10 November 2022
EMA/COMP/835868/2022
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 04-06 October 2022

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 Chair opened the meeting by welcoming all participants. Due to the coronavirus (COVID-19) pandemic, 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 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 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.

Restrictions applicable to this meeting are captured in the List of participants included in the minutes.

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. All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of the agenda

The agenda for 04-06 October 2022 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 06-08 September 2022 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. delpazolid - EMA/OD/0000091801

Yes Pharmaceutical Development Services GmbH; Treatment of tuberculosis (TB)

COMP Rapporteur: Eva Malikova

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

- Prevalence

The sponsor provided a prevalence estimate based primarily on the WHO report from 2019 and supportive publications. The European Centre for Disease Control (ECDC) does not appear to have been consulted. The COMP was of the opinion that a broader source of relevant epidemiological studies and registers should be used. A revised estimate should therefore be provided by the sponsor.

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

In the written response, the sponsor provided a revised prevalence estimate. In 2020, a total of 33,148 TB cases have been reported and the incidence for the European region was estimated to be 7.3 per 100,000 population. The number of cases with drug-susceptibility testing (DST) results for all laboratory confirmed TB cases varied between 100% (Cyprus, Denmark, Estonia, Iceland, Lithuania, Malta, Norway, Slovenia, and Sweden) and 3.4% (France). Therefore, the multidrug-resistant tuberculosis (MDR-TB) prevalence for France is likely not reflecting the actual situation as compared to the countries reporting 100% DST results. In total, approximately 3.8 % of all notified TB cases in 2020, for which a DST result was available, were laboratory confirmed MDR-TB and about 28% of these cases are confirmed to be XDR-TB. Generally, successful treatment outcome for TB cases in the EU/EEA is 71.8% after 12 months, this number is lower for MDR-TB (52.4% after 24 months) and even less for extensively drug-resistant tuberculosis (XDR-TB) (38.5% after 36 months) with a higher number of deaths reported amongst these cases (14.5 and 15.4%, respectively) (ECDC/WHO 2022).

The incidence for each country of the EU was used to estimate the prevalence. Taking into account that the treatment duration for drug-susceptible TB is approximately 6 months and that more than 70% of all notified TB cases in 2019 were cured after 1 year, the prevalence was calculated using an average duration of 9 months (ECDC/WHO 2022; WHO 2021). Therefore, the prevalence was estimated according to the following formular:

Prevalence = Incidence per 10,000 x mean duration of disease

According to this calculation, the average prevalence for all EU countries would be 0.5 per 10,000. In their deliberations the COMP noted that the prevalence of tuberculosis continues to drop in Europe and agreed to a prevalence estimate of less than 1 in 10,000. The Committee recommended granting the orphan designation.

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

The intention to treat the condition with the medicinal product containing delpazolid was considered justified based on preliminary clinical data showing an acceptable reduction in early bacterial load.

The condition is chronically debilitating and life-threatening due to haemoptysis, bronchiectasis, diffuse pulmonary destruction, and the possibility of extra-pulmonary infection.

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 delpazolid will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that showed improved reduction in early bacterial load when compared to treatment with standard of care with isoniazid, rifampin, pyrazinamide and ethambutol. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for delpazolid, for treatment of tuberculosis, was adopted by consensus.

2.1.2. iodine (^{124}I) evuzamitide - EMA/OD/0000096114

Regresponse Limited; Diagnosis of AL amyloidosis

COMP Rapporteur: Darius Matusevicius

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:

- Prevalence

The prevalence calculation for a diagnostic should be based on the number of patients potentially expected to be exposed to the diagnostic tool. If the number of persons requiring administration for diagnosis of a condition exceeds the number of persons affected by the condition, then the estimation of fulfilment of the criterion of rarity should be based on the number of persons that are candidates for being administered the product on an annual basis.

The sponsor was specifically asked to clarify the expected use of the product within the overall diagnostic algorithm of the condition. The sponsor was requested to revise their prevalence calculation and final estimate accordingly.

Reference is made to 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) and "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

In the written response, the sponsor presented a revised prevalence calculation for a population that would be possible candidates for utilizing the proposed diagnostic agent (^{124}I) evuzamitide. The revised calculation results in a prevalence estimate of 1.44 persons per 10.000 in the EU. Because patients would not be scanned more frequently than yearly, this figure represents the maximum number of candidates that would be administered (^{124}I) evuzamitide on an annual basis.

The sponsor considers the following three aspects in their revised calculation:

1. Number of patients that have been diagnosed with AL amyloidosis (0.63 per 10,000).
2. Number of patients who have AL amyloidosis but have not been diagnosed (0.62 per 10,000).
3. Calculation Based on Prevalence Estimates from the Amyloidosis Diagnostic Algorithm.

There is only one scenario within the algorithm as per Hasib Sidiqi (2021), where it is anticipated that (^{124}I) evuzamitide PET imaging could be utilized and which is not already covered by the above prevalence estimate approaches 1 and 2: patients with a negative Bone Marrow Biopsies (BMB) + fat biopsy but a strong suspicion for AL amyloidosis, to

either obviate the need for an organ biopsy or to guide the location of the organ biopsy (0.19 per 10,000).

The COMP concluded that the sponsors revised prevalence calculation and final estimate of approximately 1.4 per 10,000 persons in the EU could be acceptable. The planned oral explanation was therefore cancelled.

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

The intention to diagnose the condition with the medicinal product containing iodine (^{124}I) evuzamitide was considered justified based on non-clinical data in a valid model of the condition and based on preliminary clinical data showing sensitivity and specificity of Positron Emission Tomography imaging with the proposed product for the diagnosis of systemic AL amyloidosis.

The condition is chronically debilitating and life-threatening due to the accumulation of fibril deposits which disrupts normal tissue structure and function, notably in the heart, kidneys, liver, peripheral nervous system, gastrointestinal tract, and soft tissues.

The population of patients eligible for diagnosis of the condition was estimated to be approximately 1.4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of diagnosis of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing iodine (^{124}I) evuzamitide will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data showing sensitivity and specificity of Positron Emission Tomography imaging with the proposed product for the diagnosis of systemic AL amyloidosis, including the heart. This cannot be expected from currently available diagnostic methods. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for iodine (^{124}I) evuzamitide, for treatment of diagnosis of AL amyloidosis, was adopted by consensus.

2.1.3. - EMA/OD/0000096494

Treatment of multiple system atrophy

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 12 September 2022, prior to responding to the list of issues.

2.1.4. cannabidiol - EMA/OD/0000097127

EUDRAC GmbH; Treatment of 22q11.2 deletion syndrome (22qDS)

COMP Rapporteur: Ingeborg Barisic

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

- Medical plausibility

The COMP considered that the clinical data presented by the sponsor is very limited. The sponsor was therefore requested to present any additional data that might be available to support medical plausibility for the use of their product in the treatment of 22qDS.

The sponsor was also requested to further contextualize the results from the three patients treated for 6 weeks to allow a decision on this data being possibly indicative of a real treatment effect, considering the uncontrolled nature of the study.

The sponsor was further requested to clarify any concomitant therapies used for the symptomatic treatment in the three patients from the ongoing phase 1/2 study (ZYN2-CL-031).

In the written response, the sponsor presented 14 week efficacy data from their ongoing single-arm, uncontrolled phase 1/2 study (initial application 6 weeks only) on 16 patients (initial application 3 patients only) and for four efficacy outcome measures/scales (initial application 2 scales only). The sponsor compared the individual patient's baseline values to the ones obtained following cannabidiol administration (intra-patient comparison).

Twenty (20) patients were enrolled in the trial, 16 of whom had evaluable data for efficacy analyses at Week 14. Thirteen (13) patients continued into Period 2. The mean age of patients enrolled in the trial was 9.9 (4 to 15) years and twelve (60%) of the patients were male. Findings on medical history at baseline were consistent with a diagnosis of 22qDS and included 60% of patients with congenital abnormalities (e.g. aberrant aortic arch, cleft palate), and 45% with ear and labyrinth disorders (e.g. conductive deafness). A range of psychiatric disorders were present including anxiety, attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) consistent with the literature for 22qDS. Patients enrolled in Study ZYN2-CL-031 receiving any medication were required to be on a stable therapy for 3 months prior to enrolment. Those subjects were permitted to continue their current treatments for 22qDS during their participation in Study ZYN2-CL-031. The sponsor explains that while 14 of the 20 subjects were on concomitant medications, the majority of medications were not for symptomatic treatment of 22qDS.

The following questionnaires and scales were administered during Period 1 at Visit 2 (Day 1), Visit 3 (Week 6) and Visit 4/Early Termination (Week 14):

- Anxiety, Depression and Mood Scale (ADAMS): mean % improvement of total score from baseline of 45.3% (p-value: 0.0005) at week 14. Mean percent improvement across the ADAMS subscales, ranged from 38% to 64% (General Anxiety [45%), Depressed Mood [50%], Social Avoidance [41%], Obsessive/compulsive Behavior [64%, and Manic/hyperactive Behavior [38%]).
- Aberrant Behaviour Checklist -Community (ABC-C): mean percent improvement from baseline to week 14 across the ABC-C subscales, ranged from 16.5% to 52.1%, with mean % improvement in irritability 36.3%, hyperactivity 16.5%, social withdrawal 27.6%, stereotypic behaviour 52.1%, inappropriate speech 18.3%.
- Paediatric Anxiety Rating Scale-Revised (PARS-R): mean % improvement of total score from baseline of 40.6% (p-value: 0.0005) at week 14.
- Clinical Global Impression-Improvement (CGI-I): mean % improvement from baseline to week 14 of 75% (Any Improvement) and 62.5% (Much or Very Much Improved) respectively.

- In conclusion, the results of Period 1 of this open-label trial of children and adolescents aged 4 to 18 years diagnosed with 22qDS show that:
- the proposed product showed a positive trend towards improvement in all efficacy measures (PARS-R, ADAMS, ABC-C, and CGI-I).
- These results support further study of the proposed product in a randomized, well-controlled trial for the treatment of behavioural symptoms of 22qDS in paediatric and adolescent patients.

The COMP considered that the newly available data allowed a positive conclusion on medical plausibility, as there was a generally positive trend in clinically relevant behavioural and mood symptoms over the initial 14 weeks of the phase II study. The planned oral explanation was therefore cancelled.

The Committee agreed that the condition, 22q11.2 deletion 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 was considered justified based on preliminary clinical data suggesting a positive trend in improving behavioural and mood symptoms in treated patients.

The condition is life-threatening and chronically debilitating due to cognitive deficits and behavioural symptoms as well as congenital heart disease, hypocalcaemia, respiratory failure, immunodeficiency due to partial or full athymia, and infections resulting from T cell deficiency.

The condition was estimated to be affecting approximately 3.3 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, for treatment of treatment of 22q11.2 deletion syndrome, was adopted by consensus.

2.1.5. tricaprilin - EMA/OD/0000096942

Veristat Spain S.L.; Treatment of West syndrome

COMP Rapporteur: Julian Isla

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

West Syndrome should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00). It is noted that the recent revision of the classification of the condition as a subset of Infantile epileptic spasms syndrome by the International League Against Epilepsy (ILAE) Task Force on Nosology and Definitions should be further elaborated.

- Life-threatening and debilitating nature of the condition

The sponsor was requested to further elaborate on the life-threatening or chronically debilitating nature of the condition. From the data provided and the sponsor's arguments it was not well substantiated that the condition can be defined as being life-threatening or chronically debilitating.

- Number of people affected

The sponsor provided a prevalence estimate which was primarily based on West Syndrome, however if it is concluded that the condition will be amended to Infantile epileptic spasms syndrome, the sponsor should provide a revised prevalence estimate.

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".

- Significant benefit

If it is concluded that the condition should be amended, the sponsor should address the significant benefit as there are more medicinal products which are authorised treatments for this broader condition.

The sponsor was asked to further elaborate on their current clinical development programme.

- In the written response, the sponsor considered the ILAE reference (Zuberi et al., 2022) provided by the COMP. The sponsor acknowledged its recommendation to consider treating West Syndrome (WS) as a distinct medical entity or a valid subset of Infantile Epileptic Spans Syndrome (IESS). The sponsor indicated that they would like to maintain WS (also referred to as Infantile Spasms (IS) in the United States but not Europe) as a distinct medical condition given its unique and well-defined diagnostic features, namely:
    - onset of epileptic spasms in infancy (typically 3-5 months)
    - distinct EEG pattern (hypsarrhythmia)
    - developmental delay or regression

The sponsor highlighted that the term IESS was proposed by the COMP in line with ILAE to encompass WS as well as infants presenting with epileptic spasms who do not fulfil all the diagnostic criteria for WS. Classically, the criteria for WS are composed of three characteristics: epileptic spasms, hypsarrhythmia, and developmental stagnation or regression. The proposed classification of IESS recognizes that in some cases patients may lack one of these three criteria; for example, the developmental impact may not be apparent or hypsarrhythmia may not be present.

The criteria outlined for IESS by Zuberi et al. list the mandatory criteria for diagnosis which differ from more typical WS criteria. The primary differences are in EEG findings and comorbidities. For EEG, IESS includes multifocal or focal epileptiform discharges in addition to hypsarrhythmia. For comorbidities IESS allows for developmental slowing after spasms onset to be absent.

The COMP discussed the arguments raised by the sponsor and deliberated on the applicability of the ILAE 2022 revision where epileptic symptoms are given more prominence than the concept of syndrome. In their conclusions the COMP accepted the

sponsor's argumentation regarding the uniqueness of WS and agreed to continue accept it as an orphan condition. As a result, the remaining questions raised were considered resolved and the oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing tricaprilin was considered justified based on non-clinical in vivo data showing a dose-dependent reduction in spasms associated with the condition.

The condition is chronically debilitating in particular due to the recurrence of epileptic seizures and long-term developmental disabilities, cognitive impairment and psychiatric symptoms and can be life threatening.

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 tricaprilin will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate that the product could be used to treat spasms which do not respond to currently authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tricaprilin, for treatment of West syndrome, was adopted by consensus.

2.1.6. propranolol - EMA/OD/0000096322

Mario Negri Institute For Pharmacological Research; Treatment of familial Cerebral Cavernous Malformation (fCCM)

COMP Rapporteur: Michel Hoffmann

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 familial cerebral cavernous malformation the sponsor was requested to further elaborate on:

- the in vivo non-clinical data presented, specifically considering that the positive effect of propranolol appears to be limited to a prophylactic use in the experimental model with no apparent effect on the already formed lesions;
- the relevance of the clinical data presented given the low number of events, and the claim that the hazard ratio observed could be interpreted as a promising signal.

In the written response, and during an oral explanation before the Committee on 4 October 2022, the sponsor’s response included, amongst others, the following arguments/data.

Regarding the available in vivo non-clinical data in models of the condition, and the questions raised on the prophylactic use of the proposed product, the sponsor elaborated on

the previously introduced studies from Li et al., 2021 and Oldenburg et al., 2021. In this study from Oldenburg et al., 2021, propranolol reduced the number of cerebellum lesions, and increased pericyte coverage. However, when propranolol treatment was started at postnatal day 14, no effect on lesion number or area was observed. This suggests that propranolol reduced new lesions but did not have an impact on the existing ones. In order to justify the lack of effect on the therapeutic setting, the sponsor emphasised that when propranolol treatment was started, in the non-clinical in vivo model, CCM lesions were absent or very low, so that the effect of the treatment on a pre-existing lesion was challenging to determine. In addition, it was further emphasised the inherent challenges associated with this type of CCM model, which could be restrictive in the possibility of examining the use of propranolol in the treatment modality. These arguments could be considered of particular relevance for the medical plausibility justification.

Regarding the relevance of the clinical data presented and the low number of events in both primary endpoints, the sponsor pointed at the exploratory nature of the clinical study given the longer follow-up needed to observe a meaningful effect. As part of the argumentation, the sponsor estimated a 10.1% 2-year risk of the primary outcome in fCCM patients with standard care (Horne et al, 2016). Assuming a 50% reduction of clinical events with propranolol, the sponsor estimates that at least 834 patients (556 propranolol: 278 control) would have been needed to achieve a study powered at a significance level, which in the sponsor's view would constitute an unrealistic scenario. However, in the presented pilot study with 83 patients randomised in a 2:1, a clinically meaningful effect, would be excluded by the defined upper confidence interval. The sponsor concluded that the hazard ratio observed and the de novo CCM could serve as a promising signal instead. However, given the exploratory nature of the study, such arguments were not accepted by the committee.

In conclusion, while the sponsor's clarifications are not considered to address all uncertainties in regard to the clinical data presented, the COMP considered the totality of the data to be sufficient to fulfil the requirements for an initial orphan designation in the applied condition.

The COMP recommended the sponsor to seek EMA protocol assistance on their future planned development.

The Committee agreed that the condition, familial cerebral cavernous malformations, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing propranolol was considered justified based on non-clinical data from a valid model demonstrating a stabilization in the vasculature, as shown by reduction on the cerebrovascular lesions size and number, and preliminary clinical data that indicate a potential effect on the cerebral cavernous malformation brain lesions.

The condition is chronically debilitating due to focal seizures and various neurological deficits determined by the localisation of the lesion, and life-threatening due to severe brain or brainstem haemorrhage.

The condition was estimated to be affecting approximately 3 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 propranolol, for treatment of familial cerebral cavernous malformations, was adopted by consensus.

2.1.7. atorvastatin - EMA/OD/0000096338

Mario Negri Institute For Pharmacological Research; Treatment of familial Cerebral Cavernous Malformation (fCCM)

COMP Rapporteur: Michel Hoffmann

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 familial cerebral cavernous malformations the sponsor was requested to further elaborate on:

- the in vivo non-clinical data presented, specifically considering that the positive effect of atorvastatin appears to be limited to a prophylactic and not therapeutic effect on the model of the condition;
- the clinical data presented, considering that efficacy results are not presented for the specific subset of patients receiving atorvastatin, and that a variety of add-on therapies that are not specified were included in the study.

In the written response, and during an oral explanation before the Committee on 4 October 2022, the sponsor presented their position. The sponsor elaborated on the mechanism of action of the proposed product based on the available non-clinical data in models of the condition. The sponsor indicated that loss of the CCM complex leads to the gain of endothelial MEKK3 signalling that in turn leads to overexpression of downstream transcription factors KLF2 and KLF4 and to an increase in Rho-associated protein kinase (ROCK) activity. ROCK is therefore a therapeutic target candidate in CCM to decrease lesion burden. Along this line, atorvastatin has been tested initially in models of less severe CCM disease, CCM1 and CCM2. As part of the non-clinical studies, it was clarified that lesion burden was halved by atorvastatin compared with placebo control. Further, mean non-haem iron deposition in lesions decreased by 70% with atorvastatin compared to placebo. These results could indicate that inhibitors of ROCK may not only decrease the number of lesions, but also inhibit haemorrhages through a decrease in endothelial permeability. These arguments could be considered of particular relevance for the medical plausibility justification. Regarding the relevance of the clinical evidence presented, the sponsor acknowledged the difficulty to interpret the data considering the wide variety of medicines used in the patient population, such other statins, and a variety of add-on therapies. The clinical justification was therefore not accepted by the committee, and the focus was placed exclusively on the non-clinical data.

In conclusion, while the sponsor's clarifications are not considered to address all uncertainties such as those on the clinical evidence, the COMP considered the totality of the data to be sufficient to fulfil the requirements for an initial orphan designation in the applied condition.

The COMP recommended the sponsor to seek EMA protocol assistance on their future planned development.

The Committee agreed that the condition, familial cerebral cavernous malformations, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing atorvastatin was considered justified based on non-clinical data from a valid model demonstrating a reduction on the lesion burden and inflammatory cell infiltration, and recurrent haemorrhage.

The condition is chronically debilitating due to focal seizures and various neurological deficits determined by the localisation of the lesion, and life-threatening due to severe brain or brainstem haemorrhage.

The condition was estimated to be affecting approximately 3 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 atorvastatin, for treatment of familial cerebral cavernous malformations, was adopted by consensus.

2.1.8. pegcetacoplan - EMA/OD/0000096917

Apellis Ireland Limited; Treatment of C3 glomerulopathy (C3G) with and without immune complexes

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:

- Condition

The sponsor was requested to justify for this targeted therapy that the proposed condition is a separate disease entity or a valid subset of the already accepted orphan designation for this product of '*Treatment of C3 glomerulopathy*". The symptoms, prognosis, and the presence of complement component 3 (C3) pathway abnormalities in both disorders are largely overlapping, and transitions from C3G to immune-complex membranoproliferative glomerulonephritis (IC-MPGN) and vice versa in biopsies have been observed in patient cohorts.

In the written response, and during an oral explanation before the Committee on 5 October 2022, the sponsor emphasised that according to current scientific literature and within the nephrology community primary IC-MPGN is a separate disease entity from C3 glomerulopathy (Fakhouri 2020; KDIGO 2021).

However, the sponsor also agreed that the IC-MPGN population is rather heterogenous. More recent data suggests that primary IC-MPGN derives not only from immune complex (IC)-triggered classical pathway (CP) activation but that an underlying complement deficiency can also be present in the setting of IC deposits and therefore complement dysregulation (including complement alternative pathway) may also play a key role in primary IC-MPGN disease pathophysiology (Fakhouri 2020; Kirpalani 2020; Noris 2021; KDIGO 2021; Iatropoulos 2018). As the field matures, C3G and primary IC-MPGN may someday be viewed as separate diseases under a single umbrella term.

Based on these considerations the COMP concluded that "treatment of C3 glomerulopathy with and without immune complexes" is a more suitable condition wording, for the purpose of an orphan designation for this C3 targeting therapy.

The COMP emphasised that this new orphan condition covers patients with C3 glomerulopathy and patients with primary or idiopathic immune complex membranoproliferative glomerulonephritis that are considered eligible for treatment with pegcetacoplan, i.e. those with C3 deposits and/or low circulating serum C3 levels.

Following review of the application by the Committee, it was agreed to rename the indication to treatment of C3 glomerulopathy with or without immune complexes.

The Committee agreed that the condition, C3 glomerulopathy with or without immune complexes, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing pegcetacoplan, was considered justified based on preliminary clinical data showing elevation of serum C3 levels and reduction in proteinuria.

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

The condition was estimated to be affecting approximately 1.3 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 pegcetacoplan, for treatment of treatment of C3 glomerulopathy with or without immune complexes, was adopted by consensus.

2.1.9. - EMA/OD/0000088236

Treatment of ovarian cancer

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

- Intention to diagnose, prevent or treat

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of ovarian cancer the sponsor should further elaborate on the results of the monotherapy treatment in the applied condition and provide, if any available, non-clinical data or any comparative data with placebo on top of baseline therapy.

- Number of people affected

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

The COMP considered the proposed incidence is underestimated and taking into account that the current prevalence is close to threshold of 5 in 10,000 the sponsor should re-calculate the prevalence and perform a sensitivity analysis of the reported calculations.

- 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 since the data used for the indirect comparisons were based on the combination and not the monotherapy treatment.

In the written response, and during an oral explanation before the Committee on 5 October 2022, the sponsor focused on the results from the study, which showed according to the sponsor that the combination with pembrolizumab, provided a clinically meaningful effect in a similar patient population to that studied in the different study, with an ORR of 28.6% and a durable response of 54 weeks. In addition the sponsor referred the evidence of the anti-tumour activity of IL-2 that has been reported to literature.

However, the COMP considered that as the effects cannot be clearly attributed to the proposed product, based on the very limited data with the proposed product as monotherapy the medical plausibility cannot be justified.

Regarding the updated calculation of the prevalence provided by the sponsor, a sensitivity analyses resulted in adjusted prevalence in the range of 4.6 to 4.8 per 10,000 depending on how tumours were defined, and the source of data used. The COMP agreed with the methodology used and considered that the prevalence is 4.9 per 10,000 which is very close to the sponsor' proposed figure (4,8 per 10,000).

Finally, the arguments on the significant benefit were based on the preliminary clinical evidence of the pembrolizumab combination therapy, with a reported ORR of 28.6% and a DCR of 71.4%. In addition, the observed responses were durable, with a median DOR of 12.4 months (54 weeks). The data from the study demonstrated that pembrolizumab monotherapy had modest benefit in the PROC patient population with an ORR of 9.9% and a DCR of 37.4% reported in heavily pre-treated patients. However, the COMP considered that the ORR observed in another study was on a combination treatment and the effects cannot be clearly attributed to the proposed product and the argument on the significant benefit is not acceptable.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 5 October 2022, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000082375

Treatment of ovarian cancer

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 2022 meeting.

2.2.2. - EMA/OD/0000091248

Treatment of haemophilia B

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 2022 meeting.

2.2.3. copper nanocluster conjugated to acetate, histidinate and ascorbate - EMA/OD/0000095176

Satt Sayens; Treatment of Menkes disease

COMP Rapporteur: Giuseppe Capovilla

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

The intention to treat the condition with the medicinal product containing copper nanocluster conjugated to acetate, histidinate and ascorbate was considered justified based on non-clinical in vivo data in a valid model of the condition showing improvements in brain physiology and mitochondrial respiratory chain activity, movement coordination and motor skills, fur pigmentation and survival.

The condition is chronically debilitating in particular due to progressive neurodegeneration and marked connective tissue dysfunction with vascular, urogenital, and skeletal abnormalities. The condition is also life-threatening with death before the third year of life in the most severe cases.

The condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for copper nanocluster conjugated to acetate, histidinate and ascorbate, for treatment of Menkes disease, was adopted by consensus.

2.2.4. - EMA/OD/0000096261

Treatment of progressive supranuclear palsy

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the November 2022 meeting.

2.2.5. - EMA/OD/0000096686

Diagnosis of ATTR amyloidosis

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 2022 meeting.

2.2.6. - EMA/OD/0000096688

Treatment of autosomal dominant polycystic kidney disease (ADPKD)

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 2022 meeting.

2.2.7. rovatirelin - EMA/OD/0000096385

MDC RegAffairs GmbH; Treatment of spinocerebellar ataxia

COMP Rapporteur: Robert Nistico

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

The intention to treat the condition with the medicinal product containing rovatirelin was considered justified based on non-clinical data showing improved locomotor activity in a valid model of the condition and also based on published clinical data indicating an improvement of scale for the assessment and rating of ataxia scores in patients with spinocerebellar ataxia.

The condition is chronically debilitating due to slowly progressive incoordination of gait which is often associated with poor coordination of hands, speech and eye movements.

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.

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 rovatirelin, for treatment of spinocerebellar ataxia, was adopted by consensus.

2.2.8. adeno-associated viral vector serotype 9 containing the human *ABCD1* gene - EMA/OD/0000098317

Voisin Consulting Life Sciences; Treatment of adrenoleukodystrophy

COMP Rapporteur: Giuseppe Capovilla

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 adeno-associated viral vector serotype 9 containing the human *ABCD1* gene was considered justified based on data on a non-clinical model of the condition showing improvement in biochemical markers and functional performance in the grip strength test.

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 sexual dysfunction, progressive stiffness and gait disturbance, sphincter dysfunction leading to incontinence, 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.

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 *ABCD1* gene, for treatment of adrenoleukodystrophy, was adopted by consensus.

2.2.9. - EMA/OD/0000098623

Treatment of gastro-entero-pancreatic neuroendocrine tumours

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 2022 meeting.

2.2.10. (R)-deuteropioglitazone hydrochloride - EMA/OD/0000098673

Poxel; Treatment of adrenoleukodystrophy

COMP Rapporteur: Darius Matusevicius

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 (R)-deuteropioglitazone hydrochloride was considered justified based on non-clinical in vivo data in a model of the condition showing improvements in open field neurologic test scores (total distance and freezing time).

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 sexual dysfunction, progressive stiffness and gait disturbance, sphincter dysfunction leading to incontinence, 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.

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 (R)-deuteropioglitazone hydrochloride, for treatment of adrenoleukodystrophy, was adopted by consensus.

2.2.11. N-(4-(4-amino-5-(3-fluoro-4-((4-methylpyrimidin-2-yl)oxy)phenyl)-7-methyl-7H-pyrrolo[2,3-d] pyrimidin-6-yl)phenyl)methacrylamide hydrochloride - EMA/OD/0000099049

EUDRAC GmbH; Treatment of biliary tract cancer

COMP Rapporteur: Jana Mazelova

Following review of the application by the Committee, it was agreed to rename the indication to treatment of biliary tract cancer.

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

The intention to treat the condition with the medicinal product containing N-(4-(4-amino-5-(3-fluoro-4-((4-methylpyrimidin-2-yl)oxy)phenyl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenyl)methacrylamide hydrochloride was considered justified based on durable tumour responses observed in FGFRi-naïve and FGFR2 fusion+ patients with cholangiocarcinoma.

The condition is chronically debilitating due to development of hepatic insufficiency, progressive biliary obstruction followed by complications such as infections, and life-threatening with a low overall median survival of less than one year following diagnosis.

The condition was estimated to be affecting approximately 1.7 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 N-(4-(4-amino-5-(3-fluoro-4-((4-methylpyrimidin-2-yl)oxy)phenyl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenyl)methacrylamide hydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the proposed product is effective in patients who have been pre-treated with the currently authorised treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for N-(4-(4-amino-5-(3-fluoro-4-((4-methylpyrimidin-2-yl)oxy)phenyl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenyl)methacrylamide hydrochloride, for treatment of biliary tract cancer, was adopted by consensus.

2.2.12. - EMA/OD/0000099136

Treatment of perinatal asphyxia

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 2022 meeting.

[Post-meeting note: The sponsor withdrew the application for orphan designation on 21October 2022].

2.2.13. adeno-associated virus serotype 5 vector encoding C1-esterase inhibitor - EMA/OD/0000099342

Biomarin International Limited; Treatment of hereditary angioedema

COMP Rapporteur: Elisabeth Penninga

The Committee agreed that the condition, hereditary angioedema, 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 virus serotype 5 encoding C1-esterase inhibitor was considered justified based on non-clinical data in a valid disease model demonstrating reductions in vascular permeability.

The condition is life-threatening and chronically debilitating due to recurrent attacks of oedema in various parts of the body that may cause airway obstruction leading to asphyxia.

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 adeno-associated virus serotype 5 encoding C1-esterase inhibitor will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a valid disease model demonstrating a durable effect on

normalizing C1-INH levels following a single administration. This cannot be expected from currently authorized medicinal products, which necessitate repeated administrations. The Committee considered that this could translate into a clinically relevant advantage.

A positive opinion for adeno-associated virus serotype 5 encoding C1-esterase inhibitor, for treatment of hereditary angioedema, was adopted by consensus.

2.2.14. - EMA/OD/0000099427

Treatment of small cell lung cancer

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 2022 meeting.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

2.5.1. melatonin - EMA/OD/0000103671

Treatment of retinopathy of prematurity

An oral explanation took place before the Committee on 4 October 2022.

A negative trend of COMP was observed by consensus.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the appeal, on 5 October 2022, prior to final opinion.

2.6. Nominations

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

COMP rapporteurs were appointed for 15 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 17 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment in solid organ transplantation

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

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. Zynlonta – loncastuximab tesirine - EMEA/H/C/005685, EU/3/21/2481, EMA/OD/0000094879

ADC Therapeutics (NL) B.V.; Treatment of diffuse large B-cell lymphoma

COMP Rapporteurs: Frauke Naumann-Winter; Maria Elisabeth Kalland

A list of issues was adopted on 8 September 2022.

An oral explanation was held on 4 October 2022.

An opinion recommending the removal of Zynlonta, loncastuximab tesirine for treatment of diffuse large B-cell lymphoma (EU/3/21/2481) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

4.1.2. Mycapssa - octreotide acetate - EMEA/H/C/005826/0000, EU/3/13/1170, EMA/OD/0000086000

Amryt Pharmaceuticals Designated Activity Company; Treatment of acromegaly

COMP Rapporteurs: Vallo Tillmann; Lyubina Racheva Todorova

A list of issues was adopted on 8 September 2022.

The oral explanation scheduled on 4 October 2022, was cancelled.

An opinion recommending not to remove Mycapssa, octreotide acetate (oral use) for treatment of acromegaly (EU/3/13/1170) 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. Livmarli – maralixibat - EMEA/H/C/005857, EU/3/13/1214, EMA/OD/0000078931

Mirum Pharmaceuticals International B.V.; Treatment of Alagille syndrome

COMP Rapporteurs: Elisabeth Johanne Rook; Olimpia Neagu

An opinion recommending not to remove Livmarli, maralixibat, EU/3/13/1214 from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

[Post-meeting note: The COMP adopted the opinion by written procedure following its October 2022 meeting.]

4.2.2. – etranacogene dezaparvovec - EMEA/H/C/004827, EU/3/18/1999, EMA/OD/0000087180

CLS Behring GmbH; Treatment of haemophilia B

The status of the procedure at CHMP was noted.

4.2.3. Ebvallo – tabelecleucel - EMEA/H/C/004577, EU/3/16/1627, EMA/OD/0000076907

Atara Biotherapeutics Ireland Limited; Treatment of post-transplant lymphoproliferative disorder

COMP Rapporteurs: Karri Penttila; Frauke Naumann-Winter

An opinion recommending not to remove Ebvallo, tabelecleucel, EU/3/16/1627 from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

[Post-meeting note: The COMP adopted the opinion by written procedure following its October 2022 meeting.]

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 10 applications.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

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

5.1. After adoption of CHMP opinion

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

None

7.1.3. Strategic Review & Learning meetings

Feedback was noted from the COMP SRLM under the Czech Presidency of the Council of the EU held F-2-F on 21-23 September 2022 in Bonn, Germany.

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 3rd October 2022.

7.1.5. Principal Decisions Database

Document tabled:

The COMP acknowledged the importance of adding further topics to the database.

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)

Documents were tabled for information.

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

Documents were tabled for information.

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)

There was an update provided on the orphan cluster meeting with FDA and its implementation of the US Federal Act for Amyotrophic Lateral Sclerosis.

Another update was provided on FDA and recent developments in the US regarding Diffuse large B-cell lymphoma (DLBCL) prevalence.

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 2022

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2022 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. Real World Evidence (RWE) update

The deputy director of the DARWIN EU® Coordination Centre, presented an update on the DARWIN EU® establishment and use of RWE, and the available standard analyses. There were exchanges on how COMP could request studies using DARWIN EU® and the suitability of the data sources to be onboarded in the network.

Further information on DARWIN EU® and its Advisory Board can be found here: https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu#advisory-board-section

8.2. Follow up on expert consultation group on Inherited Retinal Dystrophies (IRD)

The COMP undertook a review to ascertain the state of the art in Inherited Retinal Diseases (IRD) for 'conditions' and what would be the best set of condition terms for Orphan Designation. The review included a literature review, overview of previous OD in IRDs and an expert consultation.

Based on in depth consideration, supported by the outcome of the expert and consultation, the COMP adopted a new approach for designating conditions in IRDS. The COMP decided that three options should be available for conditions for orphan designation depending on the application. The updated COMP recommendations will be published on the EMA website.

The three approaches that will be available for COMP to designate as conditions in IRD depending on the application are as follows:

- For therapies that are relatively broadly applicable in IRDs, terms in table 1 below offer a new strategy for orphan designated conditions for these kinds of products. This does not preclude the need for multiple orphan designations if a particular broad therapy could target more than one group. Setting the condition at the term level (e.g. *Cone-dominant phenotype)* is the expectation.

- For targeted gene therapies, the condition can include the term "inherited retinal diseases" plus the gene target to ensure that the broadest applicable scope of treatable patients will be included.
- Finally, occasional singular orphan designations outside the Box 1 structure may still be necessary for non-gene therapy products as some conditions which are recognised as IRDs do not fit the Box 1 ontology (ex. X-linked retinoschisis).

Sponsors should fully justify the chosen approach to setting the condition in the orphan designation application which will be reviewed by COMP. Sponsors with existing ODs in IRD are requested to amend their OD before Marketing Authorisation or protocol assistance in case the old designation would not cover the intended target patient population

Table 1 clinical grouping for Inherited retinal diseases for the purpose of orphan designation

1. Non-syndromic IRD
1.1. *Cone-dominant phenotype*
1.2. Rod-dominant phenotype
1.3. Macular dystrophy
2. Syndromic IRD
2.1. *Cone-dominant phenotype*
2.2. Rod-dominant phenotype
2.3. Macular dystrophy
3. Inherited choroidal dystrophies
4. Hereditary vitreoretinopathies

8.3. Innovative therapies project

The working group presented the project. The project aims to provide a description of the data to support the medical plausibility used for the various types of innovative products. The next steps are to draft a manuscript for the first set of products analysed and continue to collect data for the subsequent products.

9. List of participants

including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 04-06 October 2022 meeting.

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Chair	Netherlands	No interests declared	
Armando Magrelli	Member (Vice-Chair)	Expert recommended by EMA	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No restrictions applicable to this meeting	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Elli Loizidou	Member	Cyprus	No interests declared	
Jana Mazelova	Member	Czechia	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Cecile Dop	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Zsofia Gyulai	Member	Hungary	No interests declared	
Enrico Costa	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No restrictions applicable to this meeting	
Michel Hoffmann	Member	Luxembourg	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Robert Nistico	Member	Malta	No restrictions applicable to this meeting	
Elisabeth Johanne Rook	Member	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Joao Rocha	Member	Portugal	No restrictions applicable to this meeting	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Ines Alves	Member	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on:	2.2.13. adeno-associated virus serotype 5 vector encoding C1-esterase inhibitor - EMA/OD/0000099342 Biomarin International Limited; Treatment of hereditary angioedema
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Maria Cavaller Bellaubi	Expert - in Webex*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Marika van Leeuwen	Expert - via Webex*	Netherlands	No restrictions applicable to this meeting	
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 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/