ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Adaptive Design Workshop

ISCTM Autumn Meeting 2012

Marina del Rey, California

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Working Group Members

Radhi Abdulnabi Vlad Dragalin
Jean Dries Ginger Haynes Judy Kando
Justine Kent Pilar Lim John March
Olga Marchenko Tom Parke
Jose Pinheiro Joanne Severe Ibo Turkoz
Norris Turner Peter Zhang

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Study Proposal

- Study Design:
  - Multicenter
  - Double-blind, randomized, placebo-controlled
  - Parallel-group
  - Dose-response study in male and female subjects with schizophrenia
  - Multiple fixed doses of Compound X as a monotherapy after 6 weeks of treatment in subjects with schizophrenia
- Primary objective:
  - Evaluate the efficacy via change from baseline in the total Positive and Negative Syndrome Scale (PANSS) score
  - Minimal effectiveness = 10 point difference from placebo (SD = 20)

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Treatment of Schizophrenia

INCLUSION

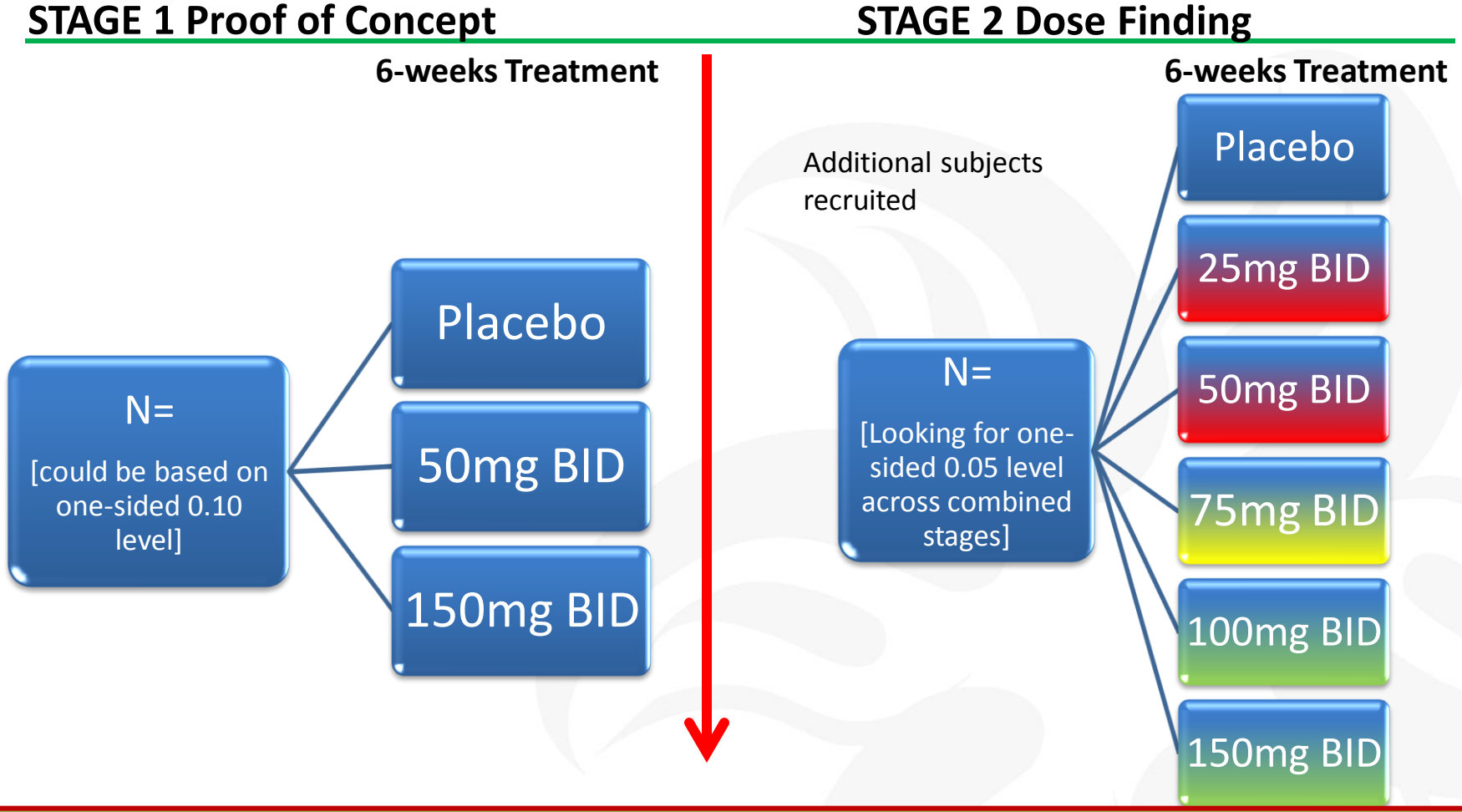
- Diagnosis of schizophrenia
- Male or female, age 18-65
- PANSS total score range 50-120

EXCLUSION

- DSM-IV diagnosis other than schizophrenia
- Dx of Substance Dependence within 6 months of screening
- Significant or unstable medical condition
- Previous or current use of clozapine due to treatment resistance
- Documented hx of no clinical response to 2 or more antipsychotics
- Significant risk of suicidality or violent behavior

Possible Phase II Study Design

Can we combine Phase II A and B?



Transition: Drop/add doses depending on efficacy. If 50mg BID cannot be differentiated from Placebo, then in STAGE 2 drop 25mg BID and 50mg BID

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Adaptive Design

Pros

- More efficient
  - Shorter duration
  - Fewer patients
  - More likely to demonstrate an effect of a drug if one exists
- Ability to use predictive probabilities and to build hierarchical models
- Use historical data *and* available patient information generated in the trial
- Can evaluate broader dose-response relationship

Cons

- Making many decisions during a trial can increase the chance of making a wrong decision
  - Abandoning a dose too soon
- Designs can be complicated
- Time and cost of running simulations
- Operational challenges (i.e., availability and distribution of doses)
- Need electronic data capture
- Unsure of acceptance by key individuals/regulatory bodies

Barry DA. *Nature Reviews* 2006
FDA Draft Guidance for Industry on Adaptive Design Clinical Trials for Drugs and Biologics. Feb 2010

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Compare 2 Designs

1. Fixed design of 2 separate trials, a 2a and 2b.
   a) Test 2 doses in 2a to determine whether to continue and which doses to test in 2b
   b) Test 2 doses in 2b – either low set with 150 mg (25mg, 50mg & 150mg) or high set (100mg & 150mg)
   c) Choose minimum effective dose (MED) from 2b to take to phase 3
2. Adaptive design of 'seamless 2a/2b',
   a) Start testing 2 doses
   b) Then open up other doses
   c) Adapt allocation to target 'MED'
   d) Allow early stopping for futility or success