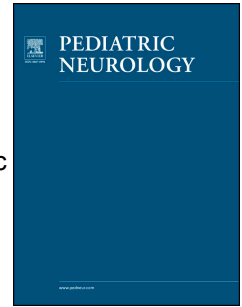# Journal Pre-proof

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A Phase 2 Study of AMO-02 (tideglusib) in Congenital and Childhood Onset Myotonic Dystrophy Type 1 (DM1)

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Abstract:

Background: GSK3β is an intracellular regulatory kinase that is dysregulated in multiple tissues in Type 1 myotonic dystrophy (DM1), a rare neuromuscular disorder that manifests at any age. AMO-02 (tideglusib) inhibits GSK3β activity in preclinical models of DM1 and promotes cellular maturation as well as normalizing aberrant molecular and behavioral phenotypes. This Phase 2 study assessed the pharmacokinetics, safety and tolerability, and preliminary efficacy, of AMO-02 in adolescents and adults with Congenital and Childhood-onset DM1.

Methods: Sixteen subjects (aged 13 to 34) with Congenital and Childhood-onset DM1 received 12 weeks of single-blind fixed-dose oral treatment with either 400 mg (n=8) or 1000 mg (n=8) of AMO-02 (NCT02858908). Blood samples were obtained for pharmacokinetic assessment. Safety assessments, such as laboratory tests and ECGs, as well as efficacy assessments of syndromal, cognitive and muscular functioning, were obtained.

Results: AMO-02 plasma concentrations conformed to a two-compartment model with first-order absorption and elimination, and dose-dependent increases in exposure (area-under-the-curve, or AUC) were observed. AMO-02 was generally safe and well-tolerated. No early discontinuations due to adverse events nor dose adjustments of AMO-02 occurred. The majority of subjects manifested clinical improvement in their CNS and neuromuscular symptoms after 12 weeks of treatment compared to the placebo baseline, with a larger response noted at the 1000 mg/day dose level. AMO-02 exposure (cumulative AUC) was significantly correlated (p<0.01) with change from baseline on several key efficacy assessments.

Conclusion: AMO-02 has favorable pharmacokinetic and clinical risk/benefit profiles meriting further study as a potential treatment for Congenital and Childhood-onset DM1.

Introduction:

Myotonic dystrophy Type 1 (DM1) is a rare, genetically determined neuromuscular disorder affecting individuals across the lifespan. DM1 occurs secondary to an expansion triplicate repeat in the untranslated 3' region of the *DMPK* gene located on chromosome 19. This leads to the production of dysfunctional RNA which increases total levels of GSK3β and active GSK3β, an intracellular regulatory kinase, as confirmed in studies of brain and muscle tissue of transgenic mouse models as well as in patient tissues (*Jones et al; 2012; Jones et al; 2015; Wei et al; 2018;)*. GSK3β activation causes mis-splicing of downstream effectors responsible for differentiation of muscle tissue and the formation of synapses in the central nervous system. Recent evidence indicates that correction of GSK3β activation with AMO-02 (tideglusib) in DM1 transgenic mice reduces the mutant RNA associated with the DMPK expansion triplicate repeat and subsequently improves the postnatal survival of these mice (Wang et al; 2019). Correction of GSK3 β also reduced mutant, pathogenic RNA in human cells from CMD1 and DM1 patients (Wang et al; 2019).

From a clinical perspective, DM1 patients experience substantial impairment in cognition, sleep regulation, communication skills, muscle functioning and quality of life. DM1 is a familial disorder and genetic anticipation occurs across generations, with congenital and childhood onset presentations often accompanied by life-threatening features such as muscular weakness and compromised respiration at birth that can culminate in early mortality. Intellectual disability and co-occurring features of autism spectrum disorder are also common in this population (Ekstrom et al; 2008). While mexiletine was recently approved in the European Union for the symptomatic treatment of myotonia in adults, there are no approved treatments for other aspects of DM1 nor for younger individuals affected with this disorder (Stunnenberg et al; 2018).

The Congenital and Childhood onset forms of DM1 are typically associated with significant medical morbidity and there are no treatments available that can ameliorate the key pathological features of this condition. Furthermore, there have been no previous clinical trials devoted to individuals affected by early-onset DM1. The goal of this study was to assess the pharmacokinetics as well as the initial safety, tolerability and efficacy of AMO-02 (tideglusib), a novel, orally administered GSK3β enzyme inhibitor, as a potential treatment for adolescents and adults with Congenital and Childhood onset DM1.

Methods:

This Phase 2 proof-of-concept clinical trial enrolled individuals with Congenital or Childhood onset DM1. All subjects had preceding diagnostic confirmation of DM1 via genetic testing as well as documentation of the onset of symptoms during infancy or early childhood. The subjects with Congenital DM1 had a history of one or more of the following signs or symptoms that was evident within the first week after birth: hypotonia, generalized weakness, respiratory insufficiency, feeding difficulties, and/or clubfoot or

another musculoskeletal deformity. The subjects with Childhood onset DM1 had at least 2 signs or symptoms (not caused by another, unrelated condition) that were evident prior to 12 years of age and that could be clearly assigned to DM1, including muscle weakness, myotonia, difficulty using hands (including fine motor problems), excessive daytime sleepiness, problems with upper or lower gastrointestinal functioning, problems with concentration or focusing (including symptoms of attention-deficit/hyperactivity disorder), and learning difficulties (including dyslexia).

The subjects were all enrolled at a single investigative site, a specialty center for DM1 in the United Kingdom. The subjects were ambulatory and had a Clinical Global Impressions of Severity (CGI-S) score of 4 (moderately ill) or greater upon entry to the study. The subjects were not receiving any stimulant medications, and other treatments and therapies had to be stable for at least 4 weeks prior to the commencement of the single-blinded placebo run-in. A history of clinically significant renal, hepatic, cardiovascular, endocrine or respiratory disease was exclusionary.

Treatment involved a 2-week single-blind placebo period and 12 weeks of fixed-dose oral treatment with either 400 mg (n=8) or 1000 mg (n=8) of AMO-02 administered once each morning. A 2-week follow-up period occurred after the study medication was discontinued. Subjects were enrolled into the 1000 mg arm first and then the 400 mg arm, so the Investigator and study personnel were not blinded to the dose. The study medication, including the placebo, was packaged in sachets of 400 mg and 600 mg dose strengths that, at the time of dosing, were opened and mixed in water by caregivers. The contents were stirred vigorously prior to being ingested as a liquid suspension by the subjects.

Outcome measures included plasma levels (for pharmacokinetic assessment), standard safety assessments, and efficacy rating scales completed by clinicians, caregivers, and subjects, as well as performance-based/functional measures that are often used in the routine clinical assessment of individuals with neuromuscular disorders. Safety and tolerability were assessed via laboratory assessments, vital signs, electrocardiograms, and with open-ended queries for adverse events.

Blood samples were taken for pharmacokinetic analysis after 2 weeks and 12 weeks of treatment with AMO-02. On the days when pharmacokinetic blood samples were drawn, the study medication was administered in the clinic, and pre-dose and post-dose blood levels were obtained, separated by at least 2 hours. Lymphocytes were collected from blood samples obtained before, during and after treatment with AMO-02 to analyze levels of GSK3β protein and other associated kinases.

A population pharmacokinetic model that included prior information from a prior AMO-02 Phase I trial in healthy subjects was used to estimate pharmacokinetic parameters of the enrollees in this study. Individual AUC, Cmax, and Css values were derived from simulated profiles using post hoc parameter estimates in a rich sampling scheme (i.e. a sample every 5 minutes). Select pharmacokinetic parameters (i.e. AUC and Cmax) were used to assess potential correlations between systemic exposure and treatment response based on several measures of efficacy.

The efficacy assessments utilized in this study could be classified into four categories: *muscle function* (10 meter walk/run test, handgrip strength and relaxation time, lung function, actigraphy, timed nine-hole peg test, dual-energy x-ray absorptiometry/DXA imaging), c*linician completed rating scales* (Clinical Global Impressions (CGI) Severity and Improvement, Clinician Completed Domain Specific Causes for Concern Visual Analogue Scale: Myotonic Dystrophy), *assessments of c*o*gnitive functioning and associated neurodevelopmental symptoms* (Ohio State University Autism Rating Scale, Ohio State

University Autism Rating Scale Clinician Global Impression - Improvement, Peabody Picture Vocabulary Test) and *subject or caregiver completed rating scales* (Top 3 Concerns).

Adverse event (AE) data were summarized as frequencies and percentages, and described in terms of severity and relationship to the study treatment. AEs were summarized separately for non-treatment emergent events (e.g. during placebo run-in) and treatment emergent events (during active treatment). Objective safety assessments (e.g. laboratory values) were summarized by visit. Changes in safety parameters over time were evaluated, and shift tables at time points of interest were generated. The safety and tolerability data were reviewed on a serial basis (e.g. every 3 months) by an independent data safety and monitoring committee.

Analyses of changes in efficacy variables from baseline to each time point were performed using mixed effect model repeated measures (MMRM) with baseline value as a covariate, dose group and visit as fixed effects, and a treatment-by-visit interaction. Adjusted least square mean estimates were produced by dose group and study visit and were analyzed with two-sided 95% confidence intervals and p-values.

Additionally, a concordant trend analysis was completed in which 10 pre-defined efficacy variables included in the study were analyzed simultaneously to determine the likelihood of the pattern of efficacy results representing a false positive finding (an example of this analytic approach is found in Glaze et al; 2017).

Because this was a Phase 2 proof-of-concept study in a clinical population that had not previously been studied in a clinical trial context, with no prior information available on potential or expected magnitudes of change-from-baseline in efficacy measures in association with treatment, no corrections were made for multiple comparisons when p-values were generated. In this regard, the study was posited to be hypotheses-generating, and the goal of diminishing the risk of a Type 2 error was prioritized over the risk of encountering a Type 1 error.

The study was approved by a central ethics committee in the United Kingdom. Consent was obtained for all subjects prior to screening, in most cases consent was provided by the subject's parent or legally authorized representative, where the subject was less than 16 years old or did not have the capacity to consent for themselves. Assent was obtained from all subjects that could not consent for themselves. The study was registered on Clinicaltrials.gov (NCT02858908) and on the EU Clinical Trials Register (2016-000067-16).

Results:

Sixteen subjects between the ages of 13 and 34 y.o. were enrolled in the study, including 10 males and 6 females with an overall mean of 21 years of age and a standard deviation of 5.8 years. Fourteen of these individuals had the congenital form of DM1 while 2 had the childhood onset form.

The pharmacokinetic profile of AMO-02 was best described by a two-compartment model with first order absorption and elimination. Estimated clearance and the volume of distribution parameters remained the same across the two dose levels evaluated in this study, indicating that the pharmacokinetics of AMO-02 are generally linear (see Table 1, below). There was no evidence of accumulation, metabolic inhibition, or induction observed during treatment. Body weight was a

covariate effect on clearance and volume of distribution. Previous Phase I studies indicated that higher plasma concentrations and exposures occur when AMO-02 is co-administered with a fatty meal. However, in this study, the timing of last food intake did not appear to influence systemic exposure, as assessed by AUC and Cmax.

Dose (mg)	1000 mg	400 mg
C_{MAX} (ng/mL)	1170.95 (573.3-1450.16)	513.54 (342.95-615.45)
C_{MIN} (ng/mL)	5.65 (3.47-16.21)	4.17 (2.16-11.34)
C_{SS} (ng/mL)	141.62 (68.83-220.29)	56.89 (30.71-74.47)
t_{max} (h)	0.7 (0.6-1.22)	0.75 (0.3-0.99)
$t_{1/2}$ (h)	1.7 (1.04-2.56)	2.05 (1.31-5.45)
AUC(0-12) (ng/mL·h)	3145.76 (1571.4-5109.46)	1218.16 (660.3-1713.85)
AUC(0-24) (ng/mL·h)	3398.68 (1651.9-5287.1)	1365.54 (737.21-1787.29)

Table 1 AMO-02 Pharmacokinetic Parameters (median, 5th and 95th quantiles).

CMAX: maximum (or peak) serum concentration; CMIN: minimum serum concentration; CSS: steady-state concentration; tmax: time to serum concentration; t1/2: drug half-life; AUC: total area under the serum drug concentration-time curve both up to 12h (0-12) and 24h (0-24) after AMO-02 administration.

All subjects completed the study, and no subjects required dose adjustments of the study medication at any point in time. AMO-02 was generally safe and well-tolerated, with no early discontinuations due to adverse events. The most common on-treatment adverse event was nasopharyngitis, mild in severity, which was experienced by 31% of subjects. All adverse events were mild or moderate in severity, except one event of bilateral knee pain at the 400 mg/day dose level, considered unrelated to study drug. There were no serious adverse events. One subject in each dose group experienced on-treatment elevations in alanine aminotransferase (ALT) where values were higher than 1.5 times the upper limit of the normal reference range, above baseline. All liver function test elevations were not deemed to be clinically significant by the investigator and typically self-resolved while treatment was still ongoing. No patients experienced elevated bilirubin values or associated symptoms.

AMO-02 rendered clinical benefit to the majority of subjects after 12 weeks of treatment, with a larger magnitude of response generally apparent at the 1000 mg/day dose level. Improvements were most

evident in the subjects' cognitive functioning, fatigue and ability to perform activities of daily living, as well as in the neuromuscular symptoms of several of the subjects. In addition, co-occurring autism symptoms improved in several subjects (see Figure 3B). The heatmaps in Figure 5 and Figure 6 visualize the changes to symptoms in all subjects with variable phenotypes at baseline.

There were no statistically significant effects of placebo treatment during the 2-week baseline placebo run-in period (data not shown). The clinician-completed and caregiver-completed rating scales (shown in Figures 1, 2, 3 and 4 and Table 2) revealed large treatment-associated effects, these effects being statistically significant across the period of treatment with AMO-02.
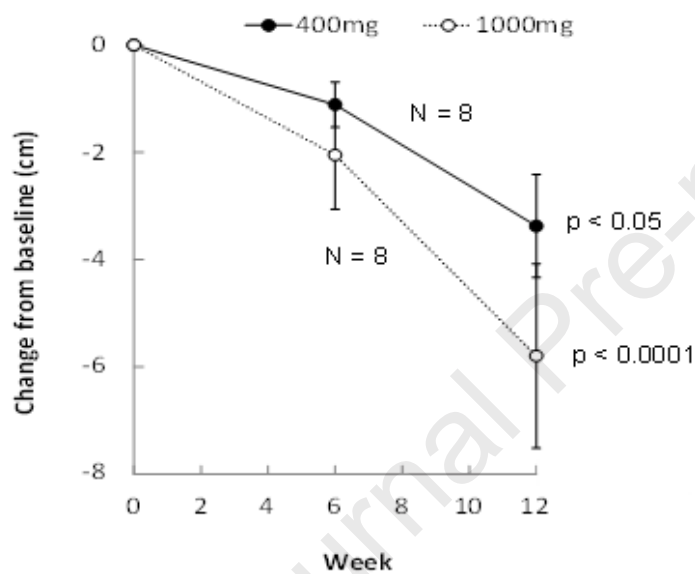

Figure 1: Change from end of placebo baseline in the Clinician-Completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy total score in cm comparing both 400 and 1000 mg/day dosages. Data are Mean ± sem from the MMRM analysis with p-values compared to end of placebo, which coincides with start of treatment at week 0, with data analyzed at mid-treatment (week 6) and end of treatment (week 12).
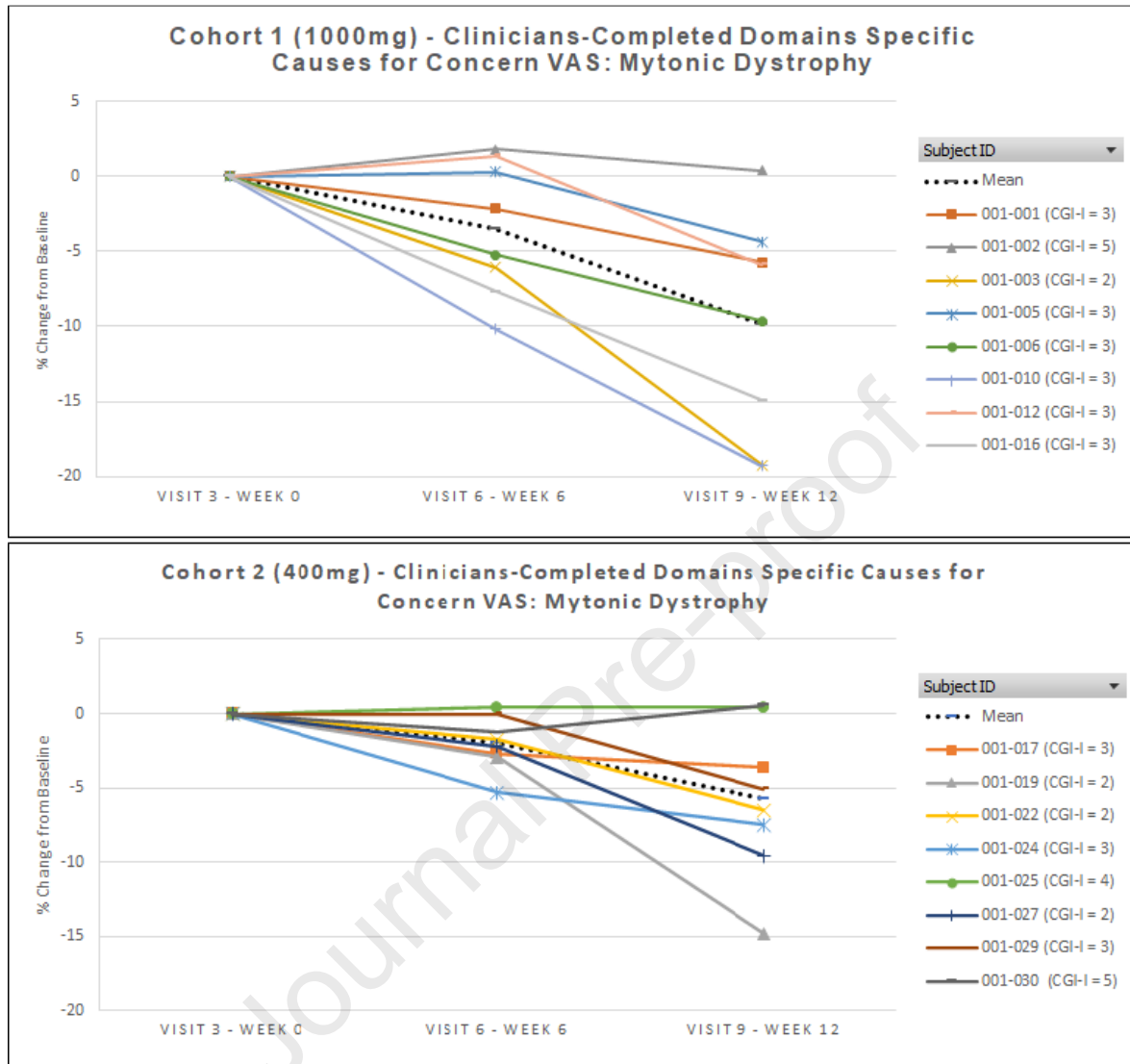
Figure 2: Individual Subject Clinician-Completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy with Week 12 CGI-I score in the legend.

Subject ID	Age (years)	CGI-S at Baseline	Number of CTG repeats at Baseline	Clinician-Completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy Total Score		
				Baseline	Week 12	Change from Baseline
Cohort 1 (1000 mg)						
001-001	23	6	1680	50.7	47.8	-2.9
001-002	34	5	1011	49.5	49.7	0.2

001-003	18	4	456	60.8	49.1	-11.7
001-005	17	6	1141	69.1	66.1	-3
001-006	22	4	1139	49.9	45.1	-4.8
001-010	23	4	1172	73.6	59.4	-14.2
001-012	19	6	1113	58.1	54.7	-3.4
001-016	18	4	711	44.2	37.6	-6.6
Cohort 2 (400 mg)						
001-017	22	6	1381	52.4	50.5	-1.9
001-019	26	4	330	47.9	40.8	-7.1
001-022	32	4	726	50.8	47.5	-3.3
001-024	17	5	600	68	62.9	-5.1
001-025	15	5	1763	74.2	74.5	0.3
001-027	16	4	1085	54.2	49	-5.2
001-029	13	6	1401	99	94	-5
001-030	21	5	875	54.7	55	0.3

Table 2: Age at enrolment, disease severity (CGI-S) and the mode number (the most common repeat length at sampling) of CTG repeats at baseline. Clinician-Completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy Total Score at baseline, end of treatment (Week 12) and change from baseline.
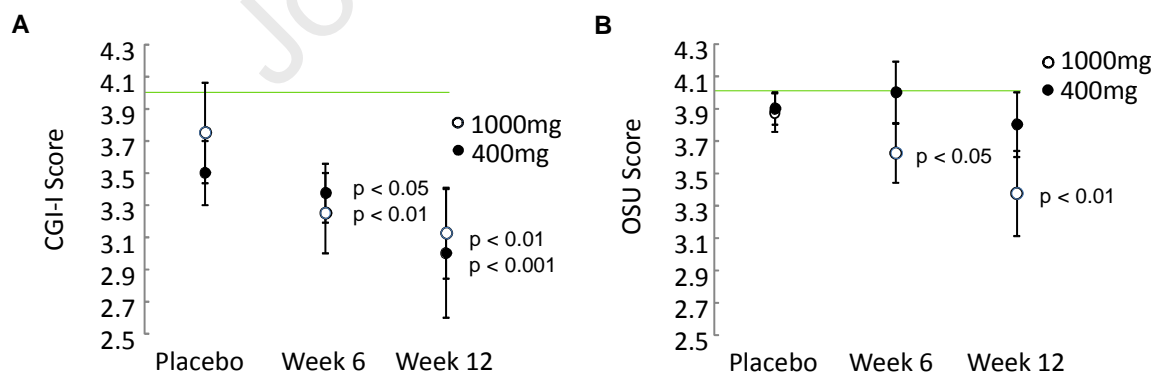

Figure 3: Clinical Global Impression – Improvement Scale (A) and in the OSU Autism Rating Scale Clinician Global Impression – Improvement (B) values comparing the 400 and 1000 mg/day dosages at end of placebo (week 0), mid-treatment (week 6) and end of treatment (week 12). Data are Mean ± sem from the MMRM analysis with N = 8 subjects per dose group.
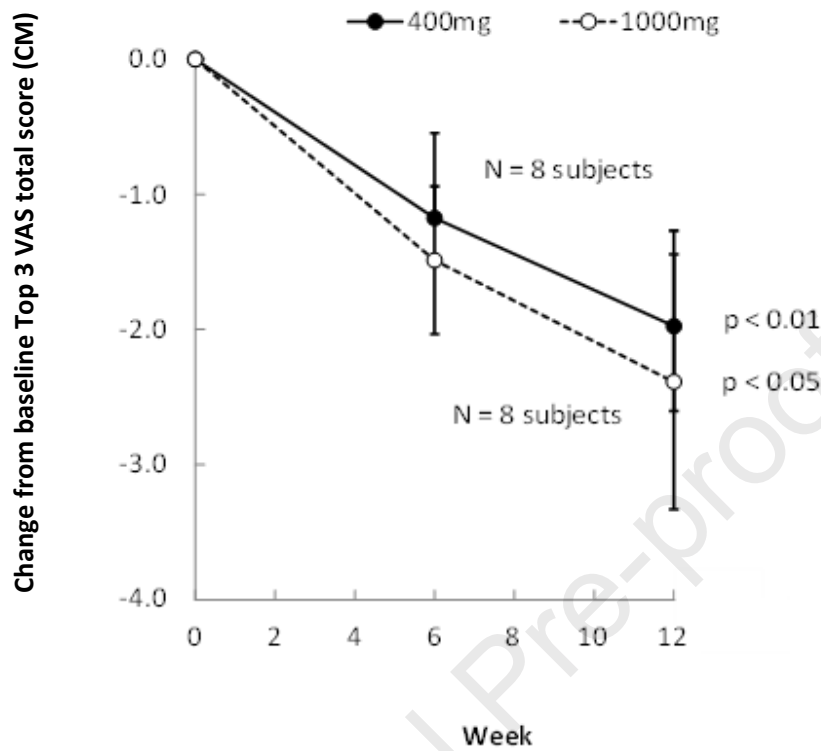
Figure 4: Change from end of placebo baseline in the Caregiver Top 3 Concerns Rating Scale VAS total score in cm comparing both 400 and 1000 mg/day dosages. Data are Mean ± sem from the MMRM analysis with p- values compared to end of placebo which coincides with start of treatment at week 0, with data analyzed at mid-treatment (week 6) and end of treatment (week 12).
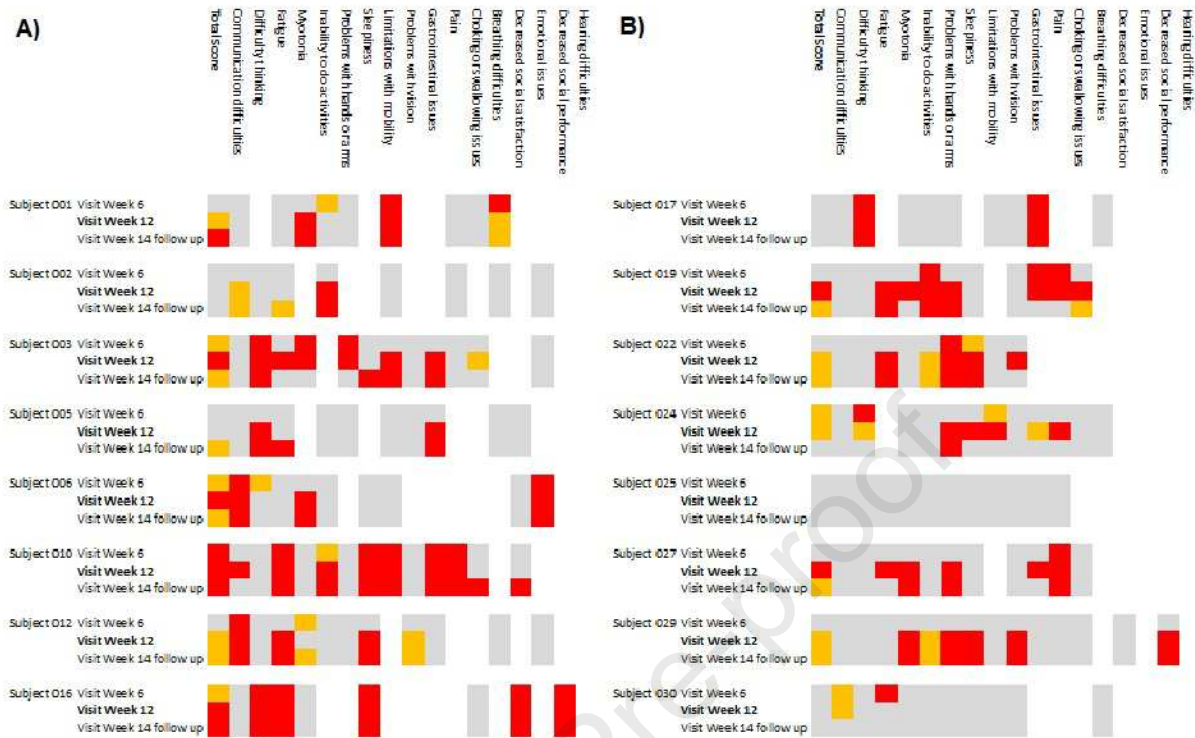
Figure 5: Each colored area shows the change relative to Baseline for the Clinician-Completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy. Where WHITE represent data points where no baseline deficit was detected, GRAY represent data points where a baseline deficit was recorded and no benefit was detected, RED represent data points where a baseline deficit was recorded and a treatment response above the threshold for minimally clinically meaningful benefit was shown (change of 10% or greater) and AMBER represent data points where a baseline deficit was recorded and a treatment response trending to the threshold for minimally clinically meaningful benefit was shown (change of 5-10%). A) Cohort 1 – 1000 mg; B) Cohort 2 – 400 mg.
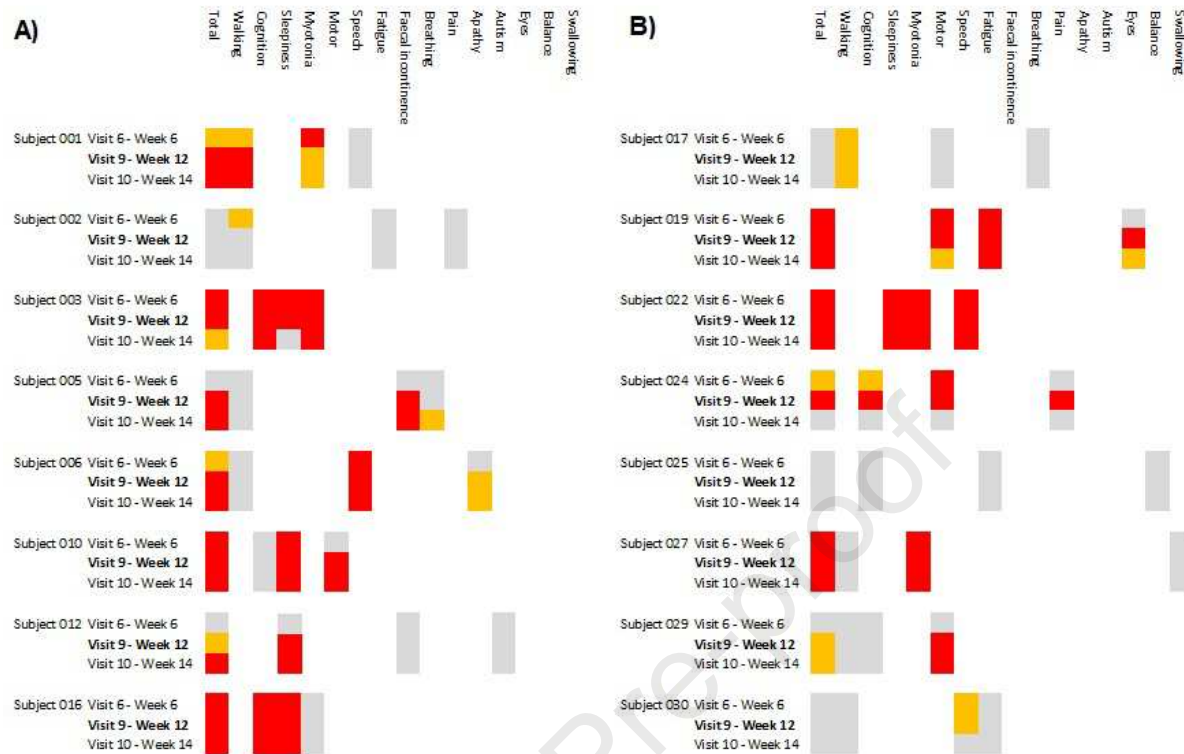
Figure 6: Each colored area shows the change relative to Baseline for the Caregiver Top 3 Concerns VAS. Where WHITE represent data points where no baseline deficit was detected, GRAY represent data points where a baseline deficit was recorded and no benefit was detected, RED represent data points where a baseline deficit was recorded and a treatment response above the threshold for minimally clinically meaningful benefit was shown (change of 10% or greater) and AMBER represent data points where a baseline deficit was recorded and a treatment response trending to the threshold for minimally clinically meaningful benefit was shown (change of 5-10%). A) Cohort 1 – 1000 mg; B) Cohort 2 – 400 mg.

Phenotypic variability at baseline was the norm rather than the exception in the group of subjects enrolled in this study. A wide range of values at baseline contributed to greater-than-expected intra-subject and inter-subject variability in the performance-based/functional neuromuscular assessments, and accordingly, this limited the informativeness of these assessments. Results from the functional neuromuscular assessments are summarized in Table 3. Some symptoms, such as myotonia (hand grip relaxation), were not present in all subjects, therefore rendering average change from baseline ineffective at detecting improvement, which was evident in some subjects (see Figure 7).

Assessment	Cohort	Baseline (week 0) Mean (SD)	EOT (week 12) Mean (SD)	Change from Baseline
10m Walk/Run Test – preferred speed (s)	1000 mg*	9.77 (2.67)	9.10 (1.34)	-0.66
	400 mg	9.80 (1.47)	9.15 (1.73)	-0.65
Hand Grip – dominant hand (kg)	1000 mg	13.08 (7.14)	14.09 (7.72)	1.01
	400 mg	15.62 (6.19)	14.13 (6.86)	-1.49
Relaxation time – dominant hand (s)	1000 mg	0.72 (0.49)	0.65 (0.41)	-0.07
	400 mg*	0.98 (0.66)	0.60 (0.29)	-0.38

Forced Vital Capacity (l)	1000 mg	2.17 (0.91)	2.15 (0.93)	-0.02
	400 mg	2.41 (1.03)	2.42 (1.16)	0.01
Nine Hole Peg Test (s)	1000 mg*	25.76 (11.08)	23.59 (8.26)	-2.17
	400 mg	25.71 (4.53)	24.76 (3.83)	-0.95
Peabody Picture Vocabulary Test (age-based standard score)	1000 mg	63.9 (20.17)	63.8 (15.81)	-0.1
	400 mg	80.9 (20.92)	79.8 (22.23)	-1.1
DXA - total lean muscle mass (kg)	1000 mg	37.86 (8.11)	38.27 (8.27)	0.41
	400 mg	37.35 (8.66)	37.74 (8.48)	0.39

Table 3: Summary of unadjusted mean and standard deviation at Baseline and End of Treatment (12 weeks) for functional neuromuscular assessments. Where marked with an *, analysis completed on adjusted treatment means (LS Means) for change from baseline were statistically significant at the $p<0.05$ level. Actigraphy is not included because device wear-time was not consistently sufficient across all subjects to produce interpretable data.
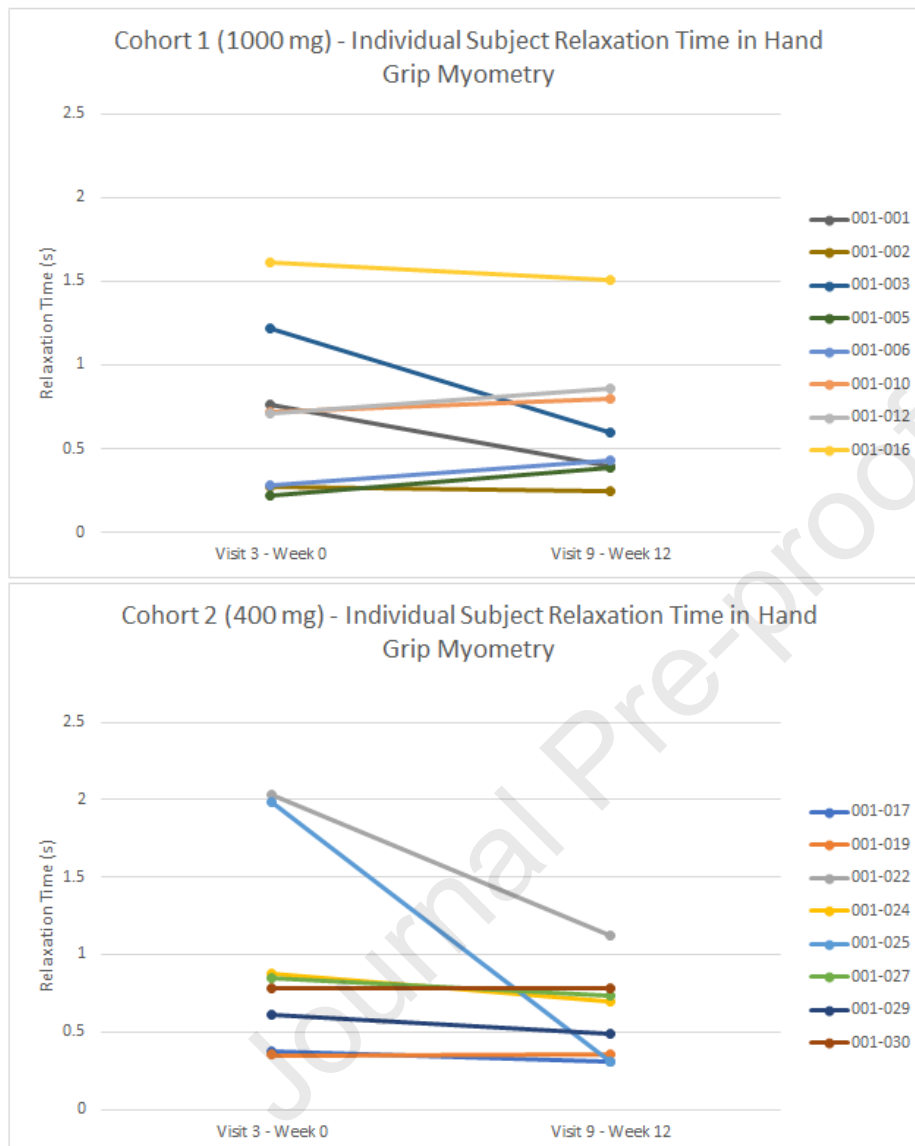
Figure 7: Average time taken from 3 attempts to relax dominant hand grip on a myometer from maximum contraction at Baseline and after 12 weeks of treatment.

The concordant trend analysis confirmed these findings by revealing a clear dose-response relationship that favored the 1000 mg over the 400 mg dose.

A pharmacokinetic/pharmacodynamic analysis revealed that cumulative Area Under the Curve (AUC) significantly correlated ($p<0.01$) with the CGI-I scores and change from baseline for both the Caregiver Top Three Concerns and the Clinician-completed Domain Specific Causes for Concern VAS: Myotonic Dystrophy. Additionally, a greater on-treatment reduction in lymphocyte GSK3β levels was observed in subjects classified as responders vs non-responders, as defined by CGI-I scores.

Discussion:

This is the first clinical trial conducted in the early-onset version of this rare neuromuscular disorder. In this study, AMO-02 was generally safe and well-tolerated, with a fully reversible elevation in ALT being the only notable objective finding in some subjects. AMO-02 improved multiple aspects of the subjects' symptomatology, including neuromuscular symptoms as well as the cognitive symptoms that are often under-appreciated in this condition but which can contribute greatly to the medical morbidity and functional deficits in affected individuals. In addition, co-occurring autism symptoms improved in several subjects, consistent with preliminary finding suggesting that GSK3 inhibitors may be beneficial to individuals with neurodevelopmental disorders (Yuskaitis et al., 2010).

The most informative assessments of efficacy in this study were the clinician-completed and caregiver-completed rating scales. These rating scales are essentially composite assessments, and they revealed large treatment-associated effects, these effects being statistically significant across the period of AMO-02 treatment. The treatment response data were consistent across the rating scales, reflecting signals of efficacy in multiple symptom domains (e.g. CNS and muscles) that are commonly affected in this condition.

Phenotypic variability is the norm rather than the exception in DM-1, and this study included subjects with both Congenital and Childhood-onset forms of DM-1. Therefore, rating scales that take into account clinician or caregiver causes for concern, appeared to provide a better tool for detecting change than solely functional assessments. The heat maps (Figure 5 and Figure 6) highlight how some subjects improved in domains where other subjects had no disabling symptoms present at baseline. The functional outcome measures provided objective support to clinician-observed and caregiver-elicited markers of change during treatment.

The Clinician-completed Domain Specific Causes for Concern (VAS) used in this study represents an important innovation in this orphan therapeutic area. It was derived from a measure previously validated in natural history and intervention studies in DM1 (Heatwole et al., 2012; Johnson et al; 2016). It is also being validated in an ongoing natural history study in children and adolescents with Congenital DM1 (NCT03059264). This rating scale was developed with the collaborative assistance of therapeutic area experts and has been vetted and refined in collaboration with the United States Food and Drug Administration. A refined version of the scale will serve as the primary outcome measure in a forthcoming Phase 2/3 study in children and adolescents with Congenital DM1 (NCT03692312).

The changes from baseline in the Clinician-completed Domain Specific Causes for Concern (VAS) scores appear to track with CGI-I scores so that clinically significant improvements (i.e. CGI-I scores of 3 or better) were correlated with reduced scores of 5-10% in the Clinician-completed Domain Specific Causes for Concern (VAS). Due to the small sample size in this proof-of-concept study, an analysis of the influence of potential response modifiers such as age, severity, and number of genetic repeats was not undertaken.

The results from this small Phase 2 study indicate that AMO-02 may represent a potential treatment for Congenital and Childhood onset DM1. While this was a relatively small study (n=16) with no randomized placebo-controlled arm, the initial findings in this rare disease population indicate that the 1000 mg dose may have the best prospect of establishing a consistent efficacy signal. Correlation between AMO-02 exposure and observed efficacy in several endpoints supports these conclusions. The continuing

improvement that was evident towards the end of dosing with AMO-02 suggests that the magnitude of clinical benefit is likely to increase further with a longer dosing period. Accordingly, additional clinical trials appear warranted.

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