From promising molecules to orphan drugs: Early clinical drug development

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Summary
Phase-1 (also known as "First-in-Man") clinical trials initiate the early clinical development of possible new medicines. Patient participation in this early phase of clinical trials is rather limited. After successful phase 1 trials, further phase 2 and phase 3 clinical trials in patients may lead to a marketing authorization. In the first 15 years of the European Union Orphan Drug Directive, 4.5% of the orphan drug applications were authorized. However, for many of these orphan drugs, no phase 1 studies were required, as these products were already well known pharmaceutical substances, with a clearly defined pharmacological profile. Furthermore, for 19 orphan drugs, already authorized by the European Medicines Agency (EMA), the original rare indication was extended to another rare disease and no phase 1 trials were needed. Phase 1 studies need to be performed in a sufficient number of volunteers even for medicinal products intended for a very limited number of patients.

Keywords: Rare diseases, orphan drugs, exploratory clinical trial, phase-1, first-in-man

1. Introduction
Clinical research is scientifically sound, and ethically acceptable, research involving humans and conducted by certified investigators according to Good Clinical Practice (www.efgcp.eu) in order to improve our knowledge of a disease or its treatment (www.ecrin.org, www.clinicaltrials.gov, www.clinicaltrial registrer.eu, https://clinicaldata.ems.europa.eu/web/cdp/home, http://ec.europa.eu/health/documents/eudralex/index_en.htm). Clinical trials evaluate the efficacy and safety of one or more investigational medicinal product(s) for a specific disease. On average, approximately 10 percent of potential therapeutics that effectively pass preclinical development make it to market (1). Since the famous 1747 scurvy trial conducted by James Lind (2), potential therapies for rare diseases have often languished in early clinical development. This can, in part, be explained by the low odds of success, the small number of participants, unknown/sparse natural history, high staff turnover and the sometimes high cost of development due to increased complexity and administrative burdens. Some diseases may be rare in some parts of the world, and not so rare in other parts of the world, so that these areas would be more practical for clinical trial development at research naïve sites (for example sickle-cell disease). Biomarker identification, and adaptive clinical trial design, may increase the chances of success. Pivotal trials for recently approved orphan drugs for cancer are more likely to use nonrandomized, unblended trial designs and surrogate endpoints to assess efficacy (3,4). Information on medicines in clinical trial can be found in the Investigator Brochure of the product. A European Union Portal and Database will be implemented in October 2018. Devices are excluded here as they follow different legislation. Observational studies such as case and cohort studies, are not clinical trials but studies to understand the disease and propose possible medical intervention.

Phase 1 clinical trials ("First-in-Man") initiate the testing of candidate future medicinal products in humans (www.bapu.be, www.kks-netzwerk.de, www.agah.eu). They involve a small number of healthy volunteers and sometimes also research subjects with a specific condition (Dose Limiting Toxicity in patient volunteers) potentially relevant to the
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In a recent phase 1 clinical trial with a gene silencing compound for the treatment of Huntington disease (IONIS HTT Rx) patients were studied and not volunteers. All clinical trials have inclusion and exclusion criteria that screen possible candidates for the study. In phase 1 trials, doctors slowly increase the dose of the drug and the subjects are carefully monitored as the dose is increased; safety parameters (recorded in adverse event forms: severe/serious adverse reactions/events, suspected unexpected serious adverse drug reaction), pharmacodynamic and pharmacokinetic parameters are measured. Trial@home systems may record several parameters with electronic devices outside the study center. For patients with rare diseases without treatment the risk-benefit balance may be somewhat different than for patients with treatable disorders. Legal and ethical principles about human experimentation are defined in the Declaration of Helsinki of the World Medical Association, the EU Clinical Trials Directive (EC 2001/EC) and the International Council of Harmonization of Technical Requirements for Registration of Pharmaceuticals for humans Use (www.ich.org). The EU Clinical Trial Regulation 536/2014 is expected to come into force in 2018. A positive outcome of a phase 1 clinical trial is no guarantee of the safety and efficacy of the final product in patients.

In 2003, the Office of Rare Diseases Research (ORDR) established the Rare Diseases Clinical Research Network (RDCRN: www.rarediseasesnetwork.org) with (phase 1) clinical trial data from multiple clinical consortia conducting research with orphan drugs (9,10). The Orphanet website (http://www.orpha.net/consor/cgi-bin/ResearchTrials_ClinicalTrials.php?Lng=EN) contains information on clinical trials in patients with rare diseases. Orphan designation can be granted at any point during the clinical development process: more often in phase 2 (in 88 percent of instances), and not in phase 1. Due to current transparency initiatives, it is likely that much more clinical trial data will become publicly available over the next few years. Phase 1 trials will be more commonly represented than any other, with fewer trials available from each successive phase. The National Institute of Health (NIH) recently issued their policy to include phase 1 studies in their registering and reporting of clinical trials. This could be promising for researchers in the areas of rare disease diagnosis, prevention and treatment. For some designated orphan drugs such as olipudase (designated by the Food and Drug Administration on 08MAR2000) a within-patient dose-escalation strategy was required (11,12). In a sample of 605 candidate orphan drugs designated by the European Medicines Agency (EMA) between 2002 and 2012 only 110 (18 percent) (13) were in phase 1 and in another sample of 1406 EMA orphan drug applications between 2000 and 2014 only 183 (13 percent) (14) were in phase 1. The GlaxoSmithKline Clinical Data Sharing System contains 17 phase 1 trials with an orphan designation for rare neurological disorders, rare cancers and rare autoimmune diseases (15). In Japan, 5 sites are active in phase 1 clinical trials for Duchenne Muscular Dystrophy (16).

Patient participation (also called "shared decision making") in this early stage of clinical development is rather limited (17,18). The European Federation of Pharmaceutical Industries and Associations (EFPIA) published some considerations in their Code Of Practice (http://transparency.efpia.eu/the-efpia-code-2). In the participation ladder of Arnstein (19), it is called tokenism: placation, consultation and informing. Patient involvement in phase 1 clinical trials designs is not feasible, as these trials are performed under very strict guidelines defined by the sponsor. However, patient preferences (20,21) are useful to study the pharmacokinetics and pharmacodynamics of the new substance by the preferred route of administration (eventually with retard release galenical forms). Understanding the text of the informed consent is an issue that eventually can be verified by patients: the information should be adapted to the patients' needs and capacity of understanding. Ultimately, only the patients themselves can evaluate the real-life consequences (risk-benefit ratio) of possible serious/severe side-effects already detected in this early stage of clinical investigation.

Ongoing rare disease research, stimulated by initiatives such as the Rare Disease Research Consortium (http://www.irdrc.org/wp-content/uploads/2015/09/IRDiRC_State-of-Play-2015.pdf), and the EU Horizon 2020, will result in an ongoing expansion of orphan drug authorizations by the competent authorities, such as the EMA, the Food and Drug Administration (FDA) and Therapeutic Goods Administration (TGA). Academic investigator-initiated clinical trials, or non-commercial experiments, are not exceptional for rare disorders (https://kce.fgov.be/sites/default/files/page_documents/KCE_246_Public_funded_clinical_trials_Report.pdf). However these trials require the same legal regulations and Good Clinical Practice (GCP) guidelines (22) as commercial trials, also supervised by a clinical trial coordinator, following Standard Operating Procedures.

2. First 15 years of EMA orphan drug directive

In the first 15 years of the EMA’s Orphan Drug Directive (EC 141/2000), 2,340 applications were submitted, with 1,599 (72 percent) positive opinions having been formulated, 602 (27 percent) having been withdrawn by the sponsor and 21 (1 percent) receiving a final negative opinion by the Committee of Orphan
Medicinal Products (COMP). This resulted in 1,581 orphan drug designations and 111 authorized orphan medicinal products for rare conditions. The most frequently designated include acute myeloid leukemia, cystic fibrosis, pulmonary arterial hypertension, glioma, pancreatic carcinoma, ovarian cancer, multiple myeloma, chronic lymphoblastic leukemia and hepatocellular carcinoma. 4.7 percent of the original 2,340 applications received a final orphan drug market authorization; half the general score for all potential therapeutics that pass preclinical development. Figure 1 gives a graphic representation of these data. Orphan drugs often have more years of market exclusivity,
as protected marketing starts the day marketing authorization is received, and not upon orphan drug designation. Several new legal procedures (Adaptive Pathways, Breakthrough Therapy Designation, Accelerated Approval, Fast-track Designation, Priority Review, Expanded Access, etc) open new possibilities in market protection.

Table 1 represents the 53 EMA authorized orphan drugs that contain an active pharmaceutical ingredient for which no phase 1 clinical trials were required, as these chemicals were already established pharmaceutical compounds with well-documented safety data and pharmacodynamic and pharmacokinetic parameters. These out-of-patent repurposed pharmaceutical ingredients received a designation as an orphan drug and ten years of market protection for a rare disease indication without phase 1 clinical trials. Moreover for several of these substances there was already some evidence about the specific rare disease indication through a scientific publication in the open medical literature (see Table 1, column "1st use"). Preclinical research was also not necessary. Cholic acid is the active ingredient of two orphan drugs (Kolbam and Orphacol) for the same rare indication (inborn errors of primary bile acid synthesis) and everolimus for two different rare indications: tubular sclerosis as Votubia and renal cell carcinoma as Afinitor. Both substances were well known substances with an already established pharmaceutical profile for which development began in phase 2 or phase 3.

Table 2. EMA orphan drugs with multiple rare diseases indications

| Name       | Rare diseases                                                                 | Year |
|------------|-------------------------------------------------------------------------------|------|
| ADCETRIS   | Treatment of anaplastic large cell lymphoma                                   | 2012 |
|            | Treatment of Hodgkin lymphoma                                                 | 2012 |
| CARBAGLU   | Treatment of N-acetylglutamate synthetase (NAGS) deficiency                   | 2003 |
|            | Treatment of isovaleric acidemia                                               | 2011 |
|            | Treatment of methylmalonic acidemia                                            | 2011 |
|            | Treatment of propionic acidemia                                                | 2011 |
| CRESEMA    | Treatment of invasive aspergillosis                                            | 2015 |
|            | Treatment of mucormycosis                                                     | 2015 |
| GLIVEC     | Treatment of chronic myeloid leukaemia                                         | 2001 |
|            | Treatment of malignant gastrointestinal stromal tumours                        | 2002 |
|            | Treatment of acute lymphoblastic leukaemia                                     | 2006 |
|            | Treatment of chronic eosinophilic leukaemia                                   | 2006 |
|            | Treatment of dermatofibrosarcoma protuberans                                  | 2006 |
|            | Treatment of myelodysplastic/myeloproliferative diseases                       | 2006 |
| ICLUSIG    | Treatment of acute lymphoblastic leukaemia                                     | 2011 |
|            | Treatment of chronic myeloid leukaemia                                         | 2013 |
| IMBRUVICA  | Treatment of chronic lymphocytic leukaemia                                     | 2014 |
|            | Treatment of mantle cell lymphoma                                              | 2014 |
|            | Treatment of lymphoplasmatic lymphoma                                          | 2015 |
| JAKAVI     | Treatment of chronic idiopathic myelofibrosis                                 | 2012 |
|            | Treatment of myelofibrosis                                                    | 2012 |
| LENIMA     | Treatment of follicular thyroid cancer                                         | 2015 |
|            | Treatment of papillary thyroid cancer                                          | 2015 |
| NEXVAR     | Treatment of renal cell carcinoma                                              | 2006 |
|            | Treatment of hepatocellular carcinoma                                          | 2007 |
|            | Treatment of follicular thyroid cancer                                         | 2014 |
| RAVICTI    | Treatment of argininosuccinic aciduria                                        | 2015 |
|            | Treatment of carbamoyl-phosphate synthase-1 deficiency                         | 2015 |
|            | Treatment of citrullinaemia type 1                                             | 2015 |
|            | Treatment of hyperargininaemia                                                 | 2015 |
|            | Treatment of ornithine carbamoyltransferase deficiency                         | 2015 |
|            | Treatment of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria | 2015 |
| REVLIMID   | Treatment of multiple myeloma                                                  | 2007 |
|            | Treatment of myelodysplastic syndromes                                        | 2013 |
| SIGNIFOR   | Treatment of Cushing's disease                                                 | 2012 |
|            | Treatment of acromegaly                                                       | 2014 |
| SOLIRIS    | Treatment of paroxysmal nocturnal haemoglobinuria                             | 2007 |
| SPRYCEL    | Treatment of atypical haemolytic uremic syndrome                              | 2011 |
|            | Treatment of acute lymphoblastic leukaemia                                     | 2006 |
| TORIZEL    | Treatment of chronic myeloid leukaemia                                         | 2006 |
| TRACLEER   | Treatment of mantle cell lymphoma                                              | 2009 |
|            | Treatment of pulmonary arterial hypertension                                  | 2002 |
|            | Treatment of systemic sclerosis                                                | 2007 |
| VIDAZA     | Treatment of acute myeloid leukaemia                                          | 2008 |
| YONDELIS   | Treatment of soft tissue sarcoma                                               | 2007 |
|            | Treatment of myelodysplastic syndromes                                         | 2008 |
| ZAVESCA    | Treatment of Gaucher Disease                                                  | 2002 |
|            | Treatment of Niemann-Pick disease, type C                                      | 2009 |
In Table 1 you also can find the designation and the authorization date by EMA together with the days between designation and authorization. You also can find the year of synthesis of the primary ingredient and the years between the chemical synthesis and the year of the first report in the medical literature (“1st use”). Further you can find the Anatomical Therapeutic Chemical-code (column “ATC”), molecular weight (indicating the molecular size), the Divided Daily Dose in mg (column “DDD/mg”) and the route of administration (column ”Route”: Oral, Parenteral, Buccal). Blank items in the table are data still to be determined by the official organizations.

In Table 2 you will find 19 orphan drugs with multiple rare disease indications for which the market has been extended but no phase 1 clinical trials were needed for the extensions. Based on new evidence, the marketing authorization holder extended the use of its product to other non-lead therapeutic indications within the same rare condition. Although such extensions are of benefit to patients, it may be considered that the variation of the marketing authorization should only be allowed after formal verification that the new therapeutic indications are of significant benefit when compared to existing treatments. Rare disease trials are less likely to use blinding and randomization than trials in other areas (23).

In the early years of the Orphan Drug Directive, mainly academic centers, public research organizations and small and medium sized, public and private, enterprises were involved in orphan drug discovery, research and development especially for Advanced Therapy Medicinal Products (three EMA orphan drug authorizations: Glybera, Holoclac, Strimvelis). Exploratory studies to demonstrate safety and proof of concept/initial efficacy of these complex medicines are difficult to set up especially for gene editing products. Primary endpoints including safety, dose finding and secondary endpoints including biodistribution, and pharmacodynamic/pharmacokinetic parameters will be needed. For radio-active orphan drugs (several designations but no authorizations yet) precautions needed for the production as well as for their administration (24).

3. Conclusion

For every new molecular entity (NME) there comes a time when it will be given for the first time in man. The predictive power of human efficacy and safety by animal testing or computer simulation today is relatively poor. It is important that this early testing in humans is performed by certified investigators under strict conditions so as not to lose a valuable new treatment or spend too much money for the research and development of a disappointing (orphan) drug. Digital technology, by using more modern electronic tools to collect data, can help to bring costs down. Only when the active compound of the designated orphan drug is an already well known pharmaceutical ingredient phase 1 randomized clinical trials are not required. In all other cases (NME) phase 1 studies need to be performed in a sufficient number of volunteers even for medicinal products intended for a very limited number of patients.

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