10 October 2019
EMA/COMP/499116/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 10-12 September 2019

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

10 September 2019, 09:00-19:00, room 2A

11 September 2019, 08:30-19:10, room 2A

12 September 2019, 08:30-15:30, room 2A

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.

Further information with relevant explanatory notes can be found at the end of this document.

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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Table of contents

1. Introduction

1.1. Welcome and declarations of interest of members and experts

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 the restricted involvement of some meeting participants in upcoming discussions 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. 23 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

The COMP was pleased to welcome Ms Gloria Maria Palomo Carrasco replacing Mr Fernando Mendez Hermida as member for Spain.

1.2. Adoption of agenda

The agenda for 10-12 September 2019 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 16-18 July 2019 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. 18-(p-(^{131}I)-iodophenyl)octadecyl phosphocholine - EMA/OD/0000009805

Voisin Consulting S.A.R.L.; Treatment of multiple myeloma

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:

- 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 multiple myeloma the sponsor was asked to further

elaborate on the presented preliminary clinical data. In order to attribute the preliminary treatment effect to the proposed product it was considered necessary to provide context from the published literature of dexamethasone therapy in the same patient population.

- Number of people affected

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

The sponsor was requested to provide the most up-to-date incidence figure of multiple myeloma in Europe, i.e. ECIS.

The sponsor was requested to further justify the proposed disease durations based on only one data source (Blimark, 2018) and to propose an adequate disease duration.

- Significant benefit

The acceptability of significant benefit was considered subject to the answers requested under "Intention to diagnose, prevent or treat".

In the written response, and during an oral explanation before the Committee on 10 September 2019, the sponsor elaborated on the available preliminary clinical evidence and contextualised this evidence with published literature on the use of high dose and low-dose dexamethasone. Furthermore, the sponsor highlighted that the proposed product was provided in combination with low-dose dexamethasone and there is no clinical evidence to suggest that low-dose dexamethasone on its own has a relevant clinical effect. Moreover, the sponsor stressed that the preliminary clinical data showed responses in heavily pre-treated patients, who received and failed authorised regimens with or without dexamethasone. The COMP discussed with the sponsor the low number of observed very good partial and partial responses, and the maturity of data with currently short duration of responses. However, the majority of COMP members concluded that the currently available evidence is sufficient to support the assumption of medical plausibility and significant benefit in heavily pre-treated patients that failed currently authorised treatment options.

The Committee agreed that the condition, treatment of 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 18-(p-(^{131}I)-iodophenyl)octadecyl phosphocholine was considered justified based on non-clinical data demonstrating antitumor efficacy in monotherapy and preliminary clinical data showing antitumor efficacy when the proposed product is used in combination with low-dose dexamethasone.

The condition is chronically debilitating in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions, and life-threatening with a reduced life expectancy.

The condition was estimated to be affecting approximately 4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing 18-(p-(^{131}I)-iodophenyl)octadecyl phosphocholine will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data showing that heavily pre-treated patients respond to treatment with the

proposed product in combination with low-dose dexamethasone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 18-(p-(^{131}I)-iodophenyl)octadecyl phosphocholine, for treatment of multiple myeloma, was adopted by majority (25 out of 26 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.

2.1.2. - EMA/OD/0000004356

Treatment of progressive supranuclear palsy

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 26 August 2019, prior to responding to the list of issues.

2.1.3. - EMA/OD/0000009156

Treatment of endophthalmitis

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 9 August 2019, prior to responding to the list of issues.

2.1.4. besilesomab - EMA/OD/0000004428

Therapharm Deutschland GmbH; Treatment in haematopoietic stem cell transplantation

COMP Rapporteur: Martin Mozina

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

- Intention to diagnose, prevent or treat

The COMP noted that the sponsor appeared to be targeting primarily multiple myeloma patients and had associated data with the product in treatment of patients with amyloidosis. With the data provided it appeared that the target condition is multiple myeloma.

The sponsor was asked to comment on whether the product aims at improving the success of haematopoietic stem cell transplantation (HSCT) in general (e.g. engraftment) or whether it aims at improving the outcome of the underlying condition, multiple myeloma.

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).

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potential improved safety in the condition.

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

In the written response, and during an oral explanation before the Committee on 10 September 2019, the sponsor provided further clarification that the product could be used in conditions other than multiple myeloma where HSCT takes place. The sponsor then further elaborated on the preliminary clinical data that they hold with the product used in the proposed condition. Of particular interest was the response rate in patients treated with the sponsor's product with high dose melphalan vs high dose melphalan used with the standard combination. The sponsor reported that each patient treated with their product achieved a clinical benefit as opposed to the standard of care and melphalan high dose. The COMP considered that this could translate into a clinically relevant advantage which would support the basis of significant benefit.

The Committee agreed that the condition, treatment of in haematopoietic stem cell transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing besilesomab was considered justified based on preliminary clinical data showing good engraftment outcomes following conditioning treatment with the sponsor's product;

The condition is life-threatening and chronically debilitating due to susceptibility to severe infections, complications associated with graft vs host disease and failure to engraft;

The condition was estimated to be affecting 0.8 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing besilesomab will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data that support the use of besilesomab in combination with other products showing a lower rate of engraftment failure to current standard of care. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for besilesomab, for treatment in haematopoietic stem cell transplantation, was adopted by consensus.

2.1.5. anti-neonatal Fc receptor human monoclonal antibody - EMA/OD/0000003541

Biopharma Excellence GmbH; Prevention of haemolytic disease of the foetus and newborn (HDFN)

COMP Rapporteur: Ingeborg Barisic

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

A critical review of the sources used for the calculation of the population at risk (e.g. whether studies were population-based, any potential bias, etc) was missing. The sponsor was asked to justify the inclusion/choice of the sources selected for the estimation of the population at risk, including why the ones presented were considered the most relevant sources, and no more recent studies were included in the calculations.

For better transparency of the prevalence calculation, data on the country-specific fertility rate and the country-specific female population between 15 and 49 years of age was

requested as well. In addition, a literature search presenting the epidemiological studies related to ABO incompatibility should support the assumption that ABO incompatibility affects approximately 15-20% of all pregnancies, and that 10% of those develop HDFN.

Given the variability between different sources in relation to the extent of the population at risk, the sponsor was asked to perform a sensitivity analysis and to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

In the written response, the sponsor further justified the calculations of the patient population at risk of HDFN. The sponsor determined the percentage of pregnant women testing positive for circulating anti-RBC (red blood cells) antibodies by indirect antiglobulin test (IAT) and the percent of ABO alloimmunised women with a foetus or newborn that develop HDFN. A systematic literature search yielding 15 studies representing the most recent data available from the EU/EEA to report the incidence of IAT positivity and ABO-HDFN was presented. The articles were classified into main or supportive evidence to further justify the source upon critical review taking into account: the sample size of the reference population; the time period studied; the number of institutions involved in collecting samples; the type of institutions participating in study (e.g. specialty or university hospital); and whether the study was population-based or nationwide.

Based on the above, the frequency of IAT positive pregnant women in the EU/EEA was calculated on data from 9 countries, with 7/9 studies being considered main evidence, as they were population-based, nationwide studies based on large study cohorts. The conservative estimate for this population was 1.6/10,000 in the EU/EEA. The frequency of ABO-dependent HDFN was determined using studies from 2 countries, as only 2 population-based, nationwide studies based on large study cohorts were available. The sponsor concluded with a frequency of ABO-dependent HDFN of 0.5-0.7/10,000 individuals based on these studies but decided to provide a higher estimate, coming from EU based treatment guideline, which estimate the frequency of ABO-dependent HDFN at 2.0/10,000 in the EU.

The overall population at risk was therefore estimated to be 3.6 in 10,000 in the EU.

The COMP considered that the sponsor' calculations were acceptable, and communicated to the sponsor that the oral explanation was cancelled.

The Committee agreed that the condition, prevention of haemolytic disease of the foetus and newborn, is a distinct medical entity and meets the criteria for orphan designation.

The intention to prevent the condition with the medicinal product containing anti-neonatal Fc receptor human monoclonal antibody was considered justified based on non-clinical studies showing inhibition of the transfer of immunoglobulins (antibodies) across the placenta in valid models of the condition.

The condition is life-threatening and chronically debilitating due to the development of haemolytic anaemia often requiring red blood cells transfusion, of jaundice, thrombocytopenia, cholestasis, foetal hydrops that can lead to intrauterine death in the most severe forms, and kernicterus that can lead to neurodevelopmental impairment.

The population of patients eligible for prevention of the condition was estimated to be approximately 3.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of prevention of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing anti-neonatal Fc receptor human monoclonal antibody will be of significant benefit to the population at risk of developing the condition. The currently authorised methods act by neutralizing only maternal antibodies associated with D antigen of Rhesus groups. The sponsor provided non-clinical data that demonstrated that the proposed product can reduce the passage across the placenta of maternal antibodies associated to different types of antigens. The Committee considered that this constitutes a clinically relevant advantage for the population at risk of developing the condition because it could potentially prevent haemolytic disease of the foetus and the newborn from all types of incompatibilities between maternal and foetal blood.

A positive opinion for anti-neonatal Fc receptor human monoclonal antibody, for prevention of haemolytic disease of the foetus and newborn, was adopted by consensus.

2.1.6. pemigatinib - EMA/OD/0000005753

Incyte Biosciences Distribution B.V.; Treatment of myeloid or lymphoid neoplasm associated with FGFR1 rearrangement

COMP Rapporteur: Armando Magrelli

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

- Intention to diagnose, prevent or treat

The COMP expressed its preference to designate "treatment of myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2" in accordance with the latest 2016 revision of the World Health Organisation Classification of myeloid neoplasms and acute leukaemia. The sponsor was asked to consider revising the condition, or alternatively justify myeloid or lymphoid neoplasm associated with FGFR1 rearrangement 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 is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

- Number of people affected

For the calculation 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 revise or confirm the current prevalence estimate in accordance with the above considerations for the definition of the condition.

In the written response, and during an oral explanation before the Committee on 10 September 2019, the sponsor acknowledged the most recent version of the WHO classification of myeloid neoplasms and acute Leukaemia (2016) and elaborated on the similarities and differences between the different sub-entities in the relevant category "treatment of myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2". The sponsor highlighted that the concerned sub-entities are characterised by distinct and non-overlapping underlying molecular abnormalities and that also some of the clinical presentations can differ, e.g. the WHO acknowledged that eosinophilia might not occur across all sub-types. The COMP appreciated

this discussion but believed that the naming of the condition for the purpose of orphan designation should follow the overarching categorisation by the WHO on the basis of the common pathophysiological, histopathological and clinical features. Therefore, the COMP considered that the orphan condition should be amended to "treatment of myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2".

The sponsor accepted the change in condition and re-calculated the prevalence accordingly. The prevalence was estimated by the formula combining incidence and disease duration. The incidence was derived from the Surveillance, Epidemiology and End Results (SEER) cancer program in the USA, by assuming that the condition affects 10%-20% of hypereosinophilic syndromes (HES). The disease duration was estimated to be 17.5 years based on published literature data. The US prevalence was extrapolated to the European population resulting in a final prevalence estimate of 0.31 to 0.63 per 10,000. The COMP concluded to designate less than 0.7 per 10,000.

The Committee agreed that the condition, treatment of myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing pemigatinib was considered justified based on preliminary clinical data suggesting that patients affected by myeloid or lymphoid neoplasm associated with FGFR1 rearrangement respond to treatment.

The condition is life-threatening and chronically debilitating due to the clonal proliferation of myeloid and/or lymphoid precursors, eosinophilia, lymphoid aggregates, and often myelofibrosis.

The condition was estimated to be affecting less than 0.7 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 provided sufficient justification for the assumption that the medicinal product containing pemigatinib will be of significant benefit to those affected by the condition. The sponsor provided clinical data that show responses in patients affected by myeloid or lymphoid neoplasm associated with FGFR1 rearrangement, who have received previous systemic chemotherapy in accordance with best standard of care including authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for pemigatinib, for treatment of myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2, was adopted by consensus.

2.1.7. - EMA/OD/0000004857

Treatment of cystic fibrosis

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 cystic fibrosis the sponsor was asked to further elaborate on: whether the type of background therapy has been evenly distributed between the active and placebo arm and whether CFTR (cystic fibrosis transmembrane conductance) modulators were allowed. Additionally, the sponsor should discuss the relevance of the observed mean log changes *versus* placebo in inflammatory markers and whether they were statistically significant.

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor was requested to detail the results of the phase 2 study with particular attention to the distribution of the background therapy among the groups and provide any other 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 11 September 2019, the sponsor further elaborated how the clinical data supported the medical plausibility and significant benefit. The discussion on medical plausibility highlighted that the study had been conducted before the introduction of CFTR-modulator therapy and that it could not be therefore considered in the evaluation of effect. The value of the effect on neutrophil activating as a surrogate endpoint was discussed as well as the data on mucous elasticity. The COMP was of the opinion that the medical plausibility could be supported with the limited data that was submitted showing the log reduction in induced sputum NE (neutrophil elastase) levels after 4 weeks treatment but that the data was very limited and more data would have been ideal to be able to see the effect on FEV1 (forced expiratory volume in one second). An anti-inflammatory effect was accepted.

Concerning significant benefit, the sponsor proposed that the anti-inflammatory effect seen in the clinical data submitted could support the basis of an additive effective on top of standard of care. The COMP however did not agree as no change in FEV1 was established and thus the claim of a better mucolytic action which would be associated with improved lung function had not been substantiated by an improvement in lung function which the sponsor was trying to claim as the clinically relevant advantage.

The mucolytic effects were not for example contextualised within the use of dornase alfa or the use of hydrator treatment such as mannitol or hypertonic saline solution. The COMP considered that the clinical data was too limited to establish if there was indeed a clinically relevant advantage or not, and thus recommended that the product should not be granted an orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 September 2019, prior to final opinion.

2.1.8. - EMA/OD/0000008878

Treatment of acute myeloid leukaemia

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

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potential improved efficacy in the condition. The data presented suggest the intention to use the product in combination with other treatments in patients affected by relapsed/refractory acute myeloid leukaemia (R/R AML).

The sponsor was requested to further discuss the arguments provided for significant benefit and to explain the intended positioning of the product in the currently recommended treatment algorithm for AML. The sponsor was asked to elaborate on the results from non-clinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. The sponsor was requested to provide a relevant discussion supported by data regarding the several products used in the R/R AML in addition to provide the available results from the ongoing clinical study. In the written response, and during an oral explanation before the Committee on 11 September 2019, the sponsor clarified that the intended therapeutic indication would encompass all patients (refractory to first line treatment) that are not eligible to receive intensive chemotherapy. The sponsor identified three populations of patients who would fall under this description. It was noted that the model of refractory AML was generated with the use of patient-derived cytarabine resistant cell lines. The COMP then inquired if any data exist to demonstrate improved efficacy over azacitidine or other demethylating agents, which can also be used in first- or second line treatment of AML in the same clinical setting (ineligible to receive intensive chemotherapy). The sponsor conceded that there were no *in vivo* data to support the claim of improved efficacy over azacitidine.

The COMP considered the available data to be premature for the purpose of demonstrating significant benefit over all authorised treatment options.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 September 2019, prior to final opinion.

2.1.9. 4-oxo-4H-chromene-2-carboxylic acid (2-(2-4-(2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl)-phenyl-2H-tetrazol-5-yl)-4,5-dimethoxy-phenyl)-amide - EMA/OD/0000006325

Boyd Consultants Limited; Treatment of soft tissue sarcoma

COMP Rapporteur: Bozenna Dembowska-Baginska;

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 calculation 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 particular, the sponsor was requested to discuss the duration of the proposed condition, taking into consideration survival and late relapses, in order to justify the use of a complete or a partial prevalence.

The sponsor was asked to re-calculate the prevalence estimate based on relevant and updated epidemiological studies and registries for the proposed orphan condition and 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

Significant benefit is argued on the basis of both improved safety and a major contribution to patient care. However, both of these aspects would pre-suppose a comparable efficacy in the target indication and require a data-driven comparison *versus* the authorised products. The latter is now missing. It is not clear how the provided observations in a non-clinical model and in two treated patients support this assumption.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from non-clinical studies and clinical observations, in order to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 11 September 2019, the sponsor submitted further clinical observations in line with the initial data presented. It was reported that the first patients with cutaneous angiosarcoma have received at least six weeks of treatment, consisting of the proposed product and an oral formulation of paclitaxel. It was reported that all patients showed visible reduction of the tumour within one or two weeks of treatment, and several complete responses based on RECIST v1.1 criteria were reported.

With regards to the issue of prevalence, the sponsor referred to a recent publication by Saltus, *et al*., pointing to a median overall survival of 5.83 years. Based on this it was argued that the appropriate epidemiological index to report the rarity of soft tissue sarcoma would be 5-year partial prevalence, which was calculated to be 2.2 per 10,000 also taking into consideration NORDCAN and UKGPR sources. The sponsor also embarked in an effort to calculate 10-year partial prevalence, as a sensitivity analysis, which gave a mean number of 4.56 per 10,000 from the different sources.

The COMP reflected on the appropriate index to be used for the assessment of the rarity criterion, taking into consideration the heterogeneity of the orphan indication. It was firstly pointed out that the survival exceeds 5 years. The Committee also considered that people who may be considered as 'cured' in terms of survival, could in some cases still be considered as "affected by the condition" for example in case of chronic disabilities as a consequence of treatment. With this in mind it was concluded that, as a proxy of the number of people alive and affected by the condition, the 10-year partial prevalence would be useful. It was concluded that the condition affected approximately 4.56 per 10,000 at the time of designation.

As for the scientific benefit issue, the sponsor discussed data from a breast cancer study, where the proposed product (oral paclitaxel and the p-gp inhibitor) is studied *versus* IV paclitaxel, and argued a numerically improved efficacy and safety. With regards to the available data in angiosarcoma, the characteristics of the patients with complete remission were discussed, pointing out that they were elderly patients with comorbidities, who would otherwise be unlikely to receive IV paclitaxel treatment, and were treated with oral paclitaxel at home. The COMP considered that paclitaxel was a recommended treatment in first line angiosarcoma, and that the use of the proposed product would allow for oral dosing of paclitaxel, thereby enlarging the pool of patients amenable to treatment. The assumption that the combination treatment would be appropriate for a group of elderly patients

otherwise unfit for standard chemotherapy, was considered justified based on the available clinical data

The Committee agreed that the condition, treatment of soft tissue sarcoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 4-oxo-4H-chromene-2-carboxylic acid (2-(2-4-(2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl)-phenyl-2H-tetrazol-5-yl)-4,5-dimethoxy-phenyl)-amide was considered justified based on preliminary clinical observations in elderly patients with cutaneous angiosarcoma who responded to treatment following administration of this p-glycoprotein pump inhibitor enhancing the absorption of an orally administered formulation of paclitaxel.

The condition is chronically debilitating with a high recurrence and metastasis rate, and life-threatening with an overall 5-year survival rate of approximately 60%.

The condition was estimated to be affecting approximately 4.56 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 provided sufficient justification for the assumption that the medicinal product containing 4-oxo-4H-chromene-2-carboxylic acid (2-(2-4-(2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl)-phenyl-2H-tetrazol-5-yl)-4,5-dimethoxy-phenyl)-amide will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical observations in angiosarcoma patients who responded to treatment following administration of this p-glycoprotein pump inhibitor enhancing the absorption of an orally administered formulation of paclitaxel. This supported the assumption that the combination treatment would be appropriate for a group of elderly patients otherwise unfit for standard chemotherapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 4-oxo-4H-chromene-2-carboxylic acid (2-(2-4-(2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl)-phenyl-2H-tetrazol-5-yl)-4,5-dimethoxy-phenyl)-amide, for treatment of soft tissue sarcoma, was adopted by consensus.

2.1.10. paclitaxel - EMA/OD/0000006386

Boyd Consultants Limited; Treatment of soft tissue sarcoma

COMP Rapporteur: Bozenna Dembowska-Baginska;

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 calculation 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 particular, the applicant was requested to discuss the duration of the proposed condition, taking into consideration survival and late relapses, in order to justify the use of a complete or a partial prevalence.

The sponsor was asked to re-calculate the prevalence estimate based on relevant and updated 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.

- Significant benefit

Significant benefit was argued on the basis of both improved safety and a major contribution to patient care. However, both of these aspects would pre-suppose a comparable efficacy in the target indication and require a data-driven comparison *versus* the authorised counterparts. The latter is now missing. It is not clear how the provided observations in a non-clinical model and in two treated patients support this assumption.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from non-clinical studies and clinical observations, in order to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 11 September 2019, the sponsor submitted further clinical observations in line with the initial data presented. It was reported that the first patients with cutaneous angiosarcoma have received at least six weeks of treatment, consisting of the proposed product and a -oxo-4H-chromene-2-carboxylic acid (2-(2-4-(2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl)-phenyl-2H-tetrazol-5-yl)-4,5-dimethoxy-phenyl)-amide. It was reported that all patients showed visible reduction of the tumour within one or two weeks of treatment, and several Complete Responses based on RECIST v1.1 criteria were also reported.

With regards to the issue of prevalence, the sponsor referred to a recent publication by Saltus *et al*., pointing to a median OS of 5.83 years. Based on this it was argued that the appropriate epidemiological index to report the rarity of STS would be 5-year partial prevalence, which was calculated to be 2.2 per 10,000 also taking into consideration NORDCAN and UKGPR sources. The sponsor also embarked in an effort to calculate 10-year partial prevalence, as a sensitivity analysis, which gives a mean number of 4.56 per 10,000 from the different sources.

The COMP reflected on the appropriate index to be used for the assessment of the rarity criterion, taking into consideration the heterogeneity of the orphan indication. It was firstly pointed out that the survival exceeds 5 years. The Committee also considered that people who may be considered as 'cured' in terms of survival, could in some cases still be considered as "affected by the condition" for example in case of chronic disabilities as a consequence of treatment. With this in mind it was concluded that, as a proxy of the number of people alive and affected by the condition, the 10-year partial prevalence would be useful. It was concluded that the condition affected approximately 4.56 per 10,000 at the time of designation.

As for the scientific benefit issue, the sponsor discussed data from a breast cancer study, where the proposed product (oral paclitaxel and -oxo-4H-chromene-2-carboxylic acid (2-(2-4-(2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl)-phenyl-2H-tetrazol-5-yl)-4,5-dimethoxy-phenyl)-amide) is studied *versus* IV paclitaxel, and argued a numerically improved efficacy and safety. With regards to the available data in angiosarcoma in particular, the characteristics of the patients with complete remissions were discussed, pointing out that they were elderly patients with comorbidities, who would otherwise be unlikely to receive IV paclitaxel treatment, and were treated with oral paclitaxel at home.

The COMP considered that paclitaxel is a recommended treatment in first line angiosarcoma, and that the use of the proposed product would allow for oral dosing of paclitaxel, thereby enlarging the pool of patients amenable to treatment. The assumption that the combination treatment would be appropriate for a group of elderly patients otherwise unfit for standard chemotherapy, was considered justified based on the available clinical data.

The Committee agreed that the condition, treatment of soft tissue sarcoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing paclitaxel was considered justified based on clinical observations in elderly patients with cutaneous angiosarcoma who responded to treatment with the proposed product in combination with the p-glycoprotein inhibitor 4-oxo-4H-chromene-2-carboxylic acid (2-(2-4-(2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl)-phenyl-2H-tetrazol-5-yl)-4,5-dimethoxy-phenyl)-amide.

The condition is chronically debilitating with a high recurrence and metastasis rate, and life-threatening with an overall 5-year survival rate of approximately 60%.

The condition was estimated to be affecting approximately 4.56 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 oral paclitaxel and 4-oxo-4H-chromene-2-carboxylic acid (2-(2-4-(2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl)-phenyl-2H-tetrazol-5-yl)-4,5-dimethoxy-phenyl)-amide will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations in elderly patients with cutaneous angiosarcoma who responded to treatment with the proposed product in combination with the p-glycoprotein inhibitor 4-oxo-4H-chromene-2-carboxylic acid (2-(2-4-(2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl)-phenyl-2H-tetrazol-5-yl)-4,5-dimethoxy-phenyl)-amide. This supports the assumption that the combination treatment would be appropriate for a group of elderly patients, otherwise unfit for standard chemotherapy. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.11. nirogacestat - EMA/OD/0000009203

Voisin Consulting S.A.R.L.; Treatment of soft tissue sarcoma

COMP Rapporteur: Brigitte Schwarzer-Daum

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 calculation 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 particular, the applicant was requested to discuss the duration of the proposed condition, taking into consideration survival and late relapses, in order to justify the use of a complete or a partial prevalence.

The sponsor was asked to re-calculate the prevalence estimate based on relevant and updated 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.

In the written response, and during an oral explanation before the Committee on 11 September 2019 the sponsor submitted an estimate of 2.5 per 10,000 people, based on incidence data from national cancer registries across the EU and an estimate of median survival of 6.8 years. The COMP has noted that the incidence of the condition remained stable over many years and was reported as such in recent publications. A recent publication by Saltus *et al*., points to a median overall survival of 5.83 years. The Committee further noted that people who may be considered as 'cured' in terms of survival, could in some cases still be considered as "affected by the condition", for example in case of chronic disabilities as a consequence of treatment. With that in mind, it was concluded that, as a proxy of the number of people alive and affected by the condition, that a 10-year partial prevalence could be useful. It was concluded that the condition affected approximately 4.56 per 10,000 at the time of designation.

The Committee agreed that the condition, treatment of soft tissue sarcoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing nirogacestat was considered justified based on preliminary clinical data where there was an improvement in Overall Response Rate (ORR) after treatment in patients with recurrent, refractory, progressive desmoid tumours.

The condition is chronically debilitating with a high recurrence and metastasis rate, and life-threatening with an overall 5-year survival rate of approximately 60%.

The condition was estimated to be affecting approximately 4.6 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 have been authorised in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing nirogacestat will be of significant benefit to those affected by the condition. The sponsor provided clinical data that demonstrate improvement in the overall response rate in patients with recurrent, refractory, progressive desmoid tumours after therapy with nirogacestat. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.12. - EMA/OD/0000009840

Treatment of cystic fibrosis

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

In order to justify the significant benefit of the proposed product the sponsor was requested to provide details (methodology, graphs, statistical analysis) of the mentioned studies where the product is compared to authorised medicines.

The sponsor was asked to support with data and discuss in detail any additional argument proposed in support of the significant benefit (e.g. potential clinical benefit across a wider range of CF mutations than the currently authorised CFTR modulators).

In the written response, and during an oral explanation before the Committee on 11 September 2019, the sponsor described a non-clinical *in vitro* study in which the proposed product had been used in combination with a currently authorised CF treatment, Symdeko (tezacaftor/ivacaftor). In this study, human bronchial epithelial cells treated with the proposed product demonstrated significantly increased airway surface liquid (ASL) volume compared to Symdeko, and the combination of the two products resulted in significant additional ASL volume increase.

The COMP extensively discussed this study. While it was acknowledged that a reduction of airways surface liquid *in vivo* in the airways of CF patients would be beneficial, it would be difficult at this stage to correlate the changes of ASL *in vitro* to potential benefits at the level of mucus clearance *in vivo* in patients. As such, even though several members would have been favourable to a positive opinion at this stage of development, taking into account the relative immaturity of the data and the uncertainty around the clinical translation of ASL *in vitro* measurements, the COMP expressed a negative trend.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 September 2019, prior to final opinion.

2.1.13. melatonin, sorafenib - EMA/OD/0000006955

Worphmed S.r.l.; Treatment of hepatocellular carcinoma

COMP Rapporteur: Brigitte Schwarzer-Daum;

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:

- Medical plausibility

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of hepatocellular carcinoma the sponsor was invited to provide *in vivo* (not *in vitro*) data with the proposed combination (the two active substances used concomitantly in the same experiment) in models of hepatocellular carcinoma or in affected patients.

- Significant benefit

The arguments on significant benefit were based on the potential improved efficacy in the condition by the two proposed active substances used in combination. The applicant cites two *in vitro* studies, claiming synergy in exerting cytotoxicity and inhibiting proliferation.

However, no *in vivo* observations with the proposed combination were available. The sponsor was invited to provide *in vivo* (not *in vitro*) data with the proposed combination

(the two active substances used concomitantly in the same experiment) in models of hepatocellular carcinoma or in affected patients.

Moreover, data-driven comparisons were also expected for all authorised medicines. This would include all authorised tyrosine kinase inhibitors (sorafenib, lenvatinib).

In the written response, and during an oral explanation before the Committee on 11 September, the sponsor provided a general discussion on the clinical practice guidelines for hepatocellular carcinoma (HCC), its staging and treatment, the authorised first line treatments and the sponsor's intention to combine melatonin with sorafenib with a view to improve efficacy and reduce the adverse effects of sorafenib. Sections from the SmPCs of authorised products in hepatocellular cancer were copied in the application, as well as previous designations for the same indication were listed. Such references were not considered directly relevant as answers to the raised issues. The sponsor also referred to a company's US orphan designations for another product (containing melatonin alone) in hepatocellular carcinoma, as well as some US-filed patents for a liquid formulation of melatonin.

In terms of *in vivo* data in HCC models with the melatonin-sorafenib combination, as requested by the COMP, such data were not provided in the responses. Instead, two publications were added to support the sponsor's position, a publication by Chen *et al.*, 2018, which includes some animal data with melatonin and etoposide, and a publication by Zhou *et al*., 2019, that investigates the combination *in vitro* in HCC cells and reports increase in sorafenib sensitivity by melatonin. This data is outlined below:

- In particular, the publication by Chen *et al*., reports that melatonin inhibits *in vitro* proliferation, migration, and invasion of HCC cells and suppresses their DNA repair capacity, increasing their sensitivity to etoposide and radiation. Moreover, in an i*n vivo* HCC model melatonin suppressed tumour growth and enhanced etoposide (but not sorafenib as proposed for designation) inhibitory effects.
- In the publication by Zhou *et al*., melatonin is reported to increase the *in vitro* sensitivity of HCC cells to sorafenib by inhibiting autophagy through the PERK-ATF4-Beclin1 pathway. In the same paper the importance of PERK (PKR-like ER stress kinase) and Beclin1 protein is also elucidated based on clinical observations correlating those biomarkers to more advanced HCC disease.
- The applicant also referred to a submitted (not yet published) paper, that reports inhibition of VEGF-induced angiogenesis in the chicken chorioallantoic membrane *in vivo* model by melatonin.

During the oral explanation and as per the list of issues, the sponsor was asked again to provide any observations of the effects of the proposed combination product *in vivo* in HCC settings. It was confirmed by the sponsor that no such data existed at that point in time. The COMP then pointed out to the sponsor that outcomes such as delay of tumour growth, tumour regression, or improved survival should have been studied *in vivo* in hepatocellular cancer models or in affected patients, in order to provide evidence for the fulfilment of the orphan designation criteria. Such outcomes would have been clinically relevant, while at this point in time the described effects on cell cultures could not allow for drawing any clinically relevant conclusions.

In the absence of such data the COMP considered that the medical plausibility, as well as the significant benefit *versus* other existing authorised products, could not be evaluated and therefore the orphan designation could not be granted.

The COMP considered that the sponsor referred to bibliographic studies reporting increased cytotoxicity of the two active substances combined *in vitro* in hepatocellular cancer cells. Such *in vitro* data were considered insufficient to support medical plausibility as they could not be translated to *in vivo* clinically relevant effects, such as tumour growth inhibition or improved survival; in the absence of data related to the combination in relation to the disease at stake, the intention to treat the condition (medical plausibility) of the combination of the two compounds could not be upheld.

The condition was estimated to be affecting approximately 1.3 in 10,000 persons in the European Union, at the time the application was made.

The condition is chronically debilitating and life-threatening due to increased mortality and liver dysfunction. Median survival without therapy can be greater than 36 months for stage 0 and A, 16 months for stage B, 4-8 months for stage C and less than 4 months for stage D.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has not provided sufficient justification for the assumption that the medicinal product containing melatonin, sorafenib will be of significant benefit to those affected by the condition.

The sponsor has referred to bibliographic studies reporting increased cytotoxicity of the two active substances combined *in vitro* in hepatocellular cancer cells. Such *in vitro* data were considered insufficient by the COMP to support the demonstration of the significant benefit of the combination *versus* existing therapies. In the absence of comparative data of improved antineoplastic activity, evidence was lacking to establish a clinically relevant advantage or major contribution to patient care of the proposed combination *versus* the authorised treatments.

A negative opinion for melatonin, sorafenib, for treatment of hepatocellular carcinoma, was adopted by consensus. The sponsor will have 90 days to appeal from the COMP decision.

[*Post-meeting note: The COMP adopted the opinion by written procedure following its September meeting.]*

2.1.14. autologous CD34+ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene - EMA/OD/0000010152

Vertex Pharmaceuticals (Ireland) Limited; Treatment of beta thalassemia intermedia and major

COMP Rapporteur: Armando Magrelli;

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 beta-thalassaemia intermedia and major the sponsor should explain the relevance of *ex vivo* data obtained to date for the potential magnitude of

the clinical effect. Please clarify the timelines of the intended clinical studies and when additional data would be available.

- Significant benefit

The evidence for the significant benefit was based on *ex vivo* data from patient cells. The sponsor was requested to further discuss the arguments provided for significant benefit against all authorised products including Zynteglo.

Furthermore, the sponsor was asked to provide more information on the planned clinical development.

In the written response, and during an oral explanation before the Committee on 12 September 2019, the sponsor discussed in particular the available clinical data from one patient who was treated with the product to date. The patient had a severe thalassaemia and achieved transfusion independence, which was maintained for the entire 6 months of the follow-up (until this submission of the orphan designation). The COMP asked about the sponsor's clinical development plans and all assumptions of significant benefit over Zynteglo were discussed. The COMP discussed with the sponsor whether any uncertainties exist about the long-term consequences of replacing adult 'beta' globin with foetal 'gamma' globin. The sponsor stated that in other indications where foetal haemoglobin is used and in people naturally maintaining foetal haemoglobin expression, no negative impact of such replacement was observed to date. Although the product was early in development, the totality of evidence from *ex vivo* and clinical studies was considered sufficient for the assumption that the product could address the underlying pathology in the condition by restoring normal levels of haemoglobin. This would reduce the need for blood transfusion and consequently any use of iron chelators. The sponsor, based on the available observations, envisioned clinically relevant improvement in severe patients, also those who are currently poorly studied or explicitly excluded from the indication of Zynteglo. These early assumptions will have to be confirmed at the time of marketing authorisation.

The Committee agreed that the condition, treatment of beta-thalassaemia intermedia and major, 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 cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene was considered justified based on *in vitro* data showing the increased expression of foetal haemoglobin and early clinical data in a patient who achieved transfusion independence with 6 months follow up.

The condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these, in particular in beta-thalassaemia major patients.

The condition was estimated to be affecting approximately 0.8 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing autologous CD34+ haematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that suggest a disease modifying potential of the product in patients restoring clinically acceptable levels of

haemoglobin. This would compare favourably to other current methods of treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous CD34+ haematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene, for treatment of beta-thalassaemia intermedia and major, was adopted by consensus.

2.1.15. - EMA/OD/0000002080

Treatment of hypoparathyroidism

Action: For information

Note: Withdrawal request received on 13 August 2019.

2.1.16. - EMA/OD/0000009969

Prevention of complications in end-stage renal disease patients on peritoneal dialysis

Action: For information

Note: Withdrawal request received on 27 August 2019.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000006190

Treatment of amyotrophic lateral 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 October meeting.

2.2.2. lonapegsomatropin - EMA/OD/0000007487

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

COMP Rapporteur: Vallo Tillmann

The Committee agreed that the condition, treatment of growth hormone deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing lonapegsomatropin was considered justified based on clinical data showing a significant effect on growth velocity in children affected by the condition.

The condition is chronically debilitating due to delayed puberty and deficits in facial, dental and genital development, associated with reduced bone mass with increased risk of developing osteopenia, osteoporosis, and bone fractures. Patients also experience severe psychosocial problems linked to the very short stature.

The condition was estimated to be affecting approximately 4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing lonapegsomatropin will be of significant benefit to those

affected by the condition. The sponsor provided clinical data showing significantly increased growth velocity in children affected by the condition compared with the currently authorised standard of care growth hormone treatments. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for lonapegsomatropin, for treatment of growth hormone deficiency, was adopted by consensus.

2.2.3. propranolol hydrochloride - EMA/OD/0000007627

Recordati Rare Diseases; Treatment of retinopathy of prematurity

COMP Rapporteur: Tim Leest

The Committee agreed that the condition, treatment of retinopathy of prematurity, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing propranolol hydrochloride was considered justified based on clinical data showing lack of progression of first-stage retinopathy to more severe stages in premature newborns treated with the proposed product.

The condition is chronically debilitating due to potential visual loss that may progress to blindness in the most severe cases.

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 propranolol hydrochloride, for treatment of retinopathy of prematurity, was adopted by consensus.

2.2.4. (16E)-14-methyl-20-oxa-5,7,14,26-tetraaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene–citric acid - EMA/OD/0000007659

Clinical Network Services (NL) B.V.; Treatment of glioma

COMP Rapporteur: Dinko Vitezic

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

The intention to treat the condition with the medicinal product containing (16E)-14-methyl-20-oxa-5,7,14,26-tetraaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene–citric acid was considered justified based on non-clinical data in a model of refractory glioblastoma showing a synergistic effect of the product and temozolomide and early clinical data demonstrating long term control of the disease in some patients.

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

The condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (16E)-14-methyl-20-oxa-5,7,14,26-tetraaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene–citric acid will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrated that a small proportion of patients who were refractory to the standard of care, achieved a prolonged disease control or partial response of the disease when treated with a combination of the proposed product and temozolomide. The Committee considered that this would constitute a clinically relevant advantage.

A positive opinion for (16E)-14-methyl-20-oxa-5,7,14,26-tetraaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene–citric acid, for treatment of glioma, was adopted by consensus.

2.2.5. - EMA/OD/0000007780

Treatment of mantle 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 October meeting.

2.2.6. Combination of two adeno-associated viral vectors of serotype 8 containing the 5'- and the 3'- half coding sequences of human *ABCA4* fused to inteins - EMA/OD/0000008501

Fondazione Telethon; Treatment of Stargardt disease

COMP Rapporteur: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing combination of two adeno-associated viral vectors of serotype 8 containing the 5'- and the 3'- half coding sequences of human *ABCA4* fused to inteins was considered justified based on the effects of the product in a non-clinical model of the condition resulting in reduction in accumulation of lipofuscin in the retinal pigment epithelial cells.

The condition is chronically debilitating, in particular due to loss of visual acuity and central vision loss, which may progress to complete blindness.

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

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

A positive opinion for combination of two adeno-associated viral vectors of serotype 8 containing the 5'- and the 3'- half coding sequences of human *ABCA4* fused to inteins, for treatment of Stargardt disease, was adopted by consensus.

2.2.7. - EMA/OD/0000009633

Treatment of autosomal recessive congenital ichthyosis (ARCI)

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 October meeting.

2.2.8. - EMA/OD/0000009997

Treatment of non-infectious uveitis

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 October meeting.

2.2.9. - EMA/OD/0000010168

Treatment of soft-tissue sarcoma

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 October meeting.

2.2.10. - EMA/OD/0000010228

Treatment of acute myeloid leukaemia

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 October meeting.

2.2.11. - EMA/OD/0000011311

Treatment of CDKL5 deficiency disorder

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 October meeting.

2.2.12. 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide-methane sulfonic acid salt - EMA/OD/0000012038

Quality Regulatory Clinical Ireland Limited; Treatment of graft-versus-host disease

COMP Rapporteur: Frauke Naumann-Winter

The Committee agreed that the condition, treatment of graft-versus-host disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide-methane sulfonic acid salt was considered justified based on preliminary clinical data in patients with chronic graft-versus-host disease showing a significant improvement in a validated primary endpoint of overall response rate.

The condition is chronically debilitating and life-threatening in particular due to intestinal inflammation causing diarrhoea, abdominal pain, nausea and vomiting, as well as due to hepatotoxicity, skin and mucosal damage, sicca syndrome, cholestasis,

arthritis, obliterative bronchiolitis and the need for immunosuppression that increases susceptibility to infections.

The condition was estimated to be affecting approximately 0.8 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide-methane sulfonic acid salt will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate responses in previously treated patients as well as a reduction in corticosteroid use. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide-methane sulfonic acid salt, for treatment of graft-versus-host disease, was adopted by consensus.

2.2.13. leriglitazone - EMA/OD/0000012140

Minoryx Therapeutics S.L.; Treatment of Friedreich's ataxia

COMP Rapporteur: Bruno Sepodes

The Committee agreed that the condition, treatment of 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 leriglitazone was considered justified based on non-clinical data in several valid models of the condition showing improved motor function upon treatment.

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

A positive opinion for leriglitazone, for treatment of Friedreich's ataxia, was adopted by consensus.

2.2.14. - EMA/OD/0000012303

Treatment of Duchenne muscular dystrophy

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 October meeting.

2.2.15. (S)-2-isobutyrylamino-pentanedioic acid 5-amide 1-{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butyl)-21-hydroxy-5-(4-hydroxy-benzyl)-15-isobutyl-4,11-dimethyl-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-bicyclo[16.3.1]docos-12-yl]-amide} - EMA/OD/0000012576

MDC RegAffairs GmbH; Treatment of Netherton syndrome

COMP Rapporteur: Zsofia Gyulai

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

The intention to treat the condition with the medicinal product containing (S)-2-isobutyrylamino-pentanedioic acid 5-amide 1-{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butyl)-21-hydroxy-5-(4-hydroxy-benzyl)-15-isobutyl-4,11-dimethyl-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-bicyclo[16.3.1]docos-12-yl]-amide} was considered justified based on early clinical data showing improvement on the Netherton syndrome total lesional sign score among other clinically relevant endpoints as compared to a vehicle control.

The condition is chronically debilitating and life-threatening due to dehydration, recurrent infections, failure to thrive and malnutrition especially during the neonatal period, and cutaneous infections, increased risk for skin cancer, alteration of physical appearance, and psychological burden on patients later in life.

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.

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

A positive opinion for (S)-2-isobutyrylamino-pentanedioic acid 5-amide 1-{[(2S,5S,8S,11R,12S,15S,18S,21R)-2,8-bis-((S)-sec-butyl)-21-hydroxy-5-(4-hydroxy-benzyl)-15-isobutyl-4,11-dimethyl-3,6,9,13,16,22-hexaoxo-10-oxa-1,4,7,14,17-pentaaza-bicyclo[16.3.1]docos-12-yl]-amide}, for treatment of Netherton syndrome, was adopted by consensus.

2.2.16. - EMA/OD/0000012626

Treatment of ATTR amyloidosis

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 October meeting.

2.2.17. 2'-O-(2-methoxyethyl)-D-ribose antisense oligonucleotide targeting glial fibrillary acidic protein messenger ribonucleic acid - EMA/OD/0000012628

Ionis Development (Ireland) Limited; Treatment of Alexander disease

COMP Rapporteur: Robert Nistico

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

The intention to treat the condition with the medicinal product containing 2'-O-(2-methoxyethyl)-D-ribose antisense oligonucleotide targeting glial fibrillary acidic protein messenger ribonucleic acid was considered justified based on non-clinical data showing the ability to reduce glial fibrillary acidic protein expression in the nervous system, resolution of Rosenthal fibre pathology, as well as improvement of weight gain and grip strength in several valid models of the condition.

The condition is chronically debilitating due to weakness, spasticity and ataxia, swallowing difficulties, dysarthria, dysphonia as well as psychomotor retardation and cognitive decline. The condition is life-threatening with median survival of 14 to 25 years depending on disease type.

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

A positive opinion for 2'-O-(2-methoxyethyl)-D-ribose antisense oligonucleotide targeting glial fibrillary acidic protein messenger ribonucleic acid, for treatment of Alexander disease, was adopted by consensus.

2.2.18. - EMA/OD/0000012715

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 October meeting.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

COMP coordinators were appointed for 32 applications.

2.7. Evaluation ongoing

The Committee noted that evaluation was on-going for 12 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of post-polycythaemia vera myelofibrosis

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 biliary tract cancer

The finalised letter was circulated for information.

3.2.2. -

Treatment of naevoid basal-cell carcinoma syndrome (Gorlin syndrome)

The finalised letter was circulated for information.

3.2.3. -

Treatment of medullary thyroid carcinoma

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of gastrointestinal stromal tumours

The new request was noted.

3.3.2. -

Treatment of graft-versus-host disease

The new request was noted.

3.3.3. -

Treatment of Duchenne muscular dystrophy

The new request was noted.

3.3.4. -

Treatment of amyotrophic lateral sclerosis

The new request was noted.

3.3.5. -

Treatment of congenital adrenal hyperplasia

The new request was noted.

4. Review of orphan designation for orphan medicinal products at time of initial marketing authorisation

4.1. Orphan designated products for which CHMP opinions have been adopted

None

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

4.2.1. Xospata - gilteritinib - EMEA/H/C/004752, EMA/OD/175/17, EU/3/17/1961, EMA/OD/0000006592

Accelerated assessment

Astellas Pharma Europe B.V.; Treatment of acute myeloid leukaemia

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. In its written response, and during an oral explanation before the Committee on 11 September 2019, the sponsor addressed all issues previously identified.

An opinion recommending not to remove Xospata from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

[Post-meeting note: The COMP adopted the opinion by written procedure following its September meeting.]

4.2.2. - polatuzumab vedotin – EMEA/H/C/004870, EMA/OD/231/17, EU/3/18/2013, EMA/OD/0000003161

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

The status of the procedure at CHMP was noted.

4.2.3. – enasidenib - EMEA/H/C/004324, EMA/OD/253/15, EU/3/16/1640, EMA/OD/0000007422

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

The status of the procedure at CHMP was noted.

4.2.4. – glutamine – EMEA/H/C/004734, EMA/OD/016/12, EU/3/12/1011

Emmaus Medical Europe Limited; Treatment of sickle cell disease

The status of the procedure at CHMP was noted.

[Post-meeting note: The marketing authorisation application was withdrawn after the CHMP September meeting]

4.3. Appeal

None

4.4. On-going procedures

COMP rapporteurs were appointed for 3 applications.

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. Adcetris - brentuximab vedotin - Type II variation – EMEA/H/C/002455/II/0070

Takeda Pharma A/S;

a) Treatment of cutaneous T-cell lymphoma, EMA/OD/100/11, EU/3/11/939

b) Treatment of anaplastic large cell lymphoma, EMEA/OD/072/08, EU/3/08/595

c) Treatment of Hodgkin lymphoma, EMEA/OD/073/08, EU/3/08/596

CHMP rapporteur: Paula Boudewina van Hennik

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

5.2.2. Vyndaqel – tafamidis – EMEA/H/C/002294/X/0049/G, EMEA/OD/032/06, EU/3/06/401, EMA/OD/0000003853

Pfizer Europe MA EEIG; Treatment of familial amyloid polyneuropathy

CHMP rapporteur: Joseph Emmerich; CHMP co-rapporteur: Bruno Sepodes

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

5.2.3. Jorveza – budesonide – EMEA/H/C/004655/X/0007/G, EMA/OD/078/13, EU/3/13/1181, EMA/OD/0000013431

Dr. Falk Pharma GmbH; Treatment of eosinophilic oesophagitis

CHMP rapporteur: Martina Weise; CHMP co-rapporteur; Tomas Boran;

The status of the procedure at CHMP was noted.

5.3. Appeal

None

5.4. Ongoing procedures

COMP co-ordinators were appointed for *2* applications.

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. Strategic Review & Learning meetings, 27-28 May 2019, Rome, Italy

The minutes for the SLRM under the Romanian presidency held on 27-28 May in Rome were discussed and adopted.

7.1.2. Strategic Review & Learning meeting– joint COMP/CAT/PDCO, 21-22 November 2019, Helsinki, Finland

The Draft agenda for the SLRM under the Finish presidency to be held on 21-22 November in Helsinki was presented.

7.1.3. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 10 September 2019.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

The documents were tabled for information.

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

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

The COMP was informed that the PCWP/HCPWP met on 25 September 2019.
The PCWP HCPWP Work plan 2019-2022 was presented and adopted.

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

The PCWP met on 25 September 2019.

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

The HCPWP met on 24 September 2019.

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 2019

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2019 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. EMA Business Pipeline activity and Horizon scanning

COMP noted the Q3/2019 update of the Business Pipeline report for the human scientific committees.

8.2. IRIS

The COMP received an EMA presentation on the best practices.

9. 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/

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 10-12 September 2019 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Chair	Netherlands	No interests declared	
Armando Magrelli	Member (Vice-Chair)	Italy	No interests declared	
Tim Leest	Member	Belgium	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Nectaroula Cooper	Member	Cyprus	No interests declared	
Lenka Kovarova	Member	Czech Republic	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Bruno Sepodes	Member	Expert recommended by EMA	No interests declared	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Geraldine O'Dea	Member	Ireland	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Elizabeth 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	
Eva Malikova	Member	Slovakia	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Angelo Loris Brunetta	Member	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on:	4.2.3. enasidenib - EMEA/H/C/004324, EMA/OD/253/15, EU/3/16/1640, EMA/OD/0000007422
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in.