Mini-Review

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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.clinicaltrialsregister.eu*, *https://clinicaldata.ema.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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disease studied (*5-7*). Innovative trial design such as "combined integrated protocol/basket trial design" can streamline early clinical drug development in rare diseases (*8*). 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 20/2001/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 (phase1) 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.irdirc.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

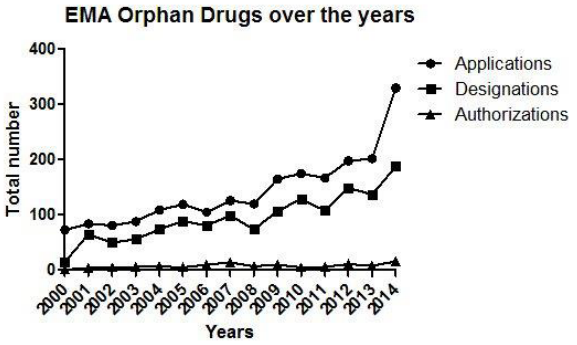

Figure 1. EMA orphan drug authorizations over the years

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,

Table 1. EMA orphan drugs without new molecular entities

No.	Product	Active ingredient	Route	Molec weight	ATC	DDD/mg	Designation	Authorization	Days	Synthesis	1ste use	Years
1	Trisenox	Arsenic Trioxide	P	197.80	L01XX27	9	2000/10/18	2002/03/05	503	1963	1996	33
2	Zavesca	Miglustat	O	219.30	A16AX06	300	2000/10/18	2002/11/20	763	1979	1994	15
3	Carbaglu	Carglumic Acid	O	190.20	A16AA05	200	2000/10/18	2003/01/24	828	1942	2004	62
4	Busilvex	Busulfan	P	246.30	L01AB01		2000/12/29	2003/07/09	922	1953	1988	35
5	Ventavis	Iloprost	B	360.50	B01AC11	0.15	2000/12/29	2003/09/16	991	1980	1994	14
6	Xagrid	Anagrilide	O	292.50	L01XX35	2	2000/12/29	2004/11/16	1418	1976	1979	3
7	Orfadin	Nitisinone	O	329.20	A16AX04	20	2000/12/29	2005/02/21	1515	1986	1992	6
8	Glivec	Imatinib	O	589.70	L01XE01	600	2001/02/14	2001/08/27	194	1996	1996	0
9	Tracleer	Bosentan	O	551.60	C02KX01	250	2001/02/14	2002/05/15	455	1992	1994	2
10	Pedea	Ibuprofen	P	206.30	C01EB16	30	2001/02/14	2004/07/29	1261	1964	1979	15
11	Prialt	Ziconotide	P	2639.10	N02BG08	0.012	2001/07/09	2005/02/21	1323	1987	1992	5
12	Cystadane	Betaine	O	117.10	A16AA06	6000	2001/07/09	2007/02/15	2047	1957	1981	24
13	Wilzin	Zinc Acetate	O	219.50	A16AX05	150	2001/07/31	2004/10/13	1170	1912	1992	80
14	Savene	Dexrazoxane	P	268.30	V03AF02	1500	2001/09/10	2006/07/28	1782	1969	2000	31
15	Litak	Cladribine	P	285.70	L01BB04		2001/09/18	2004/04/14	939	1960	1993	33
16	Onsenal	Celecoxib	O	381.40	L01XX33	800	2001/11/20	2003/10/17	696	1995	2000	5
17	Thalidomide	Thalidomide	O	258.23	L04AX02	100	2001/11/20	2008/04/16	2339	1957	1963	6
18	Diacomit	Stiripentol	O	234.30	N03AX17	1000	2001/12/05	2007/01/04	1856	1973	1978	5
19	Evoltra	Clofarabine	P	303.70	L01BB06		2002/02/05	2006/05/29	1574	1987	1999	12
20	Vidaza	Azacitidine	P	244.20	L01BC07		2002/02/06	2008/12/17	2506	1964	1972	8
21	PhotoBarr	Porfimer Sodium	P	1179.36	L01XD01		2002/03/06	2004/03/25	750	1987	1993	6
22	Lysodren	Mitotane	O	320.00	L01XX23	3000	2002/06/12	2004/04/28	686	1945	1973	28
23	Nexobrid	Bromelain	T		D03BA03		2002/07/30	2012/12/20	3796	1961	2014	53
24	Gliolan	5 Aminolevulinic Acid	O	131.10	L01XD04		2002/11/13	2007/09/07	1759	1950	1993	43
25	Firdapase	Amifampridine	O	109.10	N07XX05	40	2002/12/18	2009/12/23	2562	1935	1984	49
26	Orphacol	Cholic Acid	O	408.57	A05AA03		2002/12/18	2010/12/16	2920	1939	1990	51
27	Peyona	Caffeine Citrate	O	408.57	A05AA03	400	2002/12/18	2010/12/16	2920	1959	1975	16
28	Xyrem	Sodium Oxybate	O	126.09	N07XX04	7500	2003/02/03	2005/10/18	988	1929	1979	50
29	Tobi	Tobramycin	B	467.51	J01GB01	300	2003/03/17	2010/09/23	2747	1967	1996	29
30	Siklos	Hydroxycarbamide	O	76.05	L01XX05	250	2003/07/09	2007/06/29	1451	1869	1987	118
31	Revatio	Sildenafil	O	666.70	G04BE03	60	2003/12/12	2005/10/28	686	1992	2002	10
32	Kuvan	Sapropterin	O	314.20	A16AX07		2004/06/08	2008/12/02	1638	1963	1977	14
33	Cayston	Aztreonam	B	435.40	J01DF01	4000	2004/06/21	2009/09/21	1918	1981	1984	3
34	Mepact	Mifarmurtide	P	1237.50	L03AX15	0.7	2004/06/21	2009/03/06	1719	1981	1992	11
35	Defitelio	Defibrotide	P		B01AX01		2004/07/29	2013/10/22	3372	1975	1998	23
36	Inovelon	Rufinamide	O	238.20	N03AF03	1400	2004/10/20	2007/01/16	818	1986	2005	19
37	Esbriet	Pirfenidon	O	185.22	L04AX05	2400	2004/11/16	2011/02/28	2295	1970	1995	25
38	Ceplene	Histamine	P	184.10	L03AX14	0.5	2005/04/11	2008/10/07	1275	1938	1970	32
39	Atriance	Nelarabine	P	297.30	L01BB07		2005/06/16	2007/08/22	797	1988	1998	10
40	Bronchitol	Mannitol	B	182.17	R05CB16	800	2005/11/07	2012/04/13	2349	1957	1978	21
41	Torisel	Temsirolimus	P	1030.30	L01XE09	1000	2006/04/06	2007/11/19	592	1994	2004	10
42	Plenadren	Hydrocortisone	O	362.46	H02AB09	30	2006/05/22	2011/11/03	1991	1937	1955	18
43	Vyndagel	Tafamidis	O	308.11	N07XX08	20	2006/08/28	2011/11/16	1906	2004	2011	7
44	Tepadina	Thiotepa	P	189.20	L01AC01		2007/01/29	2010/03/15	1141	1954	1968	14
45	Raxone	Idebenone	O	338.44	N06BX13		2007/02/15	2015/09/10	3129	1975	1992	17
46	Afinitor	Everolimus	O	958.20	L01XE10		2007/06/05	2009/08/03	790	1994	2006	12
47	Quinsair	Levofloxacine	B	361.37	J01MA12	500	2008/09/23	2015/03/30	2379	1986	2002	16
48	Xaluprine	Mercaptopurine	O	152.18	L01BB02		2009/04/30	2012/03/09	1044	1952	1976	24
49	Signifor	Pasireotide	P	1107.26	H01CB05	1.2	2009/10/08	2012/04/24	929	2002	2010	8
50	Votubia	Everolimus	O	958.20	L01XE10		2010/08/04	2011/09/02	394	1994	2006	12
51	Procysbi	Cysteamine	O	77.15	A16AA04	2000	2010/09/20	2013/09/10	1086	1940	1978	38
52	Granupas	p Aminosalicylic Acid	O	153.14	J04AA01	12000	2010/12/17	2014/04/09	1209	1890	1946	56
53	Ketoconazole	Ketoconazol	O	531.44	J02AB02		2012/04/23	2014/11/21	942	1978	1985	7

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 acidaemia	2011
	Treatment of methylmalonic acidaemia	2011
	Treatment of propionic acidaemia	2011
CRESEMBA	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	2013
	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
LENVIMA	Treatment of follicular thyroid cancer	2015
	Treatment of papillary thyroid cancer	2015
NEXAVAR	Treatment of renal cell carcinoma	2006
	Treatment of hepatocellular carcinoma	2007
	Treatment of follicular thyroid cancer	2014
	Treatment of papillary 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
	Treatment of atypical haemolytic uremic syndrome	2011
SPRYCEL	Treatment of acute lymphoblastic leukaemia	2006
	Treatment of chronic myeloid leukaemia	2006
TORISEL	Treatment of renal cell carcinoma	2007
	Treatment of mantle cell lymphoma	2009
TRACLEER	Treatment of pulmonary arterial hypertension	2002
	Treatment of systemic sclerosis	2007
VIDAZA	Treatment of acute myeloid leukaemia	2008
	Treatment of myelodysplastic syndromes	2008
YONDELIS	Treatment of soft tissue sarcoma	2007
	Treatment of ovarian cancer	2009
ZAVESCA	Treatment of Gaucher Disease	2002
	Treatment of Niemann-Pick disease, type C	2009

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.

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, Holoclar, 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 need to be made 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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