20 January 2022
EMA/COMP/778269/2021
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 07-09 December 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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Table of contents

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 7-9 December 2021 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 3-5 November 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. efgartigimod alfa - EMA/OD/0000064907

Argenx; Treatment of chronic inflammatory demyelinating polyneuropathy (CIDP)

COMP Rapporteur: Darius Matusevicius

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

- Significant benefit

The arguments on significant benefit were based on an alternative mechanism of action and the potential improved efficacy in the condition.

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

In the written response, the sponsor presented additional preliminary results from the Stage A of their ongoing study. It included patients on active treatment with immunoglobulin (intravenous or subcutaneous immunoglobulins [IVIg or SCIg]) or corticosteroids until the end of the screening phase, and also allows treatment-naïve patients, including patients not receiving CIDP treatment for at least 6 months. Patients were treated with efgartigimod subcutaneously for a maximum of 12 weeks to demonstrate clinical improvement, as defined by the evidence of clinical improvement (ECI) criteria. Patients who had not shown ECI at two consecutive visits (i.e., confirmed ECI) by week 12, as well as patients who withdraw early from Stage A, were considered non-responders.

The COMP noted that, in the preliminary observation, patients with unstable CIDP and with functional limitations despite previous treatment with currently authorized products (corticosteroids or IVIg/SCIg) respond to the treatment. Key clinical parameters (inflammatory neuropathy cause and treatment - INCAT, Inflammatory Rasch-built Overall Disability Scale - I-RODS scales and/or grip strength) supports the assumption that efgartigimod could provide significant benefit over authorized products. This response is similar to the one presented in treatment of naive patients' group.

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

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

The intention to treat the condition with the medicinal product containing efgartigimod alfa was considered justified based on preliminary clinical data showing a reduction in inflammation and an improvement in muscle strength.

The condition is chronically debilitating and life threatening due to an impairment of motor and sensory functions, resulting in inability to walk without help in a majority of patients.

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 efgartigimod alfa will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a reduction in inflammation and an improvement in muscle strength in patients with unstable chronic inflammatory demyelinating polyneuropathy with functional limitations despite previous treatment with currently authorised medications. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for efgartigimod alfa, for treatment of chronic inflammatory demyelinating polyneuropathy, was adopted by consensus.

2.1.2. - EMA/OD/0000054314

Treatment of high-grade B-cell lymphoma

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 22 November 2021, prior to responding to the list of issues.

2.1.3. - EMA/OD/0000068582

Treatment of multiple myeloma

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 30 November 2021, prior to responding to the list of issues.

2.1.4. - EMA/OD/0000069661

Treatment of sarcoidosis

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 11 November 2021, prior to responding to the list of issues.

2.1.5. - EMA/OD/0000056828

Treatment of upper tract urothelial carcinoma (UTUC)

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

- Intention to diagnose, prevent or treat

The arguments provided by the sponsor were not considered sufficient to justify upper tract urothelial carcinoma as a distinct medical entity for the purpose of orphan medicinal product designation. The sponsor was invited to discuss the overlaps between various types of urothelial cancer, in the context of the fact that both UTUC and bladder cancer arise from the same tissue type.

- Prevalence

The prevalence calculation was an extrapolation based on incidence data for bladder cancer as well as the assumption that bladder cancer and UTUC make up 90% and 10% of urothelial carcinoma, respectively. The robustness of the data and assumptions used for this calculation was requested to be discussed in more detail.

- Significant benefit

To support the argument for significant benefit based on a clinically relevant advantage, the sponsor was asked to include a more detailed discussion to clarify the target population for which the product is envisaged. A direct or indirect comparison of efficacy was found necessary to support significant benefit over authorized products.

In the written response, and during an oral explanation before the Committee on 7 December 2021, the sponsor included an extensive discussion on the nature and origin of the urothelial tissues in the upper and lower urinary tract. During the oral explanation, the sponsor pointed out that the morphological similarities between upper and lower urothelial tissues are mainly found in a healthy state. The different embryonic origins of the tissues,

which result in different lymphatic drainage, and mutation frequencies associated with UTUC and UCB affect disease progression and response to treatment. According to the sponsor, knowledge on the two diseases is constantly generated and published, and it is likely that UTUC will be accepted as a distinct medical entity in a few months-years. A discussion took place on the lack of international classification of the disease and that two ICD-11 codes are clustered for UTUC, especially since this is a hierarchical classification system and the two combined codes are based on localization. The question regarding the robustness of the assumptions used for the prevalence calculation was not addressed in great detail. With regards to the significant benefit, the sponsor clarified that the target population was patients with low-grade UTUC, for which nephron-sparing surgery is the standard of care, although it is often the case that patients with low-grade UTUC will go on to receive nephroureterectomy as the disease is highly recurrent. The sponsor stated that the products listed in the summary report are authorised for treatment of locally advanced or metastatic disease and would not be expected to be used in patients with low-grade disease. Therefore, the sponsor argued that an indirect or direct comparison is not appropriate.

Although some of the issues were properly addressed and/or clarified, the COMP did not consider that the sponsor had justified UTUC as a distinct medical entity in the context of the current EU regulatory framework.

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

2.1.6. chimeric peptide of human glucagon-like peptide-1, glucagon and gastric inhibitory polypeptide analogues linked to a human immunoglobulin Fc fragment - EMA/OD/0000069185

JVM Europe B.V.; Treatment of primary biliary cholangitis (PBC)

COMP Rapporteur: Geraldine O'Dea

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

- Significant benefit

The sponsor at this stage was positioning the product as a second line therapy analogous to obeticholic acid. However, in reality second line therapy is ursodeoxycholic acid (UDCA) and obeticholic acid in combination. In addition, therapy with UDCA can delay/prevent progression of fibrosis in patients with PBC. Based on the pre-clinical study design, it is possible that the therapy modified the development of fibrosis rather than reduced pre-existing fibrosis and it is not clear whether the same effect would have been demonstrated by treatment with UDCA.

Therefore, the sponsor was requested to justify the positioning of the proposed product as second line therapy and to demonstrate significant benefit compared to UDCA.

In the written response, the sponsor presented evidence from additional non-clinical in vivo studies to support the assumption of significant benefit of the proposed product over UDCA and its treatment (and preventive) effects on fibrosis. The non-clinical in vivo efficacy study in one of the disease models suggest that the proposed product halts progression of fibrosis and possibly also reduce existing fibrosis in this model. Therefore, the presented additional data was considered acceptable by the COMP to support significant benefit of the proposed

product vs authorized therapies, for the purpose of initial orphan designation. The oral explanation was therefore cancelled.

The Committee agreed that the condition, primary biliary 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 in vivo data in valid disease models showing marked reduction of portal inflammation, parenchymal necrosis, bile duct hyperplasia, and liver fibrosis.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 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/to the population at risk of developing the condition. The sponsor has provided non-clinical in vivo data in valid disease models showing a reduction in liver fibrosis compared to the effects observed with authorized products. 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 biliary cholangitis, was adopted by consensus.

2.1.7. - EMA/OD/0000047544

Treatment of generalised pustular psoriasis (GPP)

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

While the sponsors arguments for GPP as a distinct disease entity from psoriasis are acknowledged, the COMP did not agree with this position. While certain aspects in the underlying pathophysiology may be different in the various psoriasis types, there is also considerable overlap.

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of GPP the sponsor was requested to further elaborate on:

- the unique features of GPP allowing to differentiate from other types of psoriasis (e.g. palmoplantar pustulosis),

- the overlaps in triggers, pathophysiology, clinical presentation and treatment approaches and responses between GPP and other types of psoriasis.

- 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 provide a prevalence calculation of the final proposed condition.

- Significant benefit

The claim of significant benefit was requested to be established with regards to authorized medicinal products in the final proposed condition.

In the written response and during an oral explanation on 8 December 2021, the COMP carefully considered the sponsor's responses but concluded that the totality of currently available information does not allow a definite conclusion over GPP being a distinct medical entity and outside of the overarching disease spectrum of psoriasis. The COMP emphasized that the committee operates within a regulatory framework which selects the overarching disease entity instead of disease subsets for the purpose of orphan designations. While deviations from this concept are possible, clear supportive evidence is considered necessary. In the case of GPP, there appears to be some overlap with other forms of psoriasis such as the more common plaque psoriasis (*Psoriasis vulgaris*, PV). Treatment response has been reported in GPP patients also to classes of medicinal products successfully used in PV, such as IL-17 antagonists and anti-TNF agents. Furthermore, GPP and PV sometimes co-present in patients and its link to plaque psoriasis lesions is not yet fully clear. During the oral hearing the sponsor also mentioned a possible crosstalk downstream of the IL-36 and the IL-17 pathways. Another knowledge gap appeared to be the spectrum of underlying genetic factors contributing to GPP. In about 30% of GPP patients a mutation in the IL-36R encoding gene can be identified, leading to IL-36 overactivation. Mutations in the *AP1S3*, *MPO* and *SERPIN3* genes have also been linked to GPP. However, in a large proportion of patients the underlying genetic predisposing factors are not known (Uppala *et al.*, 2021, Cell Mol Immunol. 2021 Feb;18(2):307-317. doi: 10.1038/s41423-020-0519-3. Epub 2020 Aug 19). Also, environmental factors such as specific viral or bacterial infections or exposure to triggering drugs have been reported as being linked with pustular psoriasis and GPP flares. While the COMP did not dispute the role of IL-36 as driving disease factor in a subset of GPP patients nor the distinct clinical presentation of GPP vs PV, the committee did not consider that the totality of data is sufficient to conclude on GPP being a distinct disease entity, outside of the psoriasis disease spectrum.

While two COMP members agreed to the sponsor's description of GPP as a distinct medical entity, overall the COMP committee considered that the most appropriate overarching disease entity for the purpose of orphan designation is 'treatment of psoriasis'.

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

2.1.8. - EMA/OD/0000067714

Treatment of isolated optic neuritis

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

- Intention to diagnose, prevent or treat

The COMP was of the opinion that optic neuritis is the appropriate condition. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

- Significant benefit

The sponsor was requested to discuss significant benefit of the proposed product applied for versus authorized medicinal products, i.e. corticosteroids, in the final orphan condition.

In the written response, the sponsor accepted the change of the condition to optic neuritis (ON). The sponsor declined to attend the oral explanation. With respect to the responses submitted in relation to the significant benefit question, the COMP discussed the robustness of the sponsor's responses within the context of the established use of corticosteroids to treat the condition. The sponsor presented older and more recent studies (2001-2014) showing the limitation of corticoids in the treatment of ON. In the sponsor's opinion, there is an unmet medical need for treatment of ON. The potential positive effect of the proposed product is highlighted again with data from the same studies as in a previous submission.

The COMP was of the opinion that the sponsor did not provide any new data supporting the significant benefit of proposed product over corticosteroids. The fact that corticosteroids only have a limited effect in the treatment of ON was not considered a relevant argument as there is no data to show that the proposed product would bring a significant benefit over corticosteroids. It was concluded that it was not possible at this time to recommend granting of the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 9 December 2021, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. navtemadlin - EMA/OD/0000065122

Yes Pharmaceutical Development Services GmbH; Treatment of Merkel cell carcinoma

COMP Rapporteur: Brigitte Schwarzer-Daum

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

The intention to treat the condition with the medicinal product containing navtemadlin was considered justified based on preliminary clinical data showing responses in heavily pre-treated patients with advanced Merkel cell carcinoma.

The condition is chronically debilitating due to aggressive skin lesions and neuroendocrine features and life-threatening with limited life expectancy in patients with advanced disease state.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing navtemadlin will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that showed responses in heavily pre-treated patients with advanced disease who have no other therapeutic options. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for navtemadlin, for treatment of Merkel cell carcinoma, was adopted by consensus.

2.2.2. insulin human - EMA/OD/0000065934

Sirius Regulatory Consulting EU Limited; Prevention of retinopathy of prematurity

COMP Rapporteur: Tim Leest

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 insulin human was considered justified based on non-clinical in vivo data which showed an improvement regarding the avascular area following Oxygen-Induced-Retinopathy and better vessel density at Day 14.

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

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

A positive opinion for insulin human, for prevention of retinopathy of prematurity, was adopted by consensus.

2.2.3. mRNA encoding human glucose-6-phosphatase variant S298C - EMA/OD/0000067342

Moderna Biotech Spain S.L.; Treatment of glycogen storage disease type Ia (GSD1a)

COMP Rapporteur: Lyubina Racheva Todorova

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

The intention to treat the condition with the medicinal product containing mRNA encoding human glucose-6-phosphatase variant S298C was considered justified based on non-clinical in vivo studies in a model of the condition, which show dose-dependent improvement of fasting blood glucose levels and hG6Pase-α S298C levels and activity in the liver.

The condition is life-threatening due to complications arising from hypoglycaemic events and chronically debilitating due to the risk of such events, the need for regular consumption of meals throughout the night, and organ dysfunction due to substrate accumulation.

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

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

A positive opinion for mRNA encoding human glucose-6-phosphatase variant S298C, for treatment of glycogen storage disease type Ia, was adopted by consensus.

2.2.4. fasudil hydrochloride - EMA/OD/0000068027

Granzer Regulatory Consulting & Services; Treatment of amyotrophic lateral sclerosis

COMP Rapporteur: Robert Nistico

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

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

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure. The survival of the patients is usually limited to 2-3 years.

The condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing fasudil hydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate that fasudil can attenuate motor decline in a valid model of the condition. In addition, preliminary clinical data showed a positive trend in motor function in combination with the only approved medicinal product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for fasudil hydrochloride, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.5. - EMA/OD/0000068060

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 January meeting.

2.2.6. N-sulfoglucosamine sulfohydrolase fused to a humanised monoclonal antibody targeting human transferrin receptor- EMA/OD/0000068755

Artemida Pharma Europe Limited; Treatment of mucopolysaccharidosis Type IIIA, Sanfilippo syndrome

COMP Rapporteur: Julian Isla

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

The intention to treat the condition with the medicinal product containing N-sulfoglucosamine sulfohydrolase fused to a humanised monoclonal antibody targeting human transferrin receptor was considered justified based on non-clinical in vivo studies that show dose-dependent reduction of heparan sulfate levels in organs as well as the brain and CSF, and dose-dependent reduction of pathologic substrate accumulation in CNS tissues.

The condition is life-threatening and chronically debilitating due to complications arising from SGSH deficiency, including severe neurological symptoms, organ failure, and death in the second or third decade of life.

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 N-sulfoglucosamine sulfohydrolase fused to a humanised monoclonal antibody targeting human transferrin receptor, for treatment of mucopolysaccharidosis type IIIA (Sanfilippo A syndrome), was adopted by consensus.

2.2.7. gadolinium-chelated polysiloxane nanoparticles - EMA/OD/0000069392

Nh Theraguix; Treatment of glioma

COMP Rapporteur: Brigitte Schwarzer-Daum

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

The intention to treat the condition with the medicinal product containing gadolinium-chelated polysiloxane nanoparticles was considered justified based on non-clinical in vivo studies showing a survival benefit when combining the product with radiotherapy and temozolomide.

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 2.7 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 gadolinium-chelated polysiloxane nanoparticles will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate that combining the product with radiotherapy, as well as radiotherapy and temozolomide, results in improved survival. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for gadolinium-chelated polysiloxane nanoparticles, for treatment of glioma, was adopted by consensus.

2.2.8. - EMA/OD/0000069751

Treatment of pancreatic cancers

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 January meeting.

2.2.9. - EMA/OD/0000070454

Treatment of amyotrophic lateral sclerosis (ALS)

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 January meeting.

2.2.10. olorofim - EMA/OD/0000070461

F2G Biotech GmbH; Treatment of invasive scopulariopsis

COMP Rapporteur: Olimpia Neagu

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

The intention to treat the condition with the medicinal product containing olorofim was considered justified based on preliminary clinical data showing complete response in patients who had failed to respond to previous combination antifungal therapy.

The condition is life-threatening due to infections caused by *Scopulariopsis spp*. being associated with high mortality among immunocompromised patients.

The condition was estimated to be affecting approximately 0.005 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 olorofim will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing complete response in patients who had failed to respond to previous combination antifungal therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for olorofim, for treatment of invasive scopulariopsis, was adopted by consensus.

2.2.11. 5-((4'-(3,3-difluorocyclobutyl)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-4-carboxylic acid - EMA/OD/0000071191

Voisin Consulting Life Sciences; Treatment of primary hyperoxaluria

COMP Rapporteur: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing 5-((4'-(3,3-difluorocyclobutyl)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-4-carboxylic acid was considered justified based on non-clinical in vivo data showing decrease in urinary oxalate and increase in urinary glycolate.

The condition is life-threatening and chronically debilitating due to recurrent nephrolithiasis and progressive nephrocalcinosis leading to renal insufficiency. The majority of the patients develop end stage renal disease during the 3rd to 5th decade of life.

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 5-((4'-(3,3-difluorocyclobutyl)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-4-carboxylic acid will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate that the proposed product achieved higher reduction in 24h urinary oxalate compared to the authorised medicinal product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 5-((4'-(3,3-difluorocyclobutyl)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-4-carboxylic acid, for treatment of primary hyperoxaluria, was adopted by consensus.

2.2.12. 5' moe^{m}C-(sp)-moe^{m}C-(p)-moeA-(p)-moe^{m}C-(p)-moeG-(p)-moeA-(p)-d^{m}C-(sp)-dA-(sp)-dT-(sp)-dA-(sp)-dT-(sp)-dT-(sp)-dT-(sp)-dT-(sp)-dT-(sp)-d^{m}C-(sp)-moeT-(p)-moeA-(sp)-moe^{m}C-(sp)-moeA 3' - EMA/OD/0000071211

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 5'-moe^{m}C-(sp)-moe^{m}C-(p)-moeA-(p)-moe^{m}C-(p)-moeG-(p)-moeA-(p)-d^{m}C-(sp)-dA-(sp)-dT-(sp)-dA-(sp)-dT-(sp)-dT-(sp)-dT-(sp)-dT-(sp)-dT-(sp)-d^{m}C-(sp)-moeT-(p)-moeA-(sp)-moe^{m}C-(sp)-moeA 3' was considered justified based on non-clinical in vivo data in a model of the condition showing a reduction in seizures and interictal spikes and improvement in survival.

The condition can be 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 5'-moe^{m}C-(sp)-moe^{m}C-(p)-moeA-(p)-moe^{m}C-(p)-moeG-(p)-moeA-(p)-d^{m}C-(sp)-dA-(sp)-dT-(sp)-dA-(sp)-dT-(sp)-dT-(sp)-dT-(sp)-dT-(sp)-dT-(sp)-d^{m}C-(sp)-moeT-(p)-moeA-(sp)-moe^{m}C-(sp)-moeA 3', for treatment of *SCN2A* developmental and epileptic encephalopathy, was adopted by consensus.

2.2.13. adeno-associated virus serotype 9 expressing the human fukutin-related protein and target sequence of the miR-208a - EMA/OD/0000071268

Atamyo Therapeutics; Treatment of limb girdle muscular dystrophy (LGMD)

COMP Rapporteur: Zsofia Gyulai

The Committee agreed that the condition, limb-girdle muscular dystrophy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated virus serotype 9 expressing the human fukutin related protein and target sequence of the miR-208a was considered justified based on non-clinical in vivo data showing an improvement in global muscle strength and serum and muscle tissue biomarkers.

The condition is chronically debilitating due to muscle wasting, consequent reduced mobility and debilitating fatigue and potentially life threatening due to respiratory complications.

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 adeno-associated virus serotype 9 expressing the human fukutin related protein and target sequence of the miR-208a, for treatment of limb-girdle muscular dystrophy, was adopted by consensus.

2.2.14. melatonin - EMA/OD/0000071311

Worphmed S.r.l.; Treatment of pre-eclampsia

COMP Rapporteur: Geraldine O'Dea

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

The intention to treat the condition with the medicinal product containing melatonin was considered justified based on data in non-clinical in vivo models demonstrating a lowering of blood pressure and reducing urine protein content as well as favourable effects on foetal

outcome; and based on clinical data suggesting an extended time interval from diagnosis to delivery.

The condition is life-threatening due to seizures and risk of maternal and foetal death.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing melatonin will be of significant benefit to those affected by the condition. The sponsor has provided clinical data from literature suggesting that melatonin use as adjunct to anti-hypertensive standard of care therapy extended the time interval from diagnosis to delivery. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for melatonin, for treatment of pre-eclampsia, was adopted by majority (22 out of 27 votes).

The divergent positions (*Brigitte Schwarzer-Daum, Ines Alves, Julian Isla, Martin Mozina, Zsofia Gyulai)* were appended to this opinion.

The Norwegian COMP member agreed with the above-mentioned recommendation of the COMP.

2.2.15. azithromycin dihydrate - EMA/OD/0000071547

Vale Pharmaceuticals 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 azithromycin dihydrate was considered justified based on literature data showing reduction of deaths and cases of bronchopulmonary dysplasia in preterm neonates and infants.

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

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

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

A positive opinion for azithromycin dihydrate, for prevention of bronchopulmonary dysplasia, was adopted by consensus.

2.2.16. trans N-ethyl-2-((4-(7-((4-(ethylsulfonamido)cyclohexyl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide sesquifumarate - EMA/OD/0000071656

Syndax Europe B.V.; Treatment of acute myeloid leukaemia

COMP Rapporteur: Frauke Naumann-Winter

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 trans N-ethyl-2-((4-(7-((4-(ethylsulfonamido)cyclohexyl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide sesquifumarate was considered justified based on preliminary clinical data showing responses in patients with relapsed/refractory acute myeloid leukaemia.

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

The condition was estimated to be affecting approximately 1.3 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 trans N-ethyl-2-((4-(7-((4-(ethylsulfonamido)cyclohexyl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide sesquifumarate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data which showed responses in heavily pretreated patients with relapsed/refractory acute myeloid leukaemia. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for trans N-ethyl-2-((4-(7-((4-(ethylsulfonamido)cyclohexyl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide sesquifumarate, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.17. sirolimus - EMA/OD/0000071679

Maxia Strategies-Europe Limited; Treatment of bronchiolitis obliterans syndrome (BOS)

COMP Rapporteur: Eva Malikova

The Committee agreed that the condition, bronchiolitis obliterans syndrome, 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 data in a valid non-clinical disease model demonstrating a reduction of fibrous luminal airway obliterations and based on clinical data suggesting improved survival in patients treated with immunosuppressive regimens containing sirolimus.

The condition is chronically debilitating based on bronchiolar obstruction and fibrosis of bronchioles and life threatening due to the progressive nature of the condition leading to death caused by pulmonary insufficiency.

The condition was estimated to be affecting approximately 4.4 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 sirolimus, for treatment of bronchiolitis obliterans syndrome, was adopted by consensus.

2.2.18. adeno-associated virus vector serotype 2 expressing the human MT-*ND4* codon-optimised gene - EMA/OD/0000071835

IQVIA RDS Spain S.L.; Treatment of Leber's hereditary optic neuropathy

COMP Rapporteur: Tim Leest

The Committee agreed that the condition, Leber's hereditary optic neuropathy, 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 2 expressing the human MT-*ND4* codon-optimised gene was considered justified based on preliminary clinical data showing an improvement in visual acuity which was sustained over a period of at least 60 months.

The condition is chronically debilitating due to visual loss and development of blindness.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated virus vector serotype 2 expressing the human MT-*ND4* codon-optimised gene will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a sustained improvement in visual acuity in the ND4 mutation patient population which is not shown with the only authorised medicinal product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus vector serotype 2 expressing the human MT-*ND4* codon-optimised gene, for treatment of Leber's hereditary optic neuropathy, was adopted by consensus.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

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

COMP coordinators were appointed for 16 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 14 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of myasthenia gravis

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 tuberous sclerosis

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 multiple myeloma

The finalised letter was circulated for information.

3.2.2. -

Treatment of multiple myeloma

The finalised letter was circulated for information.

3.2.3. -

Treatment of primary hyperoxaluria

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of primary IgA nephropathy

The new request was noted.

3.3.2. -

Treatment of cystic fibrosis

The new request was noted.

3.3.3. -

Treatment of neuronal ceroid lipofuscinosis

The new request was noted.

3.3.4. –

Treatment of unresectable recurrent glioblastoma/gliosarcoma

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. 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

COMP Rapporteurs: Darius Matusevicius; Armando Magrelli

A list of issues was adopted on 05 November 2021.

An oral explanation was held on 08 December 2021.

An opinion recommending the removal of Uplizna, inebilizumab, EU/3/17/1856 from the EC Register of Orphan Medicinal Products was adopted by consensus.

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 December meeting.]

4.1.2. Nexviadyme - avalglucosidase alfa - EMEA/H/C/005501/0000, EU/3/14/1251, EMA/OD/0000048959

Genzyme Europe B.V.; Treatment of Pompe's disease

COMP Rapporteurs: Armando Magrelli; Cécile Dop

A list of issues was adopted on 27 July 2021.

An oral explanation was held on 07 December 2021.

An opinion recommending the removal of Nexviadyme, avalglucosidase alfa, EU/3/14/1251 from the EC Register of Orphan Medicinal Products was adopted by consensus.

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 December meeting.]

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

4.2.1. Ngenla - somatrogon - EMEA/H/C/005633/0000, EU/3/12/1087, EMA/OD/0000063709

Pfizer Europe MA EEIG; Treatment of growth hormone deficiency

COMP Rapporteurs: Vallo Tillmann; Geraldine O'Dea

An opinion recommending not to remove Ngenla, somatrogon, EU/3/12/1087 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 December meeting.]

4.2.2. Oxbryta - 2-hydroxy-6-((2-(1-isopropyl-1h-pyrazol-5-yl)pyridin-3-yl) methoxy)benzaldehyde - EMEA/H/C/004869/0000, EU/3/16/1769, EMA/OD/0000074918

Global Blood Therapeutics Netherlands B.V.; Treatment of sickle cell disease

COMP Rapporteurs: Elisabeth Johanne Rook; Enrico Costa

An opinion recommending not to remove Oxbryta, 2-hydroxy-6-((2-(1-isopropyl-1h-pyrazol-5-yl)pyridin-3-yl) methoxy)benzaldehyde, EU/3/16/1769 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 December meeting.]

4.2.3. - tebentafusp - EMEA/H/C/004929/0000, EU/3/21/2397, EMA/OD/0000068646

Accelerated assessment

Immunocore Ireland Limited; Treatment of uveal melanoma

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 7 applications.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Polivy – polatuzumab vedotin – EMEA/H/C/004870/II/0012, EU/3/18/2013, EMA/OD/0000074173

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

CHMP Rapporteur: Alexandre Moreau, CHMP Co-Rapporteur: Jan Mueller-Berghaus

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

5.2.2. Reblozyl – luspatercept – EMEA/H/C/004444/II/0009

Bristol-Myers Squibb Pharma EEIG

Rapporteur: Daniela Philadelphy, CHMP Co-Rapporteur: Ewa Balkowiec Iskraa) Treatment of beta-thalassaemia intermedia and major EU/3/14/1300, EMA/OD/0000072540

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

b) Treatment of myelodysplastic syndromes EU/3/14/1331

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

5.2.3. Yescarta – axicabtagene ciloleucel – EMEA/H/C/004480/II/0046, EMA/OD/078/15, EU/3/15/1553

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

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

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

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for 2 applications.

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 that Mrs Lenka Gaidadzi mandate as COMP member representing Czechia has ended.

The COMP noted the new membership - Mrs Elli Loizidou replacing Mr Vasileios Loutas as member for Cyprus.

7.1.2. Vote by proxy

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

Frauke Naumann-Winter gave a proxy to Elisabeth Johanne Rook to vote on behalf of Frauke Naumann-Winter during part of December 2021 COMP meeting.

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

The Portuguese COMP member presented the feedback from the joint COMP/PDCO meeting, held on 19 November 2021, Lisbon, Portugal. The COMP noted the feedback and thanked the host for organising the successful meeting.

7.1.4. Protocol Assistance Working Group (PAWG)

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

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

Documents were tabled for information.

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

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

Documents were tabled for information.

7.4. 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

The COMP discussed the proposed draft work plan for 2022. The members were invited to add any topics and activities or sign up as contributors until January 2022 COMP meeting, when the work plan is planned to be adopted.

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. Lifecycle Regulatory Submissions Metadata Project

The COMP noted the presentation about the Lifecycle Regulatory Submissions Metadata Project.

The purpose of this project is to deliver effective generation of evidence in support of benefit/risk decision making from data-driven interrogation of scientific information within lifecycle regulatory submissions.

This EMA project was presented with emphasis on tools to facilitate the identification and investigation of unstructured documents in support of committee members and assessors. There was strong support by the committee in the potential of this concept for COMP work. Ideas were shared about elements (metadata) of particular interest to COMP members.

A call was made to invite interested COMP members to contribute in the Data Standardisation Strategy.

8.2. EMA Business Pipeline activity and Horizon scanning

The document was tabled for information.

8.3. Feedback from the ENCePP Plenary

The COMP noted the feedback from the ENCePP plenary held on 18th November 2021.

Activities of the ENCePP Steering Group and Working Groups (WGs), the renewal of the WGs, and the proposed new ENCePP activities were also presented and discussed.

9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 7-9 December 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	Member (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	
Dinko Vitezic	Member via WebEx	Croatia	No interests declared	
Lenka Gaidadzi	Member via WebEx	Czechia	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	
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 interests declared	
Elisabeth Johanne Rook	Member via WebEx	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member via WebEx	Norway	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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	
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	
Jeanette McCallion	Expert via WebEx*	Ireland	No interests declared	
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/