15 April 2021
EMA/COMP/180661/2021
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 16-18 March 2021

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

Disclaimers

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

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

Note on access to documents

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

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Table of contents

1. Introduction

1.1. Welcome and declarations of interest of members and experts

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

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

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

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

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

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

1.2. Adoption of agenda

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

1.3. Adoption of the minutes

The minutes for 16-18 February 2021 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. - EMA/OD/0000038966

Treatment of pulmonary hypertension (PH) associated with interstitial 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

In view of the COMP, the proposed condition is a subset of PH Group 3: Pulmonary hypertension due to lung diseases and/or Hypoxia. Pulmonary hypertension associated with interstitial lung disease (PH-ILD) 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 is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

The sponsor proposed PH-ILD as a valid orphan condition based on the WHO classification of pulmonary hypertension and the distinct pathophysiological features. However, in the proposed new 2018 classification of the World Symposium on Pulmonary Hypertension (WSPH), this entity does not exist anymore. There are also significant overlaps between PH-ILD and other subgroups belonging to the PH Group 3 of the WHO classification. These overlaps may explain why clinical trials typically include all Group 3 patients, without specifying ILD as inclusion criterion.

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of Pulmonary hypertension associated with interstitial lung disease the sponsor was asked to further elaborate on:

a) the most recent classification systems of PH that would support the delineation of PH-ILD,

b) the overlap of PH-ILD with underlying orphan diseases such as idiopathic pulmonary fibrosis,

c) the specificity of the clinical data in patients included in the clinical study RIN-PH-201 with the proposed product for the treatment of PH-ILD, and the interpretation of the results obtained in the study,

d) the inclusion criteria in the clinical studies with the proposed product and whether the efficacy of the product is expected (and supported by data) also outside of PH-ILD given the broad inclusion criteria in the trials.

- Number of people affected

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

The sponsor was asked to re-calculate the prevalence estimate to reflect the final proposed condition.

In the written response, and during an oral explanation before the Committee on 16 March 2021, the sponsor extended the explanation of why they think the PH-ILD is a distinct medical entity appropriate for an orphan designation. The COMP discussed with the sponsor the newest classification systems and terminology around the proposed entity. The COMP specifically asked if there are overlaps between the various subgroups belonging to PH Group 3 of the WHO Classification and the sponsor acknowledged similarities, but also distinctive features such as development of fibrosis. The sponsor conceded that the delineation of other subgroups within Group 3 would be challenging and required more dedicated research. The COMP therefore considered it is not appropriate to move the

designation practice to a lower level of granularity in the PH classification, and as such the proposed indication was not acceptable.

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

2.1.2. - EMA/OD/0000048469

Treatment of non-functioning pituitary adenomas

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 March 2021, prior to responding to the list of issues.

2.1.3. - EMA/OD/0000047634

Treatment of ovarian cancer

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 treat

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of ovarian cancer the sponsor was asked to further elaborate on:

a) the results obtained in vitro for the treatment of ovarian cancer, with reference to the tissue of origin of the cell line used in the experiments;

b) the relevance of the nonclinical model used for the treatment of ovarian cancer, and the interpretation of the results obtained in the experiments.

- Number of people affected

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

The sponsor was requested to justify the assumed duration of the condition based on up to date references and referring to EU27 states. The sponsor was asked to re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition. Given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

- Significant benefit

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

In the written response, and during an oral explanation before the Committee on 17 March 2021, the sponsor addressed the raised issues.

As regards to the available non-clinical data, the statistical considerations were further explained, with relation to the reported tumour size inhibition. On the number of affected individuals, the sponsor proposed an estimate of 4.9 per 10,000 by assuming a duration of 61 months, derived in turn from an extrapolation of 2012 SEER (US) data. Finally, with regards to the issue of significant benefit, the expectation of improved efficacy or efficacy in combination was discussed based on the mechanism of action, emphasizing that the expression of the product target has been correlated with adverse outcomes. The add-on effects to docetaxel in an in vivo model were also elaborated.

The COMP remained sceptical regarding the duration of the proposed condition, as well as the justification of significant benefit. In particular, there was an absence of in vivo data in models of the condition or affected patients, that would allow for a data-driven comparison vis a vis the standard of care.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 March 2021, prior to final opinion.

2.1.4. S-[5-(omega-methoxypoly(oxyethylene)-2-oxopentyl)]-L-cysteinylglycyl-L-serinylglycylgylcyl-L-isoleucyl-L-lysyl-L-glutamyl-L-phenylalanyl-L-leucyl-L-glutaminyl-L-arginyl-L-phenylalanyl-L-isoleucyl-L-histyl-L-isoleucyl-L-valyl-L-glutaminyl-L-serinyl-L-isoleucyl-L-isoleucyl-L-asparaginyl-L-threonyl-L-serinamide, acetate salt - EMA/OD/0000048121

Almirall S.A.; Treatment of cutaneous T-cell lymphoma (CTCL)

COMP Rapporteur: Maria Elisabeth Kalland

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

- Significant benefit

The sponsor presented data from a clinical study in which 5 of 19 patients achieved clinically meaningful responses. Pre-treatment history of patients had been presented but it was not correlated to the individual outcomes of these patients. This makes the assessment of significant benefit difficult.

The sponsor was asked to detail the individual clinical results of patients listed in the medical history table in order to support the arguments of improved efficacy of the product in the proposed condition. Further discussion of the observed responses (also the delayed ones) would be also informative.

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

In the written response, and during an oral explanation before the Committee on 17 March 2021, the sponsor provided more detailed information on patients enrolled in the clinical study in terms of their history of pre-treatment, disease stage at study onset and treatment effects observed.

The sponsor explained also the clinical outcomes for three treated patients who had previously received Poteligeo, by way of referring to global response scores (GRS) and modified severity-weighted assessment tool (mSWAT).

The sponsor acknowledged that it is difficult to contextualise the results vis-à-vis Poteligeo, but argued also that many patients may not be eligible to this treatment because of safety concerns, while there is a potential for the proposed product to be positioned as early as possible in the treatment algorithm of CTCL. The COMP did not accept improved safety arguments as they are considered premature at this stage of product development. However, the totality of evidence in patient population pre-treated with all authorised products was accepted as sufficient at this stage for the assumption of improved efficacy in the condition.

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

The intention to treat the condition with the medicinal product containing S-[5-(omega-methoxypoly(oxyethylene)-2-oxopentyl)]-L-cysteinylglycyl-L-serinylglycylgylcyl-L-isoleucyl-L-lysyl-L-glutamyl-L-phenylalanyl-L-leucyl-L-glutaminyl-L-arginyl-L-phenylalanyl-L-isoleucyl-L-histyl-L-isoleucyl-L-valyl-L-glutaminyl-L-serinyl-L-isoleucyl-L-isoleucyl-L-asparaginyl-L-threonyl-L-serinamide, acetate salt was considered justified based on preliminary clinical data showing partial or complete responses in heavily pre-treated patients.

The condition is chronically debilitating due to the development of cutaneous lesions, generalised erythroderma, and lymphadenopathy. Ulceration of tumours, with secondary bacterial infections, is linked to morbidity and death. The overall five-year survival rates vary between 24% and 68% according to the subtype of cutaneous T-cell lymphoma.

The condition was estimated to be affecting approximately 2.4 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 S-[5-(omega-methoxypoly(oxyethylene)-2-oxopentyl)]-L-cysteinylglycyl-L-serinylglycylgylcyl-L-isoleucyl-L-lysyl-L-glutamyl-L-phenylalanyl-L-leucyl-L-glutaminyl-L-arginyl-L-phenylalanyl-L-isoleucyl-L-histyl-L-isoleucyl-L-valyl-L-glutaminyl-L-serinyl-L-isoleucyl-L-isoleucyl-L-asparaginyl-L-threonyl-L-serinamide, acetate salt will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing meaningful clinical responses in patients who have previously failed multiple lines of currently authorised treatment options. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for S-[5-(omega-methoxypoly(oxyethylene)-2-oxopentyl)]-L-cysteinylglycyl-L-serinylglycylgylcyl-L-isoleucyl-L-lysyl-L-glutamyl-L-phenylalanyl-L-leucyl-L-glutaminyl-L-arginyl-L-phenylalanyl-L-isoleucyl-L-histyl-L-isoleucyl-L-valyl-L-glutaminyl-L-serinyl-L-isoleucyl-L-isoleucyl-L-asparaginyl-L-threonyl-L-serinamide, acetate salt, for treatment of cutaneous T-cell lymphoma, was adopted by consensus.

2.1.5. - EMA/OD/0000052275

Treatment of eosinophilic oesophagitis

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

- Number of people affected

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

The sponsor was requested to provide a prevalence estimate taking into consideration the latest diagnostic criteria that have been revised in 2017 (*Gastroenterology.* 2018 Oct;155(4):1022-1033.e10).

As it seemed that the sponsor had excluded part of the population affected by the condition, the sponsor was asked to indicate on which population the prevalence calculation was based on.

The sponsor was asked to re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition. Given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor was requested to perform a sensitivity analysis of the reported calculations.

- Significant benefit

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 results of the clinical observations of concomitant treatment with budesonide, compared to budesonide alone.

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

As regards to the question on prevalence, the sponsor refuted the relevance of the post-2017 subgroup of the Navarro et al., publication (*Aliment Pharmacol Ther*. 2019; 49:1116–1125), on the basis of the limited amount of studies (n=4, of which 3 pertained to Spanish regions), on the dates for collection of data and the exclusion of earlier publications, as well as on the analysis methodology that may have resulted in an over-representation of smaller studies. On the other hand, an increase in the prevalence of the condition was also acknowledged by the applicant and the higher value of the overall Confidence Intervals of the overall Navarro conclusion (less than 4.75 /10,000) was offered by way of sensitivity analysis. The COMP remained sceptical with regards to the statutory threshold being respected. The impact of the recent diagnostic changes, the apparent geo-epidemiological differences, and the relevance of the cited publications were points of concern.

As for the significant benefit issue, the observations on one patient that received budesonide plus the study drug were further discussed. It is noted that the patient had been on oral budesonide for approximately one year as treatment for eosinophilia, as well as on Fluticasone propionate nasal as treatment for asthma. After 14 weeks of treatment with the product, this patient responded with histological and clinical criteria. These observations were contextualised versus budesonide-receiving patients in the placebo group. The COMP considered that the paucity of data would render the justification of the significant benefit difficult.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 March 2021, prior to final opinion.

2.1.6. amivantamab - EMA/OD/0000048721

Janssen-Cilag International N.V.; Treatment of non-small cell lung cancer with EGFR alterations

COMP Rapporteur: Brigitte Schwarzer-Daum

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

- Intention to diagnose, prevent or treat

Non-small cell lung cancer with EGFR 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 is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

- Number of people affected

The sponsor had provided a prevalence calculation for a subset of non-small cell lung cancer namely non-small cell lung cancer with EGFR alterations. This appears to be a subset of non-small cell lung cancer adenocarcinoma. The sponsor was asked to re-calculate the prevalence estimate based on relevant epidemiological studies and registers for non-small cell lung cancer and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor was requested to perform a sensitivity analysis of the reported calculations.

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

In the written response, and during an oral explanation before the Committee on 16 March 2021, the sponsor did not address the question on prevalence as they did not consider changing the condition. The sponsor argued that non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) alterations may be considered as a distinct medical entity for the purpose of orphan designation, because of biological characteristics that differentiate it from other types of NSCLC that do not harbour the EGFR alterations. They were of the opinion that these differences arise from distinct pathophysiologies, which are, in turn, reflective of distinct risk factors for each of the subpopulations of the disease. The sponsor noted that the patient diagnostic pathway for lung cancer now also includes molecular screening as well as imaging studies and histological assessment of tumour tissue samples and patient history and clinical examination.

The sponsor argued that the use of targeted therapies directed at tumours with specific biological alterations represent a new era of precision medicine, which they believe has led to the important appreciation of the heterogenous nature of the group of diseases collectively referred to as NSCLC. The sponsor stated that the EMA in their Regulatory Science to 2025 strategic reflection highlight the need to support developments in precision medicine, which include targeted drugs aimed at stratified populations (EMA, 2020). This means that only small subclasses of otherwise common tumours are targeted by these precision medicines, which can often be quite rare. They were of the opinion that EMA's personalised medicine workshop (2017) highlighted that for personalised medicines to become more widely applicable, the clinical research and regulatory paradigms need to be adapted. It was also noted that the sponsor proposed aligning the approach for the

recognition of the proposed condition to the (biomarker) approach followed for non-Hodgkin lymphomas. The COMP considered that the current guidance on orphan designation does not support a personalised medicine approach.

Furthermore, the sponsor provided a diagnostic algorithm which was derived from https://www.esmo.org/Patients/Patient-Guides/Non-Small-Cell-Lung-Cancer. In addition to this reference the COMP also consulted the ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Annals of Oncology 28 (Supplement 4): iv1–iv21, 2017 and Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up† – *Ann Oncol* (2018) 29 (suppl 4): iv192–iv237 which targets physicians.

It was considered that neither guideline states that the proposed condition is distinct, but that it rather comes under the concept of Personalised Medicines and that "Several molecular drivers for oncogene addiction represent strong predictive biomarkers and excellent therapeutic targets". EGFR is named as one of these molecular drivers. It is a relevant tumour entity within the context of non-small cell lung cancer but not a standalone condition distinct from non-small cell lung cancer. It was not clear why NSCLC with EGFR alterations should be considered a distinct entity as opposed to the other NSCLC biomarker tumour entities such as ALK, ROS1, MET, KRAS, and PIK3CA.

EGFR mutations vary overtime, thus highlighting the variability of this type of tumour. This variability indicates that the specificity, which is an important consideration for the purpose of the claim of a distinct medical condition, is not as evident as argued by the sponsor. It was also noted that mutations that lead to EGFR overexpression (known as upregulation or amplification) have been associated with a number of cancers, including adenocarcinoma of the lung (40% of cases), anal cancers, gliobastoma (50%) and epithelial tumors of the head and neck (80-100%). For instance, in glioblastoma a specific mutation of EGFR, called EGFRvIII, is often observed. Mutations, amplifications or misregulations of EGFR or family members are implicated in about 30% of all epithelial cancers. The COMP noted that the specificity of the mutation is not unique to NSCLC and that there is overlap with other cancers.

The COMP was of the opinion that non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) alterations is a subset of NSCLC and that it is not acceptable as a standalone distinct medical entity for the purpose of orphan designation, on the basis of overlapping characteristics with other NSCLC populations. Established classification was also considered in that regard. ICD-11 states in the introduction that *"progress in oncology has clearly demonstrated that a site-only based categorization of malignant and benign tumours provides limited information for prevention, treatment, and prognosis for persons that are affected by a tumour. The field of genetic markers is rapidly changing. Whereas for some tumours, such markers have been used for many years, for others, this is not the case. As such, with the exception of haematological tumours, genetic markers were not used for classification in ICD. They are, however, included in the Chapter 21, Extension codes, and can be added as a second code to the relevant code from the neoplasms chapter to fully describe the relevant tumour entity"*.

It was noted that an ICD-11 extension code is not available for EGFR alterations in lung cancer. The sponsor anticipates that the NSCLC classification based on genetic alterations will become recognised in classification systems in the future, but agreed with the COMP that currently that is not the case.

The sponsor was targeting a relevant tumour entity with their product which, however, is different from a distinct medical entity from an orphan regulation perspective.

It was concluded that the sponsor could not establish that the proposed condition could be an orphan condition. The sponsor has not established that the proposed condition is separate and distinct from the broader condition of non-small cell lung cancer. The variable nature of the EGFR mutations in the proposed condition and the overlap with other oncological conditions with EGFR alterations could not be clarified by the sponsor thus raising doubts about the distinctiveness of the proposed condition. There are no international classifications that define the proposed condition as unique.

Therefore, it is non-small cell lung cancer that should have been considered for the purpose of the orphan designation.

The intention to treat the condition with the medicinal product containing amivantamab was considered justified based on objective responses in patients with non-small cell lung cancer.

The sponsor has established that the condition applied for is chronically debilitating and life-threatening.

The sponsor has not established that non-small cell lung cancer affects not more than 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing amivantamab will be of significant benefit to those affected by the condition. In particular, the sponsor has provided preliminary clinical data which show that the product could be used in patients who are resistant to other therapies. The COMP considered that this constitutes a clinically relevant advantage.

A negative opinion for amivantamab, for treatment of non-small cell lung cancer with EGFR alterations, was adopted by consensus.

[Post-meeting note: The COMP adopted the opinion by written procedure following its March meeting. The sponsor will have 90 days to appeal from the COMP decision.]

2.1.7. cevostamab - EMA/OD/0000042673

Roche Registration GmbH; Treatment of multiple myeloma (MM)

COMP Rapporteur: Karri Penttila

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

- 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 asked to elaborate on the positioning of cevostamab in the treatment armamentarium for relapsed/refractory multiple myeloma (RRMM). A treatment history of the patients and a discussion on how the available data support the positioning of the product was requested.

The sponsor was asked to discuss the long-term benefit of cevostamab. So far, the follow-up time after the treatment with cevostamab is very limited. Especially, more mature duration of response is of interest.

In the written response, the sponsor justified the benefit of cevostamab in the setting of relapsed MM in later lines of therapy and also presented data in patients with penta-refractory disease.

In the study that was discussed, 32 patients had penta-refractory disease (refractory to two PIs, two IMiDs, and one anti-CD38 mAb) and had received at least 4 prior lines of therapy. With the caveat of the limitations of cross-trial comparison, the ORR in this subgroup of penta-refractory cevostamab-treated patients (42%) compared favorably with that of selinexor-treated patients on STORM study (25.3%) and belantamab mafodotin-treated patients DREAMM-2 study (32%).

Moreover, a greater percentage of patients treated with cevostamab achieved stringent complete response (sCR) and CR (6.5% and 3.5% with cevostamab vs. 1% and 0% with Sd). With a median follow-up of 5.5 months, 4/13 cevostamab responders in this subgroup have a DOR of at least 6 months and the median duration of response (DOR) is not evaluable. The estimated DOR rate at 6 months is 64% (95% CI: 30%, 98%). The COMP considered the written response satisfactory and cancelled the oral explanation.

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

The intention to treat the condition with the medicinal product containing cevostamab was considered justified based on preclinical data and preliminary clinical data showing anti-cancer activity in patients affected by the condition.

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

The condition was estimated to be affecting approximately 4.0 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 cevostamab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing a response in heavily pre-treated patients with progressive disease who are refractory or intolerant to alternative treatment options. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.8. - EMA/OD/0000044231

Treatment of pancreatic cancer

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

- Intention to diagnose, prevent or treat

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of pancreatic cancer the sponsor was asked to further elaborate on any updated results of the recently completed clinical study.

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potential improved efficacy in the condition based on an indirect comparison.

The sponsor was requested to discuss the comparability of the juxtaposed studies and provide any updated results from the ongoing or completed studies. The sponsor was also requested to discuss the previous treatments of the studied patients and elaborate on the comparison versus the authorised products for the sought indication.

In the written response, and during an oral explanation before the Committee on 18 March 2021, the sponsor addressed the raised issues. The mechanism of action was further discussed, revolving around oxidative cell death, and the available clinical observations were also elaborated. Some observations in soft tissue sarcoma and pancreatic cancer have been presented which were not deemed relevant for the specific designation procedure, but importantly some additional data in pancreatic cancer patients were also included.

In particular, updated information from a clinical study in metastatic pancreatic cancer were put forward, arguing notable long-term survival for a subset of the studied population. Improvements in the number of circulating tumour cells were also reported.

The COMP enquired about any objective responses in the treated cohort of patients, their depth and duration. Since the paucity of observations in that regard did not allow a contextualisation versus the authorised treatments, the significant benefit was not considered justified at that point in time.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 March 2021, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000037733

Treatment of systemic sclerosis

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

[Post-meeting note: The sponsor withdrew the application for orphan designation on 29 March 2021.]

2.2.2. - EMA/OD/0000047579

Treatment of chronic lymphocytic leukaemia/small lymphocytic 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 April meeting.

2.2.3. - EMA/OD/0000047784

Treatment of multiple system atrophy

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 April meeting.

2.2.4. - EMA/OD/0000049059

Treatment of generalised pustular psoriasis (GPP)

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 April meeting.

2.2.5. - EMA/OD/0000049823

Treatment of cystic fibrosis

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 April meeting.

2.2.6. ganglioside GM1 - EMA/OD/0000049973

3R Pharma Consulting GmbH; Treatment of amyotrophic lateral sclerosis

COMP Rapporteur: Robert Nistico

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

The intention to treat the condition with the medicinal product containing ganglioside GM1 was considered justified based on non-clinical data in a valid model of the condition showing reduction of the decline of motor function.

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ganglioside GM1 will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that the product reduces the decline of motor function in a model of the condition, which has not been observed with the only authorised comparator, riluzole. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for ganglioside GM1, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.7. - EMA/OD/0000050198

Treatment of glioma

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 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 25 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 19 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of pancreatic cancer

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 Gaucher disease

The discussion was postponed.

3.1.3. -

Treatment of growth hormone deficiency

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

3.2. Finalised letters

3.2.1. -

Treatment of Fabry disease

The finalised letter was circulated for information.

3.2.2. –

Treatment of relapsed or refractory multiple myeloma

The finalised letter was circulated for information.

3.2.3. -

Treatment of sickle cell disease

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of glioma

The new request was noted.

3.3.2. -

Treatment of mucopolysaccharidosis type I

The new request was noted.

3.3.3. -

Diagnosis of AL amyloidosis

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. Epidyolex - cannabidiol - EMEA/H/C/004675/II/0005, EMA/OD/165/17, EU/3/17/1959, EMA/OD/0000033940

GW Pharma (International) B.V.; Treatment of tuberous sclerosis

COMP Rapporteurs: Elisabeth Johanne Rook; Dinah Duarte; CHMP Rapporteur: Kirstine Moll Harboe; CHMP Co-Rapporteur: Ondřej Slanař

A list of issues was adopted on 21 January 2021.

An oral explanation was held on 16 March 2021.

An opinion recommending not to remove Epidyolex, cannabidiol (EU/3/17/1959) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

4.1.2. Orladeyo – berotralstat - EMEA/H/C/005138/0000, EMA/OD/003/18, EU/3/18/2028, EMA/OD/0000045564

BioCryst Ireland Limited; Treatment of hereditary angioedema

COMP Rapporteurs: Martin Mozina; Dinko Vitezic

A list of issues was adopted on 21 January 2021.

An oral explanation was held on 17 March 2021.

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

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

4.1.3. Sibnayal – potassium - EMEA/H/C/005407, EMA/OD/016/17, EU/3/17/1888, EMA/OD/0000032257

Advicenne Pharma S.A.; Treatment of distal renal tubular acidosis

COMP Rapporteurs: Elisabeth Johanne Rook; Lenka Gaidadzi

A list of issues was adopted on 03 December 2020.

An oral explanation was held on 17 March 2021.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 18 March 2021, 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. – satralizumab - EMEA/H/C/004788, EMA/OD/014/16, EU/3/16/1680, EMA/OD/0000016001

Roche Registration GmbH; Treatment of neuromyelitis optica spectrum disorders

The status of the procedure at CHMP was noted.

4.2.2. – elivaldogene autotemcel - EMEA/H/C/003690/0000, EMA/OD/009/12, EU/3/12/1003, EMA/OD/0000044429

Accelerated Assessment

bluebird bio (Netherlands) B.V; Treatment of adrenoleukodystrophy

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 3 applications.

4.5. Orphan Maintenance Reports

Documents were tabled for information

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

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

Vertex Pharmaceuticals (Ireland) Limited; Treatment of cystic fibrosis

COMP Rapporteurs: Armando Magrelli; Elisabeth Johanne Rook; CHMP Rapporteur: Johann Lodewijk Hillege

An opinion recommending not to remove Kaftrio, ivacaftor/tezacaftor/elexacaftor (EU/3/18/2116) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

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

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

Vertex Pharmaceuticals (Ireland) Limited; Treatment of cystic fibrosis

COMP Rapporteurs: Gloria Maria Palomo Carrasco; Armando Magrelli; CHMP Rapporteur: Maria Concepcion Prieto Yerro

An opinion recommending not to remove Kalydeco, ivacaftor (EU/3/08/556) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

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

5.3. Appeal

None

5.4. On-going procedures

None

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. Strategic Review & Learning meetings

None

7.1.2. Protocol Assistance Working Group (PAWG)

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

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report from CHMP

Documents were tabled for information.

7.2.2. COMP-CAT Working Group

The COMP-CAT Working Group met remotely on 15 March 2021.

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

Translating Real-World Data into Real-World Evidence and its Applications to the Liver, PSC, and the Rare Diseases Forums

The COMP noted the information.

7.7. COMP work plan

None

7.8. Planning and reporting

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

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

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

8.1. Inter-Committee SAG Oncology

The discussion was postponed.

8.2. EMA Business Pipeline activity and Horizon scanning

The document was tabled for information.

8.3. Revision of the EU legislation on medicines for children and rare diseases

The COMP noted the update from the EC representative.

8.4. Safety concerns in orphan gene therapies

The COMP was updated on the recent safety information regarding some gene therapies.

Furthermore, it was noted that the EMA has begun a safety review of the medicine Zynteglo, a gene therapy authorised to treat the rare blood condition beta thalassaemia. The review of Zynteglo was initiated on 18 February 2021, at the request of the European Commission, under Article 20 of Regulation (EC) No 726/2004.

8.5. Patient involvement in CHMP orphan drug evaluation

An update was provided to COMP on the new pilot phase for CHMP early contact with patient / consumer organisations. To enhance timely participation, contact is established with patient organisations at start of new orphan MAA assessments.

The aim is to enable patients to share aspects such as quality of life, treatment options and unmet medical needs so CHMP is well-aware of all these aspects from the beginning. Also facilitates further interactions with patients, as the procedure progresses, as needed.

This is in line with CHMP work plan objective: 'Incorporate additional and regular processes to capture and include patients' views and preferences in benefit/risk evaluations' and EMA's RSS recommendations: 'enhance methods to systematically incorporate patient data in regulatory decision-making'.

During the one-year pilot, the patient organisations will be contacted at the start of orphan MAA's once published on EMA website (no confidential information shared).

EMA Public and Stakeholders Engagement Department (S-PH) reaches out to organisations covering therapeutic area via EMA's network of 'eligible' organisations, using template 'letter'. CHMP/Rapporteurs can request clarification on input but not expected to feedback. They decide if the information received provides added value and whether to use it when assessing the dossier, and whether merits being included in AR. To assess contribution and value of patient input during pilot, a short questionnaire will be sent to (co-)Rapporteurs and CHMP topic leads, and to patient organisations for feedback. The COMP will be informed about the input received from eligible organisations.

9. List of participants

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

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Chair	Netherlands	No interests declared	
Armando Magrelli	Member	Italy	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	
Vasileios Loutas	Member	Cyprus	No interests declared	
Lenka Gaidadzi	Member	Czechia	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Cecile Dop	Member	France	No interests declared	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Robert Nistico	Member	Malta	No interests declared	
Elisabeth Johanne Rook	Member	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No restrictions applicable to this meeting	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Angelo Loris Brunetta	Member	Patients' Organisation Representative	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Virginie Hivert	Expert* - via WebEx	Patients' Organisation Representative	No restrictions applicable to this meeting	
Annemieke van der Waal	Expert* - via WebEx	Netherlands	No restrictions applicable to this meeting	
	Patient expert* - via telephone	European Union - EMA	No restrictions applicable to this meeting	
	Patient expert* - via telephone	European Union - EMA	No restrictions applicable to this meeting	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

10. Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission

OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

Orphan Designation *(section 2 Applications for orphan medicinal product designation)*

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures (including protocol assistance), national incentives for research and development, 10-year market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.

Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

Protocol Assistance *(section 3 Requests for protocol assistance with significant benefit question)*

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Maintenance of Orphan Designation *(section 4 Review of orphan designation for orphan medicinal products for marketing authorisation).*

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/