16 April 2015
EMA/COMP/105033/2015
Procedure Management and Business Support Division

# Committee for Orphan Medicinal Products (COMP)

## Minutes of the 17-19 March 2015 meeting

Some documents mentioned in the agenda/minutes cannot be released at present within the framework of Regulation (EC) No 1049/2001 on access to documents because 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** Adoption of the agenda, EMA/COMP/105029/2015

The agenda was adopted with no amendments.

**1.2** Adoption of the minutes of the previous meeting, 10-12 February 2015 EMA/COMP/25297/2015

The minutes were adopted with no amendments.

**1.3** Declaration of conflicts of interest

In accordance with the Agency's Policy and Procedure on the handling of conflicts of interests, participants in this meeting were asked to declare any conflict of interests on the matters for discussion (in particular any changes, omissions or errors to the already declared interests). No new or additional conflicts of interest were declared.

# 2. Applications for orphan medicinal product designation[1]

## 2.1. For opinion

**2.1.1 Human reovirus type 3 Dearing strain** for treatment of pancreatic cancer, Oncolytics Biotech (UK) Limited - EMA/OD/302/14
*[COMP co-ordinator: B. Bloechl-Daum]*

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of pancreatic cancer, the sponsor should further elaborate on the preliminary clinical studies and the results from these studies with regards to any effects that can be attributed to the product. Any updated information available from these studies should be presented to the COMP.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potentially improved efficacy in the condition.

The sponsor should detail the results of any clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of patients. A discussion of the population where add-on effects have been observed should be clearly described.

In the written response, and during an oral explanation before the Committee on 17 March 2015, the sponsor further elaborated on the available clinical studies and provided updated results regarding progression free survival and overall survival when the product was added on to gemcitabine. The sponsor compared these results with literature clinical studies regarding mono-therapy with

[1] The procedures under assessment discussed by the COMP are considered confidential. COMP meeting reports and subsequent minutes will contain additional details on these procedures once these are finalised. Access to documents in relation to these procedures is possible after marketing authorisation is granted according to the Agency policy on access to documents (EMA/127362/2006).

gemcitabine, and based on this indirect comparison argued that there are improved effects that can be attributed to the addition of product under review.

The COMP reflected on the comparability of the populations between the referenced literature studies and the sponsor's results, and on the new mechanism of action in the context of the results observed. Overall, the medical plausibility and significant benefit were considered acceptable since the trends of the preclinical and clinical studies were pointing towards an improved efficacy in combination with authorised products for the condition.

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 human reovirus type 3 Dearing strain was considered justified based on preclinical data in models of the condition and preliminary clinical data showing improved survival in treated patients affected by the condition.

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

The condition was estimated to be affecting less than 2 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing human reovirus type 3 Dearing strain may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data in models of the condition and preliminary clinical data that support improved survival when the product is combined with currently available products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for human reovirus type 3 Dearing strain for treatment of pancreatic cancer was adopted by consensus.

### **2.1.2** Product for treatment of follicular lymphoma - EMA/OD/275/14

*[COMP co-ordinator: B. Bloechl-Daum]*

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

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and in particular to elaborate on the potential clinically relevant advantage of the proposed product in relation to rituximab and to idelasib.

The sponsor is also invited to present any available preclinical and/or clinical data supporting the claim of significant benefit in the context of the current therapeutic management of patients, including rituximab and idelasib.

In the written response, and during an oral explanation before the Committee on 17 March 2015, the sponsor discussed the pharmacological target, pharmacokinetics and pharmacodynamics of the product vis a vis the authorised counterparts. It was argued that the product as a monotherapy appears to have a broad spectrum of activity in indolent and aggressive non-Hodgkin lymphomas including

patients with advanced, heavily pre-treated follicular lymphoma. The sponsor also discussed what was viewed as a favourable safety profile, with transient adverse effects.

The COMP considered that in the absence of direct or indirect data-driven comparisons supporting a clinically relevant advantage or major contribution to patient care in the context of the available treatments, the assumption of significant benefit could not be considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 March 2015, prior to final opinion.

### **2.1.3** Product for treatment of Leber congenital amaurosis - EMA/OD/309/14

*[COMP co-ordinator: A. 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:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Leber congenital amaurosis (LCA), the sponsor should further elaborate on:

  - the particulars of the formulation used, including proof of absence of effects of the vector alone in the studied settings
  - the relevance of the preclinical models used for the treatment of Leber congenital amaurosis, and the interpretation of the results obtained in the experiments,
  - the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition.

In the written response, and during an oral explanation before the Committee on 17 March 2015, the sponsor provided additional explanations on the basis of using retinitis pigmentosa models to draw conclusions for the proposed condition as applied for designation. This bridging was based on the early onset of retinal degeneration, and the rapid evolution and severity of the phenotype in the used models. In addition, the commonalities between retinitis pigmentosa and leber's congenital amaurosis were further elaborated, in particular on the grounds that several different genetic mutations affect cyclic GMP signalling pathways. The sponsor acknowledged that there were animal models of LCA that had not been used.

The COMP considered that that specific models for the proposed condition as applied for designation have not been used and that the medical plausibility could not be therefore considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 March 2015, prior to final opinion.

### **2.1.4** Product for treatment of systemic sclerosis - EMA/OD/306/14

*[COMP co-ordinator: K. Westermark]*

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

- Intention to diagnose, prevent or treat

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

- the data generated from the preclinical model used, its relevance for the treatment of systemic sclerosis and the interpretation of the results obtained in the experiments.

- Number of people affected

The prevalence calculation appears to be quite low and it appears that there are some methodological issues regarding its calculation.

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

For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

- Significant benefit

The sponsor proposes that the product offers an alternative mode of action.

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

In the written response, and during an oral explanation before the Committee on 17 March 2015, the sponsor elaborated on studies performed with the proposed product in a preclinical model of delayed type hypersensitivity. The sponsor reported that administration of the product prior to the hypersensitivity challenge reduces cumulative inflammatory score. The sponsor also provided an updated prevalence calculation and assumed that a significant benefit may be expected by an alternative mechanism of action.

The COMP considered that in the absence of data in a specific model of the condition with the proposed product as applied for designation, the medical plausibility could not be considered justified. In addition, no data have been submitted that would allow for a translation of an alternative mechanism of action to a clinically relevant advantage or major contribution to patient care.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 March 2015, prior to final opinion.

### 2.1.5 **Rintatolimod** for treatment of Ebola virus disease, NV Hemipsherx BioPharma Europe - EMA/OD/310/14

*[COMP co-ordinator: A. Lhoir]*

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

- Intention to diagnose, prevent or treat

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

- the relevance of the results obtained in HIV to the proposed indication "treatment of Ebola virus disease";

- the methodology of the *in vitro* experiments on the Hela cell line, and the clinical relevance of the results;
- the evidence that binding of the proposed product to the VP35 protein of Ebola virus would result in displacing the native viral dsRNA, and the evidence that when this happens, it would translate into an activity of the product. In relation to this the sponsor is also invited to explain the scientific rationale and supporting literature of the hypothesis that the displaced Ebola viral dsRNA would induce an immune response;
- the details of the methodology and of the results of the experiments on the Ebola minigenome.

In the written response, and during an oral explanation before the Committee the sponsor presented additional data for consideration to the COMP. The data included more details on the inhibition of the Ebola minigenome in human embryonic stem cells, and new data on a preclinical model using an adapted Ebola virus, reporting a significant survival advantage for the treated subjects.

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

The intention to treat the condition with the medicinal product containing rintatolimod was considered justified based on preclinical data showing increased survival in models of Ebola virus infection.

The condition is life-threatening due to severe, fluid-depleting diarrhoea leading to hypotension and shock, with diffuse haemorrhage in the severe forms of the disease.

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

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

A positive opinion for rintatolimod, for treatment of Ebola virus disease, was adopted by consensus.

### 2.1.6 **Rimeporide** for treatment of Duchenne muscular dystrophy, EUDRAC Limited - EMA/OD/307/14

*[COMP co-ordinator: P. Evers]*

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Duchenne muscular dystrophy, the sponsor should further elaborate on:

- the results obtained in preclinical studies. The sponsor should describe the experimental set-up and study outcomes in more detail and elaborate on numbers of mice per treatment groups, how presented figures were derived, details on histological assessment, as well as any available data on functional outcomes in valid preclinical models of the condition.

In the written response, and during an oral explanation before the Committee on 18 March 2015, the sponsor further elaborated on the validity of the preclinical settings and provided new data from a long-term study in one of those models.

With regards to using a sarcoglycan deficient preclinical model, the sponsor stressed that dystrophin and sarcoglycans are part of the same complex connecting the muscle cell cytoskeleton to the extracellular matrix. Therefore, the commonly used dystrophin null model and the delta sarcoglycan-null model share a common pathogenic basis. Further, the sponsor referred to literature data supporting the commonalities across muscular dystrophies in particular through a shared calcium dependent mechanism.

With regards to the additional data provided, the sponsor reported the results of a 41 week study showing histological improvements in terms of muscle inflammation, fibrosis and fibre diameter in a variety of muscles. It was noted that this study does not confirm any functional endpoints in terms of muscle strength measurements, but this was attributed to the mild phenotype and the effects of the product that would be expected to slow muscle wasting.

The COMP considered that the preclinical model used was relevant for the orphan application in question, based on the pathogenetic mechanism and the phenotype of cardiomyopathy.

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

The intention to treat the condition with the medicinal product containing rimeporide was considered justified based on preclinical data with the product showing improved histopathological outcomes in a specific model of the condition, which were further supported by an increase in survival in a relevant cardiomyopathy preclinical model.

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

The condition was estimated to be affecting 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing rimeporide may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data supporting improved histological and survival outcomes which are not limited to a specific mutation, thereby targeting a broader patient population. The Committee considered that this constitutes a clinically relevant advantage.

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

### **2.1.7** Product for treatment of Duchenne muscular dystrophy - EMA/OD/257/14

*[COMP co-ordinator: P. Evers]*

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Duchenne muscular dystrophy, the sponsor should further elaborate on:

- the results obtained in preclinical studies. The sponsor should describe study outcomes in more detail and present data from all different treatment groups, different doses, etc.
- any available data on functional outcomes in valid preclinical models of the condition;

In the written response, and during an oral explanation before the Committee on 18 March 2015, the sponsor elaborated on the anabolic effects of this product in healthy preclinical settings, in terms of both body weight gain and increases in muscle volume. The sponsor also discussed results in a valid preclinical model of the proposed condition, and reported increased lower leg muscle volume but without any effects in functional endpoints such as grip strength.

The COMP considered that in the absence of clinically relevant functional endpoints in a valid model of the condition, it would be difficult to justify the medical plausibility, and consequently also the significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 March 2015, prior to final opinion.

### 2.1.8 **Recombinant monoclonal anti- T cell immune response cDNA 7 - IgG1 – antibody** for prevention of organ rejection following solid organ transplantation, Nekonal S.a.r.l. - EMA/OD/308/14

*[COMP co-ordinator: K. Westermark]*

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of organ rejection following solid organ transplantation, the sponsor should further elaborate on:

- the relevance of the bibliographical data submitted regarding the sponsor's proposed product. The bibliographical data submitted is based on similar but different products and the results obtained may be different for the sponsor's proposed product had it been used;
- the sponsor should clearly indicate if they have a product with which they could do similar studies.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the comparative pre-clinical study with tacrolimus to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. The relevance of these results should be presented within the context of their proposed product and the lack of efficacy seen with tacrolimus.

In the written response, and during an oral explanation before the Committee on 18 March 2015, the sponsor further addressed the issues raised. In particular with regards to significant benefit it was proposed that the product would not be used as a replacement of current treatments and therefore not superior to them but on the contrary that it would be used in combination with current treatments particularly in those patients with high immunological risk who are sensitized to the human leukocyte

antigen which represents nearly a third of these patients. The sponsor highlighted that this population represented the highest unmet therapeutic need to prevent organ rejection.

Following review of the application by the Committee, it was agreed to rename the active substance to "recombinant monoclonal IgG1 antibody against T-cell immune response cDNA 7" and the condition originally proposed by the sponsor as "prevention of graft rejection following solid organ transplantation".

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

The intention to prevent the condition with the medicinal product containing recombinant monoclonal IgG1 antibody against T-cell immune response cDNA 7 was considered justified based on pre-clinical in vivo data where subjects, having received engrafted organs, survive longer.

The condition is life-threatening and chronically debilitating due to the loss of function and reduced survival of the transplanted organ.

The population of patients eligible for prevention of the condition was estimated to be approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of prevention of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant monoclonal IgG1 antibody against T-cell immune response cDNA 7 may be of significant benefit to the population at risk of developing the condition. The sponsor has provided pre-clinical data that demonstrate that the use of their product in combination with tacrolimus prolongs the survival of engrafted subjects when compared to the use of tacrolimus only. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant monoclonal IgG1 antibody against T-cell immune response cDNA 7, for prevention of graft rejection following solid organ transplantation was adopted by consensus.

### **2.1.9** Product for treatment of amyotrophic lateral sclerosis - EMA/OD/278/14

*[COMP co-ordinator: V. Stoyanova]*

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of amyotrophic lateral sclerosis (ALS), the sponsor should:

  - further elaborate on the extent of effects with the product in the preclinical models of the condition, in particular with regards to the statistical differences of the results observed;
  - provide any further available data in relevant models of the condition that would support clinically relevant outcomes in the proposed condition.

- Number of people affected

For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition as per the above mentioned document. It is the sponsor's responsibility to justify that the number of people affected by the proposed condition is less than the statutory threshold.

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preclinical studies to justify either a clinically relevant advantage or a major contribution to patient care.

In particular, the sponsor should elaborate on the efficacy differences between groups of different gender.

A comparative discussion based on data, over authorised medicinal products for the proposed orphan indication is expected to support the claims of significant benefit.

In the written response, and during an oral explanation before the Committee on 18 March 2015, the sponsor further elaborated on the issues raised.

With regards to the issues of medical plausibility, the sponsor discussed the preclinical settings used, and presented survival data at two time points, showing a statistically significant improvement compared to controls. Furthermore, the sponsor discussed prevention of weight loss which had been observed in the preclinical studies, as an endpoint that may support a delay in disease progression. No further functional endpoints such as grip strength or motor skills were discussed. For the prevalence issue, the sponsor has re-calculated the prevalence based on European epidemiological resources and concluded that the average prevalence of ALS in Europe is 0.6 in 10,000 people. Finally with regards to significant benefit, the sponsor has elaborated on theoretical grounds on the basis of a different mechanism of action compared to riluzole. It was argued that an additive effect could be expected in patients treated with the combination of these two agents.

The COMP considered that the significant benefit could not be justified based solely on a theoretical discussion without data. Considering that the sponsor's main outcome was improvement of survival, a comparison would be expected over riluzole, which also prolongs survival in patients affected by the condition. In the absence of such a data-driven comparison, either direct or indirect, the significant benefit criterion could not be considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 March 2015, prior to final opinion.

### 2.1.10 **Echothiophate iodide** for treatment of Stargardt's disease, JJGConsultancy Ltd - EMA/OD/295/14

*[COMP co-ordinator: K. Westermark]*

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Stargardt's disease, the sponsor should present further details on the methodology, and the results of the open label clinical trial discussed in the application.

In the written response, and during an oral explanation before the Committee on 18 March 2015, the sponsor further elaborated on the results from the clinical study and reported that treatment with the product resulted in significant improvement in visual acuity which developed rapidly and was maintained over the study period, with a trend for continued improvement over time. It was also pointed out that the patient population for the vast majority of patients had severe disease.

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

The intention to treat the condition with the medicinal product containing ecothiophate iodide was considered justified based on preliminary clinical data showing improvement in visual acuity in patients treated with the proposed product.

The condition is chronically debilitating due to progressive loss of vision leading to severe vision impairment in nearly half of the patients and complete blindness in the most severe cases.

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.

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 ecothiophate iodide, for treatment of Stargardt's disease, was adopted by consensus.

**2.1.11** Product for treatment of trigeminal neuralgia- EMA/OD/244/14
*[COMP co-ordinator: A. Corrêa Nunes]*

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

- Number of people affected

The sponsor has proposed a prevalence calculation based on a literature search which appears to be an underestimation. For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor should describe and justify the methodology used for the prevalence calculation as well as present a sensitivity analysis.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition thereby offering a clinically relevant advantage.

Another sodium channel blocker, carbamazepine, is on some EU markets with the approved indication for this condition. The sponsor is requested to justify the assumption of significant benefit over this authorised medicinal product for the proposed orphan indication.

The sponsor should detail the results of any clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the absence of any relevant data in the condition as applied for significant benefit cannot be established.

In the written response, and during an oral explanation before the Committee on 18 March 2015, the sponsor discussed the assumptions used for the prevalence estimation. In particular, the sponsor considered the duration of condition to be from age 50 up to the average life span in each respective country and excluded symptomatic trigeminal neuralgia (in contrast to classical “essential or idiopathic” trigeminal neuralgia). The sponsor also rejected several literature studies pointing towards a higher than 5/10,000 prevalence rate, based on diagnostic uncertainties and use of administrative data. The sponsor used two literature studies, corrected to include only “classical” cases, for the calculation of prevalence. With regards to significant benefit, the sponsor discussed data from a phase II study with the product, supporting reductions in the number and severity of paroxysms in patients affected by the condition.

The COMP considered that the level of uncertainty of the prevalence calculation remained high, and that several literature studies exist that challenge the statutory threshold. Therefore the prevalence criterion had not been justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 March 2015, prior to final opinion.

### 2.1.12 1-(4-(N-Glycylamido) phenyl)-3-trifluoromethyl-5-(phenanthren-2-yl)-pyrazole-hydrochloride for treatment of cryptococcosis, Arno Therapeutics UK, Limited - EMA/OD/300/14

*[COMP co-ordinator: A. Lorence]*

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

- Intention to diagnose, prevent or treat

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

  - the relevance of the preclinical models used for the treatment of cryptococcosis, and the interpretation of the results obtained in the experiments, in particular with regards to the fact that treatment starts with the inoculation of the pathogen.
  - the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition.

- Significant benefit

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

In the written response, and during an oral explanation before the Committee on 18 March 2015, the sponsor further addressed the issues raised. With regards to the preclinical settings, it was clarified that the product was not administered at the same time, but twenty four hours after the intravenous administration of the pathogen challenge, when subjects were treated with the proposed product and/or fluconazole. The sponsor also provided histological data that support that at the time of the administration of the product, there is already detectable established pathogen burden in the brain of the preclinical subjects. Based on these clarifications, the COMP considered that these were treatment

and not preventive settings, and that the justification of medical plausibility was acceptable. Furthermore, it was considered that significant benefit, is also supported by these preclinical data, which showed improved results when the product was combined to fluconazole.

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

The intention to treat the condition with the medicinal product containing 1-(4-(N-glycylamido)phenyl)-3-trifluoromethyl-5-(phenanthren-2-yl)-pyrazole-hydrochloride was considered justified based on data in a preclinical model of the condition, showing a reduction in brain fungal burden in combination with fluconazole.

The condition is life-threatening and chronically debilitating in particular due to the development of pulmonary cryptococcosis that leads to cryptococcal meningitis or meningoencephalitis and rarely, other forms such as cutaneous infection and peritonitis.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 1-(4-(N-glycylamido)phenyl)-3-trifluoromethyl-5-(phenanthren-2-yl)-pyrazole-hydrochloride may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data in a relevant model of the condition that support an assumption of improved efficacy when used as an add-on to already authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 1-(4-(N-glycylamido)phenyl)-3-trifluoromethyl-5-(phenanthren-2-yl)-pyrazole-hydrochloride, for treatment of cryptococcosis, was adopted by consensus.

### 2.1.13 1-(4-(N-Glycylamido) phenyl)-3-trifluoromethyl-5-(phenanthren-2-yl)-pyrazole-hydrochloride for treatment of tularemia, Arno Therapeutics UK, Limited - EMA/OD/301/14

*[COMP co-ordinator: A. Lorence]*

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

- Intention to diagnose, prevent or treat

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

  - the relevance of the preclinical model used for the treatment of tularaemia, and the interpretation of the results obtained in the experiments,
  - the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition.

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

In the written response, and during an oral explanation before the Committee on 18 March 2015, the sponsor further elaborated on the raised issues. With regards to the timing of administration of the product in the in vivo preclinical model used, the sponsor asserted that the potent virulence of the pathogen strain used in the experiments necessitates early administration of the therapy. With regards to the results in this model, the sponsor stated that statistical improvements in survival had been observed with the product alone and in combination with gentamycin. The COMP considered that for the purpose of designation, even if the settings could have further benefitted by a delay in administration, the results would be relevant for the application taking into account the virulence of the pathogen as well as other supporting data from preclinical studies in vitro. The significant benefit could also be considered on the basis of this data supporting improved effects on survival in combination with gentamycin.

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

The intention to treat the condition with the medicinal product containing 1-(4-(N-glycylamido)phenyl)-3-trifluoromethyl-5-(phenanthren-2-yl)-pyrazole-hydrochloride was considered justified based on preclinical data in a relevant model of the condition showing improved survival in combination with gentamycin.

The condition is chronically debilitating due to the development of lymphadenopathy, pneumonia, diarrhoea, and cutaneous ulcers, with a protracted recovery.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 1-(4-(N-glycylamido)phenyl)-3-trifluoromethyl-5-(phenanthren-2-yl)-pyrazole-hydrochloride may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data in a relevant model of the condition showing improved survival in combination with gentamycin. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 1-(4-(N-glycylamido)phenyl)-3-trifluoromethyl-5-(phenanthren-2-yl)-pyrazole-hydrochloride, for treatment of tularaemia, was adopted by consensus.

### **2.1.14** Product for treatment of invasive candidiasis - EMA/OD/294/14

*[COMP co-ordinator: N. Sypsas]*

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

- Intention to diagnose, prevent or treat

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

- the relevance of the preclinical model used for the treatment of invasive candidiasis, and the interpretation of the results obtained in the experiments,
- the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. There are no data in the context of the proposed condition that would allow at this point in time the justification of a clinically relevant advantage or a major contribution to patient care.

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

In the written response, and during an oral explanation before the Committee on 18 March 2015, the sponsor further elaborated with regards to the issues raised.

As for the settings of the in vivo preclinical model tested, the sponsor clarified that the treatment with the product was initiated after challenge with the pathogen, at a time where fungal burden may already be identified. The sponsor argued that the product had a novel mechanism of action and has demonstrated antifungal activity in vitro as a single agent against multiple Candida species, including strains with variable resistance to fluconazole and regardless of underlying mechanism of resistance.

The COMP considered that although the in vivo model used was indeed an established preclinical model for invasive candidiasis, there were uncertainties with regards to the small number of tested subjects, the marginal statistical significance, and the absence of data on non-albicans Candida species. More importantly, even if the medical plausibility was to be considered, there are no data to document the significant benefit in vivo versus authorised counterparts.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 March 2015, prior to final opinion.

### **2.1.15** Product for treatment of congenital venous malformations - EMA/OD/282/14

*[COMP co-ordinator: D. Krievins]*

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

- Intention to treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of the condition and given the inconsistencies with regards to the terminology of different types of congenital vascular malformations among researchers and clinicians, the sponsor should further elaborate on why the product could not be used for the treatment of other types of congenital vascular malformations. The sponsor should also discuss the positioning of the product among authorised embolization techniques.

- Number of people affected

For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor is basing their prevalence estimate on one publication which is in contradiction with two other studies also cited by the sponsor, without justification.

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

In the written response, and during an oral explanation before the Committee on 19 March 2015, the sponsor asserted that the product would not be suitable in high-flow situations such as those malformations that have an arterial component and also pointed out the uncertainty surrounding its behaviour in the lymphatic system. The Committee considered that this view may be challenged as it was not supported by data and by the fact that in clinical practice the arterial part of a malformation may be treated independently.

With regards to the prevalence calculations, the sponsor estimated the prevalence to be as high as 5/10,000. The COMP reflected on the case-definition, on the evolution of diagnostic means used in everyday clinical practice, and on how this evolution might have influenced the epidemiology of the condition. It was considered that based on the uncertainty of the definitions, epidemiology and the already calculated prevalence of 5/10.0000, the prevalence criterion was not justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 March 2015, prior to final opinion.

**2.1.16 Fluciclovine ($^{18}$F)** for diagnosis of glioma, Blue Earth Diagnostics Ltd - EMA/OD/280/14
*[COMP co-ordinator: B. Bloechl-Daum]*

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

- Number of people affected

For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor bases their prevalence estimate on the annual incidence of glioma and malignant primary brain tumours in Europe. To reflect more closely the number of patients being candidates for the diagnostic procedure using the product in Europe, the sponsor should provide an estimate of the incidence of all malignant and non-malignant brain tumours, based on European data and registries.

In the written response, the sponsor provided a revised prevalence estimate calculation.

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

The intention to diagnose the condition with the medicinal product containing fluciclovine ($^{18}$F) was considered justified based on pre-clinical and preliminary clinical data suggesting an accurate delineation of low and high grade glioma compared to contrast-enhanced MRI.

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

The population of patients eligible for diagnosis of the condition was estimated to be approximately 1.5 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing fluciclovine ($^{18}$F) may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical and preliminary clinical data in patients affected by the condition suggesting an accurate delineation of low and high grade glioma compared to contrast-enhanced MRI. The Committee considered that this constitutes a clinically relevant advantage.

Since there was no quorum for the adoption of the COMP opinion during the meeting, it was agreed to circulate the draft opinion for adoption via written procedure.

**Post meeting note:**

A positive opinion on orphan medicinal product designation for fluciclovine ($^{18}$F), for treatment of glioma, was adopted by consensus via written procedure on 25 March 2015.

**2.1.17 Lenalidomide** for treatment of marginal zone lymphoma, Celgene Europe Limited - EMA/OD/284/14
*[COMP co-ordinator: K. Kubáčková]*

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:

- Orphan condition

After plenary discussion in the COMP the sponsor is invited to merge the three applications of different marginal zone lymphomas (splenic, nodal, extranodal) presented into one single application targeting "marginal zone lymphoma" as orphan condition.

- Number of people affected

Based on merging the three applications the sponsor is invited to provide a prevalence estimate for marginal zone lymphoma as a whole.

In the written response, the sponsor merged the intiatial three applications (splenic, nodal, extranodal) as per the COMP's recommendation and provided updated documentation. The COMP noted that the reasons for merging include the common origin from post-germinal centre marginal zone B cells for the 3 subtypes, a similar immunophenotype and similar management. In addition it was noted that most trials include patients of the three subtypes, as it is also the case of the present application. Following review of the application by the Committee, it was agreed to rename the indication to "treatment of marginal zone lymphoma".

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

The intention to treat the condition with the medicinal product containing lenalidomide was considered justified based on preclinical and preliminary clinical data showing antitumor activity of the product in models of the proposed condition and in patients affected by the condition.

The condition is chronically debilitating and life-threatening due to lymphadenopathy, splenomegaly, mucosa and bone marrow involvement with development of pancytopenia and increased risk of opportunistic infections. Five-year survival ranges from 30% to up to 90%.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing lenalidomide may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate improved efficacy when the product was used in combination with some of the currently authorized products for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for lenalidomide, for treatment of marginal zone lymphoma, was adopted by consensus.

## 2.2. For discussion / preparation for an opinion

**2.2.1** Product for treatment of ovarian cancer - EMA/OD/314/14
*[COMP co-ordinator: B. Bloechl-Daum]*

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

**2.2.2** Product for treatment of Huntington's disease - EMA/OD/325/14
*[COMP co-ordinator: V. Stoyanova]*

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

**2.2.3 Adeno-associated viral vector serotype 5 containing the human CHM gene** for treatment of choroideraemia, HORAMA SAS - EMA/OD/312/14
*[COMP co-ordinator: A. Magrelli]*

The Committee agreed that the condition, choroideraemia, 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 5 containing the human *CHM* gene was considered justified based on pre-clinical in vivo data which showed an expression of the gene in the eyes of subjects deficient in the target gene.

The condition is chronically debilitating due to nyctalopia, loss of visual fields, tunnel vision, and eventually vision loss.

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

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

A positive opinion for adeno-associated viral vector serotype 5 containing the human *CHM* gene, for treatment of choroideraemia, was adopted by consensus.

**2.2.4** Product for treatment of mucopolysaccharidosis IIIC - EMA/OD/322/14
*[COMP co-ordinator: A. Magrelli]*

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond to the list of issue in writing before the April Committee meeting.

**2.2.5** Product for treatment of chronic lymphocytic leukaemia/ small lymphocytic lymphoma- EMA/OD/006/15
*[COMP co-ordinator: K. Kubáčková]*

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

**2.2.6** Product for prevention of oral mucositis in head and neck cancer patients undergoing radiation therapy - EMA/OD/317/14
*[COMP co-ordinator: B. Dembowska-Bagińska]*

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

**2.2.7** Product for treatment of myasthenia gravis - EMA/OD/318/14
*[COMP co-ordinator: J. Torrent-Farnell]*

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

**2.2.8 Human recombinant mesencephalic, astrocyte-derived neurotrophic factor** for treatment of retinitis pigmentosa, Clinipace GmbH - EMA/OD/327/14
*[COMP co-ordinator: K. Westermark]*

Following review of the application by the Committee, it was agreed to rename the active substance to "recombinant human mesencephalic astrocyte-derived neurotrophic factor".

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

The intention to treat the condition with the medicinal product containing recombinant human mesencephalic, astrocyte-derived neurotrophic factor was considered justified based on pre-clinical in vivo data showing protection of rods and cones as well as reduction in apoptosis of these cells.

The condition is chronically debilitating due to the development of nyctalopia and tunnel vision that progress to total blindness.

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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for human mesencephalic astrocyte-derived neurotrophic factor, for treatment of retinitis pigmentosa, was adopted by consensus.

**2.2.9 Nitric oxide** for treatment of cystic fibrosis, Biological Consulting Europe Ltd - EMA/OD/319/14
*[COMP co-ordinator: J. Eggenhofer]*

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 nitric oxide was considered justified based on preliminary clinical data showing reduction of bacterial load in patients affected by cystic fibrosis treated with the proposed product.

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

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing nitric oxide may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing the large spectrum anti-infective activity of the product in patients affected by cystic fibrosis, accompanied by improvement of lung function in some patients. The mechanism of action of the product, targeting multiple functions of different types of infectious agents, carries the potential lack of development of resistances. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by cystic fibrosis.

A positive opinion for nitric oxide, for treatment of cystic fibrosis, was adopted by consensus.

**2.2.10 Phenol, 4-[2-(aminomethyl)-4-thiazolyl]-2,6-bis(1,1-dimethylethyl) monohydrochloride** for treatment of Huntington's disease, Ipsen Pharma - EMA/OD/311/14
*[COMP co-ordinator: A. Andrić]*

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

The intention to treat the condition with the medicinal product containing phenol, 4-[2-(aminomethyl)-4-thiazolyl]-2,6-bis(1,1-dimethylethyl)monohydrochloride was considered justified based on pre-clinical in vivo data which showed an improvement in motor function, a reduction of neurological damage as well as increased survival.

The condition is chronically debilitating due to severe behavioural and cognitive disturbances, progressive motor dysfunction and potentially fatal complications.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing phenol, 4-[2-(aminomethyl)-4-thiazolyl]-2,6-bis(1,1-

dimethylethyl)monohydrochloride may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo data that demonstrate that there was a reduction in neurological damage, improvement in motor function as well as increased survival following treatment with the product. The Committee considered that this may translate into a clinically relevant advantage.

A positive opinion for phenol, 4-[2-(aminomethyl)-4-thiazolyl]-2,6-bis(1,1-dimethylethyl)monohydrochloride, for treatment of Huntington's disease, was adopted by consensus.

**2.2.11** Product for treatment of plasma cell myeloma- EMA/OD/277/14
*[COMP co-ordinator: K. Kubáčková]*

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

**2.2.12 Sodium 2-hydroxylinoleate** for treatment of neuroblastoma, Ability Pharmaceuticals SL - EMA/OD/326/14
*[COMP co-ordinator: B. Dembowska-Bagińska]*

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

The intention to treat the condition with the medicinal product containing sodium 2-hydroxylinoleate was considered justified based on preclinical data in models of the condition showing inhibition of tumour progression, reduction in metastases and improved survival.

The condition is life threatening and chronically debilitating due to its aggressive nature and frequency of metastatic disease. Symptoms include: Horner's syndrome, paralysis, ptosis, hypertension and watery diarrhoea.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sodium 2-hydroxylinoleate may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the product has synergistic effects in combination with cisplatin with regards to tumour progression and development of metastases, and has efficacy in cells resistant to cisplatin. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sodium 2-hydroxylinoleate, for treatment of neuroblastoma, was adopted by consensus.

**2.2.13** Product for treatment of myasthenia gravis - EMA/OD/321/14
*[COMP co-ordinator: V. Stoyanova]*

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

**2.2.14** Product for treatment of malignant mesothelioma - EMA/OD/324/14
*[COMP co-ordinator: A. Magrelli]*

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

**2.2.15** Product for treatment of non-infectious uveitis - EMA/OD/320/14
*[COMP co-ordinator: A. Magrelli]*

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

**2.2.16** Product for treatment of Rett syndrome - EMA/OD/316/14
*[COMP co-ordinator: I. Barisic]*

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

**2.2.17 Xenon** for treatment of perinatal asphyxia, Neuroprotexeon Ltd - EMA/OD/315/14
*[COMP co-ordinator: M. Možina]*

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

The intention to treat the condition with the medicinal product containing xenon was considered justified based on data in preclinical models of the condition and preliminary clinical data in full-term and near-term neonates showing anticonvulsant effects as an adjunctive to therapeutic hypothermia.

The condition is chronically debilitating due to the long lasting neurological and developmental sequelae. The condition is also life threatening, with high mortality associated with the most severe cases.

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.

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 xenon, for treatment of perinatal asphyxia, was adopted by consensus.

## 2.3. Appeal procedure

None

## 2.4. Evaluation on-going

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

### 2.5. Validation on-going

The Committee was informed that validation was on-going for forty two applications for orphan designation.

## 3. Requests for protocol assistance

**3.1** For treatment of pancreatic cancer [Coordinator: B. Bloechl-Daum]

The COMP adopted the proposed answers on the significant benefit issues.

**3.2** For treatment of amyloid light-chain amyloidosis [Co-ordinator: K. Westermark]

The COMP adopted the proposed answers on the significant benefit issues that were presented in February.

**3.3** For treatment of active ulcerative colitis [Co-ordinator: K. Westermark]

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

**3.4** For treatment of glioma [Coordinator: B. Bloechl-Daum]

The Committee was briefed on the significant benefit issues. The COMP discussed the draft answers and proposed changes. It was agreed that the revised answers would be circulated for adoption via written procedure.

**3.5** For treatment of paroxysmal nocturnal haemoglobinuria [Co-ordinator: K. Westermark]

The Committee was briefed on the significant benefit issues in preparation of the April meeting.

**3.6** For diagnosis of gastro-entero-pancreatic neuroendocrine tumours [Co-ordinator: K. Westermark]

The Committee was briefed on the significant benefit issues in preparation of the April meeting.

## 4. Overview of applications

**4.1** Update on applications for orphan medicinal product designation submitted/expected

COMP co-ordinators were appointed for 2 applications submitted and 34 upcoming applications.

**4.2** Update on orphan applications for Marketing Authorisation

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

# 5. Review of orphan designation for orphan medicinal products for Marketing Authorisation

## 5.1. Orphan designated products for which CHMP opinions have been adopted

**5.1.1** Tolvaptan for treatment of autosomal dominant polycystic kidney disease; Otsuka Pharmaceutical Europe Ltd (EU/3/13/1175) [COMP Co-ordinator: A. Correa-Nunes]

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

The sponsor should provide a prevalence calculation for autosomal dominant polycystic kidney disease in the EU-EEA at the time of review of the criteria for designation at the time of marketing authorisation. The prevalence calculation should refer to the orphan indication as designated and not the therapeutic indication subject of the marketing authorisation application.

For the calculation and presentation of the prevalence data it is advised to refer to the "Points to consider on the calculation and reporting of a prevalence of a condition for orphan designation".

A sensitivity analysis of all the assumptions used is also expected.

In its written response, and during an oral explanation before the Committee on 17 March 2015, the sponsor reviewed further published studies on the issue since the designation of 2013 but rejected them, mainly on the basis of population sampling and generalizability. In addition to direct studies, the sponsor also used an indirect method of calculation, based on ERA-EDTA registry data, starting from patients with the condition that needs renal replacement therapy (RRT). This was corrected upwards by provisioning for patients with no need for RRT (assuming that 23% of diagnosed patients need renal replacement) and for patients who remain undiagnosed (assuming that 85% of patients are diagnosed).

The COMP, after reviewing the supplemental information provided by the sponsor, reflected on the case definition, the scope of the indication and the epidemiological changes across time. Previous opinions of the COMP on the issue were also taken into consideration.

Based on the paucity of data submitted and the uncertainty of the assumptions made by the sponsor, it was considered that it has not been established that the number of people affected by the condition remained below the European statutory threshold. In particular, it was considered difficult to account for the number of patients with milder forms of the condition, and therefore the prevalence criterion could not be established at the time of the review.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the product from the EC Register of Orphan Medicinal Products on 18 March 2015, prior to final opinion of the COMP on the maintenance of criteria for designation.

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

**5.2.1** Tasimelteon for treatment of non-24-hour sleep-wake disorder in blind people with no light perception; Vanda Pharmaceuticals Limited (EU/3/10/84)

**5.2.2** Lenvatinib; Eisai Ltd

a) treatment of papillary thyroid cancer (EU/3/13/1121)

b) treatment of follicular thyroid cancer (EU/3/13/1119)

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond to the list of issue in writing before the April Committee meeting.

## 5.3. On-going procedures

**5.3.1** Amikacin; Insmed Limited:

a) treatment of Pseudomonas aeruginosa lung infection in cystic fibrosis (EU/3/06/387)

b) treatment of nontuberculous mycobacterial lung disease (EU/3/14/1259)

**5.3.2** Blinatumomab for treatment of acute lymphoblastic leukaemia; Amgen Europe B.V. (EU/3/09/650)

**5.3.3** Mifepristone for treatment of hypercortisolism (Cushing's syndrome) of endogenous origin; FGK Representative Service GmbH (EU/3/11/925)

**5.3.4** Isavuconazonium sulfate; Basilea Medical Ltd:

a) treatment of invasive aspergillosis (EU/3/14/1284)

b) treatment of mucormycosis (EU/3/14/1276)

**5.3.5** Cysteamine hydrochloride for treatment of cystinosis; Orphan Europe S.A.R.L. (EU/3/08/578)

**5.3.6** Cysteamine hydrochloride for treatment of cystinosis; Lucane Pharma (EU/3/14/1341)

**5.3.7** Autologous tumour-derived immunoglobulin idiotype coupled to keyhole limpet haemocyanin for treatment of follicular lymphoma; Biovest Europe Ltd (EU/3/06/394)

**5.3.8** Efmoroctocog alfa for treatment of haemophilia A; Biogen Idec Ltd (EU/3/10/783)

**5.3.9** Panobinostat for treatment of multiple myeloma; Novartis Europharm Limited (EU/3/12/1063)

**5.3.10** Human heterologous liver cells (for infusion); Cytonet GmbH&Co KG

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EU/3/10/821)

b) treatment of ornithine-transcarbamylase deficiency (EU/3/07/470)

c) treatment of citrullinaemia type 1 (EU/3/10/818)

d) treatment of hyperargininaemia (EU/3/10/819)

e) treatment of argininosuccinic aciduria (EU/3/10/820)

**5.3.11** Ibrutinib for treatment of lymphoplasmacytic lymphoma; Janssen-Cilag International NV (EU/3/14/1264)

**5.3.12** Carfilzomib for treatment of multiple myeloma; Amgen Europe B.V. (EU/3/08/548)

**5.3.13** Recombinant human parathyroid hormone for treatment of hypoparathyroidism; NPS Pharma UK Ltd (EU/3/13/1210)

**5.3.14** Dexamethasone acetate for treatment of multiple myeloma; LABORATOIRES CTRS (EU/3/10/745)

**5.3.15** Susoctocog alfa for treatment of haemophilia A; Baxter AG (EU/3/10/784)

**5.3.16** Lumacaftor / ivacaftor for treatment of cystic fibrosis; Vertex Pharmaceuticals (U.K.) Ltd., (EU/3/14/1333)

**5.3.17** Sirolimus for treatment of chronic non-infectious uveitis; Santen Oy (EU/3/11/898)

**5.3.18** Glyceryl tri-(4-phenylbutyrate); Hyperion Therapeutics Limited:

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EU/3/10/733)

b) treatment of ornithine carbamoyltransferase deficiency (EU/3/10/734)

c) treatment of citrullinaemia type 1 (EU/3/10/735)

d) treatment of argininosuccinic aciduria (EU/3/10/736)

e) treatment of hyperargininaemia (EU/3/10/737)

f) treatment of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome) (EU/3/10/738)

g) treatment of citrullinaemia type 2 (EU/3/10/739)

**5.3.19** Idebenone for treatment of Leber's hereditary optic neuropathy; Santhera Pharmaceuticals (Deutschland) GmbH (EU/3/07/434)

**5.3.20** Lenalidomide for treatment of mantle cell lymphoma; Celgene Europe Limited (EU/3/11/924)

**5.3.21** Recombinant human lysosomal acid lipase for treatment of lysosomal acid lipase deficiency; Synageva BioPharma Ltd (EU/3/10/827)

**5.3.22** L-Asparaginase for treatment of acute lymphoblastic leukaemia; medac Gesellschaft fuer klinische Spezialpraeparate mbH (EU/3/04/258)

**5.3.23** Asfotase alfa for treatment of hypophosphatasia; Alexion Europe SAS (EU/3/08/594)

**5.3.24** Chimeric monoclonal antibody against GD2 for treatment of neuroblastoma; United Therapeutics Europe Ltd (EU/3/11/879)

**5.3.25** Selexipag for treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension; Actelion Registration Ltd. (EU/3/05/316)

**5.3.26** 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride for treatment of narcolepsy; Bioprojet (EU/3/07/459)

**5.3.27** Herpes simplex 1 virus-thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes for adjunctive treatment in haematopoietic cell transplantation; MolMed S.p.A. (EU/3/03/168)

# 6. Procedural aspects

**6.1** Significant Benefit Working group

The Working group on significant benefit met on 18 March. No report was given to the COMP.

**6.2** NCA/COMP Consultation on proposed process improvements for Orphan procedures (review and reconnect) – Workshop update

Postponed to April.

**6.3** Evaluation (and communication) of the Benefit/Risk Balance of medicinal products

Postponed to April.

# 7. Any other business

None

# Date of next COMP meeting: 14-16 April 2015

# List of participants

including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 17-19 March 2015 meeting.

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Bruno Sepodes | Chair | Expert recommended by EMA | No interests declared | |
| André Lhoir | Member | Belgium | No interests declared | |
| Irena Bradinova | Member | Bulgaria | No interests declared | |
| Adriana Andrić | Member | Croatia | No interests declared | |
| Elena Kaisi | Member | Cyprus | No interests declared | |
| Jens Ersbøll | Member | Denmark | No interests declared | |
| Vallo Tillmann | Member | Estonia | No interests declared | |
| Karri Penttilä | Member | Finland | No interests declared | |
| Annie Lorence | Member | France | No interests declared | |
| Frauke Naumann-Winter | Member | Germany | No interests declared | |
| Nikolaos Sypsas | Member | Greece | No restrictions applicable to this meeting | |
| Judit Eggenhofer | Member | Hungary | No interests declared | |
| Sigurdur B. Thorsteinsson | Member | Iceland | No interests declared | |
| Geraldine O'Dea | Member | Ireland | No interests declared | |
| Dainis Krievins | Member | Latvia | No restrictions applicable to this meeting | |
| Michel Hoffmann | Member | Luxembourg | No interests declared | |
| Albert Vincenti | Member | Malta | No interests declared | |
| Violeta Stoyanova | Member | Netherlands | No interests declared | |
| Lars | Member | Norway | No interests declared | |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Gramstad | | | | |
| Bożenna Dembowska-Bagińska | Member | Poland | No restrictions applicable to this meeting | |
| Ana Corrêa Nunes | Member | Portugal | No interests declared | |
| Flavia Saleh | Member | Romania | No interests declared | |
| Zuzana Batova | Member | Slovak Republic | No interests declared | |
| Martin Možina | Member | Slovenia | No restrictions applicable to this meeting | |
| Josep Torrent-Farnell | Member | Spain | No interests declared | |
| Kerstin Westermark | Member | Sweden | No restrictions applicable to this meeting | |
| Daniel O'Connor | Member | United Kingdom | No interests declared | |
| Pauline Evers | Member | Patients' Organisation Representative | No interests declared | |
| Lesley Greene | Member (Vice-Chair) | Patients' Organisation Representative | No restrictions applicable to meetings | |
| Birthe Byskov Holm | Member | Patients' Organisation Representative | No restrictions applicable to meetings | |
| Aikaterini Moraiti | Member | Expert recommended by EMA | No interests declared | |
| Ingeborg Barisic | Member | Expert recommended by EMA | No restrictions applicable to this meeting | |
| Giuseppe Capovilla | Member | Expert recommended by EMA | No interests declared | |
| Virginie Hivert | Eurordis | Patients' Organisation Representative | Participation in the meeting as observer allowed | |
| Mohamed Ameziane | Expert | Netherlands | No interests declared | |

| Name | Role | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Conny Klaassen | Expert | Netherlands | No interests declared | |
| A representative from the European Commission attended the meeting | | | | |
| Meeting run with support from relevant EMA staff | | | | |

* Experts were only evaluated against the product(s) they have been invited to talk about.