9 December 2021
EMA/COMP/647448/2021
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 03-05 November 2021

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

The agenda for 3-5 November 2021 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 5-7 October 2021 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. cedazuridine, decitabine - EMA/OD/0000066742

Otsuka Pharmaceutical Netherlands B.V.; Treatment of acute myeloid leukaemia (AML)

COMP Rapporteur: Maria Elisabeth Kalland

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

- Number of people affected

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

The sponsor was asked to estimate the complete prevalence indirectly by using crude incidence data from ECIS. The proposed duration of disease should be based on literature data from the European community. Data from national registries where prevalence of AML may be specifically reported should be explored. Sensitivity analyses of the reported calculations should be provided to reflect the variability and uncertainties from the different sources used.

- Significant benefit

The arguments on significant benefit were based on the potential improved efficacy in the condition and the major contribution to patient care.

The sponsor was requested to discuss the assumption of an improved efficacy of the fixed-dose combination tablets over approved treatment options for the target AML patients who are ineligible for intensive chemotherapy. The claim for major contribution to patient care of the proposed product needs to be substantiated with available data.

In the written response, the sponsor provided an updated prevalence calculation of AML in the EU of 1.69 per 10,000 based on a Dutch registry reporting 1.69 for 20-year prevalence. The COMP considered that this figure is in line with figures recently approved and rounded it up to 1.7.

For the demonstration of significant benefit, the sponsor did not provide additional data but claimed that the advantages associated with the change in route of administration (from intravenous (IV) and subcutaneous (SC) to oral tablet) supports the major contribution to patient care claim. In addition, the sponsor claimed that the preliminary efficacy data from the ongoing phase 3 study is comparable to decitabine (IV) and azacitidine (SC), two approved monotherapy treatments for AML patients who are ineligible for intensive chemotherapy.

The COMP considered that the preliminary clinical data showed similar efficacy compared to currently approved therapies for AML patients who are ineligible for intensive induction chemotherapy and that the oral fixed-dose combination might reduce the burden of parenteral therapies. The oral explanation with the sponsor was therefore cancelled.

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

The intention to treat the condition with the medicinal product containing cedazuridine, decitabine was considered justified based on preliminary clinical data showing responses in de novo or secondary acute myeloid leukaemia.

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

The condition was estimated to be affecting approximately 1.7 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 cedazuridine and decitabine will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data which demonstrate similar efficacy with currently approved therapies for AML patients who are ineligible for intensive induction chemotherapy. The oral fixed-dose combination might reduce the burden of parenteral therapies.
The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for cedazuridine and decitabine, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.1.2. 6-(4-(tert-butyl)phenoxy)pyridin-3-amine hydrochloride - EMA/OD/0000066191

Yes Pharmaceutical Development Services GmbH; Treatment of acute lymphoblastic leukaemia (ALL)

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

It remains elusive how much the positive treatment effect observed in only one patient and no follow-up information can be attributed to the proposed product, considering the combined therapeutic approach including also other agents to specifically target additional genetic alterations frequently detected in leukaemic cells such as BCL2, ABL1 and CD-38. The sponsor was requested to further substantiate their claim for significant benefit.

In addition, the sponsor was asked to describe their plans for a clinical development in patients with ALL/T-cell ALL.

In the written response, the sponsor provided data from in vivo non-clinical xenograft (PDX) models comparing the product to standard of care.

Following transplantation, tumour burden was monitored following administration with either vehicle or the proposed product. The treatment with the proposed product resulted in prolonged survival in the model organism compared to the vehicle group. A decrease in cleaved N1-ICD was observed. This data showed that the proposed product exhibits in vivo anti-tumour efficacy against NOTCH positive patient derived xenograft models of human tumours that were clinically relapsed/refractory. The proposed product proved to be effective in cell-killing in all tested PDX models, while most of the models were refractory to dexamethasone, and one was refractory to Ara-C and nelarabine. These findings suggest that the proposed product has improved efficacy over drugs that are used as standard of care for the treatment of T-ALL.

Furthermore, synergistic drug interactions were found between the product and Ara-C and the product and nelarabine in several PDX models. This synergy was independent from NOTCH1 mutational status, indicating that the product may have additive/synergistic effects when added to standard of care therapeutics used in T-ALL independently of the patient's Notch status.

Moreover, the sponsor clarified that a phase I clinical trial is currently ongoing which also includes a confirmatory cohort to collect safety and early efficacy data in adult patients with Notch positive relapsing/refractory T-ALL. A phase II study of the product in combination with venetoclax in adolescent and young adult patients with relapsed/refractory T-ALL (independently of the Notch status) is planned.

The COMP considered that the additional data provided addressed the issue of significant benefit. The oral explanation was therefore cancelled.

The Committee agreed that the condition, acute lymphoblastic leukaemia, 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-(tert-butyl)phenoxy)pyridin-3-amine hydrochloride was considered justified based on non-clinical data in a valid disease model suggesting a positive effect on survival.

The condition is chronically debilitating and life-threatening depending on the response to treatment, with acute leukaemic forms being fatal in a few weeks if left untreated. Symptoms include persistent fever, infections, anaemia, fatigue, breathlessness, bone and joint pain and ultimately bone marrow failure and organ damage.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 6-(4-(tert-butyl)phenoxy)pyridin-3-amine hydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in valid disease models suggesting a positive effect on survival. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 6-(4-(tert-butyl)phenoxy)pyridin-3-amine hydrochloride, for treatment of acute lymphoblastic leukaemia, was adopted by consensus.

2.1.3. autologous T cells ex vivo modified with a lentiviral vector encoding a chimeric antigen receptor specific for CD1a - EMA/OD/0000062804

Onechain Immunotherapeutics S.L.; Treatment of acute lymphoblastic leukaemia/ lymphoblastic lymphoma

COMP Rapporteur: Maria Elisabeth Kalland

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 condition should be changed from acute lymphoblastic leukaemia/ lymphoblastic lymphoma to acute lymphoblastic leukaemia.

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the efficacy results obtained with the in vivo proof-of-concept study in T-ALL transplanted study subjects.

The sponsor was requested to further discuss the arguments provided for significant benefit and to justify the assumption of improved efficacy of the proposed product over authorised medicinal products for the target patient population including nelarabine.

In the written response, the sponsor agreed to change the condition from acute lymphoblastic leukaemia/ lymphoblastic lymphoma to acute lymphoblastic leukaemia.

For the demonstration of significant benefit, the sponsor argued that the proposed CD1a-targeted immunotherapy is intended for the treatment of T-cell ALL where there are limited treatment options for patients with relapsed/refractory disease. Blinatumomab, inotuzumab ozogamicin, and autologous T-cells genetically modified ex vivo using a lentiviral vector encoding an anti-CD19 CAR are specific for the treatment of patients with relapsed/refractory B-cell ALL. These medicinal products do not offer any benefit to patients with T-cell ALL.

Based on the mechanism of action of tyrosine kinase inhibitors (TKIs), imatinib, dasatinib, and ponatinib are specific for the treatment of ALL cases with tyrosine kinase activity, specifically Philadelphia chromosome positive (Ph+) and some Ph-negative (Ph-)-like ALL cases. These products are therefore not effective in T-cell ALL, considering that Ph-positivity is occasional in this type of ALL.

The sponsor argued that the proposed product is not expected to substitute clofarabine, nelarabine, and idarubicin, but is expected to be a curative option for patients with relapsed/refractory T-cell ALL who are not eligible for SCT and who have failed to previous treatment with these products. The proposed product is therefore sought as an alternative to SCT when the only next option is palliative therapy.

The COMP agreed that the significant benefit can be justified based on non-clinical data in a valid model that demonstrate efficacy of the CD1a-targeted immunotherapy for treatment of T-cell ALL where there are limited options for patients with relapsed/refractory disease. The oral explanation was therefore cancelled.

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

The intention to treat the condition with the medicinal product containing autologous T cells ex vivo modified with a lentiviral vector encoding a chimeric antigen receptor specific for CD1a was considered justified based on non-clinical data showing anti-leukaemic activity.

The condition is chronically debilitating and life-threatening depending on the response to treatment, with acute leukaemic forms being fatal in a few weeks if left untreated. Symptoms include persistent fever, infections, anaemia, fatigue, breathlessness, bone and joint pain and ultimately bone marrow failure, and organ damage.

The condition was estimated to be affecting less than 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 autologous T cells ex vivo modified with a lentiviral vector encoding a chimeric antigen receptor specific for CD1a will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a valid model that demonstrate efficacy of the CD1a-targeted immunotherapy for the treatment of T-cell acute

lymphoblastic leukaemia and there are limited options for patients with relapsed/refractory disease. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous T cells ex vivo modified with a lentiviral vector encoding a chimeric antigen receptor specific for CD1a, for treatment of acute lymphoblastic leukaemia, was adopted by consensus.

2.1.4. chimeric peptide of human glucagon-like peptide-1, glucagon and gastric inhibitory polypeptide analogues linked to a human immunoglobulin Fc fragment - EMA/OD/0000066630

JVM Europe B.V.; Treatment of primary sclerosing cholangitis (PSC)

COMP Rapporteur: Lyubina Racheva Todorova

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

- 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 any additional non-clinical in vivo or preliminary clinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 3 November 2021, the sponsor argued that although ursodeoxycholic acid (UDCA) is approved across the EU and has been widely studied as a therapy for PSC, its efficacy remains unproven, and therefore UDCA should not be considered a satisfactory treatment. This change would not be acceptable to the COMP but the arguments used by the sponsor for why UCDA is not satisfactory can be used in support for the significant benefit.
The sponsor provided details of 5 published clinical studies and a meta-analysis performed on 8 (eight) randomised clinical trials comprising 567 patients (Triantos et al., 2011). Based on these data the sponsor provided evidences that the use of UDCA does not improve biochemical parameters. Moreover, there are clear data for lack of effect on liver fibrosis. In contrast, the proposed product effectively lowered transaminase levels and liver fibrosis markers in one independent non-clinical model of the condition.
In conclusion, all studies presented by the sponsor (scientific publications) support the thesis that UDCA does not have or only has a minimal beneficial effect on the natural course of the disease.

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

The intention to treat the condition with the medicinal product containing chimeric peptide of human glucagon-like peptide-1, glucagon and gastric inhibitory polypeptide analogues linked to a human immunoglobulin Fc fragment was considered justified based on non-clinical data demonstrating reduction of liver fibrosis.

The condition is chronically debilitating and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased

risk of developing hepatocellular cancer. Common findings include pruritus, hyperlipidaemia, hypothyroidism, deficiency of fat-soluble vitamins and osteopenia.

The condition was estimated to be affecting less than 3.8 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 chimeric peptide of human glucagon-like peptide-1, glucagon and gastric inhibitory polypeptide analogues linked to a human immunoglobulin Fc fragment will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data in a valid model of the condition showing that the product reduced liver fibrosis. This is an aspect of the condition not achieved with the use of ursodeoxycholic acid. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for chimeric peptide of human glucagon-like peptide-1, glucagon and gastric inhibitory polypeptide analogues linked to a human immunoglobulin Fc fragment, for treatment of primary sclerosing cholangitis, was adopted by consensus.

2.1.5. - EMA/OD/0000061806

Treatment of aneurysmal subarachnoid haemorrhage

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 15 October 2021, prior to responding to the list of issues.

2.1.6. macitentan - EMA/OD/0000057224

Janssen-Cilag International N.V.; Treatment of chronic thromboembolic pulmonary hypertension (CTEPH)

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 potential improved efficacy as well as a major contribution to patient care in the condition.

The sponsor was requested to provide a discussion on the efficacy of macitentan vs treprostinil and to further discuss the arguments for major contribution to patient care.

In the written response, the sponsor argued that based on the clinical data available so far, macitentan 75 mg is expected to be indicated for CTEPH patients in WHO FC II to IV, thus benefitting a greater proportion of CTEPH patients than treprostinil, which is only approved for FC III and IV.

In MERIT-1 study, the treatment effect on pulmonary vascular resistance (PVR) and exercise capacity was consistent in all pre-specified subgroups including in patients with WHO FC II, and WHO FC III-IV. In line with the arguments of significant benefit over riociguat; the effect of macitentan in class II could support a significant benefit over treprostinil as this would be a broader target patient population.

The sponsor also provided an indirect comparison between macitentan and treprostinil based on the MERIT-1 study and the CTREPH study, which was a 24-week, randomized, double-blind, controlled, Phase 3 study resulting in the approval of treprostinil. The sponsor noted that the CTREPH trial targeted a population with more severe disease and, therefore, the studies might not be completely suitable for comparison of outcomes. The COMP accepted the significant benefit based on a broader patient population and the oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing macitentan was considered justified based on clinical data showing improvement of pulmonary vascular resistance and in the 6-minute walking test in patients with the condition.

The condition is life-threatening and chronically debilitating due to impairment of physical ability with symptoms including dyspnoea and fatigue and 5-year survival rates as low as 16% for untreated patients with chronic thromboembolic pulmonary hypertension.

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 macitentan will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the product can be used in a broad patient population with WHO function class II, III and IV. The currently authorised products cover a more restricted patient population. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for macitentan, for treatment of chronic thromboembolic pulmonary hypertension, was adopted by consensus.

2.1.7. - EMA/OD/0000062530

Treatment of acute myeloid leukaemia

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 19 October 2021, prior to responding to the list of issues.

2.1.8. - EMA/OD/0000064296

Treatment of narcolepsy

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 15 October 2021, prior to responding to the list of issues.

2.1.9. - EMA/OD/0000066935

Treatment of epilepsy with myoclonic-atonic seizures

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 19 October 2021, prior to responding to the list of issues.

2.1.10. - EMA/OD/0000064393

Treatment of Dravet syndrome (DS)

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

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potential improved efficacy in the condition, as adjunct to standard of care. No relevant data had been presented on the concomitant use of the proposed product together with fenfluramine or cannabidiol, or following their previous use. The sponsor was requested to elaborate the significant benefit over these two approved medicinal products for Dravet Syndrome.

In the written response, and during an oral explanation before the Committee on 4 November 2021, the sponsor referred again to the previously presented analysis from the study of concomitant anti-seizure medications (ASMs) in the patient population with DS. With regards to the two authorized ASMs in DS, cannabidiol (Epidyolex) and fenfluramine (Fintepla), Fintepla has not been used in any of the DS patients in the study and cannabidiol (including dietary supplements) only in 2/25 patients in the placebo group but not concomitant with the proposed product. This means that no data has been presented on the concomitant use of Fintepla and Epidyolex with the proposed product.

The sponsor stressed again that in the primary analysis of seizure frequency during the maintenance period for all subjects (i.e. DS and Lennox-Gastaut syndrome) and for the DS subjects in the study there was a significant decrease from baseline in the median number of reported seizures per 28 days for subjects receiving the proposed product. The sponsor maintained that, considering the novel mechanism of action and the observed reduction of seizure frequencies in the Phase 2 clinical trial when taken concomitantly with several other antiseizure medications, it can be reasonably expected that the proposed product has the potential to provide add-on benefit to Epidyolex and Fintepla as well. The sponsor intends to confirm that expectation at time of orphan maintenance.

In addition, the sponsor provided an in-depth comparison of known safety information with adverse drug reactions and drug-drug interaction that are known to limit the utility of Fintepla and Epidyolex but thus far do not represent major concerns for the proposed product. Based on current clinical data, the sponsor expects that the proposed product may have a more benign safety profile as compared to currently authorized ASMs.

The COMP acknowledged the additional information provided by the sponsor but concluded that it was not sufficient to support significant benefit over all currently authorized ASMs in the EU, i.e. especially Fintepla and Epidyolex. While the COMP welcomed the development of a new medicinal product for the treatment of DS with a novel mechanism of action, extrapolation of efficacy based on the data was not considered acceptable in the adjunct therapy of the proposed product with Fintepla and Epidyolex. Furthermore, the COMP pointed out that the data provided for the proposed product on safety were too preliminary to support significant benefit vs currently authorized ASMs based on safety grounds.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 4 November 2021, prior to final opinion.

2.1.11. anti-(endothelin-1 receptor subtype A) IgG4 humanised monoclonal antibody - EMA/OD/0000064736

Gmax Biopharm Belgium; Treatment of pulmonary arterial hypertension (PAH)

COMP Rapporteur: Lenka Gaidadzi

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

A clinically relevant advantage was argued on the basis of improved efficacy. However, significant benefit of the proposed product over the medicinal products authorized for the treatment of PAH in the drug classes of nitric oxide pathway modulators (PDE-5 inhibitors, soluble guanylate cyclase stimulator) and prostacyclin derivatives (prostacyclins, prostacyclin receptor agonist) have not been provided.

The applicant was requested to discuss significant benefit of the proposed product vs the drug classes of nitric oxide pathway modulators and prostacyclin derivatives.

In the written response, the sponsor provided an indirect comparison of efficacy data, i.e. the six-minute walk test (6MWT), between the proposed product to drugs targeting prostacyclin and nitric oxide pathways, based on available data from literature. The published data indicated that the average 6MWD increases for drugs in prostacyclin pathway and nitric oxide pathway are around 25.8m and 41.7m, respectively. While the 79m increase of 6MWD in average is observed in patients receiving the lowest dose of the proposed product (300mg dose, Q4W, totally for 12 weeks) in the ongoing phase 1b study.

The COMP considered that the additional information addressed the issue on significant benefit and the oral explanation was therefore cancelled.

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

The intention to treat the condition with the medicinal product containing Anti-(endothelin-1 receptor subtype A) IgG4 humanised monoclonal antibody (GMA301) was considered justified based on non-clinical in-vivo data in a relevant disease model and clinical data which suggest that the product is effective in reducing key pathological aspects of the disease and increasing the patients' distance walked over a span of 6 minutes (six minute walk test).

The condition is life-threatening and chronically debilitating due to progressive dyspnoea and right heart failure, leading to premature death.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing anti-(endothelin-1 receptor subtype A) IgG4 humanised

monoclonal antibody will be of significant benefit to those affected by the condition. The sponsor has provided relevant data from a valid non-clinical disease model and a clinical study which compared favorably with regards to efficacy to currently authorized medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for anti-(endothelin-1 receptor subtype A) IgG4 humanised monoclonal antibody, for treatment of pulmonary arterial hypertension, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. garadacimab - EMA/OD/0000042546

CSL Behring GmbH; Treatment of hereditary angioedema

COMP Rapporteur: Martin Mozina

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 garadacimab was considered justified based on preliminary clinical data showing a significant reduction in attacks in patients with the condition.

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 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing garadacimab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing a significant reduction in attacks in patients with the condition which compares favourably to authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for garadacimab, for treatment of hereditary angioedema, was adopted by consensus.

2.2.2. - EMA/OD/0000047544

Treatment of generalised pustular psoriasis

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 December meeting.

2.2.3. - EMA/OD/0000054314

Treatment of high-grade B-cell lymphoma

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

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 22 November 2021.]

2.2.4. - EMA/OD/0000056828

Treatment of upper tract urothelial carcinoma

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 December meeting.

2.2.5. allogeneic fetal mesenchymal stem cells - EMA/OD/0000061939

Boost Pharma ApS; Treatment of osteogenesis imperfecta

COMP Rapporteur: Dinah Duarte

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 allogeneic fetal mesenchymal stem cells was considered justified based on clinical cases showing improved lengthwise growth and significant reduction of fractures.

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.

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 allogeneic fetal mesenchymal stem cells, for treatment of osteogenesis imperfecta, was adopted by consensus.

2.2.6. vatiquinone - EMA/OD/0000064102

PTC Therapeutics International Limited; Treatment of Alpers-Huttenlocher syndrome

COMP Rapporteur: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing vatiquinone was considered justified based on preliminary clinical data suggesting an improvement in disease symptoms including seizure frequency (as compared to patient’s baseline values).

The condition is life-threatening due to premature death from hepatic failure or status epilepticus within 3 months to 12 years after onset of first symptoms and chronically debilitating due to refractory seizures, movement disorders, cognitive decline and loss of vision;

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 vatiquinone, for treatment of Alpers-Huttenlocher syndrome, was adopted by consensus.

2.2.7. retinol palmitate - EMA/OD/0000064241

Real Regulatory Limited; Prevention of bronchopulmonary dysplasia

COMP Rapporteur: Eva Malikova

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

The intention to prevent the condition with the medicinal product containing retinol palmitate was considered justified based on non-clinical data showing reduced alveolar tissue damage and bibliographic clinical data showing reduced incidence of bronchopulmonary dysplasia with the proposed product.

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

The population of patients eligible for prevention of the condition was estimated to be approximately 2 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of prevention in the European Union for the population at risk of developing the condition.

A positive opinion for retinol palmitate, for treatment of bronchopulmonary dysplasia, was adopted by consensus.

2.2.8. 3-(ethoxydifluoromethyl)-6-(5-fluoro-6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyrazine - EMA/OD/0000064779

Real Regulatory Limited; Treatment of SCN2A developmental and epileptic encephalopathy (SCN2A-DEE)

COMP Rapporteur: Giuseppe Capovilla

The Committee agreed that the condition, SCN2A 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 3-(ethoxydifluoromethyl)-6-(5-fluoro-6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyrazine was considered justified based on non-clinical in vivo data in a model of the condition showing a reduction in focal seizures.

The condition is chronically debilitating due to the occurrence of pharmaco-resistant epilepsy starting in the first years of life, autistic spectrum disorders, severe neurodevelopmental delay and can be life threatening in the most severe cases, due to sudden unexpected death in epilepsy or pulmonary infections secondary to general hypotonia.

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

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

A positive opinion for 3-(ethoxydifluoromethyl)-6-(5-fluoro-6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyrazine, for treatment of SCN2A developmental and epileptic encephalopathy, was adopted by consensus.

2.2.9. 3-(ethoxydifluoromethyl)-6-(5-fluoro-6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyrazine - EMA/OD/0000064784

Real Regulatory 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 3-(ethoxydifluoromethyl)-6-(5-fluoro-6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyrazine was considered justified based on non-clinical in vivo data in a model of the condition which showed a dose dependent inhibition of audiogenic seizures.

The condition is chronically debilitating due to early onset, pharmaco-resistant epilepsy and severe neurodevelopmental delay. Also reported are hearing problems, bone fractures secondary to prolonged seizures, laryngomalacia, scoliosis, and microcephaly. Gastrointestinal disorders are common. 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 0.01 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/for the population at risk of developing the condition.

A positive opinion for 3-(ethoxydifluoromethyl)-6-(5-fluoro-6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyrazine, for treatment of SCN8A developmental and epileptic encephalopathy, was adopted by consensus.

2.2.10. - EMA/OD/0000064907

Treatment of chronic inflammatory demyelinating polyneuropathy

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 December meeting.

2.2.11. crofelemer - EMA/OD/0000064955

Napo EU S.p.A.; Treatment of short bowel syndrome

COMP Rapporteur: Olimpia Neagu

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

The intention to treat the condition with the medicinal product containing crofelemer was considered justified based on non-clinical in vivo data and preliminary clinical data suggesting an anti-diarrhoea effect.

The condition is chronically debilitating due to severe nutritional deficiency, metabolic and/or septic complications and life-threatening due to liver failure and end stage renal disease.

The condition was estimated to be affecting approximately 0.4 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 crofelemer will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data and preliminary clinical data that demonstrate that the product may be used as complementary treatment option to the currently authorized medicine due to its faster onset of treatment effect and due to its direct anti-diarrhoea effect. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for crofelemer, for treatment of short bowel syndrome, was adopted by consensus.

2.2.12. atrasentan - EMA/OD/0000065051

Voisin Consulting Life Sciences; Treatment of primary IgA nephropathy

COMP Rapporteur: Dinah Duarte

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 atrasentan was considered justified based on non-clinical data showing a reduction of albuminuria and in urine albumin to creatinine ratio.

The condition is life-threatening and chronically debilitating due to progressive loss of kidney function leading to kidney 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 atrasentan will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that atrasentan can treat a broader patient population than the approved product, which only targets a subset of primary IgA nephropathy patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for atrasentan, for treatment of primary IgA nephropathy, was adopted by consensus.

2.2.13. copper (^{64}Cu) chloride - EMA/OD/0000065120

Advanced Center Oncology Macerata - S.r.l.; Treatment of glioma

COMP Rapporteur: Robert Nistico

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

The intention to treat the condition with the medicinal product containing copper (64Cu) chloride was considered justified based on non-clinical in vivo data that show significant tumour volume reduction and increased survival in a model of the condition, as well as preliminary clinical data showing antitumor activity of the product.

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

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

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 copper (^{64}Cu) chloride will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data showing enhanced antitumor effects of the product as compared to temozolomide. In addition, the sponsor has provided preliminary clinical data that demonstrate effects in monotherapy in patients with recurrence after treatment with temozolomide and radiotherapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for copper (^{64}Cu) chloride, for treatment of glioma, was adopted by consensus.

2.2.14. ribonucleoprotein complex composed of two sgRNA and a Cas9 nuclease targeting the human *COL7A1* gene - EMA/OD/0000065281

Branca Bunus Limited; Treatment of epidermolysis bullosa

COMP Rapporteur: Gloria Maria Palomo Carrasco

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

The intention to treat the condition with the medicinal product containing a ribonucleoprotein complex composed of two sgRNA and a Cas9 nuclease targeting the human *COL7A1* gene was considered justified based on non-clinical data in a model of the condition showing successful expression of the truncated gene, as well as deposition of type VII collagen in treated skin.

The condition is life-threatening and chronically debilitating due to blister formation in response to minor friction or trauma, resulting in multiple complications that include life-threatening infections, failure to thrive, and predisposition to the development of squamous cell carcinoma.

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 ribonucleoprotein complex composed of two sgRNA and a Cas9 nuclease targeting the human *COL7A1* gene, for treatment of epidermolysis bullosa, was adopted by consensus.

2.2.15. N-[1-((5-cyanopyridin-2-yl)methyl)-1H-pyrazol- 3-yl]-2-[4-(1-(trifluoromethyl)cyclopropyl) phenyl]acetamide - EMA/OD/0000065820

Neurocrine Therapeutics Limited; Treatment of epileptic encephalopathy with continuous spike-and-wave during sleep (EECSWS)

COMP Rapporteur: Giuseppe Capovilla

The Committee agreed that the condition, epileptic encephalopathy with continuous spike-and-wave during sleep, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing N-[1-((5-cyanopyridin-2-yl)methyl)-1h-pyrazol-3-yl]-2-[4-(1-(trifluoromethyl)cyclopropyl)phenyl]acetamide was considered justified based on non-clinical in vivo data showing a reduction in seizures in a model of the condition.

The condition is chronically debilitating due to neurocognitive regression and neuropsychological impairment.

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

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

A positive opinion for N-[1-((5-cyanopyridin-2-yl)methyl)-1h-pyrazol-3-yl]-2-[4-(1-(trifluoromethyl)cyclopropyl)phenyl]acetamide, for treatment of epileptic encephalopathy with continuous spike-and-wave during sleep, was adopted by consensus.

2.2.16. norrin (25-133), Lys86Pro - EMA/OD/0000067316

Maxia Strategies-Europe Limited; Treatment of familial exudative vitreoretinopathy

COMP Rapporteur: Tim Leest

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

The intention to treat the condition with the medicinal product containing Norrin (25-133), Lys86Pro was considered justified based on non-clinical in vivo data in relevant disease models demonstrating the ability of this product to promote capillary regrowth, induce the formation of non-fenestrated intraretinal vessels, inhibit the development of pathological neovascularization and reduce vascular permeability.

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

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 norrin (25-133), Lys86Pro, for treatment of familial exudative vitreoretinopathy, was adopted by consensus.

2.2.17. - EMA/OD/0000067714

Treatment of isolated optic neuritis

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 December meeting.

2.2.18. unesbulin - EMA/OD/0000068074

PTC Therapeutics International Limited; Treatment of soft tissue sarcoma

COMP Rapporteur: Frauke Naumann-Winter

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 unesbulin was considered justified based on non-clinical data showing tumour growth inhibition and preliminary clinical data in leiomyosarcoma patients who showed objective responses to treatment with the product.

The condition is chronically debilitating 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 unesbulin will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical showing tumour growth inhibition and preliminary clinical data as add on to authorized medicine showing responses in heavily pre-treated patients who had failed existing treatments. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.19. - EMA/OD/0000068582

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 December meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 30 November 2021.]

2.2.20. adeno-associated virus vector serotype 9 encoding the human *GRN* gene - EMA/OD/0000068610

Scendea (NL) B.V.; Treatment of frontotemporal dementia

COMP Rapporteur: Darius Matusevicius

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

The intention to treat the condition with the medicinal product containing adeno-associated virus vector serotype 9 encoding the human *GRN* gene was considered justified based on non-clinical data showing elevate levels of progranulin protein in the brain.
The condition is life-threatening and chronically debilitating due to neurological and cognitive impairment and with limited life-expectancy;
The condition was estimated to be affecting approximately 3.8 in 10,000 persons in the European Union, at the time the application was made.
The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for adeno-associated virus vector serotype 9 encoding the human *GRN* gene, for treatment of frontotemporal dementia, was adopted by consensus.

2.2.21. 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-thiocytidylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioadenylyl-(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)-P-thioadenylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-p-thioguanoylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioadenylyl-(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)-P-thioguanylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioadenylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioadenylyl-(3'-O->5'-O)-2'-O-(2-methoxyethyl)-P-thioguanylyl-(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-uridine sodium salt - EMA/OD/0000068887

AdRes EU B.V.; Treatment of cystic fibrosis (CF)

COMP Rapporteur: 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)-P-thioguanylyl-(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)-P-thioadenylyl-(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)-P-thioguanoylyl-(3’-O->5’-O)-2’-O-(2-methoxyethyl)-P-thioadenylyl-(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)-P-thioguanylyl-(3’-O->5’-O)-2’-O-(2-methoxyethyl)-P-thioadenylyl-(3’-O->5’-O)-2’-O-(2-methoxyethyl)-P-thioadenylyl-(3’-O->5’-O)-2’-O-(2-methoxyethyl)-P-thioguanylyl-(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-uridine sodium salt was considered justified based on non-clinical in vitro/ex vivo data in respiratory epithelial cells from CF patients carrying at least one *CFTR* allele with the 3849+10Kb C-to-T mutation showing restoration of *CFTR.*

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)-P-thioguanylyl-(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)-P-thioadenylyl-(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)-P-thioguanoylyl-(3’-O->5’-O)-2’-O-(2-methoxyethyl)-P-thioadenylyl-(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)-P-thioguanylyl-(3’-O->5’-O)-2’-O-(2-methoxyethyl)-P-thioadenylyl-(3’-O->5’-O)-2’-O-(2-methoxyethyl)-P-thioadenylyl-(3’-O->5’-O)-2’-O-(2-methoxyethyl)-P-thioguanylyl-(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-uridine sodium salt will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vitro/ex vivo data showing restoration of CFTR in cells from patients heterozygous and also homozygous for the 3849 +10kb C-to-T mutation, not 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)-P-thioguanylyl-(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)-P-thioadenylyl-(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)-P-thioguanoylyl-(3’-O->5’-O)-2’-O-(2-methoxyethyl)-P-thioadenylyl-(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)-P-thioguanylyl-(3’-O->5’-O)-2’-O-(2-methoxyethyl)-P-thioadenylyl-(3’-O->5’-O)-2’-O-(2-methoxyethyl)-P-thioadenylyl-(3’-O->5’-O)-2’-O-(2-methoxyethyl)-P-thioguanylyl-(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-uridine sodium salt, for treatment of cystic fibrosis, was adopted by consensus.

2.2.22. - EMA/OD/0000069185

Treatment of primary biliary cholangitis

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

2.2.23. troriluzole hydrochloride - EMA/OD/0000069239

Biohaven Pharmaceutical Ireland DAC; Treatment of spinocerebellar ataxia

COMP Rapporteur: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing troriluzole hydrochloride was considered justified based on preliminary clinical data suggesting attenuation of disease progression in patients with spinocerebellar ataxia.

The condition is chronically debilitating due to slowly progressive incoordination of gait which is often associated with poor coordination of hands, speech, and eye movements.

The condition was estimated to be affecting approximately 0.3 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for troriluzole hydrochloride, for treatment of spinocerebellar ataxia, was adopted by consensus.

2.2.24. octreotide acetate - EMA/OD/0000069399

Granzer Regulatory Consulting & Services; Treatment of idiopathic intracranial hypertension

COMP Rapporteur: Darius Matusevicius

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

The intention to treat the condition with the medicinal product containing octreotide acetate was considered justified based on bibliographical clinical data showing an improvement in visual acuity and a reduction in intractable headaches.

The condition is chronically debilitating due to impaired vision and refractory headache.

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

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

A positive opinion for octreotide acetate, for treatment of idiopathic intracranial hypertension, was adopted by consensus.

2.2.25. - EMA/OD/0000069661

Treatment of sarcoidosis

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 December meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 11 November 2021.]

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 16 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 15 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 multiple myeloma

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 primary hyperoxaluria

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 soft tissue sarcoma

The finalised letter was circulated for information.

3.2.2. -

Treatment of glioma

The finalised letter was circulated for information.

3.2.3. -

Treatment of haemophilia A

The finalised letter was circulated for information.

3.2.4. -

Treatment of glioma

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of primary IgA nephropathy

Postponed.

3.3.2. -

Treatment of myasthenia gravis

The new request was noted.

3.3.3. -

Treatment of tuberous sclerosis

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. Aspaveli – pegcetacoplan - EMEA/H/C/005553, EU/3/17/1873, EMA/OD/0000072952

Swedish Orphan Biovitrum AB (publ); Treatment of paroxysmal nocturnal haemoglobinuria

COMP Rapporteurs: Karri Penttila; Armando Magrelli

An opinion recommending not to remove Aspaveli, pegcetacoplan, EU/3/17/1873 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. Tavneos – avacopan - EMEA/H/C/005523/0000

Vifor Fresenius Medical Care Renal Pharma France

COMP Rapporteurs: Elisabeth Johanne Rook; Darius Matusevicius

a) Treatment of microscopic polyangiitis, EMA/OD/149/14, EU/3/14/1372, EMA/OD/0000063037

b) Treatment of granulomatosis with polyangiitis, EMA/OD/150/14, EU/3/14/1373, EMA/OD/0000062280

The status of the procedure at CHMP was noted.

An opinion recommending not to remove Tavneos, avacopan, EU/3/14/1372 and EU/3/14/1373 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 November meeting.]

4.2.2. Lonapegsomatropin Ascendis Pharma - lonapegsomatropin - EMEA/H/C/005367, EU/3/19/2213, EMA/OD/0000059751

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

COMP Rapporteurs: Elisabeth Rook; Vallo Tillmann

The status of the procedure at CHMP was noted.

An opinion recommending not to remove Lonapegsomatropin Ascendis Pharma, lonapegsomatropin, EU/3/19/2213 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 November meeting.]

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

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

COMP Rapporteurs: Bożenna Dembowska-Bagińska; Elisabeth Johanne Rook

The status of the procedure at CHMP was noted.

An opinion recommending not to remove Voraxaze, glucarpidase, EU/3/02/128 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 November meeting.]

4.2.4. Uplizna – inebilizumab - EMEA/H/C/005818/0000, EMA/OD/267/16, EU/3/17/1856, EMA/OD/0000055830

Viela Bio B.V.; Treatment of neuromyelitis optica spectrum disorders

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 December meeting.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 5 applications.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

None

5.3. Appeal

None

5.4. On-going procedures

None

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP membership

The COMP noted Mrs Vlasta Zavadova as new COMP member representing Liechtenstein.

7.1.2. Vote by proxy

None

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

The COMP noted the final agenda and organisational details of the meeting.

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 29 October 2021.

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

Postponed

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report

Documents were tabled for information.

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

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

None

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

None

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

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

None

7.7. COMP work plan

None

7.8. Planning and reporting

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

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2021 were circulated.

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

8.1. Real World Evidence pilot with COMP

Action: For discussion

The COMP noted the follow-up presentation from the June plenary. The ongoing initiative in Real World Evidence (RWE) can be grouped into two categories: i) to study and characterise Real World Data/Evidence included in applications with the aim to provide guidance to applicants; ii) for the network to be able to generate RWE to support the committee's decision making. The presentation focused on the latter.

A catalogue of data sources was under development (Q4 2022). The network could generate RWE through studies performed on the data sources accessible through the EMA framework contract, and from 2022 onwards, through DARWIN EU.

The EMA presented the progress on the proof of concept for COMP The objectives are:

- to collect as many examples as possible where RWE could be useful to support decision-making,
- to provide at least two RWE analyses and evaluate their added value,
- to determine feasibility and an optimal approach for processes and selection of data sources.

Furthermore, two situations were identified when to request an analysis:

i). During a specific regulatory procedure: identified preparing and commenting the assessment reports, or during the discussions.

ii). Outside the context of a specific regulatory procedure: for particular diseases of interest, when information is lacking.

The identified steps for proof of concept with COMP are:

1. Send email proposing a research question

2. TDA-DAT will quickly look at the databases available in-house

3. A short teleconference is organised with the requesters to review preliminary results

4. TDA-DAT will prepare the draft results

5. The report is delivered to the requesters

6. The report is published on the EU PAS Register for transparency

An example on narcolepsy was presented to show how to request an analysis.

9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 3-5 November 2021 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova - Beninska	Chair via WebEx	Netherlands	No interests declared	
Armando Magrelli	Vice-chair via WebEx	Expert recommended by EMA	No interests declared	
Brigitte Schwarzer-Daum	Member via WebEx	Austria	No restrictions applicable to this meeting	
Tim Leest	Member via WebEx	Belgium	No interests declared	
Lyubina Racheva Todorova	Member via WebEx	Bulgaria	No interests declared	
Dinko Vitezic	Member via WebEx	Croatia	No interests declared	
Lenka Gaidadzi	Member via WebEx	Czechia	No interests declared	
Elisabeth Penninga	Member via WebEx	Denmark	No interests declared	
Vallo Tillmann	Member via WebEx	Estonia	No interests declared	
Karri Penttilä	Member via WebEx	Finland	No interests declared	
Cecile Dop	Member via WebEx	France	No restrictions applicable to this meeting	
Frauke Naumann-Winter	Member via WebEx	Germany	No interests declared	
Zsofia Gyulai	Member via WebEx	Hungary	No interests declared	
Geraldine O'Dea	Member via WebEx	Ireland	No interests declared	

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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Giuseppe Capovilla	Member via WebEx	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert via WebEx*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Franziska Wolter	Expert via WebEx*	Germany	No interests declared	
	Patient expert via WebEx*	Netherlands	No interests declared	
	Patient expert via WebEx*	Netherlands	No interests declared	
	Observer via WebEx*		Confidentiality agreement	
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/