13 April 2022
EMA/COMP/157930/2022
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Draft minutes for the meeting on 15-17 March 2022

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

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

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced that no restriction in the involvement of meeting participants in upcoming discussions was identified as included in the pre-meeting list of participants and restrictions.

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 22 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

The agenda for 15-17 March 2022 was adopted with no amendments.

1.3. Adoption of the minutes

COMP minutes for 15-17 February 2022 were adopted with no amendments.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. - EMA/OD/0000072331

Treatment of X-linked protoporphyria (XLP)

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 09 March 2022, prior to responding to the list of issues.

2.1.2. cannabidiol - EMA/OD/0000075999

GW Pharma (International) B.V.; Treatment of epilepsy with myoclonic-atonic seizures (EMAS)

COMP Rapporteur: Giuseppe Capovilla

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

- Intention to diagnose, prevent or treat

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of epilepsy with myoclonic-atonic seizures the sponsor was asked to further elaborate on:

- the types of seizures that have been considered as convulsive;

- the benefit obtained with a partial reduction of the seizures.

- Significant benefit

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

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preliminary clinical data to justify the assumption of significant benefit over authorised medicinal products for the seizures present in the proposed orphan condition.

In the written response the sponsor highlighted that they used the EMA guidelines on the design of add-on antiseizure medication (ASM) clinical trials which cite use of the 50% responder analysis for determining whether clinical meaningfulness has been achieved (CHMP/EWP/566/98 Rev.3). This criterion was used in the Extended Access Trial which included EMAS patients, submitted to support the medical plausibility. The COMP accepted that the reductions in seizures was supportive of the medical plausibility.

Regarding significant benefit: 50% of patients with EMAS do not respond adequately to antiseizure medications (ASMs). In the expanded access trial, where several EMAS patients were enrolled, it was noted that many were on several ASMs and were still having seizures. Following treatment with cannabidiol some of the patients had reductions in seizure despite the treatment with ASMs. The COMP accepted this data for the purpose of supporting significant benefit.

The COMP decided to cancel the oral explanation and recommend granting the orphan designation.

The Committee agreed that the condition, epilepsy with myoclonic-atonic seizures, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing cannabidiol was considered justified based on preliminary clinical data showing a 50% reduction in seizures in patients who have previously received antiseizure medicines.

The condition is chronically debilitating as some of the patients do not respond well to antiseizure medications and are pharmacoresistant. They can also present with cognitive deficits and behavioural disturbances.

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 cannabidiol will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a 50% reduction in seizures in patients who are resistant to previous treatment with multiple antiseizure medications. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for cannabidiol, for treatment of epilepsy with myoclonic-atonic seizures, was adopted by consensus.

2.1.3. norucholic acid - EMA/OD/0000072395

Dr. Falk Pharma GmbH; Treatment of primary biliary cholangitis (PBC)

COMP Rapporteur: Olimpia Neagu

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

- Significant benefit

The arguments on significant benefit were based on a potential improved efficacy in the condition.

The sponsor was required to provide more detailed information to support the significant benefit of the proposed product, which is intended to be used alone or in combination with ursodeoxycholic acid (UDCA) in the treatment of patients with PBC.

In addition, the sponsor was asked to further discuss the efficacy arguments and to justify the assumption of a significant benefit of the proposed product over already authorised medicinal products for the proposed orphan 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.

The sponsor submitted a written response describing two non-clinical models which are well characterized for cholestatic liver disease: the Mdr2 (-/-) and the non-clinical model with ligated bile ducts.

In these non-clinical in vivo studies, the potentially better effects of norucholic acid (NCA) over UDCA in ameliorating several pathologic features of PBC were observed. For example, in studies with bile duct ligated in the non-clinical model, significant amelioration of liver injury was shown with NCA but not with UDCA (Fickert 2013). In contrast to UDCA treatment, treatment with NCA in Mdr2 / non-clinical model led to a marked reduction of liver enzymes (ALP and ALT), oxidative stress and attenuation of inflammatory mRNA expression of genes such as IL-1β, inducible nitric oxide synthase and macrophage inflammatory protein 2 (Fickert 2006). Furthermore, NCA reduced the size of hepatic granulomas, a specific histological feature in PBC, and hepatic fibrosis in a non-clinical model of hepatic schistosomiasis (Sombetzki 2015).

Potential benefits of using NCA and UDCA were presented in preliminary clinical data from study NUC-7/ Bio showed that when the product was used in combination there could be a clinical benefit in patients with PBC. There appears to be a synergistic effect on anti-

inflammatory, anti-lipotoxic, anti-fibrotic and anti-proliferative actions of both UDCA and NCA.

Obeticholic acid (OCA) is a selective and potent agonist for farnesoid receptor X (FXR), considered a key regulator of bile acid, inflammatory, fibrotic and metabolic pathways. FXR activation decreases bile acid concentrations by suppressing de novo cholesterol synthesis, as well as increasing the transport of bile acids from hepatocytes and thus reducing liver exposure to bile acids. This mechanism of action is different from that of the NCA which induces bicarbonate-rich hypercholeresis.

The results of clinical trials on the use of OCA in the treatment of patients with PBC and preliminary clinical data on the use of NCA in patients with non-PBC cholestatic liver disease have shown that the efficacy of the two drugs appears to be similar. Serum ALP levels (a surrogate biomarker for cholestatic liver disease) were reduced by comparable proportions by 25% for OCA and 26% for NCA, respectively. The sponsor was of the opinion that this synergistic effect could be beneficial in patients who were no longer responding adequately to UDCA. A similar line of approach was considered for OCA which the COMP accepted when the limitations of toxicity were considered.

Regarding the comparison of NCA versus cholestyramine, the sponsor suggests that cholestyramine and NCA are two complementary therapeutic options for the treatment of PBC which treat two different aspects of the disease and their clinical benefit cannot be directly compared.

The bile sequestrant cholestyramine is recommended as first-line therapy for the treatment of cholestatic pruritus (EASL guidelines 2017) and the only approved drug for the treatment of PBC-associated pruritus. Cholestyramine does not treat cholestasis and has no effect on disease progression or survival. In contrast, NCA improves cholestasis and targets the underlying liver injury and thus may improve the survival of patients with PBC.

The COMP considered that the questions had been adequately answered and the oral explanation was 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 norucholic acid was considered justified based on non-clinical in vivo data in models of the condition showing induction of bile flow and bile excretion as well as an anti-inflammatory effects and a reduction in the proliferation of hepatocytes and cholangiocytes.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing norucholic acid will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate an additional benefit in the reduction of liver injury when the product is used in combination

with ursodeoxycholic acid. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for norucholic acid, for treatment of primary biliary cholangitis, was adopted by consensus.

2.1.4. n-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine - EMA/OD/0000076085

iCoat Medical AB; treatment in solid organ transplantation

COMP Rapporteur: Martin Mozina, 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:

- Intention to diagnose, prevent or treat

Ischaemia-reperfusion injury in solid organ transplantation should be justified as a distinct medical entity or a valid subset. Considering the mechanism of action and timing of administration of this product, the COMP is of the opinion that the more suitable overarching condition is 'treatment in solid organ transplantation', for the purpose of this orphan designation.

- Number of people affected

The sponsor was requested to re-calculate the prevalence estimate in line with the final condition. For the estimation and presentation of the prevalence estimate the sponsor is advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

- Significant benefit

In light of the final condition, the sponsor was asked to justify the assumption of significant benefit within the context of authorised medicinal products, such as immunosuppressive therapy.

In the written response, the sponsor agreed with the change to the overarching condition "treatment in solid organ transplantation". The issue was therefore considered solved by the COMP.

Regarding the number of people affected, the sponsor concluded that their previous prevalence calculation and final estimate of 0.67 per 10,000 persons is still valid for the condition "treatment in solid organ transplantation". The COMP agreed with an up-rounded prevalence estimate of 0.7 per 10,000.

With regards to the significant benefit, the sponsor stated that authorized medicinal products for treatment in solid organ transplantation mainly consists of immunosuppressive therapies: glucocorticosteroids (e.g prednisolone), anti-metabolites (e.g. azathioprine), calcineurin inhibitors (e.g. tacrolimus, cyclosporine), mTOR inhibitors (e.g. everolimus), antibodies (ATG, anti-IL2R, anti-CD3, anti-CD25, anti-CD152).

The listed treatments target the adaptive immune system and focus mainly on T- and B-cell responses. Currently there is a lack of therapies that target the innate immune response that is associated with ischemia-reperfusion injury during organ transplantation. Immunosuppressive therapies are given systemically before, during or after organ

transplantation but do not target the molecular and cellular events triggered by ischemia-reperfusion injury. Events that are predominantly mediated by the innate immune system i.e. complement system and thrombo-inflammation.

The proposed product is differentiated from currently available treatments by targeting three important features:

- Timing: A transient coating to prevent the immediate ischemia-induced insult to the allograft and resulting suboptimal function.
- Mode of action: Targeting the innate immune system and vascular dysfunction. Hence, preventing thrombo-inflammation and organ injury, as shown in multiple preclinical studies.
- Administration: Local administration (ex-vivo intravascular) to the organ.

The sponsor's data for the proposed product as discussed above, provides support for a significant benefit with respect to reduced renal cell death and transplant outcomes in multiple in vivo preclinical studies. By targeting the innate immune activation, locally and preventatively, the proposed product addresses a vacant area in the solid organ transplant treatment landscape, potentially acting synergistically with existing immunosuppressive regimes to prevent delayed graft function and improve long-term graft survival.

In conclusion, the COMP considered that the sponsor addressed all issues satisfactorily and the oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing N-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine was considered justified based on pre-clinical *in vivo* data in valid models of the condition which demonstrate a reduction in ischemia reperfusion associated injury in recipients of organs injected with the product prior to transplantation.

The condition is chronically debilitating and life threatening due to delayed graft function following transplantation.

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.

In addition, although satisfactory methods of prevention of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing n-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine will be of significant benefit to the population at risk of developing the condition. The sponsor has provided non-clinical in vivo data that demonstrate a reduction in ischemia reperfusion associated injury in recipients of donor organs which is not observed with current standard of care therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for n-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine, for treatment of solid organ transplantation, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. glofitamab - EMA/OD/0000070101

Roche Registration GmbH; Treatment of mantle cell lymphoma

COMP Rapporteur: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing glofitamab was considered justified based on preliminary clinical data which showed high overall response rates in heavily pretreated patients with relapsed/refractory disease who responded to treatment with the product.

The condition is chronically debilitating due to lymphadenopathy, night sweats, fever, and weight loss and life-threatening with a median survival of 3 to 5 years.

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 glofitamab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in heavily pretreated patients with relapsed/refractory disease who responded to treatment with the proposed product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for glofitamab, for treatment of mantle cell lymphoma, was adopted by consensus.

2.2.2. adeno-associated virus serotype 9 containing human *MYBPC3* gene - EMA/OD/0000071657

Yes Pharmaceutical Development Services GmbH; Treatment of hypertrophic cardiomyopathy due to mutations in the *MYBPC3* gene encoding cardiac myosin-binding protein C

COMP Rapporteur: Eva Malikova

The Committee agreed that the condition, hypertrophic cardiomyopathy due to mutations in the *MYBPC3* gene encoding cardiac myosin-binding protein C, 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 containing human *MYBPC3* gene was considered justified based on non-clinical *in vivo* data in a valid model of the condition showing an improvement in ejection fraction, left ventricular wall thickness and survival.

The condition is life-threatening due to sudden cardiac death and chronically debilitating due to progressive heart failure in the severe forms. Most patients are asymptomatic and have a normal life expectancy.

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.

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 serotype 9 containing human *MYBPC3* gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate an improvement in ejection fraction and survival which could obviate the need for currently authorised medicines for the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus serotype 9 containing human *MYBPC3* gene, for treatment of hypertrophic cardiomyopathy due to mutations in the *MYBPC3* gene encoding cardiac myosin-binding protein C, was adopted by consensus.

2.2.3. - EMA/OD/0000072068

Treatment of focal segmental glomerulosclerosis (FSGS)

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 April meeting.

2.2.4. - EMA/OD/0000073629

Treatment of glioma

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 April meeting.

2.2.5. adeno-associated virus vector serotype 9 encoding human gigaxonin gene - EMA/OD/0000074838

Raremoon Consulting Esp S.L.; Treatment of giant axonal neuropathy

COMP Rapporteur: Gloria Maria Palomo Carrasco

The Committee agreed that the condition, giant axonal 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 9 encoding human gigaxonin gene was considered justified based on non-clinical in vivo data in models of the condition showing reduced neuronal intermediate filament inclusions, sustained expression of gigaxonin levels as well as the improvement of motor performance.
The condition is chronically debilitating due to the disorder in the lower limb gait, muscle weakness, ataxia, and gradual upper limb dysfunction which begins around 3 years of age. It is life-threatening due to respiratory failure. Most patients die during the second or third decade of life.
The condition was estimated to be affecting approximately 0.002 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 human gigaxonin gene, for treatment of giant axonal neuropathy, was adopted by consensus.

2.2.6. - EMA/OD/0000075402

Treatment of cystic fibrosis

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 April meeting.

2.2.7. human papillomavirus type 16-derived empty nanoparticle conjugated to approximately 200 molecules of a phthalocyanine-based photosensitizer - EMA/OD/0000075682

FGK Representative Service GmbH; Treatment of uveal melanoma

COMP Rapporteur: Dinko Vitezic

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

The intention to treat the condition with the medicinal product containing human papillomavirus type 16-derived empty nanoparticle conjugated to approximately 200 molecules of a phthalocyanine-based photosensitizer was considered justified based on preliminary clinical data which showed high vision preservation rates and tumour control in patients with choroidal melanoma who have not received prior therapy.

The condition is life-threatening with a reduced survival in relapsed/refractory disease and chronically debilitating especially due to enucleation and in metastatic disease due to pain, organ failure, and treatment burden.

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 human papillomavirus type 16-derived empty nanoparticle conjugated to approximately 200 molecules of a phthalocyanine-based photosensitizer will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data which demonstrate that the proposed product showed high vision preservation rates and tumour control in patients with choroidal melanoma who have not received prior therapy which cannot be achieved with the current available treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for human papillomavirus type 16-derived empty nanoparticle conjugated to approximately 200 molecules of a phthalocyanine-based photosensitizer, for treatment of uveal melanoma, was adopted by consensus.

2.2.8. devimistat - EMA/OD/0000076090

IQVIA RDS Ireland Limited; Treatment of biliary tract cancer

COMP Rapporteur: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing devimistat was considered justified based on preliminary clinical data in combination with gemcitabine and cisplatin demonstrating anti-tumour responses in treatment naïve patients affected by the condition.

The condition is chronically debilitating due to development of hepatic insufficiency, progressive biliary obstruction followed by complications such as infections, and life-threatening with a low overall median survival of less than one year following diagnosis.

The condition was estimated to be affecting approximately 1.5 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 devimistat will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the proposed product targets a broader patient population within the proposed orphan condition than the currently authorised product which is restricted to a molecular subset of the disease. The Committee considered that this constitutes a clinically relevant advantage

A positive opinion for devimistat, for treatment of biliary tract cancer, was adopted by consensus.

2.2.9. tiratricol - EMA/OD/0000076343

Rare Thyroid Therapeutics International AB; Treatment of resistance to thyroid hormone type beta

COMP Rapporteur: Vallo Tillmann

The Committee agreed that the condition, resistance to thyroid hormone type beta, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing tiratricol was considered justified based on clinical data from published case reports in patients with heterozygous and homozygous forms of the disease, demonstrating improvement of their hypothyroid and/or thyrotoxic symptoms.

The condition is chronically debilitating due to hypothyroid and/or thyrotoxic symptoms and life-threatening in patients with homozygous forms of the disease related to cardiac disorders.

The condition was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for tiratricol, for treatment of resistance to thyroid hormone type beta, was adopted by consensus.

2.2.10. - EMA/OD/0000076540

Treatment of essential thrombocythemia

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 April meeting.

2.2.11. - EMA/OD/0000076545

Prevention of spaceflight-related radiation and microgravity

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 April meeting.

2.2.12. - EMA/OD/0000076679

Treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN)

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 April meeting.

2.2.13. - EMA/OD/0000077023

Treatment of Angelman syndrome

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

2.2.14. (2S)-4-[2-methoxyethyl-[4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]amino]-2-(quinazolin-4-ylamino)butanoic acid - EMA/OD/0000077175

Pharma Gateway AB; Treatment of primary sclerosing cholangitis

COMP Rapporteur: Elisabeth Johanne Rook

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 (2S)-4-[2-methoxyethyl-[4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]amino]-2-(quinazolin-4-ylamino)butanoic acid was considered justified based on in vivo data in a valid model of the condition, which showed significantly reduced liver fibrosis and reduction of liver enzymes that are biomarkers of cholestasis and liver damage.

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

The condition was estimated to be affecting less than 3.2 in 10,000 persons in the European Union, at the time the application was made.

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

medicinal product containing (2S)-4-[2-methoxyethyl-[4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]amino]-2-(quinazolin-4-ylamino)butanoic acid 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 (2S)-4-[2-methoxyethyl-[4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]amino]-2-(quinazolin-4-ylamino)butanoic acid, for treatment of primary sclerosing cholangitis, was adopted by consensus.

2.2.15. - EMA/OD/0000077200

Treatment of COVID-19 related ARDS and survival

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 April meeting.

[Post-meeting note: The sponsor withdrew the application for orphan designation on 28 March 2022.]

2.2.16. - EMA/OD/0000077207

Treatment of epidermolysis bullosa

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 April meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 1 April 2022.]

2.2.17. obecabtagene autoleucel - EMA/OD/0000077237

Autolus GmbH; Treatment of acute lymphoblastic leukaemia

COMP Rapporteur: Bozenna Dembowska-Baginska

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 obecabtagene autoleucel was considered justified based on preliminary clinical data showing high rate of responses in heavily pre-treated patients.

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. The invasion of tumour cells in the bloodstream, the bone marrow and/or the lymphatic system result in lack of normal blood cells, bone marrow failure, and organ damage.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing obecabtagene autoleucel will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate high rate of responses in heavily pre-treated patients with relapsed/refractory acute lymphoblastic leukaemia. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for obecabtagene autoleucel, for treatment of acute lymphoblastic leukaemia, was adopted by consensus.

2.2.18. adeno-associated viral vector serotype 8 encoding B-domain deleted liver specific codon optimized bioengineered chimeric human porcine factor VIII, under a synthetic hepatic combinatorial bundle promoter - EMA/OD/0000077493

MDC RegAffairs GmbH; Treatment of haemophilia A

COMP Rapporteur: Karri Penttila

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 8 encoding B-domain deleted liver specific codon optimized bioengineered chimeric human porcine factor VIII, under a synthetic hepatic combinatorial bundle promoter was considered justified based on non-clinical in vivo data showing an increase in the serum level of Factor VIII.

The condition is chronically debilitating due to recurrent bleeding in joints, gastrointestinal tract or in surgery, which may also be life-threatening.

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 adeno-associated viral vector serotype 8 encoding B-domain deleted liver specific codon optimized bioengineered chimeric human porcine factor VIII, under a synthetic hepatic combinatorial bundle promoter will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical in vivo data that demonstrate a sustained increase in serum Factor VIII which would obviate the need for continuous replacement therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 8 encoding B-domain deleted liver specific codon optimized bioengineered chimeric human porcine factor VIII, under a synthetic hepatic combinatorial bundle promoter, for treatment of haemophilia A, was adopted by consensus.

2.2.19. adeno-associated virus serotype C102 containing the human *GLA* gene - EMA/OD/0000077524

Pharma Gateway AB; Treatment of Fabry disease

COMP Rapporteur: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing adeno-associated virus serotype C102 containing the human *GLA* gene was considered justified based on preliminary clinical data showing either a decrease in serum glycolipid substrate levels or a continued maintenance of low serum glycolipid substrate levels after discontinuation of enzyme replacement therapy.

The condition is chronically debilitating due to recurrent episodes of severe pain that do not respond to standard analgesic, and life-threatening due to renal failure, cardiovascular and cerebrovascular complications.

The condition was estimated to be affecting approximately 2.6 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 adeno-associated virus serotype C102 containing the human *GLA* gene will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data which demonstrates that a single administration of the product leads to long-term alpha-galactosidase A activity, which would obviate the need for regular treatment with the currently authorized products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus serotype C102 containing the human *GLA* gene, for treatment of Fabry disease, was adopted by consensus.

2.2.20. - EMA/OD/0000077548

Treatment of inherited retinal dystrophies due to defects in the *RPGR* gene

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 April meeting.

2.2.21. - EMA/OD/0000077756

Treatment of epidermolysis bullosa

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 April meeting.

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 36 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 mucopolysaccharidosis type I

The discussion was postponed.

3.1.2 -

Treatment of acute myeloid leukaemia

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 primary IgA nephropathy

The finalised letter was circulated for information.

3.3. New requests

3.3.1 -

Treatment of multiple myeloma

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

None

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

4.2.1. – arimoclomol - EMEA/H/C/005203/0000, EU/3/14/1376, EMA/OD/0000064667

Orphazyme A/S; Treatment of Niemann-Pick disease, type C

The status of the procedure at CHMP was noted.

[Post-meeting note: Marketing Authorisation Application had been withdrawn after the CHMP March meeting.]

4.2.2. - betulae cortex dry extract (DER 5-10: 1), extraction solvent n-heptane 95% (w/w) - EMEA/H/C/005035/0000, EU/3/10/845, EMA/OD/0000070235

Amryt Pharmaceuticals Designated Activity Company; Treatment of epidermolysis bullosa

The status of the procedure at CHMP was noted.

4.2.3. Carvykti - ciltacabtagene autoleucel - EMEA/H/C/005095/0000, EU/3/20/2252, EMA/OD/0000060914

Janssen-Cilag International N.V.; 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 April meeting.

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

Calliditas Therapeutics AB; Treatment of primary IgA nephropathy

The status of the procedure at CHMP was noted.

4.2.5. - mosunetuzumab - EMEA/H/C/005680/0000, EU/3/21/2517, EMA/OD/0000082933

Accelerated assessment

Roche Registration GmbH; Treatment of follicular lymphoma

The status of the procedure at CHMP was noted.

4.2.6. Kymriah – tisangenlecleucel - EMEA/H/C/004090/II/0044, EU/3/21/2464, EMA/OD/0000054173

Novartis Europharm Limited; Treatment of follicular 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 April meeting.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 1 application.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. 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

COMP Rapporteurs: Karri Penttila; Maria Elisabeth Kalland; CHMP Rapporteur: Alexandre Moreau; CHMP Co-Rapporteur: Jan Mueller-Berghaus

An opinion recommending not to remove Polivy, polatuzumab vedotin (EU/3/18/2013) 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 March meeting.]

5.3. Appeal

None

5.4. On-going procedures

The COMP noted the review of orphan designation for OMP for MA extension - On-going procedures

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP membership

None

7.1.2. Vote by proxy

None

7.1.3. Strategic Review & Learning meetings

The COMP noted the agenda for the joint COMP/PDCO Strategic Review & Learning meeting –meeting under the French Presidency of the Council of the EU was he to be held virtually on 31 March 2022 and topics to be discussed.

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely 14 March 2022.

7.1.5. Principal Decisions Database

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

7.1.6. Data protection notice - processing of scientific committees' members/alternates' contact details

The COMP noted the information about the data protection notice.

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)

The COMP re-nominated Tim Leest as representative to the PCWP for a new three-year mandate (June 2022 to May 2025). Further discussions on the HCPWP nomination are expected at the next COMP meeting.

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

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

None

7.7. COMP work plan

None

7.8. Planning and reporting

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

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

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

8.1. Introducing DARWIN EU® Coordination Centre and next steps for RWE

The COMP noted the presentation about the project. The process about conduct of studies in DARWIN EU® was presented. The implementation roadmap consists of 3 phases. DARWIN EU® is expected to be fully operational in 2025/2026. The next steps will be the formation of the coordination centre and to set up the project management etc.

In 2022, the onboarding of the 1st data partners will take place – primary care data, specialist use and hospital care data. Over 5 years, there will be 380 studies conducted.

The use of RWE in scientific committees has followed the pilot conducted with PRAC between 2019 and 2021. Furthermore, the pilot in SAWP has already started and the pilot is starting with COMP, PDCO and CAT.

The overview of ongoing and finalised studies was given per the type of studies. COMP example regarding narcolepsy was described. A reminder of the process for delivering RWE was presented. In addition, the members were instructed to visit the DARWIN EU® webpage and to subscribe to the to the Big Data Highlights newsletter by sending an email to: bigdata@ema.europa.eu.

COMP members are encouraged to continue sending requests for RWE.

8.2. Study on real world evidence

It was acknowledged that studies procured through the EMA new framework contract (since September 2021) is one of the workstreams to generate RWE at the agency. The COMP noted the presentation about treatment patterns and outcomes collected via real world evidence.

8.3. Orphan Maintenance Assessment Report (OMAR) updates

The discussion was postponed.

8.4. EMA Business Pipeline activity and Horizon scanning

The document was tabled for information.

9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 15-17 March 2022 meeting.

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Chair	Netherlands	No interests declared	
Armando Magrelli	Member (Vice-chair)	Expert recommended by EMA	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No restrictions applicable to this meeting	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Elli Loizidou	Member	Cyprus	No interests declared	
Jana Mazelova	Member	Czechia	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Cecile Dop	Member	France	No restrictions applicable to this meeting	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Enrico Costa	Member	Italy	No restrictions applicable to this meeting	
Irena Rogovska	Member	Latvia	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
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No restrictions applicable to this meeting	
Elisabeth Johanne Rook	Member	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Ines Alves	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Maria Cavaller Bellaubi	Expert via WebEx*	Patients' Organisation Representative	No restrictions applicable to this meeting	

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