KINECT 4: A phase 3, 1-year, open-label trial of valbenazine in adults with tardive dyskinesia


Important Information

INDICATION & USAGE
INGREZZA® (valbenazine) capsules is indicated for the treatment of adults with tardive dyskinesia.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
INGREZZA is contraindicated in patients with a history of hypersensitivity to valbenazine or any components of INGREZZA. Rash, urticaria, and reactions consistent with angioedema (e.g., swelling of the face, lips, and mouth) have been reported.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
Background: KINECT 3 pivotal trial

FDA approval of INGREZZA® (valbenazine) capsules was based on positive results from the KINECT 3 pivotal study. KINECT 3 was a phase 3, randomized, double-blind, placebo-controlled, parallel, fixed-dose study evaluating the efficacy and safety of INGREZZA 40 mg or 80 mg, administered once daily for the treatment of adults with tardive dyskinesia (TD).

KINECT 3 study design included

- 6-week double-blind, placebo-controlled treatment period: Patients randomized 1:1:1 to INGREZZA 40 mg, INGREZZA 80 mg, or placebo.
- 42-week double-blind treatment extension period, for up to 48 weeks of treatment. Patients receiving placebo were re-randomized 1:1 to INGREZZA 40 mg or INGREZZA 80 mg.
- Patients initially randomized or re-randomized to the 80 mg group received 40 mg for the first week.
- Investigators could decrease the 80 mg dose once at any time during the study due to tolerability. Patients were discontinued if the new dose was not tolerated.
- 4-week washout, for a total duration of up to 52 weeks.

KINECT 3 primary endpoint and results

- Primary efficacy endpoint was change in AIMS dyskinesia score (sum of items 1–7) from baseline to Week 6 for INGREZZA 80 mg vs placebo.
- INGREZZA reduced TD severity at 6 weeks, with results you can start to see as early as 2 weeks.
- Mean change from baseline to Week 6 was –3.2 for INGREZZA 80 mg vs –0.1 for placebo (P ≤0.001).
- Reduction in TD severity was also seen with INGREZZA 40 mg (–1.9, P<0.01).
- AIMS score reduction by ≥50% from baseline was observed in more patients taking INGREZZA vs placebo.
- INGREZZA provided continued reduction of TD severity through 48 weeks.

KINECT 4 study objective

KINECT 4 was a phase 3, open-label study conducted to further evaluate the long-term safety and tolerability of INGREZZA 40 mg or 80 mg, administered once daily. In addition, long-term effectiveness of treatment was assessed.

Study population

In this long-term, open-label study, INGREZZA was studied in a broad population of adult patients with various underlying diagnoses and treatment regimens.

<table>
<thead>
<tr>
<th>KEY INCLUSION CRITERIA</th>
<th>SELECT STUDY DEMOGRAPHICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable psychiatric status</td>
<td>Of the 167 participants who entered the study, 103 (61.7%)</td>
</tr>
<tr>
<td>18 to 85 years of age</td>
<td>completed 48 weeks of treatment and a 4-week washout period</td>
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<tr>
<td></td>
<td>Mean age was 57.4 years of age</td>
</tr>
<tr>
<td>Patients had one of these diagnoses</td>
<td>73% had a diagnosis of schizophrenia or schizoaffective disorder</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>27% had a mood disorder</td>
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<tr>
<td>Schizoaffective disorder</td>
<td></td>
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<tr>
<td>Mood disorder</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of DRBA-induced TD for ≥3 months before screening</td>
<td>88.3% were taking antipsychotics</td>
</tr>
<tr>
<td>Moderate to severe TD based on qualitative assessment at screening</td>
<td>65% were taking antidepressants</td>
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<tr>
<td></td>
<td>27% were taking anticholinergics</td>
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</table>

DRBA, dopamine receptor blocking agent.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS & PRECAUTIONS

Somnolence

INGREZZA can cause somnolence. Patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by INGREGA.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
KINECT 4 methodology

In the KINECT 4 study, eligible patients entered a 48-week treatment period with once-daily INGREZZA followed by a 4-week washout period.\(^5\)

All patients received INGREZZA 40 mg for 4 weeks. The dosage was then escalated to 80 mg once daily based on individual patient tolerability and clinical response to be reflective of real-world care.\(^4\)

- At the end of Week 4 (first postbaseline visit), the dose was escalated to 80 mg if both of the following conditions were met:
  1. Clinical Global Impression of Change-TD (CGI-TD) score of ≥3 and
  2. Acceptable safety and tolerability with 40 mg, based on investigator’s judgment\(^5\)

- A dose reduction to 40 mg was permitted once any time after dose escalation due to tolerability. Patients were discontinued if the 40 mg dose was not tolerated\(^5\)

KINECT 4 allowed patients to maintain the 40 mg dose after 4 weeks based on tolerability and treatment response\(^5\)

- 27.6% of patients were maintained on the 40 mg dose for tolerability or because they already experienced an adequate response

Assessments\(^5,^b\)

<table>
<thead>
<tr>
<th>SAFETY ANALYSES</th>
<th>EFFICACY MEASURES ASSESSED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-emergent adverse events (TEAEs)</td>
<td>Abnormal Involuntary Movement Scale (AIMS) change from baseline(^c,d)</td>
</tr>
<tr>
<td>Psychiatric status</td>
<td>Clinical Global Impression of Change-TD (CGI-TD)</td>
</tr>
<tr>
<td>Treatment-emergent akathisia or parkinsonism</td>
<td>Patient Global Impression of Change-TD (PGIC)</td>
</tr>
<tr>
<td>Emergence of suicidal ideation or behavior</td>
<td>AIMS response rates(^e)</td>
</tr>
<tr>
<td>12-lead electrocardiogram (ECG)</td>
<td></td>
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<tr>
<td>Vital signs and laboratory assessments</td>
<td></td>
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</tbody>
</table>

\(^a\) All study assessments were analyzed descriptively.

\(^b\) AIMS was scored at baseline and at Weeks 8, 12, 24, 36, 48, and 52 by site raters, who were study investigators (generally psychiatrists).

\(^c\) For continuity with earlier valbenazine studies, AIMS was also scored by consensus between 2 central AIMS video raters (movement disorder neurologists) at limited visits (baseline, Week 8 [first visit after dose escalation], and Week 52 [after washout]). Raters were blinded to treatment and study visit.

\(^d\) AIMS response defined as ≥50% improvement from baseline in the total score (sum of items 1–7).
### Long-term safety profile

In the KINECT 4 study, the majority of TEAEs were mild or moderate in intensity and few led to premature discontinuation.5

### Treatment emergent adverse reactions (TEAEs) reported in ≥3% of all patients5

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>INGREZZA 40 MG (n=163) (%)</th>
<th>All INGREZZA treateda (n=153) (%)</th>
<th>INGREZZA 40 MG (n=35) (%)</th>
<th>INGREZZA 80 MG (n=107) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>1.2%</td>
<td>8.5%</td>
<td>8.6%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Headache</td>
<td>4.3%</td>
<td>5.2%</td>
<td>5.7%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1.2%</td>
<td>4.6%</td>
<td>2.9%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>0.6%</td>
<td>4.6%</td>
<td>8.6%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.6%</td>
<td>3.9%</td>
<td>5.7%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Fall</td>
<td>0.0%</td>
<td>3.9%</td>
<td>2.9%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.7%</td>
<td>3.9%</td>
<td>8.6%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.0%</td>
<td>3.9%</td>
<td>0.0%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3.7%</td>
<td>3.9%</td>
<td>0.0%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Back pain</td>
<td>0.6%</td>
<td>3.3%</td>
<td>2.9%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.6%</td>
<td>3.3%</td>
<td>0.0%</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

*a Includes 11 patients who had a dose reduction from 80 mg to 40 mg after Week 4.
BL, baseline.

- After Week 4, <15% of all participants had serious TEAEs (13.7%) or TEAE leading to discontinuation (11.8%)5

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**Psychiatric status generally remained stable during the clinical study.**

No clinically important changes in akathisia or parkinsonism.5

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### IMPORTANT SAFETY INFORMATION (continued)

#### WARNINGS & PRECAUTIONS (continued)

#### QT Prolongation

INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

#### Parkinsonism

INGREZZA may cause parkinsonism in patients with tardive dyskinesia. Parkinsonism has also been observed with other VMAT2 inhibitors. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
Long-term effectiveness

In the KINECT 4 study, sustained TD improvements were observed with INGREZZA 40 mg. The effectiveness of INGREZZA 80 mg was also studied.5

Mean change from baseline in AIMS dyskinesia total score by site raters5,a

![Graph showing mean change from baseline in AIMS dyskinesia total score by site raters.](image)

Patients on INGREZZA 40 mg saw a 10-point reduction in their mean AIMS score at 48 weeks, as assessed by site raters5

- Mean AIMS total score change from baseline to Week 8 was −4.5 for INGREZZA 40 mg and −3.5 for INGREZZA 80 mg, as assessed by central video raters.

AIMS response rates by central video and site raters5,a

![Graph showing AIMS response rates by central video and site raters.](image)

After treatment washout, some loss of TD improvement was observed6

Consistent with findings from the KINECT 3 extension study, continued treatment with INGREZZA may be required to maintain TD reductions.3,5

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5 AIMS response defined as ≥50% improvement from baseline in the total score (sum of items 1–7).
6 Data are not shown for 11 participants who had a dose reduction from 80 mg to 40 mg after Week 4.
7 AIMS, Abnormal Involuntary Movement Scale; BL, baseline; OL, open-label; SEM, standard error of the mean.
8 Mean AIMS total score change from baseline to Week 8 was −4.5 for INGREZZA 40 mg and −3.5 for INGREZZA 80 mg, as assessed by central video raters.
9 AIMS, Abnormal Involuntary Movement Scale.
Long-term treatment with INGREZZA® (valbenazine) capsules 40 mg may be appropriate for some patients

Maintain or adjust back to INGREZZA 40 mg based on your patient’s individual treatment needs.

Even at the lowest dose, long-term effectiveness of once-daily INGREZZA was observed through 48 weeks.

- INGREZZA demonstrated sustained improvements in TD
- ~49% and 55% of patients on INGREZZA 40 mg achieved rigorous thresholds of TD improvement at 8 weeks, as measured by AIMS response by central video raters and site raters, respectively.

Long-term tolerability with no new safety concerns demonstrated with INGREZZA.

- Majority of TEAEs were mild or moderate in intensity and few led to premature discontinuation
- Psychiatric stability was generally maintained throughout the study

AIMS response defined as ≥50% improvement from baseline in the total score (sum of items 1-7).

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS
The most common adverse reaction (≥5% and twice the rate of placebo) is somnolence. Other adverse reactions (≥2% and >Placebo) include: anticholinergic effects, balance disorders/falls, headache, akathisia, vomiting, nausea, and arthralgia.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying INGREZZA full Prescribing Information.