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Adaptive Design in Phase 2: Potential Treatment for Insomnia Disorder

Margaret Moline, PhD
Senior Director
International Project Team Lead, E2006

Challenges When Developing Sleep-Promoting Drugs

- Insomnia not one symptom type
  - Difficulty initiating sleep, maintaining sleep, waking too early
  - Combination of types
- Drug should work well on the first night and in the longer term, without potential for tolerance and dependence following repeated use
- Sleep-promoting effect needs to last across the night, but not into the morning
  - FDA focusses on potential for residual morning sleepiness, especially for morning driving
- Balance between efficacy and safety critical

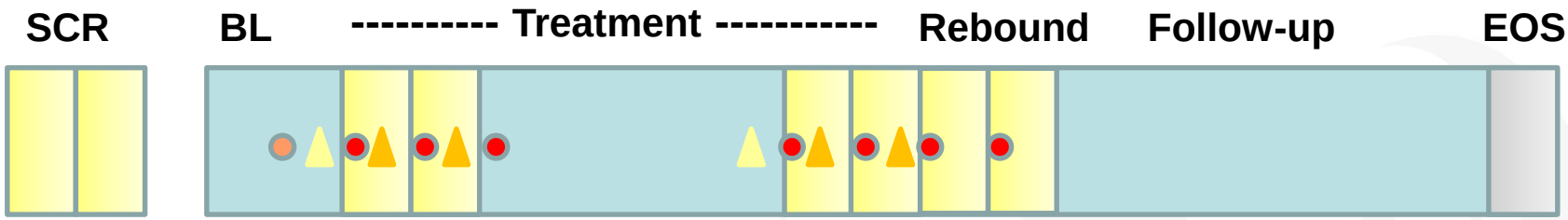
Phase 2 Study Planned after POC Achieved in SAD Study

- Program needed to accelerate development
  - Second in class
  - Preserve patent life
- Sleep studies amenable to adaptive design approach
  - Fast recruitment
  - Objective, rapidly reporting endpoints permitting IAs to occur frequently
- Advantages over traditional crossover for Phase 2 sleep compounds
  - More subjects enrolled onto doses likely to be used in future studies
  - More doses studied concurrently
  - Can stop early for success or futility, hence saving time, subjects exposed and resources

2 Primary Objectives Used to Identify Doses for Phase 3

- Identify a dose or doses of E2006 that maximize efficacy and minimize next-day residual sleepiness in subjects with chronic insomnia at the beginning of treatment
  - Comparing the effect of 6 doses of E2006 with placebo using a ***composite utility function*** incorporating change from baseline on sleep efficiency (SE) and change from baseline on the Karolinska Sleepiness Scale (KSS) at 1 hour after morning waketime after dosing on D2/D3
- Compare the effect of 6 doses of E2006 with placebo on the KSS at 1 hour after morning waketime D15/D16 in subjects with chronic insomnia
  - Confirms that doses identified in first primary objective are not associated with an emerging signal of sleepiness

A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, *Bayesian Adaptive Randomization Design*, Dose Response Study of the Efficacy of E2006 in Adults and Elderly Subjects with Chronic Insomnia



Placebo
E2006 1 mg
E2006 2.5 mg
E2006 5 mg
E2006 10 mg
E2006 15 mg
E2006 25 mg

All Placebo D16/17 for Rebound Insomnia Assessment

= 8h PSG recording

= KSS/DSST/RTI (morning residual sleepiness)

= POMS/WFB (mood and daytime functioning)

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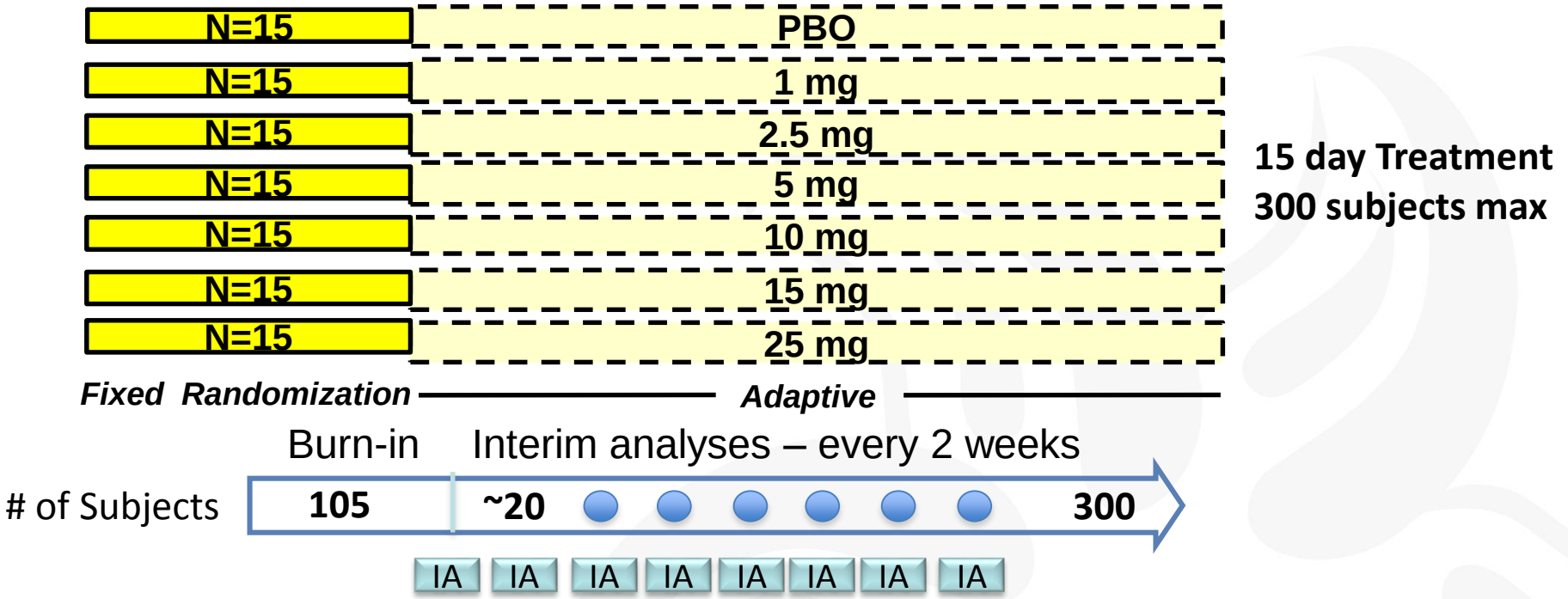
Development of the Primary Objectives

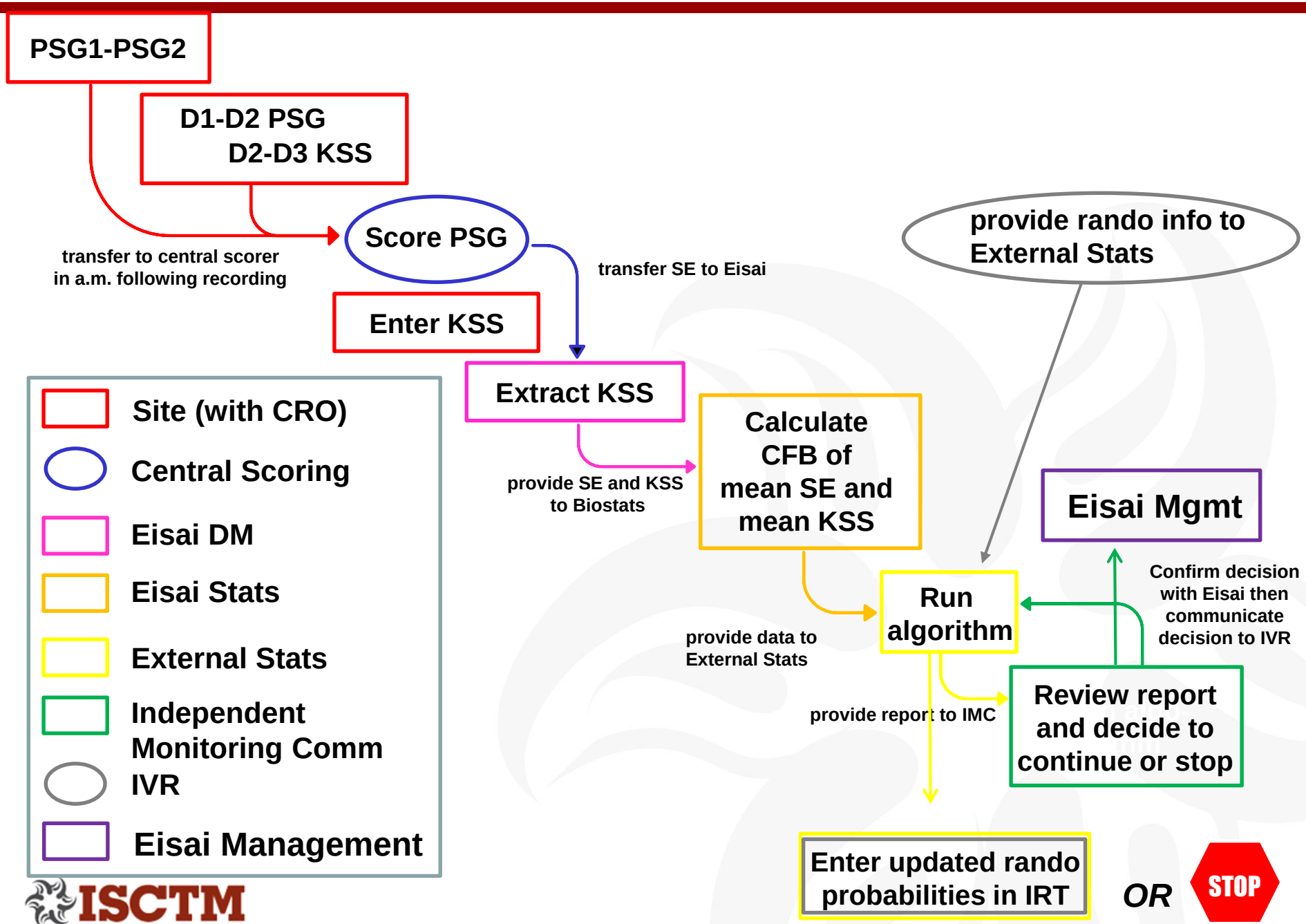
- First Primary Objective
  - SE used as it combines LPS and WASO endpoints
  - D1/D2 used to show an immediate effect on efficacy
  - KSS evaluates subjective sleepiness, so clinically very important to assess residual morning sleepiness
  - Utility function developed to combine the above
    - Defined minimally clinically significant CfB for SE (D1/D2) and KSS (D2/D3)
      - CfB compared to placebo was considered to be 6% for SE and 4 units for KSS
      - Simulations produced to review possible different dose response scenarios
- Second Primary Objective
  - KSS on D15/D16 determined if residual sleepiness present after dosing for 2 weeks
  - KSS for D15/D16 acceptable if the lower boundary of a 90% confidence interval was less than 4 units (mean difference of CfB in KSS 1 hour after waketime of dose relative to placebo)
  - *Study could not stop for early success if the above definition of acceptable KSS was not met*

Operationalizing the Adaptive Design Process



At each Interim Analysis (IA)

- Analyze current study data
- Assess for early success of a dose or futility of all doses
- Update randomization allocations
- RAR = Response Adaptive Randomization



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Bayesian Adaptive Design
Response Adaptive Randomization

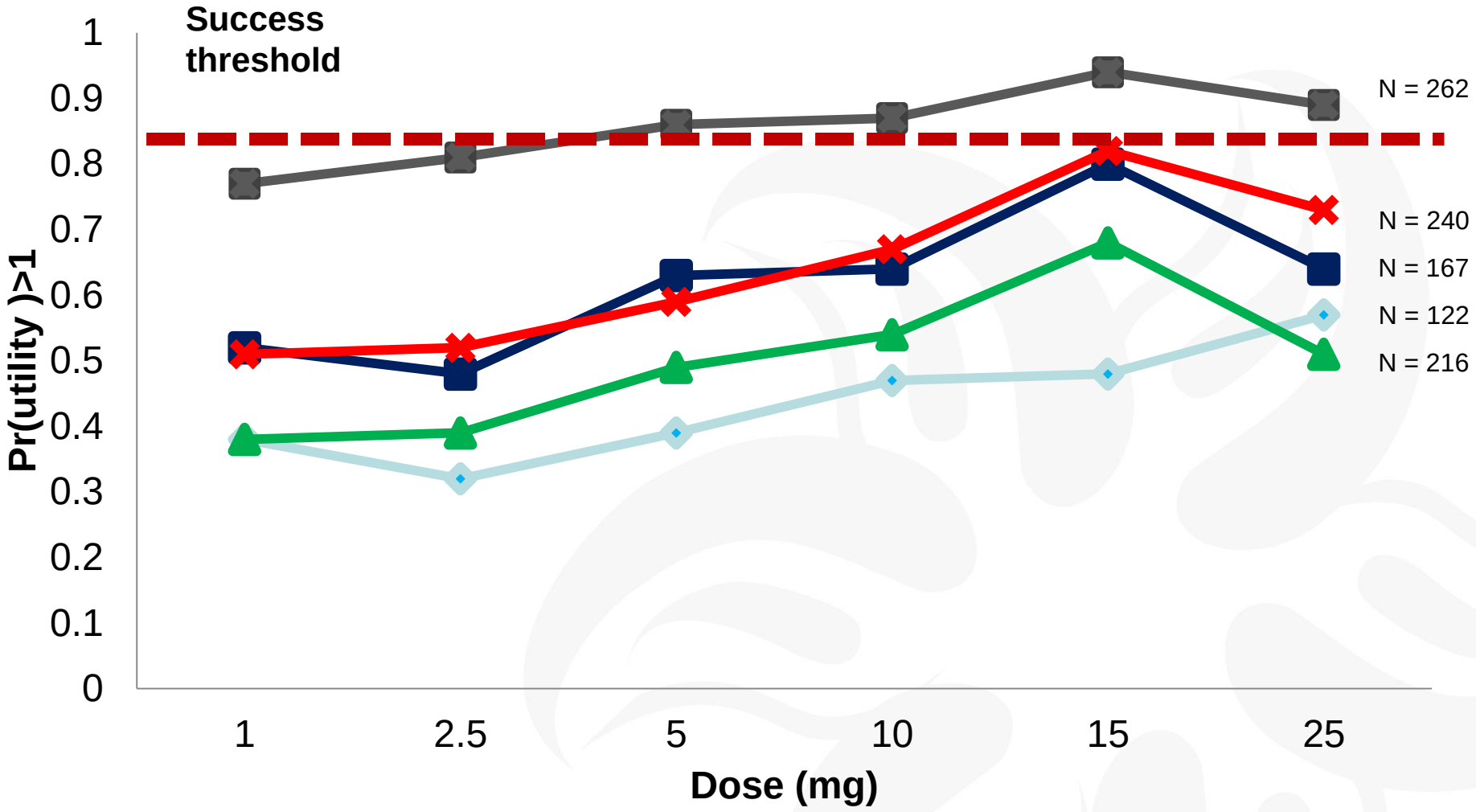
- Adaptive design study used accrued data reviewed on an interim basis by an independent monitoring committee
- Decisions made in a blinded manner
  - Sponsor, investigators, sites and patients will be completely blinded to the interim analyses
- Utility definition: Utility function balancing efficacy and safety determined that a dose had utility if

  SE ≥ 5% higher versus placebo

  and

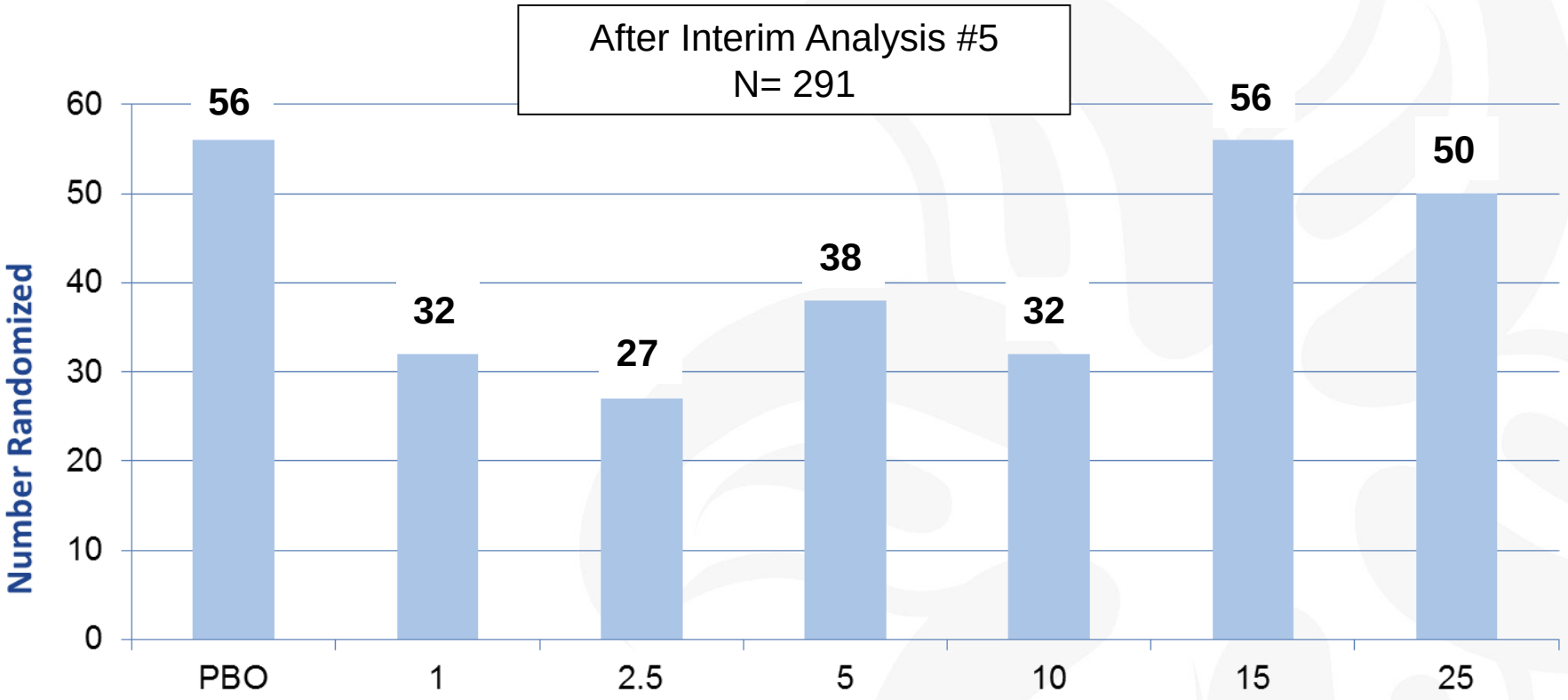
  KSS ≤ 4 points higher than placebo
  - Interim analysis on available data for these endpoints every 2 weeks
  - When a given dose reached 85% probability of being a dose with utility >1, study would stop for success
  - If not stopped, randomization adapted according to utility of dose, with more subjects allocated to 'better' doses
  - By the 5th interim analysis (n=262), the study stopped for success
    - At that time all doses above 5 mg met the 85%
  - Final Bayesian analysis (n=291), all doses except 1 mg met the threshold for success
- Early futility threshold
  - If there was <20% probability that the "best" dose has sufficient utility

Probability of Success at Interim Analyses



Response Adaptive Randomization

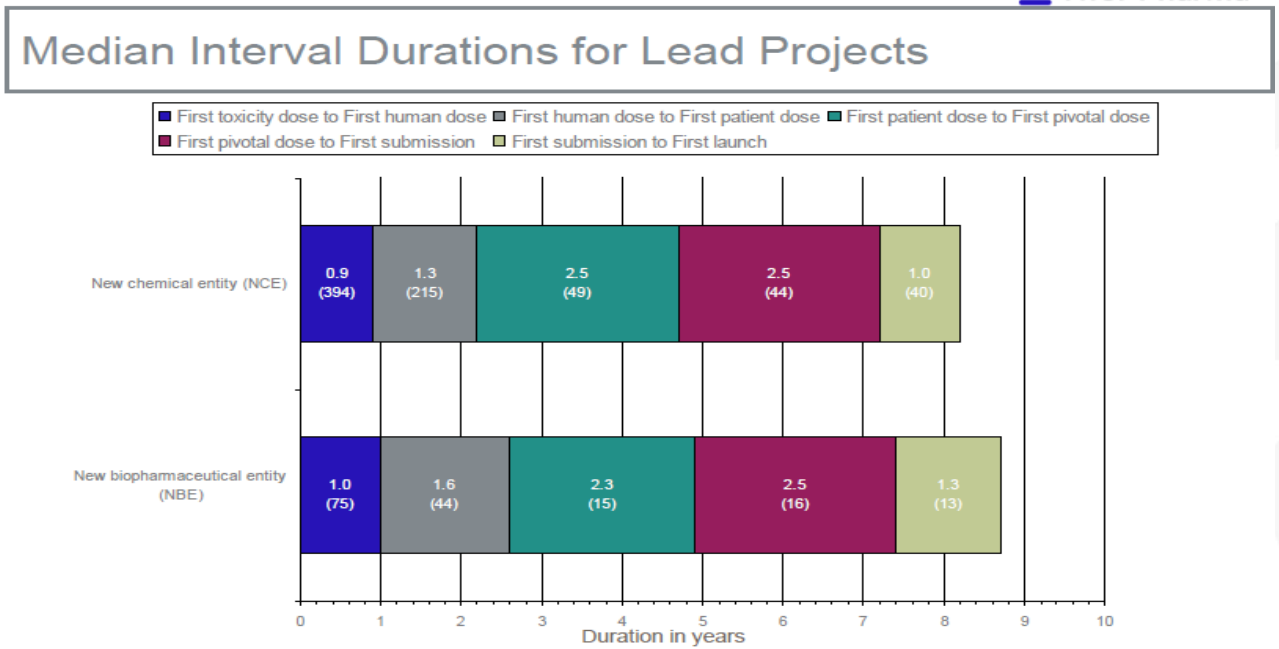
- Resulted in different number of subjects allocated to each dose



Important Time Savings

- Phase 2B: First subject dosed to meeting success criteria was 16.5 weeks (27 weeks: FPI to TLGs)

Vifor Pharma



Composite profiles are created by combining values for each interval completed by lead projects during 2004-2008. n = interval duration in years, (n) = number of lead projects that completed each interval, where the start and end milestone dates for the interval are available. Data are shown where (n) ≥ 3 for the first three intervals. Each interval represents a different cohort of projects. For explanation of the composite profile refer to Appendix 1.

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Lessons Learned

- Need to ensure recruitment and enrollment is appropriately paced to avoid issues with next IA
  - Recruitment that is too rapid could be problematic
  - Study based IAs on time - every 2 weeks - rather than # of subjects to account for uncertainty in recruitment rate
- Processes for each IA must be conducted on time to avoid compromising next IA
  - Testing each step of the adaptive process in a dry run is critical
- Understand that not all data will be cleaned by the time of the IA
  - Focus on key variables

Conclusions

- Novel design allowed for wide dose range to be tested concurrently without issues inherent in typical Phase 2 crossover designs
- Doses successfully identified for Phase 3 program
- Rapid progression to full development milestone