

Clinical and Regulatory Challenges in Developing New Treatments for Rare Diseases

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Conflict of Interests

A - Z

Too many to mention

Clinical and Regulatory Challenges

- Wide-spread belief that clinical development and regulatory approval of Orphan indications is easier and needs lower FDA and/or CHMP requirements/standards.
- Many Sponsors believe that approval by FDA of Sarepta for DMD suggests development of drugs for rare diseases is “low-hanging fruit”.
- FDA and CHMP have previously stated
 - There is no compromise on the quality of the evidence establishing efficacy and safety for orphan drugs.
 - CHMP rejected Ralaxone for DMD stating results of 66 patient placebo-controlled study were inadequate; FDA previously indicated the same position

FDA Reactions to Approval of Sarepta

- FDA Commissioner stated that the paper of the Sarepta study was “misleading” and should be retracted.
- Head of FDA’s Office for New Medicines stated that
 - “Path taken by Sarepta NOT a good model for other development programs.”
 - CDER Director had expressed concerns at the small study size and its lack of clear efficacy

This presentation discusses the issues of level/quality of evidence required from the perspective of two ongoing Phase 3 programs for orphan pediatric indications.

Development Program for an orphan, pediatric
progressive disorder
“Ataxia Telangiectasia”

Disease Background - Ataxia Telangiectasia

- Ataxia Telangiectasia (AT) is a rare, autosomal recessive disorder characterised by cerebellar ataxia, telangiectasias, immune defects, infections
- Progressive neurological disorder of childhood that destroys part of the motor control area of the brain, leading to a lack of balance and coordination
- Prevalence estimated to be 1 to 2.5 per 100,000 (< 10,000 AT patients in the US),
- High incidence of neoplasm, insulin resistance
- Wheelchair bound by 10 -15 years of age; reduced life expectancy by 10-20 years
- Neurological deterioration is the major driver of morbidity and poor QoL
- No comprehensive natural history study; no effective treatment
- Sponsor's open-label, 6-month study performed in AT patients (Chessa et al, 2014) indicated statistically significant improvements in neurological symptoms, global assessment, ocular motility, adaptive behavior

Sponsor's Proposal for Phase 3

- Single, double-blind, placebo-controlled, randomized, 2-non-overlapping dose ranges, 6-month Global study in 180 patients capable of independent ambulation (>6 years)
- Primary efficacy measure; mean change in International Cooperative Ataxia Rating Scale (ICARS) for pharmacological assessment of the cerebellar syndrome
 - ICARS: Psychometric properties already include
 - inter-rater reliability
 - internal consistency
 - criterion-related validity
 - construct validity
 - treatment sensitivity in controlled studies in AT

FDA / CHMP Feedback on Sponsor's proposal

- Wanted 1 year placebo-controlled study for efficacy and safety; following discussion, agreed to 6 months for efficacy and 1 year for safety
- Need to propose a Primary outcome measure designed to assess functional improvement in specific domains, e.g. motor/cognitive function
- Questioned use of ICARS as Primary measure; could not name alternative
- Required data on validity of ICARS for patients below age of 10 years (Sponsor performed study to validate measure in 6-10 years old)
- Train raters on ICARS; remote KOL raters to perform consensus ratings to criterion; video baseline ratings for future if site rater changes

FDA / CHMP Feedback on Sponsor's Proposal cont.

- ICARS rater not be involved with any other efficacy or safety assessments
- Report on training will need to be submitted to Health Authorities
- Need to demonstrate “clinical meaningfulness” of change in ICARS;
- Want CGI as ‘Co-Primary’ (no known CGI for AT); Sponsor developed/ validated in field
- Global improvement should be assessed by blinded rater, without access to prior global assessments or information about the primary outcome measure
- Describe how clinicians will rate the CGI-C and CGI-S, i.e. what guidelines will be used

FDA-Requested Changes: Efficacy (1)

'Modified' International Cooperative Ataxia Rating Scale (ICARS) in patients with ataxia telangiectasia (AT)

FDA: "The clinical meaningfulness of change on the ICARS is not clear. The change in eye movements is one example of an assessment where improvement cannot be directly interpreted to be clinically meaningful. However, subsections of the scale that assess specific activities such as walking and self-care tasks may be useful for assessing efficacy."

"You should propose a primary outcome measure designed to assess functional improvement in the specific domains of interest."

FDA-Requested Changes: Efficacy (2)

- To evaluate the effect of treatment compared to placebo, in this population on the **Clinical Global Impression of Change from baseline (CGI-C)**
 - **FDA:** *“Global co-primary endpoint should assess **changes in global function or improvement** rather than providing a global rating of disease specific symptoms. A separate, blinded member of the study team should assess global function without the ability to access information for global assessments from prior visits or information about the primary outcome measure.”*
 - *“We recommend that you **replace the CGI-C with the CGI-S** as a co-primary endpoint. The CGI-C has the potential to introduce recall error in that it requires the clinician to compare the patient’s current status to their status from an earlier time point.”*
 - *“Please describe how **clinicians will arrive at the CGI-C** score (e.g., “very much improved,” “much improved,” etc.)”*

FDA-Requested Changes: Efficacy (3)

Other Secondary Efficacy Objectives

- To evaluate the effect of treatment compared to placebo, in this population on the following efficacy measures:
 - **Clinical Global Impression of Severity (CGI-S)** of neurological symptoms of AT
 - **FDA: Please provide these data to the Agency, as well as details on how clinicians will arrive at scores for the 5 domains of the CGI-S that you developed** (i.e., what were the anchors for the response options for each domain, e.g., severe versus very severe). Additionally, please explain how the general CGI-S score will be calculated (e.g., sum, average).

Efficacy Measures: Secondary

Clinical Global Impression of Severity of AT (CGI-S-AT)

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Original Article

Development of global rating instruments for pediatric patients with ataxia telangiectasia



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CGI-S of AT

Severity	Ataxia (walking)	Dysarthria	Dysmetria	Extrapyramidal CMTD	Eye movements
0-none	none	none	none	none	normal
1-mild	Mild instability, no falls or staggering steps, runs better than walks, narrow gate ataxia	Some slurring of speech but all sentence understandable	Over/undershooting less than 2 cm, no bradykinesia	CMTD present with cognitive or motor activation, does not interfere with function	Saccadic breakdown of smooth pursuit, sometimes dysmetric saccades but no saccade latency
2-moderate	Moderate instability, staggering steps and falls or wide based gait	Some words not understandable, needs to repeat phrase to be understood	Over/undershooting 2-5 cm, no bradykinesia	CMTD present significantly with motor and cognitive activation, function affected but not impaired	Oculomotor apraxia appears sometimes OMA , may be some latency of saccades
3-severe	Walks with support of accompanying person (one hand held)	Some words not understandable, needs to repeat phrase to be understood	Over/undershooting 2-5 cm with bradykinesia	CMTR present without activation or at rest and impair function significantly	Always OMA, significant saccade latency, small hypometric saccades
4-very severe	Needs bilateral support for walking/ cannot walk with bilateral support	Speaks in single words, incomprehensible	Over/undershooting more than 5 cm, with bradykinesia	CMTR present without activation or at rest, making function impossible	Total ophthalmoplegia

CMTD: chorea, myoclonus, dystonia, tremor; CMTR: chorea, myoclonus, tremor, rigidity

Guideline for Rating Severity of Ataxia Telangiectasia

Overall Rating of Severity	Guideline for Rating
0- not ill at all / asymptomatic	A rating of 0 (not ill/asymptomatic) could be made only if there were no symptoms, or a rating of mild on only one symptom domain
1-mildly ill	A rating of 1 (mild) could be made only if there were not more than 2 domains rated greater than mild
2-moderately ill	A rating of 2 (moderate) could be made only if there were not more than 2 domains rated greater than moderate
3-severely ill	A rating of 3 (severe) could be made only if there were not more than 2 domains rated greater than severe
4-very severely ill	A rating of 4 (very severe) could be made only if there were at least 2 domains rated as severe and two rated as very severe

Development of a new treatment for Rett
Syndrome, an Orphan Paediatric Neurological
Condition

Characteristics of Rett Syndrome (RTT)

- Severe neurodevelopmental disorder affecting females: prevalence -one in 10-20000 females.
- >95% of clinically diagnosed individuals present mutations in the X-linked gene encoding the transcriptional regulator, methyl-CpG-binding protein 2 (MeCP2).
- Characterized by normal development up to ~18 months, followed by a regression characterized by a loss of acquired fine and gross motor skills and the development of neurological, cognitive and autonomic dysfunction
- Loss of ability to conduct daily life activities (>10 years), walk i.e. use of wheelchair (10-13 years), swallow (>13 years), or communicate (>14 years), in most cases
- Disease characterized by presence of sleep abnormalities >80%, seizures >70%, **respiratory abnormalities >70%**, severe intellectual impairment >90%, motor abnormalities >90%
- Increased mortality at the ages of 20 (22% increase; 23% vs 1%) and 35 (39% increase; 41% vs 2%) (Anderson, 2014)
- Management – currently there are no approved treatments available that affect the course of the disease, and management is purely symptomatic

Characteristics of Rett Syndrome (RTT)

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- Loss of ability to conduct daily life activities (>10 years), walk i.e. use of wheelchair (10-13 years), swallow (>13 years), or communicate (>14 years), in most cases.

Respiratory Abnormalities in Rett Syndrome

- Breathing abnormalities are found in approximately 70 percent of patients with RTT at some stage of their life
- Onset of respiratory dysregulation noted at ages 3-5 years in RTT patients; maximum severity ages 5-15
- Breathing abnormalities include alternating periods of hyperventilation and apneas (up to 80 episodes of 10 secs or greater duration per hr during waking time), breath-holds terminated by Valsalva's maneuvers, forced and deep breathing, and apneustic breathing
- Frequent breath-holds/apnea cause cyanosis and loss of consciousness, and are associated with abnormal cardiorespiratory coupling
- Apnea with overshoot of heart rate response result in hypoxia and oxidative stress, which impacts on cardiorespiratory homeostasis/ prolonged QT syndrome
- **25% of deaths in RTT are sudden and unexpected and might result from complications of cardiorespiratory dysfunction** (Kerr 1997, Julu 1997; Julu 2008; Byard 2006)

Proposed Program For Respiratory Symptoms in Rett Syndrome Patients

Sponsor's Proposal (prior to HA input):

- **3-month, uncontrolled study with clinical plethysmographic recordings (n=20)**

Multiple HA inputs led to

- Revised to **single-blind, randomized 3-month study in 60 hospitalized pts at 2 fixed doses**
- Further revised to **double-blind, randomized study in 60 pts at 2 fixed doses with plethysmographic recordings for 3 hours at home**
- Revised to **double-blind, 6-month randomized placebo-controlled study in 90 pts at 2 fixed doses with automated recordings for 8 hours at home**

Sponsor's Final Protocol following HA input

- **6-month randomized placebo-controlled with 2 fixed doses using automated recordings for 8 hours/day for 3 consecutive days per week with remote, independent interpretation**
- **Additional changes requested; secondary measures, oxygen saturation, morphology of respiratory symptoms, cognition, effect on most common symptoms, effects on rating scales, statistical methods, etc.**

Regulatory Feedback on Proposed Program

- Consolidated Feedback
 - Scientific advice (SA) meetings with HA in Germany, UK, Spain, EMA/CHMP, Canada, and FDA
 - Feedback from above meetings
 - Clinical trial needs to be at least 6 months duration ,have fixed doses and more patients **if approval is to be based on one trial**
 - General agreement (ALL) that **robust, significant beneficial effects** needed on primary efficacy measure
 - Reduction in apneic episodes must be demonstrated objectively, reliably, and **over extended periods of time**
 - Need information on device, e.g. concurrence with clinical plethysmography, validation, if used elsewhere, variability, feasibility data, how used; provide data from feasibility study
 - All wanted secondary efficacy measure- e.g., CGI, or Caregiver-rated Global Improvement, measures would be **necessary** to support a MAA/NDA for this high-risk population.