IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Meeting report series

Report of the 15th Therapies Scientific Committee Meeting

Vienna, Austria
May 14, 218

Participants

Dr Diego Ardigò, Parma, Italy – Chair
Dr Virginie Hivert, Paris, France – Vice Chair
Dr Seng H. Cheng, Framingham, USA
Dr Michela Gabaldo, Milan, Italy
Dr Sandrine Marreaud, Brussels, Belgium
Dr Anne Pariser, Bethesda, USA
Dr Karin Rademaker, Utrecht, the Netherlands
Dr Ken Sakushima, Tokyo, Japan
Prof Maurizio Scarpa, Wiesbaden, Germany/ Padova, Italy
Dr Josep Torrent i Farnell, Barcelona, Spain

Dr Anneliene Jonker, Scientific Secretariat, Paris, France

Apologies

Dr Annemieke Aartsma-Rus, Leiden, the Netherlands
Dr Robin Conwit, Bethesda, USA
Mr Yann Le Cam, Paris, France

Agenda

1. Roundtable and introductions
2. TSC membership
3. Update on ongoing/ completed activities/ Task Forces
    a. SPCT TF paper update
    b. PCOM TF paper update
    c. DMR TF follow-up
4. Brainstorming on TSC follow-up to completed Task Forces

   a. TSC free discussion on potential follow-ups to completed TFs and past initiatives
5. Overview of TSC activities
6. Activity C
   a. Review of approach, plan, and timelines
   b. Review and approval of the first draft of tools (Development Board, Building Blocks, and Block Form)
   c. Brainstorming and prioritization on Building Blocks list
   d. Building Blocks form
   e. Planning of the workshop
7. Update on the IRDiRC counter
   a. Review of data generated with the new counter and discussion on finalization of counting rules
   b. Planning for the counter paper

REPORT

1. Roundtable and introductions

Diego Ardigo, the Chair of the Therapies Scientific Committee (TSC), welcomed all participants and invited them to introduce themselves. He is R&D Rare Diseases Unit Head at Chiesi Farmaceutici.

Virginie Hivert is the Therapeutic Development Director of EURORDIS, and previously worked at Orphanet, based in Paris, France; she has been involved in IRDiRC in various roles since its beginning, now as Vice Chair of the TSC.

Michela Gabaldo is Head of Alliance Management & Regulatory Affairs Manager at San Rafaele Telethon Institute for Gene Therapy (SR-TIGET), and has been highly involved in the development of Strimvelis, approved last year for the treatment of ADA-SCID.

Anneliene Jonker is the Project Manager of the IRDiRC Scientific Secretariat (Sci Sec).

Sandrine Marreaud is the Head of EORTC's Medical and Pharmacovigilance Department, and she is the coordinator of their fellowship program. She has more than 20 years of experience in running clinical trials with rare cancer patients.

Anne Pariser is the Director of the Office of Rare Diseases Research (ORDR) and works to advance diagnosis and treatment for rare diseases through research. Anne Pariser previously worked at the Food and Drug Administration (FDA), mainly on the development of drug and biological products for rare diseases.

Karin Rademaker's area of expertise is pharmaceutics for children and rare diseases. She runs the R&D department of the University Medical Center of Utrecht and trains hospital pharmacists and clinical pharmacologists.

Maurizio Scarpa is the Chair of the Board of the European Reference Networks, the Coordinator of the European Reference Network for Rare Heridatary Metabolic Diseases (METABERN), the Director of the Rare Disease Center, the Helios Dr Horst Schmidt Kliniken, and a Professor of pediatrics at the University of Padova.

Josep Torrent i Farnell is a Professor of Clinical Pharmacology and Therapeutics with an interest in orphan drugs, and has been involved in IRDiRC since the start. He was a former Chair of the TSC, and has also previously served on the EMA's Committee for Orphan Medicinal Products (COMP).

2. TSC membership

The TSC currently has 13 members, with three members that will finalize their second mandate in 2019, leaving some possibilities for new members to join. Ideally the group has about 15 members, but can be enlarged up to 20.

Looking at geographical distribution of membership:

- Current distribution:
  - Europe: 9 members
  - USA: 3 members
  - Asia: 1 member
  - TSC is currently a bit Eurocentric, but has members from the USA and Japan
- Ideally would like to expand Committee with members from Australia/ South America/ Africa and if possible, additional representation from Asia.

Looking at stakeholder distribution of membership:

- Current distribution:
  - Clinician: 1
  - HTA/ Regulators: 2
  - Academics: 6
  - Industry: 2
  - PO: 2
- Ideally the Committee should be expanded with additional regulators and industry representatives
- The questionnaire the TSC held last year also confirmed the need for regulators and industry members
  - Currently difficulty recruiting a representative from EMA, due to Brexit

Potential new members

- Balance between quality of the potential member and the willingness to be active in the Committee
- Potentially, ask them to be involved in activities/ Task Forces, and then recruit active members out of this pool

→ Several TSC members will reach out for suggestions for new members

3. Update on ongoing/ completed activities/ Task Forces

3.1 SPCT TF paper update

The Steering Committee of the Small Populations Clinical Trials (SPCT) Task Force (TF), led by Simon Day, and assisted by the IRDiRC Sci Sec, has transformed the post-workshop recommendations report into a paper.

- Submitted to the *Orphanet Journal of Rare Diseases*
  - The paper was rejected at first try
- All comments are integrated, and the paper has recently been resubmitted
- Will be send to all TSC members if accepted

3.2 PCOM TF paper update

Thomas Morel and Stefan Cano, members of the Patient-Centered Outcome Measures (PCOM) TF, have transformed the post-workshop recommendations report into a paper.

- Accepted and online in *Orphanet Journal of Rare Diseases*
- Paper was previously send to all members

3.3 DMR TF paper update

The post-workshop paper of the Data-Mining and Repurposing TF is currently being transformed into a paper by the IRDiRC Sci Sec, the Chairs of the TF, and the Chairs of the TSC.

- Draft to be finalized
- Submission planned at *Orphanet Journal of Rare Diseases*
- TSC members interested in reviewing this paper, to inform Sci Sec
- Report with recommendations will be published publically once the article is accepted/ online

→ Send out paper SPCT recommendations to all TSC members, if accepted
→ Publish paper DMR recommendations

4. Brainstorming on TSC follow-up to completed Task Forces

How to do follow up so that the knowledge is further integrated and not lost in the community? How can we spread the word better on outcomes of Task Forces/ Activities?

Current model of TF is:

- TF gets approved
- Sci Sec writes State of the Art report
- Several teleconferences in preparation of workshop
- Workshop
- Report by Sci Sec
- Paper; a commentary on the report

Several remarks

- TF needs a strong leader in order to finish (on time)
- Currently little to no follow-up

Several follow-up ideas possible:

- DMR
  - DMR business model paper, to be written by Virginie and Diego
- SPCT
  - Asterix, IDeAl and InSPiRe are finished: reach out if a "final impression" document would be possible on SPCT, highlighting the critical aspects of this topic, with a forward looking view on the impact of future orphan drugs
  - Follow-up workshop planned with RD-Action at the EMA: http://www.ema.europa.eu/docs/en_GB/document_library/Agenda/2018/05/WC500249260.pdf
- PCOM
  - Follow-up survey planned within European Reference Networks (ERN)

External communication plan

- Reach-out roadshow with stakeholders and communication targets (e.g. ERNs, trade associations such as EFPIA, regulatory agencies, etc)
- Mapping of member's speaking at conferences on IRDiRC activities

5. Overview of TSC activities

- Prior to the Tokyo CA meeting, a strategic exercise was held among TSC members, a GAP analysis to generate new actions for the TSC to take on
  - Resulted in a general framework for the generation of the TSC strategy
  - What needs to be done? – Strategic imperative
  - How to do it? – Strategic tools
  - What are the stakeholders, who to communicate with? – Target stakeholders
    - Resulted in the identification of 4 strategic themes for action
- Themes and actions were presented at the Tokyo CA meeting, as were all actions from the other Scientific and Constituent Committees. Hereafter, actions were condensed by the Sci Sec, and presented for vote to the CA
  - Proposed TSC actions were approved, with over 90 % of votes for each activity

- Final list of actions of the TSC, and the outcome for each activity
  - Support the definition of a new master plan for the development and registration of innovative drugs specific for RDs
    - Activity TSC led
    - Voted for priority as ACTION C
  - Support the definition of standards for use of data collected in health care practice for RWE generation, in particular for disease understanding and treatment monitoring
    - Activity shared with CCC and FCC, ISC
    - Voted for priority as ACTION D

- Support the reframing of the current international research agenda for rare diseases pushing for focusing research efforts and funding
  - Activity TSC led
  - Voted for priority as ACTION E
- Clinical Research Network for Rare Diseases
  - Activity Shared with ISC, FCC and TSC
  - Voted for priority as ACTION G

6. Activity C

6.1 Review of approach, plan, and timelines

This project aims at creating a simple guidebook for academic and industrial drug developers describing the available tools and initiatives specific for rare disease development and how to best use them.

- Concept: there is a way to develop drugs for rare diseases, that is different from the classical drug development pathway used for blockbuster drugs
- The approach for Activity C is like a game, the framework being the game board, with all classical steps of drug-development.
- Building bricks of the game are all single initiatives and tools. Each building brick will have a description sheet that will enable developers, academic researchers, and others to decide which block to use, according to their need in the process of orphan drug-development.

Status:

- Activity proposal submitted on April 4, 2018
- First consolidated draft of tools to be defined in this meeting
- Proposal for vote at Consortium Assembly meeting on May 16, 2018

6.2 Review and approval of the first draft of tools (Development Board, Building Blocks, and Block Form

The development board represents all classical milestones in the drug-development process in a wheel, rather than a continuous line.

- Additional milestones/tasks/ single initiatives to be attached to this basic board, specific for rare disease drug-development
- This is an initial skeleton to build upon and refine, and this matter could be reflected upon in the next steps to come.

The list of building blocks represents either tools or initiatives specific for rare disease drug development. This initial list is non-exhaustive and is now open for discussion and modification, and will be discussed later in the meeting.

The issue of overlapping already financed ongoing projects (e.g. European Joint Program-EJP), such as mapping, structure coordination, increase diagnostics, policy making, etc… has been raised.
International projects/practices/tools can be added as building blocks. The Guidebook can act both ways, as to also benefit the community to questions raised in the EJP, for example. The main spirit of the Guidebook is to inform the community of what is available in the field and to use it to its best potential. That information will be handed out to developers through the form of fact sheets or building block forms.

The purpose of those Building Blocks form template is to give highlights, where to find detailed information, as well as where and when to use it for each initiative/practice/incentive.

6.3 Brainstorming and prioritization on Building Blocks list

Throughout the TSC meeting, the list of Building Blocks was discussed and completed. List will be sorted further by type and scope of the tool/initiative

- Some building blocks are missing
  - If none found, this could be a conclusion, to indicate where further tools are needed
  - Example 1: there appears to be a gap between market authorization and access
  - Example 2: there seems little to no tools for making IND, which is a hurdle for young investigators to obtain
- Several building blocks are double or appear redundant
  - To indicate what blocks would be used preferentially

6.4 Building blocks form

The building block form contains the following elements:

- Building Block (BB) Title: Headline description of the BB (e.g. “EMA Protocol Assistance”)
- References: How to find the BB (e.g. website address, literature, etc.)
- Description: Full narrative description of what the BB is
- Category: Type of BB (according to the categories defined by generating the list of BBs)
- Availability: Whether the BB is available or conceived only for:
  - Rare Diseases
  - Public/ no-profit
  - SMEs
  - Etc… (other categories)
- Geographical scope: Where the BB is available
- Scope of use: How the BB is used in RD development
- Subject: Who is entitled to activate/ have access/ use the BB

- Enablers/ Requirements: What is needed to activate/ have access/ use the BB
- Output: What is the final product of the BB (e.g. report, recommendation, certification, etc.) and its format

No additional categories were added to the form. An example of use will be send to TSC members shortly.

6.5 Planning of the workshop

The workshop is planned to take place on December 12-13, 2018, in a place to be determined, preferably somewhere sunny.

- Steering Committee for activity should contain maximum 6 people
- Total number of people involved in activity can be max 20-24 people, including TSC members interested in the topic
    - 3 subgroups of people throughout the workshop

→Send in names for potential members Activity C
→Present Activity C proposal to CA for approval
→ Send example of Building Block form that is filled out
→Start organization of the Activity C Workshop

[Post meeting note]: Activity C has been approved by the Consortium Assembly

7. Discussion on Orphan Drug Counter

Based on information obtained from the EMA and the Food and Drug Administration (FDA) websites and using the current established count methodology, i.e. orphan medicinal products (OMPs) with a marketing authorization (MA) and an orphan designation (OD) were counted until 2017, contributing to a total of 279 drugs.

- Drugs that are approved in both EMA and FDA get only counted once, upon first approval
- Drugs for which a new indication has been approved get counted; they do not get counted if they go from second-line to first-line therapy or from 12 to 4 years of age.

This leads to several questions:

- There are more than 200 drugs, but what are these drugs?
- What is the difference between drugs approved in the USA and drugs approved in the EU

For each drug, the following information is collected:

- Trade name
    - Active substance
- Approved indication

    - Disease according to Orphanet Classification
        - Allows a comparison between agencies
    - Soon: Disease group according to Orphanet Classification
- Market authorization date
- Market authorization holder
- ATC code
    - ATC
- Approved in EMA and FDA both
    - First approval
- Designation date
    - Difference between Orphan Designation (OD) and Market Authorization (MA)
- Extension
    - Indication for extension

In order to get a better overview, the Sci Sec has started an analysis, that is expected to turn into a commentary:

- Number of drugs contributing to the counter
- Total number of drugs
- Total number of approvals
- Total number of extensions for new indications
- Time delay between OD and MA
- Total number of drugs approved in the other agency
- Number of diseases that can be treated
- Difference ATC group US/ EU
- Difference OD and MA US/EU for drugs that are approved in both agencies

For the IRDiRC goals 2017-2027, we will refine the current count. Primary count from 1 January 2017

- New therapies for RD with MA, for rare indications, from US/EU/Japan

The counter structure to be put in place from January 2017

- All pharmaceutical products for rare diseases (RDPP) (with or without OD) approved by EMA, FDA, or PMDA starting from January 1, 2017
    - All RDPP approved with OD and without OD
    - All RDPPs (with or without OD) approved for an indication for which no prior active marketing authorization exists
    - New Orphan Medical Products (with or without OD)
    - All new RDPPs approved for a disease for which no prior active marketing authorization exists
    - New RDPP with at least one OD

→ Present metrics for the orphan drug count 2017-2027 to joint SC meeting

→ Finish analysis orphan drugs 2010-2017 and write commentary

→ Start orphan drug count 2017-2027

Next steps and actions

- Reach out for suggestions for new TSC members
- Send out paper SPCT recommendations to all TSC members, if accepted
- Publish paper DMR recommendations
- Send in names for potential members Activity C
- Present Activity C proposal to CA for approval
- Send example of Building Block form that is filled out
- Start organization of the Activity C Workshop
- Present metrics for the orphan drug count 2017-2027 to joint SC meeting
- Finish analysis orphan drugs 2010-2017 and write commentary
- Start orphan drug count 2017-2027