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Tourette Syndrome

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding data in the use of INGREZZA® (valbenazine) capsules for the treatment of Tourette syndrome (TS).

INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia.[1]

The use of INGREZZA for the treatment of TS is not approved by the FDA.

Valbenazine Clinical Development for the Treatment of TS

A clinical development program has been established to investigate the use of valbenazine for the treatment of TS, including one Phase Ib (T-Force) study, two Phase II (T-Forward and T-Force GREEN) studies, and one Phase IIb (T-Force Gold) study.

T-Force: Phase Ib Study

T-Force was a Phase Ib open-label, multiple ascending dose, pharmacokinetic and pharmacodynamic study (T-Force) that evaluated the safety, tolerability, and exposure-response of valbenazine in (N=28) children (6-11 years old) and adolescents (12-18 years old) with TS. Seventeen adolescents and 11 children were recruited into the study, with 2 adolescents dropping out. [2]

Participants were evaluated over 14 days of once-daily valbenazine dosing followed by seven days off-drug at 10 study centers in the United States. Each age group was further divided into three sequential dosing cohorts (low, medium, and high). Dose escalations from low to high for children and adolescents were based on the pharmacokinetic and safety data from the previous cohort in each age group. Additionally, the participants were evaluated weekly via the Yale Global Tic Severity Scale (YGTSS), the Premonitory Urge for Tics Scale, and the overall Clinical Global Impression of Tourette Syndrome Scale. [2]

In this study, valbenazine was generally safe and well tolerated. The YGTSS was assessed and after two weeks of treatment showed a mean reduction of 31% from baseline scores, with over half of the participants considered clinical responders (having a ≥ 30% reduction in the YGTSS).[2]

T-Forward: Phase II Study

The T-Forward study was a randomized, double-blind, placebo-controlled, multi-dose, parallel group, Phase II study to evaluate the safety, tolerability and efficacy of valbenazine in adults with moderate to severe Tourette syndrome (N=124; Ages 18-64). Two once-daily fixed doses of valbenazine were evaluated vs placebo in a 1:1:1 randomization.[3]

While the study showed a significant improvement in overall symptoms of TS in participants treated with valbenazine (as evidenced by the Clinical Global Impression of Change [p=0.015]), valbenazine did not demonstrate a statistically significant improvement (from baseline to week 8) in the YGTSS (the pre-specified primary endpoint) vs placebo (p=0.18). Adverse events were dose dependent and consistent with earlier clinical studies.[3]

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T-Force GREEN: Phase II Study

The T-Force GREEN study was a randomized, double-blind, placebo-controlled, multi-dose, parallel group, Phase II study of 98 children and adolescents. The safety, tolerability, and efficacy of once-daily valbenazine in pediatric TS participants was assessed vs placebo during a six-week treatment period. The study assessed two doses of valbenazine for each of the child and adolescent study arms.[4]

The study did not meet its primary endpoint, change from baseline to week 6 in the YGTSS for participants treated with valbenazine vs placebo. Exposure-response analysis showed that the selected doses for this placebo-controlled Phase II study were below the therapeutic range for adequate tic reduction in the majority of pediatric participants. For the subset of participants with valbenazine exposure in the appropriate range, there was a greater reduction in tics (mean YGTTS change: range -11.3 to -13.7) than in those with sub-therapeutic exposure (mean YGTSS change: rang -4.7 to -8.3). In this study, adverse events were consistent with those observed in previous valbenazine studies. There were a total of four discontinuations due to adverse events, two in each of the placebo and valbenazine arms.[4]

T-Force Gold: Phase IIb Study

T-Force Gold was a randomized, double-blind, placebo-controlled, dose optimization Phase IIb study to assess the safety, tolerability, and efficacy of valbenazine for the treatment of pediatric (6 – 17 years old) participants with moderate to severe TS (N=127).[5] Participants received either once-daily dosing of valbenazine or placebo using a 1:1 randomization over 12 weeks of dosing followed by two weeks off-drug. The first six weeks of the trial was a dose optimization phase, with dose escalations allowed at Week 2 or Week 4. The primary endpoint of T-Force GOLD was the change from baseline of the Yale Global Tic Severity Scale (YGTSS) Total Tic Score at Week 12.[6] The YGTSS is designed to rate the overall severity of motor and phonic tic symptoms across a range of dimensions: number, frequency, intensity, complexity and interference.

T-Force GOLD study did not meet the primary endpoint as assessed by YGTSS in children and adolescents with moderate to severe TS. The types of treatment emergent adverse events observed in this trial were consistent with those seen in other valbenazine studies.[5]

This letter and the enclosed material are provided in response to your unsolicited medical information inquiry. Please feel free to contact Neurocrine Medical Information at (877) 641-3461 or medinfo@neurocrine.com if you would like to request additional information.

References:

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.; 2018.
2. Neurocrine.com. (2017). *Neurocrine Announces Completion of Phase II Clinical Study of VMAT2 Inhibitor INGREZZA™ (valbenazine) in Adults with Tourette Syndrome* [Press release]. Retrieved from http://phoenix.corporate-ir.net/phoenix.zhtml?c=68817&p=irol-newsArticle&ID=2237914
3. http://www.neurocrine.com/home/clinical-trials/ Accessed on July 27, 2017.
4. Neurocrine.com. (2017). *Neurocrine announces Phase II Results of VMAT2 inhibitor INGREZZA® for treatment of tourette syndrome* [Press release]. Retrieved from http://phx.corporate-ir.net/phoenix.zhtml?c=68817&p=RssLanding&cat=news&id=2276016
5. Neurocrine.com. (2018). *Neurocrine Biosciences Announces Topline Data from Phase IIb T-Force GOLD Study Demonstrating Valbenazine Did Not Meet Primary Endpoint in*

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6. ClinicalTrials.gov. (2018). Safety, Tolerability, and Efficacy of NBI-98854 for the Treatment of Pediatric Participants with Tourette Syndrome. https://clinicaltrials.gov/ct2/show/NCT03325010.

Enclosures:

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.; 2018.

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