20 March 2019
EMA/CAT/191544/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Advanced Therapies (CAT)

Agenda for the meeting on 20-22 March 2019

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

20 March 2019, 14:00 – 18:30, room 0-C

21 March 2019, 09:00 – 18:00, room 0-C

22 March 2019, 09:00 – 12:00, room 0-C

Health and safety information

In accordance with the Agency's health and safety policy, delegates are to be briefed on health, safety and emergency information and procedures prior to the start of the meeting.

Disclaimers

Some of the information contained in this agenda 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 CAT meeting reports once the procedures are finalised.

Of note, this agenda is a working document primarily designed for CAT members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the agenda 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

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the CAT plenary session to be held 20-22 March 2019. See March 2019 CAT minutes (to be published post April 2019 CAT meeting).

1.2. Adoption of agenda

CAT agenda for 20-22 March 2019 meeting

1.3. Adoption of the minutes

CAT minutes for 20-22 February 2019 meeting

1.4. Technical information

2. Evaluation of ATMPs

2.1. Opinions

2.1.1. Autologous CD34+ cell enriched population that contains hematopoietic stem cells transduced with lentiglobin BB305 lentiviral vector encoding the beta-A-T87Q-globin gene - Orphan - EMEA/H/C/003691

Accelerated assessment

bluebird bio GmbH; treatment of transfusion-dependent β-thalassaemia (TDT)

Scope: Opinion

Action: for adoption

List of Questions adopted on 25.01.2019.

2.2. Oral explanations

No items

2.3. Day 180 list of outstanding issues

No items

2.4. Day 120 list of questions

No items

2.5. Day 80 assessment reports

No items

2.6. Update on ongoing initial applications

2.6.1. Viable T-cells - Orphan - EMEA/H/C/002397

Kiadis Pharma Netherlands B.V.; Adjunctive treatment in haematopoietic stem cell transplantation (HSCT) for a malignant disease

Scope: request by the applicant for a third clock stop extension .

Action: for adoption

Oral Explanation took place on 12.09.2018. List of Outstanding Issues adopted on 14.09.18 and 25.05.2018. List of Questions adopted on 08.09.2017.

2.7. New applications

2.8. Withdrawal of initial marking authorisation application

No items

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

No items

2.10. GMP and GCP inspections requests

No items

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

2.11.1. Imlygic - talimogene laherparepvec - EMEA/H/C/002771/II/0028

Amgen Europe B.V.

Rapporteur: Olli Tenhunen, CHMP Coordinator: Outi Mäki-Ikola, PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Safety: submission of an updated RMP version 4.0 in order to align the important identified and potential risks and missing information with the revised guideline Good Pharmacovigilance Practices Module V (Revision 2), resulting in the reclassification and removal of a number of identified and potential risks and missing information. Opinion

Action: for adoption

Request for Supplementary Information adopted on 07.12.2018.

2.11.2. Imlygic - talimogene laherparepvec - EMEA/H/C/002771/II/0029

Amgen Europe B.V.

Rapporteur: Olli Tenhunen, CHMP Coordinator: Outi Mäki-Ikola, PRAC Rapporteur: Brigitte Keller-StanislawskiScope: Safety: update of section 5.2 of the SmPC in order to update the pharmacokinetic properties information based on the final results from study 20120324, a phase 2, multicenter, single-arm trial to evaluate the biodistribution and shedding of talimogene laherparepvec in subjects with unresected, stage IIIB to IVM1c melanoma. This submission fulfils MEA 006.1. In addition, the Marketing authorisation holder (MAH) took the opportunity to update Annex II as per the already assessed EMEA/H/C/002771/ANX/001 procedure. Opinion

Action: for adoption

Request for Supplementary Information adopted on 22.02.2019.

2.11.3. YESCARTA - axicabtagene ciloleucel - Orphan - EMEA/H/C/004480/II/0003

Kite Pharma EU B.V.

Rapporteur: Jan Mueller-Berghaus, CHMP Coordinator: Jan Mueller-Berghaus, PRAC Rapporteur: Anette Kirstine Stark

Scope: update of the sections 4.8, 5.1 of the SmPC to add information based on a Phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive non-Hodgkin lymphoma (ZUMA-1), an addendum presenting 24-month analysis. The package leaflet has been updated accordingly. Furthermore, editorial changes have been introduced throughout the PI. Opinion

Action: for adoption

Request for Supplementary Information adopted on 25.01.2019.

2.12. Other Post-Authorisation Activities

2.12.1. Glybera (EXP) - alipogene tiparvovec - Orphan - EMEA/H/C/002145/REC/013

uniQure biopharma B.V.

Rapporteur: Christiane Niederlaender, CHMP Coordinator: Greg Markey

Scope: Clinical: LPLD registry collecting safety and efficacy data from patients that have received Glybera and are followed-up for 15 years. Annual update.

Action: for adoption

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

No items

3.2. Day 60 Evaluation Reports

No items

3.3. New Applications

4. Scientific Recommendation on Classification of ATMPs

4.1. New requests – Appointment of CAT Coordinator

4.1.1. Autologous micronized adipose tissue particles – H0005338

Intended for the treatment of scar revision, burn wound, diabetic ulcer and pressure ulcer

Scope: appointment of CAT Coordinator and adoption of timetable

Action: for adoption

4.1.2. Allogeneic haematopoietic stem and progenitor cells treated ex vivo with the protein transduction domain of the HIV-1 transactivation protein fused to MYC transcription factor – H0005341

Intended for the treatment of myelofibrosis

Scope: appointment of CAT Coordinator and adoption of timetable

Action: for adoption

4.1.3. Allogeneic haematopoietic stem and progenitor cells treated ex vivo with the protein transduction domain of the HIV-1 transactivation protein fused to MYC transcription factor – H0005340

Intended for the treatment of acute myelogenous leukaemia

Scope: appointment of CAT Coordinator and adoption of timetable

Action: for adoption

4.2. Day 30 ATMP scientific recommendation

4.2.1. Recombinant adeno-associated viral vector serotype 8 (AAV8) encoding a codon optimised cDNA encoding human Retinitis Pigmentosa GTPase Regulator (coRPGR) – H0005315

Intended for the treatment of X-linked retinitis pigmentosa (XLRP)

Scope: ATMP scientific recommendation

Action: for adoption

4.2.2. Allogeneic adult bone-marrow-derived stem cells transiently transfected with a plasmid construct encoding the intracellular domain of human Notch-1 – H0005313

Intended for the treatment of motor deficits arising from acquired brain injury, including traumatic brain injury, ischaemic stroke and haemorrhagic stroke

Scope: ATMP scientific recommendation

Action: for adoption

4.2.3. Autologous T cells transduced with a T cell receptor (TCR) targeting human Telomerase Reverse Transcriptase (hTERT) – H0005314

Intended for the treatment of various cancer types expressing hTERT

Scope: ATMP scientific recommendation

Action: for adoption

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

4.3.1. Allogeneic cord blood mononuclear cells - H0005292

Treatment of neurological disorders, autism spectrum disorders, cerebral palsy

Scope: assessment of the responses from the applicant. Revised ATMP scientific recommendation

Action: for adoption

4.4. Finalisation of procedure

4.4.1. Recombinant adeno-associated viral vector serotype-5 expressing human 21-hydroxylase gene – H0005295

Treatment of congenital adrenal hyperplasia

Scope: the European Commission raised no comments. Final ATMP scientific recommendation

Action: for information

4.4.2. Autologous skeletal muscle derived cells attached to biodegradable poly(DL-lactide-co-glycolide) microparticles combined with skeletal muscle derived cells – H0005289

Treatment of faecal incontinence and anorectal malformation

Scope: the European Commission raised no comments. Final ATMP scientific recommendation

Action: for information

4.4.3. Allogeneic, *ex vivo* expanded, umbilical cord (UC) blood-derived, haematopoietic CD34+ progenitor cells and allogeneic, non-expanded, UC blood-derived, haematopoietic mature myeloid and lymphoid cells - H0005288

Haematopoietic reconstitution of patients who are medically indicated for allogeneic haematopoietic stem cell transplantation

Scope: comments raised by the European Commission. Revised final ATMP scientific recommendation

Action: for adoption

4.4.4. *In vitro* transcribed single-stranded messenger RNA (mRNA) molecules encoding human interferon-α2b, interleukin-12, interleukin-15sushi, and Granulocyte-macrophage colony-stimulating factor – H0005291

Treatment of solid tumours

Scope: the European Commission raised some minor comments. Final ATMP scientific recommendation

Action: for information

4.4.5. Recombinant adeno-associated viral vector (AAV) containing a human micro-dystrophin gene drug substance – H0005293

Treatment of patients with Duchene muscular dystrophy (DMD)

Scope: the European Commission raised no comments. Final ATMP scientific recommendation

Action: for information

4.4.6. Plasmid vector expressing interleukin-12 gene – H0005294

Treatment of advanced melanoma

Scope: the European Commission raised no comments. Final ATMP scientific recommendation

Action: for information

4.4.7. *Ex vivo* expanded allogeneic bone marrow derived mesenchymal stromal cells – H0005290

Treatment of graft-*versus*-host disease

Scope: the European Commission raised no comments. Final ATMP scientific recommendation

Action: for information

4.4.8. Autologous dendritic cell, electroporated with messenger ribonucleic acid (mRNA) encoding tumour antigen Wilms tumour r (WT)-1 – H0005240

Clock stop: postponed to April 2019 Treatment of lung cancer

Scope: the European Commission raised no comments. Final ATMP scientific recommendation

Action: for information

4.5. Follow-up and guidance

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

5.2. CAT reports

5.3. List of Issues

5.4. Finalisation of SA procedures

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

No items

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

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. Strategic Review & Learning meeting – joint CAT/Clinical trial facilitation group (CTFG), Bucharest, Romania, 13-14 June 2019

CAT resources: Simona Badoi

Scope: initial draft agenda

Action: for discussion

Note: a half day of this SRLM will be held jointly with the CTFG.

7.2. Coordination with EMA Scientific Committees

7.2.1. Committee for Medicinal Products for Human Use (CHMP)

Scope: Summary of Outcomes (SoO) for the February 2019 meeting

Action: for information

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

None

7.4. Cooperation within the EU regulatory network

7.4.1. Question and Answer document on the use of Out-of-Specification (OOS) batches of authorised ATMPs

Scope: questions and answers describing the process and responsibilities for using OOS batches of authorised ATMPs in patients (implementation of the provision in section 11.5 of the guidelines on GMP for ATMP).

Action: for agreement

7.4.2. EDQM/Council of Europe – 4th edition of the guide to the quality and safety of tissues and cells for human application

CAT: Martina Schüssler-Lenz

Scope: CAT contribution to the consultation of the 4th edition of the guide to the quality and safety of tissues and cells for human application.

Action: for information

Note: weblink to the consultation: http://extranet.edqm.eu/dropboxout/045FeTCbK9YidCaHofWneRjQuVeHi7oxxUtyyN0mqeK/4th%20ed%20of%20TC%20Guide%20for%20open%20consultation-TO%2019%201_.zip

7.4.3. European Commission initiatives on ATMPs

Scope: update on discussions with GMO authorities;

Action: for information

Note: on the interplay between the pharma and the GMO framework, a short update was provided by the European Commission's representative at the February 2019 CAT meeting.

7.4.4. Handling of confidential information within the EU network

Action: For information

7.4.5. Reflection on principles of GMP

Scope: Presentation to CAT

Action: for discussion

Note: in January 2019, CAT discussed how to interpret 'principles of GMP' with regard to the critical starting materials for ATMPs

7.5. Cooperation with international regulators

None

7.6. CAT work plan

7.6.1. Genome editing technologies for drug development – regulatory considerations

Scope: revised CAT considerations

Action: for adoption

Note: the proposal agreed by CAT in December 2018 was presented to CHMP in January 2019. CHMP raised some comments on the extent of the CAT position. A revised wording was developed by the drafting group (meeting on 11th and 13th March 2019) taking into account the CHMP comments.

7.7. Planning and reporting

7.7.1. Planning estimates of forthcoming ATMP MAAs

Scope: Q1/2019 update of the business pipeline report for the human scientific committees

Action: for information

7.8. Others

7.8.1. Draft QWP/BWP guideline on the quality requirements for drug device combination products

Rapporteur: Abigail Moran (UK); Co-rapporteur: Nicholas Lee (IE)

CAT: Ilona Reischl

Scope: development of the guideline on drug device combinations: applicability of the guideline to ATMPs

Action: for discussion

8. Any other business

No items

Date of next CAT meeting:

Tuesday 16th to Wednesday 17th April 2019

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

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

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

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: Scientific Working Party

SME: Small and medium size enterprises

SmPC: Summary of Products Characteristics

TT: Timetable

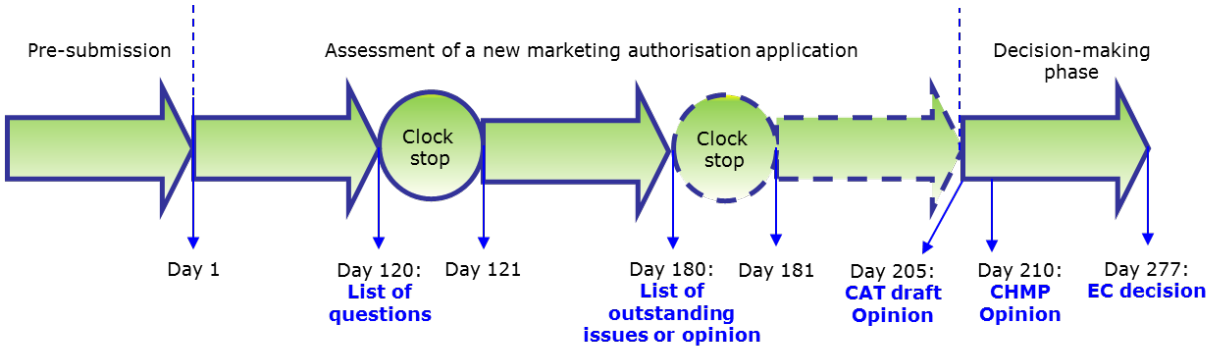
Evaluation of ATMPs (section 2)

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/