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SCIENCE MEDICINES HEALTH

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Human Medicines Division

## Committee for Orphan Medicinal Products (COMP)

### Minutes for the meeting on 16-18 February 2021

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

#### Disclaimers

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

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

#### Note on access to documents

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

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## 1. Introduction

### 1.1. Welcome and declarations of interest of members and experts

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

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

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

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

Giuseppe Capovilla gave a proxy to Armando Magrelli to vote on behalf of Giuseppe Capovilla during part of February 2021 COMP meeting.

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

### 1.2. Adoption of agenda

The agenda for 16-18 February 2021 was adopted with no amendments.

### 1.3. Adoption of the minutes

The minutes for 19-21 January 2021 were adopted with amendments and will be published on the EMA website.

## 2. Applications for orphan medicinal product designation

### 2.1. For opinion

#### 2.1.1. adeno-associated virus serotype hu68 containing the human *GALC* gene - EMA/OD/0000046077

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Pharma Gateway AB; Treatment of Krabbe disease

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 primarily used Orphanet as their source for the prevalence estimate. The COMP did not consider this as a suitable source for the establishment of the prevalence estimate. The sponsor was asked to re-calculate the prevalence estimate based on relevant EU epidemiological studies and registers for the proposed orphan 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"](#).

The sponsor was requested to justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor was asked to describe and justify the methodology used for the prevalence calculation.

In the written response, the sponsor provided a revised prevalence estimate. The calculation was based on several approaches. The first was of average birth prevalence based on crude pooling of data using the four studies identified by the sponsor and was estimated to be 0.92/100,000 births. The second was by means of a meta-analysis which also concluded with similar results showing an average birth prevalence of 0.1 in 10,000. Similarly, the lifetime risk at birth was estimated to be 0.1 per 10,000, based on the available evidence.

The COMP considered that the information provided in the response to the list of questions was acceptable. The sponsor provided an estimate of birth prevalence which is the preferred term in current publications. This is undoubtedly a rare condition, with limited information on prevalence. Therefore, the COMP considered that it is acceptable to use birth prevalence.

The Committee agreed that the condition, Krabbe 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 hu68 containing the human *GALC* gene was considered justified based on non-clinical data in 2 valid models of the condition, showing in both dose-dependent expression of the transgene and rescue of functional endpoints which include survival, body weight and clinical scoring, psychosine levels in cerebrospinal fluid, increased myelination and decreased globoid cell infiltration and neuromotor function.

The condition is life-threatening and chronically debilitating, in particular due to the development of progressive motor paralysis, ataxia and regression of cognitive development.

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

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

A positive opinion for adeno-associated virus serotype hu68 containing the human *GALC* gene, for treatment of Krabbe disease, was adopted by consensus.

Treatment of fulminant hypermetabolic crisis secondary to calcium dysregulation in skeletal muscle

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

- Intention to diagnose, prevent or treat

The sponsor was requested to justify the fulminant hypermetabolic crisis secondary to calcium dysregulation in skeletal muscle (abbreviated as FHC) as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention was drawn to the orphan regulations and relevant guidelines (especially section A of [ENTR/6283/00](#)).

The sponsor proposed the condition based on a scientific rationale regarding the commonalities between included patient populations. However, no official literature or classification systems exist that would define the condition as proposed. To justify the acceptability of the proposed condition the sponsor was asked to further clarify:

- a) common genetic or other underlying features in the proposed patient population, which would predispose them to the development of FHC due to diverse triggers,
- b) the scientific or medical rationale for the selection of a broad patient population, which necessitates a very descriptive name of the condition,
- c) any literature which would phrase or describe the condition in the way as proposed in this application.

In the written response, and during an oral explanation before the Committee on 16 February 2021, the sponsor further explained the genetic association of the proposed condition with mutation in RYR1 gene. Reference was also made to the ICD-11 classification system (8C78), which partially supports this association. The COMP questioned the broader inclusion criteria, where evidence of a genetic link has not been established. The sponsor agreed that the classification systems do not yet reflect the condition as proposed and that genetic links are not always established. The sponsor was adamant though in claiming that the proposed condition is not iatrogenic because of the underlying genetic predisposition of patients.

In addition, the sponsor acknowledged that there are no clinical guidelines or consensus literature at the moment that would support one approach to treating fulminant hypermetabolic crisis (FHC) in case of all triggers. Usually, FHC is treated in association with the underlying trigger, such as anaesthetics or neuroleptic medicines. The COMP acknowledged the rationale for the development of treatment before overt signs of hyperthermia appear. However, for the purpose of the orphan designation it was not considered appropriate to create a new condition, which would then correspond to the intended therapeutic indication. The sponsor was therefore invited to apply for separate orphan designations for all well-established condition where medical plausibility of dantrolene has been demonstrated (e.g. malignant hyperthermia).

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 February 2021, prior to final opinion.

### 2.1.3. - EMA/OD/0000043808

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#### Treatment of bronchopulmonary dysplasia

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 bronchopulmonary dysplasia (BPD) the sponsor was requested to further elaborate on any efficacy results in BPD patients that may be attributed to the proposed product. The sponsor was also asked to discuss the clinical relevance of the reported effects.

- 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 discuss the duration of the condition irrespectively of the envisioned intervention and justify the use of yearly incidence rate rather than point prevalence.

In the written response, and during an oral explanation before the Committee on 16 February 2021, the sponsor further elaborated on the raised issues.

With regards to the medical plausibility, the sponsor reiterated the available clinical observations. It was noted in particular that in an uncontrolled study with 12 infants with BPD, treatment with the product resulted in decreases in partial pressure of carbon dioxide (pCO<sub>2</sub>). Another study in infants with respiratory distress syndrome was also referred to, where treatment with the product resulted in improvements in gas exchange and respiratory mechanics.

As for the issue of the number of affected individuals, a revised estimate of 2.42 per 10,000 was proposed on the basis of the number of individuals alive and diagnosed with BPD within 10 years of diagnosis.

The COMP considered that the only relevant data for this designation procedure would be the treatment effects in patients with already established BPD. In the relevant study, the uncontrolled nature of the observations and the limited signal of gas exchange improvement, would not render the application acceptable for designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 February 2021, prior to final opinion.

### 2.1.4. - EMA/OD/0000046325

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#### Prevention of bronchopulmonary dysplasia

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

- Intention to diagnose, prevent or treat



To establish correctly whether there exists a scientific rationale for the development of the proposed product for prevention of bronchopulmonary dysplasia the sponsor was asked to further elaborate on:

- a) the relevance of the nonclinical models used for the prevention of bronchopulmonary dysplasia, and the interpretation of the results obtained in the experiments,
  - b) the results of the clinical study and the relevance of the study settings for the prevention of bronchopulmonary dysplasia as applied for designation.
- 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 justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition, taking into consideration the preventative scope of the application.

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 should perform a sensitivity analysis of the reported calculations.

In the written response, and during an oral explanation before the Committee on 16 February 2021, the sponsor elaborated on the raised issues.

Regarding the medical plausibility, the sponsor referred to the mechanism of action of the product and discussed the reduction of pro-inflammatory cytokines (in particular, IL-8) which was expected to exert beneficial effects with relevance to the pathophysiology of the condition. A published clinical study was also referred to, reporting improved outcomes in infants with severe respiratory distress syndrome. An additional four cases of treated infants with the proposed product were also discussed. As regards to the prevalence calculation, the sponsor used the prevalence of respiratory distress syndrome from a previous designation they were granted, and adjusted the EU27 population to 2020, producing a 2.86 per 10,000 estimate.

The COMP considered that while submitted clinical observations pertain to the treatment of a major risk factor for BPD, the prevention of actual cases had not been shown. As such the medical plausibility could not be considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 February 2021, prior to final opinion.

#### 2.1.5. [messenger RNA encoding Cas9, single guide RNA targeting the human \*TTR\* gene - EMA/OD/0000046448](#)

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Voisin Consulting; Treatment of ATTR amyloidosis

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:

- 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"](#).

Given the substantial uncertainty about many of the assumptions regarding the prevalence the sponsor was asked to perform a sensitivity analysis of the reported calculations.

- Significant benefit

The sponsor was requested to further discuss the arguments for significant benefit, in order to justify a clinically relevant advantage or major contribution to patient care compared to the existing authorised treatments. The sponsor was also invited to discuss the pharmacological basis for the expected long-term efficacy and provide any functional effects with the product in non-clinical or clinical settings of ATTR amyloidosis.

In the written response, and during an oral explanation before the Committee on 17 February 2021, the sponsor further elaborated on the raised issues.

As regards to the prevalence of the condition, this was revised and calculated as a sum of wildtype and mutated ATTR cases.

The sponsor performed a literature search and concluded that the ATTR prevalence due to mutations was 0.23 per 10,000 and that the wildtype ATTR amyloidosis would be approximately 1.67 per 10,000 (e.g. Lindmark et al, 2020).

With regards to the significant benefit, the sponsor stressed that the non-clinical data support a one-time only application that would eliminate the need for further treatment. In non-clinical models, sustained *TTR* gene editing was shown up to 19 months. This can be accepted as a clinically relevant advantage.

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

The intention to treat the condition with the medicinal product messenger RNA encoding Cas9, single guide RNA targeting the human *TTR* gene was considered justified based on in-vivo data supporting reduction of serum transthyretin concentrations and accumulation in several tissues in a non-clinical model of the condition.

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

The condition was estimated to be affecting approximately 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 messenger RNA encoding Cas9, single guide RNA targeting the human *TTR* gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data in a model of the condition, showing a reduction of serum transthyretin concentration and accumulation in several tissues. These effects were long-term after a single administration and may obviate the need for continuous treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for messenger RNA encoding Cas9, single guide RNA targeting the human *TTR* gene, for treatment of ATTR amyloidosis, was adopted by consensus.

#### 2.1.6. lorcaserin hydrochloride - EMA/OD/0000048780

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Premier Research Group S.L.; Treatment of Dravet syndrome

COMP Rapporteur: Julian Isla, 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:

- Significant benefit

The sponsor claimed that their product could be used in patients who are refractory to other currently authorised medicinal products for the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on data from non-clinical *in vivo* and/or preliminary clinical data to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. Further elaboration regarding known safety considerations especially in the paediatric population should be addressed.

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

In the written response, and during an oral explanation before the Committee on 17 February 2021, the sponsor reiterated many of the points discussed in the initial submission. However, during the oral explanation further elaboration on the challenges in managing patients with Dravet syndrome were discussed and how lorcaserin could have a potential additional value. The sponsor noted that patients with the condition do not all respond favourably to fenfluramine. The exact cause of this is not known, however, it may be due to variable nature of the *de novo* mutations associated with the condition which may affect the target receptor 5HTC. The COMP discussed this variable responsiveness with the sponsor and indeed the sponsor noted that they had one patient who had not been responsive to fenfluramine but responsive to lorcaserin. Serious known safety issues which led to the removal of this product from the market in Europe in 2012 were raised with the sponsor and heavily discussed by the COMP. In general, it was agreed that for the purpose of orphan designation the sponsor had adequately justified the use of the product in these patients.

In addition, the COMP listened to the testimony of a patient representative who also indicated that there was some experience in the United States of patients who had not responded to fenfluramine but to lorcaserin, or who had been switched from lorcaserin to fenfluramine in the belief that the products had the same effect only to note that the patient had to be put back on lorcaserin.

Following the discussion, the COMP considered that the argumentation and data provided as well as the variable response nature of Dravet syndrome patients to antiepileptic medication provided sufficient basis for the recommendation of granting the orphan designation.

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

The intention to treat the condition with the medicinal product containing lorcaserin hydrochloride was considered justified based on preliminary clinical data showing a clinically meaningful reduction in epileptic seizures.

The condition is chronically debilitating due to psychomotor and cognitive impairment and the occurrence of convulsive seizures, and life-threatening due to sudden unexpected death in epilepsy.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing lorcaserin hydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a reduction in epileptic seizures in patients refractory to authorised anti-epileptic medicines used in the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for lorcaserin hydrochloride, for treatment of Dravet syndrome, was adopted by majority (26 out of 27 votes). The Norwegian COMP member agreed with the above-mentioned recommendation of the COMP.

The divergent position (Elisabeth Johanne Rook) was appended to this opinion.

#### 2.1.7. [ilixadencel - EMA/OD/0000046254](#)

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Immunicum AB; Treatment of soft tissue sarcoma

COMP Rapporteur: Geraldine O'Dea

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

- Intention to diagnose, prevent or treat

Based on the current practice of the COMP and the data submitted to support this application, the COMP considered that the proposed condition should be phrased as 'treatment of gastrointestinal stromal tumours' (GIST). Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention was drawn to the Orphan regulations and relevant guidelines (especially section A of [ENTR/6283/00](#)).

The sponsor presented preliminary data in GIST patients and a rationale for the extrapolation of efficacy results from these patients to several genomically complex subtypes of soft tissue sarcoma. The COMP considered the presented data as relevant for the GIST indication only. Depending on the final agreed condition further justifications will be asked as follows.

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

- a) the clinical relevance of observations in GIST patients for the treatment of GIST, and the interpretation of the results obtained in the clinical study,

- b) individual patient narratives from the clinical study, in particular more heavily pre-treated patients,
- c) any data available in soft tissue sarcoma.
- Prevalence

The sponsor was requested to provide a calculation of prevalence of GIST as a proposed appropriate condition for this application.

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 presented preliminary data in several GIST patients who were refractory to at least 2 prior therapies, some of whom achieved partial responses. The sponsor did not present individual patient narratives to support the efficacy of the product in more heavily pre-treated patients.

The sponsor was requested to further discuss the arguments provided to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

In addition, in case there is data available in soft tissue sarcoma, an appropriate comparison should be made to the current standard of care in soft tissue sarcoma at large.

Furthermore, it would be useful to obtain more information on the ongoing study/planned development.

In the written response, and during an oral explanation before the Committee on 18 February 2021, the sponsor accepted amendment of the orphan condition to 'treatment of gastrointestinal stromal tumours'. The sponsor provided an appropriate prevalence calculation proposing the value of 2.2 in 10,000 based on current databases and literature. The COMP accepted this calculation and phrased the final accepted value as 'less than 3 in 10,000' for consistency with recent assessments. During the oral hearing the sponsor focused on further discussion of the assumptions of significant benefit. The sponsor clarified that the product will be developed as an add on to sunitinib, the second line treatment of GIST. This would correspond to the setting in which the best clinical response was observed in the submitted study. Despite the evidence being scarce and preliminary in nature, the COMP considered that there is enough data to support the positive opinion on this designation. The sponsor was encouraged, however, to seek protocol assistance in further development of this product.

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

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

The intention to treat the condition with the medicinal product containing ilixadencel was considered justified based on preliminary clinical data showing clinically relevant responses in pre-treated patients in addition to the standard of care.

The condition is chronically debilitating and life-threatening, in particular due to the high rate of relapse and development of metastatic disease resulting in poor survival.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ilixadencel will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that when the product is used in addition to the tyrosine kinase inhibitors in patients who are refractory to at least 2 previous lines of treatment prolonged disease stabilisation or partial responses can be achieved. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for ilixadencel, for treatment of gastrointestinal stromal tumours, was adopted by consensus.

## **2.2. For discussion / preparation for an opinion**

### **2.2.1. - EMA/OD/0000038966**

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Treatment of pulmonary hypertension associated with interstitial lung disease

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 March 2021 meeting.

### **2.2.2. alpha-L-iduronidase fused to Fab fragment of a humanised monoclonal antibody targeting human transferrin receptor - EMA/OD/0000041696**

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Artemida Pharma Europe Limited; Treatment of mucopolysaccharidosis type I

COMP Rapporteur: Geraldine O'Dea

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

The intention to treat the condition with the medicinal product containing alpha-L-iduronidase fused to Fab fragment of a humanised monoclonal antibody targeting human transferrin receptor was considered justified based on non-clinical in vivo data in a model of the condition showing an improvement of hepatomegaly and as well as improvement in neurological surrogate markers.

The condition is chronically debilitating due to facial dysmorphism, hepatosplenomegaly, upper airway obstruction, skeletal deformity, cardiomyopathy, cognitive impairment and life-threatening with death ensuing by adolescence if the severe form of the disease is left untreated.

The condition was estimated to be affecting approximately 0.04 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 alpha-L-iduronidase fused to Fab fragment of a humanised

monoclonal antibody targeting human transferrin receptor will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate improvement in valid neurological surrogate markers in comparison to laronidase. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for alpha-L-iduronidase fused to Fab fragment of a humanised monoclonal antibody targeting human transferrin receptor, for treatment of mucopolysaccharidosis type I, was adopted by consensus.

### 2.2.3. lefitolimod - EMA/OD/0000041862

Molecular Biology And Integral Biomathics; Treatment of small cell lung cancer

COMP Rapporteur: Irena Rogovska

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

The intention to treat the condition with the medicinal product containing lefitolimod was considered justified based on early clinical data suggesting clinically relevant improvement in overall survival of patients with a lower fraction of activated B cells at baseline.

The condition is chronically debilitating and life threatening due to its rapid progression and the development of widespread metastases, with a 5-year overall survival of 5-10%.

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.

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 lefitolimod will be of significant benefit to those affected by the condition. The sponsor has provided early clinical data that suggest that patients who had a lower proportion of activated B cells at baseline may achieve improved survival compared to patients treated with the standard of care. Indirect comparison to all other authorised treatments suggested a chance for longer survival. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for lefitolimod, for treatment of small cell lung cancer, was adopted by consensus.

### 2.2.4. - EMA/OD/0000042673

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 March 2021 meeting.

### 2.2.5. - EMA/OD/0000044231

Treatment of pancreatic 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 March 2021 meeting.

#### 2.2.6. 5-fluoro-4-(7'-fluoro-2'-methylspiro[cyclopentane-1,3'-indol]-5'-yl)-N-(5-(1-methylpiperidin-4-yl)pyridin-2-yl)pyrimidin-2-amine - EMA/OD/0000045910

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Rapport Global Strategic Services Ireland Limited; Treatment of glioma

COMP Rapporteur: Brigitte Schwarzer-Daum

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

The intention to treat the condition with the medicinal product containing 5-fluoro-4-(7'-fluoro-2'-methylspiro[cyclopentane-1,3'-indol]-5'-yl)-N-(5-(1-methylpiperidin-4-yl)pyridin-2-yl)pyrimidin-2-amine was considered justified based on increased survival in a non-clinical model of the condition.

The condition is chronically debilitating due to symptoms caused the tumour compressing the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality and cognitive impairment. The condition is also life-threatening, with poor 5-year survival of less than 5% for glioblastoma multiforme patients.

The condition was estimated to be affecting approximately 2.7 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 5-fluoro-4-(7'-fluoro-2'-methylspiro[cyclopentane-1,3'-indol]-5'-yl)-N-(5-(1-methylpiperidin-4-yl)pyridin-2-yl)pyrimidin-2-amine will be of significant benefit to those affected by the condition. The sponsor has provided in vivo evidence in a model of the condition reporting add-on effects in combination with temozolomide compared to temozolomide alone. The Committee considered that this supports the assumption of clinically relevant advantage.

A positive opinion for 5-fluoro-4-(7'-fluoro-2'-methylspiro[cyclopentane-1,3'-indol]-5'-yl)-N-(5-(1-methylpiperidin-4-yl)pyridin-2-yl)pyrimidin-2-amine, for treatment of glioma, was adopted by consensus.

#### 2.2.7. alpelisib - EMA/OD/0000047280

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Novartis Europharm Limited; Treatment of PIK3CA related overgrowth spectrum

COMP Rapporteur: Bozena Dembowska-Baginska

The Committee agreed that the condition, PIK3CA related overgrowth spectrum, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing alpelisib was considered justified based on non-clinical in vivo data in a model of the condition showing a reduction in tumour size and preliminary clinical data in patients with the condition showing a reduction in benign tumour size, oedema and a recovery of normal cardiac and musculoskeletal function.

The condition is life-threatening and chronically debilitating due to functional impairment (e.g., of walking or swallowing), renal impairment, cardiac impairment, pain, recurrent superficial infections due to the overgrowth of benign tumors and can include impaired



neurological development, seizures, thromboembolisms, pulmonary hypertension, and hemorrhages.

The condition was estimated to be affecting approximately 1.25 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 alpelisib, for treatment of PIK3CA related overgrowth spectrum, was adopted by consensus.

#### 2.2.8. - EMA/OD/0000047634

Treatment of ovarian 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 March 2021 meeting.

#### 2.2.9. herpes simplex virus 1 expressing the human *CFTR* gene - EMA/OD/0000047694

IDEA Innovative Drug European Associates (Ireland) Limited; Treatment of cystic fibrosis

COMP Rapporteur: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing Herpes simplex virus 1 expressing the human *CFTR* gene was considered justified based on in vivo data supporting expression of *CFTR* in a valid non-clinical model of the condition.

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

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 Herpes simplex virus 1 expressing the human *CFTR* gene will be of significant benefit to those affected by the condition. The sponsor has provided in vivo data supporting expression of *CFTR* in a valid non-clinical model of the condition. The data justify the assumption that the product may exert beneficial effects in all classes of *CFTR* mutations including class I mutations, for which none of the authorised products is indicated. The Committee considered that this supports the assumption of clinically relevant advantage.

A positive opinion for herpes simplex virus 1 expressing the human *CFTR* gene, for treatment of cystic fibrosis, was adopted by consensus.

#### 2.2.10. - EMA/OD/0000048121

Treatment of cutaneous T-cell lymphoma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the March 2021 meeting.

#### **2.2.11. - EMA/OD/0000048469**

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Treatment of non-functioning pituitary adenomas

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 March 2021 meeting.

#### **2.2.12. - EMA/OD/0000048721**

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Treatment of non-small cell lung cancer with EGFR alterations

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 March 2021 meeting.

#### **2.2.13. vatiquinone - EMA/OD/0000052192**

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PTC Therapeutics International Limited; Treatment of Friedreich's ataxia

COMP Rapporteur: Robert Nistico

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

The intention to treat the condition with the medicinal product containing vatiquinone was considered justified based on preliminary clinical data showing a slowing of decline in neurological function over a period of 24 months.

The condition is chronically debilitating and life threatening due to ataxia, progressive disability that requires the use of wheelchair, and cardiac involvement in the form of hypertrophic cardiomyopathy.

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 vatiquinone, for treatment of Friedreich's ataxia, was adopted by consensus.

#### **2.2.14. - EMA/OD/0000052275**

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Treatment of eosinophilic oesophagitis

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 March 2021 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**

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COMP coordinators were appointed for 19 applications.

## **2.7. Evaluation on-going**

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

# **3. Requests for protocol assistance with significant benefit question**

## **3.1. Ongoing procedures**

### **3.1.1. -**

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Treatment of Fabry disease

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

### **3.1.2. -**

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Treatment of relapsed or refractory multiple myeloma

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

### **3.1.3. -**

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Treatment of sickle cell disease

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. -**

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

The finalised letter was circulated for information.

### **3.2.2. -**

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Treatment of multiple myeloma

The finalised letter was circulated for information.

### **3.2.3. -**

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Treatment of ATTR amyloidosis-polyneuropathy

The finalised letter was circulated for information.

### **3.2.4. -**

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Treatment of ATTR amyloidosis-cardiomyopathy

The finalised letter was circulated for information.

## **3.3. New requests**

### **3.3.1. -**

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Treatment of pancreatic cancer

The new request was noted.

### **3.3.2. -**

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Treatment of Gaucher disease

The new request was noted.

### **3.3.3. -**

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Treatment of growth hormone deficiency

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. Nexpovio - selinexor - EMEA/H/C/005127, EMA/OD/087/14, EU/3/14/1355, EMA/OD/0000043722**

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Karyopharm Europe GmbH; Treatment of plasma cell myeloma

COMP Rapporteurs: Frauke Naumann-Winter; Karri Penttila

A list of issues was adopted on 03 December 2020.

An oral explanation was held on 16 February 2021.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 18 February 2021, prior to final opinion.

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

#### **4.1.2. Sogroya - somapacitan - EMEA/H/C/005030/0000, EU/3/18/2068, EMA/OD/0000033719**

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Novo Nordisk A/S; Treatment of growth hormone deficiency

COMP Rapporteurs: Elisabeth Johanne Rook; Zsofia Gyulai

A list of issues was adopted on 05 November 2020.

An oral explanation was held on 17 February 2021.

An opinion recommending not to remove Sogroya, somapacitan (EU/3/18/2068) from the EC Register of Orphan Medicinal Products was adopted by majority (27 out of 30 votes). The Norwegian COMP member agreed with the above-mentioned recommendation of the COMP.

The divergent positions (Elisabeth Johanne Rook, Elisabeth Penninga, Michel Hoffmann) were appended to this opinion.

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. Darzalex - daratumumab - EMEA/H/C/004077/II/0043 EMA/OD/207/17, EU/3/18/2020, EMA/OD/0000049819**

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Janssen-Cilag International NV; Treatment of AL amyloidosis

CHMP Rapporteur: Sinan B. Sarac; CHMP Co-Rapporteur: Blanca Garcia Ochoa

The status of the procedure at CHMP was noted.

#### 4.2.2. – duvelisib - EMEA/H/C/005381/0000

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Verastem Europe GmbH

a) Treatment of Follicular lymphoma, EMA/OD/047/13, EU/3/13/1157, EMA/OD/0000024085

The status of the procedure at CHMP was noted.

*[Post-meeting note: The sponsor formally withdrew the application for orphan designation on 25 February 2021. The sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 25 February 2021. The orphan designation withdrawal assessment report will be publicly available on the EMA website]*

b) Treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma, EMA/OD/196/12, EU/3/13/1125, EMA/OD/0000026423

The status of the procedure at CHMP was noted.

*[Post-meeting note: The sponsor formally withdrew the application for orphan designation on 25 February 2021. The sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 25 February 2021. The orphan designation withdrawal assessment report will be publicly available on the EMA website]*

#### 4.2.3. – hydrocortisone - EMEA/H/C/005105/0000, EMA/OD/020/05, EU/3/05/296, EMA/OD/0000032128

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Diurnal Europe BV; Treatment of congenital adrenal hyperplasia

The COMP adopted a list of issues that will be sent to the sponsor.

#### 4.2.4. – setmelanotide - EMEA/H/C/005089/0000

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TMC Pharma (EU) Limited

a) Treatment of leptin receptor deficiency, EU/3/18/2101, EMA/OD/0000040440

The status of the procedure at CHMP was noted.

b) Treatment of pro-opiomelanocortin deficiency, EMA/OD/063/16, EU/3/16/1703, EMA/OD/0000040443

The status of the procedure at CHMP was noted.

#### 4.2.5. – satralizumab - EMEA/H/C/004788, EMA/OD/014/16, EU/3/16/1680, EMA/OD/0000016001

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Roche Registration GmbH; Treatment of neuromyelitis optica spectrum disorders

The status of the procedure at CHMP was noted.

### 4.3. Appeal

None

#### **4.4. On-going procedures**

COMP co-ordinators were appointed for 1 application.

#### **4.5. Orphan Maintenance Reports**

Documents were tabled for information.

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

#### **5.1. After adoption of CHMP opinion**

None

#### **5.2. Prior to adoption of CHMP opinion**

##### **5.2.1. Kaftrio - ivacaftor/tezacaftor/elexacaftor - EMEA/H/C/005269/II/0001, EMA/OD/0000001208, EU/3/18/2116, EMA/OD/0000042077**

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Vertex Pharmaceuticals (Ireland) Limited; Treatment of cystic fibrosis

CHMP Rapporteur: Johann Lodewijk Hillege

The status of the procedure at CHMP was noted.

##### **5.2.2. Kalydeco - ivacaftor - EMEA/H/C/002494/II/0089, EMA/OD/010/08, EU/3/08/556, EMA/OD/0000042076**

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Vertex Pharmaceuticals (Ireland) Limited; Treatment of cystic fibrosis

CHMP Rapporteur: Maria Concepcion Prieto Yerro

The status of the procedure at CHMP was noted.

##### **5.2.3. Darzalex - daratumumab - EMEA/H/C/004077/II/0044, EMA/OD/038/13, EU/3/13/1153, EMA/OD/0000049818**

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Janssen-Cilag International NV; Treatment of plasma cell myeloma

CHMP Rapporteur: Sinan B. Sarac

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is not needed.

#### **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**

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COMP-SRLM of the Portuguese Presidency held on 11<sup>th</sup> February 2021

The Portuguese COMP member presented the outcome of meeting and discussions held. The minutes were noted.

#### **7.1.2. Protocol Assistance Working Group (PAWG)**

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The working group on Protocol Assistance met remotely on 12 February 2021.

### **7.2. Coordination with EMA Scientific Committees or CMDh-v**

#### **7.2.1. Recommendation on eligibility to PRIME – report from CHMP**

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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)**

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Documents were tabled for information.

### **7.4. Cooperation within the EU regulatory network**

#### **7.4.1. COMP Working Group on the orphan regulation**

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Conclusions of the COMP WG on the orphan regulation

Feedback was provided about the recent STAMP meeting held and the topics discussed.

### **7.5. Cooperation with International Regulators**

#### **7.5.1. Food and Drug Administration (FDA)**

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None

#### **7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)**

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None



### 7.5.3. Therapeutic Goods Administration (TGA), Australia

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None

### 7.5.4. Health Canada

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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

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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

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

## 8. **Any other business**

### 8.1.

### 8.2. **Roll-out of WebEx for COMP**

The COMP noted the roll-out of Webex starting from March. The members were invited to take part in trainings and practice sessions before the COMP March plenary.

### 8.3. **Re-engineered ITF - presentation to COMP**

The aim of the presentation was to describe to COMP how Innovation Task Force (ITF) interacts with stakeholders on early innovative developments and agree on lean process to inform and involve COMP members to relevant interactions.

In addition, the intention was to seek COMP feed-back on most relevant developments (interactions) from 2020 and to offer to prepare an in-depth analysis on a COMP selected area of interest.

ITF requests per therapeutic areas (2020) were also looked at. It was noted that 20 percent of requests are in orphan areas. It was agreed that ITF BMs information will be sent to COMP members via email.

#### **8.4. Update on CONSIGN project - EMA draft pregnancy strategy**

The aim of the strategy was to guide evidence-based decision-making about COVID-19 vaccine indications, vaccination policies, and treatment options for pregnant women.

The COMP noted the presentation.

## 9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 16-18 February 2021.

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)	Italy	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No interests declared	
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	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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 restrictions applicable to this meeting	
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 Matusевичius	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	
Angelo Loris Brunetta	Member	Patients' Organisation Representative	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Virginie Hivert	Expert *	Patients' Organisation Representative	No restrictions applicable to this meeting	
Nienke Rodenhuis	Expert*	Netherlands	No interests declared	
	Patient Expert* - via telephone	European Union - EMA	No interests declared	
	Patient Expert* - via telephone	European Union - EMA	No restrictions applicable to this meeting	
	Expert Witness* - via telephone	United States	Involvement limited to testify and give specialist advice on a specific issue by providing information and replying to any questions only.	
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/](http://www.ema.europa.eu/)