Objectives

The European Medicines Agency (EMA) policy on clinical data publication entered into force on 1 January 2015. Data have been regularly uploaded and are accessible to the public on the EMA website. For the first time, Clinical Study Reports (CSR) of the full Clinical Development have been made available. The aim of this study was to give an overview on the number and types of trials published and to analyze Clinical Development Pathways (CDP).

Background

EMA Policy 0070 -

- A European initiative for the disclosure of clinical reports with the objective to increase transparency. The development of Policy 0070 started in year 2012.
- Adopted on 2 October 2014 with entry into force on 1 January 2015.
- Initial first dossier upload on the EMA clinical data website on 20 October 2015. Detailed guidance on the implementation of Policy 0070 can be found in the documents below:
- First dossier published on 19 Dec 2016, the second on 12 April 2017 and the third on 22 Sept 2017. The history and development of Policy 0070 is illustrated in Figure 1.
- Was issued based on Article 88 of Regulation (EC) No 726/2004, which requires the Agency to “ensure an appropriate level of transparency” and to ensure the availability to the public of regulatory, scientific or technical information concerning the authorization or supervision of medicinal products which is not of a confidential nature.
- Policy 0043 (European Medicines Agency policy on access to documents related to medicinal products for human and veterinary use).

Methods

All available initial marketing applications on the EMA Clinical Data Website up to 1 April 2018 were analyzed. Data extraction was time-consuming and took place from 2 March to 31 May 2018. The methodology followed to access and navigate the EMA Clinical Data Website is described in detail by Bélkones and Schneider. A total of 3714 documents on the EMA Clinical Data Website were manually reviewed by application category and analyzed (visually as outlined using a Delphi cycle approach). For the data extraction and preparation of first analysis, all work flow was established to guarantee that all documents were treated equally. The work flow can be broken down into five individual steps, refer to Figure 2. The corresponding European Public Assessment Reports (EPAR) was also consulted as a quality control (QC) step. Dossiers permitted withdrawn or deleted. GANTIT charts were obtained from the available protocols, and the dates on the CSR on the EMA Clinical Data Website. GANTIT charts were generated in SAV version 9.4: using a specific software developed by the Programming Department in Data Science at Grünenthal GmH.

Results

From 86 dossiers published, 11 Initial Marketing Authorizations (IMA) were available from 57 applicants for 46 indications by ICH classification, refer to Figure 3. The IMAs were categorized into Type I and Type II, 15 phase I, 10 phase II and 42 clinical studies without a designated phase, refer to Figure 4. Not all studies for a CDP were available. e.g. fixed-dose combination IMAs did not necessarily contain all studies from the individual substance development pathways. Phase I reports contributed more than half of the studies made available. Figure 4 summarises phase II and III study reports were found to constitute 33% of the documents available. The median time from First Subject-In (FSI) in the first phase I to the FSI in phase II was found to be 6 months. Interquartile range (IQR) 0–18. The median time from FSI in the first phase I to the FSI in phase II was found to be 55 months (IQR: 33, 68), refer to Figure 5 and Table 1.

Time data was used for project management analysis shown in Table 1, in the third column of the table, and in GANTIT charts for the simple visualization of the CDP process, refer to Figure 6. More detailed breakdowns are shown for the lesinurad CDP in Figure 7. The work flow was established to guarantee that all sponsors make all timeline dates public.

Conclusions

- As shown for lesinurad the availability of CSRs and appendices, e.g. protocol, permit an insight into the strategic decision making process of CSRs.
- Studies were conducted after the respective phase had successfully been concluded. This is the first time that such analyses could be performed as complete CDPs were previously not available.
- Generally Phase II studies started in the latter half of the clinical developments. It appears, based on the limited number of CSRs available for analysis, that a CDP was planned according to the therapeutic indication and the physicochemical properties of the compound under development.
- The EMA Clinical Data Website provides a wealth of information that can be used to educate on clinical trials as well as project management aspects of clinical development. The more data is shared the more reliable the benchmarking of CDP timelines. This can be used as a better plan for future clinical developments.
- Process design analyses can be performed if the study reports do not have restricted data.
- The reduction of information in documents followed the EMA guidelines, however, they do not automatically permit a consistent analysis across all clinical developments. As the presentation of information appeared to be adapted biased on the parent company investigated it would not be advisable to expect that all sponsors make all timeline dates public.

References

7. Lehmann S1, Allard R2, Boehler YB3
1. TH Koeln – University of Applied Sciences, Faculty of Applied Natural Sciences, Leverkusen, Germany
2. Grünenthal GmbH, Aachen, Germany

Faculty of Applied Natural Sciences

TH Köln

Technology

Arts

Science

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Table 1: Timeline analysis of phase I and II clinical studies by International Nonproprietary Name

<table>
<thead>
<tr>
<th>Name of substance</th>
<th>Phase I: FSI to FSI</th>
<th>Phase II: FSI to FSI</th>
<th>Phase III: FSI to FSI</th>
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<tbody>
<tr>
<td>Omeprazole</td>
<td>6 months</td>
<td>12 months</td>
<td>18 months</td>
</tr>
<tr>
<td>Prednisone</td>
<td>3 months</td>
<td>9 months</td>
<td>15 months</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>4 months</td>
<td>10 months</td>
<td>16 months</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2 months</td>
<td>8 months</td>
<td>14 months</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>1 month</td>
<td>5 months</td>
<td>11 months</td>
</tr>
<tr>
<td>Benazepril</td>
<td>5 months</td>
<td>11 months</td>
<td>17 months</td>
</tr>
<tr>
<td>Lisinurad</td>
<td>8 months</td>
<td>14 months</td>
<td>20 months</td>
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<td>Carfilzomib</td>
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<td>16 months</td>
<td>22 months</td>
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<td>Atorvastatin</td>
<td>12 months</td>
<td>18 months</td>
<td>24 months</td>
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<tr>
<td>Rosuvastatin</td>
<td>14 months</td>
<td>20 months</td>
<td>26 months</td>
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</tbody>
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Figure 1: Overview of EMA Policy 0070 development

Figure 2: Work flow for data extraction and preparation of hot analaysis

Figure 3: Data availability within 15 MAs. The deviation of data available for analysis within each MAs on 1 April 2018. There are 17 MAs with no CDP, 4 MAs with one phase I studies, 8 MAs with data related to only phase II and 6 MAs with both phase I and II studies. For analysis a rare and non-core clinical study was comprised in 7 MAs. The total number of studies analyzed are including the lesinurad clinical development pathway. The non-core analyses included IMAs where analyses were possible but limited.