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SCIENCE MEDICINES HEALTH

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Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 7-9 September 2021

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

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

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some meeting participants in upcoming discussions as included in the pre-meeting list of participants and restrictions.

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

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 (i.e. 22 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

The agenda for 7-9 September 2021 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 13-15 July 2021 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. human igG1 monoclonal antibody against sortilin - EMA/OD/0000055853

Pharma Gateway AB; Treatment of frontotemporal dementia (FTD)

COMP Rapporteur: Robert Nistico

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

- Number of people affected

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"](#).

Due to the uncertainties related to the potential overlapping syndromes and underdiagnosis of the condition the COMP considered that the sponsor should describe and justify the methodology used for the prevalence calculation and provide a more conservative estimate.

In the written response, the sponsor provided an appropriate prevalence calculation using the most conservative interpretation possible of all existing EU prevalence and incidence data for frontotemporal dementia, and the most conservative estimate for median life-expectancy from disease onset.

The prevalence of FTD was estimated to be not more than 3.6 in 10,000.

The COMP accepted this calculation and phrased the final accepted value as '3.6 in 10,000' for consistency with recent assessment.

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

The intention to treat the condition with the medicinal product containing human IgG1 monoclonal antibody against sortilin was considered justified based on non-clinical data showing rescue of the behavioural deficit.

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

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

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

A positive opinion for human IgG1 monoclonal antibody against sortilin, for treatment of frontotemporal dementia, was adopted by consensus.

2.1.2. [adeno-associated virus of serotype rh10 encoding Human *MLC1* under the control of GFAP promoter - EMA/OD/0000059436](#)

Consorcio Centro de Investigación Biomédica en Red, M.P.; Treatment of megalencephalic leukoencephalopathy with subcortical cysts (MLC)

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:

- 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 megalencephalic leukoencephalopathy with subcortical cysts the sponsor was requested to clarify the following:

- a) the chosen non-clinical model does not display any phenotype deficits, and therefore cannot provide information on functional effects of the treatment which could be clinically relevant. The representativeness of the chosen model for the MLC

condition should be further justified, since there are symptomatic non-clinical models available with lowered seizure threshold, according to the literature. The sponsor was asked to explain why these models were not used to support the proof of concept of the proposed product.

- b) it is not clear from the documentation which adeno-associated vectors (AAV) serotype was used in the non-clinical studies in the model, and to what extent the experimental product is representative for the future clinical product.

In the written response, the sponsor clarified the differences between the used model (Hoegg-Beiler et al., 2014) and the symptomatic non-clinical models (Dubey et al 2015, Dubey et al 2018) reported in the literature. In the *Mlc1* model used by Dubey et al., 2018 exons 2 and 3 were eliminated, but additionally, also a green fluorescent protein (GFP) sequence was incorporated in the same locus. The expression of GFP may have additional effects that are not due to the lack of *Mlc1*. However, both models showed megalencephaly due to increased brain water content and white matter vacuolization, replicating early stages of the human disease. The sponsor also clarified that all the studies were performed with AAV2/rh10 pseudotyped vectors. This vector was chosen since it was described to efficiently transduce astrocytes in spinal cord compared to other serotypes (Petrosyan et al. 2014).

The COMP considered that all the issues related to the non-clinical model are considered adequately addressed and agreed that the intention to treat the condition with the medicinal product was considered justified based on data on a relevant non-clinical model showing reduced myelin vacuolation in cerebellum. Therefore, the COMP cancelled the oral hearing which was no longer needed.

The Committee agreed that the condition, megalencephalic leukoencephalopathy with subcortical cysts, 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 of serotype rh10 encoding human *MLC1* under the control of GFAP promoter was considered justified based on data on a relevant non-clinical model showing reduced myelin vacuolation in cerebellum.

The condition is life-threatening due to megalencephaly, loss of motor functions, epilepsy and mild cognitive decline.

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 virus of serotype rh10 encoding human *MLC1* under the control of GFAP promoter, for treatment of megalencephalic leukoencephalopathy with subcortical cysts, was adopted by consensus.

2.1.3. - EMA/OD/0000058277

Treatment of dermatomyositis (DM)

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 dermatomyositis the sponsor was asked to further elaborate on:

- a) the relevance of the nonclinical model used for the treatment of dermatomyositis, and the interpretation of the results obtained in the experiments,
 - b) 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,
 - c) any preliminary clinical data in the condition the sponsor may have.
- Significant benefit

The arguments on significant benefit were based on 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 as well as preliminary clinical data to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 8 September 2021, the sponsor explained the limitations and strengths of the non-clinical in vivo data used to support the medical plausibility. Further clarifications regarding the on-going Phase II randomized, double-blind, placebo-controlled, cross-over design study in patients with DM or polymyositis (PM) as well as the open-label extension. Explanations were given as to why the sponsor could not share the data at the time of the oral presentation. The COMP concluded that the non-clinical in vivo data was sufficient to support the medical plausibility.

The COMP then discussed the strengths and limitations of the non-clinical in vivo data in supporting a claim of significant benefit. The COM was of the opinion that the data was insufficient, as the non-clinical in vivo studies did not use adequately contextualise the potential use of the product in the target patient population proposed to support the clinically relevant advantage of this product within the context of the current management of these patients. As the sponsor indicated that the preliminary clinical data would be available shortly the COMP considered that this data would likely be more supportive of significant benefit. The COMP 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 9 September 2021, prior to final opinion.

2.1.4. - EMA/OD/0000058281

Treatment of polymyositis (PM)

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 polymyositis the sponsor was asked to further elaborate on:

- a) the relevance of the nonclinical model used for the treatment of polymyositis, and the interpretation of the results obtained in the experiments,
 - b) 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,
 - c) any preliminary clinical data in the condition the sponsor may have.
- Significant benefit

The arguments on significant benefit were based on 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 as well as preliminary clinical data to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 8 September 2021, the sponsor explained the limitations and strengths of the non-clinical in vivo data used to support the medical plausibility. Further clarifications regarding the on-going Phase II randomized, double-blind, placebo-controlled, cross-over design study in patients with DM or PM as well as the open-label extension. Explanations were given as to why the sponsor could not share the data at the time of the oral presentation. The COMP concluded that the non-clinical in vivo data was sufficient to support the medical plausibility.

The COMP then discussed the strengths and limitations of the non-clinical in vivo data in supporting a claim of significant benefit. The COMP was of the opinion that the data was insufficient, as the non-clinical in vivo studies did not use adequately contextualise the potential use of the product in the target patient population proposed to support the clinically relevant advantage within the context of the current management of these patients. As the sponsor indicated that the preliminary clinical data would be available shortly the COMP considered that this data would likely be more supportive of significant benefit. The COMP 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 9 September 2021, prior to final opinion.

2.1.5. - EMA/OD/0000061301

Treatment of invasive aspergillosis

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 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 studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

The sponsor was asked 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 7 September 2021, the sponsor provided a response in which they did not offer any additional new data and continued to rely on the non-clinical in vivo and in vitro data already provided in the initial submission. The COMP informed the sponsor that the use of in vitro data was insufficient to support the basis of a claim of significant benefit. Questions were asked, regarding how the product was going to be used and which patients could benefit. To this the sponsor foresees the product to be used in patients resistant to authorised products where they believed there was an unmet need. It was noted that the non-clinical in vivo data did not support the claim of a clinically relevant advantage as proposed and the only data that could potentially be used towards this end was the in vitro data which was not acceptable for the committee.

The COMP therefore concluded that insufficient data had been submitted to support the claim of significant benefit and thus 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 2021, prior to final opinion.

2.1.6. - EMA/OD/0000061466

Treatment of transthyretin-mediated amyloidosis (ATTR)

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

Transthyretin amyloidosis-polyneuropathy (ATTR-PN):

- In the presented data from the non-clinical disease model, it is not clear with which frequency inotersen and proposed product have been administered. Therefore, it is difficult to use this data in support of less frequent dosing being able to achieve comparative pharmacodynamic (PD) effects. The sponsor was requested to clarify the frequency of dosing of the two drugs within the 3 weeks duration of the study.
- The arguments on significant benefit were mainly based on the potential improved quality of life in the condition. The sponsor supported their claim by early clinical data showing a relevant PD effect in healthy volunteers after administrations with the proposed product once every 4 weeks. However, as no comparative data to inotersen has been presented, it is not possible to judge the relative PD effect, as compared to once weekly administration with the authorized inotersen. The sponsor was asked to present any available comparative data to inotersen from this study.
- The sponsor was also requested to discuss significant benefit of the proposed product over tafamidis.

Transthyretin amyloidosis-cardiomyopathy (ATTR-CM):

- The sponsor was asked to present any data which supports their assumption of improved efficacy of the proposed product as adjunctive treatment to tafamidis.

In the written responses and during the oral explanation, the following aspects were discussed: with regards to the subpopulation of ATTR-PN, the sponsor presented PD data from the Phase 1 adult healthy volunteer studies of inotersen and the proposed product suggests that the PD effect of proposed product in reducing serum transthyretin (TTR) is more than 30-fold greater than the PD effect of inotersen in patients with ATTR-PN. The COMP agreed that the data suggested that the proposed product may be administered at a lower and less frequent dose as compared to inotersen and that the pharmacodynamic activity of the proposed product is not inferior to the one of inotersen.

The significant benefit of the proposed product vs tafamidis was mainly supported by indirect data generated with inotersen, but not with the proposed product. While such indirect evidence is seen as controversial by the COMP, the committee also acknowledged that the proposed product is developed for a broader range of patients, i.e. including those with stage 2 polyneuropathy. Furthermore, a significant number of patients progress in their disease symptoms, despite treatment with protein stabilizers such as tafamidis. Considering this and the fact that the proposed product is expected to act via a very similar mechanism of action and is unlikely to be inferior in its efficacy vs the authorized inotersen, the COMP could possibly support the significant benefit of the proposed product in the disease subset of ATTR-PN.

With regards to the subpopulation of ATTR-CM, the sponsor presented only indirect evidence from smaller studies with and silencers (inotersen and patisiran) to support their assumption of a possibly improved efficacy of proposed product vs tafamidis (Dasgupta et al. 2020 and Fontana et al. 2020). No silencer is currently authorized for the treatment of ATTR-CM. No non-clinical or clinical data were presented that would suggest an effect of the proposed product on cardiomyopathy in ATTR-CM. Therefore, the COMP did not consider that sufficient evidence has been presented to support significant benefit of the proposed product over tafamidis in the disease subset of ATTR-CM.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 September 2021, prior to final opinion.

2.1.7. enterovirus B, echovirus 7, live - EMA/OD/0000057849

Latima SIA; Treatment of uveal melanoma

COMP Rapporteur: Marie Pauline J. Evers

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 uveal melanoma the sponsor was requested to further elaborate on:

- The positioning of the product since the data provided include all stages of the condition such as primary tumour, patients with liver metastasis and adjuvant therapy after enucleation.
- Additional data regarding the outcome of the historical survey by Rasa & Alberts, 2020.
- Details on the publication from Muceniece, 2001 on overall survival (OS) data.
- Number of people affected

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"](#).

The numbers presented by the sponsor were in the same range as in a previous application however the sponsor was invited to propose a specific figure of the final estimate.

- Significant benefit

The arguments on significant benefit were based on the assumptions regarding the potential improved efficacy and safety in the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to detail the results of any clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients.

However, assumption of significant benefit could only be justified pending acceptance of the medical plausibility.

In the written response, and during an oral explanation before the Committee on 7 September 2021, the sponsor referred to the publication from Tilgase et al., 2020 in order to support the medical plausibility. The cells from 3 human uveal melanoma cell lines (MP41, 92-1 and Mel202) detached from the cultivation surface when the proposed product was added to the culture medium. In all cell lines, treatment with multiplicity of infection (MOI) of 70 the product showed earlier cytotoxic response than the MOI of 7 groups. However, these limited in vitro data from the cell lines were not considered sufficient on their own to support medical plausibility.

Furthermore, the sponsor provided an update on the data of the retrospective survey (Rasa et al., 2020) in order to address the question on the medical plausibility. In total, this survey included 13 patients treated with the proposed product and 14 patients treated with standard treatment. However, as it was discussed in the publication, the wide inclusion criteria, the small number of patients, dissimilarities in patient characteristics and non-controlled intervals between visits and measurements prevented statistical evaluation of any differences (Rasa & Alberts, 2020).

Some further details were also presented on the Muceniece, 2001 publication. However, no data was available in this publication on the baseline tumour status of the patients and on prior treatments. The 3- and 5-year overall survival were reported to be 90% and 71% respectively. However, a large number of patients were lost to follow-up. Therefore, these results for OS are not valid.

Further to the above, based on the uncertainties regarding the validity of the published clinical data and the absence of in vivo data, the COMP considered that the arguments

presented were not sufficient to support the medical plausibility of the product for the purpose of the orphan designation.

Regarding the calculation of the prevalence the sponsor provided a prevalence estimate based on an average (8.6 years) and maximum duration of disease (17.2 years). Taking these figures of the disease duration and the highest European incidence value reported (1 per 100.000) the prevalence was estimated to be 0.86 per 10,000 and the maximum complete prevalence 1.72 per 10,000. The COMP accepted the proposed prevalence of 0.86 per 10,000 persons in the EU.

Regarding the assumption of significant benefit on the grounds of an improved efficacy and safety, the COMP considered that the clinical data for the product itself were inconclusive and a comparison versus products used in the condition could not be made. For that reason, the claim of the existence of an assumption of significant benefit (either on the basis of claimed improved efficacy/safety or on the basis of a claimed major contribution to patient care) would not be accepted. Furthermore, the COMP considered that the justification of the significant benefit could in any event not be considered, as the sponsor had failed to establish the medical plausibility of the orphan medicinal product.

The intention to treat uveal melanoma with the medicinal product containing enterovirus B, echovirus 7, live was not considered justified. The published clinical data are inconclusive and submitted data from the cell lines were not considered sufficient to support medical plausibility.

Treatment of uveal melanoma (hereinafter referred to as "the condition") was estimated to be affecting approximately 0.9 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has established that the condition is chronically debilitating and life-threatening.

However, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has not provided sufficient justification for the assumption that the medicinal product containing enterovirus B, echovirus 7, live will be of significant benefit to those affected by the condition. The sponsor argues significant benefit on the grounds of an improved efficacy and safety however, clinical data for the product itself were inconclusive and a comparison versus products used in the condition could not be made. Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is not fulfilled.

A negative opinion for enterovirus B, echovirus 7, live, for treatment of uveal melanoma, was adopted by consensus. The sponsor will have 90 days to appeal from the COMP decision.

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

2.1.8. - [EMA/OD/0000058053](#)

Treatment of gastric cancer (GC)

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 provide more clarification on how the oral formulation of product will benefit patients with GC. If available, PK and/or PD comparisons with the IV formulation would be supportive.

- Number of people affected

It was not clear how the sponsor came to the final proposal of 2.8 in 10,000. Other figures were mentioned in the application and therefore the sponsor was asked to clarify and give the figures based on which the estimate was derived.

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 arguments for significant benefit were hypothetical as there is no data in the target population with the envisaged future combination with trifluridine and tipiracil hydrochloride. The sponsor was requested to explain in which patient population and combination their product was intended to be used.

There currently seems to be no data to support that the oral formulation is safer or more efficacious than the IV formulation of the proposed product and the products approved for gastric cancer. The sponsor was asked to further justify the advantage of their product.

Finally, the impact on the treatment burden of the patients with the oral formulation was requested to be further discussed.

In the written response, and during an oral explanation before the Committee on 8 September 2021, the sponsor clarified the editorial error in the prevalence conclusion and the figure of 2.7 was accepted.

The sponsor confirmed that no PD comparisons have been done due to the lack of proven markers. The PK profile has been investigated in a phase 1 study. The sponsor also referred to several non-clinical and clinical studies (not gastric cancer specific though) in which it has been reported that metronomic dosing results in the same (or better) effect and less safety concerns as when irinotecan is given less frequently in higher doses. The COMP accepted the medical plausibility as there is clear evidence of efficacy (mainly with the IV formulation) in patients with the condition.

The sponsor referred to a study by Nukatsuka et al., 2015 in which the addition of proposed product to trifluridine and tipiracil hydrochloride in a gastric cancer xenograft-bearing non-clinical model has showed greater tumour growth inhibition than either agent alone, or vs. control. This could potentially be supportive of significant benefit over Lonsurf but also other products need to be considered.

The sponsor focused on the benefits of the oral dosing, but a "major contribution to patient care" cannot be considered unless the efficacy has been confirmed to be at least of the same magnitude as other treatment options for the patients. The COMP did not consider that the sponsor had justified the significant benefit sufficiently.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 September 2021, prior to final opinion.

2.1.9. - EMA/OD/0000058526

Treatment of acute liver failure (ALF)

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 COMP considered that prevention of acute liver failure would correspond to the development more adequately. 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 prevention of acute liver failure the sponsor was asked to further elaborate on:

- additional studies with their product in other causes of acute liver failure which were indicated in their submission.
- Number of people affected

It seems that the sponsor had excluded part of the population at risk of the condition as the prevention maybe considered the aim for the use of the product. The sponsor was asked to indicate which population the prevalence calculation is based on.

The sponsor was requested to re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition taking different causes of ALF into consideration. Given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor was asked to 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 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 non-clinical in vivo studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

The sponsor was asked to further elaborate on the results of the clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients and elaborate on the effect on patients who no longer respond to N-acetylcysteine.

In the written response, and during an oral explanation before the Committee on 8 September 2021, the sponsor accepted the COMP recommendation to change the proposed condition from treatment to prevention of acute hepatic failure. In addition, although no new data was provided, the justification of the data provided on paracetamol toxicity and the subsequent development of acute liver failure was accepted by the committee in support of medical plausibility. This was also true for the claim of significant benefit where again no additional data forthcoming but could be accepted.

The main discussion therefore focused on the prevalence estimate where it was noted that what was being proposed was a calculation primarily based on post-dose prophylaxis in patients who were admitted to hospital. The key driver of the calculation was the clinical assessment of the paracetamol toxicity and the perceived risk of developing acute liver failure.

There are many causes which can lead to acute liver failure such as paracetamol (the most common), ischaemia, drug-induced liver injury (other than paracetamol), autoimmunity, hepatitis B virus, hepatitis A virus, pregnancy, and all other causes (which appear to be larger than what the sponsor claims; Lancet 2019; 394: 869–81). The Committee discussed the reporting rates proposed by the sponsor indicating that they may not reflect the primary prevention population but more a paracetamol post-dose prophylaxis population who are screened by clinical judgement. This appeared therefore to be an under-estimate of the potential patient population at risk.

The COMP therefore considered that 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 2021, prior to final opinion.

2.1.10. ganaxolone - EMA/OD/0000061671

Marinus Pharmaceuticals Emerald Limited; Treatment of tuberous sclerosis

COMP Rapporteur: Giuseppe Capovilla, 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:

- Significant benefit

The arguments on significant benefit were based on the potential improved efficacy and safety in the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the ongoing clinical study to justify the assumption of significant benefit over cannabidiol and everolimus for the proposed orphan designation. The sponsor was invited to provide details on the population studied regarding the previous and current treatments.

In the written response, and during an oral explanation before the Committee on 8 September 2021, the sponsor clarified that based on the results of the ongoing study, the proportion of subjects who have failed prior treatment with other currently authorized antiepileptic drugs (AEDs), achieving at least a 50% reduction in TS-associated seizures

was 30% overall, including 25% in subjects receiving cannabidiol and 36% in those receiving everolimus. The COMP considered that the ability for ganaxolone to show a benefit on top of existing therapies is sufficient to support the assumption for a significant benefit for the purpose of orphan designation.

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

The intention to treat the condition with the medicinal product containing ganaxolone was considered justified based on preliminary clinical data showing a reduction in seizure frequency in patients with the condition.

The condition is chronically debilitating due to disfiguring tumours and severe neurological symptoms including treatment-resistant seizures that can lead to cognitive disability and life threatening due to the formation of multiple tumours in different organs.

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 ganaxolone will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating a reduction in seizure frequency as an add-on therapy to anti-seizure medications in patients with the condition.

A positive opinion for ganaxolone, for treatment of tuberous sclerosis, was adopted by consensus.

[2.1.11. - EMA/OD/0000062387](#)

Treatment of optic neuritis

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 28 July 2021, prior to responding to the list of issues.

[2.1.12. devimistat - EMA/OD/0000059143](#)

IQVIA RDS Ireland Limited; Treatment of Burkitt's lymphoma

COMP Rapporteur: Karri Penttila

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 Burkitt's Lymphoma the sponsor was requested to further elaborate on:

- the preliminary clinical data which should be further discussed in order to explain the relevance of the results presented.
- 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 clinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

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

In the written response, the sponsor highlighted that the current number of patients included in their trial was 8 patients. In the ongoing phase 2 trial, it has taken 2 years and 7 months to enroll 8 Burkitt's lymphoma patients. It was noted that the patients recruited had relapsed or refractory Burkitt's lymphoma patients which is highly aggressive, and patients are often unable to receive treatment as they are already too moribund or die before they can reach a treatment site. Of the 8 patients included two were not evaluable leaving only 6 patients of which only one had a complete response.

The COMP discussed the relevance of the finding of a complete response in one of the 6 patients evaluated, as well as the difficulty in treating the relapsed/refractory Burkitt's lymphoma patients. Following the discussion, the COMP was of the opinion that this level of data could be accepted within the context of an initial orphan designation in view of the difficulties in treating and recruiting the target patient population. The written responses were considered satisfactory and the oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing devimistat was considered justified based on preliminary clinical data showing a partial response.

The condition is life-threatening due to a rapid tumour growth with high tumour burden with poor survival in relapsed patients.

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 devimistat will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a response in patients with relapsed/refractory Burkitt's lymphoma. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for devimistat, for treatment of Burkitt's lymphoma, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. glofitamab - EMA/OD/0000053713

Roche Registration GmbH; Treatment of diffuse large B-cell lymphoma

COMP Rapporteur: Bozena Dembowska-Baginska

The Committee agreed that the condition, diffuse large B-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 glofitamab was considered justified based on preliminary clinical data from patients with relapsed and refractory diffuse large B-cell lymphoma who respond to treatment with glofitamab.

The condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract and bone marrow and life-threatening in patients not responding to first-line treatment.

The condition was estimated to be affecting approximately 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 glofitamab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients affected by the condition who had relapsed or did not respond to at least two prior systemic treatments. These patients showed clinically relevant responses when treated with the product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for glofitamab, for treatment of diffuse large B-cell lymphoma, was adopted by consensus.

[2.2.2. - EMA/OD/0000057352](#)

Treatment of primary biliary cholangitis

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

[2.2.3. - EMA/OD/0000058336](#)

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 meeting.

[2.2.4. - EMA/OD/0000058552](#)

Treatment of follicular 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 meeting.

[2.2.5. - EMA/OD/0000060407](#)

Treatment of Diamond-Blackfan anemia

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 meeting.

2.2.6. batiraxcept - EMA/OD/0000061114

Kinesys Consulting NL B.V.; Treatment of ovarian cancer

COMP Rapporteur: Irena Rogovska

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

The intention to treat the condition with the medicinal product containing batiraxcept was considered justified based on non-clinical data in relevant models of the condition showing a reduced tumour burden. In addition, batiraxcept in combination with paclitaxel or doxorubicin showed clinically relevant responses in patients with the condition.

The condition is chronically debilitating due to pain, weight loss, ascites and vaginal bleeding, and life-threatening, with approximately half of the patients surviving less than five years.

The condition was estimated to be affecting approximately 4.9 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing batiraxcept will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate clinically relevant responses to batiraxcept when used in combination with standard of care in patients relapsing from the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for batiraxcept, for treatment of ovarian cancer, was adopted by consensus.

2.2.7. - EMA/OD/0000061146

Treatment of retinal detachment

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 meeting.

2.2.8. humanised igG1 monoclonal antibody against SEZ6 linked to N-acetyl-calicheamicin - EMA/OD/0000061663

AbbVie Deutschland GmbH & Co. KG; Treatment of small cell lung cancer (SCLC)

COMP Rapporteur: Brigitte Schwarzer-Daum

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

The intention to treat the condition with the medicinal product containing humanised IgG1 monoclonal antibody against SEZ6 linked to N-acetyl-calicheamicin was considered justified based on non-clinical data showing antitumour activity supported by preliminary clinical data showing responses in relapsed or refractory small cell lung cancer patients.

The condition is chronically debilitating and life threatening due to its rapid progression and the development of widespread metastases, with a 5-year overall survival of 5-10%.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised IgG1 monoclonal antibody against SEZ6 linked to N-acetyl-calicheamicin will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate higher anti-tumour activity compared to cisplatin and etoposide used as first line therapy supported by preliminary clinical data showing responses in relapsed or refractory small cell lung cancer patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised IgG1 monoclonal antibody against SEZ6 linked to N-acetyl-calicheamicin, for treatment of small cell lung cancer, was adopted by consensus.

2.2.9. mocravimod - EMA/OD/0000061869

Priothera; Treatment in hematopoietic stem cell transplantation (HSCT)

COMP Rapporteur: Karri Penttila

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

The intention to treat the condition with the medicinal product containing mocravimod was considered justified based on non-clinical data in valid disease models demonstrating inhibition of acute Graft-versus-Host Disease (GVHD) while maintaining the Graft-versus-Leukaemia (GVL) effect and based on clinical data in patients receiving allogenic haematopoietic stem cell transplantation suggesting a positive trend in overall survival, when compared to matched historic control data.

The condition is life-threatening and chronically debilitating due to susceptibility to severe infections and complications such as graft-versus-host disease.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing mocravimod will be of significant benefit to those affected by the condition. The sponsor has provided clinical data in patients receiving allogenic hematopoietic stem cell transplantation (HSCT) that demonstrate that mocravimod as add-on to standard of care compares favourably with regards to overall survival vs matched historic control data. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for mocravimod, for treatment in hematopoietic stem cell transplantation, was adopted by consensus.

2.2.10. - EMA/OD/0000062259

Treatment of glioma

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 meeting.

2.2.11. - EMA/OD/0000062364

Treatment in solid organ transplantation

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 meeting.

2.2.12. [allogeneic retinal pigment epithelial cells genetically modified with a non-viral vector to express human alpha-L-iduronidase - EMA/OD/0000063084](#)

TMC Pharma (EU) Limited; Treatment of mucopolysaccharidosis I

COMP Rapporteur: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing allogeneic retinal pigment epithelial cells genetically modified with a non-viral vector to express human alpha-L-iduronidase was considered justified based on non-clinical in vivo data in a relevant disease model, showing that human native alpha-L-iduronidase enzyme was continuously produced and secreted by the medicinal product at levels that significantly reduced substrate accumulation to normal levels following a single intra peritoneal administration.

The condition is chronically debilitating due to hepatosplenomegaly, upper airway obstruction, skeletal deformity, cardiomyopathy, cognitive impairment and life-threatening with death ensuing by adolescence if the severe form of the disease is left untreated.

The condition was estimated to be affecting approximately 0.04 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing allogeneic retinal pigment epithelial cells genetically modified with a non-viral vector to express human alpha-L-iduronidase will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data which suggests long-term duration of response to one single administration of the product, mitigating the need for continuous treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic retinal pigment epithelial cells genetically modified with a non-viral vector to express human alpha-L-iduronidase, for treatment of mucopolysaccharidosis I, was adopted by consensus.

2.2.13. - EMA/OD/0000064329

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 meeting.

2.2.14. [adeno-associated viral vector serotype 5 expressing the human cone-rod homeobox gene - EMA/OD/0000064480](#)

Variant; Treatment of cone-rod dystrophy

COMP Rapporteur: Ingeborg Barisic

The Committee agreed that the condition, cone-rod 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 5 expressing the human cone-rod homeobox gene was considered justified based on non-clinical in vivo data in models of the condition demonstrating the ability of this vector to preserve cone photoreceptors and to partially restore photoreceptor function.

The condition is chronically debilitating due to the progressive and irreversible loss of sight over time.

The condition was estimated to be affecting approximately 0.33 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 5 expressing the human cone-rod homeobox gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data in a valid disease model that demonstrate the ability of this vector to preserve cone photoreceptors and to partially restore photoreceptor function. The model is representative of a patient population affected by a different mutation as compared to the one targeted by the currently authorised medicine. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 5 expressing the human cone-rod homeobox gene, for treatment of cone-rod dystrophy, was adopted by consensus.

2.2.15. [- EMA/OD/0000064772](#)

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 meeting.

2.2.16. [- EMA/OD/0000064903](#)

Treatment of systemic sclerosis

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 meeting.

2.2.17. autologous haematopoietic stem and progenitor cell population containing CD34+ cells transduced with a lentiviral vector encoding the *TCIRG1* cDNA ex vivo expanded - EMA/OD/0000064944

Fondazione Telethon; Treatment of osteopetrosis

COMP Rapporteur: Lyubina Racheva Todorova

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

The intention to treat the condition with the medicinal product containing Autologous haematopoietic stem and progenitor cell population containing CD34+ cells transduced with a lentiviral vector encoding the *TCIRG1* cDNA ex vivo expanded was considered justified based on non-clinical in vivo data in a model of the condition showing improved survival and normalisation of bone modelling.

The condition is life-threatening and chronically debilitating due to anaemia, recurrent infections, and hepatosplenomegaly associated with extramedullary haematopoiesis and bone thickening leading to bone marrow narrowing. Patients can also have blindness, facial paralysis, and deafness due to compression induced by the bone expansion. Abnormal cortical bone morphology (vertebral bodies, ribs and vertebral epiphysis), craniosynostosis as well as temperature dysregulation is noted in the more severe forms. These patients also have bone pain and cranial nerve paralysis. Survival in severe childhood forms is below 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 autologous haematopoietic stem and progenitor cell population containing CD34+ cells transduced with a lentiviral vector encoding the *TCIRG1* cDNA ex vivo expanded, for treatment of osteopetrosis, was adopted by consensus.

2.2.18. allogeneic umbilical cord mesenchymal cells-derived extracellular vesicles - EMA/OD/0000065116

Exo Biologics; Prevention of bronchopulmonary dysplasia

COMP Rapporteur: Lenka Gaidadzi

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

The intention to prevent the condition with the medicinal product containing allogeneic umbilical cord mesenchymal cells-derived extracellular vesicles was considered justified based on data in a valid non-clinical disease model and in vitro cell based assays which suggest that administration of the product can improve critical factors of the pathophysiology of the condition and reduce mortality.

The condition is life-threatening and chronically debilitating due to inflammation and scarring in the lungs, resulting in necrotizing bronchiolitis and alveolar septal injury, which compromises the oxygenation of blood.

The population of patients eligible for prevention of the condition was estimated to be less than 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 prevention in the European Union for the population at risk of developing the condition.

A positive opinion for allogeneic umbilical cord mesenchymal cells-derived extracellular vesicles, for prevention of bronchopulmonary dysplasia, was adopted by consensus.

2.2.19. selinexor - EMA/OD/0000065221

Karyopharm Europe GmbH; 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 selinexor was considered justified based on *in vivo* non-clinical data showing synergistic antitumor effects of selinexor and temozolomide and on the preliminary clinical data showing antitumor activity of selinexo monotherapy with durable responses in pretreated patients.

The condition is debilitating due to symptoms caused 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 2.4 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 selinexor will be of significant benefit to those affected by the condition. The sponsor has provided *in vivo* non-clinical data showing synergistic antitumor effects of selinexor and temozolomide and preliminary clinical data that demonstrate effects in monotherapy in patients with recurrence after temozolomide and radiotherapy. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.20. encaleret sulfate - EMA/OD/0000065287

Voisin Consulting; Treatment of hypoparathyroidism

COMP Rapporteur: Vallo Tillmann

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

The intention to treat the condition with the medicinal product containing encaleret sulfate was considered justified based on preliminary clinical data in patients with the condition which showed increase of the parathyroid hormone, increase of blood calcium (Ca) levels and decrease of urinary Ca excretion.

The condition is chronically debilitating due to neuromuscular symptoms, cognitive impairment, abnormal calcium and phosphate metabolism, and reduced bone turnover. The condition may be life-threatening due to risk of hypocalcaemia that may lead to seizures, cardiac arrhythmias, cardiomyopathy and laryngeal spasm if untreated.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing encalaret sulfate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that encalaret sulfate can increase the parathyroid hormone, increase of blood Ca levels and decrease of urinary Ca excretion. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for encalaret sulfate, for treatment of hypoparathyroidism, was adopted by consensus.

2.2.21. - EMA/OD/0000065329

Treatment of idiopathic pulmonary fibrosis

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 meeting.

2.2.22. adeno-associated virus serotype rh10 containing the human *GALC* gene - EMA/OD/0000065353

Diamond Pharma Services Ireland Limited; Treatment of Krabbe disease

COMP Rapporteur: Gloria Maria Palomo Carrasco

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

The intention to treat the condition with the medicinal product containing adeno-associated virus serotype rh10 containing the human *GALC* gene was considered justified based on based on non-clinical data in 2 valid models of the condition when the product was used alone or in combination with bone marrow transplant, showing improved survival, as well as improvement of psychosine levels in tissue, and increased myelination of peripheral nerves.

The condition is life-threatening and chronically debilitating, in particular due to the development of progressive motor paralysis, ataxia and regression of cognitive development.

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 adeno-associated virus serotype rh10 containing the human *GALC* gene, for treatment of Krabbe disease, was adopted by consensus.

2.2.23. idursulfase beta - EMA/OD/0000065415

Parexel International (Irl) Limited; Treatment of mucopolysaccharidosis type II (Hunter's syndrome)

COMP Rapporteur: Armando Magrelli

The Committee agreed that the condition, mucopolysaccharidosis type II (Hunter's syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing idursulfase beta was considered justified based on non-clinical data in a valid disease model and clinical data in mucopolysaccharidosis type II (MPS II) patients with neurological symptoms demonstrating that the product administered via the intracerebroventricular route can reduce idursulfase substrate levels in the cerebrospinal fluid (CSF) and the brain and show positive trends in improving behavioral parameters and developmental age of patients in the areas of posture/movement, cognitive adaptation and language.

The condition is seriously debilitating due to neurological decline, cardiovascular and pulmonary complications and life-threatening as indicated by the survival of the patients that can be limited to 10-15 years.

The condition was estimated to be affecting less than 0.04 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 idursulfase beta will be of significant benefit to those affected by the condition. The sponsor has provided clinical data in MPS II patients with neurological symptoms demonstrating that the product administered via the intracerebroventricular route and in addition to current standard of care (idursulfase, IV), can reduce idursulfase substrate levels in the CSF and shows positive trends in improving developmental age of patients in the areas of posture/movement, cognitive adaptation and language, as compared to standard of care alone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for idursulfase beta, for treatment of mucopolysaccharidosis type II (Hunter's syndrome), was adopted by consensus.

2.2.24. psilocybine - EMA/OD/0000065562

Comac Medical Ltd.; Treatment of fragile X syndrome

COMP Rapporteur: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing psilocybine was considered justified based on non-clinical data in a valid model of the condition showing improvements in cognition.

The condition is chronically debilitating due to developmental delay, a range of neurobehavioral and cognitive complications.

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.

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 psilocybine, for treatment of fragile X syndrome, was adopted by consensus.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

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

COMP rapporteurs were appointed for 27 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 22 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of acute myeloid leukaemia

The discussion was postponed.

3.1.2. -

Treatment of hyperphenylalaninemia

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

3.1.3. -

Treatment of polycythaemia vera

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

3.1.4. -

Treatment of soft tissue sarcoma

The discussion was postponed.

3.2. Finalised letters

3.2.1. -

Treatment of paediatric patients with severe combined immunodeficiency (SCID) receiving allogeneic haematopoietic stem cell transplantation

The finalised letter was circulated for information.

3.2.2. -

Treatment in haematopoietic stem cell transplantation

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of glioma

The new request was noted.

3.3.2. -

Treatment of haemophilia A

The new request was noted.

3.3.3. -

Treatment of acute myeloid leukaemia

The new request was noted.

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

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

None

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

4.2.1. - zanubrutinib - EMEA/H/C/004978/0000, EU/3/19/2167, EMA/OD/0000058248

BeiGene Ireland Limited; Treatment of lymphoplasmacytic 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 meeting.

[Post-meeting note: The sponsor formally withdrew the orphan designation from the EC register of orphan medicinal products, on 28 September 2021.]

4.2.2. - glucarpidase - EMEA/H/C/005467/0000, EMA/OD/049/02, EU/3/02/128, EMA/OD/0000042598

Protherics Medicines Development Europe B.V.; Adjunctive treatment in patients at risk of methotrexate toxicity

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

4.2.3. - artesunate - EMEA/H/C/005550, EU/3/20/2251, EMA/OD/0000060998

Amivas Ireland Ltd; Treatment of malaria

The status of the procedure at CHMP was noted.

4.2.4. - lonafarnib - EMA/OD/0000001643, EU/3/18/2118, EMA/OD/0000067500

EigerBio Europe Limited; Treatment of Hutchinson-Gilford Progeria Syndrome

The status of the procedure at CHMP was noted.

4.2.5. - pegcetacoplan - EMEA/H/C/005553, EU/3/17/1873, EMA/OD/0000051430

Apellis Ireland Limited; Treatment of paroxysmal nocturnal haemoglobinuria

The status of the procedure at CHMP was noted.

4.2.6. - ripretinib - EMEA/H/C/005614, EU/3/17/1936, EMA/OD/0000057360

Deciphera Pharmaceuticals (Netherlands) B.V; Treatment of gastrointestinal stromal tumours

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 meeting.

- 4.2.7. Tecartus – autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured - EMEA/H/C/005102/II/0008/G, EU/3/20/2344, EMA/OD/0000063560
-

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

CHMP Rapporteur: Jan Mueller-Berghaus; CHMP Co-Rapporteur: Rune Kjeklen

The discussion was postponed.

- 4.2.8. - lonapegsomatropin - EMEA/H/C/005367/0000, EU/3/19/2213, EMA/OD/0000059751
-

Ascendis Pharma Endocrinology Division A/S; Treatment of growth hormone deficiency

The status of the procedure at CHMP was noted.

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

B And O Pharm; Treatment of malaria

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 6 applications.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

None

5.3. Appeal

None

5.4. On-going procedures

None

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP membership

The COMP noted Mr George Dimopoulos as new COMP member representing Greece.

7.1.2. Vote by proxy

Marie Pauline J. Evers gave a proxy to Elisabeth Rook to vote on behalf of Marie Pauline J. Evers during part of September 2021 COMP meeting.

Dinko Vitezic gave a proxy to Ingeborg Barišić to vote on behalf of Dinko Vitezic during part of September 2021 COMP meeting.

Lyubina Todorova gave a proxy to Eva Malikova to vote on behalf Lyubina Todorova during part of September 2021 COMP meeting.

7.1.3. Strategic Review & Learning meeting – joint COMP/PDCO, 19 November 2021, Lisbon, Portugal

The COMP noted information about upcoming meeting.

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 3 September 2021.

7.1.5. COMP Rules of Procedure - revision

Document tabled:

[COMP Rules of Procedure Rev. 6](#)

To reflect the meeting approach for the pilot for the relaunch of face to face committee meetings, the COMP Rules of Procedure required revision. The opportunity was taken to introduce some other changes to facilitate the functioning of the committees and for consistency reasons.

The revised COMP rules of procedure were adopted by consensus.

7.1.6. Pilot – Relaunch of face to face Scientific Committee Meetings

The COMP was informed about the expected set-up for returning to Committee face-to-face meetings.

7.1.7. Election of COMP Chairperson

The COMP re-elected Violeta Stoyanova-Beninska as COMP Chairperson for 2nd three-year term.

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. CAT-COMP Working Group

The COMP-CAT Working Group met remotely on 6 September 2021.

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

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

Documents were tabled for information.

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

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

None

7.7. COMP work plan

None

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2021

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2021 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. Updated Guideline on registry-based studies

The COMP noted the updated guideline. As next steps, the guideline is intended to be adopted by CHMP. The publication of guideline is planned early Q1 2022.

8.2. EMA Business Pipeline activity and Horizon scanning

The document was 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 7-9 September 2021 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 via WebEx	Netherlands	No interests declared	
Armando Magrelli	Vice-chair via WebEx	Expert recommended by EMA	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Brigitte Schwarzer-Daum	Member via WebEx	Austria	No restrictions applicable to this meeting	
Tim Leest	Member via WebEx	Belgium	No interests declared	
Lyubina Racheva Todorova	Member via WebEx	Bulgaria	No interests declared	
Dinko Vitezic	Member via WebEx	Croatia	No interests declared	
Vasileios Loutas	Member via WebEx	Cyprus	No interests declared	
Lenka Gaidadzi	Member via WebEx	Czechia	No interests declared	
Elisabeth Penninga	Member via WebEx	Denmark	No interests declared	
Vallo Tillmann	Member via WebEx	Estonia	No interests declared	
Karri Penttilä	Member via WebEx	Finland	No interests declared	
Cecile Dop	Member via WebEx	France	No restrictions applicable to this meeting	
Frauke Naumann-Winter	Member via WebEx	Germany	No interests declared	
Zsafia Gyulai	Member via WebEx	Hungary	No interests declared	
Geraldine O'Dea	Member via WebEx	Ireland	No interests declared	
Enrico Costa	Member via WebEx	Italy	No restrictions applicable to this meeting	
Irena Rogovska	Member via WebEx	Latvia	No participation in discussions, final deliberations and voting on:	2.1.7. Enterovirus B, echovirus 7, live - EMA/OD/0000057849 Latima SIA - Treatment of uveal melanoma
Aušra Matulevičienė	Member via WebEx	Lithuania	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Michel Hoffmann	Member via WebEx	Luxembourg	No interests declared	
Robert Nistico	Member via WebEx	Malta	No restrictions applicable to this meeting	
Elisabeth Johanne Rook	Member via WebEx	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member via WebEx	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member via WebEx	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member via WebEx	Portugal	No interests declared	
Olimpia Neagu	Member via WebEx	Romania	No interests declared	
Eva Malikova	Member via WebEx	Slovak Republic	No interests declared	
Martin Mozina	Member via WebEx	Slovenia	No interests declared	
Gloria Maria Palomo Carrasco	Member via WebEx	Spain	No interests declared	
Darius Matusевичius	Member via WebEx	Sweden	No restrictions applicable to this meeting	
Pauline Evers	Member via WebEx	Patients' Organisation Representative	No interests declared	
Julian Isla	Member via WebEx	Patients' Organisation Representative	No interests declared	
Ines Alves	Member via WebEx	Patients' Organisation Representative	No restrictions applicable to this meeting	
Ingeborg Barisic	Member via WebEx	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member via WebEx	Expert recommended by EMA	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Virginie Hivert	Expert – via WebEx*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Johanna Lähteenvuo	CHMP Alternate via WebEx*	Finland	No interests declared	
Sinan B. Sarac	CHMP Member via WebEx*	Denmark	No interests declared	
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/