5 November 2021
EMA/COMP/590190/2021
Human Medicines Division

# Committee for Orphan Medicinal Products (COMP)

## Minutes for the meeting on 5-7 October 2021

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

**Disclaimers**

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

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

**Note on access to documents**

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

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# 1. Introduction

## 1.1. Welcome and declarations of interest of members and experts

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

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

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

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

## 1.2. Adoption of agenda

The agenda for 5-7 October 2021 was adopted with no amendments.

## 1.3. Adoption of the minutes

The minutes for 7-9 September 2021 were adopted with no amendments and will be published on the EMA website.

# 2. Applications for orphan medicinal product designation

## 2.1. For opinion

### 2.1.1. udonitrectag lysine - EMA/OD/0000062364

Mimetech S.r.l.; Treatment in solid organ transplantation (SOT)

COMP Rapporteur: Martin Mozina

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 an alternative mechanism of action and the potential improved protection against ischemia reperfusion injury in the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the non-clinical in vivo data they have, to justify the assumption of significant benefit within the context of authorised medicinal products that are used for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 5 October 2021, the sponsor provided additional data to support their claim of better engraftment following use of their product during the preservation of the organ. To this end, data from a non-clinical in vivo model which was not included in the original submission was presented. The sponsor highlighted that in transplantation, Ischemia/Reperfusion Injury (IRI) is known to underlie the clinical entity of Primary Graft Dysfunction (PGD), but also sets the premises for chronic rejection. The challenge is therefore to efficiently counteract IRI in donor organs to improve both early and long-term success.

The potential application of udonitrectag to mitigate IRI after lung transplantation was studied in two groups, subjected to lung transplantation after 24-hour cold ischemia. After organ transplant, study subjects were randomized to receive 2 mg/kg MT8 (MT8 group, n = 6) or saline (control group, n = 5) via intravenous route at the reperfusion phase. The survival was monitored for 6 hours starting from reperfusion. The data obtained demonstrated that udonitrectag was able to sustain survival in all treated study subjects at least six hours after the reperfusion phase; conversely, in the vehicle group only three study subjects survived. Moreover, no pulmonary oedema was observed in MT8-treated group, which instead was abundant in the control group (data not shown). These results were obtained from an exploratory study, but nonetheless provided useful data in the relevant context of SOT.

Currently available treatments cannot effectively inhibit IRI, as the drugs approved for use in the context of solid organ transplantation belong to the immunosuppressant pharmacotherapeutic group, acting on prevention of graft rejection. None of these therapeutic approaches can counteract the apoptotic process induced by metabolic injury, highlighting an unmet medical need. It was noted that this is exemplified by the fact that, every hour, six new patients are added to the waiting list, for a total of over 100,000 persons in EU actively waiting for a transplant. The scarcity of available organs means that every day six people on the waiting list die, each year over 3%. It was also noted that prolonged time of organ preservation would reduce the reliance on last-minute operating room bookings and on-call surgical staff, decreasing the currently high costs of patient admission for transplant. By increasing the potential preservation time for these organs, it could be possible to provide additional flexibility to organ procurement organizations.

The COMP gave careful consideration to the additional data submitted by the sponsor and considered it was adequate for the purpose of recommending an initial orphan designation.

The Committee agreed that the condition, treatment in 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 udonitrectag lysine was considered justified based on non-clinical in vivo data in models of the condition showing a reduction in ischemia reperfusion associated damage.

The condition is chronically debilitating and life threatening due to delayed graft function following transplantation.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing udonitrectag lysine 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 ischemia reperfusion associated injury in recipients who received organs stored with the product before transplantation. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for udonitrectag lysine, for treatment in solid organ transplantation, was adopted by consensus.

### 2.1.2. linerixibat - EMA/OD/0000057352

GlaxoSmithKline (Ireland) Limited; Treatment of primary biliary cholangitis

COMP Rapporteur: Geraldine O'Dea

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 an alternative mechanism of action which could further reduce pruritus a symptom associated with the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the clinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. Particular attention was requested regarding the use of combination treatments as well as comparative data to cholestyramine on signs and symptoms associated with the condition.

In the written response, and during an oral explanation before the Committee on 5 October 2021, the sponsor explained in their presentation that there was limited trial evidence to show cholestyramine's effectiveness on pruritus making indirect comparisons difficult. They noted in addition that they did not have direct comparison data in the GLIMMER study as patients included in the study were not on cholestyramine or had been washed out previously. It was highlighted that their Phase III GLISTEN study would provide this information when completed. To address the shortfall, real world data of cholestyramine use was presented. It had been recently reported by Hegade et al., in 2019 that less than one-quarter of patients with pruritus use this product. The sponsor noted that there is a high discontinuation rate (40-70%) due to palatability, tolerability and/or inadequate efficacy (Scaldaferri et al., 2013), and that there is poor reported uptake despite the serious and debilitating nature of pruritus (Hegade et al., 2016, Montagnese et al., 2013). Of particular note was the need for 4 hours of separation in dosing from other drugs. Finally, the effect on sleepiness or the ability to sleep at night is negligible whereas it was noted that the sponsor's product held a promise on improvements in sleep or sleep duration at night although these were just strong trends.

The COMP acknowledged the real-world data presented. The shortcomings of cholestyramine treatment were accepted as were the difficulties in indirect comparisons.

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

The intention to treat the condition with the medicinal product containing linerixibat was considered justified based on preliminary clinical data showing a reduction in pruritus and an improvement in sleep.

The condition is chronically debilitating and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular cancer. Common findings include pruritus and associated sleep disturbances, hyperlipidaemia, hypothyroidism, deficiency of fat-soluble vitamins and osteopenia.

The condition was estimated to be affecting approximately 2.8 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing linerixibat will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a reduction in pruritus and improvement in sleep in patients with uncontrolled pruritus. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for linerixibat, for treatment of primary biliary cholangitis, was adopted by consensus.

### 2.1.3. - EMA/OD/0000061146

Treatment of retinal detachment

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 retinal detachment the sponsor was requested to further elaborate on the methodology used in the non-clinical study as well as the results from it and its relevance for the development of the product in the condition:

a) in particular, it was not clear to what extent the proposed product would prevent proliferative vitreoretinopathy (PVR) from occurring, versus only attenuating the severity, and in the latter case how this attenuation would result in clinically meaningful results,

b) the histopathological scoring system used throughout the study had not been validated versus functional visual outcomes. Hence, it was difficult to know whether a difference of score 2 versus 3 would translate in a clinically meaningful improvement. The sponsor was asked to further discuss and clarify the relevance of the histopathological changes seen.

In the written response, and during an oral explanation before the Committee on 5 October 2021, the sponsor defended their position. It could be agreed with the sponsor that a measure of positive attenuation of the retinal disruption and inflammatory markers was achieved with the treatment, however, the question remained as to what degree this

positive effect would translate into a clinically and for the patient meaningful beneficial effect. The evidence, based on the histopathological data presented, included a number of assumptions that were not considered sufficiently supported or validated by the COMP.

The lack of functional outcomes or validated link to functional outcomes remained the main point of concern as the sponsor only provided indirect evidence to support medical plausibility. The COMP concluded that the presented evidence is not sufficient to support an orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 5 October 2021, prior to final opinion.

### 2.1.4. 5-fluoro-4-(4-fluoro-2-methoxyphenyl)-N-{4-[(S-methylsulfonimidoyl)methyl] pyridin-2-yl}pyridin-2-amine - EMA/OD/0000064329

Vincerx Pharma GmbH; Treatment of diffuse large B-cell lymphoma (DLBCL)

COMP Rapporteur: Elisabeth Johanne Rook

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

- Number of people affected

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

A proportion of 47.8% of non-Hodgkin lymphomas (NHL) had been used to calculate the prevalence of DLBCL in the EU. However, the figure was based on a publication by Smith et al., 2015. The sponsor was asked to perform sensitivity analysis on the percentage of DLBCL from NHL considering that the 47.8% appears to be an overestimate.

- Significant benefit

Significant benefit was claimed based on the potential efficacy of the proposed product in high grade lymphoma with MYC and BCL2 and /or BCL6 translocations, due to its mechanism of action. The sponsor was requested to further justify the significant benefit versus CAR-T cell products. An update of the literature was required on the efficacy of CAR-T cell products in these special patients' groups.

An indirect comparison is made to the median duration of response of other products. However, with only two responders available for the proposed product, it is difficult to draw conclusions on the median response for this product. A comparison with the duration of response ranges of the authorised products is considered more informative and was requested.

In the written response, and during an oral explanation before the Committee on 5 October 2021, the sponsor provided an updated prevalence calculation of DLBCL in the EU of 3.9 per 10,000 by using a proportion of 35% of NHL. The COMP considered that this figure should be rounded to 4 in order to be consistent with figures recently approved.

For the demonstration of significant benefit, the sponsor provided a literature overview of 5 single-arm studies on CART-T cell products in DLBCL patients, including double expresser lymphoma (DEL) and DHL/THL (high grade) types and compared it to preliminary clinical

data from the proposed product. The outcomes on overall response rate (ORR), progression free survival (PFS) and duration of response (DoR) were reported and compared. Most studies showed similar results of short-term efficacy (ORR/DOR) in high-grade lymphoma compared with other subgroups. In a single institution series, the DHL/THL phenotype was associated with relapse after CAR-T therapy, despite equivalent early measures of efficacy (Ghafouri et al., 2021). The COMP considered that the literature data provided on CAR-T cells in addition to the limited results from the two responders available for VIP152 which showed higher median DoR compared to CAR-T cells indicated that pre-treated patients with DHL responded to treatment with the current product. This was considered sufficient at this stage to justify the significant benefit.

The Committee agreed that the condition, diffuse large B-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 5-fluoro-4-(4-fluoro-2-methoxyphenyl)-N-{4-[(S-methylsulfonimidoyl)methyl]pyridin-2-yl}pyridin-2-amine was considered justified based on preliminary clinical data showing responses achieved in patients with double hit lymphoma.

The condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract, the central nervous system and bone marrow and life-threatening in relapsed/refractory patients.

The condition was estimated to be affecting approximately 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 5-fluoro-4-(4-fluoro-2-methoxyphenyl)-N-{4-[(S-methylsulfonimidoyl)methyl]pyridin-2-yl}pyridin-2-amine will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data which demonstrate that pre-treated patients with double hit lymphoma responded to treatment with the current product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 5-fluoro-4-(4-fluoro-2-methoxyphenyl)-N-{4-[(S-methylsulfonimidoyl)methyl]pyridin-2-yl}pyridin-2-amine, for treatment of diffuse large B-cell lymphoma, was adopted by consensus.

### 2.1.5. 2-[1-(3-{6-[(1E)-(hydroxyimino)methyl]-5-methyl-4-oxo-7-propyl-3H,4H-pyrrolo[2,1-f][1,2,4]triazin-2-yl}-4-propoxybenzenesulfonyl)piperidin-4-yl]ethyl nitrate - EMA/OD/0000064903

Topadur Pharma Deutschland GmbH; Treatment of systemic sclerosis

COMP Rapporteur: Armando Magrelli

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 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 non-clinical in vivo studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

The sponsor submitted a written response which was accepted by the COMP. The oral explanation was therefore cancelled. In the answer, additional published references were submitted regarding bosentan and its lack of efficacy in reducing and healing digital ulcers associated with the condition. The effects of endothelin-1 (ET-1) (and correspondingly bosentan) on platelet functions are inconsistent. Activation, inhibition and lack of effect have all been described (Jagroop et al., 2005). On the other hand, anti-platelet effects of NO and PDE5 inhibitors are well described (Dunkern & Hatzelmann, 2005; Gudmundsdóttir et al., 2005; Walter & Gambaryan, 2009; Gresele et al., 2011; Rondina & Weyrich et al., 2012) and TOP-N53 was shown to reduce thrombin-induced platelet aggregation and adhesion in vitro. In addition, the sponsor noted that the effects of bosentan in the non-clinical disease model of wound healing described in the literature did not consistently reproduce the results seen with the sponsor's product in vivo. Angiogenesis is critical for wound healing, again in the proliferative phase. ET-1 is a pro-angiogenic factor (Salani et al., 2000). Hence, bosentan would be expected to exert anti-angiogenic effects rather than promoting angiogenesis, which may impair wound healing.

Finally, it was noted that, in the non-clinical disease model where cutaneous wound healing was accelerated by (adenoviral, skin) overexpression of TGFβ1, bosentan impeded wound healing while (adenoviral, skin) overexpression of ET-1 accelerated wound healing (Lagares et al., 2010). An activation of dermal fibroblasts aside from pro-angiogenic effects (both are critical for the proliferative phase of wound healing) by ET-1 may explain these findings (Salani et al., 2000; Lagares et al., 2010). However, the role of ET-1 in wound healing appears inconsistent and contingent on the in vivo model selected (Makino et al., 2014). Bosentan did not affect wound healing in healthy study subjects (Lagares et al., 2010).

The COMP considered that this additional data from the public domain further helped understand the clinically relevant advantage of the sponsor's product to bosentan.

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 2-[1-(3-{6-[(1E)-(hydroxyimino)methyl]-5-methyl-4-oxo-7-propyl-3H,4H-pyrrolo[2,1-f][1,2,4]triazin-2-yl}-4-propoxybenzenesulfonyl)piperidin-4-yl]ethyl nitrate was considered justified based on non-clinical in vivo data which showed clinically relevant closure of skin dermal wounds when compared to vehicle.

The condition is chronically debilitating and life-threatening due to the deposition of collagen in the skin leading to skin ulcers 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 approximately 3.7 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 2-[1-(3-{6-[(1E)-(hydroxyimino)methyl]-5-methyl-4-oxo-7-

propyl-3H,4H-pyrrolo[2,1-f][1,2,4]triazin-2-yl}-4-propoxybenzenesulfonyl)piperidin-4-yl]ethyl nitrate will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate that an improvement in wound closures, using a topical formulation of the sponsor's product versus systemic delivery of bosentan, was noted. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-[1-(3-{6-[(1E)-(hydroxyimino)methyl]-5-methyl-4-oxo-7-propyl-3H,4H-pyrrolo[2,1-f][1,2,4]triazin-2-yl}-4-propoxybenzenesulfonyl)piperidin-4-yl]ethyl nitrate, for treatment of systemic sclerosis, was adopted by consensus.

### 2.1.6. nadunolimab - EMA/OD/0000058336

Cantargia AB; Treatment of pancreatic cancer

COMP Rapporteur: Brigitte Schwarzer-Daum

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

- Number of people affected

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

The sponsor was asked to revise the prevalence estimation based on a more conservative duration of the disease, which does not only cover the patients with metastatic pancreatic cancer but all patients with pancreatic cancer.

- Significant benefit

The arguments on significant benefit were based on 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 updated results from the ongoing clinical study (cut-off date for data presented was April 2021) to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

Regarding the indirect comparison, the COMP considered that the presented differences on overall survival (OS) based on the single arm study were not sufficient for the assumption of the significant benefit. The sponsor was requested to comment on the differences of overall response rate (ORR) observed with the combination of nadunolimab with nab-paclitaxel and gemcitabine combination in the ongoing study and the published data in similar populations treated with either nab-paclitaxel-gemcitabine alone or FOLFIRINOX.

In the written response, and during an oral explanation before the Committee on 6 October 2021, the sponsor provided an updated prevalence calculation of 2.13 by using 11 months disease duration for pancreatic cancer. The COMP considered that the prevalence is approximately 2.0 in 10,000 persons in line with previous designations.

For the demonstration of significant benefit, the sponsor provided updated efficacy information from the ongoing study based on an August 2021 cut-off date. The updated OS results for the combination of nadunolimab with nab-paclitaxel and gemcitabine combination

(NG), compared favourably with published data in the population treated with NG alone (OS 13.2 months vs 8.5 months). As of August 2021, ORR and progression free survival (PFS) (ORR 27%; PFS 5.2 months) were similar to what was seen in for NG alone (ORR 29%; PFS 5.5 months). In addition, iPFS (PFS per immune RECIST criteria) was prolonged compared to PFS. Based on the updated data the COMP concluded that the combination of nadunolimab with nab-paclitaxel and gemcitabine led to better outcome when compared indirectly to authorised treatments.

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 nadunolimab was considered justified based on preliminary clinical data indicating improved survival when the product is used in combination with nab-paclitaxel and gemcitabine in first line treatment.

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 markedly reduced life expectancy.

The condition was estimated to be affecting approximately 2.0 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing nadunolimab will be of significant benefit to those affected by the condition. Treatment in combination with currently authorised products led to better efficacy when compared indirectly to authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

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

### 2.1.7. rebastinib - EMA/OD/0000064772

Deciphera Pharmaceuticals (Netherlands) B.V.; Treatment of ovarian cancer

COMP Rapporteur: Irena Rogovska

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

- Number of people affected

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

The sponsor was requested to provide an updated estimate of prevalence based on all available data from EU sources including a sensitivity analysis.

- Significant benefit

The arguments on significant benefit were based on 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 updated results from the ongoing study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. The sponsor was also requested to provide details on the populations studied including patients' characteristics and prior lines of treatments for the purpose of an indirect comparison of the clinical trials.

In the written response, the sponsor explained further the methodology used for the prevalence calculation of 4.7 per 10,000. The registries from Netherlands and Germany provide survival rates in yearly increments for more precise approximation of disease duration, 4.62 for Netherlands and 4.7 for Germany. The sponsor claimed that these survival rates are higher than the EU average and represents 22.5% of EU-27 population. The COMP considered that the methodology used for the recalculation was based on less assumptions and a conservative approach and accepted the proposed prevalence estimate.

Regarding significant benefit, updated preliminary clinical data were presented from the ongoing, phase 1b/2 study of rebastinib. The updated efficacy data confirmed the positive trend with increase in overall response rate (ORR), complete response (CR) and partial response (PR). Regarding the indirect comparison of rebastinib with bevacizumab and taking into account the differences in the baseline characteristics of the population studied, rebastinib showed better efficacy potential especially in heavily pre-treated population. The COMP considered that the observed response rate in heavily pre-treated patients compares favourably to published data with currently authorised products and cancelled the oral hearing as it was no longer needed.

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

The intention to treat the condition with the medicinal product containing rebastinib was considered justified based on preliminary clinical data showing responses in patients with relapsed disease.

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.

The condition was estimated to be affecting approximately 4.7 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 rebastinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate responses in patients affected by the condition. Indirect comparisons showed that the observed response rate in heavily pre-treated patients compares favourably to published data from currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for rebastinib, for treatment of ovarian cancer, was adopted by consensus.

### 2.1.8. autologous CD34+ enriched cells transduced with a self-inactivating lentiviral vector containing the codon-optimized *RPS19* gene - EMA/OD/0000060407

Consorcio Centro de Investigación Biomédica en Red, M.P.; Treatment of Diamond-Blackfan anemia (DBA)

COMP Rapporteur: Enrico Costa

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

At time of initial orphan designation medical plausibility is usually expected to be supported either by non-clinical in-vivo data from a relevant disease model or by clinical data. It is noted that the main data is derived only from in vitro experiments using hematopoietic stem cells from RPS19-deficient DBA patients.

1) The sponsor was therefore asked to better justify their approach of conducting preclinical gene therapy studies with the medicinal product PGK.CoRPS19.Wpre* using hematopoietic stem cells from RPS19-deficient DBA patients rather than available non-clinical disease models.

2) The sponsor was also asked to better explain the planned non-clinical in-vivo study in the *NBSGW* study subjects and its added value.

3) In addition the sponsor was asked to better justify the absence of conditioning regimen and further substantiate it not being a possible limitation in the clinical development/use of this product in DBA.

In the written response, the sponsor clarified that the non-clinical Diamond-Blackfan anemia model does not well mimic the clinical situation, as it shows a marked bone marrow failure (BMF) phenotype, while DBA patients mostly show defects in the erythroid lineage. These differences may imply that conclusions are reached which do not optimally translate into the clinical setting.

The sponsor plans an additional in vivo non-clinical study. Their chosen model better mimics the human situation in terms of erythrocyte differentiation. This study is expected to replicate the earlier findings in that the therapeutic vector can correct the defect in erythrocyte differentiation.

It will also be evaluated whether transduced CD34+ cells from patients developed any proliferation advantage in the primitive compartment of HSCs, or only in specific lineages. If no proliferation advantage is observed at the HSC level, these data would suggest that in the clinical setting some conditioning might be required prior to transplantation to guarantee a minimum engraftment of corrected HSCs.

The additional information clarified the rationale of the chosen pre-clinical approach and choice of non-clinical models and assays used by the sponsor. The COMP considered that overall the available non-clinical in vitro and in vivo data were sufficient to support medical plausibility for the purpose of an initial orphan designation. The oral explanation was therefore cancelled.

The Committee agreed that the condition, Diamond-Blackfan anemia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing autologous CD34+ enriched cells transduced with a self-inactivating lentiviral vector containing the codon-optimized *RPS19* gene was considered justified based on pre-clinical in vitro and in vivo data demonstrating reconstitution and differentiation ability of hematopoietic progenitor cells from patients, and a reversion in the characteristic blockage in the maturation of erythroid progenitor cells.

The condition is life-threatening and chronically debilitating due to complications related to patients' malfunctioning bone marrow such as severe anemia and to an increased risk of developing haematological malignancies.

The condition was estimated to be affecting less than 0.06 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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for autologous CD34+ enriched cells transduced with a self-inactivating lentiviral vector containing codon-optimized *RPS19* gene, for treatment of Diamond-Blackfan anemia, was adopted by consensus.

### 2.1.9. - EMA/OD/0000065329

Treatment of idiopathic pulmonary fibrosis (IPF)

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 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 non-clinical in vivo data to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. In addition, the sponsor was asked to present any preliminary clinical data they may have.

In the written response, and during an oral explanation before the Committee on 6 October 2021, the sponsor reiterated the non-clinical in vivo data presented in the original package. In addition, they provided preliminary clinical data from an on-going phase II study in patients with the condition.

The clinical trial is a phase 2a, open-label, dose escalating trial evaluating αvβ6 target engagement by the proposed product in up to 12 participants with IPF. Target engagement was assessed by measuring uptake kinetics of the αvβ6 knottin PET radiotracer in the IPF lung pre- and post-dose of the proposed product, and the resulting change in pulmonary volume of distribution of the radiotracer using dynamic PET/CT scans and a 2-compartment model (lung and blood). All participants enrolled to date received standard of care treatment with nintedanib. Interim results, showed that αvβ6 is highly expressed in the fibrotic lung and that the proposed product penetrates areas of dense fibrosis to engage its target, αvβ6.

The sponsor then links these findings to data, presented in the Saini et al., 2015 publication, which demonstrates the potent and dose-dependent inhibition of αvβ6 in the

fibrotic lung provided by the proposed treatment, supporting its potential to improve clinical outcomes in patients with IPF patients. The sponsor notes that up to 40% of patients treated with nintedanib or pirfenidone cannot tolerate prolonged treatment and therefore are not afforded a durable benefit. It was therefore concluded that there was an unmet medical need in 40% of patients with IPF. The COMP accepted this new finding regarding patients who were not responding to nintedanib or pirfenidone. However, a clear link with the proposed surrogate endpoint of αvβ6 inhibition in reduction in the fibrotic process and how it translates into patient survival, could not be establish.

The COMP concluded that although the data appeared compelling, they 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 7 October 2021, prior to final opinion.

### 2.1.10. - EMA/OD/0000062259

Treatment of glioma

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 17 September 2021, prior to responding to the list of issues.

### 2.1.11. mosunetuzumab - EMA/OD/0000058552

Roche Registration GmbH; Treatment of follicular lymphoma (FL)

COMP Rapporteur: Maria Elisabeth Kalland

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

- Number of people affected

The sponsor was requested to re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition. Given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor was asked to perform a sensitivity analysis of the reported calculations. For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

In the written response, and during an oral explanation before the Committee on 5 October 2021, the sponsor further explained how data derived from population-based cancer registries were employed to estimate the prevalence of FL and provided an additional sensitivity analysis as requested. Two methodologies were used in a direct approach based on data abstracted from national cancer registries in the EU-27 and using the US SEER registry to help indicate the potential direction the prevalence was going in for FL. The sponsor arrived at a complete prevalence of 4.8 per 10,000 people through the direct method based on prevalence data extracted from the national population-based cancer registries in Slovenia and Italy. These two countries represent 14% of the EU-27 population.

Since the FL incidence is not reported in all cancer registries but can be retrieved for NHL, the sponsor also presented an indirect calculation to supplement the direct estimates for the

prevalence. The sponsor used the ECIS database for the crude incidence of NHL (19.6 per 100,000) which was multiplied by a factor of 0.183 based on the assumption that FL represents 18.3% of all NHL cases in the EU. In line with the comments from the Committee, the sponsor acknowledged that survival of FL patients is improving and provided a population-based median OS estimate range of 12.5 to 14.8 years. This correlated well with the age range seen in recent publications from Denmark, Sweden, and Spain. Following these assumptions, a sensitivity analysis of indirect prevalence estimates of FL was explored using various ranges of median OS and incidence rates. Based on the results from this analysis, the sponsor proposed a conservative estimate for the indirect method of 4.77 in 10,000 people, which could be rounded off to 4.8 in 10,000 people in the EU.

The two estimates from the direct and indirect methodologies applied are very close, and the Committee agreed to use 4.8 in 10,000 people for the EU-27 population.

The intention to treat the condition with the medicinal product containing mosunetuzumab was considered justified based on preliminary clinical data which showed that heavily pre-treated patients with relapsed/refractory follicular lymphoma achieved partial or complete responses which were durable.

The condition is life-threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction and the potential of transformation to aggressive lymphoma.

The condition was estimated to be affecting approximately 4.8 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing mosunetuzumab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate sustained partial and complete responses in a high proportion of heavily pre-treated relapsed/refractory patients with follicular lymphoma who have failed several lines of approved therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for mosunetuzumab, for treatment of follicular lymphoma, was adopted by consensus.

## 2.2. For discussion / preparation for an opinion

### 2.2.1. anti-CD38 IgG4 human monoclonal antibody - EMA/OD/0000036998

Encefa; Treatment of amyotrophic lateral sclerosis

COMP Rapporteur: Dinah Duarte

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 anti-CD38 IgG4 human monoclonal antibody was considered justified based on non-clinical in vivo data in models of the condition showing beneficial effects on survival, motor function and neurodegeneration.

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 the 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 anti-CD38 IgG4 human monoclonal antibody will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that also demonstrate beneficial effects on motor function and delay of disease progression which is not expected with the currently authorised medicine. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for anti-CD38 IgG4 human monoclonal antibody, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

### 2.2.2. - EMA/OD/0000057224

Treatment of chronic thromboembolic pulmonary hypertension

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 November meeting.

### 2.2.3. paclitaxel, polyoligo(ethylene glycol)methacrylate-co poly(vinylbenzyldithiodibutyric acid-gemcitabine) - EMA/OD/0000060140

Karma Oncology B.V.; 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 paclitaxel, polyoligo(ethylene glycol)methacrylate-co-poly(vinylbenzyldithiodibutyric acid-gemcitabine) was considered justified based on non-clinical data from valid models suggesting that treatment impairs tumour growth and prolonged survival.

The condition is chronically debilitating due to pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression and life-threatening with a markedly reduced life expectancy.

The condition was estimated to be affecting approximately 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 paclitaxel, polyoligo(ethylene glycol)methacrylate-co-poly(vinylbenzyldithiodibutyric acid-gemcitabine) will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data from valid models suggesting that treatment impairs tumour growth. Treatment in combination with currently

authorised products led to better efficacy when compared to authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for paclitaxel, polyoligo(ethylene glycol)methacrylate-co poly(vinylbenzyldithiodibutyric acid-gemcitabine), for treatment of pancreatic cancer, was adopted by consensus.

### 2.2.4. - EMA/OD/0000061806

Treatment of aneurysmal subarachnoid haemorrhage

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 November meeting.

*[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 15 October 2021.]*

### 2.2.5. fingolimod - EMA/OD/0000062237

Consorcio Centro de Investigación Biomédica en Red, M.P.; Treatment of adrenoleukodystrophy

COMP Rapporteur: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing fingolimod was considered justified based on a non-clinical in vivo model of the condition showing an improvement in locomotor performance.

The condition is life-threatening and chronically debilitating taking into consideration the two main phenotypes with which the condition presents. Cerebral adrenoleukodystrophy is associated with behavioural abnormalities, seizures, spastic tetraplegia and cognitive decline and patients usually die within a few years after the onset of symptoms. Adrenomyeloneuropathy is associated with primary adrenocortical insufficiency as well as progressive stiffness and gait disturbance, with a fatal outcome within 20 years following the onset of symptoms.

The condition was estimated to be affecting approximately 0.4 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 fingolimod will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate an improvement in locomotor function, a symptom of the later onset forms of the condition for which the only authorised product is not indicated. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for fingolimod, for treatment of adrenoleukodystrophy, was adopted by consensus.

## 2.2.6. - EMA/OD/0000062530

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 November meeting.

*[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 19 October 2021.]*

## 2.2.7. - EMA/OD/0000062804

Treatment of acute lymphoblastic leukaemia/lymphoblastic lymphoma

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

## 2.2.8. cannabidiol, dronabinol - EMA/OD/0000063093

Tetra Bio-Pharma Europe Limited; Treatment of complex regional pain syndrome (CRPS)

COMP Rapporteur: Michel Hoffmann

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

The intention to treat the condition with the medicinal product containing cannabidiol, dronabinol was considered justified based on bibliographical clinical data showing an improvement in peripheral neuropathic pain.

The condition is chronically debilitating due to symptoms such as pain, hyperesthesia or allodynia, local oedema, weakness, tremor, dystonia, as well as skin trophic changes.

The condition was estimated to be affecting approximately 4.4 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 cannabidiol, dronabinol, for treatment of complex regional pain syndrome, was adopted by majority (29 out of 30 votes).

The divergent position (Elisabeth Johanne Rook*)* was appended to this opinion.

The Norwegian COMP member agreed with the above-mentioned recommendation of the

COMP.

## 2.2.9. - EMA/OD/0000064296

Treatment of narcolepsy

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 November meeting.

*[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 15 October 2021.]*

## 2.2.10. - EMA/OD/0000064393

Treatment of Dravet syndrome

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

## 2.2.11. - EMA/OD/0000064736

Treatment of pulmonary arterial hypertension

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 November meeting.

## 2.2.12. ibrexafungerp - EMA/OD/0000064849

Dlrc Pharma Services Limited; Treatment of invasive candidiasis

COMP Rapporteur: Olimpia Neagu

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

The intention to treat the condition with the medicinal product containing ibrexafungerp was considered justified on the basis of preliminary clinical data showing a resolution of Candida infection's symptoms and a complete or partial microbiological response in patients who are refractory or relapsed to standard of care antifungal treatment.

The condition is life-threatening with above 50% mortality rate at 30-days in Intensive Care Units.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ibrexafungerp will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a complete or partial response in patients who are relapsed or refractory to the antifungal treatment available to date. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for ibrexafungerp, for treatment of invasive candidiasis, was adopted by consensus.

## 2.2.13. (14S)-8-[3-(2-{dispiro[2.0.24.13]heptan-7-yl}ethoxy)-1H-pyrazol-1-yl]-12,12-dimethyl-2lamba6-thia-3,9,11,18,23-penta-azatetracyclo[17.3.1.111,14.05,10]tetracosa-1(22),5,7,9,19(23),20-hexaene-2,2,4-trione calcium salt hydrate, deutivacaftor, tezacaftor - EMA/OD/0000065454

Vertex Pharmaceuticals (Ireland) Limited; Treatment of cystic fibrosis

COMP Rapporteur: Enrico Costa

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 (14S)-8-[3-(2-{dispiro[2.0.24.13]heptan-7-yl}ethoxy)-1H-pyrazol-1-yl]-12,12-dimethyl-2lamba6-thia-3,9,11,18,23-penta-azatetracyclo[17.3.1.111,14.05,10]tetracosa-1(22),5,7,9,19(23),20-hexaene-2,2,4-trione calcium salt hydrate, deutivacaftor, tezacaftor was considered justified based on clinical data showing improvements in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) and reductions in sweat chloride, following treatment with the product.

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 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 (14S)-8-[3-(2-{dispiro[2.0.24.13]heptan-7-yl}ethoxy)-1H-pyrazol-1-yl]-12,12-dimethyl-2lamba6-thia-3,9,11,18,23-penta-azatetracyclo[17.3.1.111,14.05,10]tetracosa-1(22),5,7,9,19(23),20-hexaene-2,2,4-trione calcium salt hydrate, deutivacaftor, tezacaftor will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that, based on direct and indirect comparisons, the product has achieved a larger reduction in sweat chloride, an acceptable pharmacodynamic marker, as compared to the other CFTR modulators approved. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (14S)-8-[3-(2-{dispiro[2.0.24.13]heptan-7-yl}ethoxy)-1H-pyrazol-1-yl]-12,12-dimethyl-2lamba6-thia-3,9,11,18,23-penta-azatetracyclo[17.3.1.111,14.05,10]tetracosa-1(22),5,7,9,19(23),20-hexaene-2,2,4-trione calcium salt hydrate, deutivacaftor, tezacaftor, for treatment of cystic fibrosis, was adopted by consensus.

### 2.2.14. D-lactic acid, glycolic acid - EMA/OD/0000065981

Neurevo GmbH; Treatment of amyotrophic lateral sclerosis

COMP Rapporteur: Robert Nistico

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

The intention to treat the condition with the medicinal product containing D-lactic acid, glycolic acid was considered justified based on non-clinical data showing improvements on neuromuscular function and histology.

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure.

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

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

medicinal product containing D-lactic acid, glycolic acid will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data suggesting that compared to riluzole, the standard of treatment, the proposed product was more effective in delaying the progression of neuromuscular impairment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for D-lactic acid, glycolic acid, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

## 2.2.15. - EMA/OD/0000066191

Treatment of acute lymphoblastic 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 November meeting.

## 2.2.16. soticlestat - EMA/OD/0000066312

Takeda Pharma A/S; Treatment of Lennox-Gastaut syndrome

COMP Rapporteur: Giuseppe Capovilla

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

The intention to treat the condition with the medicinal product containing soticlestat was considered justified based on preliminary clinical data showing a clinically meaningful reduction in epileptic seizures.

The condition is considered chronically debilitating due to the high frequency of multiple types of seizures, cognitive deterioration and behavioural disturbance.

The condition was estimated to be affecting approximately 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 soticlestat will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a reduction in epileptic seizures in patients refractory to authorised anti-epileptic medicines used in the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for soticlestat, for treatment of Lennox-Gastaut syndrome, was adopted by consensus.

## 2.2.17. - EMA/OD/0000066630

Treatment of primary sclerosing cholangitis

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 November meeting.

## 2.2.18. - EMA/OD/0000066742

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 November meeting.

## 2.2.19. - EMA/OD/0000066935

Treatment of epilepsy with myoclonic-atonic seizures

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 November meeting.

*[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 19 October 2021.]*

## 2.2.20. olverembatinib - EMA/OD/0000066944

Ascentage Pharma Europe Limited; Treatment of chronic myeloid leukaemia

COMP Rapporteur: Karri Penttila

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

The intention to treat the condition with the medicinal product containing olverembatinib was considered justified based on preliminary clinical data demonstrating antileukaemic effect in patients affected by the condition.

The condition is life threatening and chronically debilitating due to the consequences of the bone marrow dysfunction, intracranial or gastro-intestinal haemorrhagic episodes and the risk of severe infections.

The condition was estimated to be affecting less than 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 olverembatinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating antileukaemic effect in patients affected by the condition, who have failed all currently authorised therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for olverembatinib, for treatment of chronic myeloid leukaemia, was adopted by consensus.

## 2.2.21. adeno-associated viral vector serotype 9 containing the human *SURF1* gene - EMA/OD/0000067046

Raremoon Consulting Esp S.L.; Treatment of Leigh syndrome

COMP Rapporteur: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 9 containing the human *SURF1* gene was considered justified based on non-clinical in vivo data in a model of the condition showing an improvement of biomarkers relevant for the disease namely cytochrome c oxidase (COX) activity and lactic acidosis.

The condition is chronically debilitating due to neurological deficits, psychomotor delay, dysmorphic features, cardiac, renal and endocrine dysfunction, and life-threatening with most patients dying in early childhood.

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

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 adeno-associated viral vector serotype 9 containing the human *SURF1* gene, for treatment of Leigh 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 rapporteurs

COMP coordinators were appointed for 16 applications.

## 2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 25 applications for orphan designation.

# 3. Requests for protocol assistance with significant benefit question

## 3.1. Ongoing procedures

### 3.1.1. -

Treatment of soft tissue sarcoma

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 glioma

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 haemophilia A

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

### 3.1.4. -

Treatment of glioma

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 hyperphenylalaninemia

The finalised letter was circulated for information.

### 3.2.2. -

Treatment of polycythaemia vera

The finalised letter was circulated for information.

## 3.3. New requests

### 3.3.1. -

Treatment of multiple myeloma

The new request was noted.

### 3.3.2. -

Treatment of primary hyperoxaluria

The new request was noted.

### 3.3.3. -

Treatment of primary IgA nephropathy

The new request was noted.

### 3.3.4. -

Treatment of multiple myeloma

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. QINLOCK – ripretinib - EMEA/H/C/005614, EU/3/17/1936, EMA/OD/0000057360

Deciphera Pharmaceuticals (Netherlands) B.V; Treatment of gastrointestinal stromal tumours

COMP Rapporteurs: Maria Elisabeth Kalland; Frauke Naumann-Winter

An opinion recommending not to remove QINLOCK, ripretinib, EU/3/17/1936 from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

### 4.1.2. Brukinsa - zanubrutinib - EMEA/H/C/004978/0000, EU/3/19/2167, EMA/OD/0000058248

BeiGene Ireland Limited; Treatment of lymphoplasmacytic lymphoma

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the orphan designation from the EC register of orphan medicinal products, on 28 September 2021.

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

### 4.1.3. Artesunate Amivas – artesunate - EMEA/H/C/005550, EU/3/20/2251, EMA/OD/0000060998

Amivas Ireland Ltd; Treatment of malaria

COMP Rapporteurs: Cecile Dop; Elisabeth Johanne Rook

An opinion recommending not to remove Artesunate Amivas, artesunate, EU/3/20/2251 from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

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

### 4.2.1. – glucarpidase - EMEA/H/C/005467/0000, EMA/OD/049/02, EU/3/02/128, EMA/OD/0000042598

Protherics Medicines Development Europe B.V.; Adjunctive treatment in patients at risk of methotrexate toxicity

The status of the procedure at CHMP was noted.

### 4.2.2. – pegcetacoplan - EMEA/H/C/005553, EU/3/17/1873, EMA/OD/0000072952

Swedish Orphan Biovitrum AB (publ); Treatment of paroxysmal nocturnal haemoglobinuria

The COMP adopted a list of issues that will be sent to the sponsor. The Committee will discuss the submitted answers to the list of issues at the November meeting.

### 4.2.3. – artesunate - EMEA/H/C/005718/0000, EMA/OD/043/15, EU/3/15/1521, EMA/OD/0000063220

B And O Pharm; Treatment of malaria

The status of the procedure at CHMP was noted.

### 4.2.4. - lonapegsomatropin - EMEA/H/C/005367, EU/3/19/2213, EMA/OD/0000059751

Ascendis Pharma Endocrinology Division A/S; Treatment of growth hormone deficiency

The status of the procedure at CHMP was noted.

### 4.2.5. Flynpovi – eflornithine / sulindac - EMEA/H/C/005043/0000, EMA/OD/130/12, EU/3/12/1086, EMA/OD/0000061571

Cancer Prevention Pharma (Ireland) Limited; Treatment of familial adenomatous polyposis

The status of the procedure at CHMP was noted.

## 4.3. Appeal

None

## 4.4. On-going procedures

COMP co-ordinators were appointed for 2 applications.

## 4.5. Orphan Maintenance Reports

None

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

## 5.1. After adoption of CHMP opinion

None

## 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. COMP membership

None

### 7.1.2. Vote by proxy

Ingeborg Barišić gave a proxy to Dinko Vitezic to vote on behalf of Dinko Vitezic during October 2021 COMP meeting.

### 7.1.3. Strategic Review & Learning meeting – joint COMP/PDCO, 19 November 2021, Lisbon, Portugal

The COMP noted the agenda and organisational details of the meeting.

### 7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 1 October 2021.

## 7.2. Coordination with EMA Scientific Committees or CMDh-v

### 7.2.1. Recommendation on eligibility to PRIME – report

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 2021

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

### 7.8.2. Overview of orphan marketing authorisations/applications

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

# 8. Any other business

## 8.1. Update on the development of the database of principal decisions

The COMP discussed the establishment of database of principal decisions and its practical organisation. Furthermore, the topic will be keptin the next year COMP Work Plan.

# 9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 5-7 October 2021 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 via WebEx | Netherlands | No interests declared | |
| Armando Magrelli | Vice-chair via WebEx | Expert recommended by EMA | No interests declared | |
| Brigitte Schwarzer-Daum | Member via WebEx | Austria | No restrictions applicable to this meeting | |
| Tim Leest | Member via WebEx | Belgium | No interests declared | |
| Lyubina Racheva Todorova | Member via WebEx | Bulgaria | No interests declared | |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Dinko Vitezic | Member via WebEx | Croatia | No interests declared | |
| Vasileios Loutas | Member via WebEx | Cyprus | No interests declared | |
| Lenka Gaidadzi | Member via WebEx | Czechia | No interests declared | |
| Elisabeth Penninga | Member via WebEx | Denmark | No interests declared | |
| Vallo Tillmann | Member via WebEx | Estonia | No interests declared | |
| Karri Penttilä | Member via WebEx | Finland | No interests declared | |
| Cecile Dop | Member via WebEx | France | No restrictions applicable to this meeting | |
| Frauke Naumann-Winter | Member via WebEx | Germany | No interests declared | |
| Zsofia Gyulai | Member via WebEx | Hungary | No interests declared | |
| Geraldine O'Dea | Member via WebEx | Ireland | No interests declared | |
| Enrico Costa | Member via WebEx | Italy | No restrictions applicable to this meeting | |
| Irena Rogovska | Member via WebEx | Latvia | No restrictions applicable to this meeting | |
| Aušra Matulevičienė | Member via WebEx | Lithuania | No interests declared | |
| Michel Hoffmann | Member via WebEx | Luxembourg | No interests declared | |
| Robert Nistico | Member via WebEx | Malta | No interests declared | |
| Elisabeth Johanne Rook | Member via WebEx | Netherlands | No interests declared | |
| Maria Elisabeth Kalland | Member via WebEx | Norway | No interests declared | |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Bożenna Dembowska-Bagińska | Member via WebEx | Poland | No restrictions applicable to this meeting | |
| Dinah Duarte | Member via WebEx | Portugal | No interests declared | |
| Olimpia Neagu | Member via WebEx | Romania | No interests declared | |
| Eva Malikova | Member via WebEx | Slovak Republic | No interests declared | |
| Martin Mozina | Member via WebEx | Slovenia | No interests declared | |
| Gloria Maria Palomo Carrasco | Member via WebEx | Spain | No interests declared | |
| Darius Matusevicius | Member via WebEx | Sweden | No restrictions applicable to this meeting | |
| Julian Isla | Member via WebEx | Patients' Organisation Representative | No interests declared | |
| Ines Alves | Member via WebEx | Patients' Organisation Representative | No restrictions applicable to this meeting | |
| Ingeborg Barisic | Member via WebEx | Expert recommended by EMA | No restrictions applicable to this meeting | |
| Giuseppe Capovilla | Member via WebEx | Expert recommended by EMA | No interests declared | |
| Virginie Hivert | Expert via WebEx* | Patients' Organisation Representative | No restrictions applicable to this meeting | |
| Franziska Wolter | Expert via WebEx* | Germany | No interests declared | |
| Selma Arapovic Dzakula | CHMP Alternate via WebEx* | Croatia | No interests declared | |
| Meeting run with support from relevant EMA staff | | | | |

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

# 10. Explanatory notes

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

**Abbreviations / Acronyms**

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission

OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

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

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

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

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

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

Sponsor

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

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

At the time of marketing authorisation, the COMP will check 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/