the brain and spinal cord.

The condition is chronically debilitating and life threatening, in particular due to infantile onset of motor and cognitive regression, spasticity, muscle atrophy, hypotonia, cerebellar ataxia, dystonia, optic atrophy and distal sensory loss, and with a survival of less than 10 years.

The condition was estimated to be affecting approximately 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 adeno-associated viral vector serotype 9 containing the human *PLA2G6* gene, for treatment of infantile neuroaxonal dystrophy, was adopted by consensus.

### 2.2.17. sodium oxybate - EMA/OD/0000144198

Avadel Ireland; Treatment of narcolepsy

COMP Rapporteur: Tim Leest

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

The intention to treat the condition with the medicinal product containing sodium oxybate was considered justified based on clinical data showing a clinically meaningful improvement in the mean wakefulness time, Clinicians Global Impression and mean weekly number of cataplexy attacks.

The condition is chronically debilitating in particular due to excessive daytime sleepiness and cataplexy episodes, as well as life-threatening with a 1.5-fold excess mortality in narcolepsy patients relative to those without narcolepsy.

The condition was estimated to be affecting approximately 4.4 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 sodium oxybate will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate patient preference of a once-a-day to a twice a day formulation of sodium oxybate in the treatment of narcolepsy. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for sodium oxybate, for treatment of narcolepsy, was adopted by consensus.

The sponsor is strongly recommended to seek EMA Protocol Assistance to discuss the data expected to support the significant benefit of sodium oxybate vis a vis currently authorised products.

### 2.2.18. human IgG1 (296-cysteine, 301-glycine, 306-cysteine) monoclonal antibody against *TREM2* - EMA/OD/0000144261

Pharma Gateway AB; Treatment of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia

COMP Rapporteur: Elisabeth Johanne Rook

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of CSF1R-related leukoencephalopathy.

The Committee agreed that the condition, CSF1R-related leukoencephalopathy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing human IgG1 (296-cysteine, 301-glycine, 306-cysteine) monoclonal antibody against *TREM2* was considered justified based on in vitro data which showed an increase in the viability of microglia carrying the CSF1R gene mutation, supported by pharmacodynamic data in healthy volunteers which showed increase in the CSF1R levels in the cerebrospinal fluid.

The condition is chronically debilitating due to the development of early-onset cognitive decline and dementia, neuropsychiatric symptoms, parkinsonism and life threatening due to reduced life expectancy.

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

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

A positive opinion for IgG1 (296-cysteine, 301-glycine, 306-cysteine) monoclonal antibody against *TREM2*, for treatment of CSF1R-related leukoencephalopathy, was adopted by consensus.

## 2.3. Revision of the COMP opinions

None

## 2.4. Amendment of existing orphan designations

None

## 2.5. Appeal

### 2.5.1. -

Treatment of patients with light chain (AL) amyloidosis

The COMP noted the appeal from the applicant. The appeal rapporteur was appointed.

## 2.6. Nominations

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

COMP rapporteurs were appointed for 19 applications.

## 2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 11 applications for orphan designation.

# 3. Requests for protocol assistance with significant benefit question

## 3.1. Ongoing procedures

### 3.1.1. -

Treatment of spinal cord injury

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 malignant mesothelioma

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

None

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

### 4.2.1. Vanflyta - quizartinib - EMEA/H/C/005910/0000, EU/3/09/622, EMA/OD/0000134652

Daiichi Sankyo Europe GmbH; Treatment of acute myeloid leukaemia

A list of issues was adopted on 13 July 2023. An oral explanation was held on 05 September 2023.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 07 September 2023, prior to final opinion.

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

### 4.2.2. - zilucoplan - EMEA/H/C/005450/0000, EU/3/22/2650, EMA/OD/0000120845

UCB Pharma S.A.; Treatment of myasthenia gravis

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 October 2023 meeting.

### 4.2.3. – teriparatide - EMEA/H/C/005934, EU/3/20/2350, EMA/OD/0000140073

Ascendis Pharma Bone Diseases A/S; Treatment of hypoparathyroidism

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to send a written response by the October 2023 meeting.

## 4.3. Appeal

### 4.3.1. Jaypirca - pirtobrutinib - EMEA/H/C/005863, EU/3/21/2450,

Eli Lilly Nederland B.V.; Treatment of mantle cell lymphoma

COMP appeal rapporteur: Frauke Naumann-Winter; COMP appeal co-Rapporteur: Karri Penttilä

COMP noted the SAG report presented by the SAG Oncology Chair.

In the grounds for appeal, and during an oral explanation before the Committee on 05 September 2023, the sponsor aimed to address the main issues which led to the negative opinion.

The COMP upheld the negative view and an opinion recommending removing Jaypirca, pirtobrutinib, EU/3/21/2450 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.

## 4.4. 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. Adcetris - brentuximab vedotin - EMEA/H/C/002455/II/0109, EU/3/08/595, EMA/OD/0000146788

Takeda Pharma A/S; Treatment of peripheral T-cell lymphoma

CHMP Rapporteur: Johann Lodewijk Hillege; CHMP Co-Rapporteur: Jan Mueller-Berghaus

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is needed.

### 5.2.2. Adcetris - brentuximab vedotin - EMEA/H/C/002455/II/0107, EU/3/08/596, EMA/OD/0000136638

Takeda Pharma A/S; Treatment of Hodgkin lymphoma

COMP Rapporteur: Elisabeth Johanne Rook; COMP Co-Rapporteur: Frauke Naumann-Winter; CHMP Rapporteur: Johann Lodewijk Hillege; CHMP Co-Rapporteur: Jan Mueller-Berghaus

An opinion recommending not to remove Adcetris, brentuximab vedotin, EU/3/08/596 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 September 2023 meeting.*

## 5.3. Appeal

None

## 5.4. On-going procedures

COMP co-ordinators were appointed for 1 application.

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

None

# 7. Organisational, regulatory and methodological matters

## 7.1. Mandate and organisation of the COMP

### 7.1.1. COMP membership

New membership:

The Chair welcomed Ioannis Kkolos, as the new member for Cyprus.

End of membership:

The Chair thanked Elli Loizidou for her contribution as the member for Cyprus.

### 7.1.2. Vote by proxy

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

### 7.1.3. Strategic Review & Learning meetings

The COMP noted the topics and draft agenda for the face-to-face meeting to be held on 17-18 October 2023 in Madrid, Spain.

### 7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 1st September 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.

### 7.2.2. COMP-CAT Working Group

The meeting was held virtually on 4 September.

## 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)

Draft agenda for PCWP-HCPWP Joint meeting to be held on 19-20 September was tabled for information.

Meeting Summary for PCWP-HCPWP meeting held on 27-28 June was tabled for information.

### 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

None

## 7.8. Planning and reporting

### 7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 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. Update on progress on Patient Experience Data (PED)

The COMP noted the presentation on PED and its relevance for orphan medicines. Patients' views or preferences on medicines or living with a condition are particularly important for orphan medicines and rare diseases. In particular, PED can be useful to gather evidence in support of claims for major contribution to patient care (at time of initial orphan designation and at orphan maintenance review).

The two key deliverables for the Network in 2023 are:

- Reflection paper on the best EU approach to generate, collect and analyse PED;
- Explore how to improve transparency.

On the basis of the 2022 PED workshop's outcomes, EMA will enable discussions within the Network on current status, next steps and how to monitor progress. Furthermore, EMA is preparing a list of actions and priorities that will be discussed with the EU Network and also shared with stakeholders, including PCWP and HCPWP.

PED is also relevant in the context of the implementation of the new Health Technology Assessment (HTA) regulation, thus in value assessments that inform subsequent decisions by payers.

Other actions are:

1. The Agency will elaborate a reflection paper to provide advice on the best EU approach to generate and collect PED

EMA has set up an internal working group to coordinate cross-Agency expertise and draft the reflection paper, in collaboration with Network experts.

Drafting ongoing Q3-Q4 2023 and public consultation planned by Q1 2024

2. ICH guidance:

EMA supports PED global development and will contribute to ICH work on PED guidelines.

3. Agreed to continue multilateral stakeholder cooperation to obtain the best regulatory outcomes, and to explore additional engagement opportunities (e.g., focus groups or workshops) for key topics

Currently, the priority for EMA is to draft the reflection paper and publish it for consultation.

Any other multistakeholder discussion (such as focus groups or workshops) will be considered during the public consultation.

4. EU regulators will explore how to better reflect in the assessment report (AR) the way PED is assessed as well as the rationale for acceptance/exclusion for Benefit/Risk (B/R) decision-making.

- Agreed to introduce a section on PED on the AR template

- Internal reflection being initiated

The current updated PED section in CHMP AR was presented. Current D80 Clinical AR includes mention to patient reported outcomes (PROs) for efficacy assessment in 3.3.1.1.5. This will be published in October 2023. However further updates should look at how all types of PED data are presented in a dedicated section in the AR and how they are considered during B/R assessment.

For orphans, PED is also important for discussing significant benefit at time of reviewing the maintenance of the status at time of marketing authorisation application, and it can also be explored how to best reflect PED in the orphan maintenance assessment report.

Finally a call for experts to join PED expertise community was made - volunteers to participate in the drafting group of the Reflection Paper are awaited. COMP was invited to express interest.

## 8.2. EMA business pipeline activity

Documents were tabled for information.

## 8.3. Follow up on public summary of opinion on orphan designation

COMP was informed that public summaries of opinion on orphan designations are listed in the IRIS page.

# 9. List of participants

including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 5-7 September 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 | |
| Jana Mazelova | Member | Czechia | No interests declared | |
| Elisabeth Penninga | Member | Denmark | No interests declared | |
| 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 | Germany | No interests declared | |
| Zsofia Gyulai | Member | Hungary | No interests declared | |
| Enrico Costa | Member | Italy | No interests declared | |

| Name | Role | Member State or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| 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 restrictions applicable to this meeting | |
| 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 | |
| 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 | |
| Julian Isla | Member | Patients' Organisation Representative | No interests declared | |
| Ines Alves | Member | Patients' Organisation Representative | No restrictions applicable to this meeting | |
| Ingeborg Barisic | Member | Expert recommended by EMA | No restrictions applicable to this meeting | |
| Judit Molnar | Member | Expert recommended by EMA | 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 |
|---|---|---|---|---|
| Maria Cavaller Bellaubi | Expert - via WebEx* | Patients' Organisation Representative | No restrictions applicable to this meeting | |
| Lothar Bergmann | Expert - via WebEx* | Germany | No restrictions applicable to this meeting | |
| A representative from the European Commission attended the 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/