EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA policy on publication of clinical data – Update on implementation

Stakeholder webinar
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Introduction: Current scope of implementation

- Limited to phase 1: publication of clinical reports only, i.e.:
  - Clinical overviews (generally submitted in module 2.5)
  - Clinical summaries (generally submitted in module 2.7)
  - Clinical study reports (generally submitted in module 5), together with appendices 16.1.1 (protocol and protocol amendments), 16.1.2 (sample case report form) and 16.1.9 (documentation of statistical methods)

Introduction: Date of coming into effect of policy

- 1/1/2015 for any new MAAs and Article 58 applications, submitted after this date
- 1/7/2015 for extension of indication applications and line extension applications for existing CAPs, submitted after this date
- TBD later this year for all other post-authorisation applications for existing CAPs

Introduction: Preparing for implementation

- It is a major undertaking for the EMA since this is a completely new EMA activity for which several new arrangements have to be agreed internally and put into operation in the most cost-efficient way (due account to be taken of limited resources and anticipated high volume of work)
- Equally, important consequences for pharmaceutical industry to prepare for a timely implementation
- Stakeholder interaction will continue to take place, but because of the complexity of the project and the available timeframe before starting the publication of the clinical reports (currently anticipated for around mid 2016), stakeholder consultation will have to be targeted
- A meeting with all European Industry Associations took place on 8 May 2015; overall very broad support from pharmaceutical industry; comments and suggestions made have been considered and taken into account

Outline of implementation

- Five workstreams:
  1. Data receipt and filing
     - Focus on receipt, validation and internal distribution of a "Redaction proposal"[1] version at the EMA
  2. Redaction consultation
     - Focus on EMA assessment of the pharmaceutical company's proposals for redaction, followed by the final "conclusion" by the EMA
  3. Publication
     - Focus on the publication by the EMA of the "Final redacted" version
  4. Presentation
     - Focus on public access to the clinical reports for the users while such clinical reports are protected through redaction and watermarking
  5. Management of the external users
     - Focus on user registration, user account management, acceptance of the Terms of Use (ToU)

[1] "Redaction proposal" version refers to the version with redactions proposed by the pharmaceutical company

Main deliverables (1/2)

- New end-to-end business processes:
  - For each of the 5 workstreams one or more business processes have been developed
- Guidance documents on the following aspects:
  - Guidance to pharmaceutical industry on the submission of clinical reports intended for publication in accordance with EMA policy 0070
  - Guidance to pharmaceutical industry on redacting CCI in clinical reports
  - Guidance to pharmaceutical industry on the anonymisation of clinical reports for the purpose of publication in accordance with EMA policy 0070

Main deliverables (2/2)

- IT systems:
  - Identity and access management system
  - Publishing tool/system
  - Workflow and case management system

Specific features: Workstream data receipt and filing (1/4)

Submission by a company of redacted clinical reports:

- Issue: Necessary to find the most cost-efficient approach balancing
  - The work to be undertaken by a company on 2 different data sets for different purposes, respectively in the context of:
    - The scientific review process
    - The publication of the clinical reports
  - The work to be undertaken by the EMA to allow publication of the redacted clinical reports within a given timeframe once the procedure has been finalised

Specific features: Workstream data receipt and filing (2/4)

Submission by a company of redacted clinical reports (cont'd):

- Approach:
  - Short-term solution: Redacted clinical reports (proposed redactions presented initially as read-through text) to be uploaded by the company via the Gateway into EURS to "Supplemental Information"
  - Long-term and more viable solution: To explore if a format change of the eCTD can be achieved

Specific features: Workstream data receipt and filing (3/4)

Submission by a company of redacted clinical reports (cont'd):

- Approach (cont'd):
  - Clinical reports to be provided:
    - Between D181-220 of the MAA procedure
    - Within 30 calendar days post-receipt of the company's letter notifying the withdrawal of the application
    - Company to certify that the redacted clinical reports and the scientific review version are the same, the only difference being the proposed redactions

Specific features: Workstream data receipt and filing (4/4)

Submission by a company of redacted clinical reports (cont'd):

- Approach (cont'd):
  - Companies will make proposals to the EMA for redaction both for protection of personal data and for CCI protection, together with
    - A justification table for CCI proposed redactions
    - An anonymisation report on the company's approach to anonymisation of clinical reports
  - The choice of the redaction tool is for each company to decide but the requirements put by the EMA have to be met (e.g. searchability of the clinical reports to be guaranteed, hence requiring PDF text formats)
  - As regards support to SMEs the EMA will
    - Obtain a User's licence for a redaction tool that SMEs can use to create the redacted clinical reports
    - Further assist SMEs as much as possible through the provision of training and the creation of a helpdesk

Specific features: Workstream redaction consultation

- Approach:
  - Only 1 consultation round between the EMA and the company will be foreseen (i.e. one EMA "conclusion" pertaining to the consultation round although exchanges during such consultation round to provide clarification are possible)
  - EMA checking approach to proposed redactions will be risk-based concentrating on the proposed redactions of CCI
  - Guidance documents are made available to assist companies with:
    - The anonymisation of clinical reports for the purpose of publication on the EMA website
    - Redacting CCI in clinical reports

Specific features: Workstream publication (1/2)

- Approach:
  - Publication of the clinical reports will only be undertaken once the concerned procedure has been finalised, i.e.
    - Following the EC Decision granting or refusing the MA/extension of indication/line extension
    - Following receipt of the company's letter notifying the withdrawal of the application
  - The EPAR/updated EPAR will be published prior to the publication of the clinical reports

Specific features: Workstream publication (2/2)

- Approach (cont'd):
  - The EMA will publish the clinical reports within 60 calendar days following the EC Decision / 150 calendar days following receipt of the company's withdrawal letter
  - This timeframe includes 20 calendar days for a company to ask for interim relief if there is disagreement with the EMA

Specific features: Workstream presentation (1/2)

- Approach:
  - The EMA will apply a watermark to the clinical reports prior to their publication to emphasise the prohibition of their use for commercial purposes
  - The following text will be applied:

    "www.ema.europa.eu

    This document cannot be used to support any marketing authorisation application and any extensions or variations thereof"
  - See attached example on how this will be presented on the published information

Samples

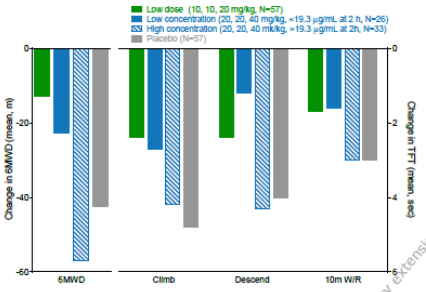
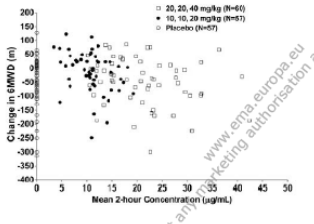


Fig. 16 Plasma concentration versus change on 6MWT



Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13 Summary of Efficacy for trial PTC124-GD-007-DMD

Title: A Phase 2b Efficacy and Safety Study of PTC124 in Subjects with Nonsense-Mutation-Mediated Duchenne and Becker Muscular Dystrophy		
Study identifier	PTC124-GD-007-DMD	
Design	multicenter, international, randomized (1:1:1), double-blind, placebo-controlled, dose-ranging study, stratified by age, corticosteroid use and baseline 6MWD	
	Duration of main phase:	48 weeks
	Duration of screening phase:	n.a.
	Duration of extension phase:	n.a. (subject to a separate protocol)
Hypothesis	Superiority	

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 4: Overview of clinical studies

Study ID (MS Section)	No. of Sites Country	Study Dates (Start - Completion)	Design / Control	Route and Regimen	Indication	No. of Patients by Treatment (Entered/ Completed)	Treatment Duration	Sex (M/F) Age Range (years)
Clinical Pharmacology (Healthy Volunteers)								
PTC124-GD-001-HV, (001) Stage 1 (5.3.3.1)	1 USA	14 Jun 2004 – 25 Jul 2004	Randomized, double-blind, placebo-controlled, dose-escalation	Oral, 5, 10, 30, 100, 150, 200 mg/kg	NA	24/24	Single dose	10/8 18-30
PTC124-GD-001-HV, (001) Stage 2 (5.3.3.1)	1 USA	30 Jul 2004 – 12 Aug 2004	Randomized, open-label crossover evaluation of food effect	Oral, 50 mg/kg with or without food	NA	13/12	Single dose	7/6 22-30
PTC124-GD-002-HV, (002) Stage 1 (5.3.3.1)	1 USA	18 Oct 2004 – 9 Dec 2004	Open-label dose-escalation	Oral, 10, 20, 30, 50 mg/kg BID	NA	24/24	7 days	12/12 18-30
PTC124-GD-002-HV, (002) Stage 2 (5.3.3.1)	1 USA	10 Jan 2005 – 3 Feb 2005	Open-label	Oral, 50 mg/kg BID	NA	7/5	14 days	4/3 18-30
PTC124-GD-010-HV, (010) (5.3.3.1)	1 USA	12 Aug 2008 – 3 Oct 2008	Open-label AME study	Oral, single dose (1775 mg ataluren + 200 µCi [^{14}C]-ataluren)	NA	14/7*	Single dose	14/0 16-50
Adequate and Well-Controlled Studies in nmDMD Patients								
PTC124-GD-007-DMD (007) (5.3.5.1)	37 Australia Canada Europe Israel USA	28 Feb 2008 – 17 Dec 2009	Randomized, placebo-controlled, 3-arm study	Oral, TID Placebo, ataluren 10, 10, 20 or 20, 20, 40 mg/kg	nmDBMD	Placebo: 57/57 10/10/20: 57/57 20/20/40: 60/59 Total: 174/173	48 weeks	174/0 5-20
Uncontrolled Studies in nmDMD Patients								
PTC124-GD-007e-DMD (007e) (5.3.5.2)	37 Australia Canada Europe Israel USA	30 Jun 2009 – 24 May 2010	Open-label extension	Oral, TID Ataluren 20, 20, 40 mg/kg	nmDBMD	173/0	Median: 21.9 weeks Range: 10.7 to 61.3 weeks	173/0 6-21
PTC124-GD-004e-DMD (004e) (5.3.5.2)	3 USA	15 Aug 2008 – 17 May 2010	Open-label extension	Oral, TID Ataluren 20, 20, 40 mg/kg	nmDMD	20/20/40: 36/0	Median: 70.9 weeks Range: 54.0 to 88.3 weeks	36/0 7-19
PTC124-GD-004-DMD (004) (5.3.4.2)	3 USA	21 Dec 2005 – 3 May 2007	Open-label, dose-escalation	Oral, TID Ataluren 4, 4, 8 mg/kg; 10, 10, 20 mg/kg; or 20, 20, 40 mg/kg	nmDMD	4/4/8: 6/6 10/10/20: 20/20 20/20/40: 12/12 Total: 38/38	4 weeks	38/0 5-17
PTC124-GD-008-DMD (008)* (5.3.5.2)	2 USA	13 Jun 2010 – 25 Mar 2010	Open-label	Oral, TID Ataluren 20, 20, 40 mg/kg	nmDBMD	6/0	2 to 7 weeks	6/0 12-20

Specific features: Workstream presentation (2/2)

- Approach (cont'd):
  - As regards multilingual aspects of the EMA website, as a starting point
    - The data protection notice and the Terms of Use will only be available in English
    - The website navigation is in English only

Other aspects (1/4)

- Re-assessment of the redactions of the published clinical reports over time?
  - Issue:
    - Redactions due to CCI will become less justified over time, e.g. because former CCI will get into the public domain
    - This is a particular challenge since published clinical reports will be permanently available on the EMA website
    - However, a regular review if the CCI is still justified over time for all published clinical reports (some 14,000 per annum) is unmanageable
  - Approach:
    - CCI redaction in the published clinical reports will be left as such
    - In case a person wanting to have access disagrees with the CCI redaction as a result of the above situation, such person will be referred to the possibilities offered under the Access to Documents scheme

Other aspects (2/4)

Publication of clinical reports prior to the anticipated closure of the project:

- Approach:
  - Closure of the implementation project is currently anticipated for the end of April 2016 (date still to be confirmed), which would be in time to publish the clinical reports submitted as of 1/1/2015 and 1/7/2015 respectively
  - In case of earlier finalisation of a procedure prior to the closure of the project (as a result of accelerated assessment or a withdrawal)
    - No publication of the clinical reports will be undertaken prior to the closure of the project
    - All the preparatory work will be done (submission by the company of the redacted clinical reports and finalisation of the redaction consultation)
  - In case the closure of the implementation project is delayed, the EMA will inform all stakeholders

Other aspects (3/4)

- Monitoring of the implementation:
  - Since this is a new EMA activity a careful monitoring of the implementation will be undertaken by the EMA
  - Six months following the start of the implementation (implementation currently scheduled for mid-2016) the EMA will review experience (this will include a satisfaction survey with the EMA stakeholders), draw-up lessons learnt, and consider more structural remedial actions in case of a high rate of non-compliance
  - Afterwards, the EMA will prepare a yearly report on experience with the implementation of the policy (the report will include a list of the non-compliant companies)
  - Reports on experience with the implementation will be made publicly available on the EMA website

Other aspects (4/4)

- Non-compliance by companies:
  - In the event of non-compliance by companies at the various stages of the process (from a company not providing clinical reports for publication at the start of the process up to a company not responding to the outcome of the redaction consultation and the further follow-up) the EMA will take remedial action (including, where appropriate, the publication of a non-compliance statement)

Next steps

- In the context of the consultation with its stakeholders the EMA will undertake the following over the next weeks:
  - Face-to-face meeting with stakeholders (6 July 2015) to discuss guidance on the
    - Anonymisation of clinical reports
    - Redaction of CCI in clinical reports

EUROPEAN MEDICINES AGENCY

Thank you for your attention

Further information

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