EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 December 2013
EMA/COMP/622526/2013
Human Medicines Research & Development Support

Committee for Orphan Medicinal Products (COMP)

Minutes of the 5 - 6 November 2013 meeting

Note on access to documents

Documents under points 1.1 and 2 to 7 cannot be released at present as they are currently in draft format or are classified as confidential. They will become public when adopted in their final form 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/622524/2013

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting, 8 - 10 October 2013 EMA/COMP/548719/2013

The minutes were adopted.

1.3 Conflicts of Interest

The Chair asked the Committee members to declare their potential conflict of interest. No conflict of interest was declared during the meeting.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5- tetrahydro-4-hydroxy-1,1-dioxido- 1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane Chloride for treatment of primary biliary cirrhosis, Lumena Pharma UK Limited - EMA/OD/121/13
[Co-ordinators: A. Corrêa Nunes / L. Fregonese]

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 was invited to explain the methodology that lead to the proposed prevalence figures from the retrieved literature sources.

- Justification of significant benefit

The sponsor was invited to discuss significant benefit versus any products authorised in the EU for the treatment of intra- and extra-hepatic cholestasis associated pruritus, in addition to the products specifically authorised for primary biliary cirrhosis including e.g. cholestyramine in addition to UDCA.

In the written response, and during an oral explanation before the Committee on 5 November 2013, the sponsor further elaborated on the two issues raised. Regarding the prevalence, the sources and methodology used by the sponsor were considered acceptable by the committee, but a higher estimate than the one proposed was considered for the purpose of designation. With regard to the significant benefit, the sponsor discussed the limited effects of UDCA on pruritus, and claimed that the proposed product would not only be expected to alleviate pruritus through reduction of bile acids but also to improve liver histology, as supported by a preclinical study in a model of cholestasis. The sponsor also discussed a preclinical model showing that the reduction of serum bile acids induced by the proposed product was higher than the reduction induced by cholestyramine.

[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).

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

The intention to treat the condition with the medicinal product containing (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido- 1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride was considered justified based on preclinical data showing reduction of serum bile acids in a cholestasis model, accompanied by some reduction of liver enzymes levels. The reduction of biliary acid levels is known to be linked to reduction of pruritus in cholestatic diseases. Since pruritus is an important and chronically debilitating symptom of primary biliary cirrhosis, the Committee considered that preliminary evidence of reduction of biliary acid levels supports the intention to treat the condition with the supposed product.

The condition is chronically debilitating and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular cancer. Common findings include pruritus which may be very distressing, usually occurring at night, hyperlipidaemia, hypothyroidism, deficiency of fat-soluble vitamins and osteopaenia. The condition was estimated to be affecting approximately 3 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 (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido- 1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing reduction of serum biliary acids and improvement of liver pathology with the proposed product. This is assumed to translate into a clinically relevant advantage for the patients affected by primary biliary cirrhosis.

A positive opinion for (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5- tetrahydro-4-hydroxy-1,1-dioxido- 1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride, for treatment of primary biliary cirrhosis, was adopted by consensus.

2.1.2 (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5- tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane Chloride for treatment of Alagille syndrome, Lumena Pharma UK Limited - EMA/OD/120/13

[Co-ordinators: A. Corrêa Nunes / L. Fregonese]

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:

- Justification of significant benefit

The sponsor states that there are no products authorised for the treatment of the condition in the European Union. However products exist that are authorised in the EU for the treatment of intra- and extra-hepatic cholestasis associated pruritus. To the knowledge of the Committee this would include also Alagille syndrome, which is a cause of intrahepatic cholestasis. The sponsor was therefore invited

to discuss significant benefit of the proposed product versus currently authorised products for treatment of cholestasis in the EU, including e.g. cholestyramine and UDCA.

In the written response, and during an oral explanation before the Committee on 5 November 2013, the sponsor discussed evidence of the very limited effects of the cholestyramine and UDCA in Alagille syndrome, with particular relevance to pruritus. The sponsor asserted that the proposed product would not only be expected to alleviate pruritus through reduction of bile acids but also to improve liver histology, as supported by a preclinical study in a model of cholestasis. The sponsor also discussed a preclinical model showing that the reduction of serum bile acids induced by the proposed product was higher than the reduction induced by cholestyramine.

The COMP considered the sponsor's responses and discussion satisfactory and it was established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

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

The intention to treat the condition with the medicinal product containing (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5- tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride was considered justified based on preclinical data showing reduction of serum bile acids in a cholestasis model, accompanied by some reduction of liver enzymes levels. The reduction of biliary acid levels is known to be linked to reduction of pruritus in cholestatic diseases. Since pruritus is an important and chronically debilitating symptom of Alagille syndrome, the Committee considered that preliminary evidence of reduction of biliary acid levels supports the intention to treat the condition with the supposed product.

The condition is life-threatening and chronically debilitating due to hepatic and cardiac dysfunction. Portal hypertension develops in up to one third of patients. Life expectancy is in most cases around 20 years and the disease is life-threatening due to liver failure, cardiac complications and blood vessel abnormalities. The condition was estimated to be affecting not more than 0.3 in 10,000 people in the European Union, at the time the application was made, based on the current available literature.

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 (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5- tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride, for treatment of Alagille syndrome, was adopted by consensus.

2.1.3 (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride for treatment of primary sclerosing cholangitis, Lumena Pharma UK Limited - EMA/OD/127/13

[Co-ordinators: A. Corrêa Nunes / L. Fregonese]

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 was invited to explain the methodology that lead to the proposed prevalence figures from the retrieved literature sources.

- Justification of significant benefit

Since UDCA seems to be authorised for the treatment of the condition in Europe, the sponsor was invited to discuss the significant benefit.

In addition products are authorised in the EU for the treatment of intra- and extra-hepatic cholestasis associated pruritus. To the knowledge of the Committee this would include also primary sclerosing cholangitis, which is a cause of intrahepatic cholestasis.

The sponsor was therefore invited to discuss significant benefit of the proposed product versus the currently authorised products for treatment of primary sclerosing cholangitis and more in general for the treatment of cholestasis in the EU.

In the written response, and during an oral explanation before the Committee on 5 November 2013, the sponsor clarified the prevalence calculations as requested. The final sponsor's estimate of 0.3 in 10,000 in the EU was considered acceptable by the COMP and justified based on a review of published European studies, accompanied by a sensitivity analysis. With regards to the significant benefit, the sponsor discussed the very limited effects of UDCA in primary sclerosing cholangitis, in particular in relation to pruritus. In contrast, it was claimed that the proposed product would not only be expected to alleviate pruritus through reduction of bile acids but also to improve liver histology, as supported by a preclinical study in a model of cholestasis. The sponsor also discussed a preclinical model showing that the reduction of serum bile acids induced by the proposed product was higher than the reduction induced by cholestyramine.

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

The intention to treat the condition with the medicinal product containing (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido- 1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride was considered justified based on preclinical data showing reduction of serum bile acids in a cholestasis model, accompanied by some reduction of liver enzymes levels. The reduction of biliary acid levels is known to be linked to reduction of pruritus in cholestatic diseases. Since pruritus is an important and chronically debilitating symptom of primary sclerosing cholangitis, the Committee considered that preliminary evidence of reduction of biliary acid levels supports the intention to treat the condition with the applied product.

The condition is chronically debilitating and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, resulting in 4-fold increased mortality as compared to age- and gender-matched population. The condition is also characterized by markedly increased risk of hepatobiliary cancer, including cholangiocarcinoma and gallbladder cancer. The condition was estimated to be affecting not more than 0.3 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 (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido- 1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride may be of significant benefit to those affected by the condition. The sponsor has provided

preclinical data showing reduction of serum biliary acids and improvement of liver pathology with the proposed product. This is assumed to translate into a clinically relevant advantage for the patients affected by primary sclerosing cholangitis.

A positive opinion for (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride, for treatment of primary sclerosing cholangitis, was adopted by consensus.

2.1.4 (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane Chloride

(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane Chloride for treatment of progressive familial intrahepatic cholestasis, Lumena Pharma UK Limited - EMA/OD/123/13
[Co-ordinators: J. Torrent-Farnell / L. Fregonese]

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:

- Justification of significant benefit

The sponsor states that there are no products authorised for the treatment of the condition in the European Union. However products exist that are authorised in the EU for the treatment of intra- and extra-hepatic cholestasis associated pruritus. To the knowledge of the Committee this would include also primary familiar intrahepatic cholestasis, which is a cause of intrahepatic cholestasis.

The sponsor was therefore invited to discuss significant benefit of the proposed product versus currently authorised products for treatment of cholestasis in the EU, including e.g. cholestyramine and UDCA.

In the written response, and during an oral explanation before the Committee on 5 November 2013, the sponsor further elaborated on the issue raised. The sponsor discussed the limited effects of UDCA in familial intrahepatic cholestasis, and based on preclinical studies, argued that the product causes a more pronounced reduction of bile acids compared to cholestyramine. The sponsor also claimed that the proposed product would not only be expected to alleviate pruritus through reduction of bile acids but also to improve liver histology, as supported by a preclinical study in a model of cholestasis. The Committee agreed that it has been established than no satisfactory methods exist that have been authorised for the condition.

The Committee agreed that the condition, progressive familial intrahepatic cholestasis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido- 1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride was considered justified based on preclinical data showing reduction of serum bile acids in a cholestasis model, accompanied by some reduction of liver enzymes levels. The reduction of biliary acid levels is known to be linked to reduction of pruritus in cholestatic diseases. Since pruritus is an important and chronically debilitating symptom of progressive familial intrahepatic cholestasis, the Committee considered that preliminary evidence of reduction of biliary acid levels supports the intention to treat the condition with the supposed product.

The condition is life-threatening and chronically debilitating due to progressive severe liver dysfunction, accompanied by portal hypertension, liver failure, cirrhosis, and higher incidence of hepatocellular

carcinoma. Symptoms develop very early, around 2 months of life. The disease ultimately leads to cirrhosis by age 10-20 years. Most affected subjects do not survive beyond 20 years of age. The condition was estimated to be affecting not more than 0.2 in 10,000 people in the European Union, at the time the application was made, based on available literature.

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 (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride, for treatment of progressive familial intrahepatic cholestasis, was adopted by consensus.

2.1.5 5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N4-[2-(isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine

for treatment of non-small cell lung carcinoma (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive, Novartis Europharm Limited - EMA/OD/113/13

[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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:

The Committee is of the opinion that non-small cell lung cancer is not a rare condition, and that the sponsor is restricting the orphan indication in patients that are “anaplastic lymphoma kinase positive”.

While the sponsor argues in its scientific application by defining the subset of ALK patients as a group with “distinct clinical, pathological and prognostic features” several aspects pertaining to the acceptability of this subset have not been addressed. In particular, the updated guideline on the format and content of the applications for orphan designation (ENTR/65283/00 Rev03) describes, inter alia, that a subset of a disease with a prevalence greater than 5 in 10,000 may be considered a valid condition if patients in that subset present distinct and unique evaluable characteristic(s) with a plausible link to the condition and if such characteristics are essential for the medicinal product to carry out its action. With reference to the above mentioned requirements the sponsor is invited to elaborate with regards to the following issues:

A. With reference to the “plausible link to the condition”:

1. As it appears that the sponsor is focusing only on EML4/ALK fusion rearrangements for the calculation of prevalence estimates, it should be clarified whether the proposed indication also comprises other ALK rearrangements, such as for example fusions with 5’ partners like KIF5B and TFG. The impact of including all possible rearrangements to the population should be clearly discussed.
2. In line with the above, the potential existence of any primary activating mutations of ALK that may render the kinase constitutively active without being fused to other 5’ partners should also be discussed, and the effect in the population addressed.
3. The definition of ALK positive tumours and the setting of the cut-off point of 15% of positive cells by the FISH test. The sponsor should elaborate on the available diagnostics to detect ALK rearrangements and provide a justification why the product might not have pharmacodynamic effects in lower cut-off points.

4. Whether it is relevant to use ALK positivity for the purpose of definition of a subset of non-small cell lung cancer, given that these rearrangements can be found in many solid tumours and haematopoietic malignancies acting as oncogenes in the pathophysiology of cancer.

5. Whether ALK-positive status of a lung tumour can be considered as a transient stage due to increasing genomic instability over the course of the disease; of note that different stages or degrees of severity of the condition may not be considered as valid conditions for designation.

6. The assertion that there may exist "some limitations" in the notion that "ALK-rearrangement defines a subset of NSCLC with distinct clinical, pathological and prognostic features"; the sponsor is invited to further elaborate on these limitations.

B. With reference to the "exclusion of effects outside the subset" sponsor is also requested to further elaborate on the following issues:

a) the role of other inhibited kinases in the pathophysiology of non-small cell lung cancer and the possible pharmacodynamic effects of the product though inhibition of these kinases.

b) To provide the internal data investigating the effects of the product in models without ALK rearrangements.

c) To support by data the note that inhibition of other kinases may not be achievable at reasonably tolerated dose and to discuss the possible pharmacodynamic effects of the product vis a vis the fact that benefit/risk considerations are not sufficient to define a distinct condition (ENTR/6283/00 Rev 03).

d) with reference to the preliminary clinical data clarify the inclusion of patients not having a confirmed EML4-ALK rearrangement and discuss the effects observed specifically in these patients.

In the written response, and during an oral explanation before the Committee on 5 November 2013, the sponsor presented the following arguments:

A. With reference to the "plausible link to the condition".

The sponsor further elaborated on the plausible link to the condition as requested : Firstly, with regards to including all possible fusion ALK rearrangements, the sponsor confirmed that fusions with other partners had already been considered. Regarding the impact of activating mutations that may render ALK constitutionally active without fusion to 5-end partners (second question), the sponsor concluded that since the promoter of ALK is not expressed in the specific tissue, such mutations would not have an impact. In the third question, regarding the setting of the cut-off point, the sponsor responded that to date there are no data to suggest any effects in levels below the 15% threshold, and provided a discussion regarding the available methods of FISH and IHC. Commenting on the issue of ALK vis a vis its involvement in other diseases, the sponsor answered by giving a parallelism of Her2 in breast and gastric cancer. With regards to the possibility of ALK representing a transient stage due to genomic instability, the applicant discussed two series of patients and stated that rearrangements were maintained during disease progression, as well as that ALK rearrangements are almost always mutually exclusive with EGFR and KRAS mutations. Finally, the sponsor acknowledged that this is a new field and the body of literature and available data over time is quite small compared to a more mature field of study.

B. With reference to the "Exclusion of effects outside the subset"

As for the exclusion of effects outside the subset, the applicant provided further additional data in preclinical models and preliminary clinical settings, to support that the activity of the product “would be predicted to be low in NSCLC without ALK rearrangements”.

The Committee agreed that the condition, non-small cell lung carcinoma (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive, is not a recognised distinct medical entity but a subset of non-small cell lung cancer.

The sponsor defines the proposed subset based on the presence of equal or more than 15% positive cells by the fluorescent in situ hybridization test.

The pharmacodynamic effects outside of the proposed population cannot be excluded; this is based on the inability of the proposed test to detect non-rearranged activated ALK, the insufficiently justified cut-off point of 15% positive cells, the availability of more sensitive detection tests that have not been used, and the limited number of kinases tested for inhibition by the product; hence it is not established that the product will be ineffective in the rest of the population with reference to the updated guideline ENTR/6283/00 Rev 03; therefore the sponsor has not established that the proposed condition is a valid condition for designation and the broader condition of “non-small cell lung cancer” should have been considered for the purpose of this application.

The intention to treat non-small cell lung cancer with the medicinal product containing 5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N4-[2-(isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine was considered justified based on preliminary clinical studies showing relevant responses in treated patients. Non-small cell lung cancer is life-threatening with 5-year overall survival reported to be approximately 15%, and chronically debilitating due to local and systemic spread of the tumour to other organs.

Non-small cell lung cancer was estimated to be affecting more than 5 in 10,000 people in the EU. This was based on 5-year partial prevalence data of approximately 6 in 10,000 people in the European Union, at the time the application was made. The product is intended for treatment of a life-threatening and seriously debilitating condition, non-small-cell lung cancer. However the sponsor did not submit the application on the basis of the second paragraph of Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products, and has not provided any data with the application that would allow an evaluation of a potential claim of insufficient return of the investment without incentives.

Although satisfactory methods of treatment of non-small cell lung cancer have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N4-[2-(isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine may be of significant benefit to those affected by non-small cell lung cancer; the sponsor has provided preliminary clinical data showing responses in patients relapsed or resistant to other authorised products, and this might result in improved efficacy of the product compared to authorised counterparts; the Committee considered that this constitutes a clinically relevant advantage.

Based on the above considerations, and having examined the application and the answers to the list of issues provided by the sponsor in writing and during an oral explanation, the COMP concludes that the requirements laid down in Article (3)(1) (a) No 141/2000 on orphan medicinal products are not fulfilled.

In the light of the overall data submitted and the discussion with the sponsor, the Committee expressed a negative trend on the application.

Post-meeting note:

A written procedure for the adoption of the opinion started on 14 October 2013. A negative opinion on orphan medicinal product designation for 5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N4-[2-(isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine, for treatment of non-small cell lung carcinoma (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive was adopted by consensus on 18 November 2013.

2.1.6 ***Lactobacillus acidophilus*** **and** ***Bifidobacterium bifidum*** for prevention of necrotizing enterocolitis, Laboratorio Farmaceutico S.I.T. s.r.l. - EMA/OD/112/13

[Co-ordinators: S. Thorsteinsson / S. Tsigkos]

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

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 population at risk and in particular the exclusion of non-premature neonates and/or neonates without low birth weight from the calculation of the number of patients eligible for prevention.

In the written response, and during an oral explanation before the Committee on 5 November 2013, the sponsor recalculated the prevalence estimate as requested. Based on literature data, it was discussed that the population eligible for this proposed prevention method consists of preterm neonates born with a weight less than 1500 gr and/or a gestational age of less than or equal to 33 weeks + 6 days. The sponsor cited literature and previous published COMP opinions on other indications to propose a new prevalence estimate.

The Committee considered that the annual number of patients eligible for prevention of NEC would be the premature neonates of less than or equal to 34 weeks. The prevalence was estimated to be less than 4.5 in 10,000 persons in the European Union, taking also into consideration the previous knowledge of the COMP regarding this population. This calculation will need to be updated and re-evaluated at the time of the review of the orphan designation criteria at the time of the marketing authorisation application.

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

The intention to prevent the condition with the medicinal product containing *Lactobacillus acidophilus* and *Bifidobacterium bifidum* was considered justified based on preliminary clinical data in very low birth weight infants, which showed a reduction in the incidence of necrotising enterocolitis in the treated population.

The condition is life-threatening due to development of short-bowel syndrome, malnutrition, and growth delay, and life-threatening due to bowel perforation, peritonitis, sepsis and mortality reported as high as in 50% of the cases. The population of patients eligible for prevention of the condition was estimated to be less than 4.5 in 10,000 people in the European Union, at the time the application was made. This was based on considering the population at risk as premature infants of less than or equal to 34 weeks of gestational age.

The sponsor has also established that there exists no satisfactory method of prevention that has been authorised in the European Union for the population at risk of developing the condition.

A positive opinion for *Lactobacillus acidophilus* and *Bifidobacterium bifidum*, for prevention of necrotising enterocolitis, was adopted by consensus.

2.1.7 Allogeneic and autologous haptenized, and irradiated cells and cell lysates, derived from glioma for treatment of glioma, ERC Belgium - EMA/OD/107/13

[Co-ordinators: H. Metz / S. Mariz]

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

To establish correctly if there exists a scientific rationale for the development of allogeneic and autologous haptenised, and irradiated cells and cell lysates, derived from glioma for treatment of glioma, the sponsor should further elaborate on:

- the composition of the sponsor's product (cells and cell lysates) and how it is produced;

- the relevance of the clinical cases submitted by the sponsor in view of limited effect in view of the very advanced stage of glioma in the patients treated;

- the sponsor is further invited to discuss the efficacy data.

- Justification of 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 should elaborate in further detail the relevance of the clinical cases that were submitted in view of the advanced stage of the patients.

The sponsor should further elaborate on the potential risks with the product and how this compares with the safety profile of current authorised medicinal products for the same condition.

In the written response, and during an oral explanation before the Committee on 5 November 2013, the sponsor further discussed the particulars of the product, the administration scheme and the mechanism of action, and elaborated on the significant benefit by discussing the safety of the product.

The COMP considered that the preclinical and preliminary clinical data from advanced-stage patients who had previously received temozolomide and who were no longer responsive to therapy justified the intention to treat. At this stage of the development it was also considered that sufficient data was submitted to support the assumption of significant benefit based on a clinically relevant advantage as some benefit was shown in patients who were refractory to temozolomide which is authorised and the recommended as the first line of therapy under current ESMO guidelines.

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

The intention to treat the condition with the product was considered justified on the grounds of preclinical and preliminary clinical data. In the preclinical data, treatment with the product resulted in inhibition of tumour volume progression in relevant xenotransplantation models. In the preliminary

clinical data, treatment of patients with relapsed malignant glioma resulted in responses with regards to tumour size.

The condition is chronically debilitating, in particular due to compression and invasion of the surrounding brain structures leading to neurological deficits, and life-threatening with poor overall survival. Survival for glioblastoma multiforme patients is less than 5% at 5 years post diagnosis. The condition was estimated to be affecting less than 3 in 10,000 people in the European Union, at the time the application was made; European epidemiological publications found in the public domain were used to calculate the prevalence.

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 allogeneic and autologous haptenised and irradiated cells and cell lysates derived from glioma may be of significant benefit to those affected by the condition. The sponsor has presented preliminary clinical data in glioma patients who have relapsed following treatment with currently available methods. In these patients, the sponsor has reported responses to treatment with regards to tumour size. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic and autologous haptenised and irradiated cells and cell lysates derived from glioma, for treatment of glioma, was adopted by consensus.

2.1.8 Product for treatment of graft versus host disease - EMA/OD/126/13

[Co-ordinators: K. Westermark / L. Fregonese]

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 was invited to re-examine the prevalence calculations taking into account also chronic GvHD, since the Committee is of the opinion, supported by scientific data on the current classification, that chronic forms should be included under the broader condition of graft versus host disease.

- Justification of significant benefit

The sponsor is requested to further elaborate on any available data to support the significant benefit of the proposed product in the treatment of graft versus host disease.

In the written response, and during an oral explanation before the Committee on 5 November 2013, the sponsor provided a recalculated prevalence estimate as requested and further elaborated on the justification of significant benefit. In particular , it was argued that the product, by acting in a multi-modal mechanism of action, would not only modulate pathogenic effector T cell responses but also prompt tissue protection and repair, and this was expected to translate into improved efficacy and safety. The COMP considered the mechanism of action to remain assumptive and considered that there was a lack of data justify the assumption of a clinically relevant advantage over other existing products.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 5 November 2013, prior to final opinion.

2.1.9 Recombinant human parathyroid hormone for treatment of hypoparathyroidism, NPS Phama UK Ltd - EMA/OD/102/13
[Co-ordinators: K. Westermark / S. Aarum]

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 has discussed the aetiology of hypoparathyroidism with regards to the post-surgical and non-surgical hypoparathyroidism. However, the exact scope of the proposed indication is not clear from the provided information. The sponsor was asked to clarify all the non-surgical forms of hypoparathyroidism that are proposed to be included in the proposed indication, in addition to the post-surgical form of the disease.

- Prevalence

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 provide a more detailed prevalence calculation taken into account all different forms of hypoparathyroidism (both post-surgical, idiopathic and other non-surgical hypoparathyroidism) corresponding to the proposed indication.

The data to support the prevalence of the post-surgical hypoparathyroidism is based on data from only a few Member States and should be substantiated with all available data.

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 6 November 2013, the sponsor clarified the scope of the proposed indication. A detailed discussion of the different aetiologies of hypoparathyroidism was provided, including a variety of non-surgical causes, and it was discussed that forms where the action of the PTH is defective would not be included in the proposedcondition. For the second question on the prevalence, the sponsor provided more information on the epidemiology of thyroid and larynx cancer, of thyroid dissection due to goiter, and of hyperparathyroidism that can be lead to post-surgical hypoparathyroidism. The sponsor also discussed in detail a Danish registry study and completed a new worst-case scenario on the overall prevalence of hypoparathyroidism.

In its discussion, the Committee considered that while a level of uncertainty remains with regard to the assumptions used in the prevalence calculation, the figures presented were well below the limit and that even when doubling of the expected rate for post-surgical hypoparathyroidism, the overall prevalence would still be below the limit. The Committee considered that the condition was estimated to be affecting less than 5 in 10,000 persons in the European Union, at the time the application was made. The sponsor was informed that additional data (e.g. from different surgical centers from different Member States including Eastern Europe) and a more robust prevalence calculation would be expected at the time of marketing authorisation application.

The Committee agreed that the condition, hypoparathyroidism, 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 parathyroid hormone was considered justified based on clinical data supporting the effect of the product in patients with hypoparathyroidism.

The condition is chronically debilitating due to neuromuscular symptoms such as paresthesia, cramps, cognitive impairment, and the abnormal calcium and phosphate metabolism that may lead to complications such as reduced bone turnover. The condition may be life-threatening due to risk of hypocalcaemia that may lead to seizures, cardiac arrhythmias, cardiomyopathy and laryngeal spasm if untreated. The condition was estimated to be affecting less than 5 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 recombinant human parathyroid hormone may be of significant benefit to those affected by the condition.

The sponsor has provided clinical data showing that patients treated with the product were able to decrease their calcium and vitamin D supplementation compared to baseline and that there may be a positive effect on the quality of life. In addition, the product replaces the hormone that is missing in patients with hypoparathyroidism which may be of benefit for the patient in the long-term. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant human parathyroid hormone, for treatment of hypoparathyroidism, was adopted by consensus.

2.1.10 Product for treatment of fragile X syndrome - EMA/OD/114/13
[Co-ordinators: V. Stoyanova / S. Mariz]

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

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

- the lack of non-clinical in vivo studies to support the proof of concept that the proposed product may work in the condition;

- the relevance of the studies which are open label and included patients who were heavily treated already with one or more psychotropic drugs. CGI was used as primary outcome measurement. Although no disease specific scales exist, other scales such as the Social Responsiveness Scale (SRS), and Attention Deficit Hyperactivity Disorder Rating Scale-IV (ADHDRS) would have been more appropriate.

- Prevalence

The sponsor was invited to perform a prevalence calculation. For further information the sponsor should refer to section 1.3 Methods for Combining Data Identified, in the guidance document *Points to Consider on the Calculation and Reporting of the Prevalence of a Condition for Orphan Designation.*

In the written response, and during an oral explanation before the Committee on 6 November 2013, the sponsor discussed further the available data with the product in a preclinical model of the

condition, and discussed the available data in preliminary clinical settings in patients affected by the condition. The sponsor also further elaborated on the prevalence calculation. However, the COMP considered there is a lack of clarity regarding the mode of action of the product and the potential for interaction with other similar products used in the treatment of patients affected by the condition. It was also considered that the endpoints studied and the results obtained in the preclinical and clinical settings were not sufficient to justify the intention to treat the condition with the applied product.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 6 November 2013, prior to final opinion.

2.1.11 Ibrutinib for treatment of follicular lymphoma, Janssen-Cilag International N.V. - EMA/OD/111/13
[Co-ordinators: B. Dembowska-Bagińska / S. Mariz]

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 is asked to recalculate the prevalence taking into account the clinical heterogeneity of the disease, its rising incidence and recent treatment approaches and to present appropriate sensitivity analyses with respect to the critical assumptions.

In its written response the sponsor further elaborated on the prevalence calculation and submitted an updated estimate. After having discussed the responses during its meeting in November 2013, the COMP concluded that currently the submitted recalculation is acceptable. It was concluded that the condition was estimated to be affecting fewer than 3.6 in 10,000 people in the European Union, at the time the application was made. It was also noted that at the time of review of the orphan criteria at the time of marketing authorisation application, the prevalence criterion will be reviewed and the COMP may request further justifications at that time.

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

The intention to treat the condition with the medicinal product containing ibrutinib was considered justified based on preliminary clinical studies in patients with relapsed or refractory disease that responded to treatment.

The condition is life-threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction and the potential of transformation to aggressive lymphoma. The condition was estimated to be affecting fewer than 3.6 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 ibrutinib may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that patients who have relapsed or are refractory to the currently available products respond to treatment with ibrutinib. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2. For discussion / preparation for an opinion

2.2.1 Product for treatment of acute myeloid leukaemia - EMA/OD/141/13
[Co-ordinators: B. Dembowska-Bagińska / L. Fregonese]

The Committee considered that the following issues require clarification by the sponsor:

- Justification of significant benefit

The sponsor is requested to further discuss and to justify with any available data the proposed grounds of significant benefit.

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 December meeting.

2.2.2 Product for treatment of acute lymphoblastic leukaemia - EMA/OD/143/13
[Co-ordinators: B. Dembowska-Bagińska / L. Fregonese]

The Committee considered that the following issues require clarification by the sponsor:

- Justification of significant benefit

The sponsor is requested to further discuss and to justify with any available data the proposed grounds of significant benefit.

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 December meeting.

2.2.3 Product for treatment of plasma cell myeloma - EMA/OD/125/13
[Co-ordinators: K. Kubáčková / S. Mariz]

The Committee considered that the following issues require clarification by the sponsor:

- Justification of significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The data submitted by the sponsor shows the potential for use in combination with bortezomib. Bortezomib is approved as a monotherapy only for patients who have received at least one prior therapy and since other products are approved for this condition it would be difficult to accept the provided data to justify significant benefit for this product. As the sponsor is conducting two studies (Phase I and Phase Ib) in patients with relapsed or refractory plasma cell myeloma, more information should be provided on these ongoing studies.

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 December meeting.

2.2.4 Product for treatment of Type 1 diabetes mellitus patients with residual beta-cell function - EMA/OD/128/13
[Co-ordinators: V. Tillmann / S. Aarum]

The Committee considered that the following issues require clarification by the sponsor:

- Orphan indication

According to the legal basis of orphan designation and in particular guideline ENTR/6283/00 Rev03, a subset of a disease which, when considered as a whole, has a prevalence greater than 5 in 10 000, could be considered a valid condition if patients in that subset present distinct and unique evaluable characteristic(s) with a plausible link to the condition and if such characteristics are essential for the medicinal product to carry out its action.

In addition, the guideline states that "different degrees of severity or stages of a disease would generally not be considered as distinct conditions". The same applies to "subsets of patients in whom the medicinal product is expected to show a favourable benefit/risk".

It is the opinion of the COMP that the proposed indication "type 1 diabetes mellitus patients with residual beta-cell function" is a stage rather than a subset of type I diabetes mellitus.

Type 1 diabetes mellitus patients with residual beta-cell function should therefore be justified as a distinct medical entity or a valid subset.

- Prevalence

In order to justify the prevalence of the proposed subset the sponsor should better elaborate on:

- the choice of the sources selected for the estimation of the prevalence of the condition, and in particular those leading to the proposed prevalence of 5.9 in 10,000 for type I diabetes as a whole. It is important to note that the COMP requires complete prevalence for designation, rather than 5-year prevalence

- the methodology used for the prevalence calculation, particularly regarding:

a) the extrapolations used to reach the proposed prevalence estimate of the patient population with residual B-cell function

b) the case definition of residual beta cell function at single patient level and across different health care practices

The sponsor is also invited to perform a sensitivity analysis of the proposed prevalence.

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 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 December meeting.

2.2.5 Product for treatment of adenovirus infection in allogeneic haematopoietic stem cell transplant recipients - EMA/OD/135/13
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

The Committee considered that the following issues require clarification by the sponsor:

- Medical plausibility

To establish correctly if there exists a scientific rationale the sponsor is invited to further elaborate on:

- the mechanism of action of the product supported by any available data;

- the relevance of the adenoviral levels monitored in the preliminary clinical study in the context of other concomitant antiviral therapies.

- any available further endpoints studied in the patients in the ongoing trial.

- Significant Benefit

The sponsor is requested to submit a significant benefit justification versus commonly used antiviral compounds in the clinical practice in patients affected by the proposed condition as applied for designation.

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 December meeting.

2.2.6 Product for prevention of neovascular glaucoma - EMA/OD/130/13

[Co-ordinators: A. Magrelli / S. Aarum]

The Committee considered that the following issues require clarification by the sponsor:

- Prevalence

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 presents data about the prevalence of NVG among patients with the most common NVG-underlying aetiologies, namely iCRVO and PDR. A corrective factor has been applied to the calculated prevalence to account for the population at high risk of NVG, the use of which has not been sufficiently justified. It also seems that the sponsor has excluded part of the population at risk of the condition, namely patients at risk of NVG with other aetiologies than iCRVO and PDR, i.e. carotid artery obstruction.

The sponsor should substantiate the sources selected for the estimation of the prevalence of the condition, in particular with regard to epidemiological information on NVG due to PDR.

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.

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 December meeting.

2.2.7 Product for treatment of epidermolysis bullosa - EMA/OD/145/13

[Co-ordinators: F. Naumann-Winter / S. Aarum]

The Committee considered that the following issues require clarification by the sponsor:

- Medical plausibility

The sponsor has presented literature data on the effects of the product on wound healing in general as well as clinical experience with the product. However, there are no data that address the mechanism of action of the product at molecular or cellular level in epidermolysis bullosa (EB).

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of epidermolysis bullosa, the sponsor is asked to clarify why preclinical studies such as *in*

vitro wound healing assays with cultured cells lacking collagen VII or one chain of laminin-332, or preclinical models of EB have not been used to analyse the effects of the product in EB.

Further, the sponsor should discuss the currently used topical treatments compared to the proposed product.

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 December meeting.

2.2.8 Product for prevention of Graft versus Host Disease - EMA/OD/146/13
[Co-ordinators: K. Westermark / L. Fregonese]

The Committee considered that the following issues require clarification by the sponsor:

- Prevalence

The sponsor is invited to recalculate the estimated population at risk of graft versus host disease taking into account the worst case scenario.

The COMP adopted a list of issues that will be sent to the sponsor for a written response.

2.2.9 Product for treatment of malignant mesothelioma - EMA/OD/138/13
[Co-ordinators: A. Magrelli / S. Mariz]

The Committee considered that the following issues require clarification by the sponsor:

- Medical plausibility

The sponsor has submitted data with a different product than the one under evaluation in non-clinical in vivo models and a clinical study. In a non-clinical in vivo study only one of the 5 tumour cell lines was used has an effect in malignant mesothelioma. The sponsor should clarify the nature of their product as it appears as different to the products used in the submitted data and the relevance of the submitted data to their product.

- Justification of 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 clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. Specific reference should be made regarding the relevance of their product versus the product in the clinical study.

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 December meeting.

2.2.10 Product for treatment of ameloblastoma - EMA/OD/110/13
[Co-ordinators: D. Krievins / S. Tsigkos]

The Committee considered that the following issues require clarification by the sponsor:

- Medical plausibility

It is understood that the product is intended for reconstruction of bone defects of the craniomaxillofacial skeleton, due to surgical treatment of tumours of the corresponding region.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of ameloblastoma, the sponsor should further elaborate on the relevance for the treatment of ameloblastoma, and if considered appropriate amend the proposed indication

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 December meeting.

2.2.11 Product for treatment of progesterone receptor negative endometrial cancer in combination with progestin therapy - EMA/OD/097/13
[Co-ordinators: B. Bloechl-Daum / S. Tsigkos]

The Committee considered that the following issues require clarification by the sponsor:

- Intention to treat

The COMP understands that the underlying condition, endometrial cancer, is not a rare condition in the EU. While the sponsor argues in that the subset follows the provisions of guideline ENTR/6283/00 this is not supported by data. In particular, the updated guideline on the format and content of the applications for orphan designation (ENTR/65283/00 Rev03) describes, inter alia, that a subset of a disease with a prevalence greater than 5 in 10,000 may be considered a valid condition if patients in that subset present distinct and unique evaluable characteristic(s) with a plausible link to the condition and if such characteristics are essential for the medicinal product to carry out its action. With reference to the above mentioned requirements the sponsor is invited to elaborate based on data with regards to the following issues:

A. With reference to the “plausible link to the condition”:

1. Further elaborate on the definition of PR positivity vis a vis the four versions appearing in the sponsor’s application (LBA 10 or 50 fmol/mg, IHC 1 or 10% stained cells) and discuss the clinical characteristics of the proposed population that would differentiate them from other endometrial cancer patients.
2. Discuss whether PR status can be considered as a transient stage due to increasing genomic instability over the course of the disease; of note that different stages or degrees of severity of the condition may not be considered as valid conditions for designation.

B. With reference to the “exclusion of effects outside the subset” sponsor is also requested to further elaborate on the following issues:

a. the mechanism of action of the proposed product in the context of pathophysiology of endometrial cancer and the possible pharmacodynamic effects that may be exerted either as a monotherapy or as part of a combination treatment

b. to address the limitations of the preclinical models in terms of absence of controls.

c. to discuss the absence of clinically relevant endpoints in the preliminary clinical study cited.

- Prevalence

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 given the substantial uncertainty about many of the assumptions regarding the prevalence, including examining other cut-off points for PR positivity.

- Justification of significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate versus all authorised products for the proposed condition.

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 December meeting.

2.2.12 Fenfluramine hydrochloride for treatment of Dravet syndrome, Brabant Pharma Limited - EMA/OD/140/13
[Co-ordinators: H. Metz / S. Tsigkos]

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

A positive opinion for fenfluramine hydrochloride, for treatment of Dravet syndrome, was adopted by consensus.

The intention to treat the condition with the medicinal product containing fenfluramine hydrochloride was considered justified based on preliminary clinical data showing reduction in the number of seizures in patients affected by the condition.

The condition is chronically debilitating due to psychomotor and cognitive impairment and the occurrence of convulsive seizures and life-threatening in particular due to generalized tonic-clonic seizures. The condition was estimated to be affecting less than 0.5 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 fenfluramine hydrochloride may be of significant benefit to those affected by the condition. This was based on an alternative mechanism of action to the authorised product, which could result in improved efficacy as supported by preliminary clinical data, showing responses as an add-on to other available treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for fenfluramine hydrochloride, for treatment of Dravet syndrome, was adopted by consensus.

2.2.13 Product for treatment of Type 1 Diabetes Mellitus patients with residual beta-cell function - EMA/OD/075/13
[Co-ordinators: V. Tillmann / L. Fregonese]

The Committee considered that the following issues require clarification by the sponsor:

- Orphan indication

According to the legal basis of orphan designation and in particular guideline ENTR/6283/00 Rev03, a subset of a disease which, when considered as a whole, has a prevalence greater than 5 in 10 000, could be considered a valid condition if patients in that subset present distinct and unique evaluable characteristic(s) with a plausible link to the condition and if such characteristics are essential for the medicinal product to carry out its action.

In addition, the guideline states that “different degrees of severity or stages of a disease would generally not be considered as distinct conditions”. The same applies to “subsets of patients in whom the medicinal product is expected to show a favourable benefit/risk”.

It is the opinion of the COMP that the proposed indication “type 1 diabetes mellitus patients with residual beta-cell function” is a stage rather than a subset of type I diabetes mellitus. Type 1 diabetes mellitus patients with residual beta-cell function should therefore be justified as a distinct medical entity or a valid subset.

- Medical plausibility

To establish if there exists a scientific rationale for the development of the proposed product for treatment of type 1 diabetes mellitus patients with residual beta-cell function the sponsor should further elaborate on the extrapolation of the cited immunologic responses to the potential clinical efficacy of the product in the proposed patient population.

- Prevalence

In order to justify the prevalence of the proposed subset the sponsor should better elaborate on:

- the choice of the sources for the estimation of the prevalence of the condition, and in particular those sources leading to the proposed prevalence of 5.9 in 10,000 for type I diabetes as a whole. It is important to note that the COMP requires complete prevalence for designation, rather than 5-year prevalence

- the methodology used for the prevalence calculation, particularly regarding:

a) the extrapolations used to reach the proposed prevalence estimate of the patient population with residual B-cell function

b) the case definition of residual beta cell function at single patient level and across different health care practices

The sponsor is invited to provide a sensitivity analysis of the proposed prevalence.

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”

- Justification of significant benefit

Assumptions of potential benefit(s) should be plausible and where possible based on sound pharmacological principles. It is to be noted that preclinical data and/or preliminary clinical information are usually required as supportive evidence. The sponsor is therefore invited to discuss any available data to support the significant benefit of the proposed product.

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 December meeting.

2.2.14 Humanized Monoclonal modified IgG4 Antibody with Bispecific Structure Targeting Factors IX, IXa, X and Xa for treatment of haemophilia A, Chugai Pharma Europe Ltd - EMA/OD/144/13
[Co-ordinators: L. Gramstad / S. Mariz]

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

The intention to treat the condition with the medicinal product containing humanized monoclonal modified IgG4 antibody with bispecific structure targeting factors IX, IXa, X and Xa was considered justified based on relevant preclinical data and preliminary clinical data.

The condition is chronically debilitating due to recurrent bleedings in joints, gastrointestinal tract or in surgery. These bleedings may be life-threatening in some patients, in particular in case of an intracranial bleeding. The condition was estimated to be affecting approximately 0.7 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 humanized monoclonal modified IgG4 antibody with bispecific structure targeting factors IX, IXa, X and Xa may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate pharmacokinetic advantages such as longer duration of action allowing fewer administrations, and the fact that it is delivered subcutaneously, which could translate to a major contribution to patient care. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for humanised monoclonal modified IgG4 antibody with bispecific structure targeting factors IX, IXa, X and Xa, for treatment of haemophilia A, was adopted by consensus.

2.2.15 Product for treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma - EMA/OD/109/13
[Co-ordinators: B. Dembowska-Bagińska / S. Mariz]

The Committee considered that the following issues require clarification by the sponsor:

- Justification of 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 preliminary study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. This should be discussed within the context of the current European guidelines.

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 December meeting.

2.2.16 Product for the treatment of hepatitis delta virus (HDV) infection - EMA/OD/132/13
[Co-ordinators: A. Corrêa Nunes / S. Tsigkos]

The Committee considered that the following issues require clarification by the sponsor:

- Medical plausibility

The proposed condition should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; your attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

The sponsor is requested in particular to further elaborate on the paragraph of the above mentioned guideline according to which "Generally the intersection of two (or more) concomitant conditions would not be considered as a valid condition. However, it could be acceptable, if such intersection resulted in a certain new evaluable characteristic essential for the pharmacological effect and the medical outcome".

- Prevalence

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".

As it seems that the sponsor may have excluded part of the population affected by the condition by using an indirect calculation method based on the population at risk. The sponsor is invited to further elaborate on the use of data in table 1 of the application to draw a conclusion on the prevalence of the proposed condition.

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.

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 December meeting.

2.2.17 **Nitric oxide** for treatment of cystic fibrosis, Novoteris - EMA/OD/095/13

[Co-ordinators: J. Eggenhofer / L. Fregonese]

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 and improvement of lung function 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 0.7 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 nitric oxide may be of significant benefit to those affected by the condition. The sponsor has provided early clinical data showing the large spectrum anti-infective activity of the product in patients affected by cystic fibrosis, accompanied by improvement of lung function. 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.

2.2.18 Product for treatment of primary sclerosing cholangitis - EMA/OD/136/13
[Co-ordinators: L. Gramstad / S. Aarum]

The Committee considered that the following issues require clarification by the sponsor:

- Justification of significant benefit

Since UDCA is authorised for the treatment of the condition in Europe, the sponsor is invited to discuss the significant benefit of the proposed product in relation to UDCA.

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 December meeting.

2.2.19 Poly[2-[(4-{[1-carboxy-2-(hexadecylcarbamoyl)ethyl]sulfanyl}-2,3-bis({2-[((2S)-2-(2-{[(2R)-2-carbamoyl-(2-{[(2S)-1-ethoxy-3-(3-hydroxy-4oxo-1,4-dihydropyridin-1-yl)-1-oxopropan-2-yl]carbamoyl}ethyl]sulfanyl}-3-{[(2S)-1-ethoxy-3-(3-hydroxy-4-oxo-1,4-dihydropyridin-1-yl)-1-oxopropan-2-yl]carbamoyl}propanamido)-3-(3-hydroxy-4-oxo-1,4-dihydropyridin-1-yl)propanoyl Ethyl ester))-methoxy]acetyl}oxy)butyl)sulfanyl]-3-(hexadecylcarbamoyl)propanoic acid]-PEG1500-ester] for treatment of dengue fever, Coté Orphan Consulting UK Limited - EMA/OD/142/13
[Co-ordinators: N. Sypsas / S. Tsigkos]

For the purpose of orphan designation, the Committee for Orphan Medicinal Products (COMP) considered that the active substance should be renamed as “poly[2-[(4-{[1-carboxy-2-(hexadecylcarbamoyl)ethyl]sulfanyl}-2,3-bis({2-[((2S)-2-(2-{[(2R)-2-carbamoyl-(2-{[(2S)-1-ethoxy-3-(3-hydroxy-4oxo-1,4-dihydropyridin-1-yl)-1-oxopropan-2-yl]carbamoyl}ethyl]sulfanyl}-3-{[(2S)-1-ethoxy-3-(3-hydroxy-4-oxo-1,4-dihydropyridin-1-yl)-1-oxopropan-2-yl]carbamoyl}propanamido)-3-(3-hydroxy-4-oxo-1,4-dihydropyridin-1-yl)propanoyl Ethyl ester))-methoxy]acetyl}oxy)butyl)sulfanyl]-3-(hexadecylcarbamoyl)propanoic acid]-poly(ethylene glycol)-ester]” .

For the purpose of orphan designation, the Committee for Orphan Medicinal Products (COMP) considered that the condition originally proposed by the sponsor should be renamed as “treatment of dengue”.

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

The intention to treat the condition with the medicinal product containing poly[2-[(4-{[1-carboxy-2-(hexadecylcarbamoyl)ethyl]sulfanyl}-2,3-bis({2-[((2S)-2-(2-{[(2R)-2-carbamoyl-(2-{[(2S)-1-ethoxy-3-(3-hydroxy-4oxo-1,4-dihydropyridin-1-yl)-1-oxopropan-2-yl]carbamoyl}ethyl]sulfanyl}-3-{[(2S)-1-ethoxy-3-(3-hydroxy-4-oxo-1,4-dihydropyridin-1-yl)-1-oxopropan-2-yl]carbamoyl}propanamido)-3-(3-hydroxy-4-oxo-1,4-dihydropyridin-1-yl)propanoyl Ethyl ester))-methoxy]acetyl}oxy)butyl)sulfanyl]-3-(hexadecylcarbamoyl)propanoic acid]-poly (ethylene glycol)-ester] was considered justified based on preclinical data showing improved survival in the treated subjects.

The condition is life-threatening due to the development of systemic plasma leakage and severe haemorrhage that may lead to shock, in the severe form of the disease. The condition was estimated to be affecting less than 0.1 in 10,000 people 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 poly[2-[(4-{[1-carboxy-2-(hexadecylcarbamoyl)ethyl]sulfanyl}-2,3-bis({2-[((2S)-2-(2-{[(2R)-2-carbamoyl-(2-{[(2S)-1-ethoxy-3-(3-hydroxy-4oxo-1,4-dihydropyridin-1-yl)-1-oxopropan-2-yl]carbamoyl}ethyl]sulfanyl}-3-{[(2S)-1-ethoxy-3-(3-hydroxy-4-oxo-1,4-dihydropyridin-1-yl)-1-oxopropan-2-yl]carbamoyl}propanamido)-3-(3-hydroxy-4-oxo-1,4-dihydropyridin-1-yl)propanoyl Ethyl ester))-methoxy]acetyl}oxy)butyl)sulfanyl]-3-(hexadecylcarbamoyl)propanoic acid]-poly(ethylene glycol)-ester], for treatment of dengue, was adopted by consensus.

2.2.20 Recombinant human type I pancreatic elastase for prevention of arteriovenous access failure in haemodialysis patients, Proteon Therapeutics Limited - EMA/OD/139/13
[Co-ordinators: D. Krievins/ D. O'Connor / L. Fregonese]

The Committee agreed that the condition, arteriovenous access failure in haemodialysis patients, is a distinct medical entity and meets the criteria for orphan designation.

The intention to prevent the condition with the medicinal product containing recombinant human type I pancreatic elastase was considered justified based on clinical data showing improvement of relevant endpoints in patients undergoing haemodialysis.

The condition is chronically debilitating and potentially life threatening as it may lead to inactive dialysis and subsequent deterioration of the renal function. The population of patients eligible for prevention of the condition was approximately 2 in 10,000 people in the European Union, at the time the application was made, based on data from international registries.

The sponsor has also established that there exists no satisfactory method of prevention that has been authorised in the European Union for the population at risk of developing the condition.

A positive opinion for recombinant human type I pancreatic elastase, for prevention of arteriovenous access failure in haemodialysis patients, was adopted by consensus.

2.2.21 Product for treatment of aneurysmal subarachnoid haemorrhage - EMA/OD/131/13
[Co-ordinators: M. Možina / S. Mariz]

The Committee considered that the following issues require clarification by the sponsor:

- Justification of significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential of using their product in combination with nimodipine to improve efficacy in the condition.

No data was submitted to support the basis of the significant benefit of using the product in combination. The sponsor should detail the results of any preclinical and clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of patients.

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 December meeting.

2.2.22 Product for treatment of acute myeloid leukemia - EMA/OD/147/13
[Co-ordinators: B. Dembowska-Bagińska / S. Mariz]

The Committee considered that the following issues require clarification by the sponsor:

- Justification of 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 preliminary clinical study in relapsed and refractory AML patients where pharmacodynamic data were used to justify the assumption of significant benefit.

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 December meeting.

2.3. Evaluation on-going

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

2.4. Validation on-going

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

3. Requests for protocol assistance

3.1. Letters

The COMP was briefed on the significant benefit issues and adopted five protocol assistance letters for the following indications:

3.1.1 Product for treatment of graft-versus-host disease

3.1.2 Product for treatment of Fabry disease

3.1.3 Product for treatment of chronic iron overload requiring chelation therapy

3.2. 1st reports

The protocol assistance advice was discussed for final adoption in the forthcoming meetings for the following indications:

3.2.1 Product for treatment of acromegaly

3.2.2 Product for treatment of chronic non-infectious uveitis

3.3. On-going procedures

The Committee noted the following on-going protocol advice procedures:

3.3.1 Product for treatment of malaria

3.3.2 Product for treatment of Wilson's disease

3.3.3 Product for treatment of hepatocellular carcinoma

4. Overview of applications

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

COMP co-ordinators were appointed for nine 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 Opsumit (Macitentan) for treatment of pulmonary arterial hypertension; Actelion Registration Ltd. (OD/023/11, EU/3/11/909, EMA/H/C/002697)
[Co-ordinators: V. Saano / L. Fregonese]

Following the discussion with the sponsor during the oral explanation on 9 October 2013 and additional data provided by the sponsor on 21 October 2013 the COMP concluded that:

The proposed therapeutic indication "long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class II to III " falls entirely within the scope of the orphan indication of the designated orphan medicinal product.

The prevalence of pulmonary arterial hypertension was estimated to remain below 5 in 10,000 at the time of the review of the designation criteria. The prevalence is still estimated at less than 1.8 in 10,000 in the EU.

The condition is chronically debilitating and life threatening due to progressive dyspnoea and right hearth failure, leading to death in an average period of 2.8 years after diagnosis;

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Opsumit may be of potential significant benefit to those affected by the orphan condition is confirmed. This is justified based on the results of the main pivotal clinical trial showing reduction of morbidity and mortality in patients already treated with currently authorised treatments for pulmonary arterial hypertension. This constitutes a clinically relevant advantage for the patients affected by the condition.

An opinion not recommending the removal of Opsumit /Macitentan (EU/3/11/909) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion (EMA/COMP/684833/2013) was adopted for publication on the EMA website.

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

5.2.1 Cholic Acid FGK for treatment of inborn errors of primary bile acid synthesis responsive to treatment with cholic acid; FGK Representative Service GmbH (EU/3/09/683) [Co-ordinators: A. Magrelli / S. Tsigkos]

The Committee held initial discussion.

5.2.2 Delamanid ((R)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole) for treatment of tuberculosis; Otsuka Novel Products GmbH (EU/3/07/524) [Co-ordinators: V. Stoyanova / L. Fregonese]

Discussion was postponed until update on progress of the MA procedure.

5.2.3 Masican N-(methyl-diazacyclohexyl-methylbenzamide)-azaphenyl-aminothiopyrrole for treatment of malignant gastrointestinal stromal tumours; AB Science (EU/3/04/251) [Co-ordinators: D. O'Connor / S. Mariz]
Discussion was postponed until update on progress of the MA procedure.

5.2.4 PAS-GR (Para-aminosalicylic acid) for treatment of tuberculosis; Lucane Pharma SA (EU/3/10/826) [Co-ordinators: V. Stoyanova / L. Fregonese]

Discussion was postponed until update on progress of the MA procedure.

5.2.5 Translarna (3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid) for treatment of Duchenne muscular dystrophy; PTC Therapeutics Ltd (EU/3/05/278) [Co-ordinators: P. Evers / S. Aarum]

Discussion was postponed until update on progress of the MA procedure.

5.2.6 Winfuran (-)-17(cyclopropylmethyl)-1,14 ß-dihydroxy-4,5 alpha-epoxy-6ß-[N-methyl-trans-3-(3-furyl) acrylamido] morphinan hydrochloride for treatment of uremic pruritus; Toray International U.K. Limited (EU/3/02/115) [Co-ordinators: S. Thorsteinsson / S. Mariz]

Discussion was postponed until update on progress of the MA procedure.

5.3. On-going procedures

5.3.1 Adempas (Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate) for treatment of pulmonary arterial hypertension including treatment of chronic thromboembolic pulmonary hypertension; Bayer Pharma AG (EU/3/07/518)

5.3.2 Cerdelga ((1R,2R)-octanoic acid[2-(2',3'-dihydro-benzo[1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-L-tartaric acid salt) for treatment of Gaucher disease; Genzyme Europe BV (EU/3/07/514)

5.3.3 Cometriq [Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate salt] for treatment of medullary thyroid carcinoma; TMC Pharma Services Ltd (EU/3/08/610)

5.3.4 Cyramza (Ramucirumab) for treatment of gastric cancer; Eli Lilly Nederland B.V. (EU/3/12/1004)

5.3.5 Folcepri (N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-D-gamma-glutamyl-(2S)-2-amino-beta-alanyl-L-alpha-aspartyl-L-cysteine to be used with folic acid) for diagnosis of positive folate receptor status in ovarian cancer; Endocyte Europe, B.V. (EU/3/12/1043)

5.3.6 Gazyva (Obinutuzumab) for treatment of chronic lymphocytic leukaemia; Roche Registration Limited (EU/3/12/1054)

5.3.7 Holoclar (former name: GPLSCD01) (Ex vivo expanded autologous human corneal epithelium containing stem cells) for treatment of corneal lesions, with associated corneal (limbal) stem cell deficiency, due to ocular burns; Chiesi Farmaceutici S.p.A. (EU/3/08/579)

5.3.8 Masiviera (formerly Kinaction) (Masitinib mesilate) for treatment of pancreatic cancer; AB Science (EU/3/09/684)

5.3.9 Neocepri (Folic acid to be used with N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-D-gamma-glutamyl-(2S)-2-amino-beta-alanyl-L-alpha-aspartyl-L-cysteine) for diagnosis of positive folate receptor status in ovarian cancer; Endocyte Europe, B.V. (EU/3/12/1044)

5.3.10 Neofordex (Dexamethasone (40 mg tablet) for treatment of multiple myeloma; Laboratoires CTRS (Cell Therapies Research & Services) (EU/3/10/745)

5.3.11 Nexavar (Sorafenib tosylate), Bayer HealthCare AG, (EMA/H/C/000690, extension of indication to include treatment of differentiated thyroid carcinoma)

- treatment of follicular thyroid cancer (EU/3/13/1199)
- treatment of papillary thyroid cancer (EU/3/13/1200)

5.3.12 Olaparib AstraZeneca AB (Olaparib) for treatment of ovarian cancer; AstraZeneca AB (EU/3/07/501)

5.3.13 Scenesse ([Nle4, D-Phe7]-alfa-melanocyte stimulating hormone, Afamelanotide) for treatment of erythropoietic protoporphyria; Clinuvel (UK) Limited (EU/3/08/541)

5.3.14 Sirturo [Bedaquiline ((1R,2S) 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-(1-naphthyl)-beta-phenyl-3-quinolineethano)] for treatment of tuberculosis; Janssen-Cilag International N.V. (EU/3/05/314)

5.3.15 Sylvant (Chimeric-anti-interleukin-6 monoclonal antibody) for treatment of Castleman's disease; Janssen-Cilag International N.V.; (EU/3/07/508)

5.3.16 Vantobra, Tobramycin (inhalation use) for treatment of *Pseudomonas Aeruginosa* lung infection in cystic fibrosis; PARI Pharma GmbH (EU/3/09/613)

5.3.17 Vimizim (Recombinant human N-acetylgalactosamine-6-sulfatase) for treatment of mucopolysaccharidosis, type IVA (Morquio A syndrome); BioMarin Europe Ltd (EU/3/09/657)

5.3.18 Vynfinit (Vincaleukoblastin-23-oic acid, O4-deacetyl-2-[(2-mercaptoethoxy)carbonyl]hydrazide, disulfide with N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-gamma-glutamyl-L-alpha-aspartyl-L-arginyl-L-alpha-aspartyl-L-alpha-aspartyl-L-cysteine) for treatment of ovarian cancer; Endocyte Europe, B.V. (EU/3/12/959)

6. Procedural aspects

6.1 The European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP)

The Committee re-appointed Dr A. Corrêa-Nunes as the COMP representative to the ENCePP Steering Group for 2014-2016 term.

6.2 Inter-Committee Scientific Advisory Group (IC-SAG) for Oncology

The Committee was briefed on the *Mandate, objectives and rules of procedure for the IC-SAG for Oncology* (EMA/684918/2012).

6.3 Creation of the inter-active PDCO/COMP working group on conditions in rare diseases

The members were asked to express their interest to join the group.

6.4 EMA policy on fee reductions for designated orphan medicinal products

The proposal for the revised EMA policy on fee reduction for designated orphan medicinal products was endorsed by the Committee.

7. Any other business

7.1 Proposal for a publication strategy (including book on rare diseases)

The topic was postponed.

7.2 Grounds of major contribution to patient care

The topic was postponed.

7.3 Similarity group

- Similarity – orphan medicines (EMA/84728/2013)

The members were asked to submit their comments by 6 December 2013 for a discussion at the December COMP meeting.

7.4 Public consultation on the *EC Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another* ENTR/6283/00 Rev 3.

The Committee was briefed on the comments received by the EC during the consultation phase.

Date of next COMP meeting: 10-12 December 2013

List of participants

Chair:

Bruno Sepodes

Vice-Chair:

Lesley Greene	Volunteer patient representative for Eurordis

COMP Members:

André Lhoir	België/Belgique/Belgien
Irena Bradinova	Бълга̀рия
Kateřina Kubáčková	Česká Republika
Vacant	Danmark
Frauke Naumann-Winter	Deutschland
Vallo Tillmann	Eesti
Geraldine O'Dea	Éire/Ireland
Annie Lorence	France
Sigurdur B. Thorsteinsson	Iceland
Armando Magrelli	Italia
Ioannis Kkolos	Κύπρος
Aušra Matulevičienė	Lietuva
Judit Eggenhofer	Magyarország
Albert Vincenti	Malta
Violeta Stoyanova-Beninska	Nederland
Lars Gramstad	Norway
Brigitte Blöchl-Daum	Österreich
Bożenna Dembowska-Bagińska	Polska
Flavia Saleh	Romãnia
Martin Možina	Slovenija
Nomination pending	Slovensko
Veijo Saano	Suomi/Finland
Kerstin Westermark	Sverige
Daniel O'Connor	United Kingdom
Birthe Byskov Holm	Volunteer patient representative for Eurordis
Pauline Evers	Patient representative representing the European Genetic Alliances Network
Aikaterini Moraiti	CHMP Representative
Vacant	EMA Representative
Vacant	EMA Representative

Observers:

Maria Mavris	Eurordis

European Commission:

Agnès Mathieu	DG Health and Consumers (present on 1st and 2nd day only)

EMA:

Stiina Aarum	Head of Orphan Medicines *Ad interim (present on 2nd day only)*
Laura Fregonese	Scientific Officer
Segundo Mariz	Scientific Officer
Stylianos Tsigkos	Scientific Officer
Federica Castellani	Scientific Officer (for 5.1.1)
Agnieszka Wilk-Kachlicka	Assistant
Frederique Dubois	Assistant

Apologies

Members:

Nikolaos Sypsas	Ελλάδα
Josep Torrent Farnell	España
Dainis Krievins	Latvija
Henri Metz	Luxembourg
Ana Corrêa-Nunes	Portugal

Observers:

Antonio Blazquez	Agencia Española de Medicamentos y Productos Sanitarios