18 January 2023
EMA/CAT/946084/2022
Human Medicines Division

Committee for Advanced Therapies (CAT)

Minutes for the meeting on 07-09 December 2022

Chair: Martina Schuessler-Lenz; Vice-Chair: Ilona Reischl

Disclaimers

Some of the information contained in these minutes are considered commercially confidential or sensitive and therefore not disclosed. Regarding 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 CAT meeting reports once the procedures are finalised.

Of note, these minutes are a working document primarily designed for CAT members and the work the Committee undertakes.

Note on access to documents

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

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1. Introduction

1.1. Welcome and declarations of interest of members, alternates and experts

The Chairperson opened the meeting by welcoming all participants.

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 on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some Committee members, alternates and experts for concerned agenda points.

Participants were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions concerning the matters for discussion. No new or additional interests or restrictions were declared. Restrictions applicable to this meeting are captured in the List of participants included in the minutes.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure. All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

The CAT agenda for 07-09 December 2022 meeting was adopted.

1.3. Adoption of the minutes

The CAT minutes for 03-04 November 2022 meeting were adopted.

2. Evaluation of ATMPs

2.1. Opinions

2.1.1. Etranacogene dezaparvovec - PRIME - Orphan - EMEA/H/C/004827

CSL Behring GmbH; Treatment of adults with Haemophilia B

Scope: Opinion

Action: for adoption

List of outstanding issues adopted on 07.10.2022. List of questions adopted on 15.07.2022.

The Rapporteurs presented the outcome of assessment of the responses to the list of outstanding issues.

CAT discussed and agreed on the specific obligation linked to the conditional marketing authorisation.

CAT agreed that the benefit-risk balance of Hemgenix in the indication as in the SmPC (section 4.1) is positive and that a conditional marketing authorisation can be recommended. The draft opinion was adopted. Norway was in agreement with the draft opinion. The draft opinion will be forwarded to the CHMP for adoption.

2.2. Oral explanations

2.3. Day 180 list of outstanding issues

2.3.1. Lenadogene nolparvovec - Orphan - EMEA/H/C/005047

GenSight Biologics S.A.; Treatment of vision loss due to Leber hereditary optic Neuropathy (LHON)

Scope: Day 180 list of outstanding issues

Action: for adoption

List of questions adopted on 19.02.2021.

The list of outstanding questions and the review timetable were adopted.

2.4. Day 120 list of questions

2.5. Day 80 assessment reports

2.6. Update on ongoing initial applications

2.7. New applications

2.8. Withdrawal of initial marketing authorisation application

2.9. Re-examination of initial application procedures under Article 9(2) of Regulation No. 726/2004

2.10. GMP and GCP inspections requests

2.11. Type II variations and variations of therapeutic indication procedure according to Commission Regulation (EC) No 1234/2008

2.11.1. Abecma - idecabtagene vicleucel - Orphan - EMEA/H/C/004662/II/0019

Bristol-Myers Squibb Pharma EEIG

Rapporteur: Rune Kjeken

Scope: Quality; opinion

Action: for adoption

The opinion was adopted.

2.11.2. Abecma - idecabtagene vicleucel - Orphan - EMEA/H/C/004662/II/0020

Bristol-Myers Squibb Pharma EEIG

Rapporteur: Rune Kjeken

Scope: Quality; opinion

Action: for adoption

The opinion was adopted.

2.11.3. Breyanzi - lisocabtagene maraleucel / lisocabtagene maraleucel - EMEA/H/C/004731/II/0004

Bristol-Myers Squibb Pharma EEIG

Rapporteur: Concetta Quintarelli

Scope: Quality; opinion

Action: for adoption

Request for supplementary information adopted on 09.09.2022.

The opinion was adopted.

2.11.4. Breyanzi - lisocabtagene maraleucel / lisocabtagene maraleucel - EMEA/H/C/004731/II/0007/G

Bristol-Myers Squibb Pharma EEIG

Rapporteur: Concetta QuintarelliScope: Quality; Request for supplementary information

Action: for adoption

The request for supplementary information was adopted.

2.11.5. Breyanzi - lisocabtagene maraleucel / lisocabtagene maraleucel - EMEA/H/C/004731/II/0009

Bristol-Myers Squibb Pharma EEIG

Rapporteur: Concetta QuintarelliScope: Quality; Request for supplementary information

Action: for adoption

The request for supplementary information was adopted.

2.11.6. CARVYKTI - ciltacabtagene autoleucel - Orphan - EMEA/H/C/005095/II/0003

Janssen-Cilag International NV

Rapporteur: Jan Mueller-Berghaus, , PRAC Rapporteur: Jo Robays

Scope: Clinical safety; opinion

Update of sections 4.4 and 4.8 of the SmPC in order to update the existing warnings on cytokine release syndrome (CRS), neurologic toxicities and grading of related events, and to update the list of adverse drug reactions (ADRs) based on previously reviewed data from studies MMY2001 and MMY2003 as well as an additional internal characterisation of neurotoxicity risk; the Package Leaflet is updated accordingly. The RMP version 2.1 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information.

Action: for adoption

The opinion was adopted.

2.11.7. CARVYKTI - ciltacabtagene autoleucel - Orphan - EMEA/H/C/005095/II/0004/G

Janssen-Cilag International NV

Rapporteur: Jan Mueller-Berghaus

Scope: Clinical safety; opinion

Grouped application comprising two type II variations as follows:

Update of section 4.4 of the SmPC in order to add a new warning on increased risk of severe/fatal Covid-19 infections following Covid-19 signal evaluation from the ongoing study 68284528MMY3002 (CARTITUDE-4) based on a cumulative review of all clinical trials, registries and literature.

Update of section 4.4 of the SmPC in order to add a new warning on risk of severe bleeding in the context of hemophagocytic lymphohistiocytosis syndrome (HLH) following a signal evaluation from the ongoing study 68284528MMY3002 (CARTITUDE-4) based on cumulative review of all clinical trials, registries and literature.

The Package Leaflet is updated accordingly.

The RMP version 2.2 has also been submitted.

Action: for adoption

The opinion was adopted.

2.11.8. CARVYKTI - ciltacabtagene autoleucel - Orphan - EMEA/H/C/005095/II/0005

Janssen-Cilag International NV

Rapporteur: Jan Mueller-Berghaus

Scope: Quality, Request for supplementary information

Action: for adoption

The request for supplementary information was adopted.

2.11.9. Imlygic - talimogene laherparepvec - EMEA/H/C/002771/II/0056

Amgen Europe B.V.

Rapporteur: Maija Tarkkanen, PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Clinical safety

Submission of the final report from study 20120139 listed as a category 3 study in the RMP in order to fulfil MEA/004. This is a multicentre, observational registry study to evaluate the survival and long-term safety of subjects who previously received talimogene laherparepvec in Amgen or BioVEX sponsored clinical trials.

Action: for adoption

Request for supplementary information adopted on 09.09.2022.

The opinion was adopted.

2.11.10. Kymriah - tisagenlecleucel - Orphan - EMEA/H/C/004090/II/0050

Novartis Europharm Limited

Rapporteur: Rune KjekenScope: Quality; opinion

Action: for adoption

Request for supplementary information adopted on 13.04.2022.

The opinion was adopted.

2.11.11. Libmeldy - atidarsagene autotemcel - Orphan - EMEA/H/C/005321/II/0011/G

Orchard Therapeutics (Netherlands) B.V.

Rapporteur: Carla Herberts, PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Quality and Clinical safety; Request for supplementary information

Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC ; the Package Leaflet and Labelling are updated accordingly. In addition, the MAH took the opportunity to remove ANX/002 from the Annex II and to introduce minor editorial changes to the PI. The RMP version 1.3 has also been submitted.

Action: for adoption

The request for supplementary information was adopted.

2.11.12. Upstaza - eladocagene exuparvovec - Orphan - EMEA/H/C/005352/II/0004/G

PTC Therapeutics International Limited

Rapporteur: Maura O'Donovan

Scope: Quality; Request for supplementary information

Action: for adoption

The request for supplementary information was adopted.

2.12. Extension applications

2.13. Other Post-Authorisation Activities

2.13.1. CARVYKTI - ciltacabtagene autoleucel - Orphan - EMEA/H/C/005095/MEA/007

Janssen-Cilag International NV

Rapporteur: Jan Mueller-Berghaus

Scope: Pharmacovigilance

Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training [From initial MAA]

Action: for adoption

The assessment of this post-authorisation measure was adopted.

2.13.2. CARVYKTI - ciltacabtagene autoleucel - Orphan - EMEA/H/C/005095/REC/009

Janssen-Cilag International NV

Rapporteur: Jan Mueller-Berghaus

Scope: Quality

Action: for adoption

The assessment of this recommendation was adopted.

2.13.3. Upstaza - eladocagene exuparvovec - Orphan - EMEA/H/C/005352/REC/005

PTC Therapeutics International Limited

Rapporteur: Maura O'DonovanScope: Quality

Action: for adoption

The assessment of this recommendation was adopted.

2.13.4. Zolgensma - onasemnogene abeparvovec - Orphan - EMEA/H/C/004750/P46/020

Novartis Europharm Limited

Rapporteur: Carla Herberts

Scope: Clinical

Paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended: Final study report, Study No. AVXS-101-CL-102 (COAV101A12102): Phase 1, open-label, dose comparison study of AVXS-101 for sitting but non-ambulatory patients with spinal muscular atrophy.

Action: for adoption

Request for supplementary information adopted on 09.09.2022.

The assessment of this post-authorisation measure was adopted. See also CAT November minutes, point 2.13.16.

2.13.5. Implementation by the MAHs of CAR-Ts of the CAT-PRAC recommendation on using EBMT as a data source for imposed or requested studies for the long-term safety and efficacy follow-up for ATMPs

Scope: Feedback from the discussion with the Rapporteurs of CAR-Ts and feedback from the PRAC discussion

Action: for discussion

Feedback was provided to CAT. CAT agreed that EBMT could be kept as data source for ongoing studies, supplementing the data from CIBMTR (when not already part of the imposed studies); for products with newer indications where the clinical experience on using CAR-T cell-based therapies is less extensive, MAH should explore and include other data sources such as national registries or specific disease registries for the indications.

2.13.6. Kymriah - tisagenlecleucel - Orphan - EMEA/H/C/004090/REC/020

Novartis Europharm Limited

Rapporteur: Rune Kjeken

Scope: Quality

Action: for adoption

The assessment of this recommendation was adopted.

3. Certification of ATMPs

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

3.1. Opinion

3.2. Day 60 Evaluation Reports

3.3. New Applications

4. Scientific Recommendation on Classification of ATMPs

Timetable:

Start of procedure:	19 December 2022
EMA coordinator's draft report:	10 January 2023
CAT coordinator's comments:	13 January 2023
Revised scientific recommendation:	16 January 2023
CAT discussion of scientific recommendation:	20 January 2023

4.1. New requests – Appointment of CAT Coordinator

4.1.1. Autologous platelet concentrate, consisting of a fibrin matrix enriched with platelets, leukocytes and of cytokines and growth factors

Treatment of patients with critical limb ischemia, in combination with mechanical lower limb revascularization (angioplasty)

Scope: Appointment of CAT Coordinator and adoption of timetable

Action: for adoption

The CAT coordinator was appointed.

4.1.2. Autologous adipose tissue derived progenitor cells in biodegradable chemically crosslinked hydrogel

Subacute spinal cord injury in adults with a complete lesion (ASIA A score)

Scope: Appointment of CAT Coordinator and adoption of timetable

Action: for adoption

The CAT coordinator was appointed.

4.1.3. Genetically engineered E. coli strain containing a plasmid expressing CRISPR-Cas against clbA, clbB and clbC

Prevention of disease progression in Familial Adenomatous Polyposis (FAP)

Scope: Appointment of CAT Coordinator and adoption of timetable

Action: for adoption

The CAT coordinator was appointed.

4.1.4. Mitochondria isolated from allogeneic umbilical-cord mesenchymal stem cells

Polymyositis/Dermatomyositis

Scope: Appointment of CAT Coordinator and adoption of timetable

Action: for adoption

The CAT coordinator was appointed.

4.1.5. Macrophage-Drug Conjugate (MDC) composed of allogenic human monocyte-derived macrophages loaded with a protein-drug conjugate

Treatment of solid tumours

Scope: Appointment of CAT Coordinator and adoption of timetable

Action: for adoption

The CAT coordinator was appointed.

4.1.6. DNA plasmid vector encoding human insulin like growth factor binding protein 2

Treatment of newly diagnosed advanced ovarian cancer after debulking surgery

Scope: Appointment of CAT Coordinator and adoption of timetable

Action: for adoption

The CAT coordinator was appointed.

4.1.7. Autologous muscle precursor cells (MPCs)

Treatment of female stress urinary incontinence

Scope: Appointment of CAT Coordinator and adoption of timetable

Action: for adoption

The CAT coordinator was appointed.

4.2. Day 30 ATMP scientific recommendation

4.2.1. Adult autologous regenerative cells

Indicated for regeneration, repair, or replacement of weakened or injured subcutaneous tissue

Scope: ATMP scientific recommendation

Action: for adoption

CAT discussed the ATMP classification report. CAT considered that following additional information should be provided by the applicant before concluding on the classification:

The procedural clock will be stopped awaiting responses from the applicant

4.2.2. Autologous adipose-derived stromal vascular fraction cells (ADSVFCs)

Indicated for the treatment of haemophilic arthropathy

Scope: ATMP scientific recommendation

Action: for adoption

CAT discussed the classification report. CAT secretariat to send the draft scientific recommendation to the European Commission for comments by 4 January 2023.

4.2.3. Allogeneic Natural Killer cells armed with anti-EGFR monoclonal antibody

Indicated for the treatment of epidermal growth factor receptor (EGFR) positive cancers

Scope: ATMP scientific recommendation

Action: for adoption

CAT discussed the classification report. CAT secretariat to send the draft scientific recommendation to the European Commission for comments by 4 January 2023.

4.2.4. Allogeneic natural killer cells armed with anti-HER2 monoclonal antibody

Indicated for the treatment of human epidermal growth factor receptor 2 (HER2) positive cancers

Scope: ATMP scientific recommendation

Action: for adoption

CAT discussed the classification report. CAT secretariat to send the draft scientific recommendation to the European Commission for comments by 4 January 2023.

4.2.5. Ex-vivo expanded allogeneic neural crest-like stem cells

Indicated for the treatment of diabetic foot ulcer

Scope: ATMP scientific recommendation

Action: for adoption

CAT discussed the classification report. CAT secretariat to send the draft scientific recommendation to the European Commission for comments by 4 January 2023.

4.2.6. Allogeneic Wharton's jelly mesenchymal stem cells (WJ-MSCs)

Indicated for the treatment of stress incontinence

Scope: ATMP scientific recommendation

Action: for adoption

CAT discussed the classification report. CAT secretariat to send the draft scientific recommendation to the European Commission for comments by 4 January 2023.

4.2.7. Autologous monocyte-derived dendritic cells electroporated with mRNAs encoding for immunostimulatory proteins caTLR4, CD40L and CD70 combined with one of the tumour-associated antigens (TAA) MAGE-C2, MAGE-A3, WT1 and NY-ESO-1

Indicated for the treatment of gastric cancer

Scope: ATMP scientific recommendation

Action: for adoption

CAT discussed the classification report. CAT secretariat to send the draft scientific recommendation to the European Commission for comments by 4 January 2023.

4.2.8. Autologous human tumour infiltrating lymphocytes

Indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)

Scope: ATMP scientific recommendation

Action: for adoption

CAT discussed the classification report. CAT secretariat to send the draft scientific recommendation to the European Commission for comments by 4 January 2023.

4.3. Day 60 revised scientific recommendation (following list of questions)

No items

4.4. Finalisation of procedure

4.4.1. Allogeneic adipose-derived mesenchymal stem cells (ADMSCs)

Intended for the treatment of osteoarthritis of the knee and hip

Scope: The European Commission raised no comments. ATMP scientific recommendation

Action: for adoption

The classification report was adopted. The product does fulfil the definitions of a somatic cell therapy medicinal product and a tissue engineered product and based on that is considered as tissue engineered product as provided in Article 2(4) of Regulation (EC) No 1394/2007.

4.5. Follow-up and guidance

No items

5. Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

5.1. New requests - appointment of CAT Rapporteurs

5.1.1. Ongoing scientific advice procedures - Appointment of CAT Peer Reviewers

Timetable:

Start of procedure at SAWP:	28.11-01.12.2022
Appointment of CAT Peer Reviewers:	07-09.12.2022
SAWP first reports:	02.01.2023
CAT Peer Reviewer comments (NC/C):	06.01.2023
CAT Peer Reviewer comments (Q):	11.01.2023
Discussion at SAWP:	09-12.01.2023
Discussion at CAT and feedback to SAWP:	18-20.2023

5.1.2. Scientific advice procedures starting at the next SAWP meeting

Timetable:

Start of procedure at SAWP:	09-12.01.2023
Appointment of CAT Peer Reviewers:	18-20.01.2023
SAWP first reports:	30.01.2023
CAT Peer Reviewer comments (NC,C):	03.02.2023
CAT Peer reviewer comments (Q):	08.02.2023
Discussion at SAWP:	06-09.02.2023
Discussion at CAT and feedback to SAWP:	15-17.02.2023

5.2. Procedures discussed at SAWP – 1st reports, D40 JRs, LoIs

5.3. Finalisation of D70 procedures – feedback from the discussion meeting

5.4. Final Advice Letters for procedures finalised the previous month

6. Pre-Authorisation Activities

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

6.1. Paediatric investigation plans

6.2. ITF briefing meetings in the field of ATMPs

6.3. Priority Medicines (PRIME) – Eligibility requests

6.3.1. Month 0 - Start of the procedure

Timetable for assessment:	
Procedure start:	28/11-01/12/2022
SAWP recommendation:	12/01/2023
CAT recommendation:	20/01/2023
CHMP adoption of report and final recommendation:	26/01/2023

6.3.2. Month 1 – Discussion of eligibility

6.3.3. Month 2 – Recommendation of eligibility

6.3.4. Ongoing support

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the CAT

7.1.1. CAT membership

New alternate member from Denmark: Bibi Fatima Syed Shah

7.1.2. Vote by proxy

No items

7.1.3. CAT Strategic Review & Learning meeting (SRLM) under the Czechia presidency, 17 – 18 November 2022 in Paris

CAT: Petr Soukup, Kristýna Řehořová Hradilková, Violaine Closson Carella, Martina Schuessler-Lenz

Scope: Feedback from the CAT SRLM

Action: for information

A short feedback was provided to CAT from the discussion at the SRLM of 17-18 November 2022.

7.2. Coordination with EMA Scientific Committees

None

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

None

7.4. Cooperation with the EU regulatory network

None

7.5. Cooperation with international regulators

7.5.1. ATMP cluster teleconference with US-FDA, Health Canada and PMDA (Japan)

CAT: Martina Schuessler-Lenz

Scope: Agenda of the teleconference of 15 December 2022

Action: for information

The draft agenda was presented.

7.5.2. International Pharmaceutical Regulators Programme (IPRP), gene and cell therapy working groups

CAT: Pille Säälik, Ivana Haunerova

Scope: Draft IPRP reflection paper: General Considerations for Materials Used in the Manufacture of Human Cell and Gene Therapy Products

Action: for discussion

The comments from CAT and BWP members on the draft IPRP reflection paper were presented. The comments were agreed and will now be sent to the IPRP drafting group.

7.6. CAT work plan

7.6.1. CAT Workplan for 2023

CAT: Martina Schüssler-Lenz

Scope: Draft CAT workplan for 2023

Action: for discussion

The draft work plan was presented and CAT discussed the proposed work plan topics. The work plan will be updated following the discussion and circulated to CAT members for final comments and identification of additional volunteers to take part in the different work plan topics. The CAT work plan 2023 will be adopted at the January 2023 CAT meeting.

7.7. Planning and reporting

7.7.1. Update of the Business Pipeline report – Q4-2022

Scope: Update of the business pipeline report for the human scientific committees

Action: for information

The information was noted.

7.8. Others

7.8.1. Good Practice Guide for the use of the EU metadata catalogue and Data Quality Framework

Scope: Presentation of the following documents for public consultation: a. Good Practice Guide for the use of the EU metadata catalogue, and b. Data Quality Framework

Action: for information

The documents are published for public consultation. The presentation was cancelled.

7.8.2. Blood/tissue establishment in third countries providing starting materials for ATMPs

CAT: Barbara Bonamassa

Scope: CAT learning: inspection of leukapheresis centres in third countries

Action: for discussion

The conclusions reached by CAT at is November meeting (see November CAT minutes, point 7.8.3) was brought to the attention of the European Commission and shared with competent authorities for safety of blood and blood components, and for tissues and cells: received comments were discussed. It was agreed to clarify that these conclusions only relate to starting materials for ATMPs and not to plasma derived medicinal products. Additional clarifications are included on the type of information that would be expected in Module 3 of the marketing authorisation application. With these amendments, the document was adopted as a CAT learning.

The CAT learning will be circulated to BWP, SAWP and the Inspector Working Group for information; CAT members were asked to circulate the CAT learning within their agencies.

7.8.3. CAT Stakeholder meeting 2023

Scope: proposals for topics to be included in the agenda of the CAT stakeholder meeting that will be organised in the first half of 2023.

Action: for discussion

An initial discussion took place. A CAT stakeholder meeting will be organised during the May 2023 CAT meeting (to be confirmed). A call for topics will be send to industry and academic stakeholders. CAT members were asked in parallel to provide some proposal for agenda points for discussion.

7.8.4. EMA-funded SMA study on spinal muscular atrophy (SMA).

CAT: Lisbeth Barkholt, Kieran Breen, Mencia de Lemus

Action: for information

EMA provided feedback on the EMA-funded study on SMA. The procedural steps and the study plan were presented. CAT will be kept informed of the progress and outcome of the study.

7.8.5. Adeno-associated viral (AAV) vector toxicities: regulatory considerations

CAT: Carla Herberts, Egbert Flory

Scope: Revised discussion paper on insertional mutagenesis and follow-up for AAV gene therapy

Action: for adoption

Carla Herberts presented the changes made to the discussion paper following comments by the non-clinical working party (NCWP). The updated paper was adopted and will be shared with CHMP, PRAC, SAWP and NCWP.

It was agreed to convert the paper into a scientific publication and to include the outcome in the revision of the GVP Module V, which will start shortly.

7.8.6. Guideline on Clinical electronic Structured Harmonised Protocol (CeSHarP)

Scope: Introduction of the clinical protocol template and the technical specification

Action: for information

EMA presented an update on the development of the ICH M11 guideline: clinical electronic structured harmonised protocol. The public consultation has been initiated (until 26 February 2023). A call for volunteers was made for CAT members who want to be review the draft M11 template. Interested CAT members should inform EMA .

A similar call for volunteers will be made to the methodological working party (MWP), and the clinical trial coordination group (CTCG) and the clinical trial expert group (CTEG) are also informed.

7.8.7. Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation

CAT: Carla Herberts, Jan Mueller-Berghaus

Scope: Presentation of the draft reflection paper

Action: for information

Carla Herberts presented the reflection paper in single-arm trials. The public consultation will start soon.

CAT members' comments on the reflection paper can be shared until 2 January 2023.

7.8.8. Methodology Working Party (MWP)

MWP chair: Kit Roes; MWP member: Kristin Karlsson

Scope: Presentation of the working of the MWP and how it can support the CAT under the new working party model

Action: for information

Kristin Karlsson presented the establishment of the MWP and the multi-annual workplan of the MWP. Guideline development will be structured under four main areas: clinical pharmacology, real world evidence, clinical trial modernisation and pharmacogenomics. MWP can support CAT in guideline development (if input on methodological issues is required) and can provide expert support to CAT e.g. on the potential better use of RWE data.
CAT was informed that a call for European Specialised Expert Communities (ESEC) will be initiated soon: this will be an open call and experts will be endorsed by CHMP.

8. Any other business

No items

Date of next CAT meeting:

18-20/01/2023

9. Explanatory notes

The Notes give a brief explanation of relevant agenda items and should be read in conjunction with the agenda.

Abbreviations / Acronyms

AAV: Adeno-Associated Virus

AR: Assessment Report

ATMP: Advanced Therapy Medicinal Product

BWP: Biologics Working Party

CAT: Committee for Advanced Therapies

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

CTFG: Clinical Trial Facilitation Group

DG: Drafting Group

EC: European Commission

EU NTC: European Union Network Training Centre

ERA: Environmental Risk Assessment

FDA: Food and Drug Administration

FL: Final Letter

GCG: Guideline Consistency Group

GCP: Good Clinical Practice

GLP: Good Laboratory Practice

GMO: Genetically-modified organism

GMP: Good Manufacturing Practice

GTMP: Gene Therapy Medicinal Product

HTA: Health Technology Assessment Bodies

HSPC: Hematopoietic Stem and Progenitor Cells

ITF: Innovative Task Force

JR: Joint Report

LoOI: List of outstanding issues

LoQ: List of questions

MA: Marketing Authorisation

MAA: Marketing Authorisation Application

MAH: Marketing Authorisation Holder

MNAT: Multinational assessment team

MSC: Mesenchymal stem cells

PDCO: Paediatric Committee

PMDA: Pharmaceuticals and Medical Devices Agency (Japan)

PIP: Paediatric Investigation Plan

PL: Package leaflet

PRAC: Pharmacovigilance and Risk Assessment Committee #

PRIME: Priority Medicines

QRD: Quality review of documents

RMP: Risk Management Plan

RP: Reflection paper

RSI: Request for supplementary information

SAs: Scientific Advices

SAG-O: Scientific Advisory Group Oncology

SAWP: Scientific Advice Working Party

SR: Summary Report

SWP: Safety Working Party

SME: Small and medium size enterprises

SmPC: Summary of Products Characteristics

TT: Timetable

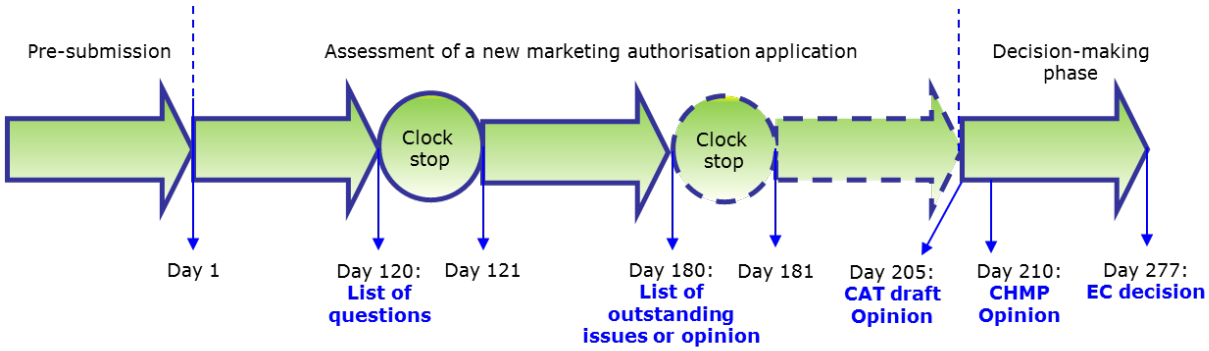
Evaluation of ATMPs (section 2)

This section lists applications for marketing authorisations of new Advanced Therapy Medicinal Products (ATMPs) that are to be discussed by the Committee. It also lists any ATMP related inspection requests (section 2.9) and Post-authorisation activities (section 2.10).

New applications (sections 2.1. to 2.12.)

Section 2.1 is for ATMPs nearing the end of the evaluation and for which the CAT is expected to adopt a draft **opinion** at this meeting on whether marketing authorisation should be granted. Once adopted, the CAT opinion is transmitted to the CHMP for final adoption. The CHMP opinion will be forwarded to the European Commission for a final legally binding decision valid throughout the EU. More information on the evaluation of ATMPs can be found here.

The other items in the section are listed depending on the stage of the evaluation, which is shown graphically below:



The assessment of an application for a new medicine takes up to 210 'active' days. This active evaluation time is interrupted by at least one 'clock-stop' during which time the applicant prepares the answers to questions from the CAT. The clock stop happens after day 120 and may also happen after day 180, when the CAT has adopted respectively a **Day 120 list of questions** (section 2.3) or a List of outstanding issues to be addressed by the company, which is listed in the agenda under sections 2.7 (**Ongoing evaluation procedures**). Section 2.7 also includes the CAT discussions at any other timepoint of the evaluation procedure of new applications.

Oral explanation (section 2.2.)

Prior to adoption of the CAT opinion, marketing authorisation applicants are normally invited to the CAT plenary meeting to address questions raised by the Committee.

Oral explanations normally relate to ongoing applications, but they can also relate to any other issue for which the CAT would like to discuss with company representatives in person.

Re-examination procedures (new applications) under article 9(2) of regulation no 726/2004 (section 2.6.)

This section lists applications for new marketing authorisation for ATMPs for which the applicant has requested a re-examination of the opinion previously issued by the CHMP. Similar to the initial evaluation of a marketing authorisation of an ATMP, CAT will adopt a draft re-examination opinion, which is transmitted to the CHMP for final adoption.

Withdrawal of applications (section 2.7.)

This section includes information on marketing authorisation applications that are withdrawn by the applicant. Applicants may decide to withdraw applications at any stage during the assessment and a CAT opinion will therefore not be issued. Withdrawals are included in the agenda for information or discussion, as necessary.

New applications (section 2.9.)

In this section, information is included on upcoming marketing authorisation applications for ATMPs, as well as information on appointment of Rapporteurs for new ATMP applications.

GMP and GCP Inspections Issues (section 2.10.)

This section lists inspections that are undertaken for ATMPs. Inspections are carried out by regulatory agencies to ensure that marketing authorisation holders comply with their obligations. Inspection can relate to good manufacturing practice (GMP), good clinical practice (GCP), good laboratory practice (GLP) or good pharmacovigilance practice (GVP).

Post-authorisation activities (section 2.12.)

This section lists type II variations, extension application according to Annex I of Reg. 1234/2008, re-examination procedures for type II variations (including extension of indication applications) for which the applicant has requested re-examination of the opinion previously issued by the CHMP and other issues concerning authorised medicines that are not covered elsewhere in the agenda such as annual reassessments, 5-year renewals, supply shortages, qualify defects. Issues that have been discussed at the previous meeting of the PRAC, the EMA's committee responsible for evaluating and monitoring safety issues for medicines, will also be included here.

Certification of ATMPs (section 3)

This section includes the scientific evaluation by the CAT of quality and non-clinical data that small and medium-sized enterprises have generated at any stage of the ATMP development process. More information on the ATMP certification procedure can be found here.

Scientific Recommendation on Classification of ATMPs (Section 4)

This section includes the scientific recommendation by the CAT on whether medicines based on genes, cells or tissues meet the scientific criteria that define ATMPs. More information on the ATMP classification procedure, including the outcomes of finalised classifications, can be found here.

Scientific Advice (section 5)

This section includes all scientific advice given to companies during the development of an ATMP. Information related to the number of ATMP related scientific advices discussed by CAT can be found in the CAT Monthly reports. Further information on SAWP can be found here.

Pre-Authorisation (section 6)

Paediatric Investigation Plan (PIP)

This section includes the discussion of an ATMP before a formal application for marketing authorisation is submitted. These cases refer for example to requests for an accelerated assessment for medicines that are of major interest for public health or can be considered a therapeutic innovation: in case of an accelerated assessment the assessment timetable is reduced from 210 to 150 days.

CAT contributes to the evaluation of a Paediatric Investigation Plan (PIPs) for ATMPs by the Paediatric Committee. These PIPs are included in this section of the Agenda.

ITF Briefing meeting in the field of ATMPs

This section refers to briefing meetings of the Innovation Task Force and International co-operations activities of the CAT

The Innovation Task Force (ITF) is a body set up to encourage early dialogue with applicants developing innovative medicines. Minutes of meetings with applicants developing ATMPs and of other ITF meetings of interest to the CAT are included in this section of the agenda. Further information on the ITF can be found here.

Priority Medicines (PRIME)

This section includes the new requests for eligibility to PRIME for ATMPs under development, the discussions in CAT of these eligibility requests and the final recommendations for eligibility of ATMPs adopted by CHMP.

CAT will appoint one of its members as the CAT sponsor for each new ATMP eligibility request who will lead the CAT discussion based on the recommendation from the SAWP.

Organisational, regulatory and methodological matters (section 7)

This section includes topics related to regulatory and procedural guidance, CAT workplan, CAT meeting organisation (including CAT membership), planning and reporting, co-ordination with other committees, working parties and scientific advisory groups.

Furthermore, this section refers to the activities of the CAT drafting groups developing scientific guidelines for gene therapy medicinal products and for cell-based medicinal products, cooperation within the EU regulatory network and international regulators as well as direct interaction with interested parties. It also includes topics of scientific interest for the Committee that are not directly related to the work of the CAT drafting groups or CAT associated working parties.

Any other business (section 8)

This section is populated with miscellaneous topics not suitable under the previous headings.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/

10. List of participants

Including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 07-09 December 2022 meeting.

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Martina Schüssler-Lenz	Chair	Germany	No interests declared	
Ilona Reischl	Member (Vice-Chair)	Austria	No interests declared	
Silke Dorner	Alternate	Austria	No interests declared	
Claire Beuneu	Member	Belgium	No interests declared	
Rozalina Kulaksazova	Member	Bulgaria	No interests declared	
Azra Selimovic	Member	Croatia	No interests declared	
Petra Sokol	Alternate	Croatia	No interests declared	
Rafaella Pontou	Member	Cyprus	No interests declared	
Petr Soukup	Member	Czechia	No interests declared	
Kristyna Rehorova Hradilkova	Alternate	Czechia	No interests declared	
Ebru Karakoc Madsen	Member	Denmark	No restrictions applicable to this meeting	
Bibi Fatima Syed Shah	Alternate	Denmark	No interests declared	
Martina Schüssler-Lenz	Chair	Germany	No interests declared	
Ilona Reischl	Member (Vice-Chair)	Austria	No interests declared	
Toivo Maimets	Member	Estonia	No interests declared	
Pille Saalik	Alternate	Estonia	No interests declared	
Heli Suila	Member	Finland	No interests declared	
Violaine Closson	Member	France	No interests declared	
Jean-Michel Race	Alternate	France	No interests declared	
Jan Mueller-Berghaus	Member (CHMP co-opted member)	Germany	No interests declared	
Egbert Flory	Alternate (to CHMP representative)	Germany	No interests declared	
Maria Gazouli	Member	Greece	No interests declared	
Angeliki Rompoti	Alternate	Greece	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Katalin Lengyel	Member	Hungary	No interests declared	
Maura O'Donovan	Member	Ireland	No interests declared	
Niamh Curran	Alternate	Ireland	No restrictions applicable to this meeting	
Concetta Quintarelli	Member	Italy	No interests declared	
Barbara Bonamassa	Alternate	Italy	No restrictions applicable to this meeting	
Una Riekstina	Member	Latvia	No interests declared	
Raimondas Benetis	Alternate (to CHMP representative)	Lithuania	No interests declared	
Nancy De Bremaeker	Member	Luxembourg	No interests declared	
John J. Borg	Member (CHMP member)	Malta	No interests declared	
Anthony Samuel	Alternate (to CHMP representative)	Malta	No interests declared	
Carla Herberts	Member	Netherlands	No interests declared	
Babs Fabriek	Alternate	Netherlands	No interests declared	
Rune Kjeken	Member	Norway	No restrictions applicable to this meeting	
Dariusz Śladowski	Member	Poland	No restrictions applicable to this meeting	
Maria Isabel Borba Vieira	Alternate (to CHMP representative)	Portugal	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Silviu Istrate	Member	Romania	No interests declared	
Katarina Vavrová	Member	Slovakia	No interests declared	
Margareta Fogelová	Alternate	Slovakia	No interests declared	
Metoda Lipnik-Stangelj	Member	Slovenia	No interests declared	
Suzana Vidic	Alternate	Slovenia	No participation in final deliberations and voting on	2.11.10 Kymriah II/50 2.13.4 Zolgensma P46/020 2.13.6 Kymriah Rec/20
Sol Ruiz	Member (CHMP co-opted member)	Spain	No interests declared	
Marcos Timón	Alternate (to CHMP representative)	Spain	No interests declared	
Alessandra Renieri	Alternate	Clinicians' Representative	No restrictions applicable to this meeting	
Kerstin Sollerbrant	Member	Patients' Representative	No interests declared	
Mencia de Lemus Belmonte	Alternate	Patients' Representative	No restrictions applicable to this meeting	
Kieran Breen	Member	Patients' Representative	No interests declared	
Federica Chiara	Alternate	Patients' Representative	No restrictions applicable to this meeting	
Andrea Laslop	Expert - via telephone*	Austria	No interests declared	
Rene Anour	Expert - via telephone*	Austria	No interests declared	
Bojana Divkovic	Expert - via telephone*	Austria	No interests declared	
Florian Klinglmüller	Expert - via telephone*	Austria	No interests declared	
Christoph Mück	Expert - via telephone*	Austria	No interests declared	
Christine Vaculik	Expert - via telephone*	Austria	No interests declared	
Jakob Paur	Expert - via telephone*	Austria	No restrictions applicable to this meeting	
Manfred Schuster	Expert - via telephone*	Austria	No interests declared	
Brigitte Mueller	Expert - via telephone*	Austria	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Harald Bernsteiner	Expert - via telephone*	Austria	No interests declared	
Melanie Ramberger	Expert - via telephone*	Austria	No interests declared	
Laura Rodriguez	Expert - via telephone*	Spain	No interests declared	
David Ordóñez	Expert - via telephone*	Spain	No interests declared	
Juan Fernando Martínez	Expert - via telephone*	Spain	No restrictions applicable to this meeting	
Gloria Palomo	Expert - via telephone*	Spain	No interests declared	
Fernando Méndez	Expert - via telephone*	Spain	No interests declared	
Concha Prieto	Expert - via telephone*	Spain	No interests declared	
Raquel Martín Palomeque	Expert - via telephone*	Spain	No interests declared	
Susana Rojo Gozalo	Expert - via telephone*	Spain	No interests declared	
Anna Vikefors	Expert - via telephone*	Sweden	No interests declared	
Karri Penttilä	Expert - via telephone*	Finland	No interests declared	
Juliane Rau	Expert - via telephone*	Germany	No interests declared	
Torbjorn Callreus	Expert - via telephone*	Malta	No interests declared	
Danila Renzo	Expert - via telephone*	Italy	No interests declared	
Antonella Isgrò	Expert - via telephone*	Italy	No interests declared	
A representative from the European Commission attended the meeting Meeting run with support from relevant EMA staff				