23 May 2019
EMA/COMP/245908/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 15-17 April 2019

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

15 April 2019, 09:00-19:30, room 2-A

16 April 2019, 08:30-19:30, room 2-A

17 April 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
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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.

1.2. Adoption of agenda

The agenda for 15-17 April 2019 was adopted with no amendments.

1.3. Adoption of the minutes

The COMP minutes for 19-21 March 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. relacorilant - EMA/OD/0000002397

Granzer Regulatory Consulting & Services; Treatment of Cushing's syndrome

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:

- 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 further discuss the arguments provided for significant benefit and to elaborate on the results from the Phase II study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

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

In the written response, the sponsor elaborated on the mechanism of action of the product (being a glucocorticoid receptor (GR) antagonist), and postulated that it would be used in patients that do not show sufficient response to current therapies or who are not candidates for available therapies due to disease aetiology or safety concerns. In particular it was pointed out that with reference to available guidelines, GR antagonist is recommended for patients with diabetes or glucose intolerance who are not candidates for surgery or who have persistent disease after surgery.

Towards this end, it was pointed out that in the available phase II study, five patients had been treated with other approved medical therapies and were titrated off their medication and enrolled in the study. These patients had only partially responded or had developed adverse events to the other therapies. Two patients had been treated with metyrapone, two with ketoconazole and one with mifepristone. In both patients treated previously with metyrapone, relacorilant showed higher efficacy based on improvement in the primary endpoints, improved glucose control and hypertension, and secondary end points, including weight loss and recovery of the HPA axis. It was also reported that relacorilant significantly improved hypertension in 1 of 2 patients previously uncontrolled with ketoconazole. The patient who was treated previously with mifepristone had developed endometrial hypertrophy which completely resolved during treatment with relacorilant.

The COMP considered that the sponsor presented sufficient clinical data to support the assumption that the product can reduce blood pressure and improve control of hyperglycemia in patients, who were not adequately managed by currently authorised products.

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

The intention to treat the condition with the medicinal product containing relacorilant was considered justified based on preliminary clinical data in patients with Cushing's syndrome showing a meaningful reduction in blood pressure and control of hyperglycaemia.

The condition is life-threatening and chronically debilitating due to the consequences of hypercortisolism, including cardiovascular disease, diabetes, clotting disorders, muscular weakness and osteoporosis, and psychiatric conditions.

The condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing relacorilant will be of significant benefit to those affected by the condition. The sponsor has provided clinical data to demonstrate that the product can reduce blood pressure and improve control of hyperglycaemia in patients, who were not adequately managed by currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for relacorilant, for treatment of Cushing's syndrome, was adopted by consensus.

2.1.2. - EMA/OD/0000003147

Treatment of lichen planopilaris

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 27 March 2019, prior to responding to the list of issues.

2.1.3. - EMA/OD/0000003085

Treatment of non-small cell lung cancer with MET alterations

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

Non-small cell lung cancer (NSCLC) with MET alterations should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention was drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00). The COMP considered NSCLC with MET alterations as a subset of NSCLC that does not fulfil the criteria for a valid subset.

The sponsor defined the proposed condition by claiming that MET alterations drive the disease. However, MET alterations are a known mechanism of treatment evasion in NSCLC, not only in MET TKI (tyrosine kinase inhibitor) resistant cancer but also in epidermal growth factor receptor (EGFR) TKI resistance (Westover et al 2018). The definition of the patient population with MET alterations is therefore elusive.

Further, the sponsor was asked to justify the exclusion of the population of NSCLC with the overexpression of MET due to reasons other than increased gene copy number or exon 14 skipping mutations (e.g. MET overexpression triggered by KRAS or EGFR mutations).

In addition, the sponsor was asked to further discuss the results on which the sponsor argues a lack of pharmacodynamic activity of the product in MET unaltered NSCLC.

- Number of people affected

The sponsor focused the prevalence calculation on the proportion of METex14, MET GCN>5 and MET amplifications within the broad NSCLC. The calculation excluded other reasons for MET overexpression in NSCLC (*e.g.* as mentioned in Bubendorf et al 2017).

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

In addition, the sponsor was asked to provide a prevalence calculation of the condition NSCLC.

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".

In the written response, and during an oral explanation before the Committee on 15 April 2019, the sponsor reinforced the arguments to establish that METex14 mutations as well as MET amplifications drive oncogenesis of NSCLC. The COMP did not contest this notion. The

sponsor, however, excluded from the proposed population all patients with MET overexpression. This was based on data demonstrating lack of efficacy of MET inhibitors in such patients. The COMP considered this argument as related to the benefit/risk assessment, which is not sufficient to establish a valid orphan condition according to the EC guidance on the content of applications. The sponsor stressed that the product is characterised by excellent target specificity and that MET overexpressing tumours are not dependent on this signalling pathway. Nevertheless, the COMP was of the opinion that the criteria for justifying a valid subset of a common condition for an orphan designation were not met. Consequently, the prevalence of the acceptable medical entity would reach above the threshold of 5 in 10,000 and the product would fail to fulfil the criteria for an orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 April 2019, prior to final opinion.

2.1.4. - EMA/OD/0000003229

Treatment in solid organ transplantation

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 the treatment in solid organ transplantation the sponsor was asked to discuss the validity of the extrapolation of the non-clinical data to support a clinically relevant effect in view of the chosen experimental settings (e.g. selection of endpoints, limited follow up, degree of mismatch of donor and recipient).

- Significant benefit

The arguments on significant benefit were based on a new mechanism of action and the potential improved efficacy in the condition. The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the clinical study to justify the assumption of significant benefit over authorised medicinal products within the context of lung transplantation.

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

In the written response, and during an oral explanation before the Committee on 16 April 2019, the sponsor provided additional data for both medical plausibility and significant benefit. The COMP accepted that the non-clinical in vivo data provided enough basis for supporting the medical plausibility of the product in the treatment of solid organ transplantation.

The COMP was of the opinion that the sponsor's product could not support the claim of significant benefit based on a clinically relevant advantage associated with the improved outcomes to standard of care (SOC). Although the sponsor showed that there was an improvement in walking distance in favour of the treatment group in combination with SOC, the improvements in pulmonary parameters, which are associated with the target graft organ, were not compelling and only showed a trend. The sponsor did not seem to be able to address this disconnect between the different outcome measures. The COMP therefore

considered that the sponsor had not conclusively established the benefit of using their product in combination with standard of care in either the acute rejection setting or in the chronic rejection setting. As a result the COMP could not recommend granting of the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 April 2019, prior to final opinion.

2.1.5. - EMA/OD/0000003185

Treatment of angioimmunoblastic T-cell lymphomas (AITL)

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 1 April 2019, prior to responding to the list of issues.

2.1.6. - EMA/OD/0000003203

Treatment of enteropathy-associated T-cell lymphoma (EATL)

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 1 April 2019, prior to responding to the list of issues.

2.1.7. - EMA/OD/0000003554

Treatment of loculated pleural effusion

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 proposed condition was based on loculation of pleural effusion. Loculation is understood in the scientific literature to be a different degree of severity or a stage in the development and evolution of pleural effusions. Therefore, the sponsor was invited to justify loculated pleural effusion as a distinct medical entity or a valid subset. Note that this was for the purpose 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).

To justify medical plausibility, the sponsor was requested to discuss the extrapolation of the results from a different substance than the product in this designation. With regards to the preliminary clinical evidence it was noted that the results stem from a small uncontrolled study. The sponsor was requested to contextualise the uncontrolled data with published literature data and to further elaborate on the trial methodology and outcomes taking into account the absence of a control arm.

- 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 proposed prevalence estimate was largely based on assumptions and excludes some patients (determined negligible) affected by the proposed condition. The sponsor was

invited to justify all assumptions based on further epidemiological data of the EU. The sponsor was asked to provide sensitivity analyses for the underlying key assumptions. A prevalence estimate for pleural effusions without taking into account loculation and other types of severity or stages was also requested.

- Significant benefit

The sponsor was requested to provide data to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. It was recommended to elaborate on the presented preliminary clinical data and the best standard of care of enrolled patients as part of the clinical trial protocol.

In the written response, and during an oral explanation before the Committee on 16 April 2019, the sponsor addressed the issues identified by the COMP. The COMP acknowledged that the assumption of medical plausibility and significant benefit could be fulfilled if the condition was acceptable.

Regarding the proposed orphan condition, the sponsor re-affirmed its position that "loculated pleural effusion" is a distinct condition that would fulfil the criteria for orphan designation. In support of this position, it was argued that loculations arise from a very specific pathophysiology that is related to pleural injury and inflammation associated with local activation of the coagulation cascade and inhibition of fibrinolysis. While the COMP acknowledged the presented pathophysiological process that is responsible for the process of fibrin deposition and loculation, the COMP considered that this pathophysiology is interrelated with the underlying condition that is pleural effusions. Therefore, the COMP considered that loculated pleural effusion is a stage in the development and/or evolution of pleural effusions. This understanding is supported by the current classification systems by Light (Light 2006) and the ACCP guidelines (Colice 2000). The sponsor has not provided sufficient published evidence to suggest that this understanding of the condition has changed.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 April 2019, prior to final opinion.

2.1.8. zanubrutinib - EMA/OD/0000004269

BeiGene Ireland Limited; Treatment of lymphoplasmatic lymphoma

COMP Rapporteur: Lyubina Racheva Todorova

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

- Number of people affected

The applicant submitted a prevalence calculation based on an extrapolation of the incidence reported in Sweden to European Union and survival as observed in the United States. The sponsor was asked to provide justification of the validity of this approach. If not the sponsor was asked to recalculate the prevalence estimate based on relevant epidemiological studies and registers from the European Economic Area for the proposed orphan condition.

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 arguments on significant benefit were based on a more selective and safer product which could offer a potential improved efficacy in the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the clinical study submitted to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition with particular consideration to the conclusions of the indirect comparisons to ibrutinib.

The sponsor was asked to detail the results from the ongoing comparison clinical trial to ibrutinib to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, and during an oral explanation before the Committee on 17 April 2019, the sponsor elaborated on the issues identified by the COMP.

Regarding prevalence, the sponsor provided a revised estimate for lymphoplasmacytic lymphoma, including Waldenstrom's macrogobulinaemia, taking into account epidemiological data from Sweden, the UK and pan-European sources. The final estimate of 1.4 per 10,000 was calculated with the formula P=I*D using the annual incidence of 1.2 per 100,000 (based on Swedish data) and mean survival of 12 years (based on the 10-year overall survival estimate of 69% across 10 European countries).

Regarding significant benefit, the sponsor provided a detailed indirect comparison of efficacy data reported in clinical trials with zanubrutinib and ibrutinib in R/R and treatment naive LPL patients. The provided indirect comparisons suggested improved outcomes, e.g. good partial response. The sponsor explained that this preliminary clinical data will be confirmed through an active comparative phase 3 trial. The COMP considered that sufficient evidence was provided for the assumption of significant benefit for the purpose of orphan designation.

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

The intention to treat the condition with the medicinal product containing zanubrutinib was considered justified based on preliminary clinical data demonstrating that patients affected by the condition respond to treatment.

The condition is life-threatening and chronically debilitating due to bone marrow dysfunction, lymphadenopathy, splenomegaly and paraproteinaemia resulting in hyperviscosity, autoimmunity, cryoglobulinaemia, coagulopathies and neuropathies.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing zanubrutinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating that relapsed/refractory patients respond to treatment. Indirect comparisons to trial data with the currently authorised product suggested improved outcomes. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for zanubrutinib, for treatment of lymphoplasmatic lymphoma, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. allogeneic skin-derived ABCD5-positive mesenchymal stem cells - EMA/OD/0000001324

Rheacell GmbH & Co. KG; Treatment of epidermolysis bullosa

COMP Rapporteur: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing allogeneic skin-derived ABCB5-positive mesenchymal stem cells was considered justified based on non-clinical data demonstrating that treatment with the product was able to reduce mortality and disease manifestations like pseudosyndactyly and coat appearance in a valid model of the condition.

The condition is life-threatening and chronically debilitating due to blister formation in response to minor friction or trauma, leading to the development of multiple complications including life-threatening infections and failure to thrive.

The condition was estimated to be affecting approximately 0.7 in 10,000 persons in the European Union, at the time the application was made.

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 allogeneic skin-derived ABCB5-positive mesenchymal stem cells, for treatment of epidermolysis bullosa, was adopted by consensus.

2.2.2. diacerein - EMA/OD/0000003013

WORPHMED World Orphan Medicines Limited; Treatment of epidermolysis bullosa

COMP Rapporteur: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing diacerein was considered justified based on literature data and preliminary clinical data in patients with the condition demonstrating a reduction of blisters.

The condition is life-threatening and chronically debilitating due to in particular severe generalised blistering resulting in poor quality of life and shortened life expectancy.

The condition was estimated to be affecting approximately 0.9 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 diacerein, for treatment of epidermolysis bullosa, was adopted by consensus.

2.2.3. - EMA/OD/0000003105

Prevention of intradialytic hypotension

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

2.2.4. emixustat hydrochloride - EMA/OD/0000003121

Pharma Gateway AB; Treatment of Stargardt's disease

COMP Rapporteur: Tim Leest

The Committee agreed that the condition, Stargardt'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 emixustat hydrochloride was considered justified based on non-clinical and on preliminary clinical data showing improvement of biomarkers relevant to the condition. In clinical setting, the product also showed improvements in electroretinogram measurements in patients affected by the condition.

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 emixustat hydrochloride, for treatment of Stargardt's disease, was adopted by consensus.

2.2.5. - EMA/OD/0000003694

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

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 May meeting.

2.2.6. - EMA/OD/0000003698

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

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 May meeting.

2.2.7. - EMA/OD/0000003833

Treatment of heat stroke

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 May meeting.

2.2.8. - EMA/OD/0000003859

Treatment of eosinophilic esophagitis

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 May meeting.

2.2.9. (S)-5-(1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethylamino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile - EMA/OD/0000003878

Pharma Gateway AB; Treatment of acute myeloid leukemia

COMP Rapporteur: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing (S)-5-(1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethylamino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile was considered justified based on preliminary clinical observations showing that patients affected by the condition respond to treatment.

The condition is life threatening and chronically debilitating due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated. The overall 5-year relative survival with the currently available treatments is approximately 22%.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (S)-5-(1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethylamino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations showing that unfit patients respond to treatment in the relapsed refractory setting, where there were no authorised treatments. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for (S)-5-(1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethylamino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.10. N-(trans-3-(5-((R)-1-hydroxyethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide - EMA/OD/0000003888

Voisin Consulting S.A.R.L.; Treatment of cystic fibrosis

COMP Rapporteur: Eva Malikova

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

The intention to treat the condition with the medicinal product containing N-(trans-3-(5-((R)-1- hydroxyethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide was considered justified based on non-clinical data showing improvement of chloride transport in *in vitro* models reflecting different cystic fibrosis mutations, and on preliminary clinical data showing improvement of lung function in patients affected by the condition.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing N-(trans-3-(5-((R)-1-hydroxyethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5- carboxamide will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate improvement of lung function when the proposed product is used in patients with F508del, the most prevalent mutation in cystic fibrosis, on top of the current standard of care for this patient population, including the CFTR (cystic fibrosis transmembrane conductance regulator) modulator Orkambi. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for N-(trans-3-(5-((R)-1-hydroxyethyl)-1,3,4-oxadiazol2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide, for treatment of cystic fibrosis, was adopted by consensus.

2.2.11. - EMA/OD/0000003941

Treatment of cyclin-dependent kinase-like 5 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 May meeting.

2.2.12. - EMA/OD/0000004036

Treatment of nontuberculous mycobacterial lung disease

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

2.2.13. - EMA/OD/0000004038

Treatment of haemophilia A

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 May meeting.

2.2.14. - EMA/OD/0000004041

Treatment of Cushing’s syndrome

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

2.2.15. - EMA/OD/0000004076

Treatment of Angelman syndrome

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

2.2.16. (S)-3-((3-(1-((6-(3,4-dimethoxyphenyl)pryazin-2-yl)amino)ethyl)phenyl)carbamoyl)-5-methylpridin-1-ium - EMA/OD/0000004127

MWB Consulting S.A.R.L.; Treatment of pulmonary arterial hypertension

COMP Rapporteur: Eva Malikova

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

The intention to treat the condition with the medicinal product containing (S)-3-((3-(1-((6-(3,4-dimethoxyphenyl)pryazin-2-yl)amino)ethyl)phenyl)carbamoyl)-5-methylpridin-1-ium was considered justified based on non-clinical data in valid models of the condition, showing attenuation of established pulmonary hypertension measured by reduction of pulmonary artery systolic pressure and right ventricular systolic pressure, and by increased lumen/media ratio of pulmonary arterioles.

The condition is life-threatening and chronically debilitating due to progressive dyspnoea and right heart failure, leading to death in approximately 3 years after diagnosis.

The condition was estimated to be affecting approximately 1.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing (S)-3-((3-(1-((6-(3,4-dimethoxyphenyl)pryazin-2-yl)amino)ethyl)phenyl)carbamoyl)-5-methylpridin-1-ium will be of significant benefit to those affected by the condition. The sponsor provided non-clinical data showing that the addition of the proposed product to the combination of a phosphodiesterase-5 inhibitor and an endothelin receptor antagonist, currently authorised for the condition, attenuated pulmonary hypertension to a higher extent than the phosphodiesterase-5 inhibitor and endothelin receptor antagonist combination alone. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for (S)-3-((3-(1-((6-(3,4-dimethoxyphenyl)pryazin-2-yl)amino)ethyl)phenyl)carbamoyl)-5-methylpridin-1-ium, for treatment of pulmonary arterial hypertension, was adopted by consensus.

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

2.2.17. sodium benzoate, sodium phenylacetate - EMA/OD/0000004137

Dipharma B.V.; Treatment of citrullinaemia type 1

COMP Rapporteur: Geraldine O'Dea

Following the review of the application by the Committee, it was agreed to rename the condition to citrullinaemia type 1.

The Committee agreed that the condition, citrullinaemia type 1, 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 less than 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 support 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 citrullinaemia type 1, was adopted by consensus.

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

2.2.18. sodium benzoate, sodium phenylacetate - EMA/OD/0000004139

Dipharma B.V.; Treatment of carbamoylphosphate synthase-1 deficiency

COMP Rapporteur: Annie Lorence

The Committee agreed that the condition, carbamoyl-phosphate synthase-1 deficiency, 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 less than 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 carbamoyl-phosphate synthase-1 deficiency, was adopted by consensus.

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

2.2.19. - EMA/OD/0000004216

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 May meeting.

2.2.20. - EMA/OD/0000004363

Treatment of maternally inherited diabetes and deafness

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 May meeting.

[*Post-meeting note: The COMP adopted the list of issues by written procedure following its April meeting.*]

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

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

COMP coordinators were appointed for twenty applications.

2.7. Evaluation ongoing

The Committee noted that evaluation was ongoing for sixteen applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of amyotrophic lateral sclerosis

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

3.1.2. -

Treatment of cystinuria

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 beta-thalassaemia intermedia and major

The discussion was postponed.

3.2. Finalised letters

3.2.1. -

Treatment of ATTR amyloidosis

The finalised letter was circulated for information.

3.2.2. -

Treatment of congenital adrenal hyperplasia

The finalised letter was circulated for information.

3.2.3. -

Treatment of hyperargininaemia

The finalised letter was circulated for information.

3.2.4. -

Treatment of adenosine deaminase-deficient-severe combined immunodeficiency

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of diffuse large B-cell lymphoma

The new request was noted.

3.3.2. -

Treatment of idiopathic pulmonary fibrosis

The new request was noted.

3.3.3. -

Treatment of tuberculosis

The new request was noted.

3.3.4. -

Treatment of Niemann-Pick disease, type C

The new request was noted.

3.3.5. -

Treatment of immune thrombocytopenia

The new request was noted.

3.3.6. -

Prevention of invasive aspergillosis

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. Soliris - eculizumab – Type II variation – EMEA/H/C/000791/II/0105, EMA/OD/087/13, EU/3/13/1185, EMA/OD/0000004454

Alexion Europe SAS; Treatment of neuromyelitis optica spectrum disorder

CHMP rapporteur: Jorge Camarero Jiménez; CHMP co-rapporteur: Alexandre Moreau;

The status of the procedure at CHMP was noted.

4.2.2. - Trientine dihydrochloride – EMEA/H/C/004111, EMEA/OD/043/03, EU/3/03/172

Univar BV; Treatment of Wilson's Disease

The status of the procedure at CHMP was noted.

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.

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

Alexion Europe SAS; Treatment of paroxysmal nocturnal haemoglobinuria

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 May meeting.

4.2.4. - 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.

4.3. Appeal

4.3.1. Trecondi - treosulfan - EMEA/H/C/004751, EMEA/OD/075/03, EU/3/04/186, EMA/OD/0000002579

medac Gesellschaft fur klinische Spezialpraparate mbH; Conditioning treatment prior to haematopoietic progenitor cell transplantation

A COMP opinion was adopted on 19 December 2018, recommending the removal of the orphan medicinal product designation from the Community Register of Orphan Medicinal Products.

In the grounds for appeal, and during an oral explanation before the Committee on 15 April 2019, the sponsor elaborated on the issue of significant benefit.

Based on the assessment of the detailed grounds for appeal and the explanations presented by the sponsor during the oral explanation, the COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated orphan medicinal product.

The prevalence of conditioning treatment prior to haematopoietic progenitor cell transplantation (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be approximately 0.67 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition remains chronically debilitating and can be life-threatening due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition is also associated with complications such as graft-versus-host disease.

Significant benefit over busulfan was accepted on the basis of a randomised controlled trial showing numerical improvements with regards to event free survival, overall survival and non-relapse mortality in patients treated with a Trecondi based regimen when compared to outcomes in patients treated with a busulfan based regimen.

Significant benefit over thiothepa was supported by clinical data from the scientific literature supporting that Trecondi based regimens in combination with thiotepa are a preferred treatment option in paediatric patients undergoing hematopoietic stem cell transplantation (HSCT) in malignant diseases.

In the context of the initial opinion of the COMP, significant benefit of Trecondi over melphalan and cyclophosphamide has not been demonstrated. Significant benefit over melphalan and cyclophosphamide was claimed on the grounds of a clinically relevant advantage. Indirect literature-based comparisons were provided to substantiate the claim that overall survival and non-relapse mortality associated with Trecondi-based conditioning regimen compare favourably to published efficacy data that were collected with other conditioning regimens that contain melphalan or cyclophosphamide. These indirect comparisons were not considered sufficiently reliable in view of potential confounding. The claim for a significant benefit of Trecondi over melphalan and cyclophosphamide on the grounds of a clinically relevant advantage was therefore not accepted.

In the context of the appeal, the sponsor presented a matched 1:1 comparison based on propensity scores, comparing the data from the pivotal trial to data from the EBMT registry, but a significant number of patients could not be matched, and as such the outcomes were not considered representative of the studied population. Therefore, the presented matched-patient analysis versus EBMT registry data was not considered conclusive evidence, and the sponsor failed to support the existence of a significant benefit. Further non-matched comparisons (including a Cox-regression analysis versus the EBMT registry data, comparisons versus CIBMTR data, juxtaposition of the clinical study data versus selected literature studies) were considered by the COMP as insufficiently robust since it had not been established that relevant characteristics of the patients and treatments were balanced across the compared populations and since such differences in patients' characteristics could influence the outcome of HSCT independently of the induction regimen used.

Therefore, the COMP considered that the provided comparisons of treosulfan with melphalan and cyclophosphamide, respectively, were insufficiently robust and did not adjust for all potential confounding factors that could have influenced the outcome of the comparisons independently of the regimens compared. Consequently, the committee considered that the sponsor failed to establish that Trecondi provides a significant benefit over melphalan and cyclophosphamide.

The COMP, having considered the detailed grounds for appeal submitted by the sponsor and all the supporting data on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;

- the criteria for designation as set out in Article 3(1)(b) are not satisfied.

An opinion recommending the removal of Trecondi, treosulfan (EU/3/04/186) for conditioning treatment prior to haematopoietic progenitor cell transplantation, from the Community Register of Orphan Medicinal Products was adopted by consensus.

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

4.4. On-going procedures

COMP rapporteurs were appointed for one application.

4.5. Orphan Maintenance Reports

None

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

5.1. After adoption of CHMP opinion

5.1.1. Imnovid – pomalidomide – Type II variation – EMEA/OD/053/09, EU/3/09/672, EMEA/H/C/002682/II/0031/G

Celgene Europe Limited; Treatment of multiple myeloma

CHMP rapporteur: Greg Markey

A list of issues was adopted on 21 March 2019.

An oral explanation was held on 15 April 2019.

An opinion recommending not to remove Imnovid from the EC Register of Orphan Medicinal Products was adopted by majority (24 out of 26 votes). The Norwegian COMP member agreed with the above-mentioned recommendation of the COMP. The divergent positions (Armando Magrelli; Eva Malikova) were appended to this opinion.

The Orphan Maintenance Assessment Report will be publicly available on the EMA website.

5.2. Prior to adoption of CHMP opinion

None

5.3. Appeal

None

5.4. On-going procedures

None

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

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

The draft agenda for the SRLM meeting in Rome under the Romanian presidency was presented. Further discussion is expected on the next COMP meeting.

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 16 April 2019.

7.1.3. Non-Clinical Working Group

The working group on Non-Clinical met on 16 April 2019.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

Document was circulated in MMD.

Document(s) tabled:
PRIME eligibility requests - list of adopted outcomes March 2019

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

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

The COMP endorsed Tim Leest as COMP representative at PCWP.

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

The COMP agreed that Dinah Duarte will continue as COMP representative in HCPWP.

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)

Action: For information

Notes: Monthly teleconference

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

Action: For information

Notes: Ad hoc basis meeting

7.5.3. The Therapeutic Goods Administration (TGA), Australia

Action: For information

Notes: Ad hoc basis meeting

7.5.4. Health Canada

Action: For information

Notes: Ad hoc basis meeting

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. Concepts of significant benefit (follow-up to COMP Work Plan 2017)

The discussion was postponed.

8.2. IRIS: a new way of supporting COMP procedures with a CRM (Customer Relationship Management software)

The COMP received a presentation on the new IRIS features.

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 15-17 April 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	
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	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Elizabeth Rook	Member	Netherlands	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Angelo Brunetta	Member	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on	5.1.1. Imnovid – pomalidomide – Type II variation – EMEA/OD/053/09, EU/3/09/672, EMEA/H/C/002682/II/0031/G
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	
Hans Scheurer	Expert witness - in person*	Myeloma Patients Europe (MPE)	Involvement limited to testify and give specialist advice on a specific issue by providing information and replying to any questions only.	5.1.1. Imnovid – pomalidomide – Type II variation – EMEA/OD/053/09, EU/3/09/672, EMEA/H/C/002682/II/0031/G
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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