Global Approaches for Rare Diseases and Orphan Drugs

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Research Methodology and Statistical Analyses for Trials of Rare Diseases and Orphan Products

Annalisa Trama
National Centre Rare Diseases
Istituto Superiore di Sanità, Italy

CentroNazionaleMalattieRare
CNMR

Status of clinical trials for pediatric orphan drugs

Analysis of the clinical trials performed for pediatric orphan drugs to describe the design of the studies

- Pediatric orphan drugs if a pediatric indication and/or pediatric dosage was reported in the package leaflet
- Data source: European Public Assessment Reports (EPAR) http://www.emea.eu.int
- No. of drugs: 23 pediatric orphan drugs analysed (out of the 43 orphan drugs authorised between 2001-2007)

Pediatric orphan drugs

EVOLTRA
EXJADE
REPLAGAL
FABRAZYME
XAGRID
CYSTADANE
BUSILVEX
SIKLOS
ELAPRASE
NAGLAZYME
MYOZYME
INOVELON
DIACOMIT
ATRIANCE
TRISENOX
TRACLEER
PEDEA
GLIVEC
ALDURAZYME
LYSODREN
CARBAGLU
ORFADIN
WILZIN

Variables collected

- General (drug, authorisation date, disease)
- PK study (No. of studies, adult/young, No. of participants, dose; discussion of PK results)
- Efficacy study (No. of studies, No. of participants; age, blind; controlled; comparator; randomised; multicentre, end points)
- Safety study (No. of studies, No.of participants; age, blind; controlled; comparator; randomised; multicentre, end points)

Type of trials: 9 pediatric orphan drugs

Trials	Total (No.)	%
PK/efficacy/safety	10	14,7
PK/safety	2	2,9
Efficacy/Safety	26	38,2
Efficacy	5	7,4
Safety	8	11,8
PK/efficacy	1	1,5
PK	15	22,1
Bibliographic	1	1,5
Total	68	100

Type of trials: 13 pediatric orphan drugs

Trials	Total (No.)	%
PK/efficacy/safety	17	24,3
PK/safety	4	5,7
Efficacy/Safety	18	25,7
Efficacy	2	2,9
Safety	13	18,6
PK/efficacy	0	0,0
PK	15	21,4
Bibliographic	1	1,4
Total	70	100

Main studies design: 9 paediatric orphan drugs

Trials	No
blind/controlled/randomised	7
open/self controlled/non randomised	5
open/active controlled/non randomised	1
open/self controlled	1

Main studies design: 13 pediatric orphan drugs

study design	N	%
Openlabel, multicentre	5	22,73
Openlabel, single centre	1	4,55
Openlabel, multicentre, randomised	1	4,55
Openlabel, multicentre, comparison with an historical control group	1	4,55
Openlabel, multicentre, self controlled	3	13,64
Openlabel, multicentre, randomised, active control	1	4,55
Randomised, double blinded, placebo controlled, multicentre	5	22,73
Randomised, double blinded, multicentre	1	4,55
Randomised, double blinded, placebo controlled, single centre,	2	9,09
Review of published data	1	4,55
Review + registries	1	4,55
Total	22	100,00

Main studies (phase): 13 pediatric orphan drugs

Phase	N	%
phase I/II	1	4,5
phase II	8	36,4
phase II/III	2	9,1
phase III	3	13,6
phase NA	8	36,4
Total	22	100,0

Main studies (participants number & age): 13 pediatric orphan drugs

	N participants	age
Evoltra	60	pediatric
Busilvex	42	adult
	61	adult
	NA	pediatric
Elaprase	96	adult + pediatric
Naglazyme	7	NA
	39	adult + pediatric
Myozyme	18	pediatric
	15	NA
	5	pediatric
Inevolin	138	adult + pediatric

Main studies (participants number & age): 13 pediatric orphan drugs *cont.*

	N participants	age
Atriance	70	pediatric
	39	adult
Diacomit	41	pediatric
	23	pediatric
Fabrazyme	58	adult + pediatric
Replagal	26	NA
	15	NA
Exjade	586	adult + pediatric
Xagrid	44	NA
	498	NA
	455	NA

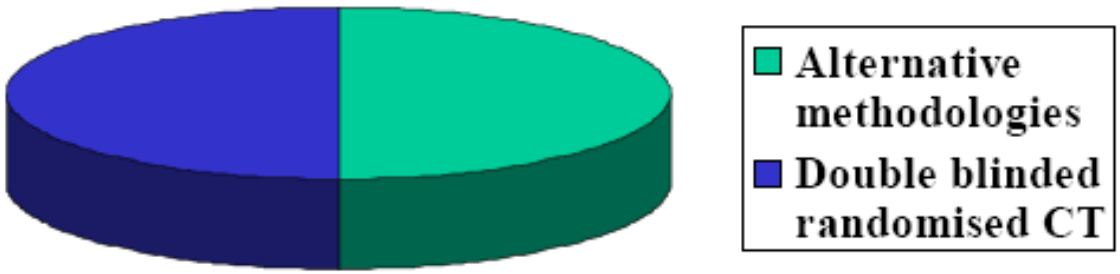
Main studies: prevalence vs No. of participants (some examples)

	N participants	Age	Disease	prevalence/ 100.000
Xagrid	44	NA	Essential thrombocythaemia	27,5
	498	NA		
	455	NA		
Inevolin	138	adult + pediatric	Lennox-Gastaut syndrome	15
Evoltra	60	pediatric	acute lymphoblastic leukemia	7,5
Fabrazyme	58	adult + pediatric	Fabry Disease	1,75
Replagal	26	NA	Fabry Disease	1,75
	15	NA		
Elaprase	96	adult + pediatric	Hunter syndrome	0,6
Naglazyme	7	NA	Mucopolysaccharidosis VI	0,16
	39	adult + pediatric		

Therapeutic needs of Paediatric Orphan Drugs

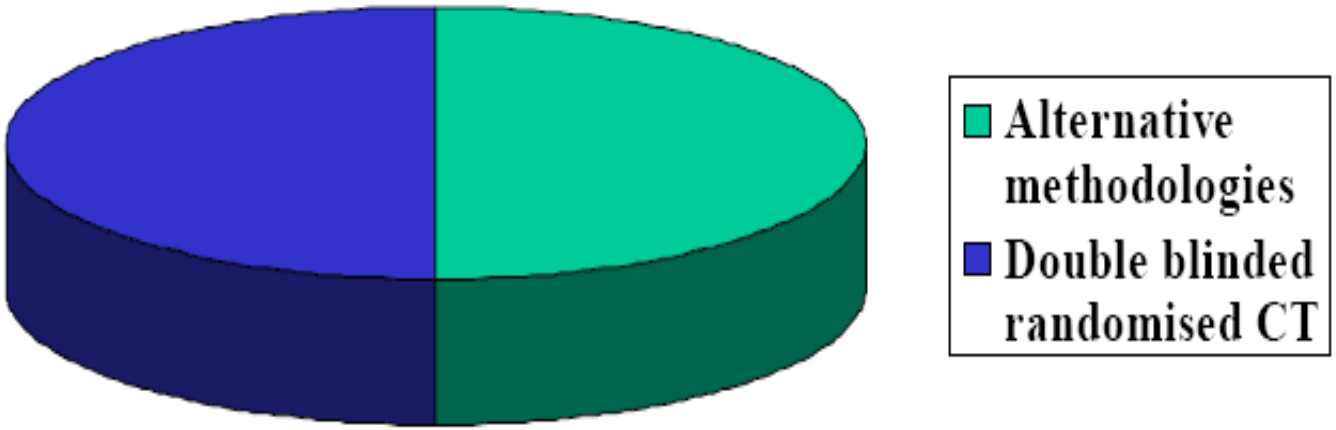
- alternative dosing regimes
- interaction studies
- combination studies (where possible)
- longer term clinical and safety assessment
- special groups (paediatrics)
- prove of clinical benefits

Overview clinical studies in OMP positive opinions



Source: Spiros Vamvakas EMEA 2005

Overview clinical studies in 10 OMP withdrawals



Source: Spiros Vamvakas EMEA 2005

Conclusions

- The benefit/risk profile is driving the opinions of the EU regulators for orphan medicinal products and not the classical or non-classical methodology of the trial (Spiros Vamvakas)

- Different study design used
  - best evidence for best decision (benefit/risk)?

- The Centralised procedures is creating a relevant mass of data which should be made available as they could serve as example of methodology for undertaking clinical trials for rare diseases