Drug Development Program for an Acute Clinical State:

Esketamine for Major Depression with Suicidal Intent Example

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Disclosures

- Former employee at FDA
- Former employee at Janssen R&D (J&J)
  - Hold some J&J stock
- Advisor to the esketamine team while at Janssen

Drug Development Programs

- All drug development programs:
  - Involve the creation of a development strategy and the clinical trials to support the strategy
  - Consider a multitude of aspects in creating the development program and clinical trials
  - Determine specific components based on the particular context
- Phase 3 trials are the typical culmination of the clinical trials for the program

Drug Development Elements Evaluated in Planning

- Indication - Objective
  - First disorder indication for new drug
  - New disorder for already approved drug
  - New population for already indicated disorder
  - Expanded benefit claim for existing indication
  - No approved drugs vs existing approved drug as model for this development program
- Clinical aspects of disorder
  - Time from onset of disorder; of targeted state of disorder
  - Acute vs Chronic clinical state for treatment
    - Duration of acute clinical state (self limited vs ongoing or escalating)
  - Severity of clinical state
  - Manifestation targets for benefit
    - Chief manifestation for benefit (Primary objective)
    - Additional manifestations for additional benefits (secondary objectives)
    - Likelihood of drug substantially affecting each manifestation
- Clinical Response aspects
  - Clinical objective during treatment
    - Improvement of acute state vs stabilization?
  - End of administration expectations or concerns
    - Return to baseline pre acute event
    - Stable but not full remission
    - Potential for rebound
  - Durability of benefit for chronic Tx
- Treatment regimen
  - Dose(s) to study
  - Route of administration
    - IV, SQ, Oral, Intranasal, Inhaled
    - Consideration clinical practice setting for suitability of route
  - Number of administrations
    - One time
    - Multiple
      - Limited course (?duration)
      - Chronic
    - Interval between administrations
- Clinical Study Design Aspects
  - COA Measurement of each manifestation
    - Sensitivity of each COA
    - Clinical interpretability of each COA
    - Relationship of COAs to eligibility criteria
  - Likelihood for showing benefit with selected COA
    - Both COA sensitivity and expected size of Tx effect
  - Duration of study
    - Practical constraints
    - Clinical responsiveness of each manifestation of interest
  - Regulatory status of the COAs
    - For specific benefit type, disorder, population
  - Endpoint definition and analysis methods

Clinical Disorder Aspects

- Identification of Target Clinical disorder
  - Major depression with severe suicidal ideation
    - Acute event within MDD population
  - Patients have both substantial severity of depression and high level of suicidal ideation
    - Mini-Intn'l Neuropschiatirc Interview (MINI) questions B3 & B10
  - Serious clinical event
    - SOC: psychiatric inpatient hospitalization and initiation or adjustment of oral antidepressants
    - Serious nature -- cannot test esketamine vs SOC; only as add-on to SOC

- Background context
  - Planned as second target indication for esketamine
    - Treatment resistant depression intended as first approval for esketamine.
  - Many years of history with ketamine had shown prompt effect on depression in this population and on suicidal ideation severity
  - Phase 2 study with esketamine had also shown depression & suicide ideation effects

Treatment Regimen Component

- Treatment regimen
  - 84 mg esketamine intra-nasal
  - Administer twice per week
  - Continue for 4 weeks

- Background
  - TRD indication found 56 and 84 mg were effective
    - ❖No limiting safety issue of 84 vs 56 mg
    - ❖Selected higher dose for potential of greater effect (size and/or %)
  - Prior known experience with ketamine and esketamine indicated that effects on depression can last for 5 days (or more) after administration
    - ❖Twice /wk is practical frequency for clinical practice
  - Esketamine not intended as chronic Tx for this indication
    - ❖4 weeks of study Tx allows time for SOC oral antidepressants to achieve effects

Clinical Study Duration Component

- Duration of phase 3 study
  - ➢ Study includes follow up after investigational treatment complete for 9 weeks

- Clinical care context
  - ➢ Prompt rebound of suicidal ideation would be a serious harmful feature of a treatment
  - ➢ Durability of decrease in suicidal ideation under continuation of SOC only needed to be understood
    - ❖Would periodic repeat course of esketamine be necessary?

Clinical Manifestations Aspect

- Clinical manifestations to target for benefit
  - Depression
  - Suicidal ideation

- Context
  - These are the two chief clinical problems for patients in the identified population
  - Precise level of “suicide risk” is not determinable
  - Demonstrating benefit on suicide rate is not practical

Study Endpoint Elements

- Endpoints
  - Selected depression as the primary endpoint
  - Selected suicidal ideation as the first secondary endpoint
  - Other endpoints and data analyses to evaluate include:
    - Rebound promptly after end of treatment
    - Durability of effect
    - Rapid onset of effect

- Context
  - Prior experience with ketamine and esketamine shows depression reliably affected with robust effect
  - Well understood COA for depression – MADRS
  - New COA needed to be developed for assessment of suicidal ideation with sensitivity to rapid effects
  - New COA only previous use in blinded controlled study was small phase 2 study

Esketamine Phase 3 Studies (ASPIRE I & II)

- Major Depression , MADRS >28
  - And need acute psychiatric hospitalization for suicidal ideation
- Placebo controlled randomized trial; 4wks blinded study Tx
  - Follow up with no study-Tx x 9wks
  - Inpatient care ~5 days, + oral antidepressants per investigator
  - Esketamine 84mg intranasal 2/wk x 4 wks or bittering agent in placebo
- Outcome Assessments
  - MADRS
  - SIBAT (includes CGI-SS-r)
  - At 4hrs post dose 1, 24 hrs, 2/wk (at study visits) through week 4
    - 2/wk decreasing to q2wks during wks 5-13 f/u period
- Endpoints
  - Primary: Change in MADRS at 24hrs
  - Secondary: CGI-SS-r change at 24 hrs
  - Other secondary: Add'l analyses of MADRS, CGI-SS-r data
    - Includes 4hr assessments and durability assessments

Study Results Summary (ASPIRE I)

- MADRS change at 24hrs
  - Mean change -12.7, -16.5 Pbo – Esketamine
    - From baseline MADRS median 42
  - Statistically significant difference in means
  - Difference generally maintained through wk 6.5
    - Fades to no difference although missing data confounds interpretation after wk4
  - No suggestion of rebound or prompt loss of benefit as oral AD takes over.

- CGI-SS-r change at 24 hrs
  - Median change -1 both groups, no statistical difference in means (ANCOVA on ranks)
    - From baseline CGI-SS-r median 4 (0-6 scale)
  - Exploratory analysis of 24 hrs data indicated odds of improvement ~ 1.9 Esket:Pbo
  - FDA other analyses also suggestive of benefit at 24hrs; not substantial evidence
  - 4hr data suggests distinct benefit for Esketamine that substantially dissipates by 24hrs
  - Phase 2 data supported expectation of suicidal ideation benefit