Clinical Trial Design Considerations for Novel Therapies in Patients Showing Inadequate Response

L Alphs, MD, PhD[1], R Anand, MD[2], R Hartman, PhD[3], SM Graham, PhD[1], U Atmuri, MS, MPharm[1]

[1]Newron Pharmaceuticals US, Inc., Morristown, NJ, USA, [2]APC, AG, St. Moritz, Switzerland, [3]NeurWrite LLC, Morristown, NJ, USA

METHODOLOGICAL QUESTION

- Many recently failed large trials with NCEs in patients showing inadequate response to standard treatment have led many companies to abandon schizophrenia drug development.
- ***What changes in trial design are important to increase the likelihood of success for novel treatments of schizophrenia?***

UNMET NEED

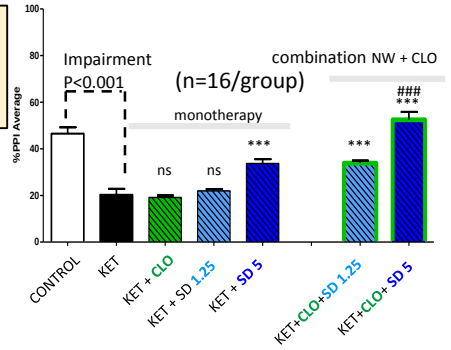
- Neuroimaging and neurotransmitter studies suggest that changes in glutamate may precede the symptoms of schizophrenia in the presence of normal dopamine levels.
- In contrast, patients who respond to antipsychotics demonstrate increased dopamine and normal glutamate levels.
- Findings suggest that glutamate modulation may have value for improving symptoms in SCZ patients with poor response to atypical antipsychotics.

PRECLINICAL PHARMACOLOGY

- Study Drug (SD) blocks voltage-gated sodium channels leading to dose-dependent inhibition of stimulated release of glutamate release
- No effect on basal glutamate release.
- Pharmacologically specific, with no affinity for over 130 different neurotransmitter receptors, ion channels, transporters and kinases.

THE COMBINATION OF INEFFECTIVE DOSES OF CLOZAPINE AND STUDY DRUG REDUCES KETAMINE-INDUCED DETERIORATION OF PPI

KET: Ketamine: 10 mg/kg, SC
SD: Study Drug 1.25 - 5 mg/kg, PO
CLO: Clozapine 3 mg/kg, IP
Statistics: 3-way, repeated-measure ANOVA; ***P<0.001 vs KET; ### P<0.001 vs NW 5 (Tukey's post-hoc))



EARLY HUMAN PHASE 2 EXPERIENCE

- Double-blind, placebo-controlled, randomized, 4-week study evaluating safety, dose-titration, and preliminary evidence of efficacy of evenamide in previously responding schizophrenia patients on stable doses of risperidone or aripiprazole.

TABLE 1. PHASE 2 STUDY EFFICACY

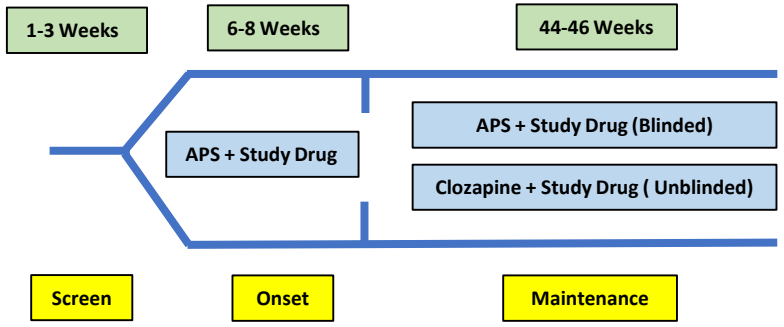
Measure	Control N = 39	Study Drug N = 50	P Value
Baseline PANSS	63.1 (8.6)	62.7 (6.5)	--
Baseline PANSS +	14.7 (2.8)	14.8 (2.8)	--
Baseline CGI-S	3.4 (0.5)	3.5 (0.5)	--
Change in PANSS +	-0.7 (3.1)	-1.9 (3.2)	p=0.046
PANSS Responders	44%	74%	p=0.0043
CGI-C responders	36%	55%	p=0.0855

SAFETY

- Most frequently reported AEs
  - Somnolence (16.0% vs. 12.8%), Headache (6.0% vs. 0); Insomnia (10.0% vs. 2.6%), Nightmare (4.0% vs 0)
  - 2 subjects (4%) discontinued for AEs on Study Drug : atrial fibrillation and seizure

NEXT OBJECTIVES

- Phase 3 clinical trials in 2 populations with schizophrenia to demonstrate possible therapeutic effects
  - Study #1: Poor responders to atypical antipsychotics
  - Study #2: Ultra-treatment resistant
    - Clozapine minimum plasma concentration of 300 ng/ml



DESIGN CONSIDERATIONS

- **Adjunctive or Monotherapy**
  - Adjunctive as an initial step to demonstrate efficacy
    - Supported by animal data
  - Requires stable baseline antipsychotic monotherapy
- **Identifiable Population of Interest**
  - Study 1: Poorly responsive to atypical antipsychotic
  - Study 2: Ultra-treatment resistant to clozapine
  - DSM-5 diagnosis
  - Moderate to severe symptom and functional deficits
  - CGI-S; BPRS; GAF; SOFAS
- **Eligibility Committee**
  - Ensure consistent eligibility criteria met across sites
- **Blinding**
  - Blinded raters
  - Independent raters for CGI and PANSS
- **Outcome Measures**
  - Symptoms (PANSS positive; CGI)
  - Functioning (GAF; SOFAS)
- **Biological Measure**
  - Striatal Connectivity Index at selected centers
- **Observation Period**
  - 6-8 weeks for onset of effect
  - 1 year for long-term safety and efficacy
- **Adherence to Treatment**
  - Plasma levels of antipsychotic and reminders
  - Recorded observation of study drug dosing
- **Safety Management**
  - International Safety Monitoring Board

CONCLUSIONS

- Results will provide deeper understanding of the biological underpinnings of inadequate antipsychotic-based treatment response
- Provides insight into understanding of role for glutamate modulation in the treatment of schizophrenia.
- Builds on increasing understanding of role of glutamate in CNS diseases

ISCTM February 2019