Kostbare geneesmiddelen, (te) duur?

Kansen aanpakken op gebied van gepast gebruik in de praktijk.
Casuïstiek en visie vanuit dure weesgeneesmiddelen

Carla Hollak, internist
AMC, Amsterdam

Sphinx
Amsterdam
Lysosome Center

amc

Disclosures

- **Geen financieel belang in farmaceutisch bedrijf**
- **Geen patenten**
- **Vergoeding reiskosten: Genzyme, Shire**

- **AMC krijgt financiele ondersteuning van Genzyme and Shire**
  - **Invoeren van data in registries**
  - **Unrestricted grant voor onderwijs op het gebied van lysosomale stapelingsziekten**
  - **Partnership in TIPharma project (optimalisatie diagnostiek ziekte van Fabry)**
  - **Participatie in muticenter studies (Genzyme)**

- *Alle financiele overeenkomsten zijn gemaakt met de AMC Research BV en in overeenstemming met de AMC Research code.*

Na EU marktvergunning…….

NICE
Zorginstituut
IQWIG, ……

Orphan drugs: 10 jaar marktexclusiviteit

- Review van orphan criteria: orphan designation (COMP)

  RARITY (prevalence) / RETURN OF INVESTMENT

  •Medical condition affecting not more than 5 in 10,000 in the EU (around 250,000 people)

  •Without incentives it is unlikely that the marketing of the product would generate sufficient return to justify the necessary investment

  SERIOUSNESS

  •Life –threatening or chronically debilitating

  ALTERNATIVE METHODS AUTHORISED

  •If satisfactory method exist the sponsor should establish that the new product will be of significant benefit

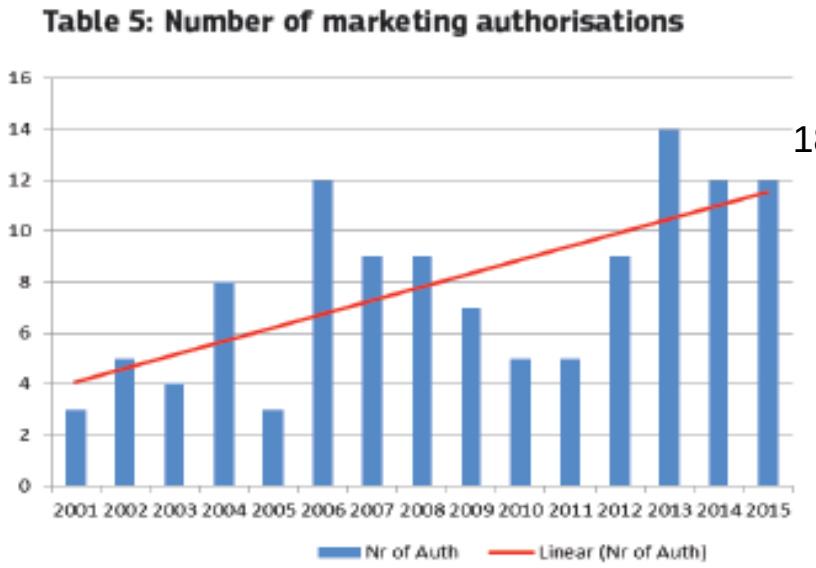
- Protocol assistance; (pre)-clinical studies
- Risk benefit assessment
- Aanbevelingen voor post-marketing studies

- Centrale authorisatie ~~=~~ nationale vergoeding
- Geen advies mbt de prijs

Orphan Designation Highlights

Orphan Designation Highlights EMA: 2001-2015

http://ec.europa.eu/health/files/orphanmp/doc/orphan_inv_report_20160126.pdf



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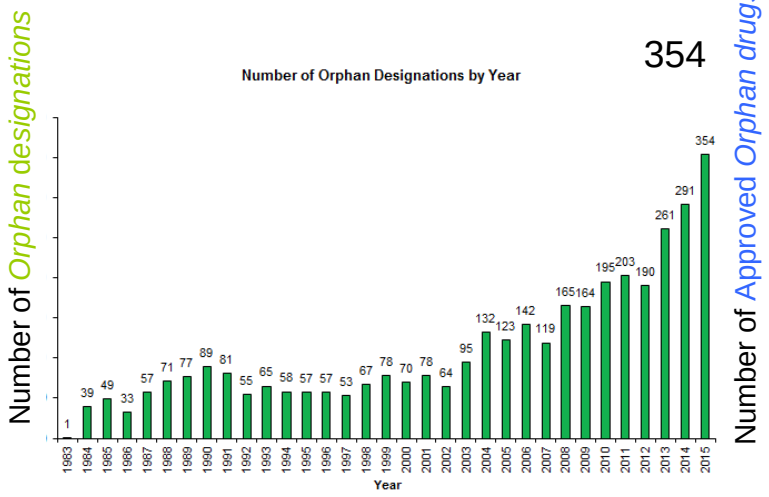
Orphan Designation Highlights FDA:1983-2015

http://www.fdalawblog.net/



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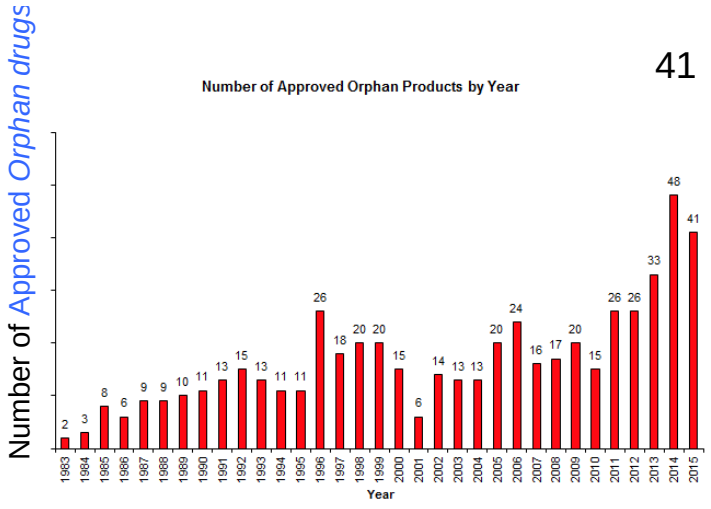

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Na marketing authorisatie

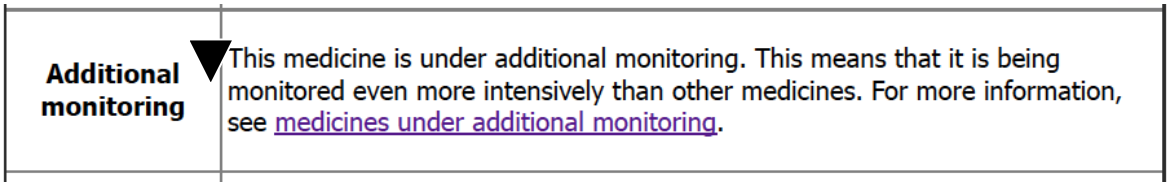
- EU 2016:117 orphan designated products geauthoriseerd
- (http://ec.europa.eu/health/human-use/orphan-medicines/developments/index_en.htm)

Discussiepunten:

- Hoge prijs (tot 1 miljoen Euro p.p.p.jaar)
  - onderbouwing niet altijd duidelijk
  - prijs verschillend per lidstaat, geheime prijsonderhandelingen

- Effectiviteit vaak onduidelijk
  - Voor zeer zeldzame aandoeningen: authorisatie under exceptional circumstances

Marketing Authorization under additional monitoring: Conditional and under Exceptional Circumstances



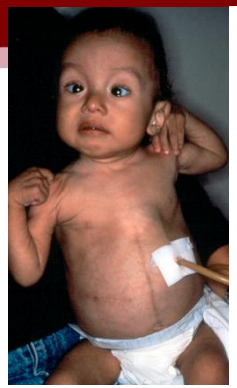
- In geval van conditional approval of under exceptional circumstances: “additional monitoring”
- Risk-management plan →
  - Post-marketing surveillance
    - Registry
    - Extra studies

} fase IV

Lysosomale stapelingsziekten

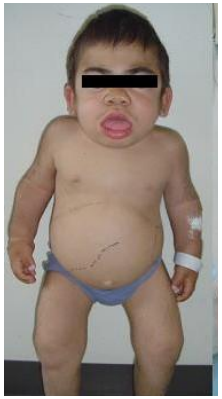
Lipidosen

Gaucher disease



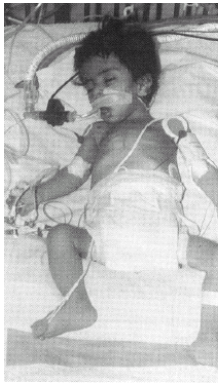
Mucopoly-saccharidosen

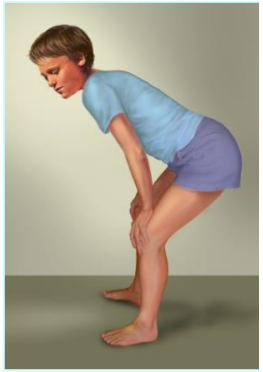
MPS 1



Glycogeen stapeling

Pompe disease





Disease	Drug	Year of authorisation	Endpoints used in pivotal trial(s)
Gaucher	*Cerezyme**	*1995*	*Spleen size*
	Zavesca (miglustat)	2002	Spleen and liver size
	Cerdelga (eliglustat)	2015	ENGAGE study: spleen volume
			ENCORE study: haematological variables and organ volumes
	Vpriv (velaglucerase alfa)	2010	hemoglobin concentration
Fabry	Fabrazyme (agalsidase bèta)	2001	renal GL-3 reduction
	Replagal (agalsidase alfa)	2001	TKT005: myocardial GL-3 levels
			TKT003: neuropathic pain
MPS I (Hurler)	Aldurazyme (laronidase)	2003	6-MWT and FVC (coprimary)
MPS II (Hunter)	Elaprase (idursulfase)	2001	6-MWT and FVC (coprimary)
MPS IV (Morquio)	Vimizim (elosulfase alfa)	2014	6-MWT
MPS VI (Maroteaux-Lamy)	Naglazyme (galsulfase)	2006	12-MWT
Niemann-Pick C	Zavesca (miglustat)	2006	HSEM velocity
Pompe	Myozyme (alglucosidase alfa)	2006	***AGLU01602 (infantile-onset): patients alive and free of invasive ventilation at age of 18 months***
			AGLU01702 (infants + children): survival
Cystinose	Procysbi (cysteamine)	2013	white blood cell cystine levels
Lysosomal acid lipase deficiency	Kanuma (sebelipase alfa)	2015	LAL-CL02: alanine aminotransferase levels
			LAL-CL03: (infantile onset) survival

Ziekte van Fabry

- X-gebonden deficientie van enzym α-Galactosidase A

Dood

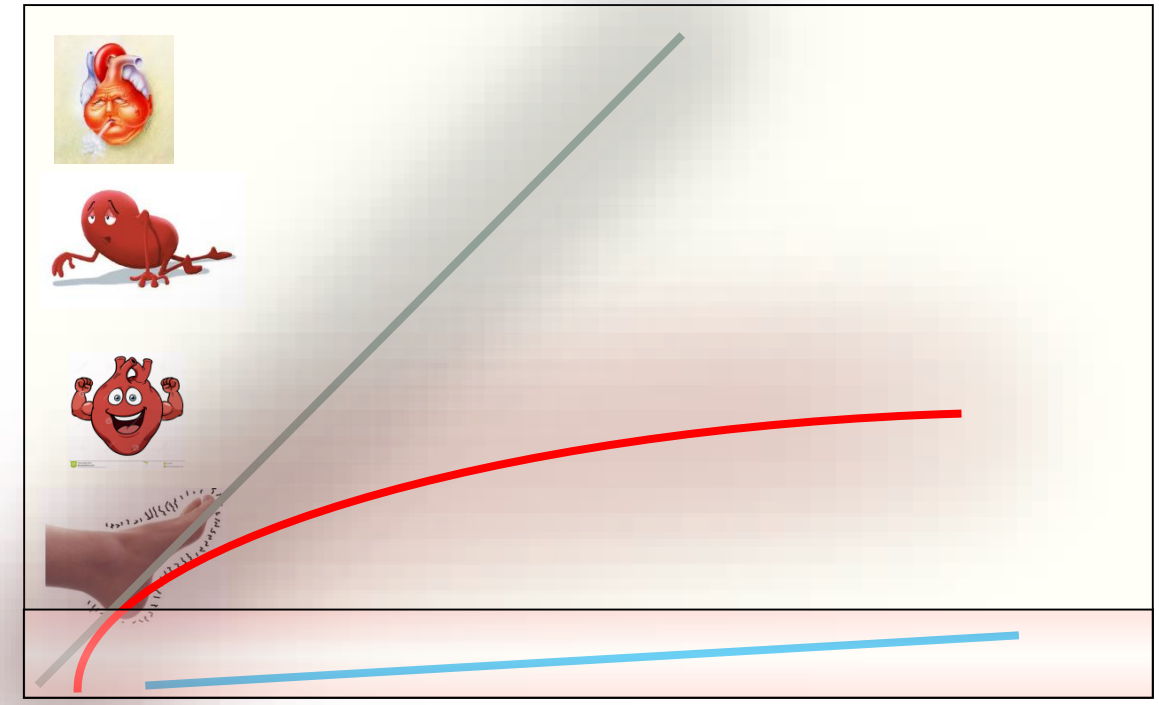
Hartfalen

Nierfalen

Cardiale hypertrofie

Proteinurie
Acroparesthesieen

Geen symptomen



Klassieke mannen

Niet-klassieke mannen/klassieke Vrouwen

Niet klassieke vrouwen

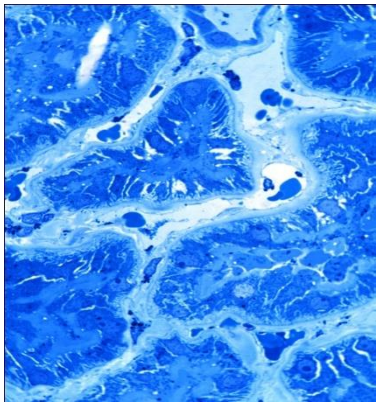
leeftijd → → → →

Klinische trials: 6 maanden

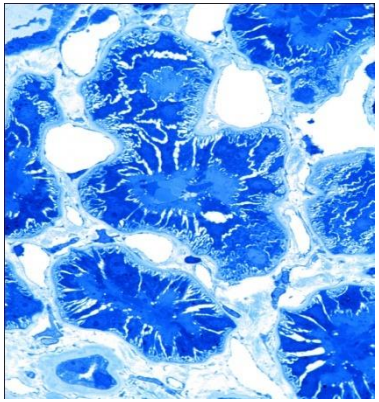
agalsidase beta
Eng et al NEJM 2001;

Clearance of storage in renal capillaries

Baseline: Score = 3

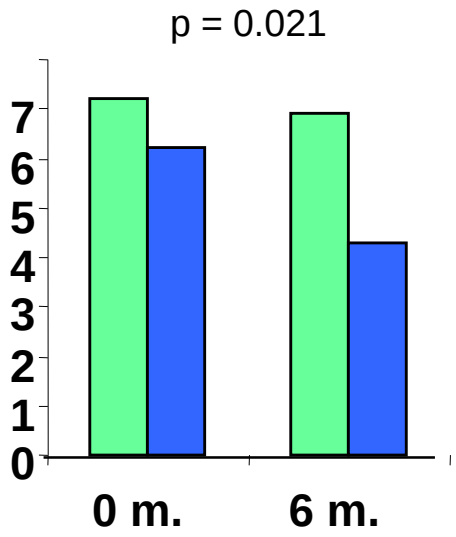


Week 20: Score = 0



agalsidase alfa
Schiffmann et al, JAMA 2001

Decrease in painscore



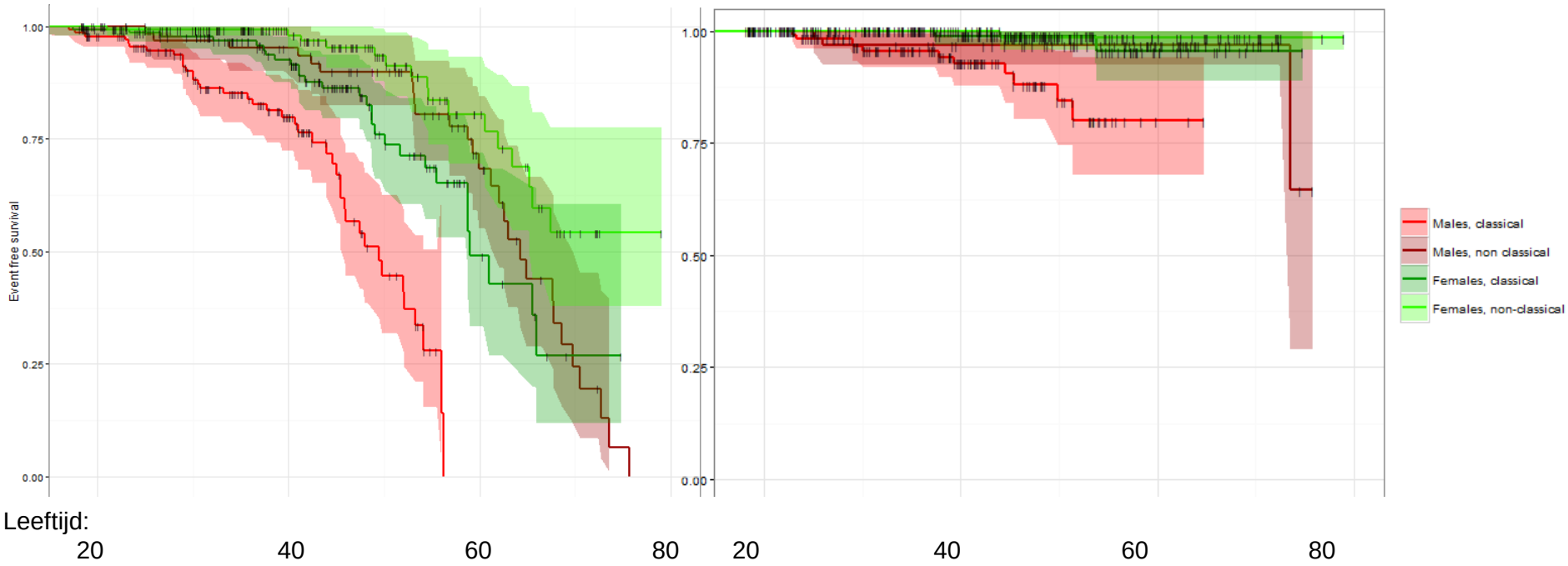
Registries: industrie of behandelcentra?

	Fabry Outcome Survey SHIRE	Fabry Registry GENZYME	GGG database
Meest recente update (pubs; eigen data)	2015: 740 behandelde patients	2016: 1044 patienten, behandeld	2016: 596 patienten, behandeld en onbehandeld; 499 volwassenen
Aantal patienten met nierfunctie data	268 (36%, baseline en 5 jaar fu)	695 (66%, alleen baseline)	485 (97% baseline, 90% follow-up)
Aantal patienten met hart data	164 (22%, baseline en 5 jaar fu)	667 (alleen baseline) *2013 studie:* 115 mannen (~20%) met > 2 jaar fu	414 (82% baseline en follow up)

Grafiek natuurlijk beloop per groep: GGG studie
(Maarten Arends)

Complicatie bij Fabry patienten

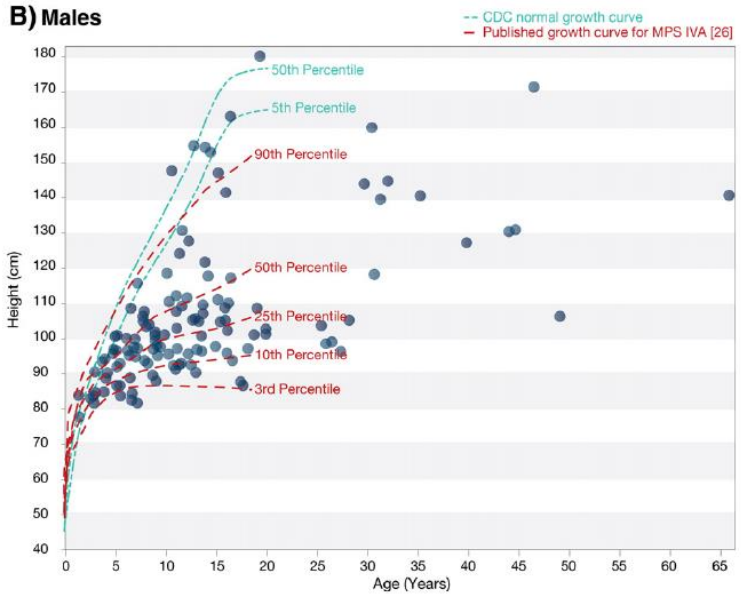
probleem met nierfunctie



137 klassieke mannen: roze
67 niet-klassieke mannen: donkerroze
147 klassieke vrouwen: donkergroen
148 niet-klassieke vrouwen: licht groen

Ziekte van Morquio A: MPS type IVA

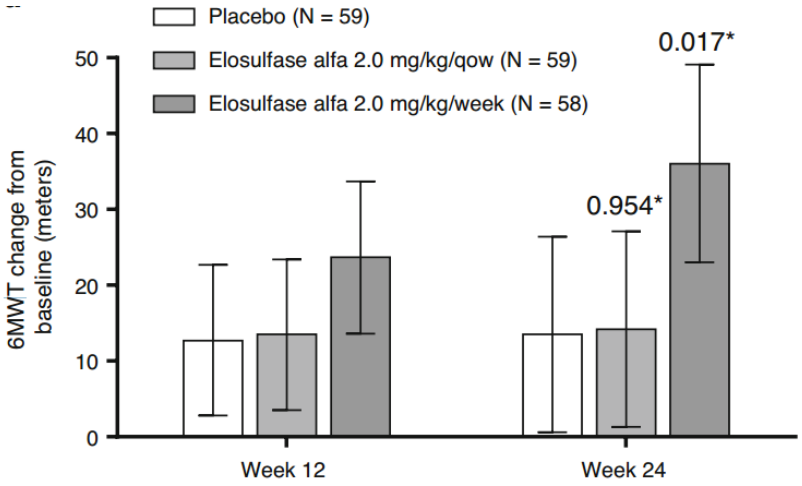
- Zeer zeldzame, autosomaal recessieve, lysosomale stapelingsziekte, deficiëntie van enzym GALNS
- Geboorte prevalentie rond de 1 : 400.000
- In Nederland op dit moment 14 patiënten met deze ziekte bekend (11 kinderen, 3 volwassenen)

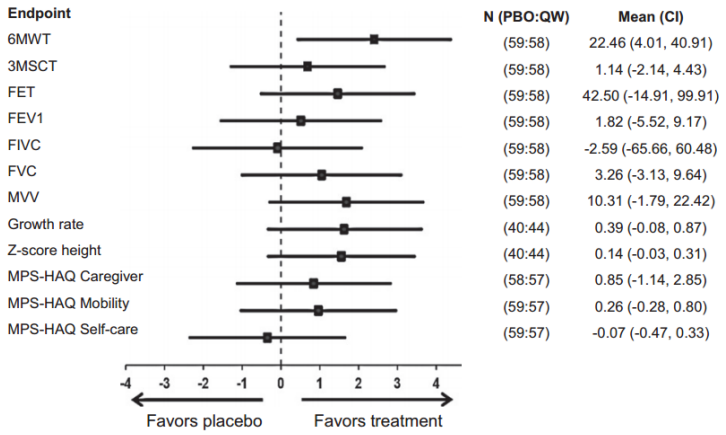


Klinische trials

- 24 weken studie
- Patienten ≥ 5 jaar
- 6MWT ≥ 30 meter; ≤ 325 meter
- 176 patienten geincludeerd (6 in Nederland)
- Rondomisatie 1 : 1 :1 over 2 mg/kg/week; 2 mg/kg/2 weken (placebo andere week); placebo 1x/week

- Authorisatie EMA: juni 2014;
- Post-marketing:
  - Registry





C. Hendriksz et al, J Inherit Metab Dis 2014;37:979

1 maart 2016:
Elosulfase alfa in Nederland geen verzekerde zorg meer

- Zorginstituut: <u>negatief standpunt</u>
  - statistisch significante verbetering van 6MWT “klinisch niet relevant”
  - Geen verbetering QoL en andere eindpunten

  → voldoet niet aan stand van wetenschap en praktijk
  - Geen veelbelovend product voor systeem van voor waardelijke toelating

Post-authorisatie verplichtingen: wordt er aan voldaan?

- 2006 - 2015: 26 producten “conditional approval”
  - 2 teruggetrokken
  - 10 regular approval
  - 14 nog altijd conditional

- Specific obligations:
  - Median 4 jaar (0.2- 7.7)
  - Vertragingen of discrepanties bij > 30%

Banzi et al. Approvals of drugs with uncertain benefit–risk profiles in Europe. European Journal of Internal Medicine 26 (2015) 572–584

Disease	Drug	Year of authorisation	Post-marketing studies (placebo-controlled, hard clinical endpoints)
Gaucher	Zavesca (miglustat)	2002	No high quality phase IV studies (one open-label extension of pivotal study, 3 open-label phase II studies, 1 open-label prospective study and 1 retrospective cohort study)
	Cerdelga (eliglustat)	2015	No post-marketing studies
	Vpriv (velaglucerase alfa)	2010	No high quality phase IV studies (only open-label phase II/III and III trials, and one retrospective cohort study)
Fabry	Fabrazyme (agalsidase bèta)	2001	**One high quality phase IV study, Fabrazyme vs placebo** (n=82, 88% men; non-significant difference in time to first clinical event favoring agalsidase beta, P=0.06)
	Replagal (agalsidase alfa)	2001	No high quality phase IV studies (only Fabry Outcome Survey registry results and several open-label studies)
MPS I (Hurler)	Aldurazyme (laronidase)	2003	No high quality phase IV studies (only one open-label extension of pivotal study and two observational studies for long-term follow-up)
MPS II (Hunter)	Elaprase (idursulfase)	2001	One open-label phase IV study, non-placebo controlled, n=28. **One high quality phase I/II randomized placebo-controlled trial, n=12.** (Rest of studies: 1 long-term extension of pivotal study, 3 retrospective, 2 Hunter Outcome Surveys, 4 open-label prospective)
MPS IV (Morquio)	Vimizim (elosulfase alfa)	2014	No post-marketing studies
MPS VI (Maroteaux-Lamy)	Naglazyme (galsulfase)	2006	One open-label, two-dose level phase IV study (n=4!), one cross-sectional survey study (n=121)
Niemann-Pick C	Zavesca (miglustat)	2006	No high quality phase IV studies (one post-approval commitment to EMA; prospective observational cohort study (n=283). Rest of studies only non-controlled open-label observational studies.)
Pompe	Myozyme (alglucosidase alfa)	2006	**One high quality randomized double-blind placebo-controlled study**, without hard clinical endpoints (6-MWT and FVC)
Cystinose	Procysbi (cysteamine)	2013	One prospective, controlled, open label, single-arm study (n=40), extension of pivotal study
Lysosomal acid lipase deficiency	Kanuma (sebelipase alfa)	2015	One post-marketing study; open-label single-arm long-term extension study (n=8)

Conclusies: post-marketing evaluatie van effectiviteit van orphan drugs laat te wensen over

- Zeer zeldzame ziekten: authorisatie op EU niveau vaak op basis van surrogaat eindpunten
- Post-marketing studies:
  - Fase IV studies
    - Specifieke populaties
    - Zelden placebo gecontroleerde
  - Registries

The drug itself has no side effects … but the number of health economists needed to prove its value may cause dizziness and nausea

Registries 2.0

Panel: **Features of post-authorisation registries**

- Disease-centred registries, instead of drug-centred registries, to enable the comparison of effectiveness of different treatments for the same indication; existing registries should be integrated in or linked to systems, such as the registries proposed
- Registries supervised by patients, health-care professionals, and other relevant stakeholders, independent of corporate activity
- Analysis of data by independent statisticians
- Obligatory data entry for all doctors treating patients across Europe
- Pivotal and extended trial data and natural history data should be included in the registry
- Registries should be launched early in the development process of orphan drugs (eg, to obtain natural history data)
- Databases should contain key factors needed for cost-effectiveness studies (eg, health-related quality of life)

Hollak CE, Biegstraaten M, Levi M, Hagendijk R.
Post-authorisation assessment of orphan drugs.
Lancet. 2015 Nov 14;386(10007):1940-1.

Aanbeveling: adaptive pathways?

- *Adaptive pathways zijn alleen zinvol als er strikte handhaving is mbt nakomen van voorwaarden*
  - Vroege markt-toegang: conditional
  - Strikte monitoring: fase IV observationele studie (registry)
    - Verplicht
    - Onafhankelijke analyses
    - Ruwe data toegankelijk voor nationale autoriteiten
    - Transparantie over prijs
    - Prijs afhankelijk van fase ontwikkeling/effectiviteit/volume