31 October 2017
EMA/COMP/649605/2017
Inspections, Human Medicines Pharmacovigilance and Committees

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 03-05 October 2017

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

03 October 2017, 09:00-19:00, room 2F

04 October 2017, 08:30-18:00, room 2F

05 October 2017, 08:30-13:00, room 2F

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 03-05 October 2017 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 05-07 September 2017 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. 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea - EMA/OD/119/17

Worldwide Clinical Trials Limited; Treatment of gastrointestinal stromal tumours

COMP coordinator: Katerina Kopečková

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 an ongoing clinical trial to support the claim of clinically relevant advantage in patients with advanced, relapsed gastrointestinal stromal tumours. Limited information on the medical history of patients enrolled in the study was provided and the duration of responses was not discussed.

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

The sponsor should detail the medical history of patients enrolled in the study and the results of clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, the sponsor detailed the medical history of patients enrolled in the clinical study. A large proportion of patients received all 3 authorised treatment options and in excess of 3 prior lines of treatment at the time of enrolment into the study. Some of these patients achieved durable stabilisation of the disease or a partial response. The Committee found the written responses of the sponsor satisfactory to further support the assumption of significant benefit and the oral hearing was subsequently cancelled.

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

The intention to treat the condition with the medicinal product containing 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea was considered justified based on clinical data in patients with relapsed or refractory gastrointestinal stromal tumours showing achievement of partial responses or stable disease.

The condition is chronically debilitating and life-threatening, in particular due to the high rate of relapse and development of metastatic disease resulting in poor survival.

The condition was estimated to be affecting approximately 1.6 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 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrated durable clinical responses in patients, who have relapsed or were refractory after treatment with best standard of care including authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea, for treatment of gastrointestinal stromal tumours, was adopted by consensus.

2.1.2. 1,4-diamino-2,3-dicyano-1,4-bis[2-aminophenylthio] butadiene - EMA/OD/120/17

Edvince AB; Treatment of non-traumatic subarachnoid haemorrhage (SAH)

COMP coordinator: Violeta Stoyanova

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 are based on the new mechanism of action and the potential improved efficacy in the condition.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the nonclinical study to justify the assumption of significant benefit to nimodipine for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 03 October 2017, the sponsor presented an additional non-clinical *in vivo* study to support the claim of significant benefit over nimodipine. In this study the proposed product was administered intracisternally and compared to subcutaneously administered nimodipine. It was noted that a subcutaneous dose of nimodipine in the model maintains a plasma concentration at or above the optimal therapeutic concentration, mimicking the human situation. The key results presented covered the rotating pole test, general behavioural patterns and *ex vivo* contractility of cerebral vessels. The COMP discussed these results and accepted the rotating pole data and the vasocontractility as valid endpoints to support the claim of significant benefit. The COMP did not accept the behavioural tests and regretted that there was no combination data with nimodipine.

Following review of the application by the Committee, it was agreed to rename the indication to treatment of non-traumatic subarachnoid haemorrhage.

The Committee agreed that the condition, non-traumatic subarachnoid haemorrhage, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 1,4-diamino-2,3-dicyano-1,4-bis[2-aminophenylthio] butadiene was considered justified based on preliminary non-clinical data showing improved motor function when compared to controls.

The condition is life-threatening and chronically debilitating due to cerebral ischemia, hydrocephalus, intracerebral haemorrhage, interventricular haemorrhage, subdural hematoma, seizures, increased intracranial pressure, left ventricular systolic dysfunction or myocardial infarction. The condition has a high mortality rate which, at 5 years, is between 65-70%.

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 1,4-diamino-2,3-dicyano-1,4-bis[2-aminophenylthio] butadiene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data supporting an improvement in cerebral vasospasm and motor function. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 1,4-diamino-2,3-dicyano-1,4-bis[2-aminophenylthio] butadiene, for treatment of non-traumatic subarachnoid haemorrhage, was adopted by consensus.

2.1.3. Melatonin - EMA/OD/127/17

Therapicon Srl; Treatment of subarachnoid hemorrhage

COMP coordinator: Brigitte Bloechl-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:

- Condition

The COMP has decided that non-traumatic subarachnoid haemorrhage is the orphan condition to be designated. The COMP requests to change the orphan condition accordingly.

- 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 non-traumatic subarachnoid haemorrhage, the sponsor should further elaborate on:

- the interpretation of the results obtained in the in *vivo* cited studies, discussing in particular the early intervention (2h) which may not reflect the clinical setting;

- the relevance of the clinical study with regards to the outcomes studied and the open design of the study being prone to bias.

- Number of people affected

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”.

The sponsor should provide a thorough literature search on epidemiology of non-traumatic subarachnoid haemorrhage including all sub-types. Please re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition. Please make sure that you use the appropriate epidemiological index. In this context, please define the disease duration and report on incidence or point prevalence.

- Significant benefit

The sponsor is requested to provide a data-driven discussion on significant benefit versus Nimodipine. The following points are in need of elaboration a) the delineation of a target group of patients and expected effects on specific manifestations b) a comparative discussion on those manifestations versus the authorised counterpart. Without any additional relevant non-clinical or clinical data, significant benefit cannot be established.

- Development

The COMP is concerned regarding the development of the product, in line of the application in a plethora of orphan indications without any development having been conducted by the sponsor. It would therefore be useful to obtain more information on the ongoing studies and planned development.

In the written response, and during an oral explanation before the Committee on 03 October 2017, the sponsor included a new article where the effects of melatonin are studied in an *in vivo* model of the condition. The COMP considered that neurological improvements in that model may be considered supportive of the application.

The sponsor elaborated on the presence of long-term fatigue as a prominent characteristic of the condition several years after the episode. The COMP also reflected on the fact that inclusion of long term effects in the condition would impact on the prevalence calculations. Overall the COMP considered that the medical plausibility is met.

With regards to prevalence, an assumption of intracranial aneurysms making up to 85% of subarachnoid haemorrhages was made, and the conclusion on prevalence was approximately 1 in 10,000 which is in accordance with previous considerations of the COMP.

Regarding the justification of significant benefit, the sponsor claimed potential significant benefit based on improved efficacy due to a different mechanism of action of melatonin. However, in line with the Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03) an alternative mechanism of action *per se* was deemed insufficient for demonstration of significant benefit.

A negative opinion for melatonin, for treatment of aneurysmal subarachnoid haemorrhage, was adopted by consensus via written procedure after the October meeting. The sponsor will have 90 days to appeal from the COMP decision.

2.1.4. C1-esterase-inhibitor human - EMA/OD/105/17

CSL Behring GmbH; Treatment in solid organ transplantation

COMP coordinator: Frauke Naumann-Winter

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 in solid organ transplantation, the sponsor should provide all data that exists with the product in solid organ transplantation, including data generated in sensitised patients (Vo *et al*, Transplantation. 2015 Feb;99(2):299-308). Regarding the presented data in patients with antibody mediated rejection, the sponsor should provide further details on the historical comparison and should discuss the outcomes with other data in the literature with similar products, e.g. Montogomery *et al*, Am J Transplant. 2016 Dec;16(12):3468-3478).

In the written response, and during an oral explanation before the Committee on 04 October 2017, the sponsor presented additional data with the proposed product from a clinical study in highly sensitised renal transplant recipients. Furthermore, the sponsor discussed published clinical data on antibody-mediated rejection from the literature with similar products. The COMP considered that the totality of clinical evidence at this point in time suggests that the product could improve kidney function in patients with antibody-mediated rejection after renal transplantation. This was sufficient to establish medical plausibility.

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

The intention to treat the condition with the medicinal product containing C1-esterase-inhibitor human was considered justified based on preliminary clinical data in patients with antibody-mediated kidney rejection suggesting that the product is able to improve kidney function.

The condition is chronically debilitating and life-threatening due to complications such as ischemia-reperfusion injury, delayed graft function, and graft rejection.

The condition was estimated to be occurring in approximately 1 in 10,000 persons per year 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 C1-esterase-inhibitor human will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data suggesting that the product is able to improve kidney function when given as an add-on to standard of care for the treatment of antibody-mediated rejection, which may translate into improved transplantation outcomes. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for C1-esterase-inhibitor human, for treatment in solid organ transplantation, was adopted by consensus.

2.1.5. - EMA/OD/110/17

Treatment of focal segmental glomerulosclerosis

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, 18 September 2017, prior to responding to the list of issues.

2.1.6. - EMA/OD/107/17

Treatment of idiopathic pulmonary fibrosis

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, 18 September 2017, prior to responding to the list of issues.

2.1.7. - EMA/OD/117/17

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, 26 September 2017, prior to responding to the list of issues.

2.1.8. N-(2-aminophenyl)-4-(1-[(1,3-dimethyl-1H-pyrazol-4-yl) methyl]piperidin)benzamide - EMA/OD/121/17

Celleron Therapeutics Limited; Treatment of peripheral T-cell lymphoma

COMP coordinator: Jens Ersbøll/Lyubina Racheva Todorova

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

- Condition

The sponsor is requested to comment on the divergence between the ESMO and their own definition of the peripheral T-cell lymphoma population as applied for designation.

- 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 peripheral T-cell lymphoma, the sponsor should further elaborate on any data specifically for peripheral T-cell lymphoma in either non-clinical or preliminary clinical settings.

- Significant benefit

With regards to the presented preliminary clinical study, the sponsor is invited to discuss the characteristics of the specific group of peripheral T-cell lymphoma patients, delineate their diagnosis and previous characteristics, present their assessment in detail and the results obtained, including the duration of responses.

In the written response, and during an oral explanation before the Committee on 04 October 2017, the sponsor referred to the latest WHO classification (Swerdlow *et al.,* 2016) and argued that the new subtypes overlap with the definitions of other peripheral T-cell lymphoma types such as angioimmunoblastic and Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). The COMP considered that the proposal was justified and that for the purpose of this designation, follicular T-cell lymphoma, and nodal peripheral lymphoma with T follicular helper (TFH) phenotype, are included in the scope of the applied indication.

Regarding medical plausibility, the sponsor referred to the effects of other products with a similar mechanism of action, which have demonstrated efficacy in this condition. The sponsor claimed also the predictive potential of a biomarker that the sponsor has developed, which allows for identification of patients that respond favourably to the product.

In addition, the sponsor provided clinical narratives for four angioimmunoblastic T-cell lymphoma patients, as well as one with PTCL (no other details on the diagnosis) and one with T-cell lymphoma without details on the diagnosis. These patients have received up to four previous lines of treatment and achieved clinically relevant and durable responses upon treatment with the proposed product.

The COMP considered that the medical plausibility may be considered justified based on the data presented and pointed to the fact that these were observed in relapsed/ refractory patients who were heavily pretreated. For these patients, there are limited options and inclusion in clinical trials is suggested in the European guidelines. Taking this into consideration the COMP considered that the significant benefit is met. A strong recommendation for protocol assistance was also voiced.

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 N-(2-aminophenyl)-4-(1-[(1,3-dimethyl-1H-pyrazol-4-yl)methyl]piperidin)benzamide was considered justified based on preliminary clinical observations in patients affected by the condition, who responded to treatment with the proposed product.

The condition is life-threatening and chronically debilitating due to poor response to therapy and high rate of relapses. Clinical presentation and course vary from an indolent clinical behaviour for years in milder subtypes, to fulminant disease in aggressive subtypes.

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing N-(2-aminophenyl)-4-(1-[(1,3-dimethyl-1H-pyrazol-4-yl)methyl]piperidin)benzamide will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in relapsed or refractory patients who responded to treatment with the proposed product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for N-(2-aminophenyl)-4-(1-[(1,3-dimethyl-1H-pyrazol-4-yl) methyl]piperidin)benzamide, for treatment of peripheral T-cell lymphoma, was adopted by consensus.

2.1.9. - EMA/OD/113/17

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:

- Number of people affected

The sponsor has proposed a prevalence calculation of 0.25 in 10,000 which is primarily based on many publications which are older than 2010. More recent publications indicate that the prevalence could be higher in males which could be due to the development of better registries. The sponsor needs to correct the prevalence to reflect the imbalance between the reporting of males and females in this condition and what the overall prevalence is in the whole population and not just in males.

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

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”.

- Significant benefit

The arguments on significant benefit are based on the major contribution to patient care.

The sponsor should further elaborate on the results of any clinical data to support the significant benefit assumption in the context of the current therapeutic management of haemophilia B patients with or without inhibitors.

In the written response, and during an oral explanation before the Committee on 04 October 2017, the sponsor provided a revised calculation of the prevalence to include the assumptions raised in the question. The calculation highlighted that the COMP had been accepting values which were an underestimate for what is probably the current situation in Europe. The proposed prevalence is closer to 0.5 in 10,000.

Regarding the claim of significant benefit, based on the limited clinical data available in 4 patients included with B-haemophilia it was not possible to establish that the proposed sub-cutaneous formulation should be used in place of the intravenous formulation used with anti-FIX inhibitors. The sponsor accepted that they needed more data to substantiate the claim of major contribution to patient care in this clinical position.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 04 October 2017, prior to final opinion.

2.1.10. Diazoxide choline - EMA/OD/115/17

Capnia (UK) Ltd; Treatment of Prader-Willi-Syndrome (PWS)

COMP coordinator: Melinda Sobor/Robert Nistico

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

- Intention to diagnose, prevent or treat

The sponsor was invited to submit the full study report including all results and statistical analyses. The sponsor was invited to further elaborate on the assessments and results of the preliminary clinical observations, specifically:

- the outcomes of the uncontrolled versus double-blind, placebo-controlled phase study.
- the baseline characteristics of the Prader-Willi-Syndrome subjects involved (age, sex, clinical characteristics other than hyperphagia, etc.) and the characteristics of responders prior to the double-blind, placebo-controlled phase.
- the effect size observed when comparing the placebo arm to the diazoxide choline controlled-release arm using both parametric and non-parametric analysis.
- the relevance and validity of the scoring systems used to assess hyperphagia and aggressive behaviours.

In the written response the sponsor provided an additional reference, pertaining to the model of the condition. In that reference authors reported that the treatment specifically improved treadmill performance in the model as opposed to fat mass, which was affected in the Prader-Willi-Syndrome model and healthy model equally.

In addition, the sponsor commented that there is no statistically significant difference in the controlled phase of the study and this is attributed to carryover effects from the open label part. There is however significant difference for the diazoxide treated group if the whole duration of study (both the open and controlled phases) is taken into consideration. The sponsor also commented on the effect sizes in hyperphagia scores. It was stated that when only the moderate and severely affected patients are taken into consideration, the mean change was clinically meaningful. The sponsor has justified the assumption of beneficial effects in hyperphagia, a prominent endpoint for the study of Prader-Willi-Syndrome. This may be accepted for the purpose of orphan designation, as the currently authorised treatment does not address this aspect of the condition. The Committee found the written responses of the sponsor satisfactory to further support the relevance of the model of the condition and the oral hearing was subsequently cancelled.

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

The intention to treat the condition with the medicinal product containing diazoxide choline was considered justified based on preliminary clinical observations supporting improvements in food-seeking behaviour in treated patients.

The condition is chronically debilitating, in particular due to cognitive impairment, maladaptive behaviour and morbid obesity, and life-threatening, with a median survival reported to be approximately 30 years.

The condition was estimated to be affecting approximately 0.3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing diazoxide choline will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations supporting improvements in food-seeking behaviour in diazoxide-treated patients, which compare favourably to the existing product that is authorised for improvement of growth and body composition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for diazoxide choline, for treatment of Prader-Willi syndrome, was adopted by consensus.

2.1.11. - EMA/OD/102/17

Treatment of sickle cell 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 current arguments on significant benefit are mainly based on improved safety. Without clinical experience, significant benefit on improved safety cannot be considered. The sponsor was asked to provide a data driven argumentation of significant benefit *versus* hydroxycarbamide to substantiate a clinically relevant advantage.

In the written response, and during an oral explanation before the Committee on 04 October 2017, the sponsor was not able to present any additional non-clinical or preliminary clinical data to substantiate a clinically relevant advantage in the context of authorised product hydroxycarbamide. The COMP concluded that additional data are needed in support of significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 04 October 2017, prior to final opinion.

2.1.12. Concizumab - EMA/OD/116/17

Novo Nordisk A/S; Treatment of haemophilia B

COMP coordinator: Karri Penttila/Fernando Méndez Hermida

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

- Intention to diagnose, prevent or treat

In order to justify the medical plausibility the sponsor is invited to clarify whether any patients of the target population (haemophilia B patients with or without allo-antibodies)

were included in the clinical trial NN7415-3813, and to provide details on the clinical response of those patients.

- Significant benefit

In order to demonstrate the significant benefit of the proposed product the sponsor is invited to further elaborate on the potential advantages of the proposed product and provide a valid comparison against authorised products in haemophilia B patients with or without allo-antibodies. In particular, the sponsor is invited to:

- provide adequate justification for the assumption that subcutaneous administration of the proposed product will be a major contribution to patient care instead of intravenous administration (as the currently used products);
- to further justify the claim of better efficacy versus long acting FIX products and versus FEIBA and NOVOSEVEN.

The sponsor is reminded that comparative discussions on significant benefit should be supported by data (non-clinical and/or clinical) in the proposed condition.

In the written response the sponsor clarified that the clinical trials included three patients with haemophilia B (without inhibitors). The trial assessed PD biomarkers including free TFPI (Tissue Factor Pathway Inhibitor), TFPI function, and thrombin generation. The results were comparable in haemophilia A and haemophilia B patients and showed decrease in residual TFPI functionality, which can translate into an increase in FXa activity (U/mL) which in turn increases the thrombin generation potential. Thrombin generation was indeed also increased in the study, and the sponsor also showed a trend towards lower bleeding rate at higher exposure levels. The COMP considered that the medical plausibility was sufficiently justified by the sponsor's written responses and the OE was cancelled.

In order to support the claims of significant benefit based on major contribution to patient care the sponsor presented data from semi-structured qualitative interviews with patients from the concizumab trial showing preference for the subcutaneous administration route (concizumab) *versus* the current standard of care treatment that is administered intravenously. The sponsor also presented a statement from the FDA "The Voice of the Patient: Hemophilia A, Hemophilia B, von Willebrand Disease and Other Heritable Bleeding Disorders" (2014) on the need for alternative route of administrations to the current intravenous treatment, including subcutaneous and oral.

The COMP considered that the data presented by the sponsor were sufficient to support the significant benefit based on major contribution to patients care for the purpose of orphan designation. Assumptions of better efficacy of concizumab *versus* the currently authorised treatments for haemophilia B were considered premature. The sponsor is recommended to seek protocol assistance for confirmation of significant benefit.

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

The intention to treat the condition with the medicinal product containing concizumab was considered justified based on preliminary clinical data showing restoration of haemostatic capability in the blood of patients affected by the condition.

The condition is life-threatening and chronically debilitating due to spontaneous bleeding episodes as well as substantially prolonged bleeding upon injury.

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 concizumab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that the subcutaneous administration route of the proposed product may be preferred by patients with haemophilia B without inhibitors in comparison with the intravenous administration route of the currently available medicinal products. The Committee considered that this constitutes a major contribution to patient care for the patients affected by the condition.

A positive opinion for concizumab, for treatment of haemophilia B, was adopted by consensus.

2.1.13. - EMA/OD/126/17

Treatment of microvillus inclusion 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

Microvillus inclusion disease should be justified as a distinct medical entity or a valid subset *versus* other congenital diarrhoeal diseases. The discussion should be substantiated by similarities or differences on histopathology, pathophysiology and clinical characteristics. Furthermore, consensus classifications could be used. For the purposes of orphan medicinal product designation, the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of microvillus inclusion disease, the sponsor should further elaborate on:

- the rationale to develop the product in the proposed condition, when the active substances might be supplied via total parenteral nutrition
- the availability of additional data to support medical plausibility
- the potential to use of total parenteral nutrition in the non-clinical model of the condition
- Number of people affected

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".

Should the sponsor or the COMP change the condition, an updated prevalence will be required.

- Significant benefit

Please provide further information on the current best standard of care in patients affected by the condition. In this context, please discuss the ingredients of total parenteral nutrition

and if the active substances are currently supplied via total parenteral nutrition. Furthermore, please discuss if the products are currently given off label as hospital preparations. Finally, please list other anti-diarrhoea medicines that are or could be used. Please substantiate significant benefit with data over these treatments.

In the written response, and during an oral explanation before the Committee on 05 October 2017, the sponsor clarified the differences between the proposed condition and other types of congenital diarrhoeal conditions by histopathology, pathophysiology, and clinical characteristics. The COMP agreed that the condition is acceptable for orphan designation. As a consequence, the prevalence calculation was also deemed acceptable.

Regarding medical plausibility and significant benefit, the sponsor provided further detail on the envisaged positioning of the product in the current treatment algorithm. The treatment is intended to be given as oral solution in addition to total parenteral nutrition with the aim to reduce and taper off total parenteral nutrition. The COMP questioned if there is any evidence to support this proposed efficacy on tapering off total parenteral nutrition. The sponsor confirmed that no additional data is available at this point in time. While the presented non-clinical data from the *in vivo* model show improvements on survival, the model in its current form cannot be used to also test the use of total parenteral nutrition. In conclusion, the COMP concluded that at this point in time there is insufficient evidence to support medical plausibility and significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 05 October 2017, prior to final opinion.

2.1.14. - EMA/OD/109/17

Treatment of chronic thromboembolic pulmonary hypertension (CTEPH)

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

In order to justify the medical plausibility of the proposed product the sponsor is invited to present more details on the baseline treatment of the patients in the clinical study (active and placebo arm) and on the clinical responses in patients with background treatment with PDE-5 inhibitors and prostanoids, respectively.

- Significant benefit

The sponsor is reminded that data (clinical/non-clinical/direct comparison/indirect comparison) would be needed in order to support any assumption of significant benefit (on clinical grounds and/or major contribution to patient care) in relation to riociguat which is currently the only authorised product for the condition.

In the written response, and during an oral explanation before the Committee on 05 October 2017, the sponsor discussed the current treatment of chronic thromboembolic pulmonary hypertension (CTEPH) and the significant benefit of the product. It was highlighted that in the clinical study, a considerable number of patients were on background treatment with prostanoids or PDE5 inhibitors and still showed improvement in the most relevant endpoints of the study. The COMP acknowledged that these data signal a potential benefit of the product used in combination with some of the products currently used in the standard of care. However, the sponsor did not present any data comparing the proposed

product to riociguat, currently authorised for CTEPH. The arguments proposed by the sponsor in relation to the better safety were considered premature. The COMP expressed a unanimous negative trend for the designation with the presented data for significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 05 October 2017, prior to final opinion.

2.1.15. - EMA/OD/067/17

Treatment of pancreatic cancer

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, 27 September 2017, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1. (1'R,6'R)-3-(Benzylamine)-6-hydroxy-3'-methyl-4-pentyl-6'-(prop-1-en-2-yl)-[1,1'-bi(cyclohexane)]-2',3,6-triene-2,5-dione - EMA/OD/142/17

Quintiles Ireland Limited; Treatment of systemic sclerosis

COMP coordinator: Brigitte Bloechl-Daum

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

The intention to treat the condition with the medicinal product containing (1'R,6'R)-3-(Benzylamine)-6-hydroxy-3'-methyl-4-pentyl-6'-(prop-1-en-2-yl)-[1,1'-bi(cyclohexane)]-2',3,6-triene-2,5-dione was considered justified based on non-clinical data showing reduction of skin fibrosis in non-clinical models of the condition.

The condition is chronically debilitating and life-threatening due to the deposition of collagen in the skin and in internal organs such as kidneys, heart, lungs and gastrointestinal tract, leading to severe complications such as pulmonary hypertension, progressive dysphagia, sclerodermal renal crisis and cardiac failure.

The condition was estimated to be affecting less than 3.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (1'R,6'R)-3-(benzylamine)-6-hydroxy-3'-methyl-4-pentyl-6'-(prop-1-en-2-yl)-[1,1'-bi(cyclohexane)]-2',3,6-triene-2,5-dione will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate an effect of the proposed product on fibrosis, the most important manifestation of the condition, which is not targeted by the currently authorised treatment. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for (1'R,6'R)-3-(benzylamine)-6-hydroxy-3'-methyl-4-pentyl-6'-(prop-1-en-2-yl)-[1,1'-bi(cyclohexane)]-2',3,6-triene-2,5-dione, for treatment of systemic sclerosis, was adopted by consensus.

2.2.2. (R)-troloxamide quinone - EMA/OD/136/17

Edison Orphan Pharma BV; Treatment of amyotrophic lateral sclerosis

COMP coordinator: Kerstin Westermark

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 (R)-troloxamide quinone was considered justified based on nonclinical *in vivo* data demonstrating a reduction in motor function deterioration.

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure. The survival of patients is usually limited to 2-3 years.

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 (R)-troloxamide quinone will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical data that demonstrate a reduction in the decline of motor function as compared to the currently authorised treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (R)-troloxamide quinone, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.3. - EMA/OD/132/17

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

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the 30-31 October meeting.

2.2.4. 4-amino-1-[(1S,4R,5S)-2-fluoro-4,5-dihydroxy-3-(hydroxymethyl)cyclopent-2-en-1-yl]pyrimidin-2-one - EMA/OD/118/17

Quintiles Ireland Limited; Treatment of pancreatic cancer

COMP coordinator: Katerina Kopečková

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 4-amino-1-[(1S,4R,5S)-2-fluoro-4,5-dihydroxy-3-(hydroxymethyl)cyclopent-2-en-1-yl]pyrimidin-2-one was considered justified based on nonclinical *in vivo* data showing a reduction in tumour size following treatment with the sponsor's product.

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 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 4-amino-1-[(1S,4R,5S)-2-fluoro-4,5-dihydroxy-3-(hydroxymethyl)cyclopent-2-en-1-yl]pyrimidin-2-one will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical *in vivo* data that demonstrate a reduction in tumour size where gemcitabine resistant cells were used and in combination with nab-paclitaxel. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 4-amino-1-[(1S,4R,5S)-2-fluoro-4,5-dihydroxy-3-(hydroxymethyl)cyclopent-2-en-1-yl]pyrimidin-2-one, for treatment of pancreatic cancer, was adopted by consensus.

2.2.5. - EMA/OD/135/17

Treatment of cerebral cavernous malformation

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 30-31 October meeting.

2.2.6. - EMA/OD/139/17

Treatment of spinal cord injury

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the 30-31 October meeting.

2.2.7. Antisense oligonucleotide targeting exon 73 in the *COL7A1* gene - EMA/OD/140/17

ProQR Therapeutics VII BV; Treatment of epidermolysis bullosa

COMP coordinator: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing antisense oligonucleotide targeting exon 73 in the *COL7A1* gene was considered justified based on non-clinical models demonstrating the correction of functional collagen VII protein production in skin cells.

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

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.

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 antisense oligonucleotide targeting exon 73 in the *COL7A1* gene, for treatment of epidermolysis bullosa, was adopted by consensus.

2.2.8. - EMA/OD/130/17

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 30-31 October meeting.

2.2.9. - EMA/OD/143/17

Treatment of myotonic disorders

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 30-31 October meeting.

2.2.10. - EMA/OD/138/17

Treatment of Fabry disease

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the 30-31 October meeting.

2.2.11. Recombinant adeno-associated viral vector serotype 9 containing human iduronate-2-sulfatase gene - EMA/OD/134/17

REGENXBIO EU Limited; Treatment of mucopolysaccharidosis type II (Hunter syndrome)

COMP coordinator: Fernando Méndez Hermida

Following review of the application by the Committee, it was agreed to rename the active substance to Recombinant adeno-associated viral vector serotype 9 containing human iduronate-2-sulfatase gene.

The Committee agreed that the condition, mucopolysaccharidosis type II (Hunter syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant adeno-associated vector serotype 9 containing human iduronate-2-sulfatase gene was considered justified based on non-clinical data in a valid non-clinical model demonstrating that a single treatment was able to improve behavioural and cognitive deficits.

The condition is chronically debilitating due to neurological decline, cardiovascular and pulmonary complications and life-threatening as indicated by the survival of the patients that can be limited to 10-15 years.

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing Recombinant adeno-associated viral vector serotype 9 containing human iduronate-2-sulfatase gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that a single

treatment was able to improve behavioural and cognitive deficits, which are currently not treatable by authorised enzyme replacement therapy products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Recombinant adeno-associated viral vector serotype 9 containing human iduronate-2-sulfatase gene, for treatment of mucopolysaccharidosis type II (Hunter syndrome), was adopted by consensus.

2.2.12. Tamoxifen citrate - EMA/OD/133/17

Duchenne UK; Treatment of Duchenne muscular dystrophy

COMP coordinator: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing tamoxifen citrate was considered justified based on non-clinical data demonstrating slowing the progression of the disease and improved muscle function.

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

The condition was estimated to be affecting less than 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tamoxifen citrate will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that the product can be used in a wider patient population than that treated with the authorised medicine. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.13. Tiratricol - EMA/OD/128/17

Medical Need Europe AB; Treatment of Allan-Herndon-Dudley-Syndrome

COMP coordinator: Michel Hoffmann

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

The intention to treat the condition with the medicinal product containing tiratricol was considered justified based on non-clinical data demonstrating a potential effect on hypothyroidism in the central nervous system and clinical data demonstrating successful management of peripheral symptoms of thyrotoxicosis.

The condition is life-threatening due to a risk of sudden cardiac arrest or aspiration pneumonia and chronically debilitating due to cognitive impairment and infantile hypotonia,

which evolves to spastic paraplegia. Other symptoms include symptoms of peripheral hyperthyroidism such as increased heart frequency, tremor, weight loss and muscular weakness.

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

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

A positive opinion for tiratricol, for treatment of Allan-Herndon-Dudley syndrome, was adopted by consensus.

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 coordinators

COMP coordinators were appointed for 26 applications submitted.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 20 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

None

3.2. Finalised letters

3.2.1. -

Treatment of paroxysmal nocturnal haemoglobinuria

The finalised letter was circulated for information.

3.2.2. -

Treatment of congenital factor VII deficiency

The finalised letter was circulated for information.

3.2.3. -

Treatment of myelodysplastic syndromes

The finalised letter was circulated for information.

3.2.4. -

Treatment in solid organ transplantation

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of spinal muscular atrophy

The new request was noted.

3.3.2. -

Treatment of plasma cell myeloma

The new request was noted.

3.3.3. -

Treatment of sickle cell disease

The new request was noted.

3.3.4. -

Treatment of chronic lymphocytic leukaemia

The new request was noted.

3.3.5. -

Treatment of idiopathic pulmonary fibrosis

The new request was noted.

3.3.6. -

Treatment of small cell lung cancer

The new request was noted.

3.3.7. -

Treatment of ornithine transcarbamylase deficiency

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. Zejula - Niraparib – EMA/OD/015/10, EU/3/10/760, EMEA/H/C/004249

Tesaro UK Limited; 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 elaborate on the following issues:

- Prevalence

The sponsor is requested to provide an updated prevalence calculation that takes into account contemporaneous epidemiological data on (a) crude incidence in combination with currently reported disease duration, and/or (b) point prevalence.

- Significant benefit

The sponsor is invited to provide a data-driven significant benefit discussion over olaparib in the patients with BRCA mutations for whom olaparib is currently authorised. This could for example be achieved by adequate indirect comparisons.

In the written response, and during an oral explanation before the Committee on 03 October 2017, the sponsor outlined its position on prevalence and significant benefit.

Regarding prevalence, further detail was provided on the previously presented prevalence calculation, without identification of new updated epidemiological data. The sponsor used crude incidence from the EUCAN database from 2012 as a basis for the prevalence calculation. Reports from Cancer Research UK were supplemented to support the assumption that age standardised incidence has not increased within the recent years. The COMP concluded that the EUCAN 2012 crude incidence (n= 44,149 with a crude incidence rate of 0.86) is an acceptable epidemiological figure to be used in 2017. The assumed disease duration of 3.3 years for the estimation of prevalence was extracted from clinical trial data published over the period of 2010-2017. The COMP questioned the accuracy of this proposed survival figure and cited data from scientific literature and epidemiological databases indicating that up to 35% of ovarian cancer patients survive 10 years or longer. In response, the sponsor suggested that long term survivors were captured by the proposed estimate as some of the clinical trials reported on long-term follow up of up to 10 years. The COMP nevertheless concluded that the reported disease duration could be an underestimate and that there remains uncertainty, because a substantial number of patients might survive longer than 3.3 years. Furthermore, the COMP explained that there exist published

prevalence data from pan-European and national cancer registries including RARECARE, which should also be used for establishing the prevalence. In conclusion, the COMP was concerned that the disease duration of 3.3 years might be an underestimate and therefore decided to conclude on a 5-year partial prevalence of 4.3, calculated from the EUCAN 2012 crude incidence (prevalence = 0.86 * 5). The COMP finally outlined that the prevalence of ovarian cancer will be closely monitored in the future due to the discussed uncertainties on the epidemiological data in the public domain.

Regarding significant benefit, the sponsor presented indirect comparisons of the outcomes of the Zejula NOVA trial and the Lynparza study 19. This approach was acknowledged by the COMP; however significant benefit was established on the grounds of a clinically relevant advantage in patients without BRCA mutation, who currently have no authorised maintenance treatment.

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of ovarian cancer (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 4.3 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating due to pain, weight loss, ascites and vaginal bleeding, and life-threatening with approximately half of the patients surviving less than five years.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, Zejula is of significant benefit to patients in the orphan condition as defined in the granted therapeutic indication. The currently authorised product Lynparza is indicated for maintenance treatment of patients with BRCA mutation. In contrast, maintenance treatment with Zejula improved progression free survival in adult patients with platinum sensitive relapsed high grade serous ovarian cancer independent of BRCA mutation status. Therefore, Zejula provides significant benefit for patients without BRCA mutation, who currently have no authorised maintenance treatment.

An opinion recommending not to remove Zejula, (3S)-3-{4-[7-(aminocarbonyl)-2H-indazol-2-yl] phenyl} piperidine tosylate monohydrate salt, niraparib (EU/3/10/760) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

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

4.2.1. Lenvima - Lenvatinib - EMA/OD/287/14, EU/3/15/1460, EMEA/H/C/003727/II/0011/G

Eisai Ltd; Treatment of hepatocellular carcinoma

CHMP rapporteur: Bart Van der Schueren; CHMP co-rapporteur: Robert James Hemmings

Coordinators were appointed.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinator was appointed for 1 application.

4.5. Public Summary of Opinions

None

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Inovelon – Rufinamide – Type II variation - EMEA/OD/047/04, EU/3/04/240,EMEA/H/C/000660/II/0045

Eisai Ltd; Treatment of Lennox-Gastaut syndrome

CHMP rapporteur: Alexandre Moreau

The status of the procedure at CHMP was noted.

5.2.2. Translarna – Ataluren - Type II variation - EMEA/OD/106/04, EU/3/05/278, EMEA/H/C/002720/II/0037

PTC Therapeutics International Limited; Treatment of duchenne muscular dystrophy

CHMP rapporteur: Johann Lodewijk Hillege

The status of the procedure at CHMP was noted.

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. COMP Strategic Review & Learning meeting, 19-21 September 2017, Lisbon, Portugal

Presentations were circulated for information.

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 03 October 2017.

7.1.3. Non-Clinical Working Group

The working group on Non-Clinical met on 04 October 2017.

7.1.4. Condition Working Group

The working group on Condition met on 05 October 2017.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Cell based ATMPs-Orphan Nomenclature

Cell based Orphan-ATMPs Nomenclature was presented.

7.2.2. Recommendations on eligibility to PRIME – report from CHMP

PRIME eligibility requests - list of adopted outcomes September 2017 was circulated.

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

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

PCWP/HCPWP joint meeting - 27-28 June 2017

PCWP/HCPWP joint meeting minutes – 27-28 June 2017 (EMA/355452/2017) were circulated for information.

7.3.2. Scientific Advice Working Party (SAWP)

The Committee was briefed on the revised SAWP mandate.

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. The 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

COMP Work Plan 2017 and draft COMP Work Plan 2018 were circulated.

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2017

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2017 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. S-REPS: a new way of supporting COMP procedures with a CRM (Customer Relationship Management software)

CRM software was presented.

8.2. Publication of review of orphan criteria report

The newly proposed procedure for publication of Orphan Maintenance Assessment Report was presented.

8.3. Preparedness of the system and capacity increase

The COMP noted the update and next steps.

8.4. COMP Workshop on Prevalence

The workshop will take place on 4 December 2017 at the EMA. Agenda was circulated for information.

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 03-05 October 2017 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bruno Sepodes	Chair	Expert recommended by EMA	No interests declared	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No restrictions applicable to this meeting	
Katerina Kopeckova	Member	Czech Republic	No restrictions applicable to this meeting	
Jens Ersbøll	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Annie Lorence	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Melinda Sobor	Member	Hungary	No interests declared	
Sigurdur B. Thorsteinsson	Member	Iceland	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Ingrid Wang	Member	Norway	No interests declared	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Fernando Mendez Hermida	Member	Spain	No interests declared	
Dan Henrohn	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No interests declared	
Kerstin Westermark	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert - in person*	Patients' Organisation	No restrictions applicable to this	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
		Representative	meeting	
Carlo La Vecchia	Expert - via telephone*			
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.

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/