# Investigation of an Adaptive Design Clinical Trial

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Society for Clinical Trials Annual Meeting

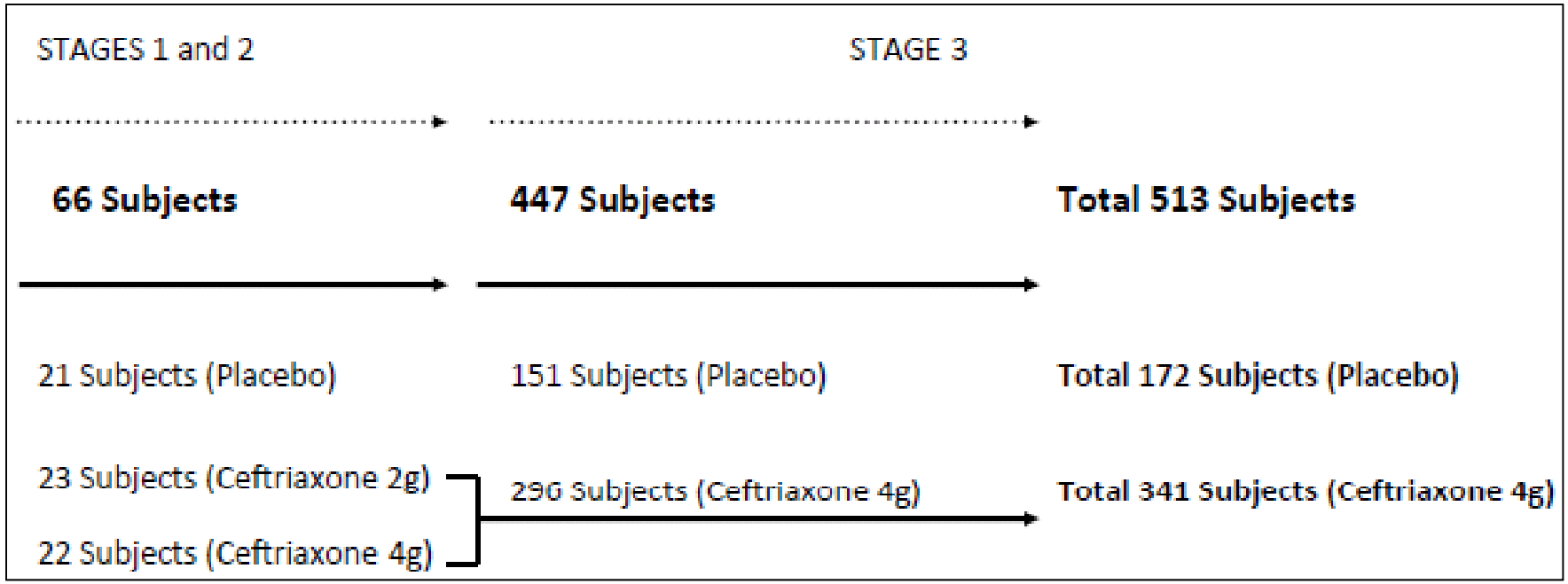
May 20, 2014

# Objective

- Review management of adaptive design study
- Look at challenges and strengths of the design
- Summarize lessons learned for future study design and management

# Ceftriaxone in ALS

- 3 phase adaptive design study
- 9 sites and 66 subjects in STAGES 1 and 2
- 58 sites and 447 subjects in STAGE 3



# Study Overview

- Study drug administered via Central Venous Catheter
  - Two infusions per day
  - Administered by caregiver in the home
- Visits every 4 weeks
- Randomization 2/3 active 1/3 placebo

# Enrollment

- STAGES 1 and 2 – PK and tolerability
  - 66 subjects at 9 sites in 1 year, 7 months

9/4/2006 - 3/19/2008 Stage One Enrollment

- 1 year, 3 months between phases

6/4/2009 – 12/14/2011 Stage Three Enrollment

- STAGE 3 – efficacy
  - 447 subjects at 58 sites in 2 years, 7 months

# STAGE 1 Site Concerns Effecting Early Enrollment

- Central Venous Catheter
  - Concerns about infections
  - Concerns about caring for the catheter at home
- Serious Adverse Events
  - Concerns about antibiotic use leading to superinfections
  - Literature suggested serious kidney issues

# Managing and Overcoming STAGE 1 Challenges

- Study nurse one on one training with experienced infusion nurses to learn proper catheter care
- Study nurses gained experience teaching caregivers to provide CVC home management
- Low rate of infection:
  - 0.24 line infections/1000 catheter days
  - 0.05 exit site infections/1000 catheter days
- Kidney stones were not common
- Gallstones found to be a significant AE
  - 24% of subjects with cholelithiasis or biliary sludge AE
  - 11% of subjects with cholelithiasis SAE

# Addressing Catheter Concerns in STAGE 3

- Training Study Staff
  - Quarterly calls with all site staff responsible for CVC training and care
  - Educate and train caregivers and subjects in line care using hands-on, written, and DVD teaching materials
- Training Participants and Caregivers
  - Administer written and practical exam to subjects and caregivers
  - Assess exit site and line for infection and change in status at each visit
- Data Showed CVC was safe:
  - Line infection 0.23/1000 catheter days
  - Exit site infection 0.12/1000 catheter days)
  - CDC predicted CVC infections: 2.9 to 11.3 per 1000 catheter days

# Ursodiol Added in STAGE 3

- Biliary AEs found to be common issues in subjects during STAGES 1 and 2 of the study
- Gastroenterologist advised on biliary issues
- Ursodiol and matching placebo added for STAGE 3
- Significantly reduced adverse events.

| CTCAE Category | STAGE 1 Events per Month | STAGE 3 Events per Month | P-value |
|---|---|---|---|
| Gastrointestinal | 0.577 | 0.137 | <.0001 |
| Hepatobiliary/ Pancreas | 0.310 | 0.081 | <.0001 |

# Sites That Participated in STAGES 1 and 2 Completed Study Start Up Tasks and Enrollment Faster in STAGE 3

- Time from protocol delivery to IRB approval averaged
  - 2.51 months in the 9 sites that participated in STAGE 1
  - 5.21 months in the 49 STAGE 3 sites
- Time from protocol delivery to STAGE 3 site activation averaged
  - 3.60 months in the 9 sites that participated in STAGE 1
  - 8.93 months in the 49 STAGE 3 sites
- Enrollment Rates in STAGE 3
  - 0.40 subjects/site/month in the 9 sites that participated in STAGE 1
  - 0.28 subjects/site/month in the 49 STAGE 3 sites

# Conclusions

- STAGE 1 sites were able to complete start up tasks more efficiently
- Able to enroll more subjects and serve as leaders throughout the three-phase study
  - Experience with CVC
  - Familiarity with protocol and operationalizing a difficult trial
  - Subjects enrolled in STAGE 1 served as references for new subjects
  - Invested in study
- Future studies – Intrinsic value in including a group of sites throughout all phases
  - Learning opportunity for Coordination Center and Sites

# Conclusions

- Three phase adaptive design led to unique challenges
  - Flexibility of funder to provide funds for unanticipated challenges
  - Subjects continued from STAGE 1 to STAGE 3 and continued taking study drug during that period
  - Retention issues
  - Unable to share data from STAGES 1 and 2 during STAGE 3 recruitment

# Acknowledgements


- NINDS
- Ceftriaxone Study Sites
- Dr. Merit Cudkowicz, MD, MSc
- Dr. Jeremy Shefner, MD, PhD

Questions?

THANK YOU!