

SESSION 6B CLINICAL TRIALS AND TRIAL DESIGN

C39 CEFTRIAXONE IN ALS: RESULTS OF STAGES 1 AND 2 OF AN ADAPTIVE DESIGN SAFETY, PHARMACOKINETIC AND EFFICACY TRIAL

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Keywords: clinical trials, ceftriaxone, pharmacokinetics

Background: The study aim is to determine the efficacy and safety of treatment with ceftriaxone in ALS. Ceftriaxone increases expression of the astrocytic glutamate transporter, EAAT2 and protects from glutamate, and superoxide dismutase mediated toxicity.

Objectives: We propose a novel study design strategy of nonstop drug development. We will apply data from an intermediate analyses of cerebrospinal fluid (CSF) penetration and safety toward the development of an efficacy study. The CSF pharmacokinetics of ceftriaxone in subjects with ALS (STAGE 1) will be followed by a safety and tolerability study for 20 weeks (STAGE 2), and then a full efficacy trial (STAGE 3). The first two STAGES are complete.

Methods: In STAGE 1, 66 subjects at ten clinical sites were enrolled, equally divided into groups receiving intravenous placebo, ceftriaxone 2g or ceftriaxone 4g daily. A plasma and CSF pharmacokinetic study was conducted at day 7. All subjects continued treatment after the STAGE 1 study and entered STAGE 2. The DSMB and part of the Steering Committee reviewed the data and decided that study should proceed to STAGE 3, at 4g/day, studying a total of 600 randomized research participants at 62 centers in US and Canada. New subjects will be randomized in a 2:1 fashion to receive treatment of (1) ceftriaxone or (2) placebo. Participants will remain in study until 52 weeks after the last participant is randomized. The co-primary outcome measures are survival and rate of change in ALSFRS-R. Secondary outcome measures include change in vital capacity, evaluation of upper and lower extremity muscles using hand-held dynamometry and quality of life and the long-term safety of ceftriaxone.

Results: STAGES 1 and 2 have been successfully completed. Ceftriaxone was found to have a volume of distribution of 13.8 liters and a plasma half-life of 8.6 hours. Plasma and CSF concentrations were closely correlated. CSF trough levels at both doses (2g and 4g) exceeded the prespecified target trough level of 1 μ M. At the 4g daily dosage, modeling predicted that CSF levels would stay above 1 μ M for 72 hours, enabling consideration of drug holidays for subjects if needed. At 20 weeks of treatment, subjects from both active

treatment dose levels met the pre-specified criteria for tolerability.

Discussion: The complexity of this study has required a team of clinical investigators from several fields, toxicologists, pharmacokineticists, project managers, data managers, and biostatisticians. We successfully achieved the goals of the first two STAGES of the trial and now are proceeding with STAGE 3.

Conclusion: The novel activities of cephalosporins provide a unique opportunity to evaluate a single agent aimed at several pathways relevant to the pathophysiology in patients with ALS.

C40 KNS-760704-CL201, PART 1: A 12-WEEK PHASE 2 STUDY OF THE SAFETY, TOLERABILITY, AND CLINICAL EFFECTS OF KNS 760704 IN ALS SUBJECTS

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Keywords: KNS-760704, clinical, neuroprotection

Background: KNS-760704 is a novel drug being developed for the treatment of ALS. This was a 12-week, double-blind, randomized, placebo-controlled study to evaluate the safety and tolerability of (6R)-4,5,6,7-tetrahydro-N6-propyl-2,6-benzothiazole-diamine dihydrochloride (KNS-760704) in ALS patients. Subjects received 50, 150, or 300mg KNS-760704, or placebo daily for 12 weeks. A secondary objective was to evaluate the effects of KNS-760704 on clinical function measures including the ALS Functional Rating Scale-Revised (ALSFRS-R) and vital capacity (VC).

Methods: Key eligibility criteria were: possible to definite ALS diagnosis, ≤ 2 years since ALS symptom onset, and vital capacity $\geq 65\%$ of predicted. Concomitant riluzole at a stable dose was permitted. Safety evaluations were conducted at Baseline and Weeks 1, 2, 4, 8, and 12. Clinical function was assessed at Baseline and Weeks 4, 8, and 12. Blood samples were collected in a subset of subjects after at least 1 week of dosing for a pharmacokinetic (PK) sub-study. Subjects completing the 12-week placebo-controlled study period (Part 1) were eligible to enter a double-blind, randomized active safety extension phase (Part 2). Reported here are Part 1 study results; Part 2 of the study will be completed by Nov 2009.

Results: A total of 102 subjects were enrolled at 20 US centers; 98 subjects (96%) completed the study. Twenty-three subjects participated in the PK sub-study. There were no deaths or treatment-related serious adverse events over 12 weeks. Two subjects (1 placebo; 1 300mg) discontinued due to adverse events (AEs). There were no per-treatment-group differences in the overall incidences of AEs, treatment-related

AEs, or pre-specified clinically significant vital sign, ECG, or laboratory abnormalities. Two subjects (300mg) had reversible CTC grade II neutropenia, one of whom restarted treatment with KNS-760704 in Part 2 without recurrence. Mean/median changes from baseline to endpoint in ALSFRS-R total scores were $-3.6/-4.0$ (placebo), $-5.0/-3.0$ (50mg), $-3.3/-2.5$ (150mg), and $-2.2/-2.0$ (300mg). Relative to the decline in the placebo group, the 300mg group showed a 39% improvement in mean ALSFRS-R change from baseline to endpoint and a 50% improvement in median ALSFRS-R change from baseline to endpoint. Mean changes from baseline to study endpoint in upright VC (% predicted) were -13.1 (placebo), -10.8 (50mg), -6.4 (150mg) and -10.7 (300mg). Pharmacokinetics were linear over the range of doses tested and $t_{1/2}$ was ~ 8 hours.

Discussion: KNS-760704 was safe and well-tolerated in this study. Encouraging dose-related and time-dependent improvements in ALSFRS-R total scores relative to the placebo group observed in this study suggest that KNS-760704 may slow the rate of motor function loss in ALS subjects. Further evaluation of KNS-760704 in larger and longer studies is merited.

C41 STAR TRIAL: SUB-ANALYSIS OF AN INTERNATIONAL, MULTI-CENTER, PLACEBO-CONTROLLED STUDY OF AVP-923 (DEXTROMETHORPHAN/QUINIDINE) FOR THE TREATMENT OF PSEUDOBULBAR AFFECT (PBA) IN AMYOTROPHIC LATERAL SCLEROSIS (ALS) PATIENTS

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Background: Pseudobulbar affect (PBA, also known as pathological laughing and crying) is characterized by exaggerated/involuntary emotional outbursts and occurs in patients with degenerative and traumatic neurological conditions including ALS. Incidence of PBA in ALS patients is particularly high (up to 50%). Dextromethorphan (DM), an NMDA-receptor antagonist and sigma-receptor agonist, reduces excitatory neurotransmission and may improve PBA. Quinidine (Q) inhibits CYP2D6 isoenzyme, slowing DM metabolism producing higher and sustained DM plasma levels. The STAR Trial has been designed to evaluate the safety and efficacy of AVP-923 for the treatment of PBA in ALS and MS patients. We report here the sub-analysis for ALS patients.

Methods: Eligible ALS patients were randomized in a 1:1:1 ratio into one of the three blinded treatment arms, to receive AVP-923-30/10 (30 mg DM/10mg Q), AVP-923-20/10 (20mg DM/10mg Q) or placebo b.i.d. for a 12-week period. Patients who completed the blinded phase of the study were eligible to participate in an open-label safety extension receiving the highest dose (AVP-923-30/10 b.i.d.) for an additional 12-week period. The main criterion for eligibility was a score of 13 or greater in the CNS-LS (Center for Neurologic Studies-Lability Scale). Primary efficacy endpoint was the number of PBA episodes recorded daily in a patient's diary; secondary efficacy endpoints were CNS-LS, NPI-Q (Neuro-Psychiatric Inventory), BDI-II (Beck Depression Inventory), SF-36 (Health

Status Survey) and CSI (Caregiver Strain Index). Safety was assessed by physical examination, vital signs, clinical laboratory tests, ECGs, and oxygen saturation. Patients were asked to record any adverse experience and all medications taken in their diaries.

Results: From a total of 251 screened ALS patients, 197 (78.5%) were enrolled over a 15-month period at 68 clinical sites in USA, Argentina and Brazil. Frequent reasons for ineligibility were concomitant depression and disallowed medications. Interim demographic and baseline data are available for 148 randomized ALS patients. Gender distribution: 42% females, 58% males. Median age was 57.2 years old (Min: 25.3; Max: 75.12). Median time from ALS diagnosis at baseline was 11 months (1; 111). Median time from PBA diagnosis in ALS patients was 6 months (1; 111). CNS-LS median score at baseline was 20 (13; 35). The last patient was enrolled on 31 March 2009 with last follow-up scheduled at the end of June, 2009.

Conclusions: The STAR trial represents the largest and longest double-blind, randomized AVP-923 study to date for the symptomatic treatment by dextromethorphan/quinidine of pseudobulbar affect in ALS patients. Safety and efficacy data on primary and secondary endpoints will be available upon presentation.

C42 REGULATORY DOCUMENTS MANAGEMENT PLATFORM: EFFICIENCY, SCALABILITY, REGULATORY COMPLIANCE AND STANDARDIZATION IN CLINICAL TRIALS IN ALS

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Keywords: clinical trials management, project management, TREAT ALS

Background: The Neurology Clinical Trials Unit (NCTU) at MGH serves as Coordination Centre for The Northeast ALS consortium's Clinical Trials Network with the goal to "translate research advances into clinical trials for patients with ALS." Several multi-site clinical trials and biomarker studies in ALS are coordinated simultaneously.

Objective: To design and develop a comprehensive and customizable Web-based platform that brings efficiency, scalability, regulatory compliance and standardization in conducting clinical trials and biomarker studies.

Methods: Web-based TREAT ALS Platform was designed and built to manage clinical studies in ALS. It is comprised of several modules that allow the Coordination Centre team to:

- Collect and maintain real-time information on: site equipment and capabilities and site members qualifications
- Follow Regulatory Documents (RD) during the life cycle of a clinical trial: from trial initiation to FDA submission.

The Platform allows users to:

- Define trial-specific roles and corresponding required RD
- Identify site member participants for trial-specific roles
- Provide RD for approval and regulatory compliance
- Verify sites' RD completion and readiness

- Generate reports for missing and expired documents
- View site and trial participants readiness in Virtual Regulatory Binder
- Flag missing and expired documents
- Accelerate trials' initiation and subjects' enrollment
- Track IRB Submissions across multiple sites and protocol versions
- Reduce time spent on IRB submissions
- Track protocol deviations
- Increase accuracy of information
- Improve regulatory compliance

Results: The Regulatory Documents Management platform:

- Deployed at the Neurology Clinical Trials Unit at MGH
- Available to all member sites of the NEALS consortium
- Site and member information collected and maintained for 130 sites
- Sites notified via e-mail to update and upload missing & expired RD
- Collected site information utilized in site selection for future trials
- Improved regulatory compliance
- Ability to track site metrics
- Faster trial startup and enrollment
- Utilized for Phase III trial of Ceftriaxone in ALS (58 sites) and Phase II trial of Lithium in ALS (36 sites)

Conclusion: All new clinical research NEALS-based initiatives will utilize the TREAT ALS platform. This platform adds efficiency, standardization and regulatory compliance to the conduct of ALS trials.

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C43 THE EFFECT OF INCLUSION CRITERIA ON OUTCOMES: INTERPRETING RESULTS IN HISTORICAL PLACEBO CONTROLLED TRIALS

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Keywords: trial design, historical controls, patient demographics

Background: Using historical placebo controls could reduce sample sizes and costs, and speed enrolment in ALS trials. The WALs Lithium study is the largest to use historical controls and was designed to test the large effect reported in an Italian study on Lithium. The large response would be

easily refuted if the outcome appears only similar to historical controls, or confirmed if the outcome appears much superior. Detecting smaller effects, however, using this trial design is still challenging. Results from past trials have differed with respect to the observed rates of decline in placebo groups, and even small differences affect assumptions about what "true" rate of decline should be used for historical comparisons. Understanding what factors affect outcomes, including variations in enrollment criteria, recruitment methods, disease timing, phenotypes, and demographics, and creating mathematical models to control for differences would be a key step in the interpretation of results.

Objectives: To explain the differences in prior placebo outcomes from different ALS clinical trials; and to present novel methods for analyzing trial data in historically controlled trials.

Methods: Using our historical placebo database (containing 748 patients) we studied rates of decline among different trials, and created mathematical models to control differences in baseline patient characteristics that could have affected outcomes.

Results: Data from 4 past trials that used the ALSFRS-R slope decline as an outcome were used. We found differences in the mean distributions of slopes during the first six months of follow-up (range: -0.80 to -1.03). We found the differences had the closest correlations with predicted rate of decline, initial forced vital capacity (FVC), and the duration of symptoms since onset. Studies that set cutoffs with lower FVC or longer symptom durations found greater rates of decline than those using more restrictive criteria. In addition, individual patients with longer disease durations, higher baseline FVC, and slower pre-trial estimated decline tended to progress slower. The effect of timing was important because distributions of disease durations varied from trial to trial, perhaps due to definitions of "timing" that affected enrolment or due to differences in healthcare demographics. When corrections to slopes were made using a linear model, the differences narrowed and were no longer statistically significant.

Discussion and Conclusions: Differing enrolment criteria will affect mean rates of decline in trials, thus influencing observations of "true" slope declines in ALS. Subtle effects on timing could relate to regional differences in healthcare or study inclusion criteria. By using linear models that correct for the differences between the enrolled cohorts, the interpretation of outcomes in historically controlled trials may be improved.