12 September 2019
EMA/COMP/403440/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 16-18 July 2019

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

16 July 2019, 08:30-19:00, room 2A

17 July 2019, 08:30-19:30, room 2A

18 July 2019, 08:30-17:00, room 2A

Disclaimers

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

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

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

Note on access to documents

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

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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 16-18 July 2019 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 18-20 June 2019 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. - EMA/OD/0000002952

Treatment of amyotrophic lateral sclerosis (ALS)

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of amyotrophic lateral sclerosis (ALS) the sponsor was asked to further elaborate on:

– the relevance of the bibliographical non-clinical data used to substantiate the claim of efficacy of the sponsor's product in the treatment of amyotrophic lateral sclerosis, and the interpretation of the results obtained in the experiments,

- the methodology, endpoints and results from the observational clinical study that was presented in the significant benefit section of the submission. In particular the sponsor was asked to further elaborate on the characteristics of patients, the endpoint chosen (ALSFRS-R), the analysis and statistics used, the effect size over disease progression and the gender influence on the results obtained. In addition, the sponsor was requested to explain how cells are manipulated before intrathecal administration.

- Significant benefit

The arguments on significant benefit were based on an alternative 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 open clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. The sponsor was asked to elaborate on the patient characteristics in particular, those who received riluzole or not.

In the written response, and during an oral explanation before the Committee on 16 July 2019, the sponsor could not explain how the expected values in the analysis based on a comparison between values observed and expected of ALSFRS-R were computed. As a result, the meaningfulness of the outcomes was difficult to understand. The COMP noted that the sponsor could not clarify the timing of evaluation, and that the effects were minimal and not consistent with disease progression (as it would be expected with the disease modifying approach). Regarding the design, the exclusion of cases who did not receive the full dose or did not decide to continue was not justified, leading the COMP to conclude that there could have been selection bias. Finally the sponsor could not clarify the effect of the proposed product over riluzole. The COMP came to the conclusion that the data submitted was inadequate to support both the medical plausibility and significant benefit and could not recommend granting the orphan designation.

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

2.1.2. - EMA/OD/0000003546

Treatment of aneurysmal subarachnoid haemorrhage

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 committee, for regulatory purposes the condition should be phrased as 'non-traumatic subarachnoid haemorrhage'. 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 presented data in a non-clinical model of the condition, which illustrated the mechanism of action of the product. However, there was little information from that data on the clinically relevant effects of the product in the condition.

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of non-traumatic subarachnoid haemorrhage the sponsor was requested to elaborate on:

- the relevance of the nonclinical data in the model of subarachnoid haemorrhage (SAH) for the treatment of non-traumatic subarachnoid haemorrhage, and the interpretation of the results obtained in the experiments,
- any further data to support the clinically relevant effects in the condition as applied for.

- Significant benefit

In this case, nimodipine was an authorised product used for the treatment of the condition. The argument for significant benefit was based on a novel mechanism of action but no comparative efficacy data was presented.

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

In the written response, and during an oral explanation before the Committee on 16 July 2019, the sponsor elaborated on the non-clinical data available to date. The methodology, the relevance of the model used and functional endpoints used were well explained and accepted by the COMP in support of medical plausibility. In support of significant benefit the sponsor described in detail the proposed mechanism of action of the product and juxtaposed it to that of nimodipine. In addition, safety concerns related to nimodipine were cited and compared to an assumed more benign safety profile of the proposed product. The COMP concluded that the novel mechanism of action *per se* in absence of data demonstrating relative efficacies of the two substances compared is not sufficient. The provided safety comparison was also not accepted because the population in which safety was shown for the proposed product was not representative of the SAH population. Therefore, the COMP considered data submitted in support of significant benefit was not sufficient at this point.

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

2.1.3. - EMA/OD/0000003683

Treatment of beta-thalassaemia intermedia and major

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 28 June 2019, prior to responding to the list of issues.

2.1.4. temozolomide - EMA/OD/0000004755

Orphelia Pharma S.A.S.; Treatment of neuroblastoma

COMP Rapporteur: Bozenna Dembowska-Baginska

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

- Significant benefit

The arguments for significant benefit were based on the potentially improved efficacy in the condition, in particular for relapsed/refractory patients. The sponsor was invited to discuss the standard of care in the target population, and provide a data-driven comparative discussion versus all authorised products, including dinutuximab.

Moreover, in case improved safety is put forward, comparable efficacy would be a prerequisite for any improved safety arguments to be considered.

In the written response, the sponsor focused on the assumption of improved efficacy, by positioning the product in relapsed/refractory patients as per the available clinical data. The comparison versus dinutuximab was not deemed to be relevant for the significant benefit, as prior to treatment any actively progressing disease should have been stabilized. It was also argued that the study protocol, which includes the authorised products, represents the standard of care, and given that the clinical observations pertain to relapsed/refractory patients, a *de facto* improved efficacy was argued. The Committee considered that this would be an acceptable argument, since the only notable addition to the products used in the condition since the time of the publication of the cited studies was dinutuximab.

The written responses were considered satisfactory and the oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing temozolomide was considered justified based on non-clinical data in a model of the condition supporting an inhibition of tumour growth, as well as clinical responses in relapsed or refractory patients receiving temozolomide.

The condition is life threatening and chronically debilitating due to its aggressive nature and frequency of metastatic disease, as well as poor survival in certain patient groups.

The condition was estimated to be affecting approximately 1.1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing temozolomide will be of significant benefit to those affected by the condition. The sponsor has referred to clinical studies in relapsed or refractory patients who responded to treatment with temozolomide. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for temozolomide, for treatment of neuroblastoma, was adopted by consensus.

2.1.5. gallium citrate - EMA/OD/0000005579

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

COMP Rapporteur: Eva Malikova

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

- Significant benefit

In order to justify the significant benefit the sponsor was invited to provide additional details on a study in which the product showed synergistic effects in combination with colistin, and discuss how the beneficial effect may be extrapolated from the intraperitoneal route of this study to the intended inhalation route in clinical use.

Similarly, the sponsor was requested to elaborate on the potential extrapolation from the clinical results obtained with intravenous gallium nitrate to the intended use via inhalation of gallium citrate.

In the written response, the sponsor further described the non-clinical experiment in a model of *Pseudomonas aeruginosa* (PA) infection (pneumonia) where the proposed product was used in combination with different antibiotics (colistin, piperacillin/tazobactam, tobramycin) that constitute the standard of care for chronic PA infection in cystic fibrosis. A synergistic effect on survival was measured with the proposed product in combination with colistin. In a similar experiment the sponsor assessed the effects of the proposed product administered via the inhalation route in combination with antibiotics. Treatment of infected mice with low dose of the proposed product and tobramycin or colistin resulted in significant decrease in lung bacterial levels relative to antibiotic monotherapy. The COMP reviewed the responses of the applicant and concluded that the non-clinical data provided with the responses, was sufficient to justify significant benefit at the current stage of development.

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 gallium citrate was considered justified based on non-clinical data showing reduction of lung bacterial loads and increased survival in models of the condition.

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

The condition was estimated to be affecting 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 gallium citrate will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data showing that the proposed product had a synergistic effect with colistin, one of the mainstays of authorised antibiotic treatments of cystic fibrosis, in reducing bacterial loads in experimental models of *Pseudomonas aeruginosa* infection. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for gallium citrate, for treatment of cystic fibrosis, was adopted by consensus.

2.1.6. - EMA/OD/0000006192

Treatment of pneumonia caused by Pseudomonas aeruginosa

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 pneumonia caused by *Pseudomonas aeruginosa* (PA) the sponsor was requested to further elaborate on:

  - The design of the pneumonia study in which the product was pre-mixed with PA for the intended therapeutic use of the product.
  - The relevance of the study in a sepsis model to the intended use in pneumonia.

- Number of people affected

In consideration of the variable frequency of CAP in the literature sources reported by the sponsor (incidence from 1.7 to 11.6 in 1000) as well as the hospitalization rates (from 20 to 50%) the sponsor was invited to significantly expand the sources of information used to estimate the incidence of community-acquired pneumonia (CAP) due to PA in the EU.

It was also not clear whether and how the incidence of CAP has been incorporated into Hospital-acquired pneumonia (HAP).

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

- Significant benefit

In order to justify the significant benefit of the proposed product the sponsor was invited to elaborate on the methodology (route of infection, time of treatment initiation), results and relevance of the prophylactic studies with tobramycin and meropenem in view of the intended therapeutic use.

In the written response, and during an oral explanation before the Committee on 16 July 2019, the sponsor presented an additional experiment in an acute model of PA pneumonia. In this experiment the administration of the proposed product occurred two hours after intratracheal infection with PA and resulted in significantly increased survival compared to a control group. This was considered sufficient to justify the medical plausibility in the proposed treatment indication, taking also into account the high bacterial loads that were used in the experiment and the very fast development of clinical disease and lethality in the model.

The sponsor expanded the sources of information consulted for the calculation of the incidence of PA pneumonia and incorporated sensitivity analyses to account for uncertainties in reporting. The COMP acknowledged that some uncertainty around the data CAP caused by PA infection is unavoidable due to the available reporting pathways for CAP but the

impact on CAP of the overall incidence of PA pneumonia is in any case very low. The revised calculations were considered overall acceptable.

In relation to the significant benefit the sponsor further discussed the two non-clinical studies in which the product was used in combination with tobramycin and meropenem. In the tobramycin study the results showed reduction of bacterial loads but the effect did not substantially differ between tobramycin, the proposed product, and the combination. The timing of administration of the proposed product prior to the experimental infection was not considered representative of the intended therapeutic use. In the meropenem study the proposed product was administered 24 and 4 hours prior to infection and meropenem (1.5 or 0.8 mg/kg) was administered two hours prior to infection. The COMP questioned the lack of effect of meropenem and the proposed product alone.

Considering the results of the studies presented by the sponsor the COMP was of the opinion that the significant benefit was not sufficiently justified.

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

2.1.7. - EMA/OD/0000003566

Treatment of acute myeloid leukaemia

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

- Intention to diagnose, prevent or treat

The sponsor presented data from one acute myeloid leukaemia (AML) patient to support medical plausibility, this amount of data may be considered anecdotal. Extrapolation of results from autologous cells to allogeneic cells is generally not accepted. Non-clinical data supporting medical plausibility was mentioned in form of citations but no data from these publications was presented.

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

- the results obtained in non-clinical models in the treatment of acute myeloid leukaemia, and the interpretation of the results obtained in the experiments,
- any additional results obtained in clinical studies with the proposed product in patients with AML to date.

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potential improved safety in the condition. Clinical data provided did not compare favourably with the standard of care and additional data on a clinically relevant advantage was needed.

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

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

In the written response, and during an oral explanation before the Committee on 16 July 2019, the sponsor explained in detail the data generated in the non-clinical *in vivo* model of AML. The COMP found the presented model suboptimal for evaluation of the product. The sponsor presented also all clinical data available to date, adding data from the ongoing clinical study in which early biomarker data for three patients was available. The COMP found the data promising but too immature at this stage for any assumptions regarding significant benefit.

2.1.8. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 July 2019, prior to final opinion. - EMA/OD/0000006345

Treatment of West syndrome

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 safety considerations and targeting infants under the age of 3 years. The applicant claimed that their alcohol-free formulation will overcome the warning indicating that the current authorised formulation is "not recommended" for children under the age of 3 years. However, according to current European regulatory recommendations, benzyl alcohol containing formulations can be used in neonates over 4 weeks. (Please refer to the 2017 document EMA/CHMP/302620/2017)

The sponsor was requested to further elaborate on the results of any clinical data they have with their formulation in infants under the age of 3 years 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 July 2019, the sponsor continued to base their claim of significant benefit on the contraindication in national SmPCs regarding alcohol content in formulations and use in neonates and infants of the proposed substance authorized for the condition. In the oral explanation, the COMP highlighted to the sponsor that the regulatory position regarding the dose of alcohol used as an excipient in oral formulation has evolved since many of the SmPCs were written. Specific reference was made to recent regulatory guidance released by the EMA in 2017 EMA/CHMP/302620/2017.), which states that benzyl alcohol containing formulations can be used in neonates over 4 weeks. In addition, the alcohol content, which the sponsor was claiming was a health hazard, was noted to be similar to that found in foodstuffs which are commonly used in the targeted infant population. The COMP concluded that it could not recommend granting the orphan designation, as significant benefit was not justified.

2.1.9. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 July 2019, prior to final opinion. - EMA/OD/0000005689

Treatment of haemophilia B

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

- Significant benefit

The arguments on significant benefit were based on a major contribution to patient care.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on data which would support the claim for major contribution to patient care to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 17 July 2019, the sponsor further elaborated on the claim of major contribution to patient care based on extrapolation of non-clinical *in vivo* pharmacokinetic data in models of the condition. This claim was further supported by data using three patients with haemophilia B where the product was used at a different dose for each patient. The main claim for major contribution to patient care was primarily based on the assumption that the delayed pharmacokinetic property leading to a once weekly formulation will lead to a reduction of factor IX replacement. There was very limited data to support this in the clinical setting. A second argument for significant benefit stated that the treatment with the proposed product would reduce the need for the inhibitor FEIBA (factor eight inhibitor bypass activity). The COMP requested the sponsor to provide further data in support of this statement, which was not forthcoming during the oral explanation. The COMP considered that insufficient data were available to support major contribution to patient care, and thus the COMP could not recommend granting the orphan designation.

2.1.10. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 July 2019, prior to final opinion. - EMA/OD/0000005861

Treatment of myelodysplastic syndromes

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 myelodysplastic syndromes, the sponsor was asked to further elaborate on:

– the mechanism of action of the product regarding anaemia and the small effect size regarding haemoglobin in the beta-thalassemia model,

– the general availability of non-clinical myelodysplastic syndromes (MDS) models to study anaemia and iron overload.

- the results obtained in the beta-thalassaemia model. The sponsor was asked to clarify whether iron overload has been studied.

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit. To further elaborate on the results from the beta-thalassaemia model and how the ability of the proposed product to reduce iron overload can be demonstrated thereby reducing the need for currently authorised iron-chelators.

In the written response, and during an oral explanation before the Committee on 17 July 2019, the sponsor elaborated on the proposed mechanism of action linking the capacity to improve anaemia and reduce iron overload in MDS patients. Furthermore, additional non-clinical data from MDS and beta thalassaemia models were presented in support of the claim that the proposed product was able to reduce iron levels. The COMP agreed that medical plausibility was justified based on non-clinical evidence in the MDS model. However, the COMP considered that insufficient data were available at that point in time to support significant benefit over erythropoietin stimulating agents that are currently authorised in MDS. The presented arguments were only theoretical in nature and not yet supported by data.

2.1.11. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation on 17 July 2019, prior to final opinion. - EMA/OD/0000006618

Treatment of haematopoietic stem cell transplantation

2.1.12. 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 3 July 2019, prior to responding to the list of issues. - EMA/OD/0000004919

Treatment of graft loss in solid organ transplantation

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 June 2019, prior to responding to the list of issues.

2.1.13. - EMA/OD/0000006189

Treatment of subarachnoid haemorrhage

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 28 June 2019, prior to responding to the list of issues.

2.1.14. peginterferon lambda-1a - EMA/OD/0000006379

Eiger Biopharmaceuticals Europe Limited; Treatment of hepatitis D virus infection

COMP Rapporteur: Nikolaos SypsasAs 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 Hepatitis D virus infection the sponsor was requested to further elaborate on:

– the relevance of the Phase II clinical trial results as the product was used in combination with antiviral medicines and the added effect of the sponsor's product. The applicant was asked to contextualise the results within expected response with the use of pegylated interferon alpha.

- Number of people affected

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

For the calculation and presentation of the prevalence estimate the sponsor is 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, the sponsor further clarified the treatment groups and results obtained in the clinical data they had submitted initially. The combination data when the product was used with an antiviral clearly showed a reduction in the Hepatitis D viral load. The sponsor also clarified the differences between the interferon lambda formulation and the interferon alpha formulation which was used off-label to treat the condition. The COMP was satisfied with the written responses from the sponsor and agreed to cancel the oral explanation and recommended granting the orphan designation for this product.

The Committee agreed that the condition, hepatitis D virus infection, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing peginterferon lambda-1a was considered justified based on preliminary clinical data showing significant reduction in viral load.

The condition is chronically debilitating and life threatening due to the development of cirrhosis, portal hypertension and liver insufficiency.

The condition was estimated to be affecting 3.8 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for peginterferon lambda-1a, for treatment of hepatitis D virus infection, was adopted by consensus.

2.1.15. naltrexone - EMA/OD/0000006314

Treatment of fibromyalgia

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

- Medical plausibility

In order to justify medical plausibility to further elaborate:

- on the methodological uncertainties and the clinical relevance of the observed marginal effect sizes of the two presented clinical trials,
- on more recent evidence to support the results from the presented trials

- Seriousness

Based on Article 3(1)(a) of Regulation (EC) No 141/200, the condition is expected to be proven life-threatening, and/or seriously debilitating, and/or serious and chronic. The sponsor provided various literature sources to support the seriously debilitating or serious and chronic aspects. These sources could not sufficiently demonstrate the seriousness in a scientifically sound, qualitative and quantitative manner. The sponsor was requested to provide a more systematic approach and present scientific literature on (a) dedicated natural history studies (b) dedicated studies investigating the impact of fibromyalgia on the quality of life. Without such scientific evidence, the argument for seriousness cannot be accepted by the COMP.

- Insufficient return of the investment

  The sponsor was asked to justify the underlying assumptions of the net present value (NPV) calculation:

- The NPV needs to include the following stages: pre-marketing authorisation (from time of orphan designation), marketing authorisation application, launch and 10-year market exclusivity period. The individual periods need to be characterised by their own cost and selling assumptions.
- The sponsor was requested to justify the assumptions that no, or only a limited clinical development package (200 patients vs 2000 patients) would be required for marketing authorisation in case of an orphan designation. Alternative NPV calculations should be presented that assume no differences in clinical development costs.
- The sponsor was asked to justify the assumptions underlying selling: the selling price and relationship with and without OD, the target of 6% of the overall patient population, and the steady increase in sales with a rate of 1/10 per year.
- The sponsor was asked to justify the assumptions underlying the COGS (cost of goods sold) in case with or without designation.
- The sponsor was asked to provide additional alternative scenarios by changing the different input and output variables.
- The sponsor was asked to present the respective two most representative NPV scenarios for with and without orphan designation incentive and justify the underlying assumptions.

In the written response, and during an oral explanation before the Committee on 18 July 2019, the sponsor acknowledged that there has not been any follow-up data regarding the

use and efficacy of naltrexone for the treatment of fibromyalgia. The COMP highlighted that the available evidence was relatively low and based on small and short pilot clinical trials. However, the limited level of evidence can be considered as sufficient for the assumption of medical plausibility at the time of initial orphan designation.

The sponsor presented additional evidence to support that the condition is "seriously debilitating" or "serious and chronic". The COMP acknowledged numerous scientific publications that investigated the impact of fibromyalgia on the quality of life of patients as perceived by them and concluded that the condition is "seriously debilitating" due to widespread pain that can be associated with depression and anxiety. Patients affected by fibromyalgia report a negative impact on their quality of life leading to social isolation and reduced ability to work and take part in daily activities.

The sponsor claimed that it is unlikely that the marketing of the medicinal product in the European Union would generate sufficient return to justify the necessary investment without orphan designating incentives. To support this claim, the sponsor presented updated NPV calculations, which covered a longer time frame (up to 13 years including the pre-marketing phase, the marketing phase, and the post-marketing phase with 10-year market exclusivity). Two base case NPV calculations were presented, which reflected developments with and without orphan designation incentives.

The COMP acknowledged with the assistance of an independent expert in health economics that the general methodology of the NPV was adequate. Nevertheless, the COMP considered that the underlying assumptions regarding (1) the sales price, (2) the overall sales figures and market penetration (3) the cost of goods (COGS), and the discount rate were not sufficiently justified. The overall sales figures were based on naltrexone sales in the USA in a different condition and were not suitably reliable. The COGS and discount rates were considered to be too high. Moreover, the claim for non-return of investment was mainly based on assumed differences in fixed costs that are associated with the clinical development in the pre-marketing phase. The COMP did not agree with the sponsor's position that orphan designation will help in reducing clinical development and associated costs. Irrespective of orphan designation or not, and a same trial design would need to be generated for the establishment of benefit/risk for marketing authorisation.

In conclusion, the sponsor failed to provide robust NPV calculations that are founded on adequate assumptions regarding development costs and revenues.

The intention to treat the condition can be considered justified on the basis of preliminary clinical observations in published literature that support improvement of symptoms in patients affected by the condition.

The condition is seriously debilitating due to widespread pain that can be associated with depression and anxiety. Patients affected by fibromyalgia report a negative impact on their quality of life leading to social isolation and reduced ability to work and take part in daily activities.

However, the sponsor has failed to establish that the expected revenues from marketing of the product in the European Union are unlikely to generate sufficient return to justify the necessary investment. The sponsor proposed several different clinical development programs for the net present value calculations. These were not sufficiently clear to be considered for a robust net present value calculation. No adequate justifications have been

provided to support the sponsor's view that costs associated with clinical development can be lower when obtaining orphan designation.

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

2.1.16. - EMA/OD/0000004401

Treatment of sarcoidosis

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 28 June 2019, prior to responding to the list of issues.

2.1.17. - EMA/OD/0000005898

Treatment of Huntington's 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:

- Significant benefit

The arguments on significant benefit were based on the potential improved safety in the condition. It was also noted that a major contribution to patient care was highlighted due to the potential of a less frequent daily dosing with the applicant's product due to its pharmacokinetics properties vs three times a day dosing for tetrabenazine. No data was submitted to substantiate this claim.

The two products are structurally related and have shown similar efficacy. It is well known that extrapolation from limited clinical studies cannot fully predict the safety of a product in its clinical setting, thus other relevant data was required to justify safety arguments in most cases. The applicant has submitted a limited indirect safety comparison.

Tetrabenazine has been in use for many years and its safety is well-established. The COMP is of the opinion that the claimed better safety profile of the applicant's product needed to be further discussed and justified including a discussion of the weaknesses of the indirect comparison, the short treatment period and the clinical relevance of the magnitude of the claimed improved safety.

In the written response, and during an oral explanation before the Committee on 17 July 2019, the sponsor proposed that the slower rate of rise to Cmax of the proposed product, associated with the chemical modification, provides a product that will have fewer and less severe adverse events than the currently authorized ones. In addition, the pharmacokinetics may allow to reduce the dosing from three times a day to twice a day. The COMP recognised that the modification in the proposed molecule can alter the dosing schedule, which could in theory lead to a major contribution to patient care. However, the sponsor had no preliminary data to support this assumption.

The sponsor continued to base their claim of better safety on published indirect comparisons with tetrabenazine. The COMP requested the sponsor to elaborate on any post marketing surveillance data to support the claims of better safety to tetrabenazine since the proposed

product has been available in the USA for the last 2 years. The presented post marketing surveillance data were deemed insufficient to support the proposed claims on improved safety. Hence, the claimed clinically relevant advantage could not be supported for the purpose of an initial orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation on 18 July 2019, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000002080

Treatment of hypoparathyroidism

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 September meeting.

2.2.2. - EMA/OD/0000003541

Prevention of haemolytic disease of the foetus and newborn (HDFN)

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 September meeting.

2.2.3. - EMA/OD/0000004356

Treatment of progressive supranuclear palsy

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 September meeting.

2.2.4. - EMA/OD/0000004428

Treatment in haematopoietic stem cell transplantation

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

2.2.5. - EMA/OD/0000004857

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 September meeting.

2.2.6. - EMA/OD/0000005753

Treatment of myeloid or lymphoid neoplasm associated with FGFR1 rearrangement

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 September meeting.

2.2.7. relacorilant - EMA/OD/0000005878

Granzer Regulatory Consulting & Services; Treatment of pancreatic cancer

COMP Rapporteur: Brigitte Schwarzer-Daum

The Committee agreed that the condition, pancreatic cancer, 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 metastatic pancreatic cancer refractory to standard therapies showing clinical benefit including confirmed partial responses.

The condition is chronically debilitating because of pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression; and life-threatening with a median survival of about 6 months.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing relacorilant will be of significant benefit to those affected by the condition. The sponsor provided clinical data that demonstrate partial responses in patients with metastatic pancreatic cancer refractory to standard therapies. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for relacorilant, for treatment of pancreatic cancer, was adopted by consensus.

2.2.8. - EMA/OD/0000006325

Treatment of soft tissue sarcoma

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

2.2.9. poly(oxy-1,2-ethanediyl), alpha-hydro-omega-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-alpha-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain - EMA/OD/0000006352

Apellis Ireland Limited; Treatment of C3 Glomerulopathy

COMP Rapporteur: Vallo Tillmann

The Committee agreed that the condition, C3 glomerulopathy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing poly(oxy-1,2-ethanediyl), alpha-hydro-omega-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-

cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-alpha-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain was considered justified based on early clinical data in patients showing elevation of serum C3 levels.

The condition is life-threatening and chronically debilitating due to the development of nephrotic syndrome and end-stage kidney disease leading to renal failure.

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

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 poly(oxy-1,2-ethanediyl), alpha-hydro-omega-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-alpha-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain, for treatment of C3 glomerulopathy, was adopted by consensus.

2.2.10. - EMA/OD/0000006386

Treatment of soft tissue sarcoma

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

2.2.11. - EMA/OD/0000006955

Treatment of hepatocellular carcinoma

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 September meeting.

2.2.12. setmelanotide - EMA/OD/0000007359

TMC Pharma (EU) Limited; Treatment of Bardet Biedl syndrome (BBS).

COMP Rapporteur: Vallo Tillmann

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

The intention to treat the condition with the medicinal product containing setmelanotide was considered justified based on preliminary clinical data showing significant decrease in hyperphagia and weight in patients with the condition.

The condition is chronically debilitating due to rod-cone dystrophy which leads to visual impairment and blindness, obesity, ataxia, renal disease, speech and learning difficulties. Less common are diabetes mellitus, congenital heart disease and anosmia.

The condition was estimated to be affecting 0.2 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 setmelanotide, for treatment of Bardet-Biedl syndrome, was adopted by consensus.

2.2.13. acetazolamide - EMA/OD/0000007386

Laboratorios Tillomed Spain, S.L.U; Treatment of periodic paralysis

COMP Rapporteur: Elisabeth Johanne Rook

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

The intention to treat the condition with the medicinal product containing acetazolamide was considered justified based on preliminary published clinical observations that suggest effects of the proposed product on muscle weakness in patients affected by hypokalemic periodic paralysis.

The condition is chronically debilitating, due to permanent weakness and muscle pain in the majority of patients, and the requirement of mobility aids in about half of the patients. The condition may also be life-threatening, in particular due to the risk of cardiac arrhythmias in hypokalaemic periodic paralysis and Andersen-Tawil syndrome.

The condition was estimated to be affecting approximately 0.2 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 acetazolamide, for treatment of periodic paralysis, was adopted by consensus.

2.2.14. 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine - EMA/OD/0000007519

Neurocrine Therapeutics Limited; Treatment of congenital adrenal hyperplasia

COMP Rapporteur: Vallo Tillmann

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

The intention to treat the condition with the medicinal product containing 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine was considered justified based on early clinical data in patients showing reductions in ACTH (adrenocorticotropic hormone), 17-OHP (17-Hydroxyprogesterone) and androstenedione levels.

The condition is life-threatening and chronically debilitating due to the development of adrenal insufficiency, virilisation in females, hyponatremia, hyperkalaemia, dehydration and hypotension.

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 provided sufficient justification for the assumption that the medicinal product containing 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine will be of significant benefit to those affected by the condition. The sponsor provided clinical data that demonstrate that patients treated with the product achieved reductions in ACTH hormone levels as well as 17-OHP and androstenedione. This control of hormone production would allow for combination treatment with glucocorticoid replacement therapy, used at lower, more physiological levels. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine, for treatment of congenital adrenal hyperplasia, was adopted by consensus.

2.2.15. 1-(2,2-diphenyltetrahydrofuran-3-yl)-N,N-dimethylmethanamine hydrochloride - EMA/OD/0000007945

Anavex Germany GmbH; Treatment of Rett syndrome

COMP Rapporteur: Giuseppe Capovilla

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

The intention to treat the condition with the medicinal product containing 1-(2,2-diphenyltetrahydrofuran-3-yl)-N,N-dimethylmethanamine hydrochloride was considered justified based on non-clinical data from valid models to suggest positive effects of the proposed product in a number of neurological tests.

The condition is life-threatening and chronically debilitating due to severe locomotor disability, sleep disturbances, seizures, respiratory complications and development of arrhythmias resulting in decreased life-expectancy.

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

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

A positive opinion for 1-(2,2-diphenyltetrahydrofuran-3-yl)-N,N-dimethylmethanamine hydrochloride, for treatment of Rett syndrome, was adopted by consensus.

2.2.16. recombinant self-complementary adeno-associated viral vector serotype 9 containing the human *CLN3* gene - EMA/OD/0000008395

Amicus Therapeutics Europe Limited; Treatment of neuronal ceroid lipofuscinosis

COMP Rapporteur: Robert Nistico

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

The intention to treat the condition with the medicinal product containing recombinant self-complementary adeno-associated viral vector serotype 9 containing the human *CLN3* gene was considered justified based on non-clinical data in a model of the condition demonstrating reduced accumulation of cellular ceroid lipofuscin, reduced microglial activation and improved motor performance upon treatment.

The condition is life-threatening and chronically debilitating due to visual, cognitive, and motor skills decline, speech impediment, behavioural problems, seizures, cerebral atrophy which lead to early death.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant self-complementary adeno-associated viral vector serotype 9 containing the human *CLN3* gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that the product will allow treatment of patients with neuronal ceroid lipofuscinosis type 3 who cannot be treated with the only authorised product for this condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant self-complementary adeno-associated viral vector serotype 9 containing the human *CLN3* gene, for treatment of neuronal ceroid lipofuscinosis, was adopted by consensus.

2.2.17. recombinant self-complementary adeno-associated viral vector serotype 9 containing the human *CLN6* gene - EMA/OD/0000008785

Amicus Therapeutics Europe Limited; Treatment of neuronal ceroid lipofuscinosis

COMP Rapporteur: Giuseppe Capovilla

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

The intention to treat the condition with the medicinal product containing recombinant self-complementary adeno-associated viral vector serotype 9 containing the human *CLN6* gene was considered justified based on non-clinical data in a model of the condition demonstrating reduced accumulation of cellular ceroid lipofuscin, reduced microglial activation and improved motor performance upon treatment.

The condition is life-threatening and chronically debilitating due to visual, cognitive, and motor skills decline, speech impediment, behavioural problems, seizures, cerebral atrophy which lead to early death.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant self-complementary adeno-associated viral vector serotype 9 containing the human *CLN6* gene will be of significant benefit to those affected by the condition. The sponsor provided non-clinical data that demonstrate that the product will allow treatment of patients with neuronal ceroid lipofuscinosis type 6 who cannot be treated with the only authorised product for this condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant self-complementary adeno-associated viral vector serotype 9 containing the human *CLN6* gene, for treatment of neuronal ceroid lipofuscinosis, was adopted by consensus.

2.2.18. - EMA/OD/0000008878

Treatment of acute myeloid leukemia

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 September meeting.

2.2.19. - EMA/OD/0000009156

Treatment of endophthalmitis

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 September meeting.

2.2.20. - EMA/OD/0000009203

Treatment of soft tissue sarcoma

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

2.2.21. adenoviral vector serotype 5 encoding the human interleukin-12 p70 transgene under the control of activator ligand veledimex - EMA/OD/0000009406

Ziopharm Oncology Limited; Treatment of glioma

COMP Rapporteur: Brigitte Schwarzer-Daum

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

The intention to treat the condition with the medicinal product containing adenoviral vector serotype 5 encoding the human interleukin-12 p70 transgene under the control of activator ligand veledimex was considered justified based on data in combination with veledimex in patients with recurrent disease who showed improved survival.

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

The condition was estimated to be affecting approximately 2.6 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 adenoviral vector serotype 5 encoding the human interleukin-12 p70 transgene under the control of activator ligand veledimex will be of significant benefit to those affected by the condition. The sponsor has provided data in combination with veledimex in patients with recurrent disease; the survival outcomes compare favourably with literature studies with the authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adenoviral vector serotype 5 encoding the human interleukin-12 p70 transgene under the control of activator ligand veledimex, for treatment of glioma, was adopted by consensus.

2.2.22. veledimex - EMA/OD/0000009454

Ziopharm Oncology Limited; Treatment of glioma

COMP Rapporteur: Brigitte Schwarzer-Daum

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

The intention to treat the condition with the medicinal product containing veledimex was considered justified based on data in combination with Adenoviral vector serotype 5 encoding the human interleukin-12 p70 transgene under the control of activator ligand veledimex in patients with recurrent disease who showed improved survival.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor provided sufficient justification for the assumption that the

medicinal product containing veledimex will be of significant benefit to those affected by the condition. The sponsor submitted supportive preliminary clinical observations with the product in combination with adenoviral vector serotype 5 encoding the human interleukin-12 p70 transgene under the control of activator ligand veledimex, in patients affected by recurrent disease; the survival outcomes compare favourably with literature studies with the authorised treatments; the Committee considered that this constitutes a clinically relevant advantage.

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

2.2.23. - EMA/OD/0000009805

Treatment of multiple myeloma

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

2.2.24. - EMA/OD/0000009840

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 September meeting.

2.2.25. clofazimine - EMA/OD/0000009964

Sebastian Canisius; Treatment of nontuberculous mycobacterial lung disease

COMP Rapporteur: Nikolaos Sypsas

The Committee agreed that the condition, nontuberculous mycobacterial lung disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing clofazimine was considered justified based on non-clinical data in valid models of the condition showing significant reduction of nontuberculous mycobacteria load with the proposed product, and on clinical data showing effective mycobacteria clearance from patients' airways.

The condition is chronically debilitating due to progressive lung damage in severe forms that respond poorly to treatment.

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 provided sufficient justification for the assumption that the medicinal product containing clofazimine will be of significant benefit to those affected by the condition. The sponsor provided published clinical data showing that the addition of oral clofazimine induced clearance of nontuberculous mycobacteria faster than the standard of care treatment alone. In non-clinical studies, the sponsor's aerosolised formulation of clofazimine significantly improved microbiological outcomes compared to

oral clofazimine. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for clofazimine, for treatment of nontuberculous mycobacterial lung disease, was adopted by consensus.

2.2.26. - EMA/OD/0000009969

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

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 September meeting.

2.2.27. - EMA/OD/0000010152

Treatment of Beta thalassemia

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 September meeting.

2.3 Revision of the COMP opinions

None

2.4 Amendment of existing orphan designations

2.4.1. Monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin E – EMA/OD/0000010120

Takeda Pharma A/S; Treatment of anaplastic large cell lymphoma; Proposed new condition: Treatment of peripheral t-cell lymphoma (PTCL).

COMP rapporteurs: Armando Magrelli / Nectaroula Cooper

The Committee agreed that the condition, peripheral 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 monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin E was considered justified based on clinical responses with the product as a monotherapy in relapsed/refractory patients, as well as clinical studies in first line in combination with existing treatments resulting in improved survival.

The condition is life-threatening and chronically debilitating due to poor response to therapy and high rate of relapses.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin E will be of significant benefit to

those affected by the condition. The sponsor has provided clinical data showing responses with the product as a monotherapy in relapsed/refractory patients, as well as clinical studies in first line in combination with existing treatments resulting in improved survival. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin E, for treatment of peripheral t-cell lymphoma, was adopted by consensus.

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 23 applications.

2.7 Evaluation on-going

The Committee noted that evaluation was on-going for 15 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1 Ongoing procedures

3.1.1. -

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

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 medullary thyroid carcinoma

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 diffuse large B-cell lymphoma

The finalised letter was circulated for information.

3.2.2. -

Treatment of beta-thalassaemia intermedia and major

The finalised letter was circulated for information.

3.2.3. -

Treatment of spinal muscular atrophy

The finalised letter was circulated for information.

3.2.4. -

Treatment of immune thrombocytopenia

The finalised letter was circulated for information.

3.2.5. -

Treatment of multiple myeloma

The finalised letter was circulated for information.

3.2.6. -

Treatment of transthyretin-mediated amyloidosis

The finalised letter was circulated for information.

3.2.7. -

Treatment of acute myeloid leukaemia

The finalised letter was circulated for information.

3.3 New requests

3.3.1. -

Treatment of post-polycythaemia vera myelofibrosis

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

Accelerated assessment

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

The status of the procedure at CHMP was noted.

4.2.2. Epidyolex – cannabidiol - EMEA/H/C/004675

GW Pharma (International) B.V;

a) Treatment of Dravet syndrome EMA/OD/083/14, EU/3/14/1339

b) Treatment of Lennox-Gastaut syndrome EMA/OD/275/16, EU/3/17/1855

COMP rapporteurs: Dinah Duarte / Giuseppe Capovilla

An opinion recommending not to remove Epidyolex 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 July meeting.]

Notes: CHMP positive opinion adopted in July 2019.

4.2.3. 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

COMP rapporteurs: Darius Matusevicius / Michel Hoffmann; CHMP rapporteur: Jorge Camarero Jiménez; CHMP co-rapporteur: Alexandre Moreau

An opinion recommending not to remove Soliris 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 July meeting.]

Notes: Status of the procedure at the CHMP: CHMP positive opinion adopted in July 2019.

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

Accelerated assessment

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

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 September meeting.

4.2.5. - 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

c) Treatment of glioma EMA/OD/116/18, EU/3/18/2097

d) Treatment of papillary thyroid cancer EMA/OD/117/18, EU/3/18/2098

The sponsor formally withdrew the application for orphan designation on 02 July 2019. The sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 02 July 2019.

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

4.3. Appeal

None

4.4. On-going procedures

COMP rapporteurs were appointed for 3 applications.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

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

5.1. After adoption of CHMP opinion

5.1.1. Imbruvica – ibrutinib - EMEA/H/C/003791/II/0046, EMA/OD/185/13, EU/3/14/1264, EMA/OD/0000002783

Janssen-Cilag International NV; Treatment of lymphoplasmacytic lymphoma

CHMP rapporteur: Filip Josephson; A list of issues was adopted on 20 June 2019.

An oral explanation was held on 17 July 2019.

The Committee confirmed that all issues previously identified in this application had been addressed.

An opinion recommending not to remove Imbruvica 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.

Notes: CHMP positive opinion adopted in June 2019.

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 meetings

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

7.1.2. Protocol Assistance Working Group (PAWG)

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

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1 Recommendations on eligibility to PRIME – report from CHMP

The documents were tabled for information.

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

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

None

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

None

7.4. Cooperation within the EU regulatory network

7.4.1 European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

7.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee

None

7.7. COMP work plan

None

7.8. Planning and reporting

7.8.1 List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2019

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2019 were circulated.

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

8.1. EMA's move to the permanent building

Update

COMP noted the information on the move of EMA to the permanent building.

8.2. -

The topic was cancelled.

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 16-18 July 2019 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Chair	Netherlands	No interests declared	
Armando Magrelli	Member (Vice-Chair)	Italy	No interests declared	
Brigitte Schwarzer-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	
Nectaroula Cooper	Member	Cyprus	No interests declared	
Lenka Kovarova	Member	Czech Republic	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Bruno Sepodes	Member	Expert recommended by EMA	No interests declared	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Frauke Naumann-	Member	Germany	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Winter				
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	
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	
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Angelo Brunetta	Member	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on:	3.2.5.
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	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	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Martin Mozina	Member	Slovenia	No interests declared	
Fernando Mendez Hermida	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Gloria Maria Palomo Carrasco	Expert - in person*	Spain	No interests declared	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
	Expert - via telephone*		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.