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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 and two Phase II (T-Forward and T-Force GREEN) studies.

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]

Subjects 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 subjects 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 subjects considered clinical responders (having a $\geq$ 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 subjects 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]

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 subjects 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]

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The study did not meet its primary endpoint, change from baseline to week 6 in the YGTSS for subjects 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 subjects. For the subset of subjects 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]

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]. Neurocrine Biosciences, Inc., San Diego, CA; 2017.
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

Enclosures:

1. INGREZZA [package insert]. Neurocrine Biosciences, Inc., San Diego, CA; 2017.
2. Important Safety Information. Neurocrine Biosciences, Inc., San Diego, CA; 2017.

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