BMS-927711 for the Acute Treatment of Migraine: A Double-Blind, Randomized, Placebo Controlled, Dose-Ranging Trial

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Migraine: Case Study of an Adaptive Design

- Migraine - episodic headache lasting 4-72 hours
  - Associated symptoms include nausea, vomiting, photophobia and phonophobia
  - Affects 12% of population (3:1 women to men)
  - Treatment: Triptans, NSAIDs and Excedrin
- Adaptive designs have been successfully used by Merck and BI migraine programs
- Study examines a novel mechanism: calcitonin gene related peptide (CGRP) receptor antagonist
Case Study CN170-003: Phase 2b Study: Objectives

- Evaluate the relative safety, efficacy and dose response of 6 different oral doses of BMS-927711 vs. placebo in patients with moderate to severe migraine
- Explore the full dose-response range
  - Ensure adequate sampling of lower doses
  - Reduce randomization to ineffective doses
- To efficiently select doses for Phase 3
Case Study CN170-003: Study Design

- Randomized, double-blind, placebo and active-controlled, parallel group, outpatient study
- Single headache
- Dose Groups
  - BMS-927711 10mg, 25mg, 75mg, 150mg, 300 mg, 600mg
  - Placebo
  - Sumatriptan 100 mg
- Primary endpoint – pain relief at 2 hours
- Fixed 1:3 randomization ratio for placebo versus other treatments used to reduce placebo response rate
Study Schematic

Screening/Baseline Phase

- Screening Visit
- Randomization

Acute Treatment Phase

- Treatment (Treatment of one migraine of moderate or severe intensity)
- Evaluation* (30 mins to 48 hours post dose)

End of Treatment Visit

- Within 7 days of treatment

- 3 - 28 days

* Data collection via electronic diary

Treatment of migraine must occur within 45 days of randomization
Other Features of the Design

• “Chase the Winners”
  – Subject allocation ratios increased for arms the model estimates to have good response rates
  – Arms can be closed down, and reopened later

• After 550 patients - possibility of early stopping
  – Early stopping based on strong evidence of success or failure

• Possibility of a formal Interim Analysis
  – Triggered by modest evidence of efficacy
  – Would not stop the study
  – Used to select effective doses for phase III
Adaptive Design: Taking the Plunge

Statistical
**Adaptation Process**

**Bayesian with Weekly Adaptation**

- **Randomizer**
  - Randomize to placebo, suma’ or BMS-’711

- **Data Interface**
  - Single Migraine
  - Data collected / processed

- **Predictive Model**
  - Estimate dose-response curve

- **Dose Allocator**
  - Weight randomization to doses most informative about ED90* & MED**

- **Terminator**
  - Decision rule
    - Continue
    - Early Stop
      - Success or Futility

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* ED90 – is the dose that attains 90% of maximal efficacy response
** MED – “Minimum Effective Dose” – Smallest dose with efficacy 15% above PBO
Randomization

- **Burn-in Period:** 336 patients
  - 84 patients to placebo
  - 36 to Sumatriptan
  - 36 to each of the 6 BMS-927711 doses
    - 12 blocks of size 28 (7:3:3:3:3:3:3:3)

- **Adaptive Phase:**
  - 2 of each 8 patients to placebo
  - 1 of each 8 to Sumatriptan
  - 5 of each 8 to the 6 BMS doses
    - Block size of 32. 8 to PBO; 4 to sumatriptan; 20 to BMS-927711
Study Design Process

- Iterative process that included Clinical, Biostats, Clinical Operations, Clinical Drug Supply, and external consultants
- Many different types of designs were evaluated: (e.g., group sequential, response adaptive)
- Required several months
- For the response adaptive alternatives, analytic estimates of power and type-I error are not tractable
  - Operating characteristics were evaluated through extensive simulations
  - Evaluating a single, response-adaptive design requires many hours of computer time
  - Interpretation of the output also requires time
Final Design - Scenarios Evaluated by Simulation

**Linear**

- Response vs. Dose
- Linear relationship

**Plateau**

- Response vs. Dose
- Plateau effect

**U-Shaped (inverted)**

- Response vs. Dose
- U-shaped curve, inverted
Mean Allocation for Linear, Plateau and U-Shaped Scenarios

Linear

Plateau

U-Shaped
Adaptive Design: Taking the Plunge

Procedural

Logistical
• Data flow outside of BMS systems
  – Data collected as electronic, patient reported outcomes (e-PRO)
  – Nightly upload of e-PRO devices to Invivodata
  – Weekly data transfers from Invivodata to Tessella for analysis
    – Early stopping and interim analysis evaluated
    – New randomization probabilities generated
  – Analyses from Tessella reviewed by Berry Consultants
  – Randomization probabilities were sent directly to the BMS IVRS group
• Possibility of an interim analysis at any time required constant data cleaning
Taking the Plunge:
Drug Supply

- The study medications were packaged as 4 pills, placed in 3 bottles, packaged in one kit
  - Only 2 kits of each type were kept in stock at each site
- Resupply was done on a just-in-time basis through express shipping
- Patients were screened, and then randomized two days before their “randomization” visit.
  - This kept the drug supply ahead of randomizations
Results
Primary Endpoint
Pain Freedom at 2 hours Post Dose

Nominal p-values from CMH tests against placebo and sample size shown beneath the bars.
Summary of Clinical Results

• Superiority over placebo demonstrated
• Overall efficacy profile similar to sumatriptan 100 mg (underpowered to make direct comparisons)
• Dose response demonstrated, with a plateau from 75 mg- 600 mg taking into consideration the totality of the efficacy data
• Well tolerated with an acceptable tolerability and safety profile
Lessons Learned

• Data Management
  – Integration of data flow from subjects and between external vendors, without passing through BMS systems.
    ▪ ePRO Device ➔ Invivodata ➔ Tessella
  – Dosing data were recorded in ePRO. The patients had to enter number of pills taken from each of 3 bottles
    ▪ Reconciliation was an issue
Lessons Learned

• Design of this complicated adaptive study took several months longer than a typical study
  • Greater efficiency will come with increased use of adaptive design
  • Simpler adaptations (e.g. sample size re-estimation) should take less time
• Rapid enrollment pushed timelines forward by 2 months
  • Team managed a “slow down of enrollment”, limiting each site to 3-5 screened patients per week
• Management of IVRS and Drug Supply
  • Just-in-Time Drug Supply
  • Patients randomized in IVRS 2 days prior to arriving for baseline visit
  • Minimized waste
Benefits of Adaptive Randomization in CN170-003

- Design allowed a richer exploration of the dose-response relationship than could have been achieved using fixed sample size alternatives
  - Relative to fixed alternatives, this design allowed for the examination of at least two more doses
  - Burn-in period assured a minimum of $n=36$ subjects per treatment arm
  - Study went to full enrollment.
    - Consistent with simulations for U-shaped dose-response scenarios
    - Other dose-response scenarios would have allowed the same richness of exploration with a smaller sample size