MYOTONIC DYSTROPHY FOUNDATION
Care and a Cure

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DEVELOPMENT OF AMO-02 FOR THE TREATMENT OF CONGENITAL MYOTONIC DYSTROPHY TYPE 1

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AMO PHARMA

Myotonic Dystrophy Type 1: Overview

- Myotonic Dystrophy Type 1 (DM1) affects individuals across the lifespan

- Congenital onset form (CDM1) affects 1 in 40,000 and is the most serious and life threatening

- Significant mortality and severe CNS symptoms

- No approved treatments for any form of DM1

- Expansion triplicate repeat in the untranslated 3´region of the DMPK gene on Chromosome 19

- Produces "toxic" RNA which induces upregulation of GSK3β – seen in brain and muscle of transgenic mouse model and patient tissues

- GSK3β activation causes mis-splicing of downstream effectors responsible for differentiation of muscle tissue and formation of synapses

- Suggests use of GSK3β inhibitor

  - **AMO-02 is an irreversible GSK3β inhibitor**

GSK3β in CDM1 Patient Tissue

Normal Muscle

Patients Affected with DM1

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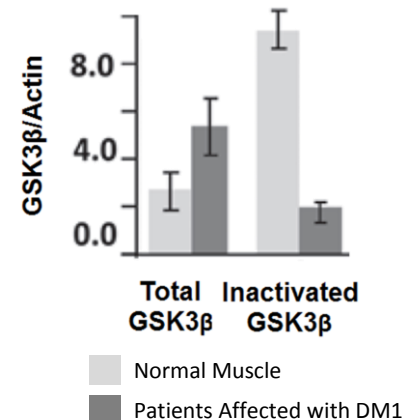
AMO-02: Summary of Pre-clinical Efficacy in DM1

- ☐ Two year research collaboration with Cincinnati Children's Hospital (Prof Luba Timchenko)
- ☐ Pre-clinical investigations of AMO-02 in DM1 were conducted using three models of Adult and Congenital DM1
  - ☐ Primary human muscle cell precursors (primary myoblasts) from Congenital DM1 patients and healthy children
  - ☐ Transgenic mouse model with skeletal muscle pathology reminiscent to Adult DM1 (HSA^{LR} mice)
  - ☐ Transgenic mouse model with skeletal muscle under-development and neuromotor defects reminiscent to Congenital DM1 (DMSXL mice)

AMO-02: Summary of Pre-clinical Efficacy in DM1 (continued)

- Conclusions from the pre-clinical investigations:
  - ✓ AMO-02 improves reduced differentiation of human myoblasts
  - ✓ Treatment of Congenital DM1 myotubes with AMO-02 corrects the total levels of BIN1 and reverses abnormal splicing of BIN1
    - AMO-02 corrects expression and splicing of multiple muscle effectors in both transgenic models
  - ✓ A single dose of AMO-02 has a positive effect on skeletal muscle histopathology in DM1 mice (HSA^{LR} and DMSXL models)
  - ✓ AMO-02 corrects the GSK3b-cyclin D3-CDK4-CUGBP1 pathway to positively impact downstream targets in brain as well as in the skeletal muscle of DMSXL mice
  - ✓ Twice weekly dosing of AMO-02 over two weeks increases grip strength in the adult female HSA^{LR} mice
  - ✓ AMO-02 improves survival and motor function in DMSXL mice

AMO-02 Phase 2 Clinical Study (AMO-02-MD-2-001): Study Design

- First clinical trial devoted to this early-onset segment of DM1 patients

- Single study site in Newcastle, United Kingdom.

- 16 adolescents and adults with congenital and juvenile-onset myotonic dystrophy

  - Ages 13 to 34 y.o.

  - Genetic diagnosis of congenital myotonic dystrophy type 1 (CDM1) since birth or since before the age of 12 years old

- 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.

- Outcome measures included plasma levels (for pharmacokinetic assessment), rating scales completed by clinicians, caregivers, and subjects, and performance-based/functional measures.

- Safety and tolerability were assessed via serial adverse event inquiry as well as serial assessments of vital signs, laboratories, and ECGs.

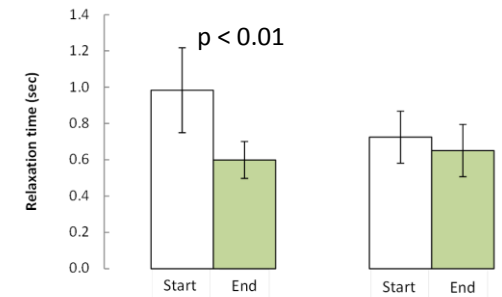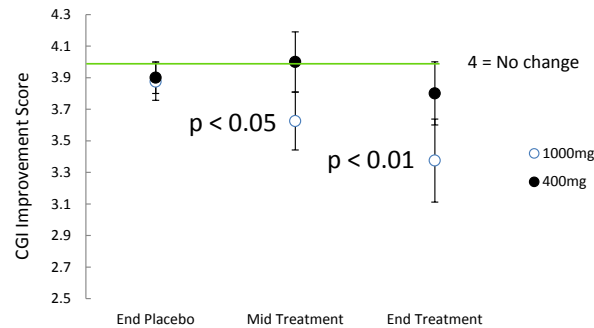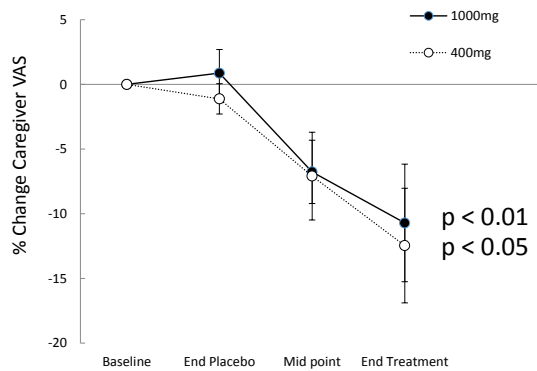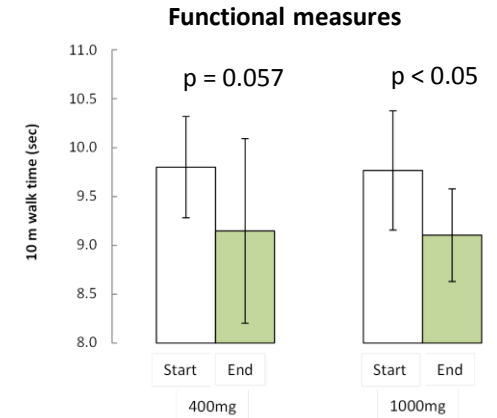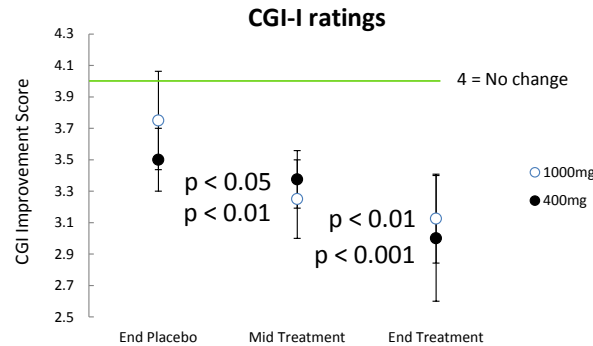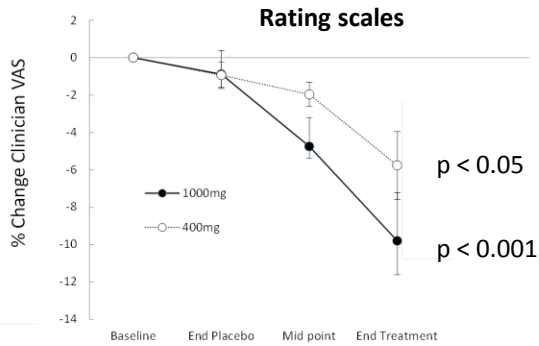# AMO-02-MD-2-001 Study: Safety and Tolerability Results

- AMO-02 was generally safe and well-tolerated, with no early discontinuations due to adverse events and no dose adjustments of the study medication were necessary.

- The most common treatment-emergent adverse event was nasopharyngitis (31%). All instances of nasopharyngitis were deemed unrelated to the study medication.

- One adverse event was deemed to be of severe intensity (knee pain in a subject taking 400 mg/day) although it was declared by the investigator to be unrelated to the study medication.

- In addition, there were no systematic irregularities in objective assessments (e.g. vital signs, ECGs, laboratory assessments).
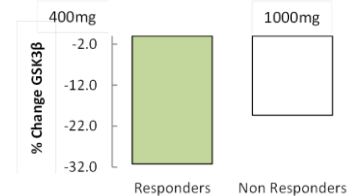
AMO-02-MD-2-001 Study: Efficacy Results

- 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.

- Phenotypic variability at baseline limited the informativeness of performance-based/functional neuromuscular assessments.

- The most informative assessments of efficacy were the clinician-completed and caregiver-completed rating scales.

- These rating scales revealed large treatment-associated effect sizes, these effects being statistically significant across the period of treatment with AMO-02.

- The treatment response data, reflected by the rating scales utilized in this study, were consistent across measures.

AMO-02-MD-2-001 Study: Efficacy Results

- **Concordant trends in 6 of 6 key endpoints with all endpoints showing superiority on drug**
  - Statistically significant changes on all endpoints for at least one dose of AMO-02
  - Numerically greater inhibition of GSK3β in responding patients

Rating scales

$p < 0.05$

$p < 0.001$

$p < 0.01$

$p < 0.05$

CGI-I ratings

4 = No change

$p < 0.05$
$p < 0.01$

$p < 0.01$
$p < 0.001$

4 = No change

$p < 0.05$

$p < 0.01$

Functional measures

$p = 0.057$

$p < 0.05$

$p < 0.01$

GSK3β inhibition

AMO-02-MD-2-001 Study: Examples of Databased Commentaries

Subject 12

- "The patient seems to be more alert"
- "From parents input, he is keeping a conversation for longer periods of time, he understands more what they tell him"
- "He started to take initiative, e.g., he changed his clothes by himself without his parents telling him to"
- "Started showing signs of affection – hugged doctor"
- "Improvement – fatigue, alert, speech, keeping a conversation"
- "He's more alert, sleeps better during the night"
- "Can walk for longer distances without complaining of fatigue"

Subject 16

- "Patient feels more energetic, less sleepy during the day and not having as many naps and she is more confident and less anxious on public situation and around strangers"
- "Patient has better concentration and better response to feedback at school and has better social interaction and less anxious around unknown people and large groups"
- "Patient – feels that her daytime sleepiness improved, is also more confident in big groups of people & is now keen to organize social events"

AMO-02-MD-001 Study: Conclusions

- These results indicate that AMO-02 may represent a potential treatment for congenital and childhood onset DM1.

- Further studies appear warranted.

- The primary clinician-completed rating scale in this study was derived from a measure previously validated in natural history and intervention studies in myotonic dystrophy.

  - It is also being validated in an ongoing natural history study in children and adolescents with congenital DM1 (NCT03059264).

  - This clinician-completed rating scale was developed with the collaborative assistance of therapeutic area experts and has been vetted and refined in collaboration with the FDA.

- The refined clinician-completed rating scale will serve as the primary outcome measure in a forthcoming Phase 2/3 registration-caliber study in children and adolescents with congenital myotonic dystrophy that will commence later this year.

A Randomized, Double-Blind Study To Evaluate The Efficacy and Safety Of Weight Adjusted Tideglusib versus Placebo For The Treatment Of Children and Adolescents with Congenital Myotonic Dystrophy

AMO-02-MD-2-003: Study Overview

- **Phase 2/3, randomized, double-blind, placebo controlled**
- **Participants**
  - Males & Females, 6-16 years old
  - Diagnosis of Congenital Myotonic Dystrophy
  - CGI-S ≥ 4

- **Enrollment**
  - Approximately 56 subjects randomized
  - Up to 10 study sites in US, UK and Canada
  - Approximately 5-10 subjects enrolled per site

- **Randomization**
  - Randomization will occur in a 1:1 manner such that each treatment group will have approximately 28 subjects
  - Randomization will be stratified by age. Subjects between ≥6 and <10 years of age, and subjects ≥10 years of age will be randomized using separate randomization lists to ensure treatment allocation is balanced between the two age groups.

AMO-02-MD-2-003: Study Design

- **Study will consist of the following phases:**
  - 2 to 4 week Screening period
  - 22 week double-blinded placebo-controlled Treatment period
  - 2 week Follow-up period or enrolment into AMO-02-MD-2-004 Extension study

AMO-02-MD-2-003: Study Endpoints

- **Primary Endpoint**
  - Clinician-Completed Congenital DM1 Rating Scale (CDM1-RS)

- **Key Secondary Endpoint**
  - Clinical Global Impression – Improvement Scale (CGI-I)

- **Secondary Endpoints**
  - Top 3 Caregiver Concerns VAS score
  - Caregiver Completed Congenital DM1 Rating Scale (CC-CDM1-RS)
  - Clinical Global Impression – Severity Scale (CGI-S)
  - DXA Scan measurement of total body lean/muscle mass

Clinician-completed Congenital DM-1 Rating Scale (CDM1-RS)

☐ The following 11 items are rated by the assessing clinician:

- ▫ Limitations with mobility or walking
- ▫ Problems with hands or arms
- ▫ Signs of fatigue
- ▫ Signs of pain
- ▫ Gastrointestinal issues
- ▫ Communication difficulties
- ▫ Impaired sleep or daytime sleepiness
- ▫ Difficulty thinking
- ▫ Myotonia
- ▫ Breathing difficulties
- ▫ Choking or swallowing issues
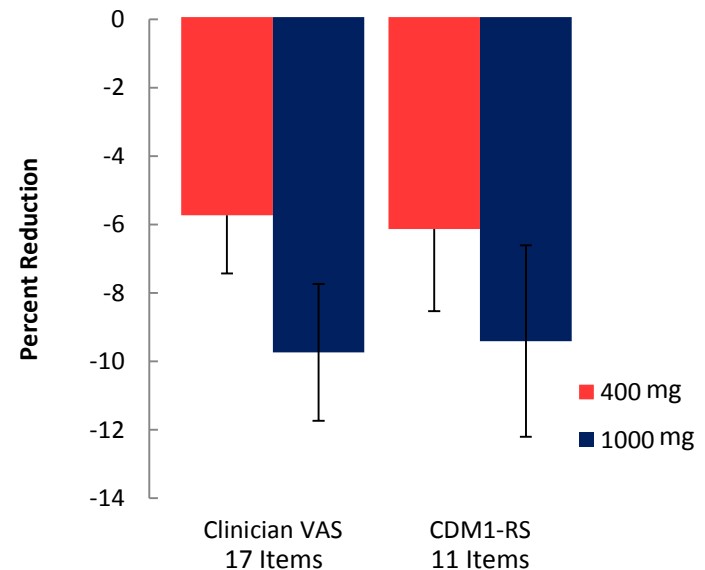
Clinician-completed Congenital DM-1 Rating Scale (CDM1-RS) (continued)

The item should be scored as 0, 1, 2, 3, or 4 based on overall severity (e.g. severity of symptoms, frequency of symptoms, context in which it occurs and functional impact).

The possible 0 to 4 rating levels for each item are:

0 = 		Symptom not present or no longer present during the relevant time frame

1 = 		Mild severity, symptom is clearly present but not pronounced, interferes little with day-to-day functioning

2 = 		Moderate severity, symptom is readily evident, intrudes on daily life to a moderate extent

3 = 		Severe, symptom is serious, markedly evident, consistently intrudes on daily life, symptom has a distinct impact on daily life

4 = 		Very severe, symptom causes pronounced and consistent impairment and is highly disruptive with regard to daily life

(The total score can range from 0 to 44)

AMO-02-MD-2-003: Study Endpoints

- **Exploratory Endpoints**
  - 10-meter walk-run test (preferred speed and fastest speed)
  - Measurement of lip strength (via lip force meter)
  - Congenital and Childhood Myotonic Dystrophy Health Index (CC-MDHI) Parent Proxy Instrument
  - Vineland Adaptive Behavior Scale – Survey Interview
  - Quantitative myometric measure of hand grip strength
  - NIH Toolbox Cognition Battery: Dimensional Change Card Sort Test
  - NIH Toolbox Cognition Battery: Picture Sequence Memory Test
  - Peabody Picture Vocabulary Test (PPVT)
  - Lymphocyte GSK-3β levels
  - Protein Biomarker and RNA Sample
  - Muscle tissue RNA (optional needle muscle biopsy)
  - Serial blood pharmacokinetics of tideglusib

# AMO-02-MD-2-003: Study Endpoints

□ **Safety Endpoints**

■ The incidence of Adverse events (AEs), including serious adverse events (SAEs), and abnormal findings between Screening and end of treatment. The incidence will also be assessed during a 2-week follow-up period after discontinuation of the study drug for those subjects not participating in the extension study AMO-02-MD-2-004.

■ The incidence of abnormal findings in objective assessments (e.g. laboratory values, ECGs, vital signs and bone mineral density) between Screening and end of treatment. The incidence of abnormal findings in objective assessments will also be assessed during a 2-week follow-up period after discontinuation of the study drug for those subjects not participating in the extension study AMO-02-MD-2-004.

AMO-02-MD-2-004: Study Overview

- **Effectively, a 32-week extension study of the preceding AMO-02-MD-2-003 study**
- **Primarily a safety/tolerability study but will utilize the same set of efficacy measures as the preceding AMO-02-MD-2-003 study**
- **Participants**
  - Males & Females, 6-16 years old
  - Have previously completed study AMO-02-MD-2-003

- **Enrollment**
  - Up to approximately 56 subjects randomized to either 600mg or 1000mg (weight adjusted)
  - Up to 10 study sites in US, UK and Canada
  - Approximately 5-10 subjects enrolled per site

- **Randomized, double-blind**
  - Randomization will occur in a 1:1 manner such that each treatment group will have up to approximately 28 subjects
  - Randomization will be stratified based on the subject's preceding treatment assignment in the AMO-02-MD-2-003 study (1000mg tideglusib weight adjusted or placebo) to ensure treatment allocation is balanced to each dose level.

AMO-02-MD-2-004: Study Design

- **Study will consist of 4 distinct phases:**
  - Eligibility Assessment
  - 4- week double-blind dose titration
  - 28-week double-blind maintenance treatment
  - 2-week follow-up period
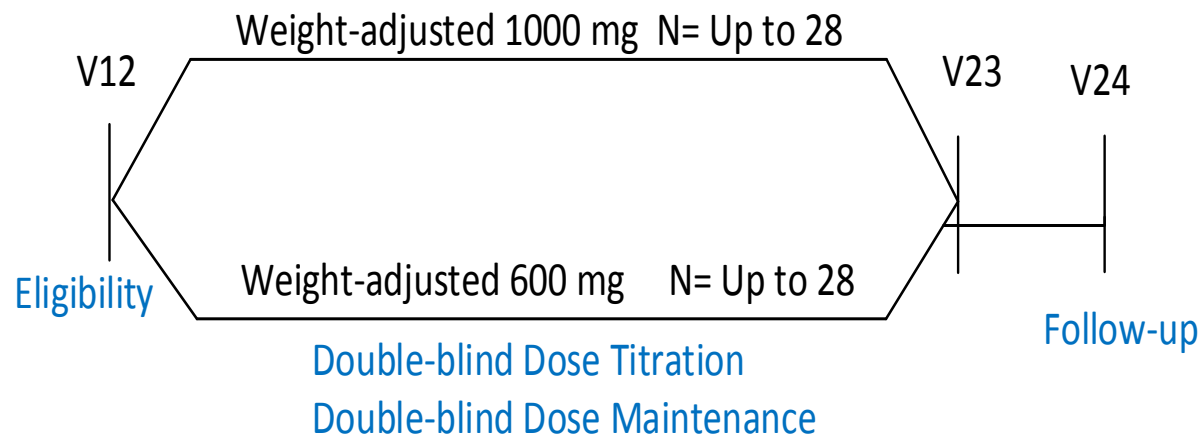
TIDE AMO-2 Autism Study: Completed in 2018

- **Congenital myotonic dystrophy is often considered to be a form of syndromal autism**

- **Therefore has similar symptoms to idiopathic autism**
  - Phase II study in idiopathic autism is a good proxy for our congenital myotonic dystrophy pivotal study

ClinicalTrials.gov
A service of the U.S. National Institutes of Health
ClinicalTrials.gov Identifier:
NCT02586935

Holland Bloorview
Kids Rehabilitation Hospital Foundation

Tideglusib vs. Placebo in the Treatment of Adolescents With Autism Spectrum Disorders (TIDE)

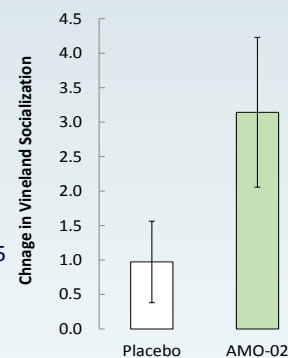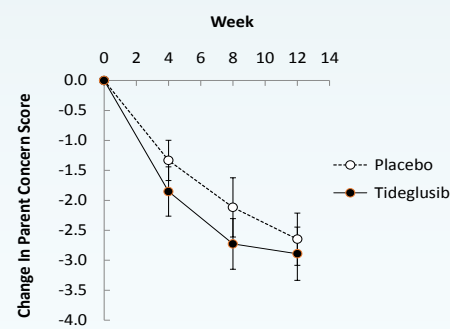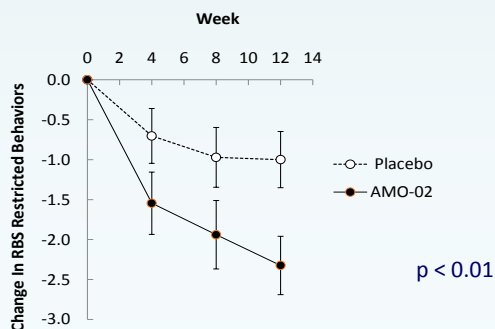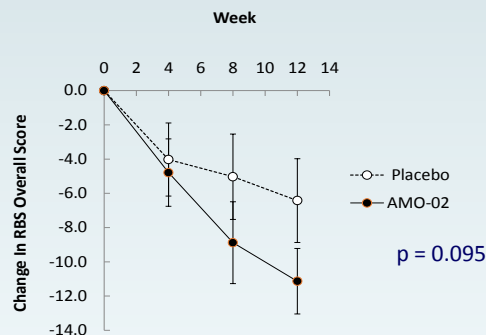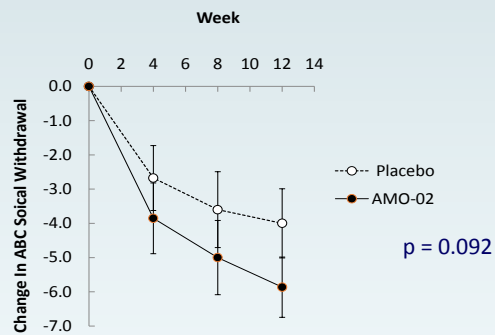| Condition	Intervention	Phase
Autism Spectrum Disorders	Drug: Tideglusib Other: Placebo	Phase 2

- **Phase 2 double-blind, placebo-controlled 1:1 parallel design**

- **N = 40 per group pediatric autism subjects**

- **12 weeks titrated dose (400 mg to 1,000 mg; oral, weight-adjusted) AMO-02**
  - Seven key outcomes

TIDE Study: Key Efficacy Endpoints and Subscales

- **Aberrant Behavior Checklist (ABC) (Primary outcome measure)**
  - Lethargy/Social Withdrawal subscale score
- **Vineland Adaptive Behavior Scales**
  - Socialization subscale score
  - Adaptive Behavior Composite subscale score
- **Repetitive Behavior Scale**
  - Overall score
  - Restricted Behavior score
- **The OSU Autism Rating Scale (OARS)**
  - Total impairment mean score

- **The Parent Chief Complaints**
  - Total score
- **Statistical analysis via Permutation test**
  - Determines the probability of observed results being down to chance
- **Biomarker analysis**
  - GSK3β phosphorylates Akt – therefore analyze phosphorylated Akt levels

TIDE Study: Efficacy Results

- **Concordant trends in 3 of 7 key endpoints with remaining endpoints showing no worsening on drug, drug consistently outperforms placebo.**

  - These concordant trends may be interpreted as early indication of efficacy/biological activity. Confirms AMO-02 adequately absorbed, crosses blood-brain barrier, engages target, and renders clinically meaningful benefit in randomized, double-blind, placebo-controlled context

- **Permutation test**

  - Determines probability of obtaining by chance alone (false-positive rate) results as good as or better than those observed in the trial under null hypothesis that drug is no different than placebo. In each iteration of the test subjects are re-randomized with equal chance of being assigned a "placebo" or "drug" label. Procedure repeated 1000 times, so should be no true difference between "drug" and "placebo" – only chance difference is possible. Counting number of iteration out of 1000 where results were as good as or better ("success") than those in the actual study, determines false-positive rate.

- **Permutation test highly significant (p<0.01). Biomarker – inhibition pAkt highly significant (p<0.001)**

Questions?