6 October 2022
EMA/COMP/772376/2022
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 6-8 September 2022

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 as included in the pre-meeting list of participants and restrictions.

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 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.

The Chair thanked the departing member for her contribution to the Committee.

1.2. Adoption of agenda

The agenda for 6-8 September 2022 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 12-14 July 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. - EMA/OD/0000093474

Treatment of Werner's syndrome (WS)

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 Werner's syndrome, the sponsor was asked to further elaborate on the availability of pre-clinical models in the proposed condition. In particular, the sponsor was requested to elaborate on the Wrn Δhel/Δhel pre-clinical model, and the reasons why it was not used, or it would not be a good candidate for the assessment of the proposed product.

In the written response, and during an oral explanation before the Committee on 6 September 2022, the sponsor's response on medical plausibility was presented and included, among others, the following arguments.

Regarding the lack of available models, the sponsor emphasised what was conveyed as part of the initial application. The sponsor argued on the inadequacy of such models, given the lack of aging features and/or a limited life span due to the lack of exon 9 duplication. This repeated region is alleged to be essential for the senescence phenotype. To support this claim, the attention was drawn to several in vitro experiments that were also included as per initial application. During the oral explanation, the COMP asked about other models identified in the literature, however, the response produced by the sponsor did not dispel the existing doubts. Overall, it was the opinion of the COMP that the arguments brought by the sponsor did not sufficiently address the questions form the COMP about other models for WS, and why they were not used.

In conclusion, the additional information provided by the sponsor was not sufficient to outweigh the previous view of the COMP that the data is considered insufficient to support the claim on medical plausibility 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 8 September, prior to final opinion.

2.1.2. human IgG4k monoclonal antibody against CD89 - EMA/OD/0000092639

Jjp Biologics Sp. z o.o.; Treatment of linear IgA bullous dermatosis

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 sponsor was requested to provide a significant benefit discussion over dapsone, authorised at a national level in various EU countries for the treatment of autoimmune bullous dermatoses including linear IgA bullous dermatosis.

In the written response, the sponsor provided a clarification on the rationale behind the non-clinical setting and elaborated on the standing challenge of assessing the efficacy and safety of authorised treatments for the condition given scarcity of available data, which appeared to be limited to small case reports, case series, and evidence, which, according to the sponsor, would not be exempt of methodological limitations and uncertainty. It was then emphasised that the targeted nature of the proposed product is alleged to have a better safety profile than the broad acting dapsone, for which an array of contraindications, drug interactions and warnings are discussed by the sponsor. In this context, the proposed product precise mechanism of action is presented as an alternative treatment for patients

not responding to dapsone, or where dapsone would not be a feasible option due to toxicity/adverse events.

In summary, the arguments based on improved efficacy and safety were not accepted. However, considering the disease modifying potential of this targeted approach, it could be conceivable that the proposed product would be targeting a broader patient population than covered by existing authorized treatments, and hence be of significant benefit for patients affected by the condition.

In conclusion, in light of the additional information provided by the sponsor, the COMP considered the totality of the data to be sufficient to support the claim on significant benefit of the proposed product compared to relevant authorized medicinal products for the purpose of an initial orphan designation.

The COMP considered the written response adequately addressed the question raised and cancelled the oral explanation.

The COMP strongly recommended the sponsor to seek EMA protocol assistance on their future planned development.

The Committee agreed that the condition, linear IgA bullous dermatosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing human IgG4k monoclonal antibody against CD89 was considered justified based on non-clinical data showing the reduction in the influx of neutrophil granulocytes into the basement membrane zone of the skin and reduction of inflammatory biomarkers, addressing the key elements of LABD blister pathogenesis.

The condition is chronically debilitating due to progressive corneal scarring, which if not promptly treated may lead to blindness, and blister formation, which may present a character of painful erosions and ulcerations affecting the skin of the thighs, extremities, trunk, and face and affecting the mucosa of the mouth and throat.

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 human IgG4k monoclonal antibody against CD89 will be of significant benefit to those affected by the condition. The sponsor has provided data that demonstrate that the product bears disease modifying potential, capable of targeting a broader patient population than covered by existing authorized treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for human IgG4k monoclonal antibody against CD89, for treatment of linear IgA bullous dermatosis, was adopted by consensus.

2.1.3. crofelemer - EMA/OD/0000085970

Napo Therapeutics S.p.A.; Treatment of microvillous inclusion disease (MVID)

COMP Rapporteur: Vallo Tillmann

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 microvillous inclusion disease, the sponsor was asked to further elaborate on:

- the relevance of the non-clinical models used for the treatment of microvillous inclusion disease, and the interpretation of the results obtained in the experiments.
- the methodology used in the non-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition.

In the written response, the sponsor, in regard to the question on medical plausibility, further elaborated on the difficulties in sourcing a viable and stable non-clinical model of the condition and how this can limit conducting pharmacodynamic studies in this setting. They noted that due to the very short life span of the study subjects, pharmacological evaluation of drugs is very difficult. Furthermore, intestinal tissues from the subjects and studies in cells from MVID patients showed decreased localisation of the apical protein sodium hydrogen exchanger (NHE3) but not cystic fibrosis transmembrane conductance regulator (CFTR). To overcome this problem the sponsor generated data in a novel MVID patient-derived enteroid model. MVID enteroids from a patient with mutations in Myosin5b (MYO5B compound heterozygote c.1576>T and c.211del;p) were grown and expanded from duodenal biopsies and characterized to verify MVID cellular phenotypes. MVID enteroids were able to grow, proliferate and expand similarly to healthy control enteroids. Crofelemer administration (apical), induced a dose-dependent decrease in the stimulated current with a maximum inhibition of 75-85% of the stimulated current and an IC50 of 17.9 mM in MVID patient-derived enteroids. Administration of crofelemer (100 µM) also significantly inhibited forskolin-stimulated fluid secretion (~40-60%) in control and MVID enteroids. Washout of crofelemer following forskolin stimulation and subsequent repeat stimulation showed ongoing significant inhibition at 2 hours, with decreased inhibition (~25-30%) at 6 hours after washout of crofelemer.

The COMP also noted that the non-clinical in vivo data which was submitted to support the MVID enteroid study was based on the cholera toxin non-clinical model of diarrhoea which was accepted as supporting data in an earlier submission. The sponsor evaluated the effects of crofelemer with collaborators from University of North-Carolina in a cholera-toxin model of diarrhoea. Crofelemer when administered 3 hours after cholera toxin (CT), showed a dose-dependent reduction in fluid accumulation levels of CT with a half-maximal inhibitory dose (ED50) of 10 mg/kg.

The committee accepted the totality of the data of the in vitro results for reduction of forskolin-mediated chloride ion current in MVID patient-derived enteroids, and in vivo CT non-clinical model are used as demonstration of expected proof-of-activity of crofelemer in MVID patients and recommended cancelling the oral explanation and granting the orphan designation.

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

The intention to treat the condition with the medicinal product containing crofelemer was considered justified based on in vitro studies in intestinal enteroids from a patient with microvillous inclusion disease which showed significant inhibition of agonist stimulated chloride ion and fluid secretion and non-clinical in vivo data which showed a reduction in diarrhoea, a symptom associated with the condition.

The condition is life-threatening and chronically debilitating due to persistent and treatment resistant diarrhoea.

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.

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 crofelemer, for treatment of microvillous inclusion disease, was adopted by consensus.

2.1.4. - EMA/OD/0000084535

Treatment of Duchenne muscular dystrophy

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 16 August 2022, prior to responding to the list of issues.

2.1.5. - EMA/OD/0000092197

Treatment of pneumonia due to *Pseudomonas aeruginosa*

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 18 August 2022, prior to responding to the list of issues.

2.1.6. inaxaplin - EMA/OD/0000090156

Vertex Pharmaceuticals (Ireland) Limited; Treatment of apolipoprotein L1-mediated kidney disease (AMKD)

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:

- Condition

The presence of the two APOL1 mutations may rather be seen as risk variants (RVs) associated with a more severe course of established conditions such as focal segmental glomerular sclerosis (FSGS) or hypertensive kidney disease (HKD), rather than a separate disease entity. The sponsor is therefore invited to further substantiate AMKD as a distinct disease entity or a valid disease subset.

Reference is made to the European Commission Guideline on the format and content of applications for designation as orphan medicinal products (Rev 5, July 2021):

https://ec.europa.eu/health/system/files/2021-12/2021-07_guideline_rev5_en.pdf

Of note, all other parts of the application including the prevalence and significant benefit discussions need to be aligned with the orphan condition finally accepted by the COMP.

In the written response, the sponsor further substantiated their position that "APOL1-mediated kidney disease (AMKD)" is a distinct disease entity which meets the criteria for orphan drug designation.

The COMP did not yet consider that at present sufficient evidence exists to support the proposed condition as an established disease entity and therefore a valid orphan condition. The proposed condition is also not reflected in current disease classification systems such as the WHO's ICD nor in current therapeutic guidelines such as the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.

However, the COMP supported the proposed condition as a valid condition subset of focal segmental glomerular sclerosis (FSGS) or hypertensive kidney disease (HKD). The committee agreed that current evidence suggests a likely causative relationship between the APOL1 mutations (either G1 or G2 mutations) and kidney disease with distinct pathophysiological characteristics such as podocyte injury, glomerular filtration defects and proteinuria. A non-clinical model of the disease which expresses APOL1 G1 or G2, but not G0, develops similar pathological changes as observed in kidneys of patients with AMKD. Furthermore, the COMP took note of the specific mechanism of action of the proposed medicinal product inaxaplin, a selective inhibitor of apolipoprotein L1 (APOL1). The product is not expected to be effective for patients with 1 or 0 APOL1 mutation, because 2 APOL1 mutations are required to cause disease. The product binds to APOL1 and inhibits its pore function in multiple human cell in vitro assays, and substantially reduces proteinuria in a non-clinical in vivo disease model that overexpresses APOL1. Furthermore, preliminary clinical data suggests that inaxaplin reduces in urinary creatinine/protein ratio in AMKD patients.

In view of the committee's acceptance of the proposed condition as a valid condition subset of FSGS or HKD, the COMP also discussed applicability of significant benefit. While it was agreed that at present no medicinal products are specifically authorized for the proposed condition AMKD, several treatment options exist for the treatment of FSGS and HKD and the mainstay of treatment currently used for patients with AMKD includes renin-angiotensin-system (RAS)-inhibitors, anti-hypertensive agents, diuretics, and SGLT2 inhibitors, systemic corticosteroids, and calcineurin inhibitors (CNIs). For the time being the COMP considered those therapies as "satisfactory methods". Nevertheless, the COMP acknowledged that such therapies may lead to no response or a transient response with a recurrence of proteinuria in patients with APOL1 mutations (either G1 or G2 mutations). Considering that preliminary clinical data suggests an additional reduction in urinary creatinine/protein ratio when inaxaplin was used concomitantly with anti-hypertensive therapy, corticosteroids and/or immunosuppressive agents, significant benefit over existing therapies was considered established by the COMP. The oral explanation was cancelled.

The Committee agreed that the condition, apolipoprotein L1-mediated kidney disease (AMKD), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing inaxaplin was considered justified based on preliminary clinical data in patients with the condition showing a reduction in urinary creatinine/protein ratio.

The condition is life-threatening and chronically debilitating due to the development of end-stage kidney disease.

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 inaxaplin will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate an additional reduction in urinary creatinine/protein ratio when their product was used concomitantly with anti-hypertensive therapy, corticosteroids and/or immunosuppressive agents. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for inaxaplin, for treatment of apolipoprotein L1-mediated kidney disease, was adopted by consensus.

2.1.7. - EMA/OD/0000090261

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 1 August 2022, prior to responding to the list of issues.

2.1.8. - EMA/OD/0000083978

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

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 validity of the proposed orphan condition subset was questioned. There is increasing evidence that also the DR4-DQ8 haplotype is associated with autoimmunity against GAD65. Furthermore, available data suggests that the proposed product may also be effective in patients negative for the DR3-DQ2 haplotype. The sponsor was therefore asked to further justify the validity of the proposed orphan condition being a valid disease subset.

- Number of people affected

The prevalence calculation and final estimate need to reflect the final agreed condition wording by COMP.

A more plausible order in the steps of the calculation would be to determine the number of T1D subjects with GAD65 autoantibodies and thereafter the % of HLA haplotypes within the GAD65+ population. The sponsor was asked to present a revised estimate based on this order.

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 7 September 2022, the sponsor maintained their view that the proposed condition "Treatment of Type 1 diabetes mellitus in individuals positive for GAD65 antibody and carrying the genetic human leukocyte antigen DR3-DQ2 haplotype" is a valid disease subset for the purpose of orphan designation.

The sponsor emphasised that in their view the necessary condition subset criteria were fulfilled:

1) Distinct and unique evaluable characteristics with a plausible link to the condition:

- While Pöllanen et al. (2022) and Wester et al. (2017) suggest an association between truncated GADA (tGADA) and HLA DR4-DQ8, the importance of truncated (t) GADA for the pathogenesis of T1D and the response to the proposed product is unknown, whilst the importance of full-length GADA (fGADA) is well established.
- These data do not excluded that DR3-DQ2 is associated with primary autoimmunity against GAD65, since it is not discernible whether fGADA/tGADA were the first autoantibodies to occur in these children, most of whom had at least two islet autoantibodies.

2) Such characteristics being essential for the medicinal product to carry out its action:

- The sponsor believed that the (borderline) beneficial effect of the proposed product on C-peptide AUC (treatment ratio 1.203; adjusted p = 0.043) in patients negative for DR3-DQ2 (Hannelius et al., 2020) was a chance finding and no clinical benefit has been shown to date for the proposed product in patients negative for DR3-DQ2. This was supported by the following arguments:

- These positive effects seem to have been driven by a single Phase II study in 70 patients (NCT00435981). The trial was completed in 2008 and has been throughout the clinical development of the proposed product the only RCT to suggest any treatment effect in patients lacking DR3-DQ2. Importantly, the trial showed a null effect on HbA1c.
- The results of the updated meta-analysis by Nowak et al. (2022a), that includes the same three RCTs from the meta-analysis by Hannelius et al. (2020) of proposed subcutaneous product plus the recently completed Phase IIb trial DIAGNODE-2 of proposed intralymphatic product support the conclusion that no effect is seen in patients lacking DR3-DQ2.
- The recently published CGM results (Nowak et al. 2022b) from the Phase IIb trial DIAGNODE-2 of three intralymphatic injections of the proposed product show a null effect in patients lacking DR3-DQ2, whilst significant benefit for time in range, hyperglycemia and glycemic variation was seen only in the patients with present DR3-DQ2.

- As regard to the bias in the baseline characteristics of patients included in the DIAGNODE-2 study (Ludvigsson et al, 2021), the sponsor clarified that all analyses are adjusted for baseline values (including C-peptide AUC and HbA1c) in the mixed model repeated measures (MMRM) analysis.

In conclusion, the sponsor brought forward additional arguments in support of the proposed condition being a valid subset and that the absence of these characteristics (GADA+/DR3-DQ2+) will render the product ineffective in the rest of the population suffering from the condition. However, the sponsor has not demonstrated that the proposed product will not also generate a treatment response in other HLA genotypes such as HLA DR4-DQ8. Therefore, the COMP did not consider the proposed condition a valid condition subset, for the purpose of orphan designation.

Regarding the number of people affected, COMP advised that a more plausible order in the steps of the prevalence calculation would be to determine the number persons with T1D with GAD65 autoantibodies and thereafter the % of HLA haplotypes within the GAD65-positive population. The sponsor has revised the prevalence calculation accordingly and provides updated calculations and references to the literature below. The final point prevalence estimate of the orphan condition in the EU following the updated calculations is 4.92 per 10,000 inhabitants.

For the main prevalence calculation, it was assumed that 50% of recently diagnosed T1D patients have detectable GADA and that 44% of them carry the HLA DR3-DQ2 haplotype. The sponsor notes that over the last five decades, there appears to be a trend for a declining frequency of the HLA DR3-DQ2 haplotype in T1D patients (Herman et al 2003; Steck et al 2011), warranting a conservative approach to estimating the average frequency of DR3-DQ2 among GADA-positive patients.

In view of the fact that the COMP did not consider the proposed condition to be a valid orphan condition subset, an in-depth discussion on the prevalence calculation and estimate was deemed obsolete.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 7 September 2022 prior to final opinion.

2.1.9. - EMA/OD/0000083743

Treatment of focal cortical dysplasia

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

Focal cortical dysplasia should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of focal cortical dysplasia the sponsor should further elaborate on:

- the relevance of the nonclinical model used for the treatment of focal cortical dysplasia, and the interpretation of the results obtained in the experiments.

- Prevalence

The proposed prevalence appears to be primarily focused on focal cortical dysplasia associated with epilepsy only. Those cases without epilepsy appear to have been omitted.

The sponsor is invited to provide a revised estimate given that cases without epilepsy have not been included leading to substantial uncertainty about many of the assumptions regarding the current prevalence.

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

- Significant benefit

The arguments on significant benefit were based on the 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 non-clinical in vivo study to justify the assumption of significant benefit over antiseizure medications for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 7 September 2022, the sponsor reiterated that focal cortical dysplasia is a distinct medical entity and referred back to the 2019 ICH 11 classification as well as the publication by Miyata, and Vinters 2002 as the basis to support their position regarding the condition. The COMP raised the issue of the recent reclassification where focal cortical dysplasia has been removed from the ILAE 2022 publication. The sponsor could not answer the question as to where the condition now stands within the current understanding of epilepsy and recognized that the citations they used could be considered out of date. The COMP therefore considered that the question regarding the validity of the condition had not been adequately answered.

The validity of the hippocampal kainic acid pre-clinical model to reproduce the type of seizures seen in the proposed condition non-clinical in vivo data submitted to support the medical plausibility was then discussed. The COMP indicated that there were better models which could have been chosen such as various pre-clinical models of mTORopathies (Nguyen and Bordey,2021) and the pre-clinical model of human PIK3CA related brain overgrowth (Roy et5 al, 2015) shows bilateral dysplastic megalencephaly, hemimegalencephaly and focal cortical dysplasia resulting in epilepsy. The COMP therefore believed the sponsor had not submitted sufficient data to support medical plausibility and significant benefit. As a result of these conclusions, the COMP considered it 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 8 September 2022 prior to final opinion.

2.1.10. isotretinoin - EMA/OD/0000092484

Granzer Regulatory Consulting & Services GmbH; Treatment of autosomal recessive congenital ichthyosis

COMP Rapporteur: Lyubina Racheva Todorova

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 treat

The sponsor was asked to discuss which subtypes of ichthyosis would be included under the proposed umbrella term "congenital ichthyosis", and those that would be excluded. Note that this is for the purposes of orphan medicinal product designation; the sponsor's

attention is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

- Number of people affected

The sponsor was reminded that should the condition be modified, a revised prevalence calculation is also expected. 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 asked to further discuss the arguments provided for significant benefit over acitretin, authorised in EU member states for treating congenital ichthyosis.

In the written response, and during an oral explanation before the Committee on 7 September 2022, the sponsor addressing the enquiries on the condition and decided to revise the condition to "Treatment of autosomal recessive congenital ichthyosis", for which prior orphan designations have been granted by the COMP. Accordingly, the sponsor provided a revised prevalence calculation which was considered acceptable and in line with previous considerations by COMP.

Addressing the assumption of significant benefit over acitretin, the sponsor conducted a detailed bibliographic search, and argued on the assumption of a superior efficacy and safety profile of the proposed product. To support this claim, the attention was drawn to the fact that the systemic retinoid levels in patients treated with the proposed product never exceeded endogenous levels observed already before administration. This could support the claim that the proposed topical formulation would be associated with a more benign safety profile than existing therapies. In addition, it was emphasised that clinical evidence with the proposed product in both paediatric and adult populations could bear particular relevance for the assumption of significant benefit, as it would have the potential to target a broader patient population than authorised treatments for the condition. This element could constitute a clinically relevant advantage.

In summary, the arguments based on improved efficacy and safety were not accepted. However, considering the evidence presented at this point in time, it could be conceivable that the proposed product would be capable of targeting a broader patient population than covered by existing authorized treatments, and hence be of significant benefit for patients affected by the condition.

The COMP strongly recommended the sponsor to seek EMA protocol assistance on their future planned development.

Following review of the application by the Committee, it was agreed to rename the indication to treatment of autosomal recessive congenital ichthyosis.

The Committee agreed that the condition, autosomal recessive congenital 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 clinical data in patients treated with the product used as a topical formulation showing improvements in investigator's global assessment and Visual Index for Ichthyosis Severity score.

The condition can be life-threatening and is chronically debilitating in particular due to manifestations such as collodion babies, the development of scales, an impairment of the epidermal barrier resulting in infections and trans epithelial water loss, hyperkeratosis interfering with sweat gland function, ectropion, conductive hearing loss, hair loss, palmoplantar and nail abnormalities, as well as the development of skin malignancies.

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 isotretinoin will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate 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 autosomal recessive congenital ichthyosis, was adopted by consensus.

2.1.11. - EMA/OD/0000083190

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

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 proposed orphan condition is not considered to be a valid disease subset. The indicated c-peptide range is mostly considered to represent an early disease stage rather than a valid condition subset with distinct and unique evaluable characteristics essential for the product to carry out its action. The sponsor is therefore invited to suggest a valid orphan condition or to further substantiate the validity of the current proposal.

Reference is made to the EC guideline ENTR/6283/00 Rev 5, p.6.

- Number of people affected

The validity of the proposed condition subset has been questioned by the COMP. The prevalence calculation and estimate will have to be in line with the final accepted condition.

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

In the written response, and during an oral explanation before the Committee on 7 September 2022, the sponsor proposed to change the condition to "Treatment of type 1 diabetes with residual β-cell function defined by stimulated C-peptide levels $\geq$0.2 nmol/L within 5 years from diagnosis". The previous upper limit of 0.6 nmol/L in C-peptide levels was replaced with a duration of maintaining a minimum C-peptide threshold of at least 0.2 nmol/L within a time span of 5 years from diagnosis.

The sponsor emphasised that their proposed condition subset identifies 1) patients with different risks of progression and with a different natural history of the disease, characteristics not expected from a mere disease stage, and 2) patients who can benefit most from immune modulating therapeutic approaches.

In support of the above the sponsor mostly re-emphasised core arguments/data already presented in the initial application. These include the non-clinical disease model and clinical data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. The COMP considered that the sponsor's responses did not provide sufficient support for the (newly) amended proposed condition to be a valid orphan condition subset for the following reasons:

- Direct extrapolation from the non-clinical in vivo data to the specific clinical setting of T1D patients with stimulated C-peptide levels ≥0.2 nmol/L within 5 years from diagnosis, is not considered acceptable.
- At present, there is insufficient evidence that the absence of these specifically defined patient characteristics (i.e. stimulated C-peptide levels ≥0.2 nmol/L within 5 years from diagnosis) will render the proposed product ineffective in the rest of the population suffering from the condition (see requirement as per EC guideline ENTR/6283/00 Rev 5, p.6).

In view of the fact that the COMP did not consider the (newly) amended proposed condition to be a valid orphan condition subset, an in-depth discussion on the prevalence calculation and estimate was deemed obsolete.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 7 September 2022, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. oxygen, sodium chloride solution 0.9% - EMA/OD/0000082252

Dlrc Pharma Services Limited; Treatment of amyotrophic lateral sclerosis (ALS)

COMP Rapporteur: Robert Nistico

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

The intention to treat the condition with the medicinal product containing oxygen, sodium chloride solution 0.9% was considered justified based on non-clinical data showing prolonged survival and improved neuromuscular function in a valid model of the condition. In addition, preliminary clinical data showed improvement in respiratory function.

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure. The survival of the patients is usually limited to 2-3 years.

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

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

medicinal product containing oxygen, sodium chloride solution 0.9% will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo and preliminary clinical data that demonstrate that the proposed product improves respiratory function when it is used as add-on to standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for oxygen, sodium chloride solution 0.9%, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.2. autologous T cells transduced with a lentiviral vector expressing a chimeric antigen receptor against CLL-1 - EMA/OD/0000086488

ELC Group s.r.o.; Treatment of acute myeloid leukemia

COMP Rapporteur: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing autologous T cells transduced with a lentiviral vector expressing a chimeric antigen receptor against CLL-1 was considered justified based on non-clinical data in a model of the condition supporting inhibition of tumour growth and increased survival, as well as preliminarily clinical data reporting complete responses in patients with relapsed/refractory acute myeloid leukaemia.

The condition is life threatening and chronically debilitating due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated.

The condition was estimated to be affecting 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 autologous T cells transduced with a lentiviral vector expressing a chimeric antigen receptor against CLL-1 will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that showed responses that were also consolidated by stem cell transplantation in patients with relapsed/refractory acute myeloid leukaemia for whom no authorised treatments exist. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous T cells transduced with a lentiviral vector expressing a chimeric antigen receptor against CLL-1, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.3. - EMA/OD/0000088236

Treatment of ovarian 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 2022 meeting.

2.2.4. epeleuton - EMA/OD/0000089323

Afimmune Limited; Treatment of sickle cell disease

COMP Rapporteur: Enrico Costa

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

The intention to treat the condition with the medicinal product containing epeleuton was considered justified based on in vivo non clinical data showing improvement of the inflammatory imbalance, prolongation of red blood cells survival, prevention of hypoxia/reoxygenation-induced abnormal vascular activation and hypoxia/reoxygenation-organ damage and disease progression.

The condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, stroke, chronic kidney disease, pulmonary hypertension, susceptibility to infections and skin ulcers and life-threatening with reduced life expectancy.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing epeleuton will be of significant benefit to those affected by the condition. The sponsor has provided in vivo non-clinical data that demonstrate the ability of epeleuton to simultaneously target several aspects of the disease such as vascular inflammation, red blood cells survival and haemolytic anaemia, while authorised treatments are only effective to treat single aspects of the disease. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for epeleuton, for treatment of sickle cell disease, was adopted by consensus.

2.2.5. velusetrag - EMA/OD/0000089368

Alfasigma S.p.A.; Treatment of intestinal pseudo-obstruction

COMP Rapporteur: Ingeborg Barisic

Following review of the application by the Committee, it was agreed to rename the indication to treatment of intestinal pseudo-obstruction.

The Committee agreed that the condition, intestinal pseudo-obstruction, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing velusetrag was considered justified based on non-clinical data showing phenotypic amelioration and improved survival after treatment with the proposed product.

The condition is chronically debilitating due to continuous or intermittent symptoms of bowel obstruction, loss of weight due to nutritional impairment, recurrent pain, anxiety and depression, and life threatening due to disease-related complications with especially poor prognosis in children.

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.

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 velusetrag, for treatment of intestinal pseudo-obstruction, was adopted by consensus.

2.2.6. adeno-associated viral vector serotype 8 containing the 3' human otoferlin coding sequence, adeno-associated viral vector serotype 8 containing the 5' human otoferlin coding sequence - EMA/OD/0000091780

Sensorion S.A.; Treatment of otoferlin gene-mediated hearing loss

COMP Rapporteur: Gloria Maria Palomo Carrasco

Following review of the application by the Committee, it was agreed rename the indication to treatment of otoferlin gene-mediated hearing loss.

The Committee agreed that the condition, otoferlin gene-mediated hearing loss, 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 8 containing the 3' human otoferlin coding sequence, adeno-associated viral vector serotype 8 containing the 5' human otoferlin coding sequence was considered justified based on data generated in a non-clinical in vivo model of the condition which showed restoration of the auditory function.

The condition is chronically debilitating due to permanent Severe-to-Profound hearing loss or deafness.

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 adeno-associated viral vector serotype 8 containing the 3' human otoferlin coding sequence, adeno - associated viral vector serotype 8 containing the 5' human otoferlin coding sequence, for treatment of otoferlin gene-mediated hearing loss, was adopted by consensus.

2.2.7. - EMA/OD/0000091801

Treatment of tuberculosis

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 2022 meeting.

2.2.8. aglatimagene besadenovec - EMA/OD/0000092213

Propharma Group The Netherlands B.V.; Treatment of glioma

COMP Rapporteur: Brigitte Schwarzer-Daum

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

The intention to treat the condition with the medicinal product containing aglatimagene besadenovec was considered justified based on non-clinical studies in a valid model of the condition showing prolonged survival as well as preliminary clinical data, in patients with glioma responding to treatment.

The condition is chronically debilitating due to symptoms caused by the tumour compressing the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality changes and cognitive decline. The condition is also life-threatening, with poor 5-year survival of less than 5% for glioblastoma grade 4 patients.

The condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing aglatimagene besadenovec will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients with glioma, treated with the product in combination with standard of care, can survive longer than otherwise expected when treated with standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for aglatimagene besadenovec, for treatment of glioma, was adopted by consensus

2.2.9. adeno-associated viral vector serotype rh.10 encoding the *CLN2* gene - EMA/OD/0000092280

Pharma Gateway AB; Treatment of neuronal ceroid lipofuscinosis

COMP Rapporteur: Darius Matusevicius

The Committee agreed that the condition, neuronal ceroid lipofuscinosis, 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 rh.10 encoding the *CLN2* gene was considered justified based on non-clinical data showing improvement in the biochemical markers, motor function and survival, and clinical data demonstrating reduction of the decline of motor functions and language skills, and improved biochemical markers when compared to historical controls.

The condition is life-threatening and chronically debilitating due to visual, cognitive, and motor skills decline, speech impediment, behavioural problems, seizures, cerebral atrophy, and ultimately premature death.

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 rh.10 encoding the *CLN2* gene will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the proposed gene therapy medicinal product

could be given as a one-time single administration with the potential of eliminating or reducing the need of periodic intracerebroventricular administrations associated with the use of Brineura. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for adeno-associated viral vector serotype rh.10 encoding the *CLN2* gene, for treatment of neuronal ceroid lipofuscinosis, was adopted by consensus

2.2.10. etidronate disodium - EMA/OD/0000093040

Qualix Dot S.L.; Treatment of ABCC6 deficiency

COMP Rapporteur: Tim Leest

Following review of the application by the Committee, it was agreed to rename the indication to treatment of ABCC6 deficiency.

The Committee agreed that the condition, ABCC6 deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing etidronate disodium was considered justified based on in vivo nonclinical data showing a reduction of ectopic calcification and on clinical data demonstrating a reduction in the rate of progression of multiple arterial calcification endpoints, including the total arterial calcification score.

The condition is chronically debilitating due to pathological mineralization and intimal proliferation that manifests in a spectrum of phenotypes. As the disease progresses, cardiovascular manifestations can occur and manifest as increased risk of ischemic stroke and early myocardial infarcts.

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.

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 etidronate disodium, for treatment of ABCC6 deficiency, was adopted by consensus.

2.2.11. sodium ({(2S)-1,4-bis[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[2.2.2]octan-2-yl}oxy)methyl hydrogen phosphate-2-amino-2-(hydroxymethyl)propane-1,3-diol (1/1/1) - EMA/OD/0000095828

AbbVie Deutschland GmbH & Co. KG; Treatment of vanishing white matter disease

COMP Rapporteur: Michel Hoffmann

The Committee agreed that the condition, treatment of vanishing white matter disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sodium ({(2S)-1,4-bis[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[2.2.2]octan-2-yl}oxy)methyl hydrogen phosphate-2-amino-2-(hydroxymethyl)propane-1,3-diol (1/1/1) was considered justified based on in vivo non clinical data in a valid model of the condition which showed improvement of motor function.

The condition is chronically debilitating and life-threatening leading to loss of ambulation, wheelchair dependency and early death.

The condition was estimated to be affecting not more than 0.1 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for sodium ({(2S)-1,4-bis[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[2.2.2]octan-2-yl}oxy)methyl hydrogen phosphate-2-amino-2-(hydroxymethyl)propane-1,3-diol (1/1/1), for treatment of vanishing white matter disease, was adopted by consensus

2.2.12. selinexor - EMA/OD/0000095946

Karyopharm Europe GmbH; 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 selinexor was considered justified based on preliminary clinical data showing reduction in spleen volume and improvement in anaemia in affected patients.

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 selinexor will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data suggesting a positive trend in efficacy in a subset of patients intolerant or refractory to currently authorized products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for selinexor, for treatment of myelofibrosis, was adopted by consensus

2.2.13. - EMA/OD/0000096114

Diagnosis of AL amyloidosis

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 2022 meeting.

2.2.14. methyl(R)-4-((3S,5R,7R,8R,9S,10S,13R,14S,17R)-7-hydroxy-10,13-dimethyl-3-((4-((pyridin-3- yimethyl)amino)butyl)amino)hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate - EMA/OD/0000096220

Maxia Strategies-Europe Limited; Treatment of Rett syndrome

COMP Rapporteur: Giuseppe Capovilla

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

The intention to treat the condition with the medicinal product containing methyl(R)-4-((3S,5R,7R,8R,9S,10S,13R,14S,17R)-7-hydroxy-10,13-dimethyl-3-((4-((pyridin-3-ylmethyl)amino)butyl)amino)hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate was considered justified based on non-clinical data from a valid in vivo model of the condition which showed improved motor function.

The condition is life-threatening and chronically debilitating due to severe neurodevelopmental delay, sleep disturbances, seizures, respiratory complications and development of arrhythmias resulting in decreased 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 methyl(R)-4-((3S,5R,7R,8R,9S,10S,13R,14S,17R)-7-hydroxy-10,13-dimethyl-3-((4-((pyridin-3- yimethyl)amino)butyl)amino)hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate, for treatment of Rett syndrome, was adopted by consensus.

2.2.15. eculizumab - EMA/OD/0000096314

Alexion Europe S.A.S.; Treatment of Guillain-Barré syndrome

COMP Rapporteur: Darius Matusevicius

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

The intention to treat the condition with the medicinal product containing eculizumab was considered justified based on non-clinical data in a model of the condition demonstrating biochemical and functional improvement, and preliminary clinical data showing an improvement in the functional grading scale compared to control.

The condition is chronically debilitating and life-threatening due to breathing difficulties and nerve damage.

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 eculizumab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the use of the proposed product as an add-on therapy to authorized medicinal products, resulted in an improvement on the functional grading scale compared to standard of care alone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for eculizumab, for treatment of Guillain-Barré syndrome, was adopted by consensus.

2.2.16. - EMA/OD/0000096322

Treatment of familial cerebral cavernous malformation

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 2022 meeting.

2.2.17. - EMA/OD/0000096338

Treatment of familial cerebral cavernous malformation

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 2022 meeting.

2.2.18. - EMA/OD/0000096494

Treatment of multiple system 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 October 2022 meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 12 September 2022.]

2.2.19. acetylleucine - EMA/OD/0000096637

IntraBio Ireland Limited; Treatment of GM1 gangliosidosis

COMP Rapporteurs: Joao Rocha, Ingeborg Barisic

The Committee agreed that the condition, GM1 gangliosidosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing acetylleucine was considered justified based on preliminary clinical data suggesting that treatment can improve motor function and cognition.

The condition is life-threatening due to a reduced life expectancy and chronically debilitating due to neurodegeneration causing cognitive decline, seizures, muscle weakness, spasticity and ataxia, as well as skeletal abnormalities, visual impairment and hepatosplenomegaly.

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.

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 acetylleucine, for treatment of GM1 gangliosidosis, was adopted by consensus.

2.2.20. - EMA/OD/0000096917

Treatment of primary immune complex membranoproliferative glomerulonephritis (IC-MPGN)

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 2022 meeting.

2.2.21. - EMA/OD/0000096942

Treatment of West 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 2022 meeting.

2.2.22. ropeginterferon alfa-2b - EMA/OD/0000096995

Aop Orphan Pharmaceuticals GmbH; Treatment of essential thrombocythaemia

COMP Rapporteur: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing ropeginterferon alfa-2b was considered justified based on the totality of bibliographic clinical data which suggests a platelet lowering effect.

The condition is life-threatening and chronically debilitating due to thrombotic and haemorrhagic episodes which can be associated with deep vein thrombosis and pulmonary embolism.

The condition was estimated to be affecting approximately 3.4 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 ropeginterferon alfa-2b will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data which suggests that the product induces hematologic remission in patients resistant or intolerant to current standard of care therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for ropeginterferon alfa-2b, for treatment of essential thrombocythaemia, was adopted by consensus.

2.2.23. - EMA/OD/0000097127

Treatment of 22q11.2 deletion syndrome (22qDS)

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 2022 meeting.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

2.5.1. - EMA/OD/0000099365

Prevention of spaceflight-related radiation and microgravity

Note: Withdrawal request received on 30 August 2022.

2.6. Nominations

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

COMP coordinators rapporteurs were appointed for 21 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 congenital alpha-1 antitrypsin deficiency

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. Livtencity - maribavir - EMEA/H/C/005787/0000

Takeda Pharmaceuticals International AG Ireland Branch

COMP Rapporteurs: Armando Magrelli; Olimpia Neagu

a) Prevention of cytomegalovirus (CMV) disease in patients with impaired cell mediated immunity deemed at risk, EU/3/07/519, EMA/OD/0000091090

An opinion recommending not to remove Livtencity, maribavir (EU/3/07/519) 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 2022 meeting.]

b) Treatment of cytomegalovirus disease in patients with impaired cell mediated immunity, EU/3/13/1133, EMA/OD/0000091101

An opinion recommending not to remove Livtencity, maribavir (EU/3/13/1133) 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 2022 meeting.]

4.2.2. Pyrukynd – mitapivat - EMEA/H/C/005540, EU/3/20/2270, EMA/OD/0000068458

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

COMP Rapporteurs: Enrico Costa; Elisabeth Johanne Rook

An opinion recommending not to remove Pyrukynd, mitapivat (EU/3/20/2270) 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 2022 meeting.]

4.2.3. - octreotide acetate - EMEA/H/C/005826/0000, EU/3/13/1170, EMA/OD/0000086000

Amryt Pharmaceuticals Designated Activity Company; Treatment of acromegaly

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 2022 meeting.

4.2.4. Enjaymo – sutimlimab - EMEA/H/C/005776, EU/3/16/1609, EMA/OD/0000082097

Genzyme Europe BV; Treatment of autoimmune haemolytic anaemia

COMP Rapporteurs: Armando Magrelli; Karri Penttila

An opinion recommending not to remove Enjaymo, sutimlimab, EU/3/16/1609 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 2022 meeting.]

4.2.5. – loncastuximab tesirine - EMEA/H/C/005685, EU/3/21/2481, EMA/OD/0000094879

FGK Representative Service GmbH; Treatment of diffuse large B-cell lymphoma

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 2022 meeting.

4.2.6. – maralixibat - EMEA/H/C/005857, EU/3/13/1214, EMA/OD/0000078931

Mirum Pharmaceuticals International B.V.; Treatment of Alagille syndrome

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 3 applications.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

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

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

COMP Rapporteurs: Maria Elisabeth Kalland; Bozenna Dembowska-Baginska; CHMP Rapporteur: Jan Mueller-Berghaus; CHMP Co-Rapporteur: Claire Beuneu

An opinion recommending not to remove Yescarta, axicabtagene ciloleucel, EU/3/14/1393 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 2022 meeting.]

5.2.2. Iclusig - ponatinib - EMEA/H/C/002695/II/0064, EU/3/09/715, EMA/OD/0000097417

Incyte Biosciences Distribution B.V.; Treatment of acute lymphoblastic leukaemia

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

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for 1 application.

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP membership

The Chair thanked Geraldine O'Dea for her contribution as a member for Ireland.

7.1.2. Vote by proxy

None

7.1.3. Strategic Review & Learning meetings

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

The COMP noted the final agenda for the meeting.

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met face-to-face on 6th September 2022.

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)

None

7.3.2. Working Party with Healthcare Professionals' Organisations (HCPWP)

None

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

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

None

7.7. COMP work plan

None

7.8. Planning and reporting

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

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

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

8.1. EMA Business Pipeline activity and Horizon scanning

Documents were tabled for information

9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 6-8 September 2022 meeting.

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Chair	Netherlands	No interests declared	
Armando Magrelli	Member (Vice-Chair)	Expert recommended by EMA	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No restrictions applicable to this meeting	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Elli Loizidou	Member	Cyprus	No interests declared	
Jana Mazelova	Member	Czechia	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Cecile Dop	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Enrico Costa	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No restrictions applicable to this meeting	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No restrictions applicable to this meeting	
Elisabeth Johanne Rook	Member	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Joao Rocha	Member	Portugal	No restrictions applicable to this meeting	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
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	
Marika van Leeuwen	Expert – via Webex*	Netherlands	No restrictions applicable to this meeting	
Dimitar Roussinov	PDCO Member	Bulgaria	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/