Universitat Autònoma de Barcelona

Session 1: Disease clustering to guide trial design and analysis

Modelling at a product level as a way to test applicability and move forward to future recommendations

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Zaandam, 18-19th September 2017

1) The applicability and potential value of novel methodology developed within the ASTERIX project within four groups of methods for six condition clusters (UMCU): *4 examples per cluster*

The four main method groups:

1. Innovative designs
2. Level of evidence
3. Study endpoints & statistical analysis
4. Evidence synthesis

Six disease clusters have been created:

1. Acute: single episodes
2. Acute: repeated episodes
3. Chronic: stable/slow progression
4. Chronic: progressive, one system/organ
5. Chronic: progressive, multiple systems/organs
6. Chronic: staged conditions

2) Simulations or modeling at a product level based on conclusions from UMCU report (*1 example per cluster*)

3) Discussion on the (potential) ethical, practical and regulatory impact of new methodology on drug development

4) Recommendations

Simulations based on conclusions from UMCU report
(*1 example per cluster*)

CLUSTER	EXAMPLES
Acute single episodes	Defitelio for the treatment of hepatic venooclusive disease
Repeated acute episodes	Ilaris for the treatment of cryopirine periodic syndromes
Chronic stable/slow progression	Revestive for the treatment of Short Bowel Syndrome
Chronic progressive led by one system/organ	Soliris for the treatment of Nocturnal Paroxysmal Hemoglobinuria
Chronic progressive multiorgan/symtem	Fabrazyme for the long-term ERT in patients with Fabry disease
Chronic staged conditions	Opsumit for the treatment of pulmonary hypertension

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Clinical Development Plan

Fabrazyme® (agalsidase beta)

Clinical development for the long-term enzyme replacement therap
confirmed diagnosis of Fabry disease

1. Index

Introduction

Background information on Fabry Disease (FD)

- ultrarare disease (500-2000 patients in EU)
- inherited enzyme deficiency, chronic life-lasting disease
- multiorgan/system damage due to GL3 (substrate) deposit: heterogeneous involvement of skin, nervous, renal, heart, hepatic
- No SOC

Rationale for the development of Fabrazyme in FD

- Strong: ERT

Scope of development

- Fabrazyme in the long-term ERT in patients with Fabry Disease

Actual clinical development plan for Fabrazyme in FD

Proof of activity/dose finding

Study FB9702-01 (US), a phase I/II supportive, dose- finding 15 patients testing 5 groups of doses (5 infusions)

PEP: GL3 plasma clearance ; SEP: GL3 clearance in endothelial vasculature, tissues

Pivotal evidence

AGAL-1- 002-98 (US, EU), a phase III RCT, DB, Pl-C, conducted in 58 patients (29 vs 29): 0 or 1q2w, for up to 20 wks, followed by OLE Study AGAL-005-99 with additional 18 months FU, all in active treatment.

PEP: GL3 clearance from the capillary endothelium of the kidney (score 0, in a 0-3 scale)

SEP: GL3 inclusions in the capillary endothelium of heart, kidney and skin; kidney tissue and urinary GL3 levels; McGill pain questionnaire; QoL, change in GFR, neuropathy impairment, autonomic function status

Results:

PEP : 69% vs 7% rate of responders

SEP:

Statistically significant differences in all endpoints based on GL3 clearance from capillary endothelium of heart, kidney and skin, from kidney and heart tissues, and from plasma

No SS differences in pain reduction, QoL, renal function

Actual clinical development plan for Fabrazyme in FD

Uncertainties and weaknesses identified

- Demonstration of efficacy based on PD markers (reduction of sphingolipids in the target organs) with a complete absence of clinical endpoints, i.e. symptoms, function, etc. Therefore, there were uncertainties on the extent to which PD changes translate into clinical outcomes.

- Changes in symptoms/function are infrequent and highly variable. Clinical trials main limitation was poor sensitivity to assess changes in symptomatic/functional endpoints: none of the clinical parameters investigated as SEP did reach SS improvements/show changes at all.

- Inference on the potential benefit of the product is assumed to derive from the hypothesis and physiopathology.

- Additional long- term efficacy and safety data were required as post-authorization commitments.

- From other information on the disease and trials with similar treatments, it can be derived that patients with more advanced disease may be more responsive to treatment, so that clinical changes may be quantified.

Assessment on applicability of methods based on UMCU report

- **Applicable:**
  - Long-short term outcomes:
  - Sequential design for small populations
  - Bayesian sample size re estimation using powers prior.
  - GAS
  - Minimisation or stratification strategies

- **Might be applicable:**
  - Multi-arm group sequential designs with a simultaneous stopping rule
  - Dynamic borrowing through empirical power priors that control type I error

- **Not applicable (with the parameters of clinical development of Fabrazyme):**
  - delayed start randomization,
  - sample size reassessment and hypothesis testing in adaptive survival trials
  - fallback tests for co-primary endpoints,
  - optimal exact tests for multiple binary endpoints
  - simultaneous inference for multiple marginal GEE models

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Study outline for alternative scenario 3

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1	**Title of study: ALTERNATIVE AGAL-1-002-98 (simulated Option 3) : fallback test for co-primary endpoints + enrichment**
2	**Investigators (Study center):**
3	**Studied period:** First Patient Enrolled 14 March 1999 Last Patient Completed 04 February 2000
4	**Objectives** **Primary:** The primary objective of the study will be to evaluate the safety and efficacy of recombinant human α-galactosidase (r-hα GAL) compared to placebo for the treatment of patients with Fabry disease. **Secondary:** Secondary objectives of the study include assessment of the efficacy of r-hα GAL compared to placebo based on changes from Baseline to Visit 11 (Week 20) of at least one of the following variables: in renal function (creatinine clearance, 24h proteinuria), Bodily Pain Domain of the SF36 , and the proportion of patients with score 0 in the composite score of GL-3 inclusions in the capillary endothelium (vasculature) of the kidney, skin, and heart. Changes in the McGill Pain Questionnaire (short form) will be secondary, but it is unexpected that differences may be detected with the anticipated sample size and time of follow-up. The change from Baseline to Visit 11 (Week 20) in composite score of GL-3 levels, as measured by Enzyme Linked Immunosorbant Assay (ELISA) in kidney tissue and urine, will be also a secondary objective.
5	**Design:** Multinational, multicenter, placebo-controlled, double-blind, randomized study of patients with a current diagnosis of Fabry disease who have had no prior treatment with r-hα GAL. Patients will receive approximately 1.0 mg/kg (0.9 to 1.1 mg/kg) of r-hα GAL or placebo every 2 weeks for 20 weeks (11 Patient Visits) for a total of 11 infusions of study medication. Twenty- eight additional days will be allowed for some of the final safety and efficacy procedures associated with Visit 11 (Week 20). Therefore, **the total duration that a patient will be involved in the study after the first infusion will be up to 168 days.**

Analysis of the practical, ethical and regulatory impact

Method assessed:	Yes	No	Depends, or not fully	Comments
Practical considerations:				
• May reduce sample size requirements				
• May shorten time to study completion				
• May ease recruitment				
Statistical assessment:				
• Improves internal validity				
• Increases stability of estimates				
• Increases sensibility to changes				
• Compliant with predetermination				
• Consistency (discuss)				
• Robustness of method (discuss)				
• Protection against type I and II errors (discuss)				
Regulatory assessment:				
• Risk of bias and credibility				
• External validity (discuss)				
• Therapeutic positioning and comparisons				
• Informative on relevance and clinical impact				
• Suitable information for risk-benefit balance				
Ethical assessment:				
• May minimise risks				
• May maximize access to treatment				
• May minimise unnecessary exposure to ineffective treatments				
• Considers patient input				

Alternative development plan (Option 1)

Sequential design for small populations (PEP: ClCr + enrichment)

Impact on practical considerations	May reduce sample size (30%?)and shorten time to completion, but recruitment might be more challenging: enriched/ open new centers
Impact on ethical aspects	May minimize exposure to the experimental arm and to placebo, thus minimizing potential risks. May delay access to treatment for patients already available.
Impact on statistical aspects	May improve internal validity and sensitivity to changes. By contrary, may reduce stability of estimates (IA), need to control for alpha error
Impact on regulatory assessment	May improve assessment of relevance and clinical impact Enriched population: weak impact on external validity Negative impact on the extent of the safety database

- **Practical advantages counterbalanced by the fact that patients are already available.**
- **General ethical advantages confronted with a delay in access to treatment to patients not enrolled/excluded**
- **May reduce the extent of an already limited safety database.**
- **In summary, advantages are not so relevant in this particular case**

Alternative development plan (Option 2)

Dose-finding with multi-arm multi-stage trial with a simultaneous stopping rule (PEP change in GL3 urine levels)

Impact on practical considerations	May shorten time to completion, but no effect at all on sample size requirements or to ease recruitment
Impact on ethical aspects	May minimize exposure to an ineffective treatment
Impact on statistical aspects	May improve robustness of the dose-selection strategy
Impact on regulatory assessment	No effect at all, if any negative on the extent of the safety database

- **It may minimize exposure to ineffective treatments, reduce time to completion, but given the little room for improvement this is not deemed a major contribution.**
- **May improve credibility of the dose-finding, but does not solve the main uncertainties identified**

In summary, the two first alternative options are based on recommendations on applicability of novel methodologies to the studies already conducted.

An alternative approach could be going beyond the actual development and modify it as much as possible, i.e. study population, number and type of endpoints, etc, so that the options to apply novel methodologies increase.

The example chosen is a good one to exemplify this approach, as an attempt to improve the actually conducted development plan.

Considerations

-Heterogeneity of the disease, with involvement of skin, kidney, heart, peripheral nervous system

-Good dynamic markers: association with clinical outcome measures not well established

multiple endpoints including clinical outcome measures (symptomatic changes, functional and QoL,) and histological changes may provide a more convincing (clinically relevant) demonstration of efficacy.

But…

Considerations II

	Sample size per group	Differences Active vs Placebo*	SD pooled	Effect Size
Fabrazyme				
Primary Outcome: Grade 0 at week 20	8-9	-69%		
Secondary outcomes:				
sensory pain score	7715	0.3	6.65	0.045
affective pain score	520	0.4	2.3	0.174
total pain score	1774	0.8	8.5	0.094
visual analog scale score	884	-0.2	1.5	0.133
present pain intensity	639	0.4	2.55	0.157
Replagal				
Creatinine Clearance; 6 Month Data. TKT003	24	-18.1	21.653	0.836
Glomerular Filtration Rate; 6 Month Data				
TKT003	48	-11	18.93	0.581
TKT010	1749	1.2	12.66	0.095
Standard Renal Histopathology: Effects of Replagal				
Normal Glomeruli	11	-0.241	0.19	1.268
Fraction of Glomeruli with Mesangial Widening	9	-0.29	0.2	1.45
The Effects of Replagal on Cardiac Disease TKT005				
Cardica GB3	47	-0.18	0.306	0.588
Left Ventricular Mass by MRI	10	-33.3	23.68	1.406
Left Ventricular Mass by Echo	411	-12.5	63.86	0.196

Table 55. GFR (mean ± st. dev) in AGAL-1-002-98 and at 6 months of AGAL-005-99

Trial	Visit	Statistic	Treatment group	
			placebo	r-hαGal
AGAL-11-002-98	Baseline	*N*	*28*	*29*
			97 ± 35	82 ± 22
	visit 11	*N*	*23*	*21*
		Mean	108 ± 39	93 ± 34
			placebo/ r-hαGal	r-hαGal/ r-hαGal
AGAL-005-99	6-month	*N*	*26*	*23*
		Mean	117 ± 41	82 ± 30

Alternative proposal :

—-GAS: not optimal as PEP due to limited sample size and functional parameters not assessable

—-Methods for multiple endpoints (i.e. like the fallback tests for co-primary endpoints and the optimal exact tests for multiple binary endpoints) +

—-enrichment (patients with clinical symptoms or functional impairment)

Alternative development Option 3

Fallback tests for co-primary endpoints (histology in several organs + renal fu

Statistical assessment:	Yes	No	Depends, or not fully	Comments
• **Improves internal validity**	Yes			
• **Increases stability of estimates**		NO		Depending on sample size, which is unmodified
• **Increases sensibility to changes**	YES			May reduce chances of failure for main endpoint with similar sample size, more chances to reach conclusive results.
• **Compliant with predetermination**	YES			
• **Consistency (discuss)**	YES			Yes, proper assessment of the multidimensional nature of the disease
• **Robustness of method (discuss)**	YES			As demonstrated in the publication
• **Protection against type I and II errors (discuss)**	YEs			Fallback method preserving from errors

Regulatory assessment:	Yes	No	Depends, or not fully	Comments
• **Risk of bias and credibility**	Contr olled			Parallel double blind design, appropriate methods for analysis
• **External validity (discuss)**	YES			Enriched population may decrease external validity, but in this case, with such a good mechanistic rationale and with consistent results in substrate clearance from other tissues, not a major issue
• **Therapeutic positioning and comparisons**	YES			Improved, allowing comparison with trials in more severe populations
• **Informative on relevance and clinical impact**	Yes			Improved substantially, since relevant variables may be conclusive from a confirmatory perspective
• **Enough information on safety**	YES			At least similar or higher, data in a more advanced (frail) set of patients
• **Suitable information for risk-benefit balance**	YES			Improved substantially

Alternative development Option 3

Fallback tests for co-primary endpoints (histology in several organs + renal func

Practical considerations:	Yes	No	Depends, or not fully	Comments
• **May reduce sample size requirements**		No		Same sample size, determined by ultrararity
• **May shorten time to study completion**		No		Same duration per patient, still too short to collect relevant clinical outcomes. Overall study duration may increase if difficult to find eligible patients with more severe disease
• **May ease recruitment**		No (worsens)		More strict inclusion criteria, less eligible patients Same chances to receive placebo, less willingness to participate

Ethical assessment:	Yes	No	Depends, or not fully	Comments
• **May minimise risks**		NO		More advanced (frail) set of patients may be more susceptible to adverse reactions
• **May maximize access to treatment**		NO		Access to the therapeutic test (I e: entering the trial and having chances to receive active) is reduced, since only severe patients may participate.
• **May minimise unnecessary exposure to ineffective treatments or placebo**		NO		Same number of patients exposed to placebo for the same period of time. On top, less patients may have acess to the active drug in the experimental setting because of strict inclusion criteria
• **Considers patient input**	Yes			QoL as one of the primary co-endpoints

- **The overall balance of an enriched design is a reduction of uncertainty at the price of slower access to active treatment for mildly diseased patients.**
- **Using fallback tests for co-primary endpoints is improving the trial at no substantial impact on other assessment parameters, and thus should be recommended as it addresses the main limitations of the actual development**

Recommendations

- The development of Fabrazyme in the treatment of Fabry´s disease is considered a representative model within the cluster of progressive multidimensional multi organ conditions. Therefore, general considerations on applicability of novel methods can reasonably be suitable options for conditions belonging to the cluster of chronic progressive conditions led by multiple organs/systems.

- *Chronic condition with a relatively low progression*
- *Multidimensional nature and heterogeneous presentation*
- *Recruitment based on prevalent cases, but low prevalence/high dispersion*
- *No effective SOC*
- *Strong scientific rationale based on pathophysiology-MoA*
- *Good PD marker (clearance of GL3), not fully conclusive of efficacy*
- *Usually prior data from registries available (not that much in this case)*

Recommendations

- In particular, new methodologies aimed to study the multidimensional nature of the condition, like the fallback tests for co-primary endpoints and the optimal exact tests for multiple binary endpoints, are highly recommended in order to generate a more complete and compelling evidence of efficacy and safety and to facilitate generalizability of the study results.

- Parallel designs needed to deal with progression and intersubject variability. Enrichment /stratification may be useful to control heterogeneity and increase sensitivity to changes

- Previous information on the clinical course can be suitable for bayesian approaches and planning of adaptions. However, sample size adaptions and sequential designs, although applicable, may not always increase efficiency if patients are already available for study entry and the use of placebo does not cast major ethical/practical concerns.

Conclusions WP5

The selection of methods guided by clustering allows a pragmatic approach that considers the different options for measuring treatment effe clinical context of the condition. As a result methodological requirements

Connecting clinical rationale, unmet patients needs and suitable methodologies

Thank you