9 September 2020
EMA/COMP/381675/2020
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 14-16 July 2020

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

14 July 2020, 08:30-19:40, remote virtual meeting

15 July 2020, 08:30-20:00, remote virtual meeting

16 July 2020, 08:30-17:45, remote virtual 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.

Further information with relevant explanatory notes can be found at the end of this document.

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

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the COMP plenary session to be held 14-16 July 2020. See July 2020 COMP minutes (to be published post September 2020 COMP meeting).

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 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 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.

Dinko Vitezic gave a proxy to Ingeborg Barisic to vote on behalf of Dinko Vitezic during the July 2020 COMP meeting.

1.2. Adoption of agenda

The agenda for 14-16 July 2020 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 16-18 June 2020 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. allogeneic umbilical cord tissue-derived mesenchymal stromal cells ex vivo expanded - EMA/OD/0000016117

MDTB Cells GmbH; Prevention of bronchopulmonary dysplasia

COMP Rapporteur: Olimpia Neagu

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 population eligible for prevention of the condition 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 sponsor was requested to re-calculate the population eligible for prevention of the condition taking into account also cases that may occur after 32 weeks gestational age.

In the written response, the sponsor calculated separately the figures of extremely preterm (below 28 weeks of gestational age), very preterm (between 28 and 31 weeks) and moderately preterm (between 32 and 36 weeks of gestational age to term) infants. In the gestational age group of moderately preterm infants (32-36 weeks of gestation), the rate of bronchopulmonary dysplasia (BPD) in survivors to 36 weeks was estimated to be 0.25%, based on published literature. Taking into account the risk of BPD in moderately preterm infants, the population eligible for prevention was estimated to be approximately 2.6 in 10,000, which was deemed acceptable by the COMP.

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 tissue-derived mesenchymal stromal cells ex vivo expanded was considered justified based on non-clinical data showing improvement of respiratory parameters and alveolar structure in valid models of the condition.

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 approximately 2.6 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 prevention in the European Union for the population at risk of developing the condition.

A positive opinion for allogeneic umbilical cord tissue-derived mesenchymal stromal cells ex vivo expanded, for prevention of bronchopulmonary dysplasia, was adopted by consensus.

2.1.2. adeno-associated virus serotype 2/8 vector containing the human pde6a gene - EMA/OD/0000024640

Institute For Ophthalmic Research; Treatment of retinitis pigmentosa

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:

- Number of people affected

The prevalence estimate provided by the sponsor appears to be an underestimate. The sponsor was requested to justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor was requested to describe and

justify the methodology used for the prevalence calculation and provide a new revised estimate.

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, the sponsor further elaborated on the issue of prevalence. The COMP recognised that it can be challenging to find reliable sources of data regarding the prevalence of retinitis pigmentosa, and an estimate of 2.2 in 10,000 was considered adequate for the purpose of an initial orphan designation.

The Committee agreed that the condition, retinitis pigmentosa, 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 2/8 vector containing the human *PDE6A* gene was considered justified based on non-clinical in vivo data in a valid model of the condition showing positive electro retinogram measurements.

The condition is chronically debilitating due to the development of nyctalopia and tunnel vision that progresses to total blindness.

The condition was estimated to be affecting approximately 2.2 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for adeno-associated virus serotype 2/8 vector containing the human *PDE6A* gene, for treatment of retinitis pigmentosa, was adopted by consensus.

2.1.3. protein-based delivery vector carrying a DNA payload encoding an RNA-guided nuclease that targets *stx* genes of Shiga toxin-producing *Escherichia coli* - EMA/OD/0000031667

Eligo Bioscience; Prevention of haemolytic uraemic syndrome

COMP Rapporteur: Geraldine O'Dea

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

The sponsor appears to have focused primarily on (Shiga toxin-producing *Escherichia coli*) STEC (all toxin-producing serogroups) driven HUS (haemolytic uraemic syndrome) and have not included the shigella toxin subgroup. Both groups should be included.

The sponsor was requested to justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor was asked to describe and justify the methodology used for the prevalence calculation.

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

In the written response, the sponsor provided an updated estimate including the *Shigella* prevalence to the STEC (Shiga toxin-producing *E. coli*) prevalence in a HUS as was requested by the COMP.

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

The intention to prevent the condition with the medicinal product containing protein-based delivery vector carrying a DNA payload encoding an RNA-guided nuclease that targets *stx* genes of Shiga toxin-producing *Escherichia coli* was considered justified based on non-clinical in vivo data which showed a substantial reduction in the target bacteria.

The condition is chronically debilitating and life-threatening, in particular due to renal failure and recurrence of the disease in the transplant.

The condition was estimated to be affecting approximately 0.24 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 protein-based delivery vector carrying a DNA payload encoding an RNA-guided nuclease that targets *stx* genes of Shiga toxin-producing *Escherichia coli*, for prevention of haemolytic uraemic syndrome, was adopted by consensus.

2.1.4. allogeneic T-cell precursors, mobilized peripheral blood-derived, ex vivo cultured - EMA/OD/0000031867

Smart Immune; Treatment in haematopoietic stem cell transplantation

COMP Rapporteur: Frauke Naumann-Winter

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 haematopoietic stem cell transplantation the sponsor was requested to further elaborate on:

  - the relevance of the non-clinical model used for the treatment of haematopoietic stem cell transplantation (HSCT), and the interpretation of the results obtained in the experiment for the proposed product using mobilised peripheral blood stem cells,
  - the methodology used in the non-clinical study as well as the results from the study and its relevance for the development of the product in the condition,
  - any preliminary clinical data that they may have with their product in the condition.

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

In the written response, the sponsor claimed a potential improvement in the outcome of HSCTs using alternative graft sources. This claim was based on immune reconstitution data in a non-clinical model, using two different graft sources. The results showed homing to the thymus and maturation of T-cells, but no clinical data or endpoints of improved outcome were provided. The oral explanation with the sponsor was cancelled.

The Committee agreed that the condition, haematopoietic 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 allogeneic T-cell precursors, mobilised peripheral blood-derived, ex vivo cultured was considered justified based on non-clinical in vivo data showing early endpoints of immune reconstitution such as engraftment of cells to the thymus and development of mature T cells.

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 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 allogeneic T-cell precursors, mobilised peripheral blood-derived, ex vivo cultured will be of significant benefit to those affected by the condition. The sponsor has provided preliminary non-clinical in vivo data that demonstrate the potential for accelerated immune reconstitution compared to unmanipulated grafts. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic T-cell precursors, mobilised peripheral blood-derived, ex vivo cultured, for treatment in haematopoietic stem cell transplantation, was adopted by consensus.

2.1.5. dextran sulfate low molecular weight - EMA/OD/0000032154

TikoMed AB; Treatment of amyotrophic lateral sclerosis

COMP Rapporteur: Darius Matusevicius

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

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor was requested to discuss the preliminary clinical observations, and the comparability of the juxtaposed populations in the presented indirect comparison to the authorised product.

In the written response, the sponsor further elaborated on the indirect comparison. Clinical studies were identified in the literature, studying the effect of riluzole as an add-on to other treatments, in populations similar in terms of patient age and baseline function. Two of such

studies were discussed in particular, NCT00818389 by Aggarwal et al, and NCT0086816 by Lenglett et al, which contained riluzole arms in their design. The first study examined the effects of lithium or placebo as an add on to riluzole (Lancet Neurol. 2010 May ; 9(5): 481–488).The second study was an randomized controlled trial (RCT) to assess the safety and efficacy of olesoxime and riluzole compared to riluzole in 512 amyotrophic lateral sclerosis (ALS) patients (European Journal of Neurology 2014, 21: 529–536).

It was proposed that the two studies provide support for this position "on the basis that they were conducted in a similar patient population and evaluated the efficacy of riluzole on Amyotrophic Lateral Sclerosis Rating Scale - Revised (ALSFRS-R) score (or rate of change of score) when used as a comparator". In both studies, riluzole was dosed at 50 mg twice a day and the sponsor notes a decline in ALSRFS score in the treated patients, in contrast to the increase observed with the sponsor's set of data.

Importantly, both studies report a decline of about -1 point/month rate which contrasts to the reported improvements in the small cohort of patients studied by the sponsor. The COMP accepted this indirect comparison for the justification of the assumption that the product may be of improved efficacy compared to riluzole and the oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing dextran sulfate low molecular weight was considered justified based on preliminary clinical observations reporting an improvement in functional scores in treated patients.

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 dextran sulfate low molecular weight will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations supporting improved functional outcomes when indirectly compared to the existing product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for dextran sulfate low molecular weight, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.1.6. bis-(3-deoxy-3-(4-(3-fluorophenyl)-1h-1,2,3-triazol-1-yl)-beta-d-galactopyranosyl) sulfane - EMA/OD/0000023667

Galecto Biotech AB; Treatment of idiopathic pulmonary fibrosis

COMP Rapporteur: Lenka Kovarova

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

In order to justify the significant benefit, the sponsor was invited to further discuss the non-clinical data in the bleomycin model in which the product was compared to pirfenidone. In particular the sponsor was asked to clarify whether any of the doses of the proposed product resulted in a higher effect than pirfenidone, and how such dose relates to the clinical dose used in humans.

The sponsor was asked to provide any available non-clinical and/or clinical data showing potential advantages (e.g. better effect, increased effect when used in combination) of the proposed product as compared to nintendanib, currently authorized for the treatment of idiopathic pulmonary fibrosis (IPF).

In the written response, and during an oral explanation before the Committee on 14 July 2020, the sponsor discussed the potential benefits of the proposed product in relation to pirfenidone and nintedanib, currently authorized for the condition.

From a non-clinical perspective, the sponsor further discussed the results of the bleomycin model study in which both pirfenidone and the proposed product were tested. In this study the sponsor showed that the same effect on lung collagen content and histological fibrosis score was achieved with doses of the proposed product that were lower than the clinical dose currently used in clinical trials, while pirfenidone was used at the clinical doses. According to the sponsor this would suggest potential higher effect of the proposed product.

In another bleomycin model study, the sponsor showed that while the proposed product was efficacious on collagen content and fibrosis score, nintedanib showed activity only on the fibrosis score and no on collagen content, which is a relevant endpoint in IPF non-clinical studies. Similarly, to pirfenidone, nintedanib in this study was used at a dose comparable to the clinical dose in humans, while the proposed product was at lower dose than the one currently chosen as the clinical dose for phase II. The use of lower doses than the expected therapeutic one in the non-clinical studies was justified by the sponsor with the uncertainties regarding dosing approaches in non-clinical phase.

The sponsor also presented an indirect comparison based on biomarker data from clinical studies. In a study of patients with or without treatment with pirfenidone and nintendanib (alone or in combination) no changes were reported in YKL-40, a biomarker that has been associated with survival in IPF in published studies. The proposed product on the other hand showed significant reduction of YKL-40 as well as other biomarkers relevant to IPF in the first human study, which was performed in IPF patients, after 14 days of treatment.

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

The intention to treat the condition with the medicinal product containing bis-(3-deoxy-3-(4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl)-beta-D-galactopyranosyl) sulfane was considered justified based on non-clinical data showing reduction of collagen content and improvement of fibrosis scores in valid models of the condition.

The condition is chronically debilitating due to progressive dyspnoea and loss of lung function, with limited exercise capability and decreased quality of life. Pulmonary hypertension usually develops. Median survival is less than five years, and death ultimately occurs due to respiratory failure.

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 bis-(3-deoxy-3-(4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl)-beta-D-galactopyranosyl) sulfane will be of significant benefit to those affected by the condition. The sponsor has provided an indirect comparison based on preliminary clinical data with the proposed product, showing higher effect on relevant IPF biomarkers than the effect reported in the literature for pirfenidone and nintedanib, currently authorized for the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for bis-(3-deoxy-3-(4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl)-beta-D-galactopyranosyl) sulfane, for treatment of idiopathic pulmonary fibrosis, was adopted by consensus.

2.1.7. - EMA/OD/0000031911

Treatment of inherited disorders of oxidative phosphorylation

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 justify the inherited disorders of oxidative phosphorylation 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 was drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

To establish the proposed medical entity as a valid orphan condition the sponsor was requested to further elaborate on:

- the overview of aetiologies and symptoms of the proposed condition,
- as far as possible, a list of conditions or groups of conditions that are included under the proposed term,
- any reference to existing classification systems and how these systems account for the diverse mitochondrial diseases included in the proposed umbrella term,
- a proposal of future clinical development to demonstrate benefit in this broad condition.

In the written response, and during an oral explanation before the Committee on 14 July 2020, the sponsor presented an extensive list of mutations associated with disorders of oxidative phosphorylation. The list exceeded 300 genes, which were grouped into classes of mitochondrial diseases and described in terms of heterogeneity of clinical characteristics within each mutation, due to the phenomenon of heteroplasmy. The Committee questioned the sponsor with regards to the clinical development plan and the expected/intended therapeutic indication at the time of marketing authorisation.

The COMP could not accept the condition as heterogenous in terms of aetiology as well as clinical characteristics as the proposed umbrella term.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 July 2020, prior to final opinion.

2.1.8. 2-(2-(18F)fluoropyridin-4-yl)-9H-pyrrolo[2,3-b:4,5-c']dipyridine - EMA/OD/0000029150

Life Molecular Imaging GmbH; Diagnosis of progressive supranuclear palsy (PSP)

COMP Rapporteur: Michel Hoffmann

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

- Intention to diagnose, prevent or treat

To establish correctly whether there exists a scientific rationale for the development of the proposed product for diagnosis of progressive supranuclear palsy the sponsor should further elaborate on:

- the results obtained from the clinical study did not address the concerns regarding specificity of the proposed diagnostics for this condition. The sponsor was asked to further elaborate on the level of specificity of their product for the proposed condition and contextualise it within the role of the neuropathological data used in the diagnosis.

In the written response, the sponsor discussed product uptake in selected PSP target regions including the globus pallidus (internus and externus), putamen, subthalamic nucleus, substantia nigra, dentate nucleus and frontal cortex. The qualitative assessment showed high sensitivity and specificity for the detection of tau deposition in globus pallidus internus region of progressive supranuclear palsy- Richardson syndrome (PSP-RS) patients and when compared to alpha-synucleopathy patients and healthy controls. Visual PET assessment also showed high in single-patient level 32 out of 40 clinically diagnosed PSP-RS patients were visually classified as PET-positive. The oral explanation with the sponsor was cancelled. The Committee agreed that the condition, progressive supranuclear palsy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to diagnose the condition with the medicinal product containing 2-(2-(18F)fluoropyridin-4-yl)-9H-pyrrolo[2,3-b:4,5-c']dipyridine was considered justified based on preliminary clinical data where the qualitative assessment showed a significant sensitivity and specificity for the detection of tau deposition in the globus pallidus internus region of progressive supranuclear palsy patients when compared to other tauopathy patients, alpha-synucleopathy patients and healthy controls. This could facilitate an earlier and more reliable diagnosis of progressive supranuclear palsy and could assist in the differentiation of the condition from other neurodegenerative diseases.

The condition is life-threatening and chronically debilitating due to progressive neurological impairment including development of parkinsonism, inability to walk, cognitive deterioration and progressive paralysis leading to premature death.

The condition was estimated to be affecting approximately 1.8 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 diagnosis in the European Union for the population at risk of developing the condition.

A positive opinion for 2-(2-(18F)fluoropyridin-4-yl)-9H-pyrrolo[2,3-b:4,5-c']dipyridine, for diagnosis of progressive supranuclear palsy, was adopted by consensus.

2.1.9. - EMA/OD/0000029026

Treatment of follicular lymphoma

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 26 June 2020, prior to responding to the list of issues.

2.1.10. humanised IgG1 monoclonal antibody against human eotaxin-2 - EMA/OD/0000030305

Granzer Regulatory Consulting & Services; Treatment of primary sclerosing cholangitis

COMP Rapporteur: Dinko Vitezic

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

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor provided data to support the notion that the product slows down the formation of liver fibrosis and inflammation. However, the sponsor was asked to further elaborate on the non-clinical data for the currently used product in the condition.

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

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

In the written response, the sponsor provided details of published non-clinical studies, including information on the models used, study design and results observed. Cumulatively, the sponsor presented 5 experiments in 2 independent models of the condition with the use of ursodeoxycholic acid (UDCA), which all indicated increase transaminase levels and lack of effect on liver fibrosis. In contrast, the proposed product effectively lowered transaminase levels and liver fibrosis markers in 3 independent models of the condition. The oral explanation with the sponsor was cancelled.

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

The intention to treat the condition with the medicinal product containing humanised IgG1 monoclonal antibody against human eotaxin-2 was considered justified based on non-clinical data demonstrating reduction of liver fibrosis and inflammation.

The condition is chronically debilitating and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular cancer. Common findings include pruritus, hyperlipidaemia, hypothyroidism, deficiency of fat-soluble vitamins and osteopenia.

The condition was estimated to be affecting approximately 2.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised IgG1 monoclonal antibody against human eotaxin-2 will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that in several models of the condition the product reduced liver inflammation and fibrosis. This was not achieved previously in comparable models of the condition with the use of ursodeoxycholic acid. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised IgG1 monoclonal antibody against human eotaxin-2, for treatment of primary sclerosing cholangitis, was adopted by consensus.

2.1.11. (4-{(E)-3-(4-fluorophenyl)-3-[4-(3-morpholin-4-yl-prop1ynyl)phenyl]allyloxy}-2-methylphenoxy)acetate - EMA/OD/0000028003

Clinical Network Services (NL) B.V.; Treatment of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

COMP Rapporteur: Darius Matusevicius

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

- 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 mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes the sponsor should further elaborate on the available clinical observations, in the context of the uncontrolled open settings of the study, the duration of treatment, and the natural course of the relapsing-remitting condition as applied for designation.

The sponsor was also invited to discuss the clinical history of the treated patients in further detail, in order to contextualise the reported effects.

In the written response, and during an oral explanation before the Committee on 15 July 2020, the sponsor contacted the investigators of the discussed clinical studies, who reported that all treated patients had a slowly progressive disease phenotype and have never experienced relapses. The significance of the results was also further elaborated, by comparing the mean improvement observed in the 12 minutes walking distance, to the results with the walking test in other conditions. It was pointed out that the "training effect" in the 6MWT (six minute walking test) has been minimal in several studies, and as such the observed differences in walking distance could be attributed to the treatment with the proposed product for designation. The sponsor also pointed out that there is a correlation between the walking distance and patient-reported outcomes in the studied cohort, adding that most of the patients who participated in the study chose to continue to the extension phase.

The COMP remained reserved based on the paucity of the available observations but at the same time acknowledged that there is a trend of improvement that may be attributed to the

proposed treatment. The preliminary clinical observations were therefore considered acceptable for the purpose establishing the intention to treat the proposed condition.

The Committee agreed that the condition, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes, is a distinct medical entity and meets the criteria for orphan designation.

The intention treat the condition with the medicinal product containing sodium (4-{(E)-3-(4-fluorophenyl)-3-[4-(3-morpholin-4-yl-prop1ynyl)phenyl]allyloxy}-2-methylphenoxy)acetate was considered justified based on preliminary clinical observations supporting improvements in exercise capacity.

The condition is life-threatening and chronically debilitating due to the recurrence of seizures, vomiting and headaches, anorexia, exercise intolerance, proximal limb weakness, sensorineural hearing loss and stroke-like episodes of transient hemiparesis or cortical blindness with the onset between the ages of 2 and 10 years.

The condition was estimated to be affecting less than 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 sodium (4-{(E)-3-(4-fluorophenyl)-3-[4-(3-morpholin-4-yl-prop1ynyl)phenyl]allyloxy}-2-methylphenoxy)acetate, for treatment of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes, was adopted by consensus.

2.1.12. - EMA/OD/0000028006

Treatment of myoclonic epilepsy with Ragged-Red Fibres

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 myoclonic epilepsy with ragged-red fibres the sponsor was asked to further elaborate on the clinical relevance of the available observations, in light of the uncontrolled nature of the study and the phenotypic heterogeneity of the condition. Further details on the clinical history of the treated patients is also requested in order to contextualise the reported effects.

In the written response, and during an oral explanation before the Committee on 15 July 2020, the sponsor further elaborated on the available data in two affected patients with the condition. The results were contextualised by referring to the progressive disease phenotype and the test used to study motor function. Taking into consideration the reported outcomes, the COMP considered that in the absence of further data in the proposed settings, it was difficult to acknowledge any clear beneficial effects with the proposed treatment in the sought condition.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 July 2020, prior to final opinion.

2.1.13. - EMA/OD/0000031991

Prevention of retinopathy of prematurity

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 prevention of retinopathy of prematurity the sponsor should further elaborate on:

  - the clinical relevance of the findings in the bibliographic data that was used to support the medical plausibility.

In the written response, and during an oral explanation before the Committee on 15 July 2020, the sponsor referred to published meta-analyses that would report lower incidence of retinopathy of prematurity (ROP) in premature neonates treated with the active substance. The COMP however remained critical in particular with regards to the bibliographic data used in such analyses, as they had different primary aims than to assess effects in ROP. The medical plausibility was therefore not considered acceptable.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 July 2020, prior to final opinion.

2.1.14. - EMA/OD/0000019700

Treatment of metastatic pancreatic ductal adenocarcinoma (PDAC)

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 9 July 2020, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000009949

Treatment of polycythaemia vera

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 September meeting.

2.2.2. - EMA/OD/0000028614

Treatment of multiple myeloma

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 September meeting.

2.2.3. allogeneic hepatoblastoma cells encapsulated in alginate, ex vivo expanded - EMA/OD/0000028963

ESPL Regulatory Consulting Limited; Treatment of acute liver failure

COMP Rapporteur: Olimpia Neagu

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

The intention to treat the acute liver failure with the medicinal product containing allogeneic hepatoblastoma cells encapsulated in alginate, ex vivo expanded was considered justified based on non-clinical in vivo data in an experimental model of the condition showing reduction in ammonaemia, improvement in blood pH and level of clotting factors and a reduction in intracranial pressure indicating a normalising of liver function.

The condition is life-threatening, with acute and rapid deterioration of liver function leading to encephalopathy with intracranial hypertension, and to the development of multi-organ failure and sepsis. Acute liver failure accounts for 11% of liver transplants in Europe, and mortality rates can be up to 85% when transplantation is not feasible.

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 allogeneic hepatoblastoma cells encapsulated in alginate, ex vivo expanded will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate an improvement in liver function through a reduction in ammonaemia and normalisation of blood clotting factors. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic hepatoblastoma cells encapsulated in alginate, ex vivo expanded, for treatment of acute liver failure, was adopted by consensus.

2.2.4. - EMA/OD/0000030250

Treatment of 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 September meeting.

2.2.5. - EMA/OD/0000030264

Treatment of KCNQ2 encephalopathy

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 September meeting.

2.2.6. - EMA/OD/0000030272

Treatment of uveal melanoma

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 September meeting.

2.2.7. - EMA/OD/0000031078

Treatment of soft tissue sarcomas

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 September meeting.

2.2.8. pentosan polysulfate sodium - EMA/OD/0000031602

Paradigm Biopharmaceuticals (Ireland) Limited; Treatment of mucopolysaccharidosis type VI

COMP Rapporteur: Geraldine O'Dea

Following review of the application by the Committee, it was agreed to rename the indication to treatment of mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome).

The Committee agreed that the condition, mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing pentosan polysulfate sodium was considered justified based on *in vivo* data in a model of the condition supporting improvements in mobility and skeletal formation, and preliminary clinical observations supporting a reduction in urinary glycosaminoglycan levels.

The condition is chronically debilitating and life-threatening due to bone dysplasia, joint restriction, organomegaly, heart disease, and corneal clouding, and reduced life span with death occurring in general up to the fifth decade of life.

The condition was estimated to be affecting approximately 0.01 per 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 pentosan polysulfate sodium will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations in patients treated with enzyme replacement therapy, showing an add-on reduction in urinary glycosaminoglycan concentration. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for pentosan polysulfate sodium, for treatment of mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome), was adopted by consensus.

2.2.9. - EMA/OD/0000032059

Treatment of Charcot-Marie-Tooth (CMT) disease

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 September meeting.

2.2.10. sodium (4-{(e)-3-(4-fluorophenyl)-3-[4-(3-morpholin-4-yl-prop1ynyl)phenyl]allyloxy}-2-methylphenoxy)acetate - EMA/OD/0000032752

Clinical Network Services (NL) B.V.; Treatment of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency

COMP Rapporteur: Lyubina Racheva Todorova

The Committee agreed that the condition, long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sodium (4-{(E)-3-(4-fluorophenyl)-3-[4-(3-morpholin-4-yl-prop1ynyl)phenyl]allyloxy}-2-methylphenoxy)acetate was considered justified based on preliminary clinical data suggesting reduction of fatigue and pain severity, and improvement in respiratory exchange ratio.

The condition is life-threatening due to risk of metabolic decompensation and chronically debilitating due to hypoketotic hypoglycaemia, myopathy, episodic rhabdomyolysis, cardiomyopathy, arrhythmias, and hepatic encephalopathy.

The condition was estimated to be affecting less than 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 sodium (4-{(E)-3-(4-fluorophenyl)-3-[4-(3-morpholin-4-yl-prop1ynyl)phenyl]allyloxy}-2-methylphenoxy)acetate, for treatment of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency, was adopted by consensus.

2.2.11. - EMA/OD/0000033107

Treatment of sickle cell disease

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 September meeting.

2.2.12. - EMA/OD/0000033552

Treatment of IgA nephropathy

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 September meeting.

2.2.13. copper histidinate - EMA/OD/0000033614

CambPharma Solutions (CY) Limited; Treatment of Menkes disease

COMP Rapporteur: Vallo Tillmann

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

The intention to treat the condition with the medicinal product containing copper histidinate was considered justified based on clinical observations supporting improved survival in treated patients.

The condition is chronically debilitating in particular due to progressive neurodegeneration and marked connective tissue dysfunction with vascular, urogenital, and skeletal abnormalities. The condition is also life-threatening with death before the third year of life in the most severe cases.

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 copper histidinate, for treatment of Menkes disease, was adopted by consensus.

2.2.14. - EMA/OD/0000034330

Treatment of sickle cell disease

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 September meeting.

2.2.15. - EMA/OD/0000034496

Adjuvant treatment of acute respiratory failure in COVID-19 patients at ICU

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 September meeting.

2.2.16. adeno-associated viral vector serotype 3b encoding shortened human *ATP7B* - EMA/OD/0000034624

Vivet Therapeutics S.A.S.; Treatment of Wilson's disease

COMP Rapporteur: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 3B encoding shortened human *ATP7B* was considered justified based on non-clinical data in a model of the condition showing reduction of urine and liver copper levels, increased ceruloplasmin activity and a durability of the transgene.

The condition is chronically debilitating and can be life-threatening due to the toxic effects of copper, first accumulating in the liver and later in the brain. The disease can present with symptoms ranging from mildly elevated transaminases to acute liver failure or liver cirrhosis, and CNS related symptoms. Around 5% of all patients are diagnosed only when they develop fulminant acute liver failure, sometimes fatal.

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 adeno-associated viral vector serotype 3B encoding shortened human *ATP7B* will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data to demonstrate that a single administration of the product may induce a long-term clinically relevant reductions in copper levels in urine and liver, resulting in reduced liver inflammation and improved ceruloplasmin activity. This would

compare favourably to a life-long treatment with currently authorised medicinal products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 3B encoding shortened human *ATP7B,* for treatment of Wilson's disease, was adopted by consensus.

2.2.17. 6-[(3s,4s)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7h-imidazo[1,5-a]pyrazin-8-one - EMA/OD/0000034662

TMC Pharma (EU) Limited; Treatment of sickle cell disease

COMP Rapporteur: Angelo Loris Brunetta

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 6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-one was considered justified based on data in non-clinical models supporting a reduction of sickle cells and vascular stasis, as well as preliminary clinical observations, supporting a reduction in vaso-occlusive crises.

The condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, acute chest syndrome, chronic kidney disease, pulmonary hypertension and susceptibility to infections, and life-threatening with reduced survival.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-one will be of significant benefit to those affected by the condition . The sponsor has provided preliminary clinical data that support add-on effects in the reduction of vaso-occlusive crises when the product is combined with hydroxyurea. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-one, for treatment of sickle cell disease, was adopted by consensus.

2.2.18. trehalose - EMA/OD/0000034728

FGK Representative Service GmbH; Treatment of mucopolysaccharidosis III

COMP Rapporteur: Gloria Maria Palomo Carrasco

Following review of the application by the Committee, it was agreed to rename the indication to treatment of mucopolysaccharidosis type III (Sanfilippo syndrome).

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

The intention to treat the condition with the medicinal product containing trehalose was considered justified based on non-clinical in vivo data showing longer survival and improvement in behavioural outcomes.

The condition is chronically debilitating due to profound cognitive and behavioural impairment, and life-threatening due to poor overall survival that is commonly limited at the end of the second or the beginning of the third decade of life.

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

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

A positive opinion for trehalose, for treatment of mucopolysaccharidosis type III (Sanfilippo syndrome), was adopted by consensus.

2.2.19. 3-(((1S,2S,3R)-2,3-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile - EMA/OD/0000035036

Merck Sharp & Dohme B.V.; Treatment of von-Hippel Lindau disease

COMP Rapporteur: Lyubina Racheva Todorova

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

The intention to treat the condition with the medicinal product containing 3-(((1S,2S,3R)-2,3-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile was considered justified based on preliminary clinical data which showed an acceptable ORR response for nonrenal cell carcinoma tumours associated with the condition.

The condition is life-threatening due to the high incidence of patients with clear cell renal cell carcinoma which leads to reduced life expectancy. It is chronically debilitating due to associated conditions including angiomatosis, retinal and central nervous system haemangioblastomas, pheochromocytoma, renal cell carcinoma, pancreatic cysts, endolymphatic sac tumour, and bilateral papillary cystadenomas of the epididymis or broad ligament of the uterus.

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.

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 3-(((1S,2S,3R)-2,3-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile, for treatment of von Hippel-Lindau disease, was adopted by consensus.

2.2.20. venglustat - EMA/OD/0000035086

Genzyme Europe B.V.; Treatment of GM2 gangliosidosis

COMP Rapporteur: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing venglustat was considered justified based on non-clinical data in a valid model of the condition showing longer survival and improved motor function.

The condition is life-threatening with a reduced life expectancy of 3 to 15 years in infantile and juvenile onset patients, and chronically debilitating in adults due to ataxia, muscle weakness, loss of motor function, sight and hearing, and development of seizures and cognitive impairment.

The condition was estimated to be affecting less than 0.4 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for venglustat, for treatment of GM2 gangliosidosis, was adopted by consensus.

2.2.21. - EMA/OD/0000035180

Diagnosis of corticobasal degeneration

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 September meeting.

2.2.22. - EMA/OD/0000035212

Treatment of Graft versus Host disease

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 September meeting.

2.2.23. - EMA/OD/0000035407

Treatment of Fabry disease

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 September meeting.

2.2.24. autologous CD34+ cells transduced with a lentiviral vector encoding glucosylceramidase beta - EMA/OD/0000035408

Clinical Technology Centre (International) Limited; Treatment of Gaucher disease

COMP Rapporteur: Robert Nistico

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

The intention to treat the condition with the medicinal product containing autologous CD34+ cells transduced with a lentiviral vector encoding glucosylceramidase beta was considered justified based on non-clinical in vivo data which show an improvement of

glucocerebrosidase activity in the spleen, a reduction of the hepatosplenomegaly phenotype, and a reduction in the severity of Gaucher cell infiltration in the spleen, liver, bone marrow, and thymus;

The condition is chronically debilitating in particular due to hepatosplenomegaly, thrombocytopenia, anaemia, bone disease, as well as neurological manifestations in the neuronopathic form of the condition, and life-threatening with reduced life expectancy.

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 autologous CD34+ cells transduced with a lentiviral vector encoding glucosylceramidase beta will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical *in vivo* data that demonstrate an improvement in enzyme levels of glucocerebrosidase in spleen, liver and bone marrow after which would obviate the need for continuous treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous CD34+ cells transduced with a lentiviral vector encoding glucosylceramidase beta, for treatment of Gaucher disease, was adopted by consensus.

2.2.25. - EMA/OD/0000035563

Treatment of anal 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 September meeting.

2.2.26. autologous T cells transduced with lentiviral vector containing a tandem chimeric antigen receptor directed against CD20 and CD19 - EMA/OD/0000035570

Miltenyi Biomedicine GmbH; Treatment of diffuse large B cell lymphoma

COMP Rapporteur: Bozenna 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 autologous T-cells transduced with lentiviral vector containing a tandem chimeric antigen receptor directed against CD20 and CD19 was considered justified based on clinical data showing that complete responses may be achieved in patients with disease relapsed and refractory to the second line treatment.

The condition is chronically debilitating due to involvement of single or multiple nodal or extra nodal sites, including the gastrointestinal tract and bone marrow and life-threatening with 5-year survival rates reported as low as 26% for the high-risk patient.

The condition was estimated to be affecting approximately 4.5 in 10,000 persons in the European Union, at the time the application was made.

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

medicinal product containing autologous T-cells transduced with lentiviral vector containing a tandem chimeric antigen receptor directed against CD20 and CD19 will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients who relapsed and were refractory to the second line therapy responded to treatment with the current product. The sponsor has also provided non-clinical data suggesting that the dual recognition of CD19 and CD20 can improve the tumour control as opposed to CAR-T cell therapies with one target. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous T-cells transduced with lentiviral vector containing a tandem chimeric antigen receptor directed against CD20 and CD19, for treatment of diffuse large B cell lymphoma, was adopted by consensus.

2.2.27. human frataxin fused to TAT cell-penetrating peptide - EMA/OD/0000035595

YES Pharmaceutical Development Services GmbH; Treatment of Friedreich's ataxia

COMP Rapporteur: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing human frataxin fused to TAT cell-penetrating peptide was considered justified based on non-clinical *in vivo* data showing improvement in cardiac parameters, ataxia and gait as well as survival.

The condition is chronically debilitating and life threatening due to ataxia, progressive disability that requires the use of wheelchair, and cardiac involvement in the form of hypertrophic cardiomyopathy.

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 human frataxin fused to TAT cell-penetrating peptide, for treatment of Friedreich's ataxia, was adopted by consensus.

2.2.28. - EMA/OD/0000035618

Treatment of acute lymphoblastic leukaemia

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 September meeting.

2.2.29. infigratinib - EMA/OD/0000035662

YES Pharmaceutical Development Services GmbH; Treatment of cholangiocarcinoma

COMP Rapporteur: Brigitte Schwarzer-Daum

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

The intention to treat the condition with the medicinal product containing infigratinib was considered justified based on preliminary clinical data, demonstrating responses in heavily pre-treated patients.

The condition is life-threatening and chronically debilitating due to biliary obstruction, late diagnosis and a median survival of less than 24 months.

The condition was estimated to be affecting approximately 1.7 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 infigratinib, for treatment of cholangiocarcinoma, 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 coordinators were appointed for 23 applications submitted.

2.7. Evaluation on-going

None

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1.

Treatment of short bowel syndrome

The Committee was briefed on the significant benefit issues.

[Post-meeting note: The COMP adopted the proposed answers on the significant benefit issues by written procedure following its July meeting.]

3.1.2.

Treatment of Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase

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

3.2. Finalised letters

3.2.1.

Treatment of ß-thalassaemia intermedia and major

The finalised letter was circulated for information.

3.2.2.

Treatment of amyotrophic lateral sclerosis

The finalised letter was circulated for information.

3.3. New requests

3.3.1.

Treatment of bullous pemphigoid

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

4.1.1. Kaftrio j elexacaftor/tezacaftor/ivacaftor - EMEA/H/C/005269, EU/3/18/2116, EMA/OD/0000020155

Vertex Pharmaceuticals (Ireland) Limited; Treatment of cystic fibrosis

COMP Rapporteurs: Armando Magrelli; Eva Malikova

An opinion recommending not to remove Kaftrio, elexacaftor/tezacaftor/ivacaftor, EU/3/18/2116 from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

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

4.2.1. – emapalumab - EMEA/H/C/004386, EU/3/10/749, EMEA/OD/153/09, EMA/OD/0000009274

Novimmune B.V.; Treatment of haemophagocytic lymphohistiocytosis

The COMP adopted a list of issues that will be sent to the sponsor. The reply to the list of questions will be discussed at the September meeting.

4.2.2. – fenfluramine - EMEA/H/C/003933, EMA/OD/140/13, EU/3/13/1219, EMA/OD/0000024920

Zogenix GmbH; Treatment of Dravet syndrome

The status of the procedure at CHMP was noted.

4.2.3. – Autologous CD34+ cell enriched population that contains hematopoietic stem and progenitor cells transduced ex vivo using a lentiviral vector - EMEA/H/C/005321/0000, EMA/OD/102/06, EU/3/07/446, EMA/OD/0000023359

Accelerated assessment

Orchard Therapeutics Limited; Treatment of metachromatic leukodystrophy

The COMP adopted a list of issues that will be sent to the sponsor. The reply to the list of questions will be discussed at the September meeting.

4.2.4. Ayvakit – avapritinib - EMA/OD/037/17, EU/3/17/1889, EMA/OD/0000030630

Blueprint Medicines (Netherlands) B.V.; Treatment of gastrointestinal stromal tumours

COMP Rapporteurs: Frauke Naumann-Winter; Maria Kalland

An opinion recommending not to remove Ayvakit, avapritinib, EU/3/17/1889 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 July meeting.]

4.2.5. – amikacin - EMEA/H/C/005264, EMA/OD/191/13, EU/3/14/1259, EMA/OD/0000030955

Insmed Netherlands B.V.; Treatment of nontuberculous mycobacterial lung

The status of the procedure at CHMP was noted.

4.2.6. - valoctocogene roxaparvovec - EMEA/H/C/004749, EMA/OD/230/15, EU/3/16/1622, EMA/OD/0000024177

Accelerated assessment

BioMarin International Limited; Treatment of Haemophilia A

The status of the procedure at CHMP was noted.

4.2.7. – acalabrutinib - EMEA/H/C/005299, EMA/OD/196/15, EU/3/16/1624, EMA/OD/0000021547

AstraZeneca AB; Treatment of chronic lymphocytic leukaemia / small lymphocytic 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 September meeting.

4.2.8. Blenrep – belantamab mafodotin - EMEA/H/C/004935/0000, EMA/OD/077/17, EU/3/17/1925, EMA/OD/0000028779

Accelerated assessment

GlaxoSmithKline (Ireland) Limited; Treatment of multiple myeloma

COMP Rapporteurs: Karri Penttila; Brigitte Schwarzer-Daum

An opinion recommending not to remove Blenrep, belantamab mafodotin, EU/3/17/1925 from the EC Register of Orphan Medicinal Products was adopted by majority.

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

The divergent positions (Tim Leest and Brigitte Schwarzer-Daum*)* were appended to this opinion.

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

4.2.9. - 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/005102/0000, EMA/OD/0000013608, EU/3/19/2220, EMA/OD/0000026061

Accelerated assessment

Kite Pharma EU B.V.; Treatment of mantle cell lymphoma

The status of the procedure at CHMP was noted.

4.2.10. – tagraxofusp - EMEA/H/C/005031, EMA/OD/064/15, EU/3/15/1567, EMA/OD/0000004627

TMC Pharma (EU) Limited; Treatment of blastic plasmacytoid dendritic cell neoplasm

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 4 applications.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Kalydeco – ivacaftor - Type II variation - EMEA/H/C/002494/II/0085, EMA/OD/010/08, EU/3/08/556, EMA/OD/0000036247

Vertex Pharmaceuticals (Ireland) Limited; Treatment of cystic fibrosis

COMP rapporteurs: Armando Magrelli; Gloria Maria Palomo Carrasco; CHMP rapporteur: Maria Concepcion Prieto Yerro

An opinion recommending not to remove Kalydeco – ivacaftor (EU/3/08/556) 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 July meeting.]

5.3. Appeal

None

5.4. On-going procedures

None

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. Strategic Review & Learning Meeting – COMP, 24-25 September 2020, Germany

The COMP discussed the organisational matters of the SRLM to be host by Germany in September 2020. Further discussion is expected next month.

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 10 July 2020.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report from CHMP

Documents were tabled for information.

7.2.2. COMP-CAT Working Group

The meeting was held virtually on 13 July 2020.

7.2.3. Final proposal for fostering collaboration between CHMP and COMP

The COMP adopted a process for closer collaboration with CHMP in the evaluation of orphan medicinal products that require comparative assessments vis-à-vis existing treatments by either Committee. The procedures concerned include initial MAAs, line extensions and type II variations for orphan medicines intended for conditions for which other treatments are already available and where the application involves claims of superiority of the new medicine over the existing therapies.

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

The topic will be further discussed in the SRLM in Germany in September.

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 2020

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2020 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

8.1.1. Guideline on registry-based studies - Consultation with EMA Committees

Comments on the Draft Guideline on registry-based studies (deadline for COMP Members: 7 August 2020)

The document was tabled for information.

9. 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/

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 14-16 July 2020 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)	Italy	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No interests declared	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	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	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	
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	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Eva Malikova	Member	Slovakia	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Bruno Sepodes	Member	Expert recommended by EMA	No interests declared	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Angelo Loris Brunetta	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Virginie Hivert	Expert*	Patients' Organisation Representative	No restrictions applicable to this meeting	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in.