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Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 10-12 May 2022

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

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

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced 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.

1.2. Adoption of agenda

COMP agenda for 10-12 May 2022 was adopted with no amendments.

1.3. Adoption of the minutes

COMP minutes for 11-13 April 2022 were adopted with amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. 3-(1-(2',3'-dimethoxy-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-4-yl)benzoic acid - EMA/OD/0000077417

ChemICare S.R.L.; Treatment of gain-of-function mutations of STIM1 and ORAI1 related diseases

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:

- Condition

The sponsor was asked to justify that the three different diseases (tubular aggregate myopathy (TAM), Stormorken syndrome (STRMK), York platelet syndrome (YPS)) could be seen as one condition due to similar underlying mutations and a common pathophysiological mechanism, and despite a broad spectrum of phenotypic expression. The sponsor was requested to discuss an appropriate overarching wording of the condition that encompasses all three diseases.

In the written responses and during the oral explanation before the Committee on 10th May, the sponsor clarified that their preferred revised condition wording is "diseases related to gain-of-function mutations of STIM1 and ORAI1". This wording is motivated by the following considerations:

Gain-of-functions mutations on STIM1 or ORAI1 show a broad range of clinical phenotypes, that may see a predominance of platelet dysfunction or of muscle weakness, or may see both components present to the same extent. When mutations/phenotype correlations have been attempted, there was no definite trend on the penetrance of the symptoms. For this reason, the resulting disorders have been described inadvertently throughout the medical literature as three distinct diseases where:

- tubular aggregate myopathy primarily affects skeletal muscles;
- Stormorken syndrome shows a more complex clinical phenotype that includes also mild bleeding tendency due to platelet dysfunction, thrombocytopenia and anaemia;
- York platelet syndrome is a form of thrombocytopenia associated with STRMK syndrome with a clinical phenotype that includes a greater tendency to bleeding and coagulation defects. Yet, also for this latter syndrome, it has now been shown that muscle weakness is present.

Despite the different phenotypic expressions, the three diseases can be seen as one single condition as they share:

a) Similar underlying mutations in the proteins responsible for SOCE (Store-operated Ca2+-entry), a cellular event that regulates Ca2+ homeostasis in several cell types. TAM, STRMK and YPS are all ascribed to STIM1 and ORAI1 gain-of-function autosomal dominant mutations. At present, thirty-one STIM1 and ORAI1 gain-of-function mutations have been described (25 on STIM1 and 6 on ORAI1) and the majority of them have been diagnosed in both TAM and STRMK patients. Furthermore, the p.I115F, p.R04W/Q and K365N STIM1 have been also reported in patients affected by YPS.

b) A common pathophysiological mechanism that consists in the over-activation of SOCE and in the subsequent Ca2+ overload, as demonstrated in cells derived from patients affected by the three diseases. This functional evidence has demonstrated a link between SOCE overactivation induced by STIM1 and ORAI1 gain-of-function mutations and the phenotypic expressions characterizing TAM, STRMK and YPS (Harris et al. 2017, Garibaldi et al. 2016).

Based on the considerations above, the COMP agreed that the following could be accepted as a valid orphan condition: "treatment of gain-of-function mutations of STIM1 and ORAI1 related diseases". This encompasses the clinical phenotypes of tubular aggregate myopathy, Stormorken syndrome and York platelet syndrome.

The Committee agreed that the condition, gain-of-function mutations of STIM1 and ORAI1 related diseases, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 3-(1-(2',3'-dimethoxy-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-4-yl)benzoic acid was considered justified based on non-clinical in vivo data in a valid disease model suggesting improvements in platelet count and muscle function.
The condition is chronically debilitating due to progressive muscle weakness possibly necessitating walking aids or wheelchairs and thrombocytopenia leading to bleeding disorders. Furthermore, cardiovascular problems, sensorineural hearing loss, hypothyroidism and intellectual disabilities have been described in patients with the condition.
The condition was estimated to be affecting approximately 0.02 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-(1-(2',3'-dimethoxy-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-4-yl)benzoic acid, for treatment of gain-of-function mutations of STIM1 and ORAI1 related diseases, was adopted by consensus.

2.1.2. sodium (4Z,7Z,10R,11E,13E,15Z,17S,19Z)10,17-dihydroxy-docosa-4,7,11,13,15,19-hexaenoate - EMA/OD/0000080709

Granzer Regulatory Consulting & Services GmbH; Prevention of retinopathy of prematurity (ROP)

COMP Rapporteur: Tim Leest

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

- 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 non-clinical results and the extrapolation possibility given the divergence between the intraperitoneal (IP) injection mode of administration used in the non-clinical setting, and the proposed topical administration via eye drop instillation.
- the interpretation of the pharmacokinetic results and their relevance for the development of the product in the condition, especially regarding the claimed half-maximal effective concentration (EC_{50}) value (e.g. how it was derived, how it relates to the aforementioned extrapolation, how the limit represented in the figure was selected).
- the rationale behind the concentration of choice used in the pharmacokinetic studies via eye drop instillation (0.1%), and how this choice should be interpreted in context of moving towards the administration in humans.

As part of the written response, the sponsor provided a clarification on the rationale behind the non-clinical setting, and elaborated on the standing challenge when developing non-clinical studies for treatment and/or prevention of eye conditions in an early post-natal setting. To clarify the available data, a relevant reference was introduced supporting the translation possibility between the available results and the sponsors' proposal. In this

additional study, treatment with the proposed product resulted on a reduction in neovascularization when administered once daily for 7 days followed through day 15 post laser-induction. While acknowledging the interpretability limitations, the COMP considered this data could be supportive for the use of the proposed product in the condition, as the neovascularisation process is one of the main features of ROP.

With regards to the interpretation of the pharmacokinetic studies, the sponsor provided a rationale for the use of the EC_{50} value, which is based on conservative literature findings from three in vitro cell-line studies including known mediators in vascularization processes (e.g., COX2, TNF alpha). In addition, the sponsor discussed the product concentration of choice (0.1%), noting that this dosing level is commonly used in eye drop research. Moreover, it is clarified that this decision is also based on past experience on topical delivery in the same model with other drug candidates from the same class of compounds. It is stated that given the relatively long exposure above the EC_{50} cut-off, the concentration used could give appropriate guidance for toxicological experiments as a "mid-point" dose to be bracketed by lower and higher doses.

In conclusion, while the sponsor's clarifications are not considered to address all uncertainties over the route of administration and pharmacokinetic studies, a positive conclusion could be drawn.

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

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

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

The intention to prevent the condition with the medicinal product containing sodium (4Z,7Z,10R,11E,13E,15Z,17S,19Z)10,17-dihydroxy-docosa-4,7,11,13,15,19-hexaenoate was considered justified based on non-clinical data showing a dual beneficial effect in neovascularization and vaso-obliteration following oxygen-induced-retinopathy.

The condition is chronically debilitating due to potential visual loss that may progress to blindness in the most severe cases.

The population of patients eligible for prevention of the condition was estimated to be approximately 1.3 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 prevention in the European Union for the population at risk of developing the condition.

A positive opinion for sodium (4Z,7Z,10R,11E,13E,15Z,17S,19Z)10,17-dihydroxy-docosa-4,7,11,13,15,19-hexaenoate, for prevention of retinopathy of prematurity, was adopted by consensus.

2.1.3. ropeginterferon alfa-2b - EMA/OD/0000077171

Aop Orphan Pharmaceuticals GmbH; Treatment of chronic myeloid leukemia (CML)

COMP Rapporteur: Karri Penttila

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

- 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 provide adequate justification of a clinically relevant advantage of the proposed product over all authorised tyrosine kinase inhibitors (TKIs) based on adequate, comparative data.

In the written response, the sponsor argued that the there is evidence that mechanisms of molecular remission induction and maintenance differ significantly between tyrosine kinase inhibitors (TKI)- and interferon (IFN)-induced remissions and temporary ropeginterferon alfa-2b maintenance therapy would complement TKIs in promoting treatment-free remission (TFR), ultimately improving the quality of life of patients, with the possibility of curing the disease. The use of INFs during or after TKI treatment is associated with longer and significantly deeper molecular response, which is a prerequisite of treatment discontinuation and TFR. Ropeginterferon alfa-2b maintenance therapy would improve the depth and durability of molecular response, providing a treatment that avoids TKI toxicity by allowing TKI and IFN discontinuation with a durable TFR in 70% of the patients treated, which has not been achieved with any TKI monotherapy so far. Thus, the significant benefit derived from ropeginterferon alfa-2b combination therapy is an expected 20% increase in the number of patients cured of CML. With the ongoing trial that studies the efficacy and safety of ropeginterferon alpha-2b in promoting TFR in CML patients, the applicant intends to gather the clinical evidence required for marketing authorisation approval in the indication of is preventing molecular relapse in CML patients, who discontinue TKI therapy in deep molecular remission.

The COMP considered the data that the sponsor has provided from several sources and different treatment scenarios seem to suggest that interferon treatment could offer a bridge to TFR and could be of benefit to numerous CML patients. Therefore, the COMP concluded that the significant benefit can be justified at the stage of the orphan designation and the oral explanation was cancelled

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

The intention to treat the condition with the medicinal product containing ropeginterferon alfa-2b was considered justified based on bibliographic data demonstrating antileukaemic effect in patients affected by the condition.
The condition is life threatening and chronically debilitating due to the consequences of the bone marrow dysfunction, intracranial or gastro-intestinal haemorrhagic episodes and the risk of severe infections.
The condition was estimated to be affecting less than 2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ropeginterferon alfa-2b will be of significant benefit to those affected by the condition. The sponsor has provided bibliographic data demonstrating that the proposed product can complement the approved authorised tyrosine kinase inhibitors in

promoting treatment-free remission, in patients affected by the condition. The Committee considered that this constitutes a clinically relevant advantage.
A positive opinion for ropeginterferon alfa-2b, for treatment of chronic myeloid leukaemia, was adopted by consensus.

2.1.4. doxorubicin - EMA/OD/0000076247

Thermosome GmbH; Treatment of soft tissue sarcoma (STS)

COMP Rapporteur: Brigitte Schwarzer-Daum

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

- Intention to diagnose, prevent or treat

Non-clinical model: the sponsor was asked to clarify whether 1) tumour growth and survival data is also available from concomitant authorised doxorubicin comparators, or from a vehicle control, together with the focused hyperthermia (HT) method (adjustable light source) and 2) whether the efficacy data with DPPG3-based thermosensitive liposome (DPPG3-TSL) can be extrapolated to DPPG2-based thermosensitive liposome (DPPG2-TSL). The sponsor was requested to clarify why the positive effects in metabolic and histopathologic response were not translating into better radiographic response effects (RECIST). In addition, the sponsor was asked to comment on the relevance of the metabolic response in the absence of radiographic response.

- Significant benefit

The sponsor was asked to discuss significant benefit of doxorubicin-loaded, DPPG2-based thermosensitive liposome (DPPG2-TSL-DOX) versus all authorised treatment options for the condition applied for.
The sponsor presented their responses to the COMP's list of questions in writing. The COMP considered that medical plausibility has been established primarily by the newly submitted comparative data in a valid non-clinical in vivo model of the applied for condition which demonstrated superior activity/efficacy of DPPG2-TSL-DOX vs vehicle and non-liposomal doxorubicin controls (all in combination with hyperthermia) on tumour growth and survival.

The COMP considered that medical plausibility has been established primarily by the newly submitted comparative data in a valid non-clinical in vivo model of the applied for condition which demonstrated superior activity/efficacy of DPPG2-TSL-DOX vs vehicle and non-liposomal doxorubicin controls (all in combination with hyperthermia) on tumour growth and survival.

It was considered that significant benefit had been established considering the following:

a) Doxorubicin is one of the most essential agents of (neoadjuvant) chemotherapy regimens in the intended target populations of patients with locally advanced high-risk STS and in patients with non-resectable STS.

b) Hyperthermia (HT) has been shown to improve response and survival parameters if combined with doxorubicin-based chemotherapy.

c) The applied for product DPPG2-DOX-TSL is expected to enhance the antitumor effect as compared to current standard of care therapy, as it is always used in combination with HT. The superior efficacy of DPPG2-TSL-DOX vs non-liposomal doxorubicin (both in

combination with HT) on tumour growth and survival has been demonstrated in a valid non-clinical model of the applied for condition.

The answers were considered sufficient and oral explanation was therefore cancelled.

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

The intention to treat the condition with the medicinal product containing doxorubicin was considered justified based on non-clinical data in a valid disease model showing tumour growth inhibition and prolonged survival.

The condition is chronically debilitating due the possible need for amputation of limbs and life-threatening with a high recurrence and metastasis rate with reduced life expectancy.

The condition was estimated to be affecting approximately 4.7 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 doxorubicin will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a relevant disease model showing better tumour growth inhibition and prolonged survival as compared to authorized non-liposomal doxorubicin, which is an essential agent in soft tissue sarcoma chemotherapy regimens. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for doxorubicin, for treatment of soft tissue sarcoma, was adopted by consensus.

2.1.5. - EMA/OD/0000080466

Prevention of risk of graft failure following allogenic hematopoietic stem cell transplantation

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 27 April 2022, prior to responding to the list of issues.

2.1.6. - EMA/OD/0000080468

Treatment of chromosome 15q11.2-13.1 duplication syndrome (dup15q)

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 chromosome 15q11.2-13.1 duplication syndrome (dup15q) the sponsor should further elaborate on:

- the relevance of the non-clinical models to show the efficacy of the proposed product in the treatment of chromosome 15q11.2-13.1 duplication syndrome (dup15q), and the interpretation of the results obtained in the experiments,
- the methodology used in the non-clinical studies (details of the seizure measurements and how these were done) as well as the results from these studies

and its relevance for the development of the product in the specific condition (dup15q),

- any preliminary clinical data which could support the efficacy in patients with dup15q.

- Number of people affected

The COMP considered that the proposed prevalence may be an overestimate and the actual value could be much lower. The sponsor was therefore asked to provide a revised estimate which could reflect a more current understanding of the incidence of the condition. For the estimation and presentation of the prevalence estimate the sponsor is advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

- Significant benefit

The arguments on significant benefit were based on an alternative mechanism of action and the potential improved efficacy in the condition. The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the non-clinical in vivo studies to justify the assumption of significant benefit over antiseizure medications (ASMs) which are used to treat the spectrum of epileptic syndromes and or seizure types in the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 11 May 2022, the sponsor provided published clinical data which showed that the proposed product could be effective in reducing seizures in patients with the condition. In a compassionate use study, the results of 8 patients who were treated with the proposed product on top of their antiseizure medication were described. These results were presented during the oral explanation.

The results of this publication were accepted by the COMP for the purpose of supporting the medical plausibility. In addition, the sponsor also provided a revised prevalence estimate. It was acknowledged by the COMP that there is very little literature in the public domain on the prevalence of this condition. The estimate of 0.2 in 10,000 was considered acceptable for the purpose of supporting an initial orphan designation.

The sponsor made reference to the compassionate use study to support the clinically relevant advantage of adding the proposed product to anti-seizure medication. The COMP raised a question on the prior or continued use of clobazam which the sponsor could not respond to. They did not know the number and type of prior antiseizure medication being used in the patients reported in the study as the study was not performed by the sponsor. Neither did the sponsor know what the percentage of patients who were resistant to ASMs but they indicated that it had been reported that there were more than two antiseizure medications used. The COMP concluded that the sponsor could not establish clearly what the added value was of adding the proposed product to the current treatment of patients with Dup15Q, nor if there was an unmet need in a portion of patients resistant to treatment. As result the committee 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 12 May 2022, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. *Escherichia coli*, strain Nissle 1917, expressing high affinity phenylalanine transporter, phenylalanine ammonia lyase and L-amino acid deaminase - EMA/OD/0000068847

Orphix Consulting GmbH; Treatment of hyperphenylalaninemia

COMP Rapporteur: Enrico Costa, Ingeborg Barisic

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

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

The intention to treat the condition with the medicinal product containing Escherichia coli, strain Nissle 1917, expressing high affinity phenylalanine transporter, phenylalanine ammonia lyase and L-amino acid deaminase was considered justified based on preliminary clinical data showing reduction of elevated blood phenylalanine levels.

The condition is chronically debilitating (if untreated) due to high blood phenylalanine levels which cause cognitive impairment.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing *Escherichia coli*, strain Nissle 1917, expressing high affinity phenylalanine transporter, phenylalanine ammonia lyase and L-amino acid deaminase will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate reduction of elevated blood phenylalanine levels in patients in which target levels cannot be achieved with the currently authorized products or in patients not eligible to receive currently authorized treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for *Escherichia coli*, strain Nissle 1917, expressing high affinity phenylalanine transporter, phenylalanine ammonia lyase and L-amino acid deaminase, for treatment of hyperphenylalaninemia, was adopted by consensus.

2.2.2. - EMA/OD/0000073118

Treatment of perinatal asphyxia

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 June 2022 meeting.

2.2.3. losartan - EMA/OD/0000075685

3R Pharma Consulting GmbH; Treatment of osteogenesis imperfecta

COMP Rapporteur: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing losartan was considered justified based on non-clinical data in a valid model of the condition showing reduced excessive bone remodelling activity and increased bone mass.
The condition is chronically debilitating due to fragile bones, multiple fractures and bone deformations leading to persistent physical and functional limitations, pain and restrictions in daily life activities.

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 losartan will be of significant benefit to those affected by the condition. The sponsor has provided on non-clinical data in a valid model of the condition showing reduced excessive bone remodelling activity which is not achieved with the currently authorised product. The Committee considered that this constitutes a clinically relevant advantage

A positive opinion for losartan, for treatment of osteogenesis imperfecta, was adopted by consensus.

2.2.4. humanised IgG4 monoclonal antibody against proliferation-inducing ligand - EMA/OD/0000075740

TMC Pharma (EU) Limited; Treatment of primary IgA nephropathy

COMP Rapporteur: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing humanised IgG4 monoclonal antibody against proliferation-inducing ligand was considered justified based on the reduction in proteinuria and the decreases of serum Immunoglobulin A observed in valid non-clinical models and the reduction of urine protein/creatinine ratio observed in patients with the condition.

The condition is life-threatening and chronically debilitating due to progressive loss of kidney function leading to renal failure requiring dialysis and transplantation.

The condition was estimated to be affecting approximately 4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised IgG4 monoclonal antibody against proliferation-inducing ligand will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data and preliminary clinical data that demonstrate that the proposed product can treat a broader patient population than the currently authorised product, which only targets a subset of primary immunoglobulin A nephropathy patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised IgG4 monoclonal antibody against proliferation-inducing ligand, for treatment of primary IgA nephropathy, was adopted by consensus.

2.2.5. - EMA/OD/0000075761

Treatment of mantle cell lymphoma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June 2022 meeting.

2.2.6. sebetralstat - EMA/OD/0000076332

Kalvista Pharmaceuticals (Ireland) Limited; Treatment of hereditary angioedema

COMP Rapporteur: Geraldine O'Dea

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

The intention to treat the condition with the medicinal product containing sebetralstat was considered justified based on preliminary clinical data showing that their product prolonged the time to use of conventional treatment.

The condition is life-threatening and chronically debilitating due to recurrent attacks of oedema in various parts of the body that may cause airway obstruction leading to asphyxia.

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 sebetralstat will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that their oral product prolonged the time to use of conventional treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sebetralstat, for treatment of hereditary angioedema, was adopted by majority (23 out of 27 votes). The Norwegian COMP member agreed with the above-mentioned recommendation of the COMP.

The divergent positions (Tim Leest, Elisabeth Johanne Rook, Martin Mozina and Julian Isla) were appended to this opinion.

2.2.7. - EMA/OD/0000076399

Treatment of fracture nonunion

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 June 2022 meeting.

2.2.8. amitriptyline - EMA/OD/0000076571

AlgoTherapeutix; Treatment of erythromelalgia

COMP Rapporteur: Elisabeth Penninga

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

The intention to treat the condition with the medicinal product containing amitriptyline was considered justified based on preliminary clinical data. Patients treated with a topical formulation of amitriptyline had a reduction of pain intensity and attack frequency.

The condition is chronically debilitating due to pain, swelling and erythema, usually in the extremities of the body.

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.

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 amitriptyline, for treatment of erythromelalgia, was adopted by consensus.

2.2.9. - EMA/OD/0000077315

Treatment of Type 1 diabetes in DQ8 positive patients with residual beta cell function

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 June 2022 meeting.

2.2.10. - EMA/OD/0000079201

Treatment of non-infectious intermediate, posterior and chronic anterior uveitis

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 June 2022 meeting.

[Post-meeting note: The COMP adopted the list of issues by written procedure following its May meeting.]

2.2.11. - EMA/OD/0000079978

Treatment of malignant mesothelioma

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 June 2022 meeting.

2.2.12. 4-[[(3S)-1-benzylpyrrolidin-3-yl]-methylamino]-2-fluoro-5-methyl-N-(1,3-thiazol-4-yl)benzenesulfonamide - EMA/OD/0000080409

Neurocrine Therapeutics Limited; Treatment of SCN8A developmental and epileptic encephalopathy (SCN8A-DEE)

COMP Rapporteur: Giuseppe Capovilla

The Committee agreed that the condition, SCN8A developmental and epileptic encephalopathy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 4-[[(3S)-1-benzylpyrrolidin-3-yl]-methylamino]-2-fluoro-5-methyl-N-(1,3-thiazol-4-

yl)benzenesulfonamide was considered justified based on non-clinical in vivo data in a valid model of the condition which showed a dose dependent inhibition of seizures.

The condition is chronically debilitating due to early onset, pharmaco-resistant epilepsy and severe neurodevelopmental delay. Also reported are hearing problems, laryngomalacia, scoliosis, and microcephaly. The condition is life-threatening due to sudden unexpected death in epilepsy or pulmonary infections secondary to general hypotonia.

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 4-[[(3S)-1-benzylpyrrolidin-3-yl]-methylamino]-2-fluoro-5-methyl-N-(1,3-thiazol-4-yl)benzenesulfonamide will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that the proposed product can treat patients with the condition who are resistant to currently authorised anti-seizure medications. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 4-[[(3S)-1-benzylpyrrolidin-3-yl]-methylamino]-2-fluoro-5-methyl-N-(1,3-thiazol-4-yl)benzenesulfonamide, for treatment of SCN8A developmental and epileptic encephalopathy, was adopted by consensus.

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

2.2.13. pirfenidone - EMA/OD/0000080460

Regintel Limited; Treatment of idiopathic pulmonary fibrosis

COMP Rapporteur: Eva Malikova

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 pirfenidone was considered justified based on non-clinical data on models of the condition showing a reduction in disease biomarkers and fibrosis score, in combination with clinical data which showed a stabilization of the forced vital capacity.

The condition is chronically debilitating due to progressive dyspnoea and loss of respiratory function, with limited exercise capability and decreased quality of life, and life-threatening due to respiratory failure.

The condition was estimated to be affecting approximately 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 pirfenidone will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate improvement in forced vital capacity when compared to historical data in patients treated with the currently

authorised products for the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for pirdenidone, for treatment of idiopathic pulmonary fibrosis, was adopted by consensus.

2.2.14. - EMA/OD/0000080688

Treatment of Brugada 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 June 2022 meeting.

2.2.15. lithium carbonate - EMA/OD/0000080823

Centre Hospitalier Universitaire Dijon Bourgogne; Treatment of TBR1-related disorder

COMP Rapporteur: Julian Isla

The Committee agreed that the condition, TBR1-related disorder, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing lithium carbonate was considered justified based on non-clinical data in a valid model demonstrating improvement of synaptic transmission and improvement of social interaction deficits.

The condition is chronically debilitating due to autism and speech delay, intellectual disability, behavioral issues and gross motor function delay.

The condition was estimated to be affecting approximately 0.02 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 lithium carbonate, for treatment of TBR1-related disorder, was adopted by consensus.

2.2.16. - EMA/OD/0000080896

Treatment of Prader-Willi Syndrome

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June 2022 meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 20 May 2022.]

2.2.17. sirolimus - EMA/OD/0000081767

Raremoon Consulting Esp S.L.; Treatment of lymphatic malformations

COMP Rapporteur: Marie Pauline J. Evers

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

The intention to treat the condition with the medicinal product containing sirolimus was considered justified based on non-clinical data in a model of the condition showing a reduction in lymphatic density, in combination with clinical data from published studies which showed an improvement on lymphatic malformation volume, functional impairment score, and health related quality of life.

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

The condition was estimated to be affecting approximately 3.3 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for sirolimus, for treatment of lymphatic malformations, was adopted by consensus.

2.2.18. - EMA/OD/0000082229

Treatment of GM1 gangliosidosis

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 June 2022 meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 17 May 2022.]

2.2.19. epcoritamab - EMA/OD/0000082687

AbbVie Deutschland GmbH & Co. KG; Treatment of follicular lymphoma

COMP Rapporteur: Maria Elisabeth Kalland

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

The intention to treat the condition with the medicinal product containing epcoritamab was considered justified based on preliminary clinical data which showed that heavily pre-treated patients with relapsed/refractory follicular lymphoma achieved partial or complete responses.

The condition is life-threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction, and the potential of transformation to aggressive lymphoma.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing epcoritamab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that showed partial and complete responses in a high proportion of heavily pre-treated relapsed/refractory patients

with follicular lymphoma who have failed several lines of approved therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for epcoritamamb, for treatment of follicular lymphoma, was adopted by consensus.

2.2.20. tamoxifen citrate - EMA/OD/0000082957

Fondazione Telethon; Treatment of neuronal ceroid lipofuscinosis

COMP Rapporteur: Darius Matusevicius

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

The intention to treat the condition with the medicinal product containing tamoxifen citrate was considered justified based on non-clinical data showing improvement in the biochemical markers and motor function.

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

The condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tamoxifen citrate will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that the product used in a non-clinical model of CLN7 improved biochemical markers and motor function. Significant benefit is assumed since the proposed product targets a different population than Brineura.

A positive opinion for tamoxifen citrate, for treatment of neuronal ceroid lipofuscinosis, was adopted by consensus.

2.2.21. - EMA/OD/0000083166

Treatment of neurofibromatosis type 2

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 June 2022 meeting.

[Post-meeting note: The COMP adopted the list of issues by written procedure following its May meeting.]

2.2.22. - EMA/OD/0000083246

Treatment of pulmonary arterial hypertension

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June 2022 meeting.

2.2.23. - EMA/OD/0000083254

Prevention of graft rejection following 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 June 2022 meeting.

2.2.24. - EMA/OD/0000083331

Treatment of Lambert-Eaton myasthenia 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 June 2022 meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 18 May 2022.]

2.2.25. - EMA/OD/0000083574

Treatment of West syndrome

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June 2022 meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 24 May 2022.]

2.2.26. 2'-O-(2-methoxyethyl) modified antisense oligonucleotide targeting *UBE3A* antisense transcript RNA - EMA/OD/0000083607

Ionis Development (Ireland) Limited; Treatment of Angelman syndrome

COMP Rapporteur: Robert Nistico

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

The intention to treat the condition with the medicinal product containing 2'-O-(2-methoxyethyl) modified antisense oligonucleotide targeting UBE3A antisense transcript RNA was considered justified based on non-clinical data in a relevant model of the condition in which the use of the proposed product resulted in improvement in motor coordination, memory, cognition, anxiety, and decrease in electroencephalographic abnormalities.

The condition is chronically debilitating due to developmental delay, motor and cognitive impairment, hyperactivity and epileptic seizures that are often treatment resistant.

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 2'-O-(2-methoxyethyl) modified antisense oligonucleotide targeting UBE3A antisense transcript RNA, for treatment of Angelman syndrome, was adopted by consensus.

2.2.27. human allogeneic keratinocytes - EMA/OD/0000083615

Evomedis GmbH; Treatment of partial deep dermal and full thickness burns

COMP Rapporteur: Armando Magrelli

The Committee agreed that the condition, partial deep dermal and full thickness burns, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing Human allogeneic keratinocytes was considered justified based on non-clinical data in a model of the condition which showed skin engraftment and wound healing stimulation.

The condition is life-threatening due to the formation of extensive scarring that causes disfigurement, pain, itching, impairment of mobility and need for surgery. The condition is also life-threatening due to multi-organ failure and sepsis.

The condition was estimated to be affecting approximately 2.9 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing Human allogeneic keratinocytes will be of significant benefit to those affected by the condition. The sponsor has provided evidence demonstrating that the product can address a different aspect of the disease compared to authorised medicines. The sponsor has provided non-clinical data that demonstrate skin engraftment and wound healing stimulation. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for human allogeneic keratinocytes, for treatment of partial deep dermal and full thickness burns, was adopted by consensus.

2.2.28. modified mRNA encoding human methylmalonyl-coenzyme A mutase containing a polymorphism at position 671 - EMA/OD/0000083787

Moderna Biotech Spain S.L.; Treatment of methylmalonic acidemia

COMP Rapporteur: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing modified mRNA encoding human methylmalonyl-coenzyme A mutase containing a polymorphism at position 671 was considered justified based on non-clinical in vivo models of the condition, showing reduction of methylmalonic acid concentration in plasma and target tissues and improvement in growth and survival.

The condition is chronically debilitating and life-threatening due to neurological, gastroenterological and haematological complications.

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 Modified mRNA encoding human methylmalonyl-coenzyme A mutase containing a polymorphism at position 671 will be of significant benefit to those affected by the condition. The sponsor has provided data from non-clinical in vivo models of the condition, demonstrating a reduction of methylmalonic acid concentration in plasma and target tissues and improvement in growth and survival, which cannot be expected from the currently authorized product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for modified mRNA encoding human methylmalonyl-coenzyme A mutase containing a polymorphism at position 671, for treatment of methylmalonic acidemia, was adopted by consensus.

2.2.29. 2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl -(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioadenylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioguanylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)- 5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioguanylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioadenine, sodium salt - EMA/OD/0000083789

AdRes EU B.V.; Treatment of cystic fibrosis

COMP Rapporteurs: Enrico Costa, Eva Malikova

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

The intention to treat the condition with the medicinal product containing 2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl -(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioadenylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioguanylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)- 5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioguanylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioadenine, sodium salt was considered justified based on non-clinical in vitro data showing increase of cystic fibrosis transmembrane conductance regulator (CFTR) activity in cells from patients with cystic fibrosis carrying the W1282X CFTR mutation.

The condition is chronically debilitating and life threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure.

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 2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl -(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioadenylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioguanylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)- 5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioguanylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioadenine, sodium salt will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vitro data showing increase of CFTR activity in cells from patients carrying the W1282X CFTR mutation, that cannot be achieved with currently authorized medicinal products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl -(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioadenylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioguanylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)- 5-methyl-P-thiouridylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioguanylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioadenine, sodium salt, for treatment of cystic fibrosis, was adopted by consensus.

2.2.30. - EMA/OD/0000083791

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 June 2022 meeting.

2.2.31. - EMA/OD/0000083873

Treatment of choroideremia

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 June 2022 meeting.

[Post-meeting note: The COMP adopted the list of issues by written procedure following its May meeting.]

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 26 May 2022.]

2.2.32. diflunisal - EMA/OD/0000083967

Turnkey Pharmaconsulting Ireland Limited; Treatment of ATTR amyloidosis

COMP Rapporteur: Zsofia Gyulai

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

The intention to treat the condition with the medicinal product containing diflunisal was considered justified based on published clinical data suggesting symptomatic improvements in patients with polyneuropathy and cardiomyopathy manifestations of the condition.

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

The condition was estimated to be affecting approximately 1.4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing diflunisal will be of significant benefit to those affected by the condition. The sponsor has provided published clinical data suggesting symptomatic improvements in patients with advanced polyneuropathy (stage 3) as well as cardiomyopathy manifestations of the condition which cannot be expected from currently authorized medicinal products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for diflunisal, for treatment of ATTR amyloidosis, was adopted by consensus.

2.2.33. - EMA/OD/0000083982

Treatment of cutaneous T-cell lymphoma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June 2022 meeting.

2.2.34. eltanexor - EMA/OD/0000084241

Karyopharm Europe GmbH; Treatment of myelodysplastic syndromes

COMP Rapporteur: Karri Penttila

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

The intention to treat the condition with the medicinal product containing eltanexor was considered justified based on preliminary clinical data showing high rate of responses in patients with high risk, primary hypomethylating agent-refractory myelodysplastic syndromes.

The condition is life-threatening and chronically debilitating in particular due to anaemia, thrombocytopenia, and neutropenia, as well as transformation into acute myeloid leukaemia.

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 eltanexor will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that primary hypomethylating agent-refractory patients with intermediate and high-risk myelodysplastic syndromes achieved high rate of responses when treated with eltanexor as single agent. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for eltanexor, for treatment of myelodysplastic syndromes, was adopted by consensus.

2.2.35. - EMA/OD/0000084283

Treatment of pulmonary arterial hypertension

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the June 2022 meeting.

2.2.36. govorestat - EMA/OD/0000084390

Drug Development and Regulation S.L.; Treatment of galactosaemia

COMP Rapporteur: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing govorestat was considered justified based on non-clinical data in a valid disease model demonstrating improvements in learning capability, cognition and fine motor coordination as well as the prevention of cataract formation.

The condition is life-threatening due to acute central nervous system pathology characterized by cerebral oedema, pseudotumor cerebri and infant seizures and chronically debilitating due to cognitive, intellectual and speech impairment as well as ataxia, cataract and behavioural problems.

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,

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 govorestat, for treatment of galactosaemia, 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

None

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 34 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. The COMP adopted the proposed answers on the significant benefit issues.

3.1.2. -

Treatment of primary biliary cholangitis

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

3.1.3. -

Treatment of myelodysplastic syndromes

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 mucopolysaccharidosis type I

The finalised letter was circulated for information.

3.2.2. -

Treatment of multiple myeloma

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of mucopolysaccharidosis II (Hunter's syndrome)

The new request was noted.

3.3.2. -

Treatment of acute myeloid leukaemia

The new request was noted.

3.3.3. -

Treatment of pancreatic cancer

The new request was noted.

3.3.4. -

Treatment of myelofibrosis

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. Yescarta - axicabtagene ciloleucel - EMEA/H/C/004480/II/0042, EU/3/15/1579, EMA/OD/0000068456

Kite Pharma EU B.V.; Treatment of follicular lymphoma

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

A list of issues was adopted on 17 February 2022.

An oral explanation to be held on 10 May 2022, was cancelled.

An opinion recommending not to remove Yescarta, axicabtagene ciloleucel (EU/3/15/1579) 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. Upstaza - eladocagene exuparvovec - EMEA/H/C/005352/0000, EU/3/16/1786, EMA/OD/0000024196

PTC Therapeutics International Limited; Treatment of aromatic L-amino acid decarboxylase deficiency

COMP Rapporteurs: Dinah Duarte; Armando Magrelli

An opinion recommending not to remove Upstaza, eladocagene exuparvovec, EU/3/16/1786 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 May meeting.]

4.2.2. Kinpeygo - budesonide - EMEA/H/C/005653/0000, EU/3/16/1778, EMA/OD/0000066260

Calliditas Therapeutics AB; Treatment of primary IgA nephropathy

COMP Rapporteurs: Armando Magrelli; Elisabeth Johanne Rook

An opinion recommending not to remove Kinpeygo, budesonide (EU/3/16/1778) 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 May meeting.]

4.2.3. Zokinvy - lonafarnib - EMEA/H/C/005271/0000, EU/3/18/2118, EMA/OD/0000067500

Eigerbio Europe Limited; Treatment of Hutchinson-Gilford Progeria Syndrome

COMP Rapporteurs: Elisabeth Johanne Rook; Armando Magrelli

An opinion recommending not to remove Zokinvy, lonafarnib, EU/3/18/2118 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 May meeting.]

4.2.4. - mitapivat sulfate - EMEA/H/C/005540/0000, EU/3/20/2270, EMA/OD/0000068458

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

The status of the procedure at CHMP was noted.

4.2.5. Xenpozyme - olipudase alfa - EMEA/H/C/004850/0000, EU/3/01/056, EMA/OD/0000072975

Accelerated assessment

Genzyme Europe B.V.; Treatment of Niemann-Pick disease

COMP Rapporteurs: Cécile Dop; Elisabeth Johanne Rook

An opinion recommending not to remove Xenpozyme, olipudase alfa, EU/3/01/056 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 May meeting.]

4.2.6. – fosdenopterin - EMEA/H/C/005378/0000, EU/3/10/777, EMA/OD/0000074822

Accelerated assessment

Comharsa Life Sciences Ltd; Treatment of molybdenum cofactor deficiency type A

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 1 application.

4.5. Orphan Maintenance Reports

Documents were tabled for information

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Yescarta - axicabtagene ciloleucel - EMEA/H/C/004480/II/0046, EU/3/15/1553, EMA/OD/0000076832

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

CHMP Rapporteur: Jan Mueller-Berghaus; CHMP Co-Rapporteur: Claire Beuneu

The status of the procedure at CHMP was noted.

5.3. Appeal

None

5.4. On-going procedures

The Review of orphan designation for OMP for MA extension - On-going procedures was noted.

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

Irena Rogovska gave a proxy to Ausra Matuleviciene to vote on behalf of Irena Rogovska during part of May 2022 COMP meeting.

7.1.3. Strategic Review & Learning meetings

The COMP noted the feedback from the joint COMP/PDCO meeting under the French Presidency of the Council of the EU held virtually on 31 March 2022.

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 06 May 2022.

7.1.5. Principal 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

None

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 COMP noted the information about the meeting.

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

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

None

7.7. COMP work plan

None

7.8. Planning and reporting

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

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

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

8.1. Discussion on RWD (update on studies)

COMP noted the update from the drafting group on a RWD project. During the discussion, outcomes measures considered feasible in RWD were discussed in view of their validity and relevance for regulatory decision making.

9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 10-12 May 2022 meeting.

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

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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	
Eva Malikova	Member	Slovak Republic	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	
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/