MYODA clinical program: A new approach unraveling drug effects through a composite outcome score encompassing ambulant to non-ambulant disease stages

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BACKGROUND

The purpose of the clinical program MYODA is to evaluate Muscle strength and function in Young boys suffering from Duchenne musculAr dystrophy under long-term oral administration of a selected daily dose of BIO101 (20-hydroxyecdysone, MAS activator) (Reference to posters P11-116-#351). Ambulant and non-ambulant DMD boys will be recruited. Heterogeneity of the clinical course has long been recognized and more recently has been captured in registry studies (Ricotti et al. 2013, 2016, Mercuri et al. 2016). Moreover, the mode of action of BIO101 and the pre-clinical proof-of-concept (PoC) suggest that the population of DMD patients who will benefit from BIO101 is quite broad and that this benefit can be shown in a variety of functions.

In order to ascertain that the benefit of BIO101 in DMD is clinically relevant, the proposed primary end-point is built in a way that allows measuring clinically relevant changes, in a broad range of subjects, ambulatory, transitional, and non-ambulatory. This composite score approach includes a defined list of key end-points, which are considered relevant endpoint for the disease state investigated and that have been used is previous studies as primary or key secondary end-points.

GUIDING PRINCIPLES

Unlike conventional design, the MYODA clinical program is composed of 3 main parts (See poster Number: P11-129-#460). The part 1 dedicated to evaluate safety and PK profiles of BIO101, part 2 that evaluates the Proof-of-Concept (PoC) and PD through specific biomarkers and a part 3 corresponding to the confirmatory – efficacy and safety step of the program. In comparing a new treatment with a control for DMD under a randomized clinical trial setting, each study patient has multiple efficacy outcomes collected over time (Table 1). Instead of defining a primary endpoint using a single outcome and identifying several secondary endpoints like most conventional studies, we present several approaches to utilize multiple outcomes simultaneously to evaluate the treatment effect, in a broad range of subjects, ambulatory, transitional, and non-ambulatory.

Multiple comparison:

To prevent from conducting multiple comparisons and avoid the need to set-up a hierarchy, all the endpoints will contribute to the final score, end-points that the subject is not able to perform at baseline, the contribution of it to the total score will be set at 0.

Calibration:

Since various scales and measured are used, calibration will be achieved, by measuring the difference from the external controls, according to the Minimal Clinically Important Difference (MCID).

Standardization:

In the confirmatory part of the study (see poster P11-129-#460 for more details on the study design), each subject will be compared, based on a matching algorithm to a group of external controls, from existing datasets and these individual comparisons will pooled across the treatment groups – for a final analysis against placebo.

Collaboration with multiple data sources for development and validation of patient categorization (e.g., CINRG, UK North Star database, AFM database); Partnership with cTAP for analysis design and collaborative access to additional data sources.

Stratification:

Stratification of the study sample according to a set of pre-defined profiles, into the 3 stages of the disease (ambulatory, in-transition and non-ambulatory disease states), but enriched, based on a trajectory analysis of progression in the comparative datasets and the part 2 population.

METHODS

The following methods are under consideration with external stakeholders and regulatory authorities, one will be selected primary for each study part (2 and 3)and the other will serve as basis for sensitivity analysis:

Method A:

A responder analysis is utilized.

Responders are defined as improving at least one MCID compared to baseline.

Method B:

For each patient, by comparing outcomes in Table 1 collected at baseline and at the end of the study; for each category, each patient is scored as -1, 0, or 1:

- -1 is assigned for clinically significant worsening;
- 1 is assigned for clinically significant improvement;
- 0 is assigned if neither -1 or 1

Adding scores across all endpoints for each patient

Comparing mean scores for two treatment groups

Method C (O'Brian):

For each endpoint and each patient, by constructing a score, for example, the individual value minus the mean, divided by the standard deviation (SD), where mean and SD are computed across all patients for the endpoint.

- Calculating the average score for each patient across all the endpoints
- Comparing mean scores between two treatment groups

Method D (Wei-Lachin) – Combining test statistics across all endpoints

For each endpoint, obtaining a test statistic for comparing average values of the endpoint between treatment groups

- Combining the test statistics (e.g., simple sum)
- Comparing combined test statistics between two treatments

Table 1. Efficacy outcomes by category

The preclinical proof-of-concept (PoC) for BIO101 suggests a variety of benefits in a broad population, in a nutshell: improvement of mobility function (running distance), strength (grip strength) and respiratory function. See more details about the pre-clinical PoC in poster# P11-116-#351.

Therefore, for the composite score, end-points that have been recently used as primary or secondary in pivotal studies in DMD are selected and categorized according to the domain, in which the benefit that BIO101 can be seen:

Mobility	Strength	Respiratory functions
Performance of upper limb (PUL) test North Star Ambulatory Assessment (NSAA) 6-minute walk test (6MWT) 10-meter run/walk time	MyoGrip Myopinch	Forced vital capacity (FVC) – percent vs. predicted Peak expiratory flow (PEF) – percent vs. predicted

SUMMARY:

- **The primary end point of the MYODA study is a composite – aiming to address the variability in the study population and to reflect the personal subject experience and benefit**
- **Utilizing the MCID method increases the scientific rigor – to ascertain that the benefit is indeed clinically meaningful**
- **Comparing to external comparators in the confirmatory part of the study is made – to standardize the study groups and avoid noise due to study procedure – the primary end point, however, compares across and between the placebo and treatment groups**