9 September 2021
EMA/COMP/424709/2021
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 13-15 July 2021

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

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

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

Participants in this meeting were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions concerning the matters for discussion. The following additional interests and/or restrictions were declared at the start or during the meeting:

Irēna Rogovska has voluntarily refrained from any participation in the EMA/OD/0000057849 procedure.

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.

Julian Isla gave a proxy to Marie Pauline J. Evers to vote on behalf of Julian Isla during part of July 2021 COMP meeting.

Dinko Vitezic gave a proxy to Ingeborg Barisic to vote on behalf of Dinko Vitezic during July 2021 COMP meeting.

Ausra Matuleviciene gave a proxy to Irena Rogovska to vote on behalf of Ausra Matuleviciene during July 2021 COMP meeting.

The COMP was pleased to welcome Mrs Inês Alves as new COMP member representing Patients' Organisation.

The COMP noted that Nikolaos Sypsas mandate as COMP member representing Greece has ended.

1.2. Adoption of agenda

The agenda for 13-15 July 2021 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 15-17 June 2021 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. adeno-associated viral vector serotype 9 containing the human *HEXA* and *HEXB* genes - EMA/OD/0000057079

Raremoon Consulting Esp S.L.; Treatment of GM2 gangliosidosis

COMP Rapporteur: Gloria Maria Palomo Carrasco

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

- Number of people affected

The sponsor had provided a prevalence estimate which was based on one publication. The COMP considered that this was a limited estimate which could be potentially different had more publications been used. The sponsor was asked to re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor was requested to perform a sensitivity analysis of the reported calculations.

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

In the written response, the sponsor provided a thorough prevalence calculation which the COMP reviewed. Additional bibliographical sources were identified containing either EU or non-EU data. The publications were retrospective epidemiology studies and natural history studies which focused on a subset defined by age of onset or disease subset and reported incidence.

Moreover, the sponsor identified data from registries, more specifically from the GM2 gangliosidosis disease registry (GM2DR). The GM2DR currently includes 114 patients with GM2 gangliosidosis, including 85 patients with Tay-Sachs disease and 29 patients with Sandhoff disease.

This analysis supports the fact that Portugal has the largest population of patients with GM2 gangliosidosis within the EU.

The sensitivity analysis that was requested from the sponsor is presented in a table that reports the prevalence based on the Incidence (per 10,000) x Survival (years) formula. The numbers used for both parameters are those reported by literature and databases.

Considering all the data presented, the revised calculation reflected the "worst-case scenario", based on the incidence reported by Pinto and colleagues, and the longest survival reported for GM2 patients which gives a final prevalence estimation of 0.4 per 10,000 inhabitants (0.005/10,000*80= 0.4/10,000). The COMP considered that they could accept the revised prevalence calculation and recommend granting the orphan designation.

The Committee agreed that the condition, GM2 gangliosidosis, 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 9 containing the human *HEXA* and *HEXB* genes was considered justified based on non-clinical in vivo data in a model of a condition showing improvement in behaviours and survival.

The condition is life-threatening with a reduced life expectancy of 3 to 15 years in infantile and juvenile onset patients, and chronically debilitating in adults due to ataxia, muscle weakness, loss of motor function, sight and hearing, and development of seizures and cognitive impairment.

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.

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

A positive opinion for adeno-associated viral vector serotype 9 containing the human *HEXA* and *HEXB* genes, for treatment of GM2 gangliosidosis, was adopted by consensus.

2.1.2. - EMA/OD/0000058580

Treatment of idiopathic pulmonary fibrosis (IPF)

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 28 June 2021, prior to responding to the list of issues.

2.1.3. - EMA/OD/0000056412

Treatment of small cell lung cancer (SCLC)

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 small cell lung cancer the sponsor was asked to further elaborate on any available in vivo nonclinical data that could provide sufficient evidence for the establishment of the medical plausibility for the orphan designation.

- Significant benefit

The sponsor was requested to provide a data driven comparison of the proposed product versus the authorised products for SCLC, in order to justify a clinically relevant advantage or major contribution to patient care. In the absence of any in vivo data with the product in the proposed condition significant benefit cannot be established.

In the written response, the sponsor did not provide any new data to support the medical plausibility. Regarding the significant benefit the sponsor argued that there is no therapeutic treatment in the EU for patients with progressive SCLC following second-line treatment apart from cyclophosphamide- doxorubicin-vincristine scheme.

During the oral explanation on 13 July 2021, the sponsor presented new data based on a non-clinical model showing anti-tumour effect of the proposed product however, because of

the small numbers of study subjects used in this model the COMP considered that the limited non-clinical data was not sufficient to support the medical plausibility.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 13 July 2021, prior to final opinion.

2.1.4. humanised igG1 monoclonal antibody against TfR1 conjugated to double stranded siRNA oligonucleotide against DMPK via a non-cleavable linker - EMA/OD/0000058262

MWB Consulting S.A.R.L.; Treatment of myotonic disorders

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:

- Intention to diagnose, prevent or treat

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

a) the relevance of the non-clinical model and methodology used for the treatment of myotonic disorders, and the interpretation of the surrogate results obtained in the experiments and their translation to functional outcomes,

b) how the results obtained in studies with other RNAi products can be extrapolated to the proposed efficacy of the product for designation,

c) the methodology used in the non-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition.

In the written response, and during an oral explanation before the Committee on 13 July 2021, the sponsor confirmed that non-clinical programme aimed to demonstrate that the product/tool compound can reduce levels of mutant DMPK mRNA in relevant tissues in non-clinical in vivo models, in vitro in DM type1 patient derived myotubes. The sponsor did not provide any further justification why this particular non-clinical model was selected having in mind that 1) this model does not have specific functional phenotype and 2) other similar disease models exists with a clear functional phenotype.

The sponsor claimed that the relevance of the data is supported by the literature indicating that CUG repeat length and degree of spliceopathy is correlated with disease severity. This is acknowledged; however, the sponsor did not present any new data indicating that correcting the pathology (reducing the mutant DMPK mRNA) will result in any functional improvement in relevant non-clinical model.

The sponsor further discussed the results of experiments described already in the original application. It could be agreed that the experiment demonstrated the reduction of target DMPK mRNA up to 7 weeks following treatment with AOC 1001. The sponsor's claim that – "the pharmacologic activity of AOC 1001 following repeat dosing was evaluated in the experiment for up to 32 weeks", - was not substantiated by data. It is acknowledged that PD biomarkers behaved similarly in the experiment and humans when comparing to other RNAi products.

However, similar data as described in Jauvin, 2017 (effect on muscle strength and body weight) are expected to be produced with AOC 1001 in order to support the hypothesis that reduction of mutant DMPK RNA will result in relevant functional outcomes. It is noted that in this particular publication use of two different ASO tool compounds resulted in different functional outcomes despite 90% silencing of mutant DMPK RNA by both compounds.

The COMP discussed at length the difficulties of conducting non-clinical in vivo studies in models of the condition with this specific product and balanced this with the need for data in the target condition myotonic disorders and in particular dystrophic myotonia type 1 for which this product is targeted. In the end the majority of the committee was of the opinion that the non-clinical model showing target RNA reduction, which is a surrogate endpoint, was sufficient to show promise of efficacy in dystrophic myotonia type 1. It was, however, noted that there were two members with a divergent opinion and who felt that the sponsor failed to clarify the uncertainties regarding the correlation of the target RNA reduction and functional outcomes in non-clinical models of the proposed condition.

The COMP agreed by a majority that it could recommend granting the orphan designation.

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

The intention to treat the condition with the medicinal product containing humanised IgG1 monoclonal antibody against TfR1 conjugated to double stranded siRNA oligonucleotide against DMPK via a non-cleavable linker was considered justified based on non-clinical in vivo model using a non-clinical specific tool compound showing target RNA reduction which is a surrogate endpoint in the submitted non-clinical models.

The condition is chronically debilitating due to muscle weakness and pain with stiffness associated with disability. These symptoms can be very debilitating leading to falls associated with fractures and serious injury.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised IgG1 monoclonal antibody against TfR1 conjugated to double stranded siRNA oligonucleotide against DMPK via a non-cleavable linker will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate a reduction in target RNA which is associated with dystrophic myotonia type 1, a population where currently there are no specifically authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for containing humanised IgG1 monoclonal antibody against TfR1 conjugated to double stranded siRNA oligonucleotide against DMPK via a non-cleavable linker, for treatment of myotonic disorders, was adopted by majority (25 out of 33 votes).

The divergent positions (Karri Penttila, Darius Matusevicius*)* were appended to this opinion.

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

2.1.5. - EMA/OD/0000056765

Treatment of chronic lymphocytic leukaemia / small lymphocytic 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 24 June 2021, prior to responding to the list of issues.

2.1.6. - EMA/OD/0000041501

Treatment of pulmonary arterial hypertension (PAH) condition

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

- Number of people affected

The proposed prevalence appeared to be an underestimate of the current prevalence estimate for this condition. The sponsor was asked to justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor was requested to describe and justify the methodology used for the prevalence calculation.

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".

- Significant benefit

The sponsor was asked to justify the assumption of significant benefit to all other authorised medicinal products for the proposed orphan condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the assumption of significant benefit compared to the 10 mg dose of the proposed product.

In the written response, and during an oral explanation before the Committee on 14 July 2021, the sponsor presented the complete prevalence estimate, which was based on a systematic literature review reporting incidence and prevalence published between 1 January 2003 and 31 August 2020.

Analyses described in the briefing document, were based on publications that included all national systematic registries (N=5) and non-systematic registries that included all pulmonary hypertension (PH) expert centers in the country (N=2), reported a complete prevalence of 0.16-0.55 per 10,000 persons.

Two sensitivity analyses were performed in response to the question:

a) sensitivity analysis 1 was based on publications that included national systematic registries (N=5) and all non-systematic registries in Europe (N=6) reported a complete prevalence of 0.15-0.55 per 10,000 persons,

b) sensitivity analysis 2 based on the assumption of a 50% under-estimation of PAH cases reported which produced a complete prevalence of 0.30-1.10 per 10,000 persons.

In conclusion the sponsor proposed a plausible range of complete prevalence of PAH in Europe to be estimated at 0.3-1.1 per 10,000 persons, with the worst-case scenario prevalence estimated to be 1.1 per 10,000 persons. The COMP accepted the worse-case scenario of 1.1 in 10,000.

A written response was provided for the question on significant benefit which was also discussed at the oral explanation. The sponsor had provided new non-clinical in vivo data. In the Sugen/Hypoxia model, it was demonstrated that the proposed product 30 mg/kg (equivalent to human 75 mg dose) administration resulted in a significantly lower mean pulmonary arterial pressure (MPAP) in comparison to selexipag use.

Also submitted, was a study comparing the proposed product 10 mg/kg (equivalent to human 30 mg dose) to iloprost using 72 hour MPAP as an endpoint showing better efficacy in the proposed product arm. It was considered that this study could not support SB as the dose of the proposed product applied was lower.

Finally, in a Sugen hypoxia PH model, the proposed product (3 and 30 mg/kg) was compared to tadalafil. It was shown that the proposed product 30 mg/kg administration resulted in statistically significant decrease of MPAP when compared to tadalafil.

The sponsor claimed an alternative mechanism of action for the higher dose of the proposed product with stronger ETB receptor inhibition which is not seen with the 10 mg dose. The COMP did not accept this argumentation as the higher 75 mg dose seemed to increase the occupancy of the receptor which did not occur at the lower dose, but is not a new mode of action per se.

The COMP noted that there was no clinical data submitted and therefore limitations to assessing a major contribution to patient.

The sponsor acknowledged that they did not have clinical data to support the need to show a major contribution to patient care and that this data could be available following the completion of their on-going clinical trial in the condition with the 75mg dose of the proposed product. The COMP concluded that there was insufficient data to support the recommendation to grant the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 July 2021, prior to final opinion.

2.1.7. loncastuximab tesirine - EMA/OD/0000054695

FGK Representative Service GmbH; Treatment of diffuse large B-cell lymphoma (DLBCL)

COMP Rapporteur: Karri Penttila

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

- 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 requested to recalculate the prevalence estimate and provide sensitivity analyses of the reported calculations on the proportion of DLBCL cases within Non-Hodgkin lymphoma (NHL) to reflect most updated sources.

- Significant benefit

The sponsor was asked to present direct/indirect comparisons of the efficacy of the proposed product versus the authorised medicinal products for the proposed orphan condition. Especially comparisons versus Pixuvri (pixantrone) and Polivy (polatuzumab vedotin) were expected to be provided.

In the written response, and during an oral explanation before the Committee on 14 July 2021, the sponsor presented the prevalence, which yield an adjusted DLBCL/NHL proportion of 33% (range: 31.4% to 37.8%), resulting in an EEA prevalence of 4.318 per 10,000 which was accepted by the COMP.

The sponsor highlighted that the proposed product is intended for a broader representative population of relapsed or refractory DLBCL patients, including patients who are eligible for stem cell transplant, patients with DLBCL transformed from indolent lymphoma, and patients with high-risk disease characteristics such as primary refractory disease (defined as patients who had no response to front-line therapy), double hit/triple hit disease, and patients who have never responded to multiple lines of therapy. The COMP concluded that the currently available evidence is sufficient to support the significant benefit in patients who relapsed and were refractory to at least two previous lines of therapies.

The Committee agreed that the condition, diffuse large B-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 loncastuximab tesirine was considered justified based on clinical data showing complete responses achieved in patients with disease relapsed and refractory to the second line treatment.

The condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract and bone marrow and life-threatening in patients not responding to first-line treatment.

The condition was estimated to be affecting approximately 4.3 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 loncastuximab tesirine will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients who relapsed and were refractory to at least two previous lines of therapies responded to treatment with the current product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for loncastuximab tesirine, for treatment of diffuse large B-cell lymphoma, was adopted by consensus.

2.1.8. - EMA/OD/0000058120

Treatment of upper tract urothelial carcinoma

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 29 June 2021, prior to responding to the list of issues.

2.1.9. - EMA/OD/0000053211

Treatment of follicular lymphoma (FL)

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

- Number of people affected

The sponsor was requested to recalculate the prevalence estimate based on more relevant and extensive data sources on FL, including ECIS (for indirect estimation), which is the most comprehensive database with EU-wide data on incidence of Non-Hodgkin lymphoma (NHL) from all member states.

More specifically the sponsor was asked to discuss:

a) the suitability of the duration of the condition used for the prevalence,

b) sensitivity analyses of the reported calculations should be provided on the proportion of FL cases within NHL to reflect the variability and uncertainties from the different sources used.

- Significant benefit

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

The sponsor was requested to further discuss the arguments provided for significant benefit and to provide further clarifications with regard of the future positioning of the drug against authorised treatments in relapsed or refractory FL.

In the written response, and during an oral explanation before the Committee on 14 July 2021, the sponsor provided sensitivity analyses for the FL incidence as percentage of NHL cases within a range of 20% - 35%, with a gaussian probability distribution (30% - 50% - 20%) skewed towards the low end at 21%. In addition, the sponsor provided sensitivity analyses on the prevalence of FL considering a 5-, 7-, 10- and 15-year disease duration Based on this analysis, the sponsor concluded that the prevalence of FL in Europe ranges from 3.69 to 4.15 per 10,000 persons, with a likely value of 3.94 per 10,000 persons according to the sponsor. The COMP concluded that the overall survival has been increasing over the last years and that the prevalence of FL is getting closer to the threshold.

For the demonstration of significant benefit, argumentation against idelalisib was provided based on better efficacy outcomes and different targeted population since the proposed product is intended for treatment in combination with rituximab in patients who have received at least one line of prior therapy and thus in earlier line than idelalisib which is indicated as monotherapy for the treatment of adult patients with FL that is refractory to two prior lines of treatment.

In addition, the sponsor argued on indirect efficacy and safety comparisons of the proposed product against obinutuzumab/bendamustine for the treatment of patients who did not respond or who progressed during or up to 6 months after treatment with rituximab-

containing regimen and against lenalidomide/rituximab for patients with short remissions after chemotherapy. However, these comparisons showed comparable efficacy and safety remains unknown at this stage of development, and therefore not suitable to support the significant benefit at this stage in time.

The COMP considered that the claim of better efficacy had not been justified against the combinations obinutuzumab/bendamustine or lenalidomide/rituximab.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 July 2021, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. bardoxolone methyl - EMA/OD/0000054645

Pharma Gateway AB; Treatment of autosomal dominant polycystic kidney disease

COMP Rapporteur: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing Bardoxolone methyl was considered justified based on clinical data in patients with the condition achieving an improvement in kidney function, as assessed by the estimated glomerular filtration rate.

The condition is chronically debilitating and potentially life-threatening due to renal manifestations such as renal cyst infection, nephrolithiasis, and kidney failure requiring dialysis, as well as due to extra renal manifestations such as intracranial aneurysms, mitral valve prolapse and diverticulosis.

The condition was estimated to be affecting approximately 4.3 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 bardoxolone methyl will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients treated with bardoxolone methyl have an increased estimated glomerular filtration rate, which cannot be achieved with the currently approved product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for bardoxolone methyl, for treatment of autosomal dominant polycystic kidney disease, was adopted by consensus.

2.2.2. - EMA/OD/0000055853

Treatment of frontotemporal dementia

The COMP adopted a list of issues that will be sent to the sponsor. The Committee will discuss the submitted answers to the list of issues at the September meeting.

2.2.3. - EMA/OD/0000057849

Treatment of treatment of uveal melanoma

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 September meeting.

2.2.4. human keratinocytes - EMA/OD/0000058028

Dizg Deutsches Institut Für Zell- Und Gewebeersatz gGmbH; Treatment of partial deep dermal and full thickness burns

COMP Rapporteur: Martin Mozina

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

The intention to treat the condition with the medicinal product containing human keratinocytes was considered justified based on preliminary published data in patients who showed good skin engraftment and overall survival following use of the product.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing human keratinocytes will be of significant benefit to those affected by the condition. The product has a different mode of treatment as compared to authorised medicines. The sponsor has provided preliminary clinical data that demonstrate a good skin engraftment and improved survival following use of the sponsor's product. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.5. - EMA/OD/0000058053

Treatment of gastric cancer

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

2.2.6. adeno-associated viral vector serotype 9 containing the human *MECP2* gene - EMA/OD/0000058171

Raremoon Consulting Esp S.L.; Treatment of Rett syndrome

COMP Rapporteur: Ingeborg Barisic

The Committee agreed that the condition, Rett syndrome, 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 9 containing the human *MECP2* gene (mini-*MECP2* gene version) was considered justified based on non-clinical data from valid models which show improved survival.

The condition is life-threatening and chronically debilitating due to severe neurodevelopmental disability, sleep disturbances, seizures, respiratory complications and development of arrhythmias resulting in decreased life-expectancy.

The condition was estimated to be affecting approximately 1.1 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 viral vector serotype 9 containing the human *MECP2* gene, for treatment of Rett syndrome, was adopted by consensus.

2.2.7. - EMA/OD/0000058277

Treatment of dermatomyositis

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 September meeting.

2.2.8. - EMA/OD/0000058281

Treatment of polymyositis

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 September meeting.

2.2.9. - EMA/OD/0000058526

Treatment of acute liver failure

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 September meeting.

2.2.10. - EMA/OD/0000059143

Treatment of Burkitt's 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 September meeting.

2.2.11. - EMA/OD/0000059436

Treatment of megalencephalic leukoencephalopathy with subcortical cysts

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 September meeting.

2.2.12. talquetamab - EMA/OD/0000060100

Janssen-Cilag International N.V.; Treatment of multiple myeloma

COMP Rapporteur: Karri Penttila

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

The intention to treat the condition with the medicinal product containing talquetamab was considered justified based on preclinical data showing that patients with relapsed or refractory multiple myeloma achieve partial or complete responses.

The condition is chronically debilitating and life-threatening due to the development of hypercalcaemia, renal insufficiency, anaemia and bone lesions.

The condition was estimated to be affecting approximately 4.3 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 talquetamab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients with relapsed and penta-refractory multiple myeloma previously treated with selinexor and belantamab mafodotin achieved partial and stringent complete responses. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for talquetamab, for treatment of multiple myeloma, was adopted by consensus.

2.2.13. adeno-associated virus serotype PTC3 expressing the human *UBE3A* gene - EMA/OD/0000060300

PTC Therapeutics International Limited; Treatment of Angelman syndrome

COMP Rapporteur: Giuseppe Capovilla

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

The intention to treat the condition with the medicinal product containing adeno-associated virus serotype PTC3 expressing the human UBE3A gene was considered justified based on non-clinical data in a relevant model of the condition in which the use of the proposed product normalises hindlimb clasping and reduces neuronal hyperexcitability and seizures frequency.

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

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

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

A positive opinion for adeno-associated virus serotype PTC3 expressing the human *UBE3A* gene, for treatment of Angelman syndrome, was adopted by consensus.

2.2.14. autologous CD34+ cells transfected with a lentiviral vector containing codon optimised *RPS19* gene - EMA/OD/0000060579

Premier Research Group S.L.; Treatment of Diamond-Blackfan Anemia

COMP Rapporteur: Enrico Costa; Expert: Angelo Loris Brunetta

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

The intention to treat the condition with the medicinal product containing autologous CD34+ cells transfected with a lentiviral vector containing codon optimised *RPS19* gene was considered justified based on in vivo data in a valid non-clinical Rps19-deficient model demonstrating that transduced Rps19-deficient bone marrow cells could reconstitute bone marrow and reduce severe anaemia.

The condition is life-threatening and chronically debilitating due to complications related to patients' malfunctioning bone marrow such as severe anaemia and due to an increased risk of developing haematological malignancies.

The condition was estimated to be affecting approximately 0.03 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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for autologous CD34+ cells transfected with a lentiviral vector containing codon optimised *RPS19* gene, for treatment of Diamond-Blackfan anaemia, was adopted by consensus.

2.2.15. cemdisiran - EMA/OD/0000061148

Alnylam Netherlands B.V.; Treatment of immunoglobulin A nephropathy (IgAN)

COMP Rapporteur: Dinah Duarte

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

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

The intention to treat the condition with the medicinal product containing cemdisiran was considered justified based on preliminary clinical data showing a reduction of proteinuria in patients with the condition.

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

The condition was estimated to be affecting approximately 3.9 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing cemdisiran will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that cemdisiran can be used in a broader patient population than the approved product, which only targets a subset of primary IgA nephropathy patients. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.16. - EMA/OD/0000061301

Treatment of invasive aspergillosis

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 September meeting.

2.2.17. - EMA/OD/0000061466

Treatment of transthyretin-mediated amyloidosis (ATTR)

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 September meeting.

2.2.18. recombinant human apolipoprotein A-I - EMA/OD/0000061524

Abionyx Pharma; Treatment of lecithin-cholesterol acyltransferase deficiency

COMP Rapporteur: Dinah Duarte

The Committee agreed that the condition, lecithin-cholesterol acyltransferase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant human apolipoprotein A-I was considered justified based on preliminary clinical data in patients showing stabilisation of estimated glomerular filtration rate, improvements in proteinuria and urine creatinine with a correction of the lipid profile by a cholesterol increase.

The condition is chronically debilitating due to corneal opacities that impair vision and the development of normochromic haemolytic anaemia, and life threatening due to renal impairment that may lead to end-stage renal disease.

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 recombinant human apolipoprotein A-I, for treatment of lecithin-cholesterol acyltransferase deficiency, was adopted by consensus.

2.2.19. - EMA/OD/0000061671

Treatment of tuberous sclerosis

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

2.2.20. adeno-associated viral vector serotype S3 containing codon-optimised expression cassette encoding human beta-glucocerebrosidase variant - EMA/OD/0000061847

Freeline Therapeutics (Ireland) Limited; Treatment of Gaucher disease

COMP Rapporteur: Gloria Maria Palomo Carrasco

The Committee agreed that the condition, Gaucher 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 viral vector serotype S3 containing codon-optimised expression cassette encoding human beta-glucocerebrosidase variant was considered justified based on in vivo data from a valid non-clinical disease model in which the sustained rescue of tissue glucocerebrosidase activity could be demonstrated following a single administration of the medicinal product for visceral target tissues of Gaucher disease, including the lung. In addition, a reduction in metabolic markers and substrate accumulation was demonstrated.

The condition is chronically debilitating in particular due to hepatosplenomegaly, thrombocytopenia, anaemia, bone disease, as well as neurological manifestations in the neuronopathic form of the condition, and life-threatening with reduced life expectancy.

The condition was estimated to be affecting less than 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 adeno-associated viral vector serotype S3 containing codon-optimised expression cassette encoding human beta-glucocerebrosidase variant will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate sustained improvement in enzyme levels of glucocerebrosidase in spleen, liver, lung, leukocytes and bone marrow following a single administration after which would obviate the need for continuous treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype S3 containing codon-optimised expression cassette encoding human beta-glucocerebrosidase variant, for treatment of Gaucher disease, was adopted by consensus.

2.2.21. adeno-associated virus serotype 9 encoding human *NGLY1* gene - EMA/OD/0000062288

Voisin Consulting; Treatment of NGLY1 deficiency

COMP Rapporteur: Vallo Tillmann

The Committee agreed that the condition, NGLY1 deficiency, 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 encoding human *NGLY1* gene was considered justified based on non-clinical in vivo data in a model of the condition showing an improvement in motor function and coordination that negatively correlated with aspartylglycosamine levels, an appropriate surrogaate marker of the condition.

The condition is chronically debilitating due to developmental delay, hypolacrimia or alacrimia, hypotonia, liver dysfunction and acquired microcephaly. Some patients also present with seizures. Life-expectancy is shortened in the majority of the cases reported.

The condition was estimated to be affecting approximately 0.001 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 encoding human *NGLY1* gene, for treatment of NGLY1 deficiency, was adopted by consensus.

2.2.22. autologous CD34+ hematopoietic stem and progenitor cells genetically modified with a lentiviral vector encoding for the human iduronate 2-sulfatase cDNA - EMA/OD/0000062317

University of Padua; Treatment of mucopolysaccharidosis Type II (Hunter's syndrome)

COMP Rapporteur: Armando Magrelli

The Committee agreed that the condition, mucopolysaccharidosis type II (Hunter's syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing autologous CD34+ haematopoietic stem and progenitor cells genetically modified with the lentiviral vector encoding for the human iduronate 2-sulfatase gene was considered justified based on in vivo data in a relevant non-clinical disease model showing prolonged survival, and effects on disease-associated neurological and skeletal abnormalities.

The condition is chronically debilitating due to neurological decline, cardiovascular and pulmonary complications and life-threatening as indicated by the survival of the patients that can be limited to 10-15 years.

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.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous CD34+ haematopoietic stem and progenitor cells genetically modified with the lentiviral vector encoding for the human iduronate 2-sulfatase gene will be of significant benefit to those affected by the condition. The sponsor has provided in vivo data in a relevant non-clinical disease model suggesting that a single administration of this medicinal product may prolong life expectancy and correct disease-associated neurological and skeletal abnormalities as compared to the currently authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous CD34+ haematopoietic stem and progenitor cells genetically modified with the lentiviral vector encoding for the human iduronate 2-sulfatase

gene, for treatment of mucopolysaccharidosis type II (Hunter's syndrome), was adopted by consensus.

2.2.23. sabatolimab - EMA/OD/0000062350

Novartis Europharm Limited; Treatment of myelodysplastic syndromes

COMP Rapporteur: Karri Penttila

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

The intention to treat the condition with the medicinal product containing sabatolimab was considered justified based on clinical data showing high rate of responses in patients with high risk myelodysplastic syndromes who were additionally treated with hypomethylating agents.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sabatolimab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that patients with intermediate and high-risk myelodysplastic syndromes achieved high rate of responses when treated with a combination of sabatolimab and the standard of care, azacitidine. This compared favourably to historical studies with azacytidine alone. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.24. - EMA/OD/0000062387

Treatment of optic neuritis

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

2.2.25. lurbinectedin - EMA/OD/0000062559

Pharma Mar S.A.; Treatment of malignant mesothelioma

COMP Rapporteur: Bozenna Dembowska-Baginska

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

The intention to treat the condition with the medicinal product containing lurbinectedin was considered justified based on preliminary clinical data in patients with the condition showing a clinically relevant effect on progression free survival.

The condition is life-threatening due to the invasion of the pleura leading to pleural effusions, dyspnoea and malignant ascites. Patients with pleural mesothelioma usually die due to increasing tumour bulk that gradually fills the hemithorax causing progressive respiratory compromise ("incarceration" of the lungs), pneumonia, or myocardial dysfunction with arrhythmias. In patients with peritoneal mesothelioma, distension due to ascites, abdominal pain, and organ impairment such as bowel obstruction are observed.

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

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 lurbinectedin will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that show progression free survival in patients who had failed treatment with the currently approved product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for lurbinectedin, for treatment of malignant mesothelioma, was adopted by consensus.

2.2.26. autologous CD34+ cell enriched population containing haematopoietic stem and progenitor cells transduced ex vivo with a lentiviral vector encoding the human ADA2 gene - EMA/OD/0000062715

Fondazione Telethon; Treatment of adenosine deaminase 2 deficiency (DADA2)

COMP Rapporteur: Elisabeth Johanne Rook

The Committee agreed that the condition, adenosine deaminase 2 deficiency (DADA2), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing autologous CD34+ cell enriched population containing haematopoietic stem and progenitor cells transduced ex vivo with a lentiviral vector encoding the human *ADA2* gene was considered justified based on human ex vivo data showing that 1) lentiviral-Adenosine Deaminase 2 (LV-ADA2) gene transfer corrects the pro-inflammatory phenotype in macrophages derived from DADA2 patients (reduction of IL-6 and TNF expression), and that 2) transduction of CD34+ cells (derived from DADA2 patients) with the LV-ADA2 can re-establish intracellular ADA2 expression without disrupting the clonogenic potential of CD34+ cells.

The condition is life-threatening and chronically debilitating due to vasculopathy and life-threatening ischemic and/or haemorrhagic stroke at young age. Case mortality for DADA2 is estimated at about 8% related to vasculopathy-associated complications and infections.

The condition was estimated to be affecting approximately 0.05 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 autologous CD34+ cell enriched population containing haematopoietic stem and progenitor cells transduced ex vivo with a lentiviral vector encoding the human *ADA2* gene, for treatment of adenosine deaminase 2 deficiency (DADA2), was adopted by consensus.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

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

COMP rapporteurs were appointed for 29 applications.

2.7. Evaluation on-going

None

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1.

- Treatment of paediatric patients with severe combined immunodeficiency (SCID) receiving allogeneic haematopoietic stem cell transplantation

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

3.1.2. -

Treatment in haematopoietic stem cell transplantation

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 pancreatic cancer

The finalised letter was circulated for information.

3.2.2. -

Treatment of myelodysplastic syndromes

The finalised letter was circulated for information.

3.2.3. -

Treatment of acute myeloid leukemia

The finalised letter was circulated for information.

3.3. New requests

3.3.1.

Treatment of acute myeloid leukaemia

The new request was noted.

3.3.2.

Treatment of hyperphenylalaninemia

The new request was noted.

3.3.3. -

Treatment of polycythaemia vera

The new request was noted.

3.3.4. -

Treatment of soft tissue sarcoma

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. Minjuvi – tafasitamab - EMEA/H/C/005436/0000, EMA/OD/215/14, EU/3/14/1424, EMA/OD/0000047254

Incyte Biosciences Distribution B.V.; Treatment of diffuse large B-cell lymphoma

COMP Rapporteurs: Elisabeth Johanne Rook; Karri Penttila

An opinion recommending not to remove Minjuvi, tafasitamab, EU/3/14/1424 from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

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

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

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

The COMP discussed a list of issues.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 4 applications.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

None

5.3. Appeal

None

5.4. On-going procedures

None

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. Strategic Review & Learning meetings

None

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 9 July 2021.

7.1.3. COMP Chair election 2021

Action: For information

The COMP noted the information about Chair election planned to take place at the end of September 2021 plenary.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report

Documents were tabled for information.

7.2.2. Update on patient involvement in CHMP

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

None

7.8. Planning and reporting

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

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

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

8.1. Complex clinical trials (CCT) – Involvement in subgroup of Clinical Trial Expert Group (CTEG)

Action: For discussion, call for volunteers

The European Commission (DG Santé B4) has initiated the development of a question and answer document on 'complex clinical trials' in collaboration with EMA and the clinical trials facilitation group (CTFG). A first draft is now available, spanning a large scope of topics (master protocols, Bayesian methodology, use of external control, biomarkers, safety, transparency and study integrity). As the next important step, the EC/EMA/CTFG drafting group is now looking for volunteers from the network to contribute to this first draft and subsequent activities expected to span over the rest of 2021, and possibly beyond.

From COMP Brigitte Schwarzer-Daum and Darius Matusevicius expressed interest to volunteer.

9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 13-15 July 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	Netherlands	No interests declared	
Armando Magrelli	Vice-chair	Expert recommended by EMA	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No restrictions applicable to this meeting	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Vasileios Loutas	Member	Cyprus	No interests declared	
Lenka Gaidadzi	Member	Czechia	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Cecile Dop	Member	France	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Enrico Costa	Member	Italy	No restrictions applicable to this meeting	
Irena Rogovska	Member	Latvia	No participation in discussions, final	2.2.3. - EMA/OD/0000057849

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			deliberations and voting on:	Latima SIA - Treatment of uveal melanoma
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	
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	
Martin Mozina	Member	Slovenia	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Ines Alves	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert via Webex*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Angelo Loris Brunetta	Expert via Webex*	Italy	No interests declared	
	Patient representa-tive*	Italy	No interests declared	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only 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/