



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

10 March 2021  
EMA/COMP/64530/2021  
Human Medicines Division

## Committee for Orphan Medicinal Products (COMP)

### Minutes for the meeting on 19-21 January 2021

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

19 January 2021, 08:30-19:35, remote virtual meeting

20 January 2021, 08:30-19:50, remote virtual meeting

21 January 2021, 08:30-17:35, remote virtual meeting

#### Disclaimers

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

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

Further information with relevant explanatory notes can be found at the end of this document.

#### Note on access to documents

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

---

**Official address** Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

**Address for visits and deliveries** Refer to [www.ema.europa.eu/how-to-find-us](http://www.ema.europa.eu/how-to-find-us)

**Send us a question** Go to [www.ema.europa.eu/contact](http://www.ema.europa.eu/contact) **Telephone** +31 (0)88 781 6000

An agency of the European  
Union



## Table of contents

|             |   |           |
|-------------|---|-----------|
| <b>1.</b>   | <b>Introduction</b>   | <b>6</b>  |
| 1.1.        | Welcome and declarations of interest of members and experts.....  | 6         |
| 1.2.        | Adoption of agenda.....   | 6         |
| 1.3.        | Adoption of the minutes .....   | 6         |
| <b>2.</b>   | <b>Applications for orphan medicinal product designation</b>  | <b>6</b>  |
| <b>2.1.</b> | <b>For opinion .....</b>  | <b>6</b>  |
| 2.1.1.      | (1R,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxamide - EMA/OD/0000043071 .....  | 6         |
| 2.1.2.      | 2-(2-{[2-(1H-benzimidazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide trihydrochloride - EMA/OD/0000043114.....  | 7         |
| 2.1.3.      | autologous CD34+ cells transduced with a lentiviral RNA vector that results in integrated cDNA encoding for functional cystinosin - EMA/OD/0000043857 .....   | 9         |
| 2.1.4.      | - EMA/OD/0000030100 .....   | 10        |
| 2.1.5.      | - EMA/OD/0000043454 .....   | 11        |
| 2.1.6.      | - EMA/OD/0000043102 .....   | 11        |
| 2.1.7.      | - EMA/OD/0000043121 .....   | 11        |
| 2.1.8.      | (2S)-2-[(2S)-4-cyclohexyl-2-{{(2S)-1-(4-fluorobenzoyl)pyrrolidin-2-yl}formamido}butanamido]-N-(1-{{(1S)-1-{{(1S)-1-{{1-[[1-{{2-{{1-[[dimethylamino)methyl]cyclobutyl}carbamoyl}ethyl}carbamoyl}-1-methylethyl}carbamoyl]-1-methylethyl}carbamoyl)-3-methylbutyl}carbamoyl}-1-methylethyl)-4-methylpentanamide acetate - EMA/OD/0000043404 ..... | 12        |
| 2.1.9.      | Autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human claudin 18.2 antigen with CD28 and CD3-zeta intracellular signalling domains - EMA/OD/0000043828 .....  | 14        |
| 2.1.10.     | - EMA/OD/0000043607 .....   | 16        |
| 2.1.11.     | - EMA/OD/0000043730 .....   | 16        |
| 2.1.12.     | rintatolimod - EMA/OD/0000043217 .....  | 17        |
| 2.1.13.     | - EMA/OD/0000043459 .....   | 18        |
| 2.1.14.     | anti-SIGLEC8 IgG1 humanised monoclonal antibody - EMA/OD/0000042924.....  | 19        |
| 2.1.15.     | - EMA/OD/0000043498 .....   | 20        |
| 2.1.16.     | 2'-O-methyl phosphorothioate RNA oligonucleotide, 5'-m <sup>5</sup> CUGm <sup>5</sup> CUGm <sup>5</sup> CUGm <sup>5</sup> CUGm <sup>5</sup> CUGm <sup>5</sup> CUGm <sup>5</sup> CUG-3' - EMA/OD/0000038364.....   | 21        |
| 2.1.17.     | autologous CD34+ hematopoietic stem and progenitor cells transfected with zinc finger nuclease mRNAs SB-mRENH1 and SB-mRENH2 - EMA/OD/0000043829 .....  | 22        |
| 2.1.18.     | - EMA/OD/0000042048 .....   | 23        |
| <b>2.2.</b> | <b>For discussion / preparation for an opinion.....</b>   | <b>23</b> |
| 2.2.1.      | 18-(p-[ <sup>131</sup> i]-iodophenyl)octadecyl phosphocholine - EMA/OD/0000041437 .....   | 23        |
| 2.2.2.      | - EMA/OD/0000041484 .....   | 24        |
| 2.2.3.      | - EMA/OD/0000043808 .....   | 24        |

|             |   |           |
|-------------|---|-----------|
| 2.2.4.      | adeno-associated virus serotype 5 containing the human <i>NR2E3</i> gene -<br>EMA/OD/0000043946 .....   | 24        |
| 2.2.5.      | dodecyl creatine ester, dodecyl creatine ester hydrochloride - EMA/OD/0000044835.....   | 25        |
| 2.2.6.      | 2-[6-(6,7-Dimethoxyquinolin-3-yl)pyridin-3-yl]-N-[3-(1,1,1-trifluoro-2-methylpropan-2-yl)-<br>1,2-oxazol-5-yl]acetamide - EMA/OD/0000045680 .....                                       | 25        |
| 2.2.7.      | Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-Cys-Asp-Met-Ala-Glu-His-Thr-Glu-Arg-Leu-Lys-<br>Ala-Asn-Asp-Ser-Leu-Lys-Leu-Ser-Gln-Glu-Tyr-Glu-Ser-Ile-NH <sub>2</sub> - EMA/OD/0000045713 ... | 26        |
| 2.2.8.      | - EMA/OD/0000046077 .....   | 27        |
| 2.2.9.      | - EMA/OD/0000046254 .....   | 27        |
| 2.2.10.     | - EMA/OD/0000046325 .....   | 27        |
| 2.2.11.     | adeno-associated virus serotype 5 containing the human <i>NR2E3</i> gene -<br>EMA/OD/0000046383 .....   | 27        |
| 2.2.12.     | adeno-associated viral vector serotype 9 expressing codon-optimized human <i>GBA</i> gene -<br>EMA/OD/0000046433 .....  | 28        |
| 2.2.13.     | - EMA/OD/0000046448 .....   | 28        |
| 2.2.14.     | - EMA/OD/0000048780 .....   | 28        |
| <b>2.3.</b> | <b>Revision of the COMP opinions .....</b>  | <b>28</b> |
| <b>2.4.</b> | <b>Amendment of existing orphan designations.....</b>   | <b>29</b> |
| <b>2.5.</b> | <b>Appeal .....</b>   | <b>29</b> |
| 2.5.1.      | tebentafusp - EMA/OD/0000047566.....  | 29        |
| <b>2.6.</b> | <b>Nominations .....</b>  | <b>31</b> |
| 2.6.1.      | New applications for orphan medicinal product designation - Appointment of COMP<br>rapporteurs.....   | 31        |
| <b>2.7.</b> | <b>Evaluation on-going.....</b>   | <b>31</b> |
| <b>3.</b>   | <b>Requests for protocol assistance with significant benefit question</b>   | <b>31</b> |
| <b>3.1.</b> | <b>Ongoing procedures .....</b>   | <b>31</b> |
| 3.1.1.      | - .....   | 31        |
| 3.1.2.      | - .....   | 31        |
| 3.1.3.      | - .....   | 31        |
| 3.1.4.      | - .....   | 32        |
| 3.1.5.      | - .....   | 32        |
| <b>3.2.</b> | <b>Finalised letters.....</b>   | <b>32</b> |
| 3.2.1.      | - .....   | 32        |
| 3.2.2.      | - .....   | 32        |
| 3.2.3.      | - .....   | 32        |
| 3.2.4.      | - .....   | 32        |
| <b>3.3.</b> | <b>New requests.....</b>  | <b>32</b> |
| 3.3.1.      | - .....   | 32        |
| 3.3.2.      | - .....   | 32        |

|             |   |           |
|-------------|---|-----------|
| <b>4.</b>   | <b>Review of orphan designation for orphan medicinal products at time of initial marketing authorisation</b>              | <b>33</b> |
| <b>4.1.</b> | <b>Orphan designated products for which CHMP opinions have been adopted .....</b>   | <b>33</b> |
| <b>4.2.</b> | <b>Orphan designated products for discussion prior to adoption of CHMP opinion ....</b>                                   | <b>33</b> |
| 4.2.1.      | Evrysdi – risdiplam - EMEA/H/C/005145/0000, EMA/OD/0000001899, EU/3/19/2145, EMA/OD/0000039037 .....                      | 33        |
| 4.2.2.      | Nexpovio - selinexor - EMEA/H/C/005127/0000, EU/3/14/1355, EMA/OD/0000043722 ....   | 33        |
| 4.2.3.      | Epidyolex - cannabidiol - EMEA/H/C/004675/II/0005, EMA/OD/165/17, EU/3/17/1959, EMA/OD/0000033940 .....                   | 33        |
| 4.2.4.      | Pemazyre – pemigatinib - EMEA/H/C/005266, EMA/OD/038/18, EU/3/18/2066, EMA/OD/0000039241 .....                            | 33        |
| 4.2.5.      | – berotrastat - EMEA/H/C/005138/0000, EMA/OD/003/18, EU/3/18/2028, EMA/OD/0000045564 .....                                | 34        |
| <b>4.3.</b> | <b>Appeal .....</b>   | <b>34</b> |
| <b>4.4.</b> | <b>On-going procedures .....</b>  | <b>34</b> |
| <b>4.5.</b> | <b>Orphan Maintenance Reports.....</b>  | <b>34</b> |
| <b>5.</b>   | <b>Review of orphan designation for authorised orphan medicinal products at time of marketing authorisation extension</b> | <b>34</b> |
| <b>5.1.</b> | <b>After adoption of CHMP opinion .....</b>   | <b>34</b> |
| <b>5.2.</b> | <b>Prior to adoption of CHMP opinion .....</b>  | <b>34</b> |
| 5.2.1.      | Galafold - migalastat - EMEA/H/C/004059/II/0029, EMA/OD/105/05, EU/3/06/368 .....   | 34        |
| <b>5.3.</b> | <b>Appeal .....</b>   | <b>35</b> |
| <b>5.4.</b> | <b>On-going procedures .....</b>  | <b>35</b> |
| <b>6.</b>   | <b>Application of Article 8(2) of the Orphan Regulation</b>   | <b>35</b> |
| <b>7.</b>   | <b>Organisational, regulatory and methodological matters</b>  | <b>35</b> |
| <b>7.1.</b> | <b>Mandate and organisation of the COMP .....</b>   | <b>35</b> |
| 7.1.1.      | Strategic Review & Learning meetings.....   | 35        |
| 7.1.2.      | Protocol Assistance Working Group (PAWG) .....  | 35        |
| <b>7.2.</b> | <b>Coordination with EMA Scientific Committees or CMDh-v .....</b>  | <b>35</b> |
| 7.2.1.      | Recommendation on eligibility to PRIME – report from CHMP .....   | 35        |
| <b>7.3.</b> | <b>Coordination with EMA Working Parties/Working Groups/Drafting Groups .....</b>   | <b>35</b> |
| 7.3.1.      | Working Party with Patients’ and Consumers’ Organisations (PCWP) .....  | 35        |
| 7.3.2.      | Working Party with Healthcare Professionals’ Organisations (HCPWP).....   | 35        |
| <b>7.4.</b> | <b>Cooperation within the EU regulatory network.....</b>  | <b>35</b> |
| 7.4.1.      | European Commission.....  | 35        |
| 7.4.2.      | COMP Working Group on the orphan regulation .....   | 36        |
| <b>7.5.</b> | <b>Cooperation with International Regulators.....</b>   | <b>36</b> |
| 7.5.1.      | Food and Drug Administration (FDA).....   | 36        |
| 7.5.2.      | Japanese Pharmaceuticals and Medical Devices Agency (PMDA).....   | 36        |

|             |   |           |
|-------------|---|-----------|
| 7.5.3.      | Therapeutic Goods Administration (TGA), Australia .....   | 36        |
| 7.5.4.      | Health Canada.....  | 36        |
| <b>7.6.</b> | <b>Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee .....</b>                    | <b>36</b> |
| <b>7.7.</b> | <b>COMP work plan .....</b>   | <b>36</b> |
| <b>7.8.</b> | <b>Planning and reporting .....</b>   | <b>37</b> |
| 7.8.1.      | List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2020/2021 ..... | 37        |
| 7.8.2.      | Overview of orphan marketing authorisations/applications.....   | 37        |
| <b>8.</b>   | <b>Any other business</b>   | <b>37</b> |
| <b>8.1.</b> | <b>Big Data Training Signpost .....</b>   | <b>37</b> |
| <b>8.2.</b> | <b>ENCePP in the time of COVID.....</b>   | <b>37</b> |
| <b>8.3.</b> | <b>.....</b>  | <b>37</b> |
| <b>8.4.</b> | <b>New Executive Director at the EMA meeting with COMP .....</b>  | <b>37</b> |
| <b>9.</b>   | <b>List of participants</b>   | <b>38</b> |
| <b>10.</b>  | <b>Explanatory notes</b>  | <b>41</b> |

## 1. Introduction

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

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

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

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

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

### 1.2. Adoption of agenda

The agenda for 19-21 January 2021 was adopted with no amendments.

### 1.3. Adoption of the minutes

The minutes for 8-10 December 2020 were adopted with no amendments and will be published on the EMA website.

## 2. Applications for orphan medicinal product designation

### 2.1. For opinion

#### 2.1.1. (1R,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxamide - EMA/OD/0000043071

Alexion Europe S.A.S.; Treatment of paroxysmal nocturnal haemoglobinuria

COMP Rapporteur: Karri Penttila

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

- Number of people affected

The sponsor used only 3 literature sources to estimate the prevalence of the condition. The estimate is significantly lower than the prevalence accepted by the COMP in the recent past.

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

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

In the written response, the sponsor provided additional literature sources and discussion of the prevalence. The paucity of available published information of the condition was acknowledged by the applicant and the COMP and the final estimate of prevalence of 0.4 in 10,000 was accepted.

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

The intention to treat the condition with the medicinal product containing (1R,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxamide was considered justified based on early clinical data showing normalisation of key haematological parameters or maintenance of treatment effect in pre-treated patients.

The condition is life-threatening and chronically debilitating due to the complications of chronic haemolysis, such as abdominal pain, infection, cytopenia, and kidney malfunction, and due to occurrence of thrombosis and haemorrhage in various organs. Vascular complications in the central nervous system are the most common cause of death.

The condition was estimated to be affecting approximately 0.4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (1R,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxamide will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that shows a complete reduction of C3 deposition on patient erythrocytes, which has been linked in published studies with the risk of extravascular haemolysis (EVH). The reduction of risk of EVH would constitute an advantage over currently authorised C5 inhibitors. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (1R,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxamide, for treatment of paroxysmal nocturnal haemoglobinuria, was adopted by consensus.

### **2.1.2. 2-(2-{[2-(1H-benzimidazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide trihydrochloride - EMA/OD/0000043114**

Vifor France S.A.; Treatment of sickle cell disease

COMP Rapporteur: Angelo Loris Brunetta

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

- Number of people affected

The sponsor provided a prevalence estimate which appears to be an under-estimate as the impact of migration does not seem to have been accounted for. The sponsor was asked to justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor was requested to describe and justify the methodology used for the prevalence calculation.

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

In the written response, the sponsor provided a revised prevalence calculation in their written response. In this response efforts were made to address the deficiencies highlighted in the initial prevalence estimate, notably the effect of migration to Europe from Africa in the last 10 years. The COMP recognised that this is a difficult task but found that the final estimate of 2 in 10,000 proposed by the sponsor was adequate for the purpose of an initial designation. This is within the range of previously accepted estimates which have used current publications.

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

The intention to treat the condition with the medicinal product containing 2-(2-{{[2-(1H-benzimidazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide trihydrochloride was considered justified based on reduction of haemolysis, decreased plasma iron level and inflammation indexes.

The condition is life-threatening and chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, acute chest syndrome, chronic kidney disease, pulmonary hypertension and susceptibility to infections.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2-(2-{{[2-(1H-benzimidazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide trihydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate a dose dependent reduction of adhesion of red blood cells and leukocytes to endothelium which led to a reduction in vessel obstruction and restoration of normal blood flow. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-(2-{{[2-(1H-benzimidazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide trihydrochloride, for treatment of sickle cell disease, was adopted by consensus.



### 2.1.3. autologous CD34+ cells transduced with a lentiviral RNA vector that results in integrated cDNA encoding for functional cystinosin - EMA/OD/0000043857

---

Clinical Technology Centre (Ireland) Limited; Treatment of cystinosis

COMP Rapporteur: Lyubina Racheva Todorova

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

- Number of people affected

The prevalence appears to be an underestimate of the current prevalence of this condition. The sponsor was asked to 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 was requested to perform a sensitivity analysis of the reported calculations.

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

In the written response, the sponsor provided a revised prevalence estimate, which was primarily based on a revised bibliography search. The sponsor used birth incidence from the worst-case scenario from Brittany in France to revise their estimate and a life expectancy of 50 years. Using these assumptions an estimate of 0.23 in 10,000 was proposed. The COMP accepted the revisions in the methodology and revised estimate which they rounded off to 0.2 in 10,000 for the purpose of the initial orphan designation.

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

The intention to treat the condition with the medicinal product containing autologous CD34+ cells transduced with a lentiviral RNA vector that results in integrated cDNA encoding for functional cystinosin was considered justified based on non-clinical in vivo data in a valid model of the condition which showed a decrease in cystine content in the kidney. Preliminary clinical data showed an improvement in renal function and a reduction in corneal clouding.

The condition is chronically debilitating and life threatening due to development of renal failure.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous CD34+ cells transduced with a lentiviral RNA vector that results in integrated cDNA encoding for functional cystinosin will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical in vivo and preliminary clinical data that demonstrate a reduction of cystine content and normalisation of renal function. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous CD34+ cells transduced with a lentiviral RNA vector that results in integrated cDNA encoding for functional cystinosin, for treatment of cystinosis, was adopted by consensus.

#### 2.1.4. - EMA/OD/0000030100

---

Treatment of uterine serous carcinoma

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

- Intention to diagnose, prevent or treat

The COMP was of the view that the appropriate orphan indication would be phrased as 'Treatment of endometrial cancer'. Uterine serous carcinoma should be justified as a distinct medical entity or a valid subset. Note that this is for the purpose of orphan medicinal product designation; the sponsor's attention was drawn to the Orphan regulations and relevant guidelines (especially section A of [ENTR/6283/00](#)).

The sponsor was invited to discuss the existing classification systems and any overlaps between the proposed condition and other subsets of endometrial cancer or other types of serous neoplasms of other origin. The sponsor was also asked to further elaborate on distinct features of the proposed orphan condition.

- Number of people affected

The sponsor provided a calculation of the prevalence of the proposed orphan condition, which is perceived as a subset of 'endometrial cancer'.

The sponsor was requested to provide a calculation of the broader condition of 'endometrial cancer' to complement the discussion of the condition.

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

- Significant benefit

The sponsor claims that there are no authorised therapies for the proposed orphan condition, which is perceived as a subset of 'endometrial cancer'.

The sponsor was asked to provide significant benefit discussion of the broader condition of 'endometrial cancer' to complement the discussion of the condition.

In the written response, and during an oral explanation before the Committee on 19 January 2021, the sponsor elaborated on distinct features of serous cells carcinoma. The sponsor's considerations mostly revolved around the benefit-risk considerations for this patient population as well as typical genetic features and poor prognosis. However, upon COMP's questions the sponsor admitted that the science in this field is still evolving, that the differential diagnosis of different endometrial cancers is still challenging and that there exists an overlap between endometrioid and serous subtypes in about 10% of cases. The COMP informed the sponsor that according to the current practice cancers are classified in most cases by organ of involvement or by tissue type. In line with the designation of e.g. ovarian cancer, the appropriate orphan indication in this case would be endometrial cancer.

However, endometrial cancer was estimated by the sponsor to be affecting 40 in 10,000 persons in the EU. Therefore, this condition does not meet the orphan criteria.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 20 January 2021, prior to final opinion.

#### 2.1.5. - EMA/OD/0000043454

Treatment of acute myeloid leukaemia

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 17 December 2020, prior to responding to the list of issues.

#### 2.1.6. - EMA/OD/0000043102

Treatment of Haemophilia A

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

- Significant benefit

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

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the clinical study to justify the assumption of significant benefit over authorised medicinal products with particular attention to emicizumab for the proposed orphan condition.

The sponsor was asked to detail the results of any clinical data to support the significant benefit assumption in the context of the current therapeutic management of haemophilia A patients.

In the written response, and during an oral explanation before the Committee on 19 January 2021, the sponsor provided additional theoretical reasons why their product may offer significant benefit versus products such as emicizumab. During their oral explanation the sponsor reiterated that they had no additional non-clinical in vivo or preliminary clinical data to be able to establish what could potentially be the clinically relevant advantage of their product over authorised medicines. Although the COMP could see the hypothetical benefits, this could not be confirmed by data. As a result, the COMP considered that it was unable to recommend granting an orphan designation for the product.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 January 2021, prior to final opinion.

#### 2.1.7. - EMA/OD/0000043121

Treatment of Haemophilia B

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

- Significant benefit

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

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

The sponsor was asked to detail the results of any clinical data to support the significant benefit assumption in the context of the current therapeutic management of haemophilia B patients.

In the written response, and during an oral explanation before the Committee on 19 January 2021, the sponsor noted hypothetical reasons why their product could offer significant benefit. No additional non-clinical in vivo and/or preliminary clinical data was provided to actually support this claim. During the oral explanation the sponsor reiterated that they had no additional data to support their claim for significant benefit. The COMP after the oral explanation deliberated and decided that insufficient data had been submitted to support significant benefit. As a result, it was agreed by consensus that the COMP could not recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 January 2021, prior to final opinion.

2.1.8. (2S)-2-[(2S)-4-cyclohexyl-2-{{[(2S)-1-(4-fluorobenzoyl)pyrrolidin-2-yl]formamido}butanamido]-N-(1-{{[(1S)-1-{{[(1S)-1-{{1-{{1-{{2-{{1-{{[(dimethylamino)methyl]cyclobutyl}carbamoyl)ethyl}carbamoyl}-1-methylethyl}carbamoyl]-1-methylethyl}carbamoyl)-3-methylbutyl]carbamoyl}-1-methylethyl)-4-methylpentanamide acetate - EMA/OD/0000043404

---

Biopharma Excellence GmbH; Treatment of leishmaniasis

COMP Rapporteur: Zsofia Gyulai

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

- Significant benefit

The sponsor presented in vitro data to support the claim of improved efficacy of the proposed product as compared to the authorised alternatives. However, the clinical positioning of the proposed product was not explained, and no in vivo comparative data was presented.

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

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from non-clinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. Further contextualisation of the results in the current clinical treatment algorithm would be also helpful.

In the written response, and during an oral explanation before the Committee on 19 January 2021, the sponsor clarified that the product is developed for use in front line treatment as monotherapy. The indirect comparison to existing products was made by comparing results obtained in non-clinical models of cutaneous leishmaniasis *in vivo* and was supported by a direct comparison *in vitro*. Limitations of an indirect comparison were acknowledged both by the COMP and the sponsor. Therefore, it was not possible to conclude on the superior efficacy of the proposed new product at this stage. However, assuming at least similar efficacy, the COMP accepted the argument that a topical formulation is likely to be associated with less systemic toxicity of the treatment. This would constitute a clinically relevant advantage. The COMP considered that the sponsor would benefit from seeking protocol assistance to support the proposed development.

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

The intention to treat the condition with the medicinal product containing (2S)-2-[(2S)-4-cyclohexyl-2-{[(2S)-1-(4-fluorobenzoyl)pyrrolidin-2-yl]formamido}butanamido]-N-(1-{[(1S)-1-{[(1S)-1-{1-[(1-{2-(1-[(dimethylamino)methyl]cyclobutyl}carbamoylethyl]carbamoylethyl}carbamoylethyl]carbamoylethyl}carbamoylethyl)-1-methylethyl]carbamoylethyl}-3-methylbutyl]carbamoylethyl}-1-methylethyl)-4-methylpentanamide acetate was considered justified based on non-clinical data demonstrating reduced parasite load and lesion size in a model of cutaneous leishmaniasis.

The condition is chronically debilitating due to weight loss, organ enlargement, recurrent episodes of fever and long-term morbidity. Cutaneous leishmaniasis causes painless chronic skin lesions ranging from nodules to large ulcers that can persist for months to years but eventually heal. Mucosal disease affects nasopharyngeal tissues and can cause gross mutilation of the nose and palate. Visceral leishmaniasis causes irregular fever, hepatosplenomegaly, pancytopenia, and polyclonal hypergammaglobulinemia. The condition is also life-threatening with five percent mortality rate in treated patients with visceral leishmaniasis.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (2S)-2-[(2S)-4-cyclohexyl-2-{[(2S)-1-(4-fluorobenzoyl)pyrrolidin-2-yl]formamido}butanamido]-N-(1-{[(1S)-1-{[(1S)-1-{1-[(1-{2-(1-[(dimethylamino)methyl]cyclobutyl}carbamoylethyl]carbamoylethyl}carbamoylethyl}carbamoylethyl)-1-methylethyl]carbamoylethyl}-3-methylbutyl]carbamoylethyl}-1-methylethyl)-4-methylpentanamide acetate will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that the product can be used topically. In a non-clinical model and in *in vitro* experiments the product indicated potency at least comparable in terms of parasite load reduction to that of the authorised comparators. In addition, the product is expected to be used as a topical treatment, which would be of advantage over the existing systemic treatments. The Committee considered that this would constitute a clinically relevant advantage.

A positive opinion for (2S)-2-[(2S)-4-cyclohexyl-2-{{(2S)-1-(4-fluorobenzoyl)pyrrolidin-2-yl}formamido}butanamido]-N-(1-{{(1S)-1-{{(1S)-1-{{1-{{(1-{{2-{{1-{{[(dimethylamino)methyl]cyclobutyl}carbamoyl}ethyl]carbamoyl}-1-methylethyl}carbamoyl]-1-methylethyl}carbamoyl)-3-methylbutyl}carbamoyl}-3-methylbutyl}carbamoyl}-1-methylethyl)-4-methylpentanamide acetate, for treatment of leishmaniasis, was adopted by consensus.

#### 2.1.9. Autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human claudin 18.2 antigen with CD28 and CD3-zeta intracellular signalling domains - EMA/OD/0000043828

---

ICON Clinical Research Limited; Treatment of gastric cancer

COMP Rapporteur: Brigitte Schwarzer-Daum

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

- Intention to treat

As regards to the data in the preliminary clinical settings, the sponsor was invited to discuss to what extent the observed effects may be attributed to the proposed product and the bridging therapy used.

- Number of people affected

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

The sponsor was invited to:

- a) elaborate on the duration of the condition taking into consideration all stages of the disease and by referring to recent sources,
- b) take into consideration the available incidence from ECIS and provide an estimate of prevalence taking into consideration the duration of the disease.

The sponsor was requested to 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 was asked to perform a sensitivity analysis of the reported calculations.

- Significant benefit

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

The sponsor was asked to detail the results of the clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients. A discussion of the depth and duration of responses in comparison to the authorised products was requested in that regard.

In the written response, and during an oral explanation before the Committee on 19 January 2021, the sponsor submitted regarding the medical plausibility updated observations from the phase I study. 22 advanced gastric cancer patients (median 2 prior

lines of therapy, range 1–5) had received the proposed product. In the updated information the sponsor reported 10 confirmed partial responders. It was also clarified that a total of 16 patients (73%) received at least 1 cycle of bridging therapy and 6 patients (27%) did not receive bridging therapy.

With regards to the rarity of gastric cancer, an additional methodology is used to calculate an estimate derived from ECIS incidence and the survival of different stages as per 2008 data from National Cancer Database (Ajani et al, 2017).

With regards to the issue of SB the sponsor further elaborated on the newly discussed set of data. It was reported that of 22 patients, 10 patients achieved confirmed partial response (PR), 1 patient with an unconfirmed PR, 6 stable disease (SD), and 5 patients with progressive disease (PD). When four patients who received only 1 prior line of systemic therapy were excluded in this analysis, an estimate of 43.8% ORR was observed for the remaining patients who received at least 2 prior lines of systemic therapy. In comparison, ORRs of 15.5% and 4.5% are reported for the two approved third-line treatments, pembrolizumab and trifluridine/tipiracil, respectively.

The COMP considered that given that the bridging therapy used in the study would introduce noise to the efficacy signal of the product, emphasis should be given to those 6 patients without bridging therapy, noting 5 out of 6 partial remissions. The sponsor was also asked during the oral explanation to elaborate on the previous treatments received by these patients.

The COMP considered that based on these observations, the significant benefit can be considered justified.

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

The intention to treat the condition with the medicinal product containing autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human claudin 18.2 antigen with CD28 and CD3-zeta intracellular signalling domains was considered justified based on responses in treated patients with advanced disease.

The condition is life-threatening with poor overall survival.

The condition was estimated to be affecting approximately 3.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human claudin 18.2 antigen with CD28 and CD3-zeta intracellular signalling domains will be of significant benefit to those affected by the condition. The sponsor has provided clinical data supporting responses in treated patients with advanced gastric cancer, who had previously received several lines of treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human claudin 18.2

antigen with CD28 and CD3-zeta intracellular signalling domains, for treatment of gastric cancer, was adopted by consensus.

#### 2.1.10. - EMA/OD/0000043607

---

Prevention of retinopathy of prematurity

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

- Intention to diagnose, prevent or treat

To establish correctly whether there exists a scientific rationale for the development of the proposed product for prevention of retinopathy of prematurity (ROP) the sponsor was requested to further elaborate on the relevance of the nonclinical models used for the prevention of retinopathy of prematurity, with regards to the intended scope (prevention rather than treatment), and relevance of studied endpoints.

In the written response, and during an oral explanation before the Committee on 19 January 2021, the sponsor provided a reply to the list of questions on significant benefit. It was noted by the COMP that no new argumentation based on the models was provided, and thus the initial doubts on the medical plausibility were not addressed. Additional data on ROP pathophysiology, the role of vascular endothelial growth factor (VEGF) and the validity of malondialdehyde (MDA) as an oxidative stress marker were provided, but it is not clear how this 'new' data is supposed to address the deficiencies noted on the data generated in the nonclinical models. The COMP requested further clarifications during the oral explanation which was not provided by the sponsor.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 20 January 2021, prior to final opinion.

#### 2.1.11. - EMA/OD/0000043730

---

Treatment of primary aldosteronism

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

- Number of people affected

The sponsor provided a prevalence estimate based on the assumption that the estimate should be based on tertiary care data. The COMP noted that the literature notes higher estimates for the prevalence as it is reported in the public domain that under-reporting is common. The proposal for the prevalence estimate, therefore, would appear to be short of what could be a more encompassing estimate.

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

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

- Significant benefit



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

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the data they have to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

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

In the written response, and during an oral explanation before the Committee on 20 January 2021, the sponsor provided response for the prevalence and significant benefit questions. The sponsor confirmed their opinion, that the use of tertiary care data was most accurate in the determination of prevalence. Concerning the comparison to spironolactone the sponsor could not offer preliminary data of comparative use or use in combination regarding relative efficacy. During the COMP plenary the discussion focused primarily around the methodology used for the prevalence calculation. The committee continued to highlight the need to include primary care data noting that even though it might be less reliable (partly due to under reporting), it is nonetheless being reported at rates varying from 2 to 6% of primary hypertension cases. The number of cases being reported in primary care would indeed then push the prevalence well above 5 in 10,000. The sponsor could not refute this observation. Concerning the question on significant benefit it was noted that the product could offer similar blood pressure controlling effects to spironolactone with a different safety profile. The potential for a better safety profile was recognised but the numbers studied with the sponsor's product are much too low for a satisfactory comparison at this early stage of development.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 20 January 2021, prior to final opinion.

#### 2.1.12. [rintatolimod - EMA/OD/0000043217](#)

---

Hemispherx Biopharma Europe; Treatment of pancreatic cancer

COMP Rapporteur: Brigitte Schwarzer-Daum

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

- Significant benefit

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

In particular, the sponsor was invited to detail the particulars of the studied populations and the historical control group discussed, in order to ensure comparability and relevance of the reported outcomes.

In the written response, the sponsor further elaborated on the studied population in the expanded access program, and included an additional control group namely group B (n=27), which is a subset of original control group obtained by selection of all patients with a time from last FOLFIRINOX dose to progression above the median time for the entire Original Control Group (n=54). In control group B, the median time of last FOLFIRINOX

dose to progression was comparable to the time between last dose of FOLFIRINOX and treatment in the experimental treatment arm. The COMP accepted the comparability of the cohorts for the purpose of the designation.

With regards to the comparisons with this additional group B, an improvement in OS of 19 vs 12 months and in PFS12.0 vs 8 m was noted by the COMP. These differences were statistically significant.

In light of the newly submitted analysis, it was considered that an improvement of survival may be attributed to the product when administered after treatment with FOLFIRINOX regimen. The oral explanation was therefore cancelled on 20 January 2021. The Committee agreed that the condition, pancreatic cancer, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing rintatolimod was considered justified based on preliminary clinical observations that support improved survival when the product is used after first line treatment.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing rintatolimod will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate improved survival when the product is used after administration of first line therapy. The Committee considered that this constitutes a clinically relevant advantage.

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

### 2.1.13. - EMA/OD/0000043459

---

Treatment of hepatocellular carcinoma (HCC)

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

- Significant benefit

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

The sponsor was requested to further discuss the arguments provided for significant benefit in the context of the current therapeutic management of patients and to elaborate on the results from clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 20 January 2021, the sponsor presented argumentation and limited data in support of significant benefit. The only data that could be considered for SB comes from 7 HCC

patients receiving the proposed product as monotherapy after failing sorafenib. Overall survival (OS) for second line of the proposed product was comparable to regorafenib as second line (indirect comparison). The COMP further discussed this point with the sponsor during the oral explanation and it became apparent that the data was insufficient to establish clinically relevant advantage to regorafenib. Moreover, it was noted that the sponsor did not compare to other products used in the treatment of this target patient population namely cabozantinib, ramucirumab and nivolumab. It was noted that developing systemic immune response against alpha fetoprotein (AFP) and human telomerase reverse transcriptase (hTERT) may not be enough because as it is not known how this translates into longer OS in HCC.

In their presentation the sponsor showed a progression delaying effect of the proposed product combined with anti-VEGF antibody in an HCC nonclinical model as well as complete response (CR) in 10% of treated group, as compared to 0% for the anti-VEGF control group. This is promising but could not be considered in support of significant benefit as it had not been done in a sorafenib refractory nonclinical model.

The following arguments were not supported by data: "The Sponsor argued for a possible combination with either of these second-line options, as the combination could translate into synergistic anti-tumoral effects of significant benefit to these HCC patients. This combination strategy would particularly be a clinical advantage for HCC patients, as this indication is known to be associated with immune cell dysfunction".

The COMP considered that the sponsor had not provided sufficient data to support significant benefit and thus could not recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 21 January 2021, prior to final opinion.

#### 2.1.14. anti-SIGLEC8 IgG1 humanised monoclonal antibody - EMA/OD/0000042924

Turnkey Pharmaconsulting Ireland Limited; Treatment of eosinophilic gastritis

COMP Rapporteur: Geraldine O'Dea

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

- Intention to diagnose, prevent or treat

Eosinophilic gastritis should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (especially section A of [ENTR/6283/00](#)).

The sponsor was invited to discuss the potential overlap between eosinophilic gastritis, and other eosinophilic gastrointestinal disorders (EGIDs), and in particular eosinophilic gastroenteritis.

In the written response, and during an oral explanation before the Committee on 20 January 2021, the sponsor discussed the interaction with the agency and with FDA and remained open to further amendments of the proposed indication. The totality of EGIDs is argued not to be a distinct medical entity, on the basis of classification systems (such as ICD-11 and MedDRA codes) which do not have collective terms, as well as with reference to

publications that refer to anatomical sites as independent entities. It was agreed with the sponsor to broaden the condition to “treatment of eosinophilic gastroenteritis” and therein include all populations with eosinophilic infiltration spanning stomach and small intestine. Therefore, all cases of EG and EGE/EE would be accounted for.

During the oral explanation the sponsor agreed to amend the proposed estimation to “treatment of eosinophilic esophagitis” and provided a revised prevalence calculation concluding at not more than 2 in 10,000. The COMP considered that the revised condition was acceptable, the prevalence would be less than 2 in 10,000, and that the criteria have been justified.

Following review of the application by the Committee, it was agreed to rename the indication to treatment of eosinophilic gastroenteritis.

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

The intention to treat the condition with the medicinal product containing Anti-SIGLEC8 IgG1 humanised monoclonal antibody was considered justified based on histological and clinical improvements in treated patients.

The condition is chronically debilitating in particular due to vomiting, retrosternal or epigastric pain, dyspepsia, bleeding and gastric outlet obstruction.

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

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

A positive opinion for anti-SIGLEC8 IgG1 humanised monoclonal antibody, for treatment of eosinophilic gastroenteritis, was adopted by consensus.

#### 2.1.15. - EMA/OD/0000043498

##### Treatment of eosinophilic enteritis

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 proposed condition should be justified as a distinct medical entity or a valid subset for the purpose of orphan designation. The sponsor was invited to clarify to what extent the different eosinophilic gastrointestinal disorders (EGIDs) can be considered as anatomical subsites of the same underlying condition. In particular the differences between eosinophilic gastritis and eosinophilic gastroenteritis should be clarified.

In the written response, and during an oral explanation before the Committee on 20 January 2021, the sponsor discussed the interaction with the agency and with FDA and remained open to further amendments of the proposed indication. The totality of EGIDs is argued not to be a distinct medical entity, on the basis of classification systems and reference to publications. Nevertheless, a potential overlap with eosinophilic gastroenteritis in particular was acknowledged. An orphan designation was awarded to eosinophilic gastroenteritis (EMA/OD/0000042924).

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 21 January 2021, prior to final opinion.

#### 2.1.16. 2'-O-methyl phosphorothioate RNA oligonucleotide, 5'-m<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUG-3' - EMA/OD/0000038364

---

Vico Therapeutics B.V.; Treatment of spinocerebellar ataxia (SCA)

COMP Rapporteur: Dinah Duarte

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

- Intention to diagnose, prevent or treat

The sponsor provided data on the changes that the administration of the product results in a reduction of the mutant proteins. Nevertheless, the relationship between the reduction of the mutant proteins and the clinical symptoms of the disease has not been adequately justified.

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of spinocerebellar ataxia the sponsor was asked to further elaborate on the interpretation of the results obtained in the nonclinical model, namely the relationship between the reduction of the mutant proteins and potential phenotypic outcomes of the disease.

In the written response, the sponsor presented the data to support that the target protein lowering will improve phenotype was based on different SCA disease models as well as on several therapeutic mechanisms. It was considered that the results of several other models of SCA have shown a plausible link/relationship between the reduction of the mutant proteins in SCA and improved motor performance. Therefore, the intention to treat the condition with the medicinal product containing 2'-O-methyl phosphorothioate RNA oligonucleotide, 5' m<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUG-3' was considered justified and oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing 2'-O-methyl phosphorothioate RNA oligonucleotide, 5'-m<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUG-3' was considered justified based on preclinical data in relevant disease model for spinocerebellar ataxia demonstrating that treatment was able to reduce the mutant protein. Based on literature data, several models of spinocerebellar ataxia have shown a plausible link/relationship between the reduction of the mutant proteins in spinocerebellar ataxia and improved motor performance, therefore the use of surrogate marker of spinocerebellar ataxia (ATXN1/ATXN3 protein reduction) is acceptable.

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

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

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

A positive opinion for 2'-O-methyl phosphorothioate RNA oligonucleotide, 5'-m<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUGm<sup>5</sup>CUG-3', for treatment of spinocerebellar ataxia, was adopted by consensus.

#### 2.1.17. autologous CD34+ hematopoietic stem and progenitor cells transfected with zinc finger nuclease mRNAs SB-mRENH1 and SB-mRENH2 - EMA/OD/0000043829

---

Genzyme Europe B.V.; Treatment of sickle cell disease (SCD)

COMP Rapporteur: Angelo Loris Brunetta

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

- Intention to diagnose, prevent or treat

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of sickle cell disease, the sponsor should further elaborate on the available data in SCD settings, including any observations in additional patients and longer follow-up data. The sponsor was also invited to elaborate on the reason of an apparent halt in recruitment of further participants in the clinical study.

These clarifications would also be necessary to establish significant benefit.

In the written response, the sponsor:

- a) clarified that the apparent halt in the study pertained to a different program for which the sponsor is not responsible,
- b) submitted updated data from the ongoing clinical study including an additional patient and prolonged follow up periods. As of December 2020, three patients have been treated with the product (out of the 6 enrolled), all of whom had experienced multiple vaso-occlusive crises (VOC) episodes in the past.

It was noted in particular that the first patient was of HbSS (homozygous genotype) and on hydroxyurea 500 mg daily for several years, had frequent hospitalizations due to 10 severe VOCs including hospitalizations within the past 2 years prior to study enrolment. Similarly, the second treated patient had a HbSS genotype and a complex medical history of numerous VOCs and receiving chronic RBC (red blood cell) exchanges since she was 7 years old. The third treated patient also had a previous history of chronic RBC transfusions and a VOC in the 2 years prior to enrolment. The sponsor notes that these patients have recently completed 52 and 13 weeks, and 29 days of follow up post autologous CD34+ hematopoietic stem and progenitor cells transfected with zinc finger nuclease mRNAs SB-mRENH1 and SB-mRENH2 infusion, respectively without recurrence of previous SCD symptoms. Increases in expression of HbF have also been reported in accordance with the assumed mechanism of action.

Based on this data it was considered that the sponsor had reported improvements in the manifestations of the disease in two patients, up to a year after treatment. Since the long-term effects may obviate the need of continuous treatment, a clinically relevant advantage versus hydroxyurea was also be considered acceptable. Therefore the oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing autologous CD34+ hematopoietic stem and progenitor cells transfected with zinc finger nuclease mRNAs SB-mRENH1 and SB-mRENH2 was considered justified based on preliminary clinical observations supporting a reduction in the number of vaso-occlusive crises.

The condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, acute chest syndrome, chronic kidney disease, pulmonary hypertension and susceptibility to infections, and life-threatening with reduced survival;

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous CD34+ hematopoietic stem and progenitor cells transfected with zinc finger nuclease mRNAs SB-mRENH1 and SB-mRENH2 will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations supporting a reduction in vaso-occlusive crises, as well as long term effects that may obviate the need of frequent treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous CD34+ hematopoietic stem and progenitor cells transfected with zinc finger nuclease mRNAs SB-mRENH1 and SB-mRENH2, for treatment of sickle cell disease, was adopted by consensus.

#### **2.1.18. - EMA/OD/0000042048**

---

Treatment of acute respiratory distress syndrome

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 5 January 2021, prior to responding to the list of issues.

## **2.2. For discussion / preparation for an opinion**

### **2.2.1. 18-(p-[<sup>131</sup>I]-iodophenyl)octadecyl phosphocholine - EMA/OD/0000041437**

---

Scendea (NL) B.V.; Treatment of lymphoplasmacytic lymphoma

COMP Rapporteur: Karri Penttila

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

The intention to treat the condition with the medicinal product containing 18-(p-[<sup>131</sup>I]-iodophenyl)octadecyl phosphocholine was considered justified based on preliminary clinical data in pre-treated patients showing high overall response rates and durability of some responses.

The condition is life-threatening and chronically debilitating due to bone marrow dysfunction, lymphadenopathy, splenomegaly and paraproteinaemia resulting in hyperviscosity, autoimmunity, cryoglobulinaemia, coagulopathies and neuropathies.

The condition was estimated to be affecting approximately 0.4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 18-(p-[<sup>131</sup>I]-iodophenyl)octadecyl phosphocholine will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that patients refractory to rituximab or ibrutinib (or both) may achieve clinically meaningful responses. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 18-(p-[<sup>131</sup>I]-iodophenyl)octadecyl phosphocholine, for treatment of lymphoplasmacytic lymphoma, was adopted by consensus.

#### 2.2.2. - EMA/OD/0000041484

---

Treatment of fulminant hypermetabolic crisis secondary to calcium dysregulation in skeletal muscle

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 February meeting.

#### 2.2.3. - EMA/OD/0000043808

---

Treatment of bronchopulmonary dysplasia

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 February meeting.

#### 2.2.4. adeno-associated virus serotype 5 containing the human *NR2E3* gene - EMA/OD/0000043946

---

Ocugen Limited; Treatment of retinitis pigmentosa

COMP Rapporteur: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing adeno-associated virus serotype 5 containing the human *NR2E3* gene was considered justified based on non-clinical in vivo data in models of the condition showing a restoration of visual function through improved electroretinogram measurements.

The condition is chronically debilitating due to the development of nyctalopia (night blindness) and tunnel vision that progresses to total blindness.

The condition was estimated to be affecting approximately 3.7 in 10,000 persons in the European Union, at the time the application was made.



In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated virus serotype 5 containing the human *NR2E3* gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate a restoration of visual function by restoring the function of the *NR2E3*, *RHO* and *PDE6B* genes which are different to the gene targeted by Luxturna. This would target a broader and different patient population. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for containing adeno-associated virus serotype 5 containing the human *NR2E3* gene, for treatment of retinitis pigmentosa, was adopted by consensus.

#### 2.2.5. [dodecyl creatine ester, dodecyl creatine ester hydrochloride - EMA/OD/0000044835](#)

---

Ceres Brain Therapeutics S.A.S.; Treatment of creatine transporter deficiency syndrome

COMP Rapporteur: Vallo Tillmann

Following review of the application by the Committee, it was agreed to rename the indication to treatment of creatine deficiency syndromes.

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

The intention to treat the condition with the medicinal product containing dodecyl creatine ester, dodecyl creatine ester hydrochloride was considered justified based on non-clinical data in two valid models of the condition showing improvements in novel object recognition.

The condition is chronically debilitating due to cognitive impairment, absence of expressive speech, severe language delay, autistic behaviour, epilepsy, and developmental delay.

The condition was estimated to be affecting approximately 0.02 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for dodecyl creatine ester hydrochloride, for treatment of creatine deficiency syndromes, was adopted by consensus.

#### 2.2.6. [2-\[6-\(6,7-Dimethoxyquinolin-3-yl\)pyridin-3-yl\]-N-\[3-\(1,1,1-trifluoro-2-methylpropan-2-yl\)-1,2-oxazol-5-yl\]acetamide - EMA/OD/0000045680](#)

---

Southwood Research Limited; Treatment of medullary thyroid carcinoma

COMP Rapporteur: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing 2-[6-(6,7-dimethoxyquinolin-3-yl)pyridin-3-yl]-N-[3-(1,1,1-trifluoro-2-methylpropan-2-yl)-1,2-oxazol-5-yl]acetamide was considered justified based on preliminary clinical observations in previously treated medullary thyroid cancer patients with advanced disease who responded to treatment with the product.

The condition is chronically debilitating in particular due to symptoms such as dysphagia, coughing, dyspnoea, flushing and diarrhoea, and life threatening with 5-year survival rates as low as 40% for patients with distant metastases.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2-[6-(6,7-dimethoxyquinolin-3-yl)pyridin-3-yl]-N-[3-(1,1,1-trifluoro-2-methylpropan-2-yl)-1,2-oxazol-5-yl]acetamide will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that show responses in patients with advanced medullary thyroid cancer who had previously failed treatment with existing products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-[6-(6,7-dimethoxyquinolin-3-yl)pyridin-3-yl]-N-[3-(1,1,1-trifluoro-2-methylpropan-2-yl)-1,2-oxazol-5-yl]acetamide, for treatment of medullary thyroid carcinoma, was adopted by consensus.

#### 2.2.7. [Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-Cys-Asp-Met-Ala-Glu-His-Thr-Glu-Arg-Leu-Lys-Ala-Asn-Asp-Ser-Leu-Lys-Leu-Ser-Gln-Glu-Tyr-Glu-Ser-Ile-NH<sub>2</sub> - EMA/OD/0000045713](#)

---

Raremoon Consulting Esp S.L.; Treatment of spinal cord injury

COMP Rapporteur: Martin Mozina

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

The intention to treat the condition with the medicinal product containing Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-Cys-Asp-Met-Ala-Glu-His-Thr-Glu-Arg-Leu-Lys-Ala-Asn-Asp-Ser-Leu-Lys-Leu-Ser-Gln-Glu-Tyr-Glu-Ser-Ile-NH<sub>2</sub> was considered justified based on non-clinical in vivo data using models of the condition showing recovery of locomotive and bladder function.

The condition is life-threatening and chronically debilitating due to sensory and motor loss of function in the limbs, with reduced life expectancy.

The condition was estimated to be affecting approximately 4.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-Cys-Asp-Met-Ala-Glu-His-Thr-Glu-Arg-Leu-Lys-Ala-Asn-Asp-Ser-Leu-Lys-Leu-Ser-Gln-Glu-Tyr-Glu-Ser-Ile-NH<sub>2</sub> will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical in vivo data that demonstrate an improvement in respiratory function in the chronic spinal cord injury setting where there are no authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-Cys-Asp-Met-Ala-Glu-His-Thr-Glu-Arg-Leu-Lys-Ala-Asn-Asp-Ser-Leu-Lys-Leu-Ser-Gln-Glu-Tyr-Glu-Ser-Ile-NH<sub>2</sub>, for treatment of spinal cord injury, was adopted by consensus.

#### 2.2.8. - [EMA/OD/0000046077](#)

---

Treatment of Krabbe disease

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

#### 2.2.9. - [EMA/OD/0000046254](#)

---

Treatment of soft tissue sarcoma

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 February meeting.

#### 2.2.10. - [EMA/OD/0000046325](#)

---

Prevention of bronchopulmonary dysplasia

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 February meeting.

#### 2.2.11. [adeno-associated virus serotype 5 containing the human \*NR2E3\* gene - EMA/OD/0000046383](#)

---

Ocugen Limited; Treatment of Leber congenital amaurosis

COMP Rapporteur: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing adeno-associated virus serotype 5 containing the human *NR2E3* gene was considered justified based on non-clinical in vivo data in a model of the condition showing an improvement in retinal function as based on electroretinogram measurements.

The condition is chronically debilitating due to loss of sight.

The condition was estimated to be affecting approximately 0.9 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated virus serotype 5 containing the human *NR2E3* gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate an improvement in retinal function associated with restoration of the *CEP290* gene, which is different to the gene targeted by Luxturna. This would target a broader and different patient population. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus serotype 5 containing the human *NR2E3* gene, for treatment of Leber congenital amaurosis, was adopted by consensus.

#### 2.2.12. [adeno-associated viral vector serotype 9 expressing codon-optimized human \*GBA\* gene - EMA/OD/0000046433](#)

---

PPD Bulgaria EOOD; Treatment of Gaucher disease

COMP Rapporteur: Robert Nistico

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 9 expressing codon-optimized human *GBA* gene was considered justified based on non-clinical in vivo data showing an improvement in motor behavioural deficits.

The condition is chronically debilitating in particular due to hepatosplenomegaly, thrombocytopenia, anaemia, bone disease, as well as neurological manifestations in the neuronopathic form of the condition, and life-threatening with reduced life expectancy.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector serotype 9 expressing codon-optimized human *GBA* gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate an improvement in motor behavioural deficit which cannot be achieved with existing replacement therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 9 expressing codon-optimized human *GBA* gene, for treatment of Gaucher disease, was adopted by consensus.

#### 2.2.13. [- EMA/OD/0000046448](#)

---

Treatment of ATTR amyloidosis

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

#### 2.2.14. [- EMA/OD/0000048780](#)

---

Treatment of Dravet syndrome

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

### 2.3. **Revision of the COMP opinions**

None

## 2.4. Amendment of existing orphan designations

None

## 2.5. Appeal

### 2.5.1. tebentafusp - EMA/OD/0000047566

---

Pharma Gateway AB; Treatment of uveal melanoma (UM)

COMP appeal rapporteur: Dinko Vitezic

In the grounds for appeal, and during an oral explanation before the Committee on 19 January 2021, the sponsor presented detailed grounds:

#### 1. Key characteristics of UM

Regarding the clinical characteristics, unlike other melanomas, UM patients present with primary ocular lesion, usually diagnosed by ophthalmologists and unlike other melanomas, UM spreads almost exclusively via blood. In addition, 50% of cases metastasize, and uniquely to UM, the first site of metastasis is the liver in 90% of cases.

According to the sponsor, the distinctive genetics and biology of UM are directly linked to the fact that authorised melanoma treatments are considered to be ineffective for metastatic UM. Although there is some minimal overlap in the initiating mutations of the three non-epithelial melanomas (i.e. inactivation in GNAQ/11), the overlap is not systematic (see section on 'leptomeningeal melanocytic neoplasms' below) and furthermore additional chromosomal alterations (e.g. monosomy 3 and polysomy 8q) are unique to, and pathognomonic for, UM, and determine the clinical course of UM patients. Non-systematic, minimal genetic overlap does not constitute similarity.

One of the differences of the histopathological characteristics is that UM arises out of completely different tissue to all other melanomas, including LM, BNLM, and epithelial and skin melanomas. Unlike the vast majority of melanomas, UM develops within non-epithelial tissues from melanocytes with distinct biology, and the tumour is generally localised in the uveal tract.

Regarding the pathophysiology characteristics, the aetiology of UM is largely unknown. The sponsor claims that unlike cutaneous melanoma, ultra-violet light is not a risk factor and UM does not exhibit the genetic signature of UVR damage. The haematogenous spread of UM to the liver requires cells to transit the heart and lungs, prior to reaching the liver. The pathology of metastatic UM helps to explain its distinctive lack of response to immunotherapies; metastatic tumour cells typically form multi-focal aggregates and nodules walled off by collagenous tissue. Anti-PD1 and CTLA-4 treatments are ineffective in UM, due to the above-described absence of cytotoxic immune cells and tumour specific factors that mediate exclusion of cytotoxic immune cells.

#### 2. International Disease Classification Systems

The WHO Classification of Tumours is the international standard for the classification of tumours. The WHO Classification of Skin Tumours (Cochran et al., 2018) clearly classifies UM as a distinct medical entity.

#### 3. Distinction between uveal melanoma and (i) leptomeningeal melanoma; and (ii) blue nevus-like melanoma

According to the sponsor, incidental and spurious overlap of mutations found in UM, malignant LMNs and BNLM does not constitute a similarity without consideration of the role of mutations in shared disease characteristics. UM, malignant LMNs and BNLM arise from non-epithelial melanocytes but produce completely different melanomas with differing disease characteristics, dissemination routes and outcomes. Malignant LMNs and BNLM share initiating mutations with UM; however, all other characteristics beyond this commonality are distinctly different. Along with the aetiology, disease characteristics rather than show similarity, the driver mutations and chromosomal changes of UM characterise its distinctiveness from all other melanomas. To further illustrate that overlap of mutations does not preclude a disease as a distinct medical entity the sponsor notes that lung, colon and gastric adenocarcinomas are epithelial in origin, but produce distinctly different adenocarcinomas in different organs, (i.e. distinct entities) with differing dissemination pathways, differing clinical courses and treatments. Moreover, they share several key driver mutations, at least one of which (epidermal growth factor receptor, EGRF) is target by licensed medicines (e.g. ramucirumab, for colorectal and gastric cancer, and non-small cell lung cancer).

Following review of the application by the Committee, it was agreed that there are differences among melanomas, in terms of distinct aetiology, histopathological, pathophysiological, clinical characteristics and treatment. About 50% of the patients develop metastasis, predominantly in the liver (>80%) which makes liver directed therapies the preferred therapeutic options in the lack of efficient systemic therapies (for example lack of activity (e.g. BRAF inhibitors) in uveal melanoma with current melanoma treatments). Based on the different therapeutic options, many clinical trials on melanoma exclude patients with uveal melanoma and there are clinical trials designed in uveal melanoma only.

The COMP acknowledged the WHO classification and they recognised that the clinical guidelines are different for cutaneous melanoma and uveal melanoma.

The COMP considered that although there is a genetic overlap between uveal and blue nevus melanoma and leptomeningeal melanoma, the aetiology, histopathological, pathophysiological and clinical characteristics and the treatment, in combination with the driver mutations of UM characterise its distinctiveness from all other melanomas.

Based on the above and taking into account the SAG advice, the COMP considered that for the purpose of the European orphan designation, the arguments presented were sufficient to consider uveal melanoma a condition suitable for orphan designation.

The condition is a distinct medical entity that would be acceptable for the purpose of orphan designation on the basis of distinct aetiology, histopathological, pathophysiological, genetic and clinical characteristics.

The intention to treat the condition with the medicinal product containing tebentafusp was considered justified based on objective responses in patients with relapsed/refractory uveal melanoma.

The condition is life-threatening with a reduced survival in relapsed/refractory metastatic disease and chronically debilitating due to vision impairment (enucleation of the affected eye) and pain.

The condition was estimated to be affecting approximately 0.88 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tebentafusp will be of significant benefit to those affected by the condition. The sponsor has provided data that show objective responses in patients with relapsed/ refractory disease. The Committee considered that this constitutes a clinically relevant advantage.

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

A positive opinion for tebentafusp, for treatment of uveal melanoma, was adopted by majority (27 out of 31 votes). The Norwegian COMP member agreed with the above-mentioned recommendation of the COMP.

The divergent positions (Brigitte Schwarzer-Daum, Armando Magrelli, Robert Nistico, Elisabeth Johanne Rook) were appended to this opinion.

## **2.6. Nominations**

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

---

COMP coordinators were appointed for 11 applications.

## **2.7. Evaluation on-going**

The Committee noted that evaluation was on-going for 14 applications for orphan designation.

## **3. Requests for protocol assistance with significant benefit question**

### **3.1. Ongoing procedures**

#### **3.1.1. -**

---

Treatment of sickle cell disease

The discussion was postponed.

#### **3.1.2. -**

---

Treatment of paediatric patients with severe combined immunodeficiency (SCID) receiving allogeneic haematopoietic stem cell transplantation

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

#### **3.1.3. -**

---

Treatment of multiple myeloma

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

#### 3.1.4. -

---

Treatment of ATTR amyloidosis-polyneuropathy

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

#### 3.1.5. -

---

Treatment of ATTR amyloidosis-cardiomyopathy

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

### 3.2. Finalised letters

#### 3.2.1. -

---

Treatment of cutaneous T-cell lymphoma

The finalised letter was circulated for information.

#### 3.2.2. -

---

Treatment of thalassaemia

The finalised letter was circulated for information.

#### 3.2.3. -

---

Treatment of glioblastoma

The finalised letter was circulated for information.

#### 3.2.4. -

---

Treatment of ornithine transcarbamylase deficiency

The finalised letter was circulated for information.

### 3.3. New requests

#### 3.3.1. -

---

Treatment of Fabry disease

The new request was noted.

#### 3.3.2. -

---

Treatment of relapsed or refractory multiple myeloma



The new request was noted.

## **4. Review of orphan designation for orphan medicinal products at time of initial marketing authorisation**

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

None

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

#### **4.2.1. Evrysdi – risdiplam - EMEA/H/C/005145/0000, EMA/OD/0000001899, EU/3/19/2145, EMA/OD/0000039037**

---

Roche Registration GmbH; Treatment of spinal muscular atrophy

The oral explanation scheduled on 20 January 2021, was cancelled.

The status of the procedure at CHMP was noted.

An opinion recommending not to remove Evrysdi, risdiplam, EU/3/19/2145 from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

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

#### **4.2.2. Nexpvio - selinexor - EMEA/H/C/005127/0000, EU/3/14/1355, EMA/OD/0000043722**

---

Karyopharm Europe GmbH; Treatment of plasma cell myeloma

CHMP Rapporteur: Blanca Garcia-Ochoa; CHMP Co-Rapporteur: Sinan B. Sarac

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 February meeting.

#### **4.2.3. Epidyolex - cannabidiol - EMEA/H/C/004675/II/0005, EMA/OD/165/17, EU/3/17/1959, EMA/OD/0000033940**

---

GW Pharma (International) B.V.; Treatment of tuberous sclerosis

CHMP Rapporteur: Mark Ainsworth; CHMP Co-Rapporteur: Ondřej Slanař

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 March meeting.

#### **4.2.4. Pemazyre – pemigatinib - EMEA/H/C/005266, EMA/OD/038/18, EU/3/18/2066, EMA/OD/0000039241**

---

Incyte Biosciences Distribution B.V.; Treatment of biliary tract cancer

COMP Rapporteurs: Frauke Naumann-Winter; Maria Elisabeth Kalland; CHMP Rapporteur: Alexandre Moreau; CHMP Co-Rapporteur: Janet Koenig

An opinion recommending not to remove Pemazyre, pemigatinib, EU/3/18/2066 from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

*[Post-meeting note: The COMP adopted the opinion by written procedure following its January 2021 meeting.]*

#### 4.2.5. [– berotralstat - EMEA/H/C/005138/0000, EMA/OD/003/18, EU/3/18/2028, EMA/OD/0000045564](#)

---

BioCryst Ireland Limited; Treatment of hereditary angioedema

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 March meeting.

### 4.3. **Appeal**

None

### 4.4. **On-going procedures**

COMP co-ordinators were appointed for 3 applications.

### 4.5. **Orphan Maintenance Reports**

Documents were tabled for information.

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

### 5.1. **After adoption of CHMP opinion**

None

### 5.2. **Prior to adoption of CHMP opinion**

#### 5.2.1. [Galafold - migalastat - EMEA/H/C/004059/II/0029, EMA/OD/105/05, EU/3/06/368](#)

---

Amicus Therapeutics Europe Limited; Treatment of Fabry disease

CHMP Rapporteur: Johann Lodewijk Hillege; CHMP Co-Rapporteur: Ondřej Slanař

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is not needed.

### **5.3. Appeal**

None

### **5.4. On-going procedures**

None

## **6. Application of Article 8(2) of the Orphan Regulation**

None

## **7. Organisational, regulatory and methodological matters**

### **7.1. Mandate and organisation of the COMP**

#### **7.1.1. Strategic Review & Learning meetings**

---

The Portuguese member presented the agenda and invitation for the COMP-SRLM of the Portuguese Presidency to take place on 11<sup>th</sup> February 2021 as remote virtual meeting.

#### **7.1.2. Protocol Assistance Working Group (PAWG)**

---

The working group on Protocol Assistance met remotely on 15 January 2021.

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

#### **7.2.1. Recommendation on eligibility to PRIME – report from CHMP**

---

Documents were tabled for information.

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

#### **7.3.1. Working Party with Patients' and Consumers' Organisations (PCWP)**

---

None

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

---

None

### **7.4. Cooperation within the EU regulatory network**

#### **7.4.1. European Commission**

---

Revision of the EU legislation on medicines for children and rare diseases

The European Commission representative at COMP updated the committee about the outcome of the public consultation on the Inception Impact Assessment and the next steps in the process.

The COMP brought forward and discussed its views with the European Commission representative on several aspects of the Inception Impact Assessment document. Specific topics were addressed upon the request of the European Commission. The COMP will continue to share results of further discussions with the EC.

#### **7.4.2. COMP Working Group on the orphan regulation**

---

The COMP discussed the reflections and recommendations from the WG on the various scenarios put forward by the European Commission in the Inception Impact Assessment. These reflections were noted by the Commission representative.

The COMP WG will continue to develop its views on the ways of specifically fostering development in areas with no or limited treatment options. Related to this, the decisive role of the definition of orphan condition and unmet need were recognised. The COMP in principle welcomes the intention to introduce a more differentiated and flexible system of incentives.

### **7.5. Cooperation with International Regulators**

#### **7.5.1. Food and Drug Administration (FDA)**

---

None

#### **7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)**

---

None

#### **7.5.3. Therapeutic Goods Administration (TGA), Australia**

---

None

#### **7.5.4. Health Canada**

---

None

### **7.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee**

None

### **7.7. COMP work plan**

The COMP work plan was discussed and agreed. The document will be available on the EMA website.

## **7.8. Planning and reporting**

### **7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2020/2021**

---

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2020/2021 were circulated.

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

---

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

## **8. Any other business**

### **8.1. Big Data Training Signpost**

The COMP noted the presentation. The aim of Big Data Training Signpost is to bridge the time gap until the curricula is available. The training courses suggested will be offered by independent providers and will not be regulatory specific. A minimum of overlap and repetitions should be expected between the various trainings and sections of the document.

EMA in collaboration with the Big Data Steering Group is preparing an EU Network skills survey on Big Data which will be used to refine the content of the curricula. The survey will be sent to all NCAs and will aim to identify any skill gaps in the draft curricula. The survey will be launched end of January 2021.

### **8.2. ENCePP in the time of COVID**

The COMP representative in the ENCePP steering group gave a presentation on the ENCePP Webinar (ENCEPP in the time of Covid) held on 20<sup>th</sup> November 2020.

Objectives of the webinar were to discuss methodological considerations for observational studies on Covid-19 and how ENCePP could promote best practice, especially for the monitoring of Covid-19 vaccines safety and effectiveness.

In addition, there were the recommendations of the HMA-EMA Big Data Task Force and the proposed Data Analysis and Real-World Interrogation Network in the European Union (DARWIN EU) presented, and discussions were held on the interface between ENCePP and the Task Force.

There were achievements of the current ENCePP Steering Group summarised, the members of the new ENCePP SG were introduced and discussions were held on proposals for a draft ENCePP mandate. The COMP noted the information.

### **8.3.**

### **8.4. New Executive Director at the EMA meeting with COMP**

The COMP welcomed Emer Cooke as new EMA Executive Director.

## 9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 19-21 January 2021 meeting.

| Name                       | Role                | Member state or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|----------------------------|---------------------|-----------------------------|---|---|
| Violeta Stoyanova-Beninska | Chair               | Netherlands                 | No interests declared                             |   |
| Armando Magrelli           | Member (Vice-Chair) | Italy                       | No interests declared                             |   |
| Brigitte Schwarzer-Daum    | Member              | Austria                     | No interests declared                             |   |
| Tim Leest                  | Member              | Belgium                     | No interests declared                             |   |
| Lyubina Racheva Todorova   | Member              | Bulgaria                    | No interests declared                             |   |
| Dinko Vitezic              | Member              | Croatia                     | No interests declared                             |   |
| Vasileios Loutas           | Member              | Cyprus                      | No interests declared                             |   |
| Lenka Gaidadzi             | Member              | Czechia                     | No interests declared                             |   |
| Elisabeth Penninga         | Member              | Denmark                     | No interests declared                             |   |
| Vallo Tillmann             | Member              | Estonia                     | No interests declared                             |   |
| Karri Penttilä             | Member              | Finland                     | No interests declared                             |   |
| Cecile Dop                 | Member              | France                      | No interests declared                             |   |
| Frauke Naumann-Winter      | Member              | Germany                     | No interests declared                             |   |
| Zsafia Gyulai              | Member              | Hungary                     | No interests declared                             |   |
| Geraldine O'Dea            | Member              | Ireland                     | No interests declared                             |   |
| Irena Rogovska             | Member              | Latvia                      | No interests declared                             |   |

| Name                         | Role   | Member state or affiliation           | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|------------------------------|--------|---------------------------------------|---|---|
| Aušra Matulevičienė          | Member | Lithuania                             | No interests declared                             |   |
| Michel Hoffmann              | Member | Luxembourg                            | No interests declared                             |   |
| Robert Nistico               | Member | Malta                                 | No interests declared                             |   |
| Elisabeth Johanne Rook       | Member | Netherlands                           | No interests declared                             |   |
| Maria Elisabeth Kalland      | Member | Norway                                | No interests declared                             |   |
| Bożenna Dembowska-Bagińska   | Member | Poland                                | No restrictions applicable to this meeting        |   |
| Dinah Duarte                 | Member | Portugal                              | No restrictions applicable to this meeting        |   |
| Olimpia Neagu                | Member | Romania                               | No interests declared                             |   |
| Eva Malikova                 | Member | Slovak Republic                       | No interests declared                             |   |
| Martin Mozina                | Member | Slovenia                              | No interests declared                             |   |
| Gloria Maria Palomo Carrasco | Member | Spain                                 | No interests declared                             |   |
| Darius Matusevicius          | Member | Sweden                                | No restrictions applicable to this meeting        |   |
| Pauline Evers                | Member | Patients' Organisation Representative | No interests declared                             |   |
| Julian Isla                  | Member | Patients' Organisation Representative | No interests declared                             |   |
| Angelo Loris Brunetta        | Member | Patients' Organisation Representative | No interests declared                             |   |
| Ingeborg Barisic             | Member | Expert recommended by EMA             | No restrictions applicable to this meeting        |   |

| Name   | Role                   | Member state or affiliation           | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|--|------------------------|---------------------------------------|---|---|
| Giuseppe Capovilla   | Member                 | Expert recommended by EMA             | No interests declared                             |   |
| Virginie Hivert  | Expert*                | Patients' Organisation Representative | No restrictions applicable to this meeting        |   |
| Steen W. Hansen  | Member of SAG Oncology | Denmark                               | No restrictions applicable to this meeting        |   |
| A representative from the European Commission attended the meeting |                        |                                       |   |   |
| Meeting run with support from relevant EMA staff                   |                        |                                       |   |   |

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



## 10. Explanatory notes

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

### **Abbreviations / Acronyms**

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission

OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

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

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

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

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

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

Sponsor

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

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

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

More detailed information on the above terms can be found on the EMA website:

[www.ema.europa.eu/](http://www.ema.europa.eu/)