20 June 2019
EMA/COMP/288904/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 21-23 May 2019

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

21 May 2019, 09:00-19:30, room 2-A

22 May 2019, 08:30-19:30, room 2-A

23 May 2019, 08:30-17:00, room 2-A

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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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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.

1.2. Adoption of agenda

The agenda for 21-23 May 2019 was adopted with no amendments.

1.3. Adoption of the minutes

The COMP minutes for 15-17 April 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. - EMA/OD/0000004216

Treatment of mantle cell lymphoma

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

- Significant benefit

The arguments on significant benefit were based on a clinically relevant advantage of improved efficacy.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the clinical study submitted to justify the assumption of significant benefit over authorised medicinal products.

In particular a comparison versus ibrutinib was expected.

The applicant was invited to elaborate on the previously received treatments of the relapse/refractory patients included in the clinical study discussed.

In the written response, and during an oral explanation before the Committee on 21 May 2019, the sponsor reply to the question the COMP raised regarding the clinically relevant advantage their product offered within the context of the treatment of mantle cell lymphoma. Indirect comparisons were made to studies with ibrutinib which were obtained from the EPAR. Comparability of the results regarding progression free survival and adverse events profile was developed. The COMP discussed the comparability of the efficacy data and patient populations. As compared with a previous submission, no post hoc statistical analysis was made to show that there was a clinically relevant advantage in using the sponsor's product over ibrutinib. The COMP also considered that not enough safety data was available to establish that the sponsor's product had a better safety profile.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 22 May 2019, prior to final opinion.

2.1.2. - EMA/OD/0000003698

Treatment of peripheral T-cell lymphoma - Not otherwise specified (PTCL-NOS)

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

Peripheral T-Cell Lymphoma - Not otherwise specified (PTCL-NOS) should be justified as a distinct medical entity or a valid subset. For the purposes of orphan medicinal product designation the sponsor's attention was drawn to the Orphan regulation and relevant guidelines (especially section A of ENTR/6283/00).

- Significant benefit

Notwithstanding the raised issue with regards to the orphan condition, the sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the available clinical studies 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 21 May 2019, the sponsor elaborated on the distinctiveness of PTCL-NOS from anaplastic large-cell lymphoma (ALCL) and other PTCL subtypes, and further elaborated on the issue of significant benefit.

With regards to the condition, there were mainly three sets of arguments used by the applicant to justify the applied condition as a valid condition for designation:

a) Arguments stemming from the evolution of knowledge

The applicant acknowledged that PTCL-NOS is a type of PTCL contained in both the 2008 and 2016 WHO classifications, and that it could be considered as a diagnosis of exclusion. However, it was stressed that the recent evolutions of diagnostic methods for nodal T-cell lymphomas currently support a distinct medical entity. These nodal PTCLs, rather than being diagnosed when all other defined conditions are ruled out, are instead a more cohesive disease state with recognized histopathologic and immunohistochemically presentations and distinct gene expression profiles. It was further elaborated that T-cell-

associated antigen profile observable by immunohistochemistry is variable, but the predominant immunophenotype is CD4+ without cytotoxic markers, with most cases expressing CD3E, CD2, and/or CD5. It was also discussed that next-generation sequencing studies have identified mutations sets commonly associated with PTCL-NOS and chromosomal deletions observed in PTCL-NOS are 13q22.3, 3q, and 9p; gains of 8q, 9p, 19q. Moreover, CD30 expression (CD30+PTCL-NOS) identifies an even more homogeneous subset of PTCL-NOS patients, which was even more relevant for the proposed treatment subject of this designation. During the oral explanation, the T-helper phenotype of the respective cells was also proposed as a distinctive characteristic of PTCL-NOS.

In evaluation of these arguments, it was noted that the differences were quantitative rather than qualitative, and that PTCL-NOS was still a subtype of PTCL which was acknowledged by the sponsor. Therefore the applicant has not advanced its position in order to align the proposed condition with the expectation for a distinct medical entity in the context of orphan designation in the EU.

b) Arguments relating to clinical considerations.

The sponsor also consulted clinical experts in T-cell lymphomas who stressed that they believed PTCL-NOS constitutes a distinct medical entity. Based on these responses, the applicant discussed that the term "PTCL-NOS" used in the classifications may be a misnomer. However, and notwithstanding the standing and agreed WHO classification, the term used was considered of lesser importance to the actual referent. What was important for the designation was whether the distinctiveness of the following clinical particularities was also discussed. Compared with most other types of PTCL, patients with PTCL-NOS have a higher median age at presentation (60 years), a male predominance (66%), and a tendency towards presentation with Stage III or IV disease (69%). Bone marrow positivity is present 22% of the time (versus 7% for ALK− ALCL and 12% for ALK+ ALCL), and most patients present with an International Prognostic Index (IPI) score of 2 or 3 (57%) (Vose *et al.*, 2008). While some similarities exist with selected other PTCL subtypes, the overall pattern of these characteristics appears, like its gene expression profile, a fingerprint unique to PTCL-NOS. The prognosis of PTCL-NOS is dismal, with 5-year overall survival (OS) of 32% across the disease type; this may be as low as 11% for patients with IPI scores of 4 or 5. This has been reported as poorer than that for ALK− ALCL (49% 5-year OS).

With respect to the clinical considerations, the applicant acknowledged similarities and proposed quantitative (rather than qualitative) differences between the subtypes. Clinical considerations such as benefit/risk considerations as well as identifying the most appropriate group of patients to treat is explicitly provisioned against in ETNR/6283/00 Rev 04.

c) Regulatory arguments

The applicant acknowledged that PTCL-NOS is a subtype of PTCL, but also noted that the COMP has also previously accepted ALCL which is also a subtype of PTCL, as applied for in the first designation procedure of the applicant. This assertion has not been put in the context of time, given that the first designation was given 7 years ago, and the COMP consistency in designating PTCL, in the last years in accordance to the WHO 2016 classification.

As regards the issue of significant benefit, the applicant referred to the available clinical studies and extrapolated observations pertaining to CD30+ PTCL-NOS to all PTCL-NOS, but

it was considered redundant if the sponsor were to show SB (scientific benefit) in the CD30+ subgroup. The sponsor outlined the design and results of study 011 (in combination therapy in previously untreated patients with CD30+ mature T-cell and NK-cell neoplasms), study 012 (monotherapy in Patients with Relapsed/Refractory PTCL) and study 014 (ECHCELON-2).

With regards to study 012 the applicant provided a list of previous treatments in the R/R PTCL-NOS patients which include CHOP, ICE and variants thereof. In that population, 7/21 ORR (overall response rate) has been reported. This would support an improved efficacy claim.

As for study 014, the pivotal trial, the applicant provides an analysis of the PTCL-NOS patients, showing a non-statistically significant trend of improvements for PFS (progression-free survival) and OS (overall survival) for those patients treated with A+CHP versus CHOP. It was also stated that those gains in efficacy were associated with a corresponding improvement in the time to subsequent therapy for PTCL-NOS patients receiving A+CHP.

Finally, a recent case series investigating the tested product monotherapy as a bridge to stem cell transplantation in patients across 12 French study centers reported outcomes for 6 PTCL patients, of whom 4 had PTCL-NOS (Garciaz, Loschi, *et al.*, 2019). It is noted that of the 6 PTCL patients, 4 patients experienced a CR (complete response) and 2 patients a PR (partial response).

In evaluation of the submitted data for the justification of significant benefit, the phase III data show a non-statistical trend of improvement of A+CHP versus CHOP, but in the monotherapy phase II of 012 study, responses were also shown in R/R PTCL patients previously having received standard of care.

Overall, the COMP considered that the proposed condition would not be acceptable as a distinct medical entity appropriate for designation in the EU, on the grounds that it is a subset of PTCL.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 23 May 2019, prior to final opinion.

2.1.3. recombinant human coagulation factor VIII Fc - von Willebrand factor - XTEN fusion protein - EMA/OD/0000004038

Swedish Orphan Biovitrum AB (publ); Treatment of haemophilia A

COMP Rapporteur: Fernando Mendez Hermida

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

- Significant benefit

The arguments on significant benefit were based on a major contribution to patient care, stemming from a prolonged half-life of the proposed factor VIII-containing product.

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

The sponsor was requested to further elaborate on the design and the results of the cited studies or any additional clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, the sponsor provided an extensive reply to the question on significant benefit raised by the COMP. The assessment by the COMP examined in detail the claims made regarding the improved pharmacokinetic properties offered by this modified formulation of Factor VIII. Of note was the relevance of the data presented in a comparative table between the sponsor's product and the other modified release Factor VIIIs currently authorised.

The COMP noted that there was no comparative data to emicizumab-kxwh which was a cause for concern and discussion. There was a general consensus that the sponsor would need to establish what the clinically relevant advantage of their product would be due to recent amendments approved for emicizumab-kxwh. It was equally noted that for the purpose of an initial orphan designation the pharmacokinetic data in the clinical setting would be acceptable, however this would not be the case at the review for the maintenance orphan designation. There was a general consensus that more robust data was needed and that the modified release formulations were making the establishment of significant benefit more difficult. This was highlighted to the sponsor who acknowledged the recent approval in March 2019 of another modified release Factor VIII which they will need to consider but which was not included in the discussion as it had not received final approval at the European Commission level at the time of submission.

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

The intention to treat the condition with the medicinal product containing recombinant human coagulation factor VIII Fc – von Willebrand factor - XTEN fusion protein was considered justified based on non-clinical data in a valid model of the condition showing better survival due to the improvement in coagulation.

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

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 recombinant human coagulation factor VIII Fc – von Willebrand factor - XTEN fusion protein will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate better prolonged half-life than the currently authorised modified release factor VIIIs. The COMP considered that this constituted a clinically relevant advantage.

A positive opinion for recombinant human coagulation factor VIII Fc – von Willebrand factor - XTEN fusion protein, for treatment of haemophilia A, was adopted by consensus.

2.1.4. - EMA/OD/0000004041

Treatment of Cushing's syndrome (hyperadrenocorticism)

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 presented non-clinical data in several models of various metabolic disorders to show the potential of the studied substance in controlling obesity, diabetes and development of fatty liver disease. Anti-corticosteroid mode of action of the studied substance was also shown. No data in a model of Cushing's syndrome or patients was presented.

To establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of Cushing's syndrome the sponsor was requested to further elaborate on:

- the relevance of the non-clinical models used for the Treatment of Cushing's syndrome, and the interpretation of the results obtained in the experiments
- the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition
- the justification of not using a Cushing's syndrome models to demonstrate medical plausibility.

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potential improved safety and efficacy in the condition. However, the sponsor did not present any data to demonstrate the potential of the studied substance in addressing the shortcomings of the authorised products in the condition in terms of safety or to demonstrate efficacy in the condition as applied for.

The sponsor was requested to further discuss the arguments provided for significant benefit and to present relevant data to compare the studied substance vis-a-vis the current standard of care.

In the written response, and during an oral explanation before the Committee on 21 May 2019, the sponsor argued that Cushing's syndrome is from the nosology perspective a subset of diabetes type 2. Therefore, according to the sponsor the models used, which are modelling the classic type 2 diabetes, could support medical plausibility. The COMP questioned the mechanism of action of the product, and the sponsor mentioned two potential modes of action, one of which was not compatible with the model used and more specific to Cushing's syndrome. In addition, the sponsor presented arguments for significant benefit, mostly based on improved efficacy of the product in preventing liver disease as well as improved safety compared to the standard of care. The COMP questioned the basis of such assumptions, considering that none of the non-clinical models used reflects fully the pathophysiology of Cushing's syndrome. In the absence of a more accurate model or clinical data the COMP found it difficult to make an assumption of significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 21 May 2019, prior to final opinion.

2.1.5. - EMA/OD/0000003941

Treatment of cyclin-dependent kinase-like 5 deficiency disorder

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 proposed to have an open discussion with the sponsor on the definition and distinctiveness of the condition. The sponsor was requested to provide a discussion on the classification and the current clinical and genetic understanding of CDKL-5- deficiency disorder in the context of variant forms of Rett syndrome. 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).

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of CDKL-5 deficiency disorder the sponsor was requested to further elaborate on the presented non-clinical data. The COMP noted that the non-clinical model reflected the genotype but not the phenotype of the human condition. The sponsor was asked to discuss the relevance of the type of outcomes and how they could be translated into clinically relevant outcomes for patients affected by the condition. Furthermore, the sponsor was requested to discuss the small effect sizes that were observed in two behavioural tests.

In the written response, and during an oral explanation before the Committee on 22 May 2019, the sponsor presented the most recent scientific literature from cohort natural history studies suggesting that up to 80% of CDKL-5 deficiency disorder patients might not fulfill the diagnostic criteria of Rett syndrome and its variants, which were outlined in the latest consensus classification of Rett syndrome from 2010. Therefore, these published reports discussed CDKL-5 deficiency disorder as distinct from Rett syndrome and its variants. The COMP acknowledged this type of research and agreed that it points to the fact that CDKL-5 deficiency disorder could be seen as a distinct entity suitable for orphan designation.

Regarding medical plausibility, the sponsor presented further details on the non-clinical data. The COMP acknowledged the validity of the non-clinical model. Nevertheless, the two specific outcomes that were studied were not considered to be the most representative with regards to the clinical phenotype. Furthermore, the observed effect sizes were fairly modest and/or without statistical significance. Overall, the COMP considered that the presented data was too premature to support medical plausibility for the purpose of orphan designation in CDKL-5 deficiency.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 23 May 2019, prior to final opinion.

2.1.6. - EMA/OD/0000004036

Treatment of nontuberculous mycobacterial lung disease

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 existed a scientific rationale for the development of the proposed product for treatment of nontuberculous mycobacterial lung disease, the sponsor was requested to further elaborate on the non-clinical data that has been collected to support efficacy in monotherapy or as add-on therapy.

The sponsor was requested to further elaborate on the presented clinical data with more details on trial methodology, enrolled patients and outcomes. In addition to explain whether there is any follow-up data from the clinical trial and/or when more mature or final data will become available.

- 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 current estimate was based on Orphanet. The sponsor was requested to provide a revised estimate that was based on primary epidemiological literature. When using incidence figures, the sponsor was asked to describe and take into account the disease duration.

- Significant benefit

In order to justify significant benefit, the sponsor was requested to further describe the enrolled patients and the patients with clinical responses in the ongoing trial in addition to more information on their previous or concomitant treatment with authorised products.

In the written response, and during an oral explanation before the Committee on 22 May 2019, the sponsor presented an updated prevalence estimate based on scientific literature, which was considered acceptable by the COMP.

For the demonstration of medical plausibility and significant benefit, the sponsor presented non-clinical data from the scientific literature with the proposed product. Furthermore, the sponsor updated the COMP on the ongoing clinical trial with the proposed product in patients affected by the condition. The COMP acknowledged the presented interim data, however was of the opinion that the data were too immature to support medical plausibility or significant benefit for the purpose of orphan designation. The sponsor was encouraged to re-apply once more data become available.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 22 May 2019, prior to final opinion.

2.1.7. gaboxadol monohydrate - EMA/OD/0000004076

FGK Representative Service GmbH; Treatment of Angelman syndrome

COMP Rapporteur: Giuseppe Capovilla

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Angelman syndrome (AS), the sponsor was requested to further elaborate on:

– the results obtained *in vivo* in non-clinical studies with regards to the extent of the motor improvements argued,

– the high response rates in the placebo group of the clinical study,

– any data in epilepsy related endpoints in either non-clinical or clinical settings.

In the written response, and during an oral explanation before the Committee on 22 May 2019, the sponsor addressed the issues as follows:

Regarding the non-clinical studies, the applicant noted that literature (Egawa *et al*.,) supports that the active substance, in addition to electrophysiological improvements in cerebellar neuronal activity, also improved ataxia/gait parameters and limb postures in AS mice. A separate unpublished study was also referred with a trend towards improving ataxia/gait dysfunction and fine motor control.

In response to the COMP's comment on the high placebo-group responses in the clinical study, it was pointed out that the definition of responder used in the study was broad, where even a single Clinical Global Impression scale-Improvement (CGI-I) of 3 (minimally improved) in just one of the ten domains was considered a responder. It was stressed that this was a much lower hurdle than a responder defined by an improvement in CGI-I (overall symptoms) alone or a responder defined as having a higher level of improvement such as a CGI-I of 2. Hence, that higher placebo responses for the analysis of the primary endpoint was not considered unexpected.

To demonstrate this, the applicant included a post-hoc responder analysis for CGI-I symptoms overall. When all categories of improvement were included (CGI-I ≤3; very much improved, much improved, minimally improved), the analysis for symptoms overall also supported the superiority of gaboxadol monohydrate relative to placebo with response rates of 66.6% and 22.2%, respectively. Gaboxadol monohydrate was also superior to placebo (32.1% vs. 7%) in the analysis of those subjects whose response was considered "much improved" (CGI-I = 2).

Finally, with regards to the effects on epilepsy, the applicant noted that there was literature supporting an anticonvulsive role for the product in other (non-AS) settings, but on the basis of non-clinical and clinical data in AS, no conclusions could be made yet. In particular the low number of the patients per group in the studied population of the main clinical study (n=27) was noted.

The COMP accepted that the non-clinical data support the potential for improved motor function in the condition, and that they were in line with the preliminary clinical observations in affected patients where symptomatology as assessed with the use of global clinical impression scales was improved upon treatment with the proposed product.

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

The intention to treat the condition with the medicinal product containing gaboxadol monohydrate was considered justified based on improved motor function in non-clinical models of the condition as well as preliminary clinical data in affected patients supporting improved symptomatology as assessed with the use of global clinical impression scales.

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

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

A positive opinion for gaboxadol monohydrate, for treatment of Angelman syndrome, was adopted by consensus.

2.1.8. - EMA/OD/0000003833

Treatment of heat stroke

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 considered that the condition for designation was heat related illness. Heat stroke should be justified as a distinct medical entity or a valid subset of heat related illness. 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).

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of heat stroke, the sponsor was requested to further elaborate on the presented published studies and provide additional studies from the published literature in the non-clinical or clinical setting. Furthermore, the sponsor was asked to discuss the absence of cooling in the presented models and how medical plausibility can be judged without reflecting the clinical management.

- Number of people affected

The sponsor was requested to provide a prevalence estimate for all heat-related illnesses without focus on a severity stage. Furthermore, the sponsor was asked to include all patients in the estimate, including non-lethal cases. For all estimates, literature resources need to be provided.

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".

- Significant benefit

The COMP considered cooling as a satisfactory method in line with treatment guidelines. The sponsor was requested to provide a data-driven discussion on significant benefit over cooling.

In the written response, and during an oral explanation before the Committee on 22 May 2019, the sponsor maintained its position that heat stroke would be distinct and not part of a continuum of heat-related illnesses. Public health posters from the USA and from Australia were presented in support of this argumentation. These posters aimed to inform the public with regards to symptoms and treatment considerations of heat exhaustion and heat stroke. The COMP was of the opinion that heat stroke is part of heat-related illnesses based on published scientific literature and classification systems. Therefore, "heat-related illness" was considered by the COMP to be the condition for orphan designation. The sponsor did not present an updated prevalence estimate for the condition with a wider definition.

Regarding medical plausibility and significant benefit, the sponsor did not present additional non-clinical or preliminary clinical data studying the proposed product in relation to cooling, which was considered to be a satisfactory method for treating patients affected by heat-related illnesses.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 23 May 2019, prior to final opinion.

2.1.9. - EMA/OD/0000003859

Treatment of eosinophilic esophagitis

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 30 April 2019, prior to responding to the list of issues.

2.1.10. (S)-6-hydroxy-2,5,7,8-tetramethyl-n-((R)-piperidin-3-yl)chroman-2-carboxamide hydrochloride - EMA/OD/0000004363

Khondrion B.V.; Treatment of maternally inherited diabetes and deafness

COMP Rapporteur: Vallo Tillmann

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 presented non-clinical data from other mitochondrial diseases, which do not feature deafness or diabetes. Therefore, no disease relevant endpoints were presented for the condition as applied for.

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of maternally inherited diabetes and deafness (MELAS) the sponsor was asked to further elaborate on:

- the relevance of the non-clinical model used for the treatment of maternally inherited diabetes and deafness, and the interpretation of the results obtained in the experiments,
- the methodology used in the non-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition,
- the methodology and results of the clinical study in patients with m.3243A>G heteroplasmy and the interpretation of the results obtained, particularly for the control of hyperglycaemia and hearing loss.

In the written response, and during an oral explanation before the Committee on 23 May 2019, the sponsor provided more details with regards to the ex vivo results from patients carrying the m.3243A>G mutation in the MT-TL1 gene and presenting with MELAS. The choice of a non-clinical model was discussed and the COMP brought to the sponsor's awareness another model of a mitochondrial disease in which aspects related to mitochondrial diabetes can be tested. However, in view of the very general mechanism of action of the product and the fact that oxidative phosphorylation is affected in all mitochondrial diseases, the COMP considered the data presented sufficient for the

assumption of medical plausibility in the condition as applied for. The Committee agreed that the condition, maternally inherited diabetes and deafness, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidine-3-yl)chroman-2-carboxamide hydrochloride was considered justified based on non-clinical data in a model of mitochondrial disease showing mobility improvement and *in vitro* data showing improvement of the oxidative phosphorylation in cells derived from patients affected by the m.3243A>G mutation in the MT-TL1 gene.

The condition is chronically debilitating due to deafness and hard to treat pseudo type 2 diabetes, macular dystrophy in about 80% of patients as well as involvement of other organs leading to muscle pain, gastrointestinal tract symptoms, nephropathy, cardiomyopathy, and neuropsychiatric symptoms.

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

A positive opinion for (S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidine-3-yl)chroman-2-carboxamide hydrochloride, for treatment of maternally-inherited diabetes and deafness, was adopted by consensus.

2.1.11. - EMA/OD/0000003105

Prevention of intradialytic hypotension

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 intradialytic hypotension as a distinct medical entity or a valid subset. 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 proposed condition appeared to be a common complication of haemodialysis in chronic kidney disease patients.

- Medical plausibility

To establish correctly whether there exists a scientific rationale for the development of the proposed product for prevention of intradialytic hypotension (IDH) the sponsor was requested to further elaborate on the provided clinical observations and in particular on:

- the baseline characteristics of the studied patients,
- the nature and appropriateness of controls,
- the outcomes (such as IDH events) in the treated patients compared to controls.

- 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 applicant appeared to be considering only a subset of patients eligible for prevention from the proposed condition and only the number of new patients per year.

The sponsor was requested to justify all of the assumptions used for the calculation, including the cut-off point of eligible patients, and provide a sensitivity analysis of the reported calculations.

- Significant benefit

The applicant was invited to consider the currently used methods of prevention of IDH as per the standards of care and provide a data-driven comparison to justify a clinically relevant advantage or major contribution to patient care.

In the written response, and during an oral explanation before the Committee on 23 May 2019, the sponsor addressed the raised issues. With regards to the proposed condition, after referring to treatment guidelines and the different factors contributing to this manifestation, the applicant noted two "distinctive characteristics"; first the presence of intravascular hypovolemia in patients who actually have fluid overload, and second the recurrent nature of IDH, due to the typical thrice-weekly schedule of haemodialysis (HD). However, both arguments supported that it is a complication of the treatment rather than a distinct entity valid for orphan designation.

As for the issue of medical plausibility, the sponsor acknowledged the limitations of the study conducted in Moldova (a non-GCP study) and looked forward for the next clinical study to be conducted. The mechanism of action via nitric oxide inhibition was also discussed as relevant in that regard. However, in the absence of non-clinical or clinical data that showed clinically relevant effects of the product in appropriate prevention settings as applied for designation the medical plausibility could not be considered met.

For the issue of the number of "people affected", a new annual incidence rate of 1.84/10,000 was provided and the applicant further defended the 30% cut-off point (more accurately: patients who develop IDH in at least 30% of sessions) as the most clinically relevant target population. For example, it was noted that Flythe *et al*., 2015 reported adjusted 2-year mortality odd ratios of 1.30 and 1.76 for the frequencies of 30%–49% and ≥50% (compared with the <5% frequency), but of 0.97 for the frequencies of 6%–29%. The following sensitivity analysis was also provided (1.5, 2 and 2.5 refer to assumed duration of the condition). The main limitation in the sponsor's justification was that it referred to benefit/risk (or even pharmaco-economic) reasons for not further broadening the target population. The sponsor also clarified during the oral explanation that the scope of the application was "secondary prevention", in patients that are already sensitive to developing IDH during the dialysis session.

Finally with regards to the issue of significant benefit, the sponsor referred to quotes from publications, according to which the available preventative and reactive interventions were helpful but there was still an unmet need in the management of the proposed complication. It was described that even for those methods that do work, they are not exempt of drawbacks. Cool-temperature dialysis, for instance, causes uncomfortable symptoms. The adjustment of dialysate sodium, like the administration of isotonic saline for the acute management of IDH, may lead to sodium loading, which is a risk factor for intradialytic thirst and subsequent intradialytic weight gain (IDWG). Greater IDWG is associated with more frequent IDH and greater cardiovascular morbidity and mortality. Importantly

however no data with the effects of the product were included in the responses, and as such the potential to address any unmet need could not be accepted.

In summary the COMP considered that several limitations existed that would not allow the consideration of the application. Firstly, the proposed condition was still regarded as a complication of IDH and not a distinct medical entity acceptable for designation. Secondly, and notwithstanding the issue of the condition, there were no data for the justification of medical plausibility and significant benefit. Thirdly, and notwithstanding the above issues, the numbers of affected patients could not be estimated in the absence of a clear target population and the ambiguous scope (secondary prevention which for the COMP would be included in a general "treatment" indication) of the application.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 23 May 2019, prior to final opinion.

2.1.12. - EMA/OD/0000003694

Treatment of adult T-cell lymphomas/leukaemias (ATLL)

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 30 April 2019, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1. 5'-cEtG-sp-cEt5MeU-sp-cEt5MeU-sp-dT-sp-dA-sp-dT-sp-dT-sp-dA-sp-dT-sp-dA-sp-dG-sp-dG-sp-dG-sp-cEt5MeC-sp-cEt5MeU-sp-cEt5MeU-3' - EMA/OD/0000002916

Dynacure S.A.S.; Treatment of centronuclear myopathies

COMP Rapporteur: Michel Hoffmann

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

The intention to treat the condition with the medicinal product containing 5'-cEtG-sp-cEt5MeU-sp-cEt5MeU-sp-dT-sp-dA-sp-dT-sp-dT-sp-dA-sp-dT-sp-dA-sp-dG-sp-dG-sp-dG-sp-cEt5MeC-sp-cEt5MeU-sp-cEt5MeU-3' was considered justified based on three non-clinical models of the condition showing improvements in muscle force, muscle histology and survival.

The condition is chronically debilitating due to generalized muscle weakness, hypotonia, hyporeflexia, poor muscle-mass, and dysmorphic features secondary to the myopathy and ophthalmoparesis.

The condition was estimated to be affecting less than 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 5'-cEtG-sp-cEt5MeU-sp-cEt5MeU-sp-dT-sp-dA-sp-dT-sp-dT-sp-dA-sp-dT-sp-dA-sp-dG-sp-dG-sp-dG-sp-cEt5MeC-sp-cEt5MeU-sp-cEt5MeU-3', for treatment of centronuclear myopathies, was adopted by consensus.

2.2.2. imidazolyl ethanamide pentandioic acid - EMA/OD/0000003591

Myelo Therapeutics GmbH; Treatment of acute radiation syndrome

COMP Rapporteur: Geraldine O'Dea

The Committee agreed that the condition, acute radiation syndrome, was a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing imidazolyl ethanamide pentandioic acid was considered justified based on beneficial effects on survival and bone marrow function in relevant *in vivo* models of the condition.

The condition is life-threatening and chronically debilitating due to haematopoietic, gastrointestinal, neurological and vascular symptoms associated with multiple organ dysfunction leading to multiple organ failure and carcinogenesis.

The condition was estimated to be affecting less than 0.01 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for imidazolyl ethanamide pentandioic acid, for treatment of acute radiation syndrome, was adopted by consensus.

2.2.3. - EMA/OD/0000003689

Treatment of Gaucher 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 June meeting.

2.2.4. rasagiline - EMA/OD/0000003838

TMC Pharma (EU) Limited; Treatment of Duchenne muscular dystrophy

COMP Rapporteur: Elisabeth Johanne Rook

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

The intention to treat the condition with the medicinal product containing rasagiline was considered justified based on non-clinical data in two models of the condition demonstrating preservation of muscle force, as well as improvements in stamina.

The condition is life-threatening and chronically debilitating due to progressive muscle weakness eventually affecting all voluntary muscles. This is followed by dilated cardiomyopathy and cardiac output decrease, leading to terminal respiratory or cardiac failure often by late adolescence. Patients rarely live beyond the age of 30 years.

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.

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 rasagiline will be of significant benefit to those affected by the condition. The sponsor provided non-clinical data that demonstrated that the product may be potentially used in a wider patient population than the one for which the currently authorised product is authorised. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for rasagiline, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.2.5. regorafenib - EMA/OD/0000003987

Bayer AG; Treatment of glioma

COMP Rapporteur: Dinko Vitezic

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 regorafenib was considered justified based on non-clinical data demonstrating anti-tumour activity and preliminary clinical data indicating prolonged survival in patients affected by relapsed glioma.

The condition is chronically debilitating due to symptoms caused by compression of the tumour on the surrounding brain tissue including headache, nausea, vomiting, seizures, neurological deficits, and cognitive impairment. The condition is life-threatening, with poor 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 provided sufficient justification for the assumption that the medicinal product containing regorafenib will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data indicating prolonged survival in patients affected by relapsed glioma compared to patients receiving an authorised treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for regorafenib, for treatment of glioma, was adopted by consensus.

2.2.6. - EMA/OD/0000004238

Treatment of spinal cord injury

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 June meeting.

2.2.7. reldesemtiv - EMA/OD/0000004268

Pharma Gateway AB; Treatment of spinal muscular atrophy

COMP Rapporteur: Bruno Sepodes

Following review of the application by the Committee, it was agreed the new active substance name, reldesemtiv.

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

The intention to treat the condition with the medicinal product containing reldesemtiv was considered justified based on preliminary clinical data showing improvements in lung function and walking distance.

The condition is life-threatening and chronically debilitating due to muscle wasting, weakness, failure to thrive, pulmonary and orthopaedic complications.

The condition was estimated to be affecting approximately 0.3 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 provided sufficient justification for the assumption that the medicinal product containing reldesemtiv will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that showed that when the product was used in combination with nusinersen there was an additive effect in muscle function (plantar-flexion). The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for reldesemtiv, for treatment of spinal muscular atrophy, was adopted by consensus.

2.2.8. - EMA/OD/0000004774

Treatment of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes

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 June meeting.

2.2.9. - EMA/OD/0000004784

Treatment of myasthenia gravis

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 June meeting.

2.2.10. recombinant adeno-associated viral vector containing a bioengineered capsid serotype AAV-Rh74 and a codon-optimised expression cassette to drive the expression of a secretable form of human acid alpha-glucosidase - EMA/OD/0000004992

Spark Therapeutics Ireland Limited; Treatment of glycogen storage disease type II (Pompe's disease)

COMP Rapporteur: Lyubina Racheva Todorova

The Committee agreed that the condition, glycogen storage disease type II (Pompe's disease), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant adeno-associated viral vector containing a bioengineered capsid serotype AAV-Rh74 and a codon-optimised expression cassette to drive the expression of a secretable form of human acid alpha-glucosidase was considered justified based on studies in a non-clinical model of the condition, which support an increase in alpha-glucosidase activity and restoration of muscle strength.

The condition is life-threatening and chronically debilitating due to accumulation of glycogen in muscle and nerve cells resulting in progressive skeletal myopathy, cardiomyopathy, and respiratory insufficiency. This leads to death within two years of birth in the infantile forms, and in the fourth decade of life in forms with later onset.

The condition was estimated to be affecting approximately 0.3 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 provided sufficient justification for the assumption that the medicinal product containing recombinant adeno-associated viral vector containing a bioengineered capsid serotype AAV-Rh74 and a codon-optimised expression cassette to drive the expression of a secretable form of human acid alpha-glucosidase will be of significant benefit to those affected by the condition. The sponsor provided data in an *in vivo* model of the condition, supporting sustained increase in alpha-glucosidase activity and improvement in muscle strength after a single administration of the product. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for recombinant adeno-associated viral vector containing a bioengineered capsid serotype AAV-Rh74 and a codon-optimised expression cassette to drive the expression of a secretable form of human acid alpha-glucosidase, for treatment of glycogen storage disease type II (Pompe's disease), was adopted by consensus.

2.2.11. - EMA/OD/0000005124

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 June meeting.

2.2.12. - EMA/OD/0000005159

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 June meeting.

2.2.13. 2-(2-{[2-(1H-benzimidazol-2-yl)ethyl]amino}ethyl)-n-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide trihydrochloride - EMA/OD/0000005305

Vifor France S.A.; Treatment of beta-thalassaemia intermedia and major

COMP Rapporteur: Ingeborg Barisic

Following review of the application by the Committee, it was agreed to rename the indication to treatment of beta-thalassaemia intermedia and major.

The Committee agreed that the condition, 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 2-(2-{[2-(1H-benzimidazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridine-2-yl)methyl]-1,3-oxazole-4-carboxamide trihydrochloride was considered justified based on improvements in anaemia and spleen size in a valid non-clinical model of the proposed condition.

The condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product 2-(2-{[2-(1H-benzimidazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridine-2-yl)methyl]-1,3-oxazole-4-carboxamide trihydrochloride will be of significant benefit to those affected by the condition. The sponsor provided data in a non-clinical model of the condition showing improvements in anaemia, which is not addressed by the currently authorised products. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for 2-(2-{[2-(1H-benzimidazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridine-2-yl)methyl]-1,3-oxazole-4-carboxamide trihydrochloride, for treatment of beta-thalassaemia intermedia and major, was adopted by consensus.

2.2.14. sodium benzoate, sodium phenylacetate - EMA/OD/0000005429

Dipharma B.V.; Treatment of argininosuccinic aciduria

COMP Rapporteur: Martin Mozina

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

The intention to treat the condition with the medicinal product containing sodium benzoate, sodium phenylacetate was considered justified based on clinical data demonstrating improved survival of patients affected by the condition.

The condition is chronically debilitating and life threatening due to the consequences of metabolic decompensation leading to developmental delay, mental disability, and other types of neurological damage.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing sodium benzoate, sodium phenylacetate will be of significant benefit to those affected by the condition. The sponsor provided clinical data demonstrating improved survival of patients affected by the condition. The data supported that the proposed product can treat patients affected by the condition in the emergency situation of acute hyperammonaemia occurring despite the chronic management of

hyperammonaemia with the currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sodium benzoate, sodium phenylacetate, for treatment of argininosuccinic aciduria, was adopted by consensus.

2.2.15. sodium benzoate, sodium phenylacetate - EMA/OD/0000005430

Dipharma B.V.; Treatment of hyperargininaemia

COMP Rapporteur: Martin Mozina

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

The intention to treat the condition with the medicinal product containing sodium benzoate, sodium phenylacetate was considered justified based on clinical data demonstrating improved survival of patients affected by the condition.

The condition is chronically debilitating and life threatening due to the consequences of metabolic decompensation leading to developmental delay, mental disability, and other types of neurological damage.

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.

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 sodium benzoate, sodium phenylacetate will be of significant benefit to those affected by the condition. The sponsor provided clinical data demonstrating improved survival of patients affected by the condition. The data supported that the proposed product can treat patients affected by the condition in the emergency situation of acute hyperammonaemia occurring despite the chronic management of hyperammonaemia with the currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sodium benzoate, sodium phenylacetate, for treatment of hyperargininaemia, was adopted by consensus.

2.2.16. - EMA/OD/0000006865

Treatment of haematopoietic stem cell transplantation

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 June meeting.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

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

COMP rapporteurs were appointed for 10 applications.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of diffuse large B-cell lymphoma

The discussion was postponed.

3.1.2. -

Treatment of idiopathic pulmonary fibrosis

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

3.1.3. -

Treatment of tuberculosis

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

3.1.4. -

Treatment of Niemann-Pick disease, type C

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

3.1.5. -

Treatment of immune thrombocytopenia

The discussion was postponed.

3.1.6. - -

Treatment of beta-thalassaemia intermedia and major

The discussion was postponed.

3.2. Finalised letters

3.2.1. -

Treatment of amyotrophic lateral sclerosis

The finalised letter was circulated for information.

3.2.2. -

Treatment of cystinuria

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of multiple myeloma

The new request was noted.

3.3.2. -

Treatment of transthyretin-mediated amyloidosis

The new request was noted.

3.3.3. -

Treatment of spinal muscular atrophy

The new request was noted.

3.3.4. -

Treatment of medullary thyroid carcinoma

The new request was noted.

3.3.5. -

Treatment of ovarian cancer

The new request was noted.

3.3.6. -

Treatment of acute myeloid leukaemia

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. Ultomiris - ravulizumab – EMA/OD/246/15, EU/3/16/1661, EMEA/H/C/004954, EMA/OD/0000004229

Alexion Europe SAS; Treatment of paroxysmal nocturnal haemoglobinuria

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 08 May, prior to responding to the list of issues. The sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 14 May 2019, prior to final opinion. The orphan designation withdrawal 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. - trientine dihydrochloride – EMEA/H/C/004111, EMEA/OD/043/03, EU/3/03/172

Univar BV; Treatment of Wilson's 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 June meeting.

4.2.2. - larotrectinib - EMEA/H/C/004919

Bayer AG;

a) Treatment of salivary gland cancer EMA/OD/213/17, EU/3/18/1995

b) Treatment of soft tissue sarcoma EMA/OD/184/15, EU/3/15/1606

The status of the procedure at CHMP was noted.

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

Accelerated assessment

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

The status of the procedure at CHMP was noted.

4.2.4. - tagraxofusp – EMEA/H/C/005031, EMA/OD/064/15, EU/3/15/1567, EMA/OD/0000004627

Accelerated assessment

TMC Pharma (EU) Limited; Treatment of blastic plasmacytoid dendritic cell neoplasm

The status of the procedure at CHMP was noted.

4.2.5. - edaravone – EMEA/H/C/004938, EMA/OD/032/15, EU/3/15/1510

Mitsubishi Tanabe Pharma Europe Ltd; Treatment of amyotrophic lateral sclerosis

The status of the procedure at CHMP was noted.

4.2.6. - onasemnogene abeparvovec – EMEA/H/C/004750, EMA/OD/028/15, EU/3/15/1509, EMA/OD/0000003028

AveXis Netherlands B.V.; Treatment of spinal muscular atrophy

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. Ongoing procedures

None.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Darzalex - daratumumab

Janssen-Cilag International NV;

a) EMEA/H/C/004077/II/0029, EMA/OD/038/13, EU/3/13/1153 Treatment of plasma cell myeloma

b) EMEA/H/C/004077/II/0030, EMA/OD/038/13, EU/3/13/1153 Treatment of plasma cell myeloma

CHMP rapporteur: Sinan B. Sarac Jiménez; CHMP co-rapporteur: Jorge Camarero

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

5.3. Appeal

None

5.4. Ongoing procedures

COMP rapporteurs were appointed for two 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 meeting, 27-28 May 2019, Rome, Italy

The agenda for the SLRM under the Romanian presidency to be held on 27-28 May was presented and adopted.

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 21 May.

7.1.3. Points to consider on the estimation and reporting on the prevalence of a condition for the purpose of orphan designation (COMP/436/01)

The COMP discussed an update of the points to consider on the estimation and reporting on the prevalence of a condition for the purpose of orphan designation (COMP/436/01). The document was adopted and will be published on the EMA website.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

The PRIME eligibility requests 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)

None

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

None

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 rapporteurships 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. Preparedness of the system and capacity increase

The COMP received a presentation by EMA on preparedness of the system and capacity increase.

8.2. Court case -

The COMP received a presentation by EMA on a court case.

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 21-23 May 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	
Brigitte Blöchl-Daum	Member	Austria	No interests declared	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	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	
Karri Penttilä	Member	Finland	No interests declared	
Annie Lorence	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member (Vice-Chair)	Italy	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	
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	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Fernando Mendez Hermida	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Angelo Brunetta	Member	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on:	3.3.1.
Bruno Sepodes	Member	Expert recommended by EMA	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	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
A representatives from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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