# Supplemental Online Content

Jankovic J, Coffey B, Claassen DO, et al. Safety and efficacy of flexible-dose deutetrabenazine in children and adolescents with Tourette syndrome: a randomized clinical trial. *JAMA Netw Open.* 2021;4(10):e2128204. doi:10.1001/jamanetworkopen.2021.28204



This supplemental material has been provided by the authors to give readers additional information about their work.

## eTable 1. Daily Dose of Deutetrabenazine by Baseline Weight Category and CYP2D6 Impairment Status

| | Weight category | | | | | |
|---|---|---|---|---|---|---|
| | 20 to <30 kg | | 30 to <40 kg | | ≥40 kg | |
| **Titration (Week 7)** | **Not impaired (n=8)** | **Impaired (n=1)** | **Not impaired (n=6)** | **Impaired (n=1)** | **Not impaired (n=29)** | **Impaired (n=7)** |
| **Maximum allowed daily dose, mg** | **30** | **18** | **42** | **24** | **48** | **36** |
| Mean (SD) daily dose, mg | 22.5 (7.0) | – | 38.0 (6.2) | – | 45.1 (6.1) | 35.1 (2.3) |
| Patients who reached the maximum allowed daily dose, No. (%) | 3 (38) | 0 | 4 (67) | 1 (100) | 23 (79) | 6 (86) |
| **Maintenance (Week 12)** | **Not impaired (n=6)** | **Impaired (n=1)** | **Not impaired (n=7)** | **Impaired (n=1)** | **Not impaired (n=28)** | **Impaired (n=6)** |
| Mean (SD) daily dose, mg | 23.0 (8.0) | – | 36.9 (5.4) | – | 44.4 (6.2) | 35.0 (2.5) |
| Patients who reached the maximum allowed daily dose, No. (%) | 3 (50) | 0 | 3 (43) | 1 (100) | 19 (68) | 5 (83) |

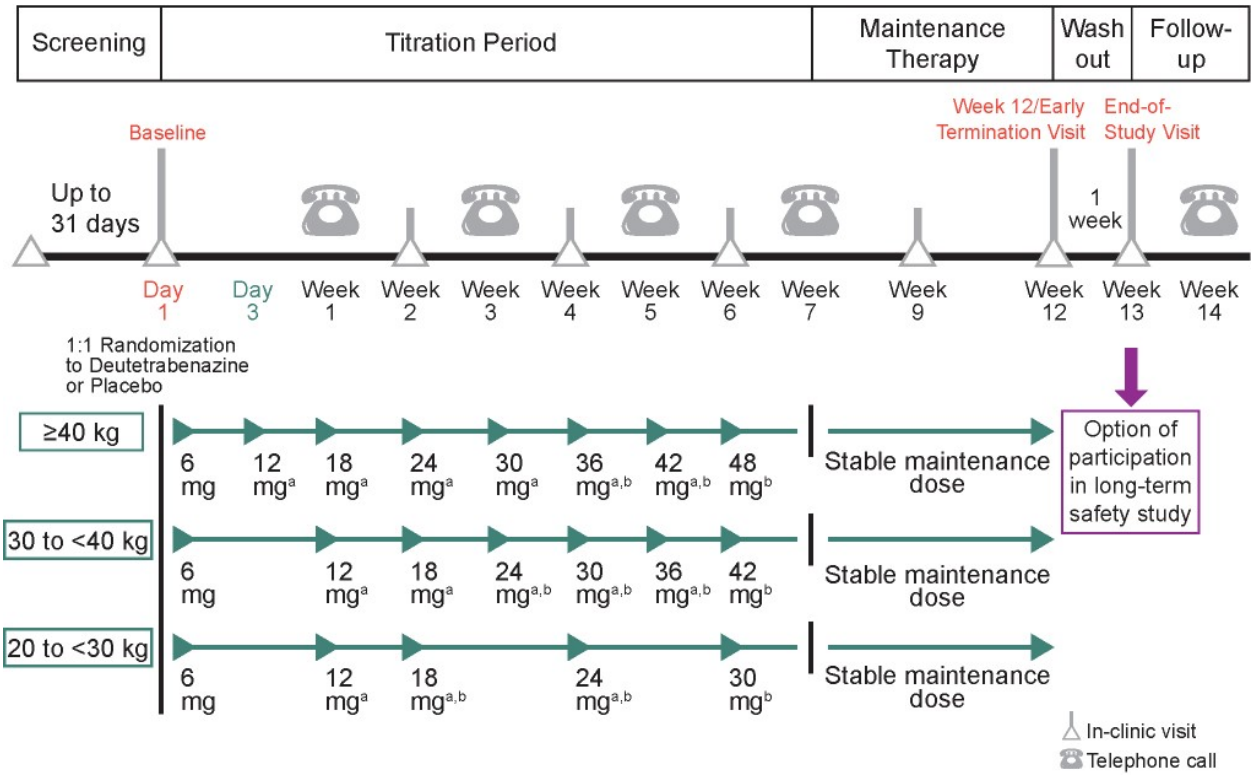
CYP2D6, cytochrome P450 2D6; SD, standard deviation.

## eTable 2. TEAEs Within the Depression and Suicide and/or Self-injury SMQs

| | Deutetrabenazine (n=58) | Placebo (n=59) |
|---|---|---|
| **Patients with ≥1 depression[a] SMQ TEAE, No. (%)** | **6 (10)** | **3 (5)** |
| ***Psychiatric disorders*** | **5 (9)** | **3 (5)** |
| Depressed mood | 2 (3) | 3 (5) |
| Middle insomnia | 2 (3) | 0 |
| Affect liability | 1 (2) | 0 |
| Initial insomnia | 1 (2) | 0 |
| Mood swings | 1 (2) | 0 |
| Depression | 0 | 0 |
| ***Nervous system disorders*** | **2 (3)** | **0** |
| Hypersomnia | 1 (2) | 0 |
| Psychomotor hyperactivity | 1 (2) | 0 |
| **Patients with ≥1 suicide/self-injury SMQ TEAE, No. (%)** | **1 (2)** | **3 (5)** |
| ***Psychiatric disorders*** | **1 (2)** | **3 (5)** |
| Suicidal ideation | 1 (2) | 3 (5) |
| Intentional self-injury | 0 | 1 (2) |

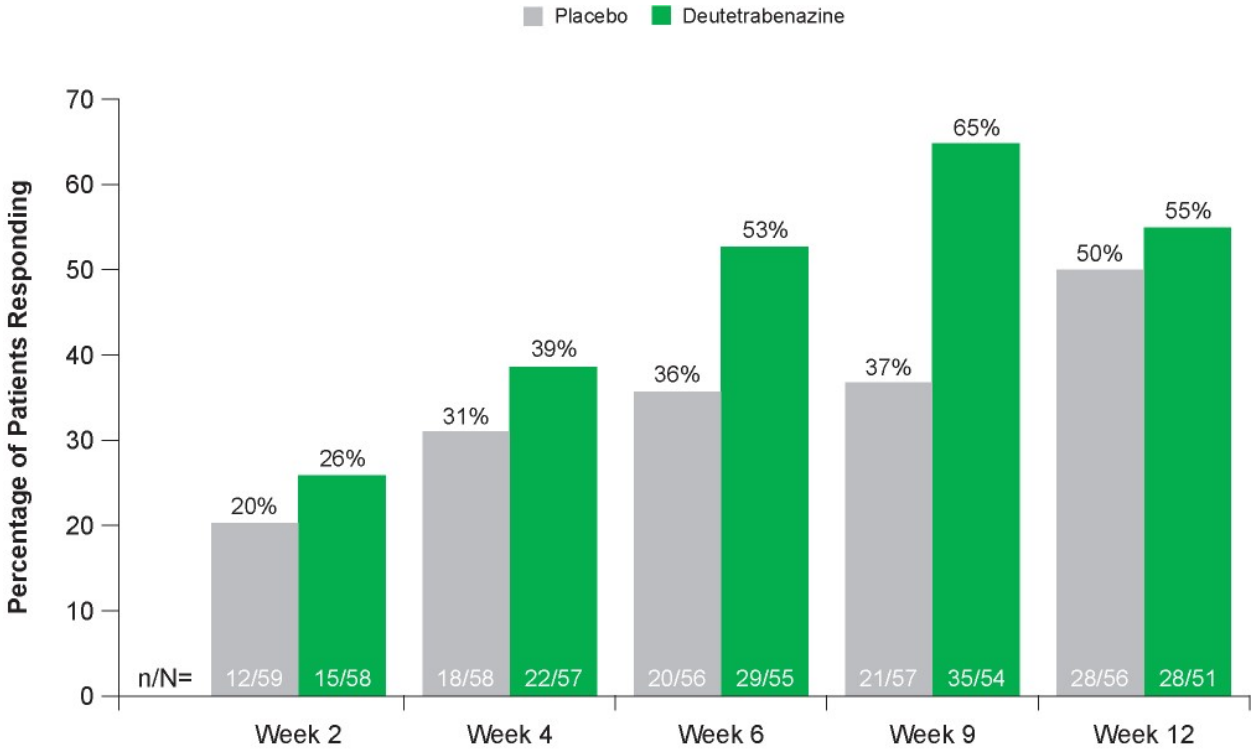
TEAE, treatment-emergent adverse event; SMQ, standardized *Medical Dictionary for Regulatory Activities* (MedDRA) query.
[a]Excludes suicide and self-injury.

## eFigure 1. Study Design



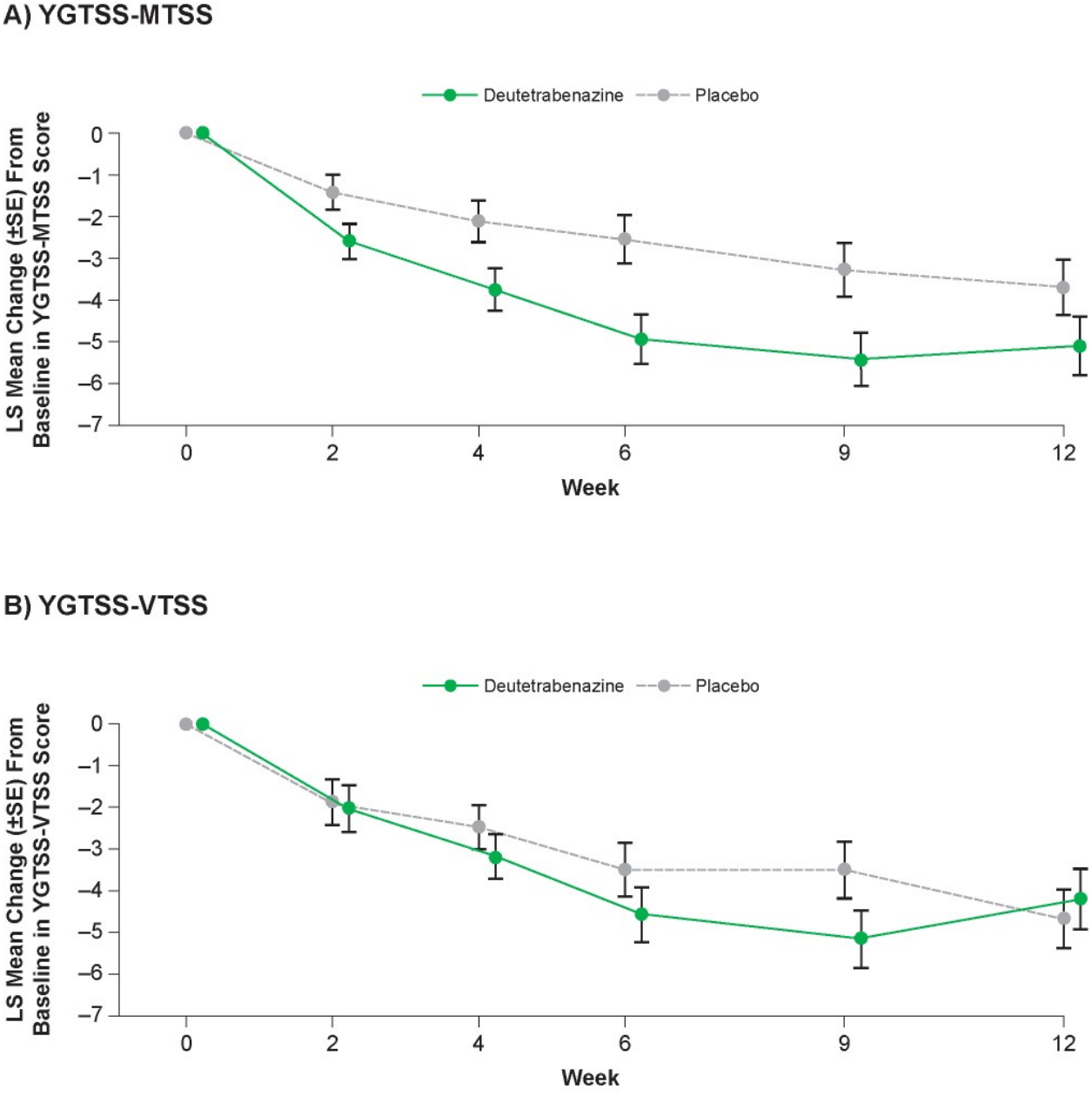

bid, twice daily; CYP2D6, cytochrome P450 2D6.
[a]If a stable dose was reached before the indicated time, the patient continued taking that dose for the remainder of the titration period and throughout the maintenance therapy dosing.
[b]The maximum total daily dose was 48 mg/day (24 mg bid) for patients weighing ≥40 kg, 42 mg/day (21 mg bid) for patients 30 to <40 kg, and 30 mg/day (15 mg bid) for patients 20 to <30 kg. For those considered CYP2D6 impaired, the maximum daily dose was 36 mg/day for patients ≥40 kg, 24 mg/day for patients 30 to <40 kg, and 18 mg/day for patients 20 to <30 kg.

**eFigure 2. Proportion of Patients With 25% or Greater Reduction From Baseline in YGTSS-TTS**




YGTSS-TTS, Yale Global Tic Severity Scale-Total Tic Score.

## eFigure 3. Change From Baseline Through Week 12 in YGTSS-MTSS and YGTSS-VTSS




YGTSS, Yale Global Tic Severity Scale; MTSS, Motor Tic Severity Score; VTSS, Vocal Tic Severity Score; SE, standard error; LS, least-squares.
[a]LS means (SE) were obtained from a mixed-model, repeated measures analysis.

## eAppendix. Full Study Inclusion and Exclusion Criteria

| **Inclusion Criteria** |
|---|
| • Patient was 6 to 16 years of age, inclusive, at baseline<br>• Patient weighed ≥44 pounds (20 kg) at baseline<br>• Patient met the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V) diagnostic criteria for Tourette syndrome (TS) and, in the opinion of the investigator, patient, and caregiver/adult, the patient's active tics were causing distress or impairment<br>• Patient had a Total Tic Score of ≥20 on the Yale Global Tic Severity Scale at screening and baseline<br>• Patient was able to swallow study medication whole<br>• Patient and caregiver/adult were willing to adhere to the medication regimen and to comply with all study procedures<br>• Patient was in good general health, as indicated by medical and psychiatric history as well as physical and neurological examination<br>• In the investigator's opinion, the patient and caregiver/adult had the ability to understand the nature of the study and its procedures, and the patient was expected to complete the study as designed<br>• Patient and caregiver/adult provided written informed consent/assent, depending on the child's age, as appropriate, according to local regulations<br>• Females who were postmenarchal or ≥12 years of age could have been included only if they had a negative beta-human chorionic gonadotropin test at baseline or were sterile<br>• Females who were postmenarchal or ≥12 years of age whose male partners were potentially fertile (ie, no vasectomy) were to use highly effective birth control methods for the duration of the study (ie, starting at screening) and for 30 days or 5 half-lives, whichever was longer after the last dose of study drug |
| **Exclusion Criteria** |
| • Patient had a neurologic disorder other than TS that could obscure the evaluation of tics<br>• The patient's predominant movement disorder was stereotypy (coordinated movements that repeat continually and identically) associated with autism spectrum disorder<br>• Patient had a confirmed diagnosis of bipolar disorder, schizophrenia, or another psychotic disorder<br>• Patient had clinically significant depression at screening or baseline<br>  ○ Note: Patients receiving antidepressant therapy could have been enrolled if on a stable dose for ≥6 weeks before screening<br>• Patient had a history of suicidal intent or related behaviors within 2 years of screening:<br>  ○ Previous intent to act on suicidal ideation with a specific plan, irrespective of level of ambivalence, at the time of suicidal thought<br>  ○ Previous suicidal preparatory acts or behavior<br>• Patient had a history of a previous actual, interrupted, or aborted suicide attempt<br>• Patient had a first-degree relative who had completed suicide<br>• Patient had clinically significant obsessive-compulsive disorder (OCD) at baseline that, in the opinion of the investigator, was the primary cause of impairment<br>• Patient had received Comprehensive Behavioral Intervention for Tics for TS or cognitive behavioral therapy for OCD within 4 weeks of screening |
| **Exclusion Criteria (cont)** |

- Patient had received any of the following concomitant medications for tics within the specified exclusionary windows of first dose:
  - Within 3 months: depot neuroleptics, botulinum toxin, or tetrabenazine
  - Within 4 weeks: cannabidiol oil and valbenazine
  - Within 21 days: reserpine
  - Within 14 days: neuroleptics (oral), typical and atypical antipsychotics, metoclopramide, levodopa, and dopamine agonists
  - Note: Use of stimulant medications, including amphetamine, methylphenidate, and lisdexamfetamine, was allowed if primary use was for the treatment of attention-deficit/hyperactivity disorder (ADHD) and dosing had been stable for ≥2 weeks before screening and no changes to dose or frequency were anticipated during the course of the study
  - Note: Use of atomoxetine was allowed if the primary use was for the treatment of ADHD and dosing had been stable for ≥4 weeks before screening and no changes to dose or frequency were anticipated during the course of the study
  - Note: Use of benzodiazepines was allowed if primary use was not for tics and dosing had been stable for ≥4 weeks before screening
  - Note: Use of topiramate (up to 200 mg/day) was allowed if dosing had been stable for ≥4 weeks before screening
  - Note: Use of guanfacine or clonidine was allowed regardless of indication (ie, if prescribed for tics or TS) if the dosing had been stable for ≥4 weeks before screening and no changes to dose or frequency were anticipated during the course of the study. If discontinuation of either medication was anticipated due to ineffectiveness, poor tolerability, or patient/caregiver preference, discontinuation was to occur ≥4 weeks prior to the screening visit
- Patient had received treatment with deep brain stimulation, transmagnetic stimulation, or transcranial direct current stimulation for reduction of tics within 4 weeks of the screening visit
- Patient had an unstable or serious medical illness at screening or baseline
- Patient had a QT interval corrected for heart rate using Fridericia's formula (QTcF) interval value >450 msec (males) or >460 msec (females) or >480 msec (with right bundle branch block) on 12-lead electrocardiogram at screening, OR required treatment with drugs known to prolong the QT interval
- Patients with a history of torsade de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure
- Patient had evidence of hepatic impairment, as indicated by the following:
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 × the upper limit of the normal range (ULN) at screening
  - Alkaline phosphatase (ALP) or total bilirubin >2 × ULN at screening
  - Note: Patients with Gilbert's syndrome were eligible to participate, if approved by the medical monitor
  - Note: Patients with abnormalities in ≥2 of the following clinical laboratory parameters were to be approved for enrollment by the medical monitor: AST, ALT, ALP, and total bilirubin
- Patient had evidence of clinically significant renal impairment, indicated by a serum creatinine >1.5 × ULN at screening
- Patient had received a monoamine oxidase inhibitor within 14 days of the baseline visit
- Patient had a known allergy to any of the components of study drug
- Patient had participated in an investigational drug or device study and received study drug/intervention within 30 days or 5 drug half-lives of baseline, whichever was longer
- Patient was a pregnant or lactating female or planned to become pregnant during the study

**Exclusion Criteria (cont)**

- Patient had a history of or acknowledged alcohol-related disorder in the previous 12 months, as defined in the DSM-V

- Patient had a positive urine drug screen test result or was unable to refrain from substance abuse throughout the study
- Patient had a DSM diagnosis based on the MINI Kid modules performed at screening that, in the opinion of the investigator, made the patient unsuitable for the study