DO EFFICACY DATA PREDICT REAL-WORLD EFFECTIVENESS OF ORPHAN DRUGS FOR METABOLIC AND ONCOLOGIC DISEASES IN THE EU?

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Introduction

• Authorization of orphan medicinal products (OMPs) is often based on few clinical studies in small patient groups, not always using hard clinical endpoints.

• Hence, long term effectiveness on clinically relevant outcomes is often uncertain at time of authorization.

• When expectations pre-marketing (efficacy) do not match real-world effectiveness (post-marketing), an efficacy-effectiveness gap exists.

Aims

Are data used for registration (*pre-marketing data*) predictive for clinically relevant outcomes in the 'real-life' setting (*post-marketing data*)?

PRE-MARKETING	POST-MARKETING
EFFICACY	EFFECTIVENESS
Can intervention work in the ideal study setting?	Does it work, generalized to real-world settings and applied to individual patients?

Methods

We used the EC register to identify all OMPs in Europe, authorized between 2000 and 2016.

Pre-marketing data:

• Data from studies that led to marketing authorization retrieved from European Public Assessment Reports.

• Metabolic OMPs: Assessment of study quality with 'COMPASS' (Clinical evidence of Orphan Medicinal Products – an ASSessment tool).

• Oncologic OMPs: Assessment of quality of evidence with ESMO-MCBS (European Society for Medical Oncology Magnitude of Clinical Benefit Scale).

Post-marketing data:

• Literature review per OMP

• Interviews with minimally two clinical experts per OMP

• Interviews with patients

Conclusions

• OMPs for metabolic and oncological diseases approved based on studies using a clinical endpoint have a higher probability of meeting expectations in real world effectiveness, than products approved based on studies with surrogate endpoints.

• Hence, the choice of surrogate endpoints may need more critical selection for the purposes of marketing authorization.

Results

Metabolic: 27 OMPs for 23 indications

Oncologic: 12 OMPs for 13 indications

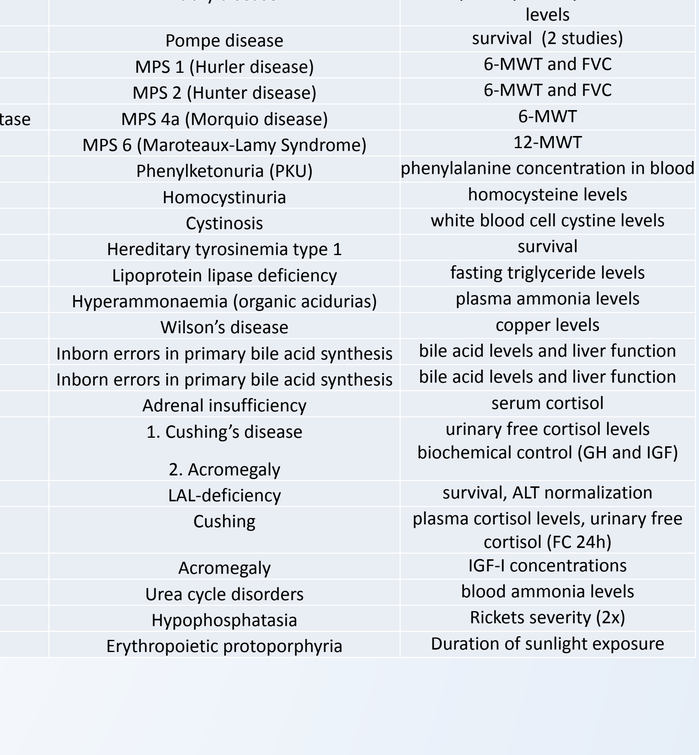

Table 1: overview of metabolic orphan diseases

Drug	Generic name	Disease	Primary endpoint
Zavesca	miglustat	1. Gaucher disease 2. Niemann-Pick C	spleen and liver size horizontal saccadic eye movement (HSEM) velocity
Vpriv	velaglucerase alfa	Gaucher disease	hemoglobin concentration
Cerdelga	eliglustat	Gaucher disease	spleen volume, haematological parameters
Fabrazyme	agalsidase bèta	Fabry disease	GL-3 reduction
Replagal	agalsidase alfa	Fabry disease	neuropathic pain, myocardial GL-3 levels
Myozyme	alglucosidase alfa	Pompe disease	survival (2 studies)
Aldurazyme	laronidase	MPS 1 (Hurler disease)	6-MWT and FVC
Elaprase	idursulfase	MPS 2 (Hunter disease)	6-MWT and FVC
Vimizim	n-acetylgalactosamine-6-sulfatase	MPS 4a (Morquio disease)	6-MWT
Naglazyme	galsulfase	MPS 6 (Maroteaux-Lamy Syndrome)	12-MWT
Kuvan	sapropterin	Phenylketonuria (PKU)	phenylalanine concentration in blood
Cystadane	betaine	Homocystinuria	homocysteine levels
Procysbi	mercaptamine	Cystinosis	white blood cell cystine levels
Orfadin	nitisinone	Hereditary tyrosinemia type 1	survival
Glybera	alipogene tiparvovec	Lipoprotein lipase deficiency	fasting triglyceride levels
Carbaglu	carglumic acid	Hyperammonaemia (organic acidurias)	plasma ammonia levels
Wilzin	zinc	Wilson's disease	copper levels
Kolbam	cholic acid	Inborn errors in primary bile acid synthesis	bile acid levels and liver function
Orphacol	cholic acid	Inborn errors in primary bile acid synthesis	bile acid levels and liver function
Plenadren	hydrocortisone	Adrenal insufficiency	serum cortisol
Signifor	pasireotide	1. Cushing's disease 2. Acromegaly	urinary free cortisol levels biochemical control (GH and IGF)
Kanuma	Sebelipase alfa	LAL-deficiency	survival, ALT normalization
Ketoconazole	ketoconazole	Cushing	plasma cortisol levels, urinary free cortisol (FC 24h)
Somavert	pegvisomant	Acromegaly	IGF-I concentrations
Ravicti	glycerol phenylbutyrate	Urea cycle disorders	blood ammonia levels
Strensiq	asfotase alfa	Hypophosphatasia	Rickets severity (2x)
Scenesse	Afamelanotide	Erythropoietic protoporphyria	Duration of sunlight exposure

Metabolic:

• 13% of the pivotal studies used a hard clinical endpoint, 87% a biomarker or function measurement as primary outcome.

• All OMPs marketed based on hard clinical endpoints, and half of the OMPs marketed based on biomarkers or function measurements showed improvement in relevant clinical outcomes post-marketing.

• Majority of pivotal studies with large differences between study vs. patient population is not predictive for real-world effectiveness.

Table 2: overview of oncologic orphan diseases

Drug	Generic name	Disease	Primary endpoint
Yondelis	trabectedine	1. Ovarian neoplasms 2. Advanced soft tissue sarcoma	1. Progression free survival 2. Time to progression
Cometriq	cabozantinib	Thyroid Neoplasms	Progression free survival
Sutent	sunitinib	1. GIST 2. pNET 3. Renal cell carcinoma	1. Time to progression 2. Progression free survival 3. Progression free survival, objective response rate
Glivec	imatinib	1. GIST 2. Dermatofibrosarcoma protuberans	1. Objective response rate, recurrence-free survival 2. Tumor response
Lysodren	mitotane	Adrenal Cortex Neoplasms	Data from 220 studies (survival time, progression free survival, ORR)
Mepact	mifamurtide	Osteosarcoma	Event free survival
Nexavar	sorafenib	1. Renal cell carcinoma 2. Hepatocellular carcinoma 3. Differentiated thyroid carcinoma	1. Overall survival 2. Overall survival, (time to progression) 3. Progression free survival
Torisel	temsirolimus	Renal cell carcinoma	Overall survival
Afinitor	everolimus	1. Breast neoplasms 2. Renal cell carcinoma 3. Pancreatic neoplasms	1. Progression free survival 2. Progression free survival 3. Progression free survival
Lynparza	olaparib	Ovarian neoplasms	Progression free survival
Unituxin	dinutuximab	Neuroblastoma	Event free survival
Lenvima	lenvatinib	Thyroid neoplasms	Progression free survival

Oncologic (preliminary):

• 52% of pivotal studies used progression-free survival as primary endpoint, while in 13% overall survival (OS) was studied.

• 67% of OMPs that were authorized based on improved OS also showed improvement in OS post-marketing. Of OMPs that were authorized based on endpoints other than survival, 39% showed improvement in OS post-marketing.

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