EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA Clinical Data Publication (CDP)

PCWP/HCPWP joint meeting
18 April 2018

Presented by Dr Karen Quigley
Documents Access and Publication Service, Office of the Deputy Director

Outline

What is EMA's Clinical Data Publication Policy?

Policy 0070 at a glance

Which data was collected during the 1st year?

CDP 1st year report

What is the experience with Industry submissions, and what can be improved?

Lessons Learned

What is happening during 2018?

Focus during this year

Policy 0070 purpose

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Policy 0070:

- 2 October 2014, Clinical Data Publication (human medicinal products)

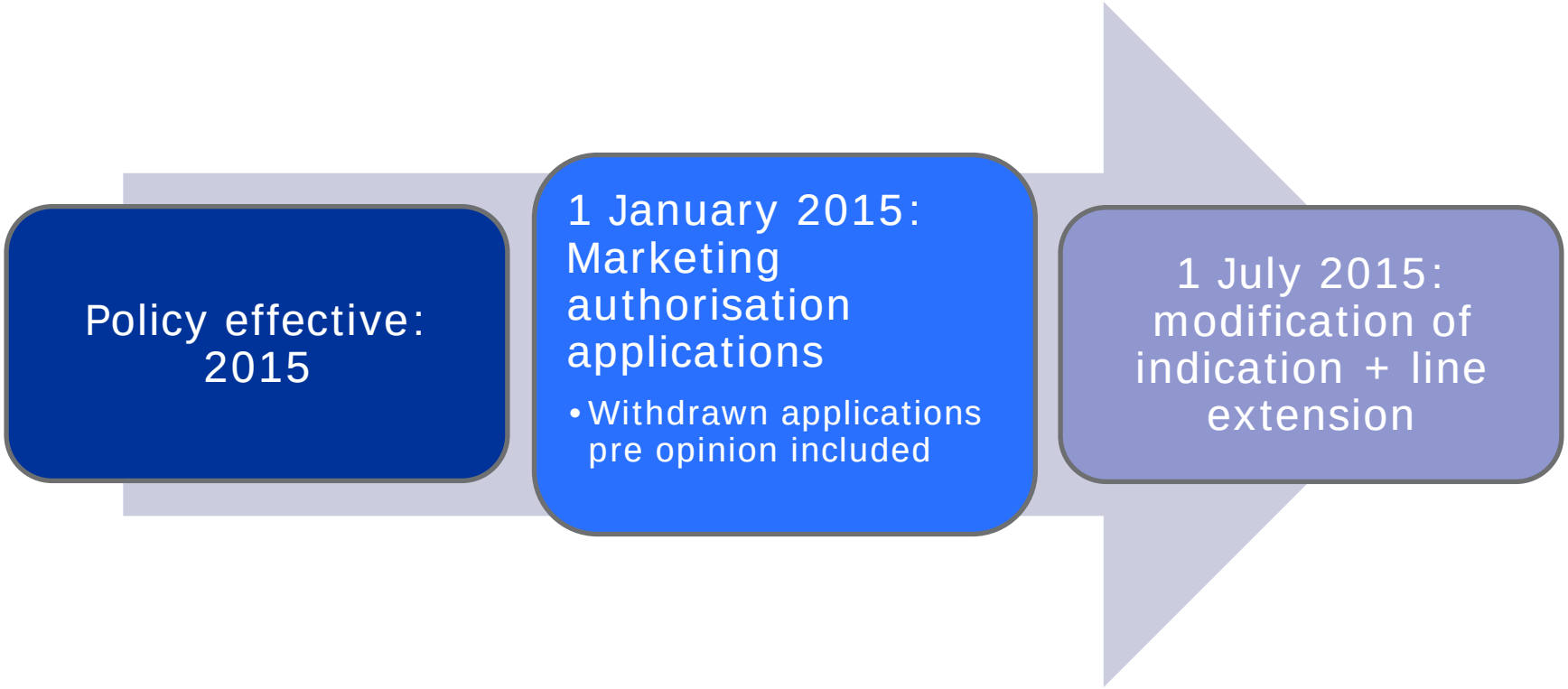
What is it:

- Publication of clinical data supporting CHMP Assessments

Benefits

- **Transparency**, continued EMA commitment
- Enables **public scrutiny**: establishes trust, confidence
- Avoids clinical trials **duplication**
- Enhanced **scientific knowledge**: value of secondary analysis

Policy 0070 scope



Type of published documents

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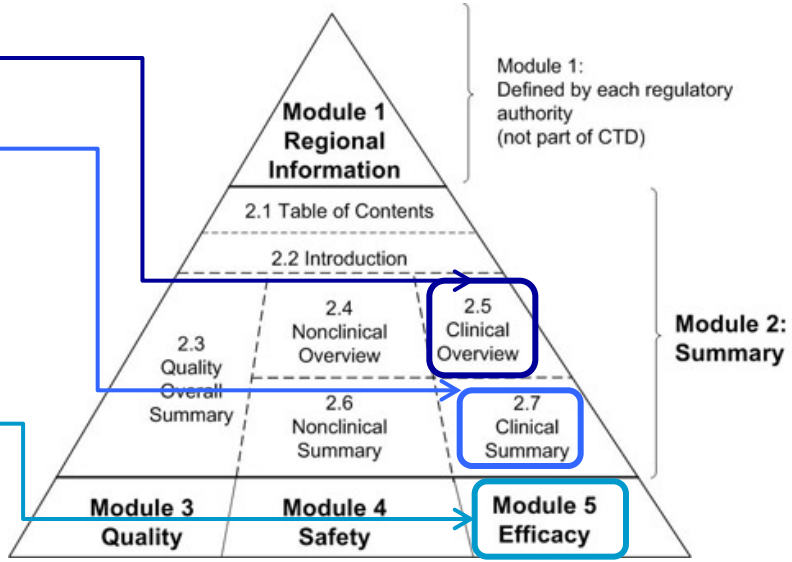
- ***Module 2.5 - Clinical Overview***
- ***Module 2.7.1 to 2.7.4 - Clinical Summary***
- ***Module 5.3 Clinical Study Reports (CSR) - Body of the reports***
- ***Module 5.3 Clinical Study Reports – 3 appendices per CSR***
  - *16.1.1 (protocol and protocol amendments)*
  - *16.1.2 (sample case report form)*
  - *16.1.9 (documentation of statistical methods)*

+

- ***Anonymisation report***



- *For all applications falling within the scope of Policy 0070 whether studies were conducted in or outside the EU*
- *No Individual Patients Data (IPD) listings*

Objective

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Pro-active and on-line Clinical Data Publication (CDP) **Access**

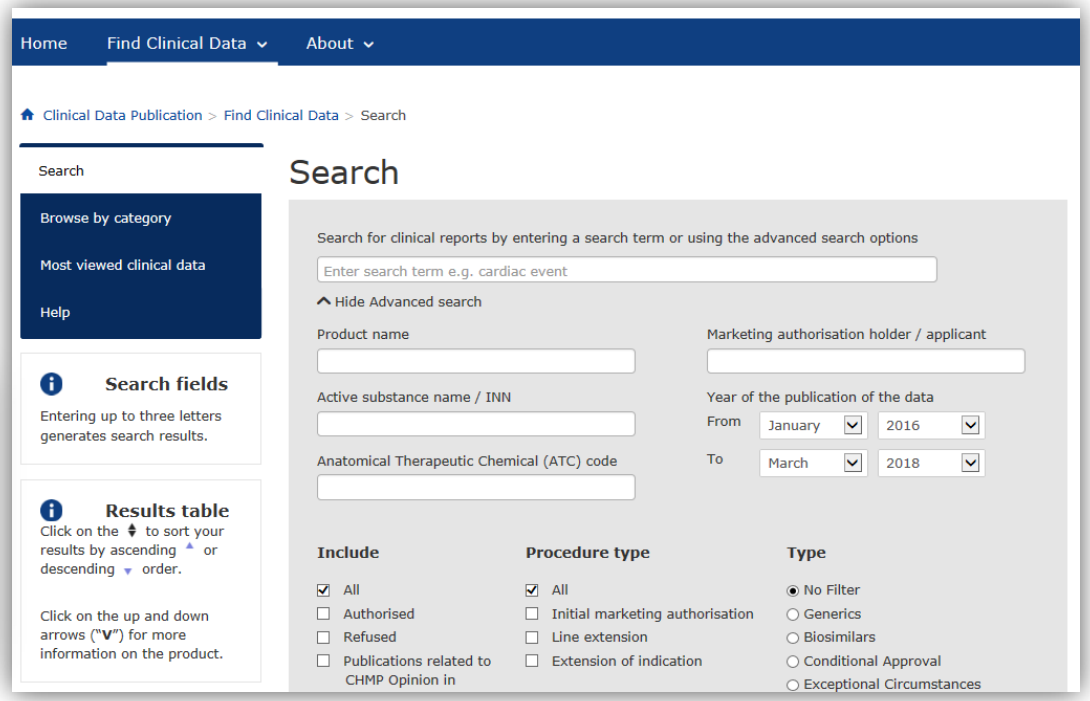
Press release

20/10/2016

Opening up clinical data on new medicines

EMA provides public access to clinical reports

As of today, the European Medicines Agency (EMA) gives open access to clinical reports for new medicines for human use authorised in the European Union (EU).



https://clinicaldata.ema.europa.eu

CDP web portal usage (since October 2016*)

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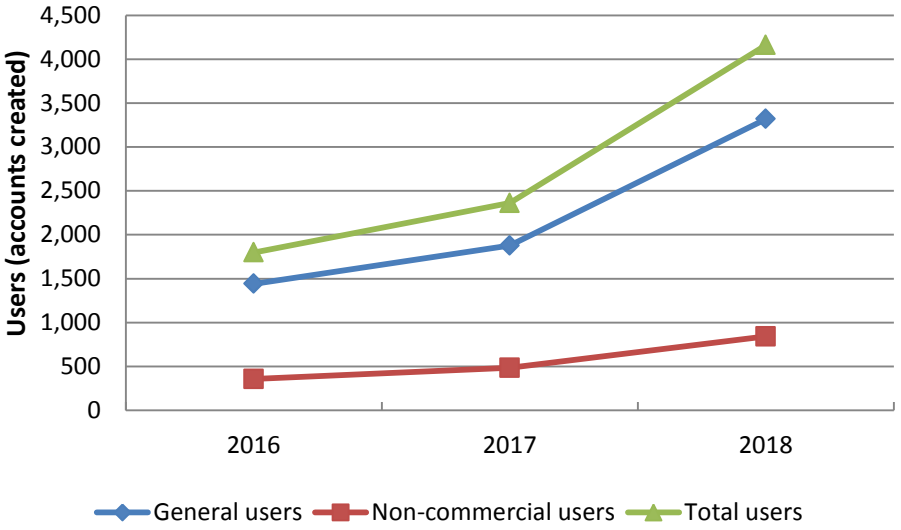
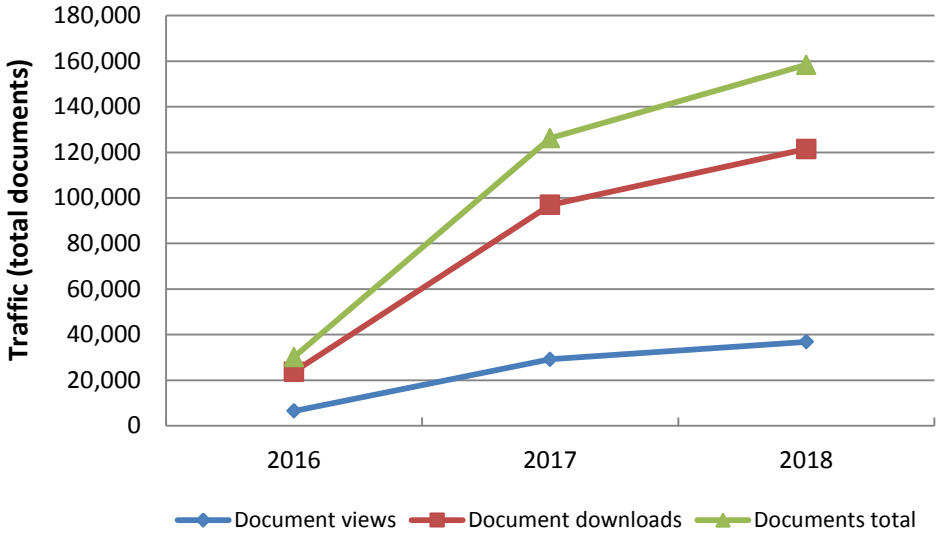
Registered accounts and documents views/downloads





Average of:

- 11 documents viewed per **general user**
- 144 documents downloaded per **non-commercial user**

*Yearly cumulative data (cut off date , Q1 2018)

CDP Report: Overview of 1st year data

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Type of published procedure	
Initial marketing authorisation	36
Extension of indication	18
Line extension	0
Total number of published procedures	54

Published documents	
Anonymisation Report	54
Module 2.5	63
Module 2.7.1-2.7.4	160
Module 5.3 (CSR)	3,002
Total number of documents	3,279
Total number of pages	1,308,244

Percentage of Commercially Confidential Information (CCI)

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	Procedures		Documents		Pages	
Total published	54		**3,279**		**1,308,244**	
CCI proposed by the MAH / Applicant	28	52%	145	4.4%		
CCI was accepted by EMA	19	35%	48*	**1.46%**	134	**0.0102%**

** documents with one or more proposed CCI redactions*

Rejection of CCI (overall/per code)

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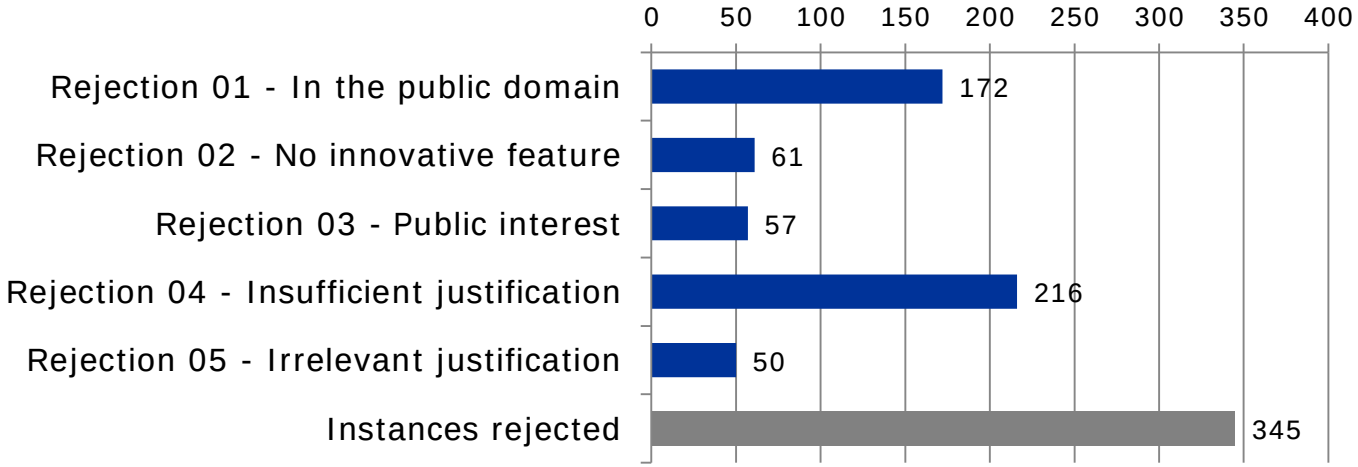
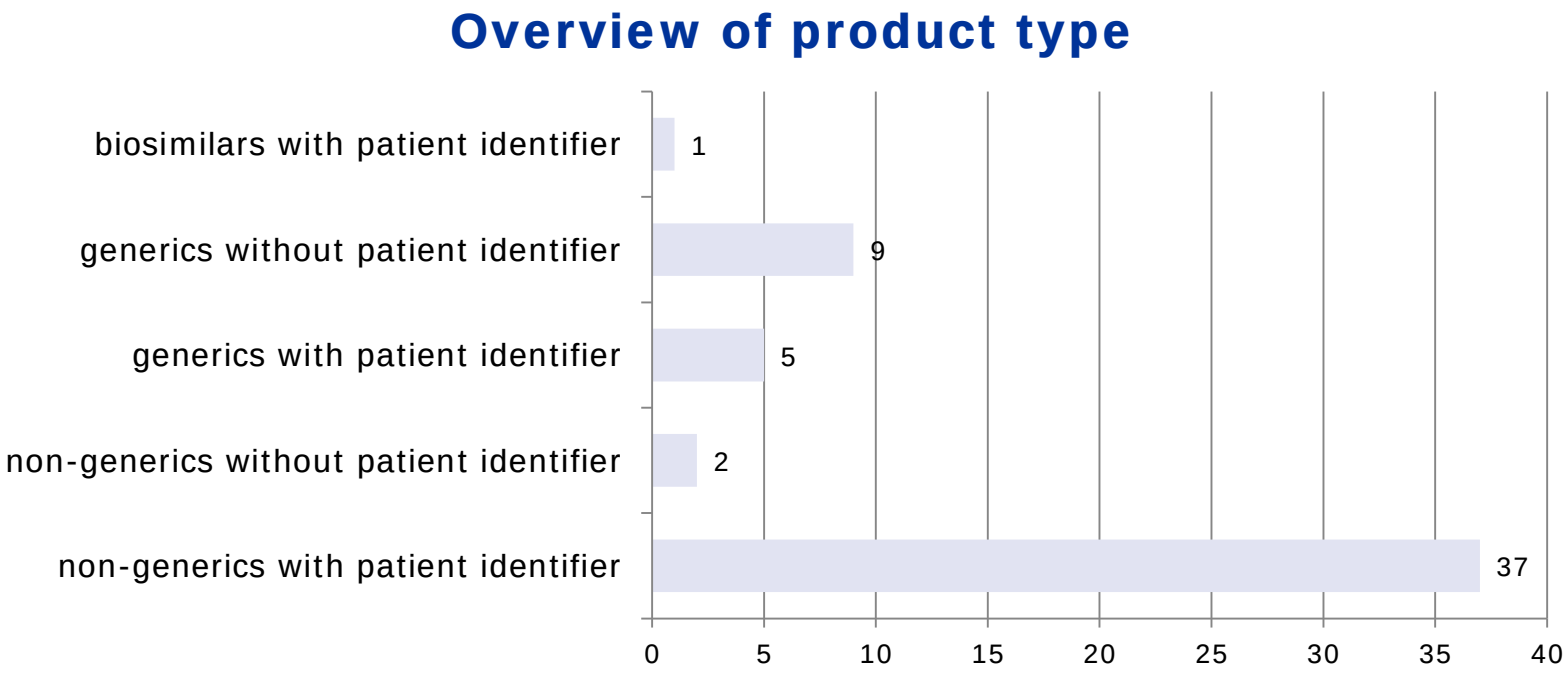
- Of **454** instances (where CCI was proposed) in **145** individual documents, **24%** were accepted and **76%** rejected.

Reasons for rejection of CCI



*An **instance** is defined as a single CCI proposal **per individual document** regardless of how many times it appears in that individual document.*

Anonymisation: overview of product type



Anonymisation: applied techniques (all procedures)

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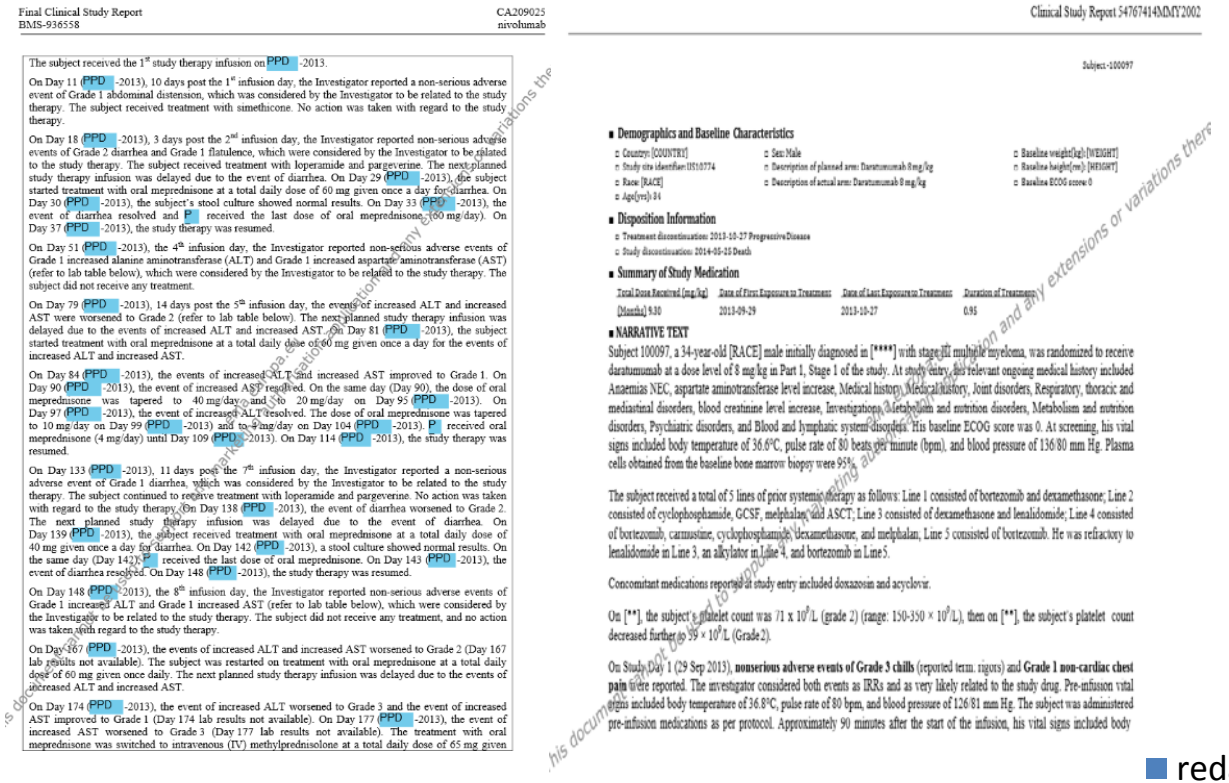


Final Clinical Study Report
BMS-936558

CA209025
nivolumab

The subject received the 1st study therapy infusion on PPD -2013.

On Day 11 (PPD -2013), 10 days post the 1st infusion day, the Investigator reported a non-serious adverse event of Grade 1 abdominal distension, which was considered by the Investigator to be related to the study therapy. The subject received treatment with simethicone. No action was taken with regard to the study therapy.

On Day 18 (PPD -2013), 3 days post the 2nd infusion day, the Investigator reported non-serious adverse events of Grade 2 diarrhea and Grade 1 flatulence, which were considered by the Investigator to be related to the study therapy. The subject received treatment with loperamide and pargeverine. The next planned study therapy infusion was delayed due to the event of diarrhea. On Day 29 (PPD -2013), the subject started treatment with oral mepredinsone at a total daily dose of 60 mg given once a day for diarrhea. On Day 30 (PPD -2013), the subject's stool culture showed normal results. On Day 33 (PPD -2013), the event of diarrhea resolved and P received the last dose of oral mepredinsone (60 mg/day). On Day 37 (PPD -2013), the study therapy was resumed.

On Day 51 (PPD -2013), the 4th infusion day, the Investigator reported non-serious adverse events of Grade 1 increased alanine aminotransferase (ALT) and Grade 1 increased aspartate aminotransferase (AST) (refer to lab table below), which were considered by the Investigator to be related to the study therapy. The subject did not receive any treatment.

On Day 79 (PPD -2013), 14 days post the 5th infusion day, the events of increased ALT and increased AST were worsened to Grade 2 (refer to lab table below). The next planned study therapy infusion was delayed due to the events of increased ALT and increased AST. On Day 81 (PPD -2013), the subject started treatment with oral mepredinsone at a total daily dose of 60 mg given once a day for the events of increased ALT and increased AST.

On Day 84 (PPD -2013), the events of increased ALT and increased AST improved to Grade 1. On Day 90 (PPD -2013), the event of increased AST resolved. On the same day (Day 90), the dose of oral mepredinsone was tapered to 40 mg/day and to 20 mg/day on Day 95 (PPD -2013). On Day 97 (PPD -2013), the event of increased ALT resolved. The dose of oral mepredinsone was tapered to 10 mg/day on Day 99 (PPD -2013) and to 4 mg/day on Day 104 (PPD -2013). P received oral mepredinsone (4 mg/day) until Day 109 (PPD -2013). On Day 114 (PPD -2013), the study therapy was resumed.

On Day 133 (PPD -2013), 11 days post the 7th infusion day, the Investigator reported a non-serious adverse event of Grade 1 diarrhea, which was considered by the Investigator to be related to the study therapy. The subject continued to receive treatment with loperamide and pargeverine. No action was taken with regard to the study therapy. On Day 138 (PPD -2013), the event of diarrhea worsened to Grade 2. The next planned study therapy infusion was delayed due to the event of diarrhea. On Day 139 (PPD -2013), the subject received treatment with oral mepredinsone at a total daily dose of 40 mg given once a day for diarrhea. On Day 142 (PPD -2013), a stool culture showed normal results. On the same day (Day 142), P received the last dose of oral mepredinsone. On Day 143 (PPD -2013), the event of diarrhea resolved. On Day 148 (PPD -2013), the study therapy was resumed.

On Day 148 (PPD -2013), the 8th infusion day, the Investigator reported non-serious adverse events of Grade 1 increased ALT and Grade 1 increased AST (refer to lab table below), which were considered by the Investigator to be related to the study therapy. The subject did not receive any treatment, and no action was taken with regard to the study therapy.

On Day 167 (PPD -2013), the events of increased ALT and increased AST worsened to Grade 2 (Day 167 lab results not available). The subject was restarted on treatment with oral mepredinsone at a total daily dose of 60 mg given once daily. The next planned study therapy infusion was delayed due to the events of increased ALT and increased AST.

On Day 174 (PPD -2013), the event of increased ALT worsened to Grade 3 and the event of increased AST improved to Grade 1 (Day 174 lab results not available). On Day 177 (PPD -2013), the event of increased AST worsened to Grade 3 (Day 177 lab results not available). The treatment with oral mepredinsone was switched to intravenous (IV) methylprednisolone at a total daily dose of 65 mg given

Clinical Study Report 54767414MMY2002

Subject-100097

Demographics and Baseline Characteristics

- Country: [COUNTRY]
- Study site identifier: IIS10774
- Race: [RACE]
- Age[yrs]: 64
- Sex: Male
- Description of planned arm: Daratumumab 8 mg/kg
- Description of actual arm: Daratumumab 8 mg/kg
- Baseline weight[kg]: [WEIGHT]
- Baseline height[cm]: [HEIGHT]
- Baseline ECOG score: 0

Disposition Information

- Treatment discontinuation: 2013-10-27 ProgressiveDisease
- Study discontinuation: 2014-05-16 Death

Summary of Study Medication

Total Dose Received [mg/kg]	Date of First Exposure to Treatment	Date of Last Exposure to Treatment	Duration of Treatment [Months]
930	2013-09-29	2013-10-27	0.95

NARRATIVE TEXT

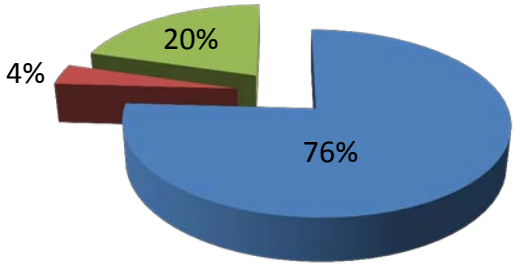
Subject 100097, a 34-year-old [RACE] male initially diagnosed in [****] with stage III multiple myeloma, was randomized to receive daratumumab at a dose level of 8 mg/kg in Part 1, Stage 1 of the study. At study entry, his relevant ongoing medical history included Anaemias NEC, aspartate aminotransferase level increase, Medical history, Medical history, Joint disorders, Respiratory, thoracic and mediastinal disorders, blood creatinine level increase, Investigations, Metabolism and nutrition disorders, Metabolism and nutrition disorders, Psychiatric disorders, and Blood and lymphatic system disorders. His baseline ECOG score was 0. At screening, his vital signs included body temperature of 36.6°C, pulse rate of 80 beats per minute (bpm), and blood pressure of 136/80 mm Hg. Plasma cells obtained from the baseline bone marrow biopsy were 95%.

The subject received a total of 5 lines of prior systemic therapy as follows: Line 1 consisted of bortezomib and dexamethasone; Line 2 consisted of cyclophosphamide, GCSF, melphalan, and ASCT; Line 3 consisted of dexamethasone and lenalidomide; Line 4 consisted of bortezomib, carmustine, cyclophosphamide, dexamethasone, and melphalan; Line 5 consisted of bortezomib. He was refractory to lenalidomide in Line 3, an alkylator in Line 4, and bortezomib in Line 5.

Concomitant medications reported at study entry included doxazosin and acyclovir.

On [**], the subject's platelet count was 71 x 10^9/L (grade 2) (range: 150-350 × 10^9/L), then on [**], the subject's platelet count decreased further to 59 × 10^9/L (Grade 2).

On Study Day 1 (29 Sep 2013), **nonserious adverse events of Grade 3 chills** (reported term: rigors) and **Grade 1 non-cardiac chest pain** were reported. The investigator considered both events as IRRs and as very likely related to the study drug. Pre-infusion vital signs included body temperature of 36.8°C, pulse rate of 80 bpm, and blood pressure of 126/81 mm Hg. The subject was administered pre-infusion medications as per protocol. Approximately 90 minutes after the start of the infusion, his vital signs included body



redaction
transformation
not applicable

Redaction vs. Transformation

Lessons learned from submissions (1/2)

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1. Pilot phases

- **85%** of the eligible companies made use of it
- **Increased quality** packages when pilot draft documents were reviewed
- Great **collaboration** from companies and **fruitful interactions** with EMA

2. Technical submissions

- **26%** of **initial** packages were invalid
- **35%** of **final** packages were resubmitted due to invalidation
- **Checklist** for *"Redaction Proposal Document"* package available in the guidance

Lessons learned from submissions (2/2)

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3. Anonymisation Report (AnR) review

- Many **AnRs not customised** to the product type
- List of quasi-identifiers **unspecific** to the package(s) characteristics
- **Inconsistencies:** AnR instructions vs. redaction/transformation of identifiers in the reports
- Lack of rationale for **full redaction of narratives**
- Impact of anonymisation on **data utility** not adequately addressed
- **EMA's comments** to be implemented or feedback to be provided

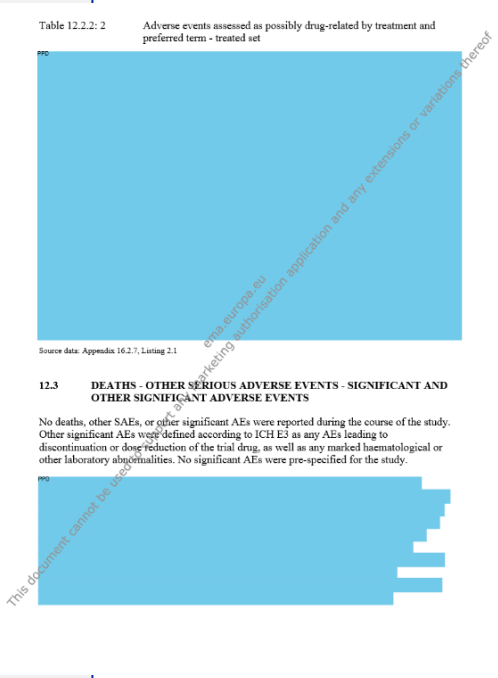
Table 12.2.2: 2 Adverse events assessed as possibly drug-related by treatment and preferred term - treated set

[redacted]

Source data: Appendix 16.2.7, Listing 2.1

12.3 DEATHS - OTHER SERIOUS ADVERSE EVENTS - SIGNIFICANT AND OTHER SIGNIFICANT ADVERSE EVENTS

No deaths, other SAEs, or other significant AEs were reported during the course of the study. Other significant AEs were defined according to ICH E3 as any AEs leading to discontinuation or dose reduction of the trial drug, as well as any marked haematological or other laboratory abnormalities. No significant AEs were pre-specified for the study.

[redacted]

What is happening during 2018?

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Focus on…

- Continue **collaboration** with industry towards:
  - Improving preparation of **CCI proposals** and rationales
  - Improving clarity and **quality** of **AnR** (revised AnR versions, need for feedback, etc.)
  - Ensuring **guidance**, templates and tool kit are used

- **TAG**: Creating **best practices** for the anonymisation of the clinical reports
  - Data **utility**, anonymisation **techniques**, new technological **developments**, attackers, **legal** issues

Last but not least!

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A big 

to all patients
who are volunteering to be part of trials
and
are making transparency on Clinical Data possible !

Any questions?

Further information

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