23 March 2023
EMA/COMP/88477/2023
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 14-16 February 2023

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

Disclaimers

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

Of note, the minutes are a working document primarily designed for COMP members and the work the Committee undertakes.

Note on access to documents

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

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

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

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced that no restriction in the involvement of meeting participants for agenda topics was identified.

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

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

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

1.2. Adoption of agenda

The agenda for 14-16 February 2023 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 17-19 January 2023 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. fosmanogepix - EMA/OD/0000083629

Pfizer Europe MA EEIG; Treatment of scedosporiosis

COMP Rapporteur: Eva Malikova

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

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potentially improved efficacy in the condition, as well as improved safety and major contribution to patient care.

The sponsor was requested to:

a) further discuss the arguments pertaining to the potentially improved efficacy versus voriconazole, by referring to in vivo studies in the sought indication,

b) detail the results of any clinical observations available to support the significant benefit assumption in the context of the current therapeutic management of patients,

c) further elaborate on the potential risks with the product and how this compares with the safety profile of currently authorised medicinal products for the same condition.

In the written response, the sponsor submitted additional justifications for significant benefit, with both indirect and direct comparisons being put forward. Importantly, the sponsor also included some newly presented preliminary clinical observations from the expanded access program, reporting some responses, in patients who had failed voriconazole therapy or could no longer be treated with voriconazole. Overall, the COMP accepted that a clinically relevant advantage of improved efficacy can be assumed, based on non-clinical data in an in vivo model of the condition, and preliminary clinical observations in patients who had previously failed voriconazole and responded to treatment with the product. The planned oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing fosmanogepix was considered justified based on improved survival and reduced fungal burden in a non-clinical in vivo model of the condition, as well as preliminary clinical observations in patients who responded to treatment with the product.

The condition is life-threatening due to disseminated infection and chronically debilitating due to skin and soft tissue infections that can lead to osteomyelitis, endocarditis, and meningitis.

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.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing fosmanogepix will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data with improved survival compared to amphotericin in an in vivo model of the condition, and preliminary clinical observations in patients who had previously failed voriconazole and responded to treatment with the product. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.2. - EMA/OD/0000116158

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

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 for the purposes of orphan medicinal product designation the condition should be revised to ''Niemann-Pick disease''. The sponsor was requested to further elaborate on whether the product could be used in other forms than Niemann-Pick C disease.

- 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 sponsor was asked to re-calculate the prevalence for the Niemann-Pick disease (including all forms) considering the changes in the condition.

- Significant benefit

The sponsor was requested to further discuss any claim of significant benefit and to substantiate such claims with any indirect comparisons (based on non-clinical and/or clinical data) of the proposed product versus the authorised product.

Furthermore, the sponsor was requested to present more information on the ongoing planned clinical development of the product, and in particular whether development in forms of Niemann-Pick disease other than type C is envisioned.

In the written response, and during an oral explanation before the Committee on 14 February 2023, the sponsor acknowledged the COMP's consideration regarding the condition and agreed with the overarching condition wording "Niemann-Pick disease" for the orphan medicinal product designation.

In addition, following the COMP's request the sponsor re-calculated the prevalence to include Niemann Pick disease (NPD) forms A or B, the sponsor presented an updated prevalence calculation and estimate. The COMP considered that the sponsor's calculation is very conservative, and that the prevalence should be retained to 0.1 per 10.000 persons in line with recent applications.

The sponsor claimed the significant benefit based on the equal efficacy and improved safety compared to miglustat based on indirect comparisons. The claim on equal efficacy was based on pharmacodynamic analysis and the levels of glucosylceramide (GlcCer), lactosylceramide (LacCer) and monosialodihexosylgangliosides (GM3) plasma concentrations. The sponsor argued that since the proposed product is an L-idose azasugar, not inhibiting intestinal disaccharidases it is expected to cause much less frequent and severe GI toxicities compared to miglustat, and that this represents a major clinical advantage since GI related adverse events have been reported being the most common reason for miglustat discontinuation. Absence of GI toxicity with the proposed product, which is supported by the Phase 1 data generated to date, may represent an important improvement of quality of life, allowing patients to be treated for longer periods, according to the sponsor.

The COMP considered that the data provided to support the significant benefit are not considered sufficient since they show only similar efficacy in comparison to miglustat for the pharmacodynamic biomarkers. In addition, the data provided for the proposed product was compared to placebo in healthy volunteers while the data on miglusat were in patients with NPD. Furthermore, the COMP consider that is too early in the development to draw any conclusion on the safety due to the limited dataset.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 February 2023, prior to final opinion.

2.1.3. - EMA/OD/0000114452

Treatment of GM1 gangliosidosis

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 the currently presented data insufficient to support medical plausibility of the proposed product for the treatment of GM1 gangliosidosis. The sponsor was therefore asked to better support their claim with any non-clinical data in the condition applied for.

- Number of people affected

The sponsor was asked to provide a calculation and final estimate of complete prevalence in the proposed condition of GM1 gangliosidosis.

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

In the written response, and during an oral explanation before the Committee on 14 February 2023, the sponsor highlighted the rarity of the condition applied for and unmet need, as there is no approved treatment for GM1 gangliosidosis to date. The sponsor pointed out that the development plan for the proposed product was primarily focused on three indications (GM2 gangliosidosis, Gaucher disease and Fabry disease), and that non-clinical data are based on non-clinical in vivo models of these conditions are also valid to derive efficacy conclusions in GM1 gangliosidosis.

COMP acknowledged the biologic rationale with the commonalities of the affected glycosphingolipid pathway, the pathophysiology of various lysosomal storage diseases in terms of clinical manifestation and burden of disease and the totality of the available data.

However, the extrapolation of efficacy between the different lysosomal storage diseases and/or from one glucosylceramide synthase inhibitor to another was not considered established. Therefore, the remaining uncertainty over relevant effects of the proposed product in GM1 gangliosidosis was considered too high to allow a positive conclusion on this application.

Furthermore, COMP noted that the prevalence question was not adequately addressed.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 February 2023, prior to final opinion.

2.1.4. - EMA/OD/0000114581

Treatment of galactosialidosis

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

COMP considered the currently presented data insufficient to support medical plausibility of the proposed product for the treatment of galactosialidosis. The sponsor was therefore requested to better support their claim with any non-clinical data in the condition applied for.

- Number of people affected

The sponsor was asked to provide a calculation and final estimate of complete prevalence in the proposed condition of galactosialidosis.

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

In the written response, and during an oral explanation before the Committee on 14 February 2023, the sponsor highlighted the rarity of the condition applied for and unmet need, as there is no approved treatment for galactosialidosis to date. The sponsor pointed out that the development plan for the proposed product was primarily focused on three indications (GM2 gangliosidosis, Gaucher disease and Fabry disease), and that non-clinical data are based on in vivo models of these conditions were also valid to derive efficacy conclusions in galactosialidosis.

COMP acknowledged the biologic rationale with the commonalities of the affected glycosphingolipid pathway, the pathophysiology of various lysosomal storage diseases in terms of clinical manifestation and burden of disease and the totality of the available data.

However, the extrapolation of efficacy between the different lysosomal storage diseases and/or from one glucosylceramide synthase inhibitor to another was not considered established. Therefore, the remaining uncertainty over relevant effects of the proposed product in galactosialidosis was considered too high to allow a positive conclusion on this application.

Furthermore, the COMP noted that the prevalence question was not adequately addressed.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 February 2023, prior to final opinion.

2.1.5. - EMA/OD/0000114584

Treatment of sialidosis

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

COMP considered the currently presented data insufficient to support medical plausibility of the proposed product for the treatment of sialidosis. The sponsor was therefore invited to better support their claim with non-clinical data in the condition applied for.

- Number of people affected

The sponsor was asked to provide a calculation and final estimate of complete prevalence in the proposed condition of sialidosis.

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

In the written response, and during an oral explanation before the Committee on 14 February 2023, the sponsor highlighted the rarity of the condition applied for and unmet need, as there is no approved treatment for sialidosis to date. The sponsor pointed out that the development plan for the proposed product was primarily focused on three indications (GM2 gangliosidosis, Gaucher disease and Fabry disease), and that non-clinical data are based on in vivo models of these conditions are also valid to derive efficacy conclusions in sialidosis.

COMP acknowledged the biologic rationale with the commonalities of the affected glycosphingolipid pathway, the pathophysiology of various lysosomal storage diseases in terms of clinical manifestation and burden of disease and the totality of the available data.

However, the extrapolation of efficacy between the different lysosomal storage diseases and/or from one glucosylceramide synthase inhibitor to another was not considered established. Therefore, the remaining uncertainty over relevant effects of the proposed product in sialidosis was considered too high to allow a positive conclusion on this application.

Furthermore, the COMP noted that the prevalence question was not adequately addressed.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 February 2023, prior to final opinion.

2.1.6. - EMA/OD/0000105112

Treatment of osteogenesis imperfecta

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 31 January 2023, prior to responding to the list of issues.

2.1.7. - EMA/OD/0000114282

Treatment of *RPE65* retinopathies

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

RPE65 retinopathies should be changed to inherited retinal dystrophies due to *RPE65* gene dysfunction.

- Significant benefit

The arguments on significant benefit were based on an alternative serotype adeno-associated viral vector which is believed to offer the potential of 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 comparative non-clinical in vivo studies to justify the assumption of significant benefit over Luxturna for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 15 February 2023, the sponsor provided a written response to the questions raised by the COMP as well as present an oral explanation. The COMP was satisfied with the response obtained from for the first question regarding the name change of the condition to inherited retinal dystrophies due to *RPE65* gene dysfunction.

The COMP agreed with the sponsor that the construct of Luxturna and the sponsor's product were similar. A discussion followed with sponsor regarding the claim of better safety and efficacy to Luxturna as the basis of significant benefit. No new data in patients was provided by the sponsor to support the potentially better safety of their product. The COMP was not convinced that a lower dose of the sponsor's product due to the difference in serotype was sufficient to support safety as there is no evidence of safety concerns with Luxturna. The COMP agreed that the SmPC for Luxturna currently does prescribe corticosteroid tapering prior and post treatment to manage potential inflammatory/immunogenic events, the absence of which may potentially be seen as a benefit. It remains a question however to what degree such a benefit could be considered as a compelling safety argument given the extensive clinical knowledge on management of ocular corticosteroid management.

The sponsor's justification for better efficacy due to the difference in serotype were based on better uptake noted in the outer nuclear layer of photoreceptors and improvement in electroretinography. The COMP questioned the validity of the findings indicating that inconsistencies appeared in the dose ranging which the sponsor could not adequately explain.

The COMP discussed the response and felt that the data provided were insufficient to establish a clinically relevant advantage regarding efficacy to Luxturna.

The COMP was therefore of the opinion that they could not recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 February 2023, prior to final opinion.

2.1.8. - EMA/OD/0000112018

Treatment of spinal muscular atrophy

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 30 January 2023, prior to responding to the list of issues.

2.1.9. - EMA/OD/0000114439

Treatment of primary sclerosing cholangitis (PSC)

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

- Significant benefit

The arguments on significant benefit were based on an alternative mechanism of action and the potential improved 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 two non-clinical in vivo studies, with particular focus on efficacy, over authorised medicinal products for the proposed orphan condition.

It is well known that extrapolation from nonclinical or early clinical studies cannot fully predict the safety of a product in its clinical setting, thus other relevant data is required to justify safety arguments in most cases.

In the written response, and during an oral explanation before the Committee on 15 February 2023, the sponsor did not provide any new information. The claim of better safety over the authorised product was based primarily on the non-clinical model showing a greater chance of having a bile infarct after use of it than with the sponsor's product. During the oral explanation the COMP challenged the sponsor regarding the dose of the authorised product used in the study which did not correspond to those normally given in the clinical setting. The sponsor acknowledged that it was a 50-fold higher dose and that it was possible that this would not reflect what would happen in a clinical setting. The lack of data in an adequate number of patients with the sponsor's product made it difficult to establish the real benefit.

The COMP concluded that they could not recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 February 2023, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000093062

Treatment of spinal cord injury

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 March meeting.

2.2.2. - EMA/OD/0000104687

Treatment of mucopolysaccharidosis type II (Hunter syndrome)

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

2.2.3. guanabenz acetate - EMA/OD/0000105611

Amsterdam UMC; Treatment of vanishing white matter disease

COMP Rapporteur: Zsofia Gyulai

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of vanishing white matter disease.

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

The intention to treat the condition with the medicinal product containing guanabenz acetate was considered justified based on non-clinical in vivo data in a valid model of the condition which showed improvement of motor function.

The condition is chronically debilitating due to loss of ambulation, cognitive impairment, spasticity, ataxia, seizures and speech problems and life-threatening due to infections and respiratory failure.

The condition was estimated to be affecting no more than 0.1 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for guanabenz acetate, for treatment of vanishing white matter disease, was adopted by consensus.

2.2.4. - EMA/OD/0000112208

Treatment of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

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 March meeting.

[Post-meeting note: The sponsor withdrew the application for orphan designation on 3 March 2023].

2.2.5. - EMA/OD/0000115658

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 March meeting.

2.2.6. 6-(4-(1-amino-3-hydroxycyclobutyl)phenyl)-1-ethyl-7-phenyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one, L-tartrate salt - EMA/OD/0000115720

FGK Representative Service GmbH; Treatment of hereditary haemorrhagic telangiectasia

COMP Rapporteur: Joao Rocha

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

The intention to treat the condition with the medicinal product containing 6-(4-(1-amino-3-hydroxycyclobutyl)phenyl)-1-ethyl-7-phenyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one, L-tartrate salt was considered justified based on non-clinical data in an in vivo model of the condition where treatment with the product inhibited the formation of arteriovenous structures in the retina.

The condition is life-threatening and chronically debilitating due to recurrent bleeding from nasal, cutaneous, or gastrointestinal telangiectasias as well arteriovenous malformations affecting the pulmonary, hepatic, and/or cerebral circulations.

The condition was estimated to be affecting approximately 1.6 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 6-(4-(1-amino-3-hydroxycyclobutyl)phenyl)-1-ethyl-7-phenyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one, L-tartrate salt, for treatment of hereditary haemorrhagic telangiectasia, was adopted by consensus.

2.2.7. bezuclastinib - EMA/OD/0000116218

FGK Representative Service GmbH; Treatment of gastrointestinal stromal tumours

COMP Rapporteur: Enrico Costa

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

The intention to treat the condition with the medicinal product containing bezuclastinib was considered justified based on clinical data showing clinically relevant responses in pre-treated patients in addition to the standard of care.

The condition is chronically debilitating and life-threatening in particular due to the high rate of relapse and development of metastatic disease resulting in a poor survival.

The condition was estimated to be affecting less than 3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing bezuclastinib will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that when the product is used in addition to sunitinib in patients who are refractory to at least 3 previous lines of treatment prolonged disease stabilisation or responses can be achieved. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for bezuclastinib, for treatment of gastrointestinal stromal tumours, was adopted by consensus.

2.2.8. - EMA/OD/0000117508

Treatment of berylliosis (chronic beryllium 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 March meeting.

2.2.9. - EMA/OD/0000118779

Treatment of amyotrophic lateral 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 March meeting.

[Post-meeting note: The sponsor withdrew the application for orphan designation on 3 March 2023].

2.2.10. fenfluramine hydrochloride - EMA/OD/0000119068

Zogenix ROI Limited; Treatment of CDKL5 deficiency disorder

COMP Rapporteur: Giuseppe Capovilla

The Committee agreed that the condition, CDKL5 deficiency disorder, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing fenfluramine hydrochloride was considered justified based on preliminary clinical data showing a reduction in tonic and tonic-clonic seizures in patients with the condition.

The condition is life-threatening and chronically debilitating due to early-onset pharmaco-resistant seizures, global developmental delay, abnormal muscle tone and hand stereotypies. A reduction of life expectancy is mainly due to respiratory problems.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing fenfluramine hydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a reduction in tonic and tonic-clonic seizures in patients who have been treated with and were resistant to several prior lines of anti-seizure medications. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for fenfluramine hydrochloride, for treatment of CDKL5 deficiency disorder, was adopted by consensus.

2.2.11. indole-3-carboxaldehyde - EMA/OD/0000120211

Adienne S.r.l.; Treatment of primary CTLA-4 checkpoint related immunodeficiencies

COMP Rapporteur: Elisabeth Johanne Rook

The Committee agreed that the condition, primary CTLA-4 checkpoint related immunodeficiencies, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing Indole-3-carboxaldehyde was considered justified based on non-clinical in vivo data from a valid model of the condition which showed that the product decreased inflammatory enteropathy, prevented body weight loss, and improved colitis symptoms.

The condition is chronically debilitating and life-threatening due to immune dysregulation, autoimmune disorders (arthritis), enteropathy, hypo-gammaglobulinemia, thrombocytopenia or neutropenia, and recurrent respiratory infections.

The condition was estimated to be affecting less than 0.01 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for indole-3-carboxaldehyde, for treatment of primary CTLA-4 checkpoint related immunodeficiencies, was adopted by consensus.

2.2.12. 5,5-dimethyl-3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrimidin-5-yl]imidazolidine-2,4-dione - EMA/OD/0000120404

Quality Regulatory Clinical Ireland Limited; Treatment of fragile X syndrome

COMP Rapporteur: Robert Nistico

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 5,5-dimethyl-3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrimidin-5-yl]imidazolidine-2,4-dione was considered justified based on non-clinical in vivo data in a valid model of the condition, showing improvement on behavioural and cognitive parameters, as compared to the control group.

The condition is chronically debilitating due to developmental delay as well as a range of behavioural and cognitive deficits.

The condition was estimated to be affecting approximately 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 5,5-dimethyl-3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrimidin-5-yl]imidazolidine-2,4-dione, for treatment of fragile X syndrome, was adopted by consensus.

2.2.13. adeno-associated viral vector serotype 1 containing the 3' portion of human *OTOF* gene, adeno-associated viral vector serotype 1 containing the 5' portion of human *OTOF* gene - EMA/OD/0000120634

Boyd Consultants Limited; Treatment of otoferlin gene (hOTOF)-mediated hearing loss

COMP Rapporteur: Ingeborg Barisic

The Committee agreed that the condition, otoferlin gene-mediated hearing loss, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 1 containing the 3' portion of human OTOF gene, adeno-associated viral vector serotype 1 containing the 5' portion of human OTOF gene was considered justified based on data generated in a non-clinical in vivo model of the condition which showed partial restoration of the auditory function.

The condition is chronically debilitating due to permanent severe-to-profound hearing loss or deafness.

The condition was estimated to be affecting approximately 0.7 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 adeno-associated viral vector serotype 1 containing the 3' portion of human *OTOF* gene, adeno-associated viral vector serotype 1 containing the 5' portion of human *OTOF* gene, for treatment of otoferlin gene-mediated hearing loss, was adopted by consensus.

2.2.14. anagrelide hydrochloride monohydrate - EMA/OD/0000109485

Sartar Therapeutics Ltd.; Treatment of gastrointestinal stromal tumours

COMP Rapporteur: Dinko Vitezic

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

The intention to treat the condition with the medicinal product containing anagrelide hydrochloride monohydrate was considered justified based on non-clinical data showing reduction in tumour volume.

The condition is chronically debilitating and life-threatening in particular due to the high rate of relapse and development of metastatic disease resulting in a poor survival.

The condition was estimated to be affecting less than 3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing anagrelide hydrochloride monohydrate will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that reported additive effects when the product is combined with existing treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for anagrelide hydrochloride monohydrate, for treatment of gastrointestinal stromal tumours, 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 18 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 9 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of multiple myeloma

The Committee was briefed on the significant benefit issues in preparation of the March meeting.

3.1.2. -

Treatment of graft-versus-host disease

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

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

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

None

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

4.2.1. – pegunigalsidase alfa - EMEA/H/C/005618, EU/3/17/1953, EMA/OD/0000109504

Chiesi Farmaceutici S.p.A.; 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 March meeting.

4.2.2. Tibsovo – ivosidenib - EMEA/H/C/005936

Les Laboratoires Servier

COMP Rapporteur: Frauke Naumann-Winter; COMP Co-Rapporteur: Maria Elisabeth Kalland

a) Treatment of biliary tract cancer, EU/3/18/1994, EMA/OD/0000115500

An opinion recommending not to remove Tibsovo, ivosidenib, EU/3/18/1994 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 February meeting.]

b) Treatment of acute myeloid leukaemia, EU/3/16/1802, EMA/OD/0000115491

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 March meeting.

4.2.3. – ivosidenib - EMEA/H/C/006174, EU/3/16/1802, EMA/OD/0000117514

Les Laboratoires Servier; Treatment of acute myeloid 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 March meeting.

4.2.4. HYFTOR – sirolimus - EMEA/H/C/005896/0000, EU/3/17/1910, EMA/OD/0000108887

Plusultra pharma GmbH; Treatment of tuberous sclerosis

COMP Rapporteur: Joao Rocha; COMP Co-Rapporteur: Elisabeth Johanne Rook

An opinion recommending not to remove HYFTOR, sirolimus, EU/3/17/1910 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 February meeting.]

4.2.5. – sodium phenylbutyrate/ ursodoxicoltaurine - EMEA/H/C/005901, EU/3/20/2284, EMA/OD/0000096503

Amylyx Pharmaceuticals EMEA; Treatment of amyotrophic lateral sclerosis

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 3 applications.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. AYVAKYT - avapritinib- EMEA/H/C/005208/II/0023, EU/3/18/2074, EMA/OD/0000127063

Blueprint Medicines; Treatment of mastocytosis

CHMP Rapporteur: Blanca Garcia-Ochoa

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

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for 1 application.

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP membership

None

7.1.2. Vote by proxy

None

7.1.3. Strategic Review & Learning meetings

None

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 10 February 2023.

7.1.5. COMP Decisions Database

The COMP acknowledged the importance of adding further topics to the database.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report

Documents were tabled for information

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

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

Documents were tabled for information

7.3.2. Upcoming ITF meetings

The COMP noted the upcoming ITF meetings.

The Overview of ITF activities during 2022 will be presented at the next meeting.

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

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

None

7.7. COMP work plan

None

7.8. Planning and reporting

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

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2023 were circulated.

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

8.1. Update on EMA sponsored RWE study for SMA

EMA provided feedback on the EMA-funded study on spinal muscular atrophy (SMA). The procedural steps and the study plan were presented. COMP will be kept informed of the progress and outcome of the study.

8.2. Revision of the PAWG COMP answer template and Orphan Designation: Preparation for the COMP discussion

The PAWG COMP answer template was agreed and finalised.

The organisational aspects of the COMP plenary presentations on orphan designations were discussed. There was a proposal made on how the discussions and presentations should be made at the plenaries so that they are most time efficient and clear.

8.3. European Specialised Expert Community (ESEC)

EMA presented the activities of the Oncology ESEC. Oncology expert can still be nominated for the Oncology ESEC: an e-mail with the experts' names and a brief description of their expertise should be sent to EMA.

Recently, a cardiovascular ESEC has been created: nominations of experts can also be sent to EMA.

8.4. Real World Evidence update, including DARWIN EU®

COMP noted the quarterly update of DARWIN EU® and RWE report. Furthermore, there was information provided on the progress and finalisation of year 1 studies, the prioritisation and selection of studies and data partners for year 2.

The EMA presented the summary of the findings of the study 'DARWIN EU – Prevalence of rare blood cancers in Europe' (EUPAS50800). This disease epidemiology study explored the contribution of real-world data to estimate prevalence of rare haematological malignancies in largely primary care databases from five European countries. The COMP noted the outcome and discussed the limitations of these results. Therefore, the committee is currently reserved with regards to the applicability of these results for the specific purposes of the orphan designation.

8.5. Committee representatives at SAWP: re-nomination

The following members were appointed:

As COMP SAWP members: Brigitte Schwarzer-Daum and Karri Penttila

As COMP SAWP alternate member: Robert Nistico

8.6. Outcome measures in Epidermolysis Bullosa

COMP noted the information on the project on outcome measures in epidermolysis bullosa. The aim of the project is to choose adequate outcome measures in new intervention studies. There will be kick-of meeting organised on the 12th April 2023. COMP members interested to take part in the kick-off meeting should contact EMA

8.7. Committees meetings dates 2025-2026

COMP noted the meetings dates.

9. List of participants

including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 14-16 February 2023 meeting.

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Chair	Netherlands	No interests declared	
Armando Magrelli	Vice-Chair	Expert recommended by EMA	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No restrictions applicable to this meeting	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Elli Loizidou	Member	Cyprus	No interests declared	
Jana Mazelova	Member	Czechia	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Cecile Dop	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Zsofia Gyulai	Member	Hungary	No interests declared	
Enrico Costa	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No restrictions applicable to this meeting	
Ruta Mameniskiene	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No restrictions applicable to this meeting	
Elisabeth Johanne Rook	Member	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Joao Rocha	Member	Portugal	No restrictions applicable to this meeting	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Ines Alves	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Maria Cavaller Bellaubi	Expert - via WebEx	Patients' Organisation Representative	No restrictions applicable to this meeting	
Meeting run with support from relevant EMA staff				

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

10. Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission

OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

Orphan Designation *(section 2 Applications for orphan medicinal product designation)*

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures (including protocol assistance), national incentives for research and development, 10-year market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.

Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

Protocol Assistance *(section 3 Requests for protocol assistance with significant benefit question)*

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Maintenance of Orphan Designation *(section 4 Review of orphan designation for orphan medicinal products for marketing authorisation).*

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/