# Lessons from a Tourette's Study

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# Patient Centric WHAT?

From a patient/caregiver point of view:

- What is a successful trial
- What is/are important treatment response/responses that the trial should demonstrate
- De-identified vs. re-contactable

# Patient Centric WHAT?

- What is a non-disruptive trial
  - Physical
  - Emotional
  - Time
  - Money
- Do you have a process to assess participant burden
  - Formal
  - Informal

# Patient Centric  WHY

- Obvious
  - Cannot conduct trials without participants
  - Cannot get quality data without trial participants correctly following protocol procedures
  - Conducted to generate data to treat patients in the future

# Patient Centric WHY

- Understand efficacy/safety differences between adults and children
- Disease course, natural history of orphan diseases not as well known
- Healthcare experience of participants/families outside trials
  - Drs. Offices
  - Hospitals
  - Labs
  - Pharmacies

# PROGRAM/STUDY DESIGN

# Program Overview

- Ecopipam has been/is being studied in the following trials for Tourette's

COMPLETED

- On open-label study in adults
- A double-blind crossover study in Children
- An open-label follow-on study in children

ONGOING

- *A double-blind study in children*
- *An open-label follow-on study in children*

# External Contacts

- Tourette Association of America
  - Chapters
  - Members
  - Meetings
- KOLs and clinicians
- FDA
- MHRA
- EMA Pediatric Committee

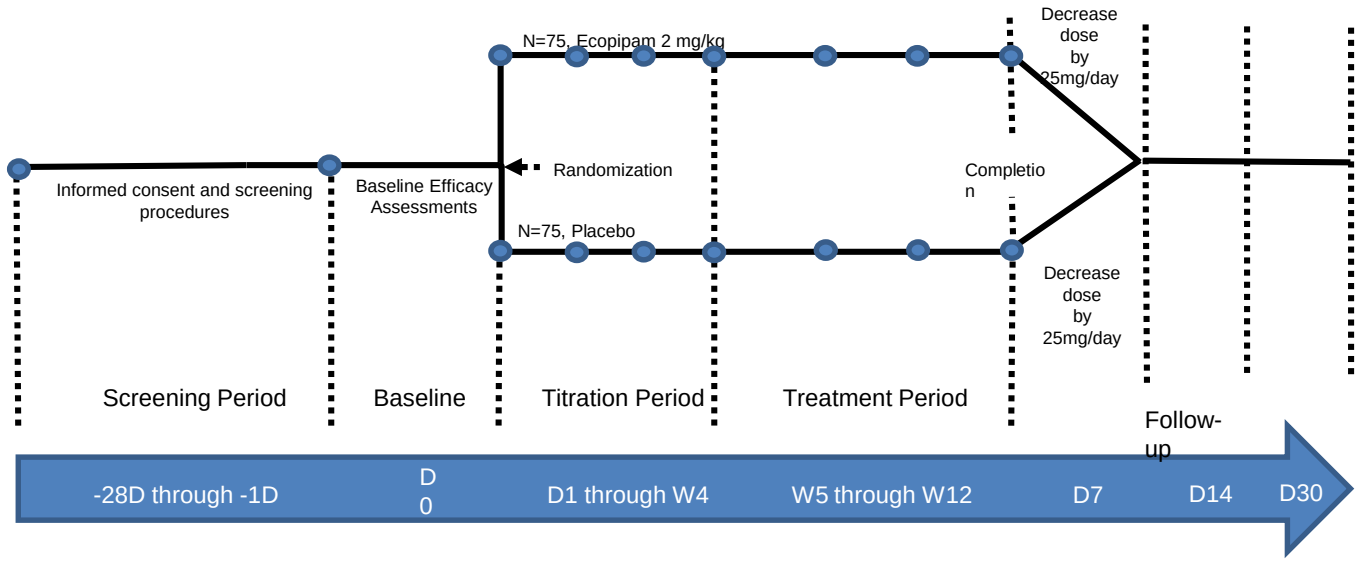
# EBS-101-CL-001 Protocol

A Multicenter, Placebo-Controlled, Double-Blind, Randomized, Parallel-Group, Phase 2b Study to Evaluate the Efficacy and Safety of Ecopipam Tablets in Children and Adolescent Subjects with Tourette's Syndrome

# Study Design

- Randomized, double-blind, parallel group, placebo-controlled, age 6-17 years
- Uptitration (4 Wks), Steady dosing (8 Wks), down-titration (1 Wk)
- Primary end point, Yale Global Tic Severity Scale
- Multiple secondary and safety end points
- Dosing based on 6 weight classes

# Study Schematic



# Assessments

EFFICACY ASSESSMENTS

- Yale Global Tic Severity Scale (YGTSS)
- Clinical Global Impression – Tourette's Syndrome of Severity (CGI- TS-S)
- Clinical Global Impression – Tourette's Syndrome of Improvement (CGI-TS-I)
- Caregiver Global Impression of Change (CaGI-C)
- Gilles de la Tourette Syndrome Quality of Life Scale (C&A-GTS-QOL)

SAFETY ASSESSMENTS

- Physical Exam and Vital Signs
- ECG Tests
- Laboratory Tests (blood and urine)
- Adverse Events
- Columbia Suicide Severity Rating Scale (CSSRS)
- Children's Depression Rating Scale (CDRS-R)
- Pediatric Anxiety Rating Scale (PARS)
- Abnormal Involuntary Movement Scale (AIMS)
- Barnes Akathisia Rating Scale (BARS)
- Swanson, Nolan and Pelham Questionnaire (SNAP-IV)
- Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)

# Major I/E Criteria

## Inclusion Criteria

- ≥ 6 and < 18 years of age
- ≥ 18 kg (~ 40 lbs.)
- TS diagnosis and both motor and vocal tics that cause impairment with normal routines
- Minimum score of 20 on the YGTSS-TTS
- Off of all medications to treat TS at least 21 days prior to Screening
- Effective contraception during the study and 30 days after for sexually active subjects

## Exclusion criteria

- Certain mood or psychiatric disorders (i.e., dementia, bipolar disorder, schizophrenia, major depressive disorder)
- Unstable medical illness or clinically significant lab abnormalities
- Risk of suicide
- Pregnant or lactating women
- Moderate to severe renal insufficiency
- Hepatic insufficiency
- Positive urine drug screen
- Unstable doses for drugs to treat anxiety, depression, ADHD
- Certain medications that would lead to drug interactions
- Recent behavioral therapy

# LESSONS

- Get multiple perspectives on design elements (I/E criteria specifically) from
  - Patients/parents
    - Academicians and
    - Smart clinicians
- Carefully evaluate and minimize study burden

# Study Set Up/Conduct

# Regulatory Interactions

- Type C Meeting with FDA NOV 2018
  - Agreement with plan to initiate Phase 2b study with suggested changes
- Scientific Advice Meeting with MHRA DEC 2018
  - Agreement with plan to initiate Phase 2b study with suggested changes
- Finalized protocol submitted to FDA/MHRA
  - Protocol amendments based on feedback
- European Pediatric Plan (PIP) procedure initiated JUN 2019
  - Refusal to issue PIP and PIP waiver granted

# Study Sites

Anticipated approximately 60 sites globally

## Countries Proposed

- US
- Canada
- France
- Germany
- Hungary
- Italy
- Poland

## Countries Approved

- US
- Canada
- France
- Germany
- Poland

# Study Progress

- First site activated in US, MAY 2019
  - MAY 2019 to AUG 2019 19 sites activated
  - *Site activation currently ongoing*
- First EU submissions: Germany and Poland MAY 2019
  - All EU submissions completed summer 2019

Pre-COVID shelter-in-place: 32 subjects randomized by Mid-March 2020

# LESSONS

- Study start up strategy clearly defined
- Stress test vendor suggested strategies
  - Manage work carefully
- Know your molecule and design study accordingly
- Understand your Pediatric EU regulatory strategy & start PIP submissions early

# Impact of COVID-19 on Trials

- EBS-101-CL-001
  - A Multicenter, Placebo-Controlled, Double-Blind, Randomized, Parallel-Group, Phase 2b Study to Evaluate the Efficacy and Safety of Ecopipam Tablets in Children and Adolescent Subjects with Tourette's Syndrome
- EBS-101-OL-001
  - A Multicenter, Open-Label, Extension Study Intended to Evaluate the Long-term Safety of Ecopipam Tablets in Children and Adolescent Subjects with Tourette's Syndrome

- Questions  Decisions
- Should subjects continue in the studies ???
- Should new subjects be enrolled in the studies ???

# Our Response

- Subject safety is paramount, best assessed by individual sites
- Trial integrity and data quality has to be maintained, assessed by study team/management
  - Assess AEs, vitals/physical labs ECG etc.

- Ensure that IMP can be delivered to subjects
- Safety/Efficacy assessments need to be completed reliably
  - Rater completed
  - PROs/Parent completed

- Protocol amendment
- Updated SAP

# Trial Status

- All aspects of study impacted
  - Site activation
  - Subject recruitment
  - Data monitoring
  - Audits
- Mixed response seen
  - Academic sites mostly stopped activities
  - Some non-academic sites stopped; others continued

As of today 76 subjects randomized

# LESSONS

- Be flexible
- Listen to sites
- Changes may need to be individualized
- Communicate as much as possible
- Use different mediums to communicate

# OVERARCHING LESSONS

- Know your patient population
- Know your molecule
- Lesson is learned only if you act on what you have learned