

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209241Orig1s000**

**MEDICAL REVIEW(S)**

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**CLINICAL REVIEW**

|  |   |
|--|---|
| <b>Application Type</b>                                | New Molecular Entity  |
| <b>Application Number(s)</b>                           | 209241  |
| <b>Priority or Standard</b>                            | Priority  |
| <b>Submit Date(s)</b>                                  | August 11, 2016   |
| <b>Received Date(s)</b>                                | August 11, 2016   |
| <b>PDUFA Goal Date</b>                                 | April 11, 2017  |
| <b>Division/Office</b>                                 | Division of Psychiatry Products/Office of New Drugs         |
| <b>Reviewer Name(s)</b>                                | Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH |
| <b>Review Completion Date</b>                          | April 4, 2017   |
| <b>Established Name</b>                                | Valbenazine   |
| <b>(Proposed) Trade Name</b>                           | Ingrezza  |
| <b>Applicant</b>                                       | Neurocrine Biosciences                                      |
| <b>Formulation(s)</b>                                  | Capsule (40 mg)   |
| <b>Dosing Regimen</b>                                  | 1-2 capsules by mouth once daily (recommended dose = 80 mg) |
| <b>Proposed Indication(s)</b>                          | Tardive Dyskinesia  |
| <b>Intended Population(s)</b>                          | Adults with tardive dyskinesia                              |
| <b>Recommendation on Regulatory Action Recommended</b> | Approve   |
| <b>Indication(s) (if applicable)</b>                   |   |

## 1 Table of Contents

---

|        |  |    |
|--------|--|----|
| 1      | Table of Contents.....   | 2  |
|        | Glossary.....  | 12 |
| 1      | Executive Summary .....  | 14 |
| 1.1.   | Product Introduction.....  | 14 |
| 1.2.   | Conclusions on the Substantial Evidence of Effectiveness .....   | 15 |
| 1.3.   | Benefit-Risk Assessment .....  | 15 |
| 2      | Therapeutic Context .....  | 24 |
| 2.1.   | Analysis of Condition.....   | 24 |
| 2.2.   | Analysis of Current Treatment Options .....  | 25 |
| 3      | Regulatory Background .....  | 27 |
| 3.1.   | U.S. Regulatory Actions and Marketing History.....   | 27 |
| 3.2.   | Summary of Presubmission/Submission Regulatory Activity .....  | 28 |
| 3.3.   | Foreign Regulatory Actions and Marketing History.....  | 32 |
| 4      | Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety..... | 32 |
| 4.1.   | Office of Scientific Investigations (OSI) .....  | 32 |
| 4.2.   | Product Quality .....  | 33 |
| 4.3.   | Clinical Microbiology .....  | 33 |
| 4.4.   | Nonclinical Pharmacology/Toxicology .....  | 33 |
| 4.5.   | Clinical Pharmacology .....  | 35 |
| 4.5.1. | Mechanism of Action .....  | 35 |
| 4.5.2. | Pharmacodynamics.....  | 35 |
| 4.5.3. | Pharmacokinetics.....  | 38 |
| 4.6.   | Devices and Companion Diagnostic Issues .....  | 42 |
| 4.7.   | Consumer Study Reviews.....  | 42 |
| 5      | Sources of Clinical Data and Review Strategy .....   | 42 |
|        | CDER Clinical Review Template 2015 Edition .....   | 2  |
|        | <i>Version date: April 9, 2015 for initial rollout (NME/original BLA reviews)</i>                              |    |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

|        |  |     |
|--------|--|-----|
| 5.1.   | Table of Clinical Studies.....   | 42  |
| 5.2.   | Review Strategy.....   | 45  |
| 6      | Review of Relevant Individual Trials Used to Support Efficacy .....  | 46  |
| 6.1.   | Study 1304: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel, Fixed-Dose Study to Assess the Efficacy, Safety, and Tolerability of Valbenazine for the Treatment of Tardive Dyskinesia .....                      | 46  |
| 6.1.1. | Study Design.....  | 46  |
| 6.1.2. | Study Results.....   | 63  |
| 6.2.   | Study 1202: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose Titration Study to Assess the Safety, Tolerability, and Efficacy of Valbenazine for the Treatment of Tardive Dyskinesia .....                            | 87  |
| 6.2.1. | Study Design.....  | 87  |
| 6.2.2. | Study Results.....   | 101 |
| 6.3.   | Study 1201: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Valbenazine for the Treatment of Tardive Dykinesia in Subjects with Schizophrenia or Schizoaffective Disorder ..... | 119 |
| 6.3.1. | Study Design.....  | 119 |
| 6.3.2. | Study Results.....   | 127 |
| 6.4.   | Study 1402: A Phase 3, Open-Label, Safety and Tolerability Study of Valbenazine for the Treatment of Tardive Dyskinesia.....   | 136 |
| 6.4.1. | Study Design.....  | 136 |
| 6.4.2. | Study Results.....   | 141 |
| 7      | Integrated Review of Effectiveness.....  | 148 |
| 7.1.   | Assessment of Efficacy Across Trials .....   | 148 |
| 7.1.1. | Primary Endpoints.....   | 148 |
| 7.1.2. | Secondary and Other Endpoints .....  | 154 |
| 7.1.3. | Subpopulations .....   | 155 |
| 7.1.4. | Dose and Dose-Response.....  | 158 |
| 7.1.5. | Onset, Duration, and Durability of Efficacy Effects .....  | 159 |
| 7.2.   | Additional Efficacy Considerations.....  | 161 |
| 7.2.1. | Considerations on Benefit in the Postmarket Setting .....  | 161 |
| 7.2.2. | Other Relevant Benefits.....   | 162 |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

|         |   |     |
|---------|---|-----|
| 7.3.    | Integrated Assessment of Effectiveness .....  | 162 |
| 8       | Review of Safety .....  | 164 |
| 8.1.    | Safety Review Approach .....  | 164 |
| 8.2.    | Review of the Safety Database .....   | 167 |
| 8.2.1.  | Overall Exposure .....  | 174 |
| 8.2.2.  | Relevant characteristics of the safety population:.....                                     | 175 |
| 8.2.3.  | Adequacy of the safety database: .....  | 177 |
| 8.3.    | Adequacy of Applicant’s Clinical Safety Assessments.....                                    | 178 |
| 8.3.1.  | Issues Regarding Data Integrity and Submission Quality .....                                | 178 |
| 8.3.2.  | Categorization of Adverse Events.....   | 183 |
| 8.3.3.  | Routine Clinical Tests .....  | 191 |
| 8.4.    | Safety Results .....  | 196 |
| 8.4.1.  | Deaths .....  | 196 |
| 8.4.2.  | Serious Adverse Events.....   | 198 |
| 8.4.3.  | Dropouts and/or Discontinuations Due to Adverse Effects .....                               | 203 |
| 8.4.4.  | Significant Adverse Events .....  | 208 |
| 8.4.5.  | Treatment Emergent Adverse Events and Adverse Reactions.....                                | 210 |
| 8.4.6.  | Laboratory Findings .....   | 216 |
| 8.4.7.  | Vital Signs .....   | 223 |
| 8.4.8.  | Electrocardiograms (ECGs).....  | 224 |
| 8.4.9.  | QT .....  | 226 |
| 8.4.10. | Immunogenicity.....   | 229 |
| 8.5.    | Analysis of Submission-Specific Safety Issues .....   | 230 |
| 8.5.1.  | Suicidal Ideation and Behavior .....  | 231 |
| 8.5.2.  | Akathisia and Extrapyrarnidal Symptoms .....  | 233 |
| 8.5.3.  | Exacerbation of Symptoms of Schizophrenia or Schizoaffactive Disorder.....                  | 236 |
| 8.5.4.  | Exacerbation of Depression in the Setting of Schizophrenia or Schizoaffactive Disorder..... | 240 |
| 8.5.5.  | Manic Symptoms .....  | 242 |
| 8.5.6.  | Depression in Patients with Underlying Mood Disorders .....                                 | 243 |
| 8.6.    | Safety Analyses by Demographic Subgroups.....   | 245 |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

|         |  |     |
|---------|--|-----|
| 8.7.    | Specific Safety Studies/Clinical Trials .....                    | 245 |
| 8.8.    | Additional Safety Explorations .....                             | 245 |
| 8.8.1.  | Human Carcinogenicity or Tumor Development .....                 | 245 |
| 8.8.2.  | Human Reproduction and Pregnancy .....                           | 246 |
| 8.8.3.  | Pediatrics and Assessment of Effects on Growth .....             | 247 |
| 8.8.4.  | Overdose, Drug Abuse Potential, Withdrawal, and Rebound .....    | 248 |
| 8.9.    | Safety in the Postmarket Setting.....                            | 249 |
| 8.9.1.  | Safety Concerns Identified Through Postmarket Experience .....   | 249 |
| 8.9.2.  | Expectations on Safety in the Postmarket Setting .....           | 252 |
| 8.10.   | Additional Safety Issues From Other Disciplines .....            | 253 |
| 8.11.   | Integrated Assessment of Safety .....                            | 254 |
| 9       | Advisory Committee Meeting and Other External Consultations..... | 254 |
| 10      | Labeling Recommendations .....                                   | 255 |
| 10.1.   | Prescribing Information .....                                    | 255 |
| 10.2.   | Patient Labeling .....   | 260 |
| 10.3.   | Non-Prescription Labeling .....                                  | 260 |
| 11      | Risk Evaluation and Mitigation Strategies (REMS) .....           | 261 |
| 11.1.   | Safety Issue(s) that Warrant Consideration of a REMS .....       | 261 |
| 11.2.   | Conditions of Use to Address Safety Issue(s) .....               | 261 |
| 11.3.   | Recommendations on REMS .....                                    | 261 |
| 12      | Postmarketing Requirements and Commitments.....                  | 261 |
| 13      | Appendices .....   | 262 |
| 13.1.   | References .....   | 262 |
| 13.2.   | Psychiatric Instruments .....                                    | 265 |
| 13.2.1. | Columbia-Suicide Severity Rating Scale (C-SSRS) .....            | 266 |
| 13.2.2. | Barnes Akathisia Rating Scale (BARS) .....                       | 270 |
| 13.2.3. | Simpson-Angus Extrapyrimal Side Effects Scale (SAS) .....        | 271 |
| 13.2.4. | Positive and Negative Syndrome Scale (PANSS) .....               | 272 |
| 13.2.5. | Calgary Depression Scale for Schizophrenia (CDSS) .....          | 287 |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

|         |   |     |
|---------|---|-----|
| 13.2.6. | Young Mania Rating Scale (YMRS).....                    | 288 |
| 13.2.7. | Montgomery-Asberg Depression Rating Scale (MADRS) ..... | 291 |
| 13.3.   | Financial Disclosure .....                              | 294 |

## Table of Tables

|  |     |
|--|-----|
| Table 1: Off-Label Treatments with Limited Supportive Evidence for Treating TD.....  | 27  |
| Table 2: Listing of Phase 2/3 Trials Submitted With NDA 209241 .....   | 43  |
| Table 3: Study 1304 - Schedule of Assessments, Placebo-Controlled Period .....   | 52  |
| Table 4: Study 1304 - Schedule of Assessments, Extension Period.....   | 53  |
| Table 5: Primary Efficacy Assessment - Abnormal Involuntary Movement Scale (AIMS) .....  | 57  |
| Table 6: Summary of Efficacy Endpoints and Classification .....  | 59  |
| Table 7: Study 1304 - Subject Disposition in Extension and Post-treatment Periods .....  | 65  |
| Table 8: Study 1304 - Important Protocol Deviations, 6-week phase .....  | 65  |
| Table 9: Study 1304 - Baseline Subject Characteristics, 6-week ITT Sample.....   | 67  |
| Table 10: Study 1304 - Baseline Characteristics, ITT Analysis Set .....  | 69  |
| Table 11: Study 1304 - Treatment Compliance, Double-Blind Period, ITT Analysis Set .....   | 70  |
| Table 12: Study 1304 - Concomitant Medications Used by $\geq 10\%$ of Subjects in Any Treatment Group During Placebo Controlled Period ..... | 72  |
| Table 13: Study 1304 - Primary Efficacy Endpoint (Applicant Analysis) .....  | 73  |
| Table 14: Study 1304 - Subgroup Efficacy Analysis (6-week AIMS Change from Baseline) .....   | 77  |
| Table 15: Study 1304 - CYP2D6 Genotype vs. Week 6 AIMS CFB.....  | 78  |
| Table 16: Study 1304 - CGI-TD, ITT Analysis Set, MMRM Analysis.....  | 81  |
| Table 17: Study 1304 - PGIC Summary, Placebo-Controlled Period, ITT Analysis Set .....   | 83  |
| Table 18: Study 1304 - TDIS Change from Baseline, Placebo-Controlled Period, ITT Analysis Set .....  | 84  |
| Table 19: Study 1304 - AIMS Change from Baseline, Extension Period, ITT Analysis Set .....   | 85  |
| Table 20: Study 1304 - Assessment of Persistence of Drug Effect .....  | 87  |
| Table 21: Study 1202 - Schedule of Assessments (abridged) .....  | 93  |
| Table 22: AIMS Score Descriptors Used by On-Site versus Central Video Raters .....   | 96  |
| Table 23: Study 1202 - Analysis Set Disposition .....  | 103 |
| Table 24: Study 1202 - Demographic Characteristics, ITT Analysis Set .....   | 105 |
| Table 25: Study 1202 - Baseline Characteristics, ITT Analysis Set .....  | 106 |
| Table 26: Study 1202 - Primary Efficacy Endpoint Analysis: PP vs. ITT Analysis Sets (Applicant Analyses) .....                               | 108 |
| Table 27: Study 1202 - Subgroup Efficacy Analysis (6-week AIMS Change from Baseline) .....   | 111 |
| Table 28: Study 1202 - CYP2D6 Genotype vs. Week 6 AIMS CFB.....  | 112 |
| Table 29: Study 1202 - CGI-TD Summary and Applicant-Submitted Analysis, Week 6, ITT Analysis Set .....                                       | 117 |
| Table 30: Study 1202 - PGIC Summary, Week 6, ITT Analysis Set .....  | 118 |
| Table 31: Study 1202 - TDRS Summary at Week 6, ITT Analysis Set .....  | 118 |
| Table 32: Study 1201 - Schedule of Assessments, Double-Blind Period (Abridged) .....   | 122 |
| Table 33: Study 1201 - Summary of Analysis Sets .....  | 129 |
| Table 34: Study 1201 - Protocol Deviations (All Randomized Subjects).....  | 130 |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

|  |     |
|--|-----|
| Table 35: Study 1201 - Subject Demographics, ITT Analysis Set .....  | 130 |
| Table 36: Study 1201 - Baseline Characteristics, ITT Analysis Set .....  | 131 |
| Table 37: Study 1201 - Primary Efficacy Endpoint, ITT Analysis Set .....   | 132 |
| Table 38: Study 1201 - Post Hoc Analyses of Primary Efficacy Measure.....  | 133 |
| Table 39: Study 1201 - CGI-TD, ITT Analysis Set .....  | 134 |
| Table 40: Study 1201 - TDRS Summary at Week 6, ITT Analysis Set .....  | 135 |
| Table 41: Study 1402 - Schedule of Assessments (Abridged).....   | 138 |
| Table 42: Study 1402 - Subject Disposition as of Data Cutoff Date.....   | 143 |
| Table 43: Study 1402 - Subject Demographics, Safety Analysis Set .....   | 144 |
| Table 44: Summary of AIMS Rating Methodology Across Studies 1201, 1202, 1304, and 1402   | 149 |
| Table 45: Comparisons Between Controlled Studies Evaluating 6-Week Efficacy Endpoints....  | 151 |
| Table 46: Comparison of 6-week AIMS Baseline and Change Scores Across Controlled Studies .....                                       | 152 |
| Table 47: AIMS Dyskinesia CFB at 6 Weeks by CGI-TD Category (ITT analysis sets, Phase 2/3 controlled studies) .....                  | 153 |
| Table 48: Studies 1202 and -1304, Exploratory Remission Criteria, ITT Analysis Set.....  | 154 |
| Table 49: Exploratory Pooled Subpopulation Analysis .....  | 157 |
| Table 50: Study 1304 - AIMS CFB Prior to and Following Treatment Discontinuation .....   | 161 |
| Table 51: Applicant Pooling of Phase 2/3 Controlled Trials for Safety Analyses.....  | 167 |
| Table 52: Applicant Pooling of Phase 2/3 Long Term Studies for Safety Analyses .....   | 169 |
| Table 53: Applicant Pooling of Phase 1 Single-dose Studies for Safety Analyses.....  | 170 |
| Table 54: Applicant Drug-Drug Interaction Studies (Analyzed Independently) .....   | 171 |
| Table 55: Applicant Phase 1 Studies in Special Populations (Analyzed Independently) .....  | 171 |
| Table 56: Applicant Phase 2 Studies of Unique Design (Analyzed Independently).....   | 172 |
| Table 57: Valbenazine Exposure to a Therapeutic Dose (per ICH guidelines & Specific to Development Program) in Safety Database ..... | 174 |
| Table 58: Safety Population, Size, and Denominators.....   | 175 |
| Table 59: Person-Years Exposure for Controlled Safety Database.....  | 175 |
| Table 60: Demographic Features of Safety Database.....   | 176 |
| Table 61: Concomitant Medications for Safety Population.....   | 177 |
| Table 62: Antipsychotic Product Groupings for Concomitant Medications .....  | 180 |
| Table 63: Grouping of Anticholinergic and Antihistaminergic products for Concomitant Medications .....                               | 181 |
| Table 64: Grouping of other CNS Active Drugs for Concomitant Medications .....   | 182 |
| Table 65: Listing of Individually Coded Foot Fractures.....  | 185 |
| Table 66: Additional Information from Applicant Regarding Foot Fractures.....  | 185 |
| Table 67: FDA Grouping of MedDRA PTs for GI, Endocrine, & Constitutional AEs .....   | 186 |
| Table 68: FDA Grouping of MedDRA PTs for Hematologic, Respiratory, & Dermatologic AEs ..   | 187 |
| Table 69: FDA Grouping of MedDRA patients for Neurologic AEs .....   | 188 |
| Table 70: FDA Grouping of MedDRA PTs for Infectious AEs.....   | 190 |
| Table 71: Raw Incidence of SAEs in Safety Database .....   | 202 |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

|   |     |
|---|-----|
| Table 73: Incidence of SAEs in Safety Database .....  | 203 |
| Table 75: Incidence of AEs Resulting in Study Discontinuation, by Dose.....   | 208 |
| Table 76: Rate of ER or Outpatient Visits in Study 1201 .....   | 209 |
| Table 77: AEs Resulting in ER or Outpatient Visit in Study 1304 .....   | 209 |
| Table 78: TEAEs from Study 1201 occurring at $\geq 2\%$ in any arm.....   | 211 |
| Table 79: TEAEs from Study 1202 occurring at $\geq 2\%$ in any arm.....   | 213 |
| Table 80: TEAEs for Study 1304 occurring at $\geq 2\%$ in any arm .....   | 215 |
| Table 81: TEAEs Across (3) Controlled-Trial Periods.....  | 216 |
| Table 82: Laboratory Parameters Significantly affected by Valbenazine.....  | 217 |
| Table 83: Mean of Sum of Squared Slopes for Different QT-RR correction methods (Study 1401)<br>.....  | 228 |
| Table 84: Study 1401, Analysis of QTcF for Valbenazine 160 mg and Moxifloxacin 400 mg .....   | 228 |
| Table 85: Summary of Studies for QT review .....  | 229 |
| Table 86: C-SSRS data for Study 1201.....   | 232 |
| Table 87: C-SSRS data for Study 1202.....   | 232 |
| Table 88: C-SSRS data for Study 1304.....   | 233 |
| Table 89: Grouping of Terms for Post-marketing Reports for the Off-Label Use of Tetrabenazine<br>.....  | 251 |
| Table 90: Adverse Reactions in 3 Placebo-Controlled Studies of 6-weeks Treatment Duration<br>Occurring in $\geq 2\%$ of Subjects and $>$ Placebo..... | 257 |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table of Figures**

|  |     |
|--|-----|
| Figure 1: Exposure-Response Analysis for Efficacy, Study 1304.....   | 36  |
| Figure 2: Exposure-Response Analysis for Prolactin Elevation, Study 1304.....  | 37  |
| Figure 3: Exposure-Response Analysis for QTc Prolongation .....  | 38  |
| Figure 4: Valbenazine Metabolic Pathways .....   | 40  |
| Figure 5: Schematic of 1304 Study Design.....  | 47  |
| Figure 6: Clinical Global Impression - Tardive Dyskinesia (CGI-TD) Scale.....  | 58  |
| Figure 7: Study 1304 - Subject Disposition Through Week 6.....   | 64  |
| Figure 8: Study 1304 - Mean AIMS Change from Baseline, Double-Blind Treatment Period, ITT Analysis Set .....                         | 74  |
| Figure 9: Study 1304 - Percent of Patients with Specific Magnitude of AIMS Total Score Improvement at Week 6 (ITT Analysis Set)..... | 75  |
| Figure 10: Study 1304 - AIMS Component Scores, Valbenazine 80 mg group, ITT Analysis Set ..  | 76  |
| Figure 11: Study 1304 - Absolute and Relative Change in AIMS at 6 Weeks, by Treatment Arm, According to Baseline AIMS .....          | 79  |
| Figure 12: Study 1304 - Percentage of Subjects Achieving Exploratory Remission Criteria .....  | 80  |
| Figure 13: Study 1304 - AIMS Change from Baseline by Treatment Group, Entire Study Duration, Central Video Raters .....              | 86  |
| Figure 14: Schematic of 1202 Study Design.....   | 88  |
| Figure 15: Study 1202 - Subject Disposition .....  | 102 |
| Figure 16: Study 1202 - Frequency of Subjects with Specified AIMS CFB at Week 6.....   | 109 |
| Figure 17: Study 1202 - AIMS Component Scores, Valbenazine group, ITT Analysis Set .....   | 110 |
| Figure 18: Study 1202 - Absolute and Relative Change in AIMS at 6 Weeks, by Treatment Arm, According to Baseline AIMS .....          | 113 |
| Figure 19: Study 1202 - Percentage of Subjects Achieving Exploratory Remission Criteria .....  | 114 |
| Figure 20: Study 1202 - AIMS CFB, On-Site Raters, ITT Analysis Set .....   | 116 |
| Figure 21: Study 1201 - Study Design Schematic.....  | 120 |
| Figure 22: Study 1201 - Subject Disposition .....  | 128 |
| Figure 23: Study 1402 - Study Design Schematic.....  | 137 |
| Figure 24: Study 1402 - AIMS Total Dyskinesia Score, Blinded Central Video Raters .....  | 146 |
| Figure 25: Study 1402 - AIMS Change from Baseline, On-Site Raters .....  | 147 |
| Figure 26: Study 1304 - AIMS CFB, Entire Study Duration, ITT Analysis Set.....   | 160 |
| Figure 27: Geometric & Arithmetic Mean Trends Relative to Dosage for Prolactin across Controlled Studies 1201, 1202, and 1304.....   | 218 |
| Figure 28: Trends in Bilirubin & Alkaline Phosphatase by Dosage across Controlled Studies 1201, 1202, and 1304 .....                 | 219 |
| Figure 29: Study 1401 Diagram.....   | 227 |
| Figure 30: Mean BARS Total Score v. Study Visit in Study 1304.....   | 234 |
| Figure 31: Mean BARS Item #4 (Global Clinical Assessment of Akathisia) v. Study Visit in Study 1304 .....                            | 235 |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Figure 33: Mean SAS Global Score v. Study Visit (Study 1304)..... 236

Figure 34: Mean Total Negative & Positive Symptom Scores from PANSS in Study 1304 ..... 238

Figure 35: Mean Total General Psychopathology Score (by PANSS) in Study 1304..... 239

Figure 36: Mean PANSS Total Score in Study 1304 ..... 240

Figure 37: Mean CDSS Total Score in Study 1304..... 241

Figure 38: YMRS Total Score in Study 1304 ..... 243

Figure 39: CFB MADRS Total Score in Study 1304 ..... 244

Figure 40: Proposed Labeling Figure - Study 1304 - Percent of Patients with Specified Magnitude of AIMS Total Score Improvement at Week 6 ..... 259

Figure 41: Proposed Labeling Figure - Study 1304 - AIMS Dyskinesia Total Score Mean Change from Baseline - Entire Study Duration (Arithmetic Mean) ..... 260

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

## Glossary

---

|         |  |
|---------|--|
| AC      | advisory committee   |
| AE      | adverse event  |
| AIMS    | Abnormal Involuntary Movement Scale                                  |
| AMBMTD  | Assessment of Most Bothersome Movement in Tardive Dyskinesia         |
| AMS     | Altered mental status  |
| ANCOVA  | analysis of covariance   |
| APA     | American Psychiatric Association                                     |
| AUC     | area under the curve   |
| BARS    | Barnes Akathisia Rating Scale  |
| BPRS    | Brief Psychiatric Rating Scale                                       |
| BRF     | Benefit Risk Framework   |
| CDER    | Center for Drug Evaluation and Research                              |
| CDISC   | Clinical Data Interchange Standards Consortium                       |
| CDSS    | Calgary Depression Scale for Schizophrenia                           |
| CDTL    | Cross-Discipline Team Leader   |
| CGI-TD  | Clinical Global Impression of Change-Tardive Dyskinesia              |
| CFB     | change from baseline   |
| CFR     | Code of Federal Regulations  |
| CMC     | chemistry, manufacturing, and controls                               |
| CNS     | central nervous system   |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms               |
| CRF     | case report form   |
| CRO     | contract research organization                                       |
| CSR     | clinical study report  |
| CSS     | Controlled Substance Staff   |
| C-SSRS  | Columbia-Suicide Severity Rating Scale                               |
| DMC     | data monitoring committee  |
| DMEPA   | Division of Medication Error Prevention and Analysis                 |
| DSM-5   | Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition |
| DSMB    | Data and Safety Monitoring Board                                     |
| EDC     | electronic data capture  |
| ECG     | electrocardiogram  |
| eCTD    | electronic common technical document                                 |
| EPS     | extrapyramidal symptoms  |
| ETASU   | elements to assure safe use  |
| FDA     | Food and Drug Administration   |
| FDAAA   | Food and Drug Administration Amendments Act of 2007                  |

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

|        |  |
|--------|--|
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GABA   | gamma-aminobutyric acid                                |
| GCP    | good clinical practice                                 |
| GCSI   | Gastroparesis Cardinal Symptom Index                   |
| ICF    | informed consent form                                  |
| ICH    | International Conference on Harmonization              |
| IND    | Investigational New Drug                               |
| iPSP   | Initial Pediatric Study Plan                           |
| ISE    | integrated summary of effectiveness                    |
| ISS    | integrated summary of safety                           |
| ITT    | intent to treat  |
| IWRS   | interactive web response system                        |
| MADRS  | Montgomery-Asberg Depression Rating Scale              |
| MedDRA | Medical Dictionary for Regulatory Activities           |
| MINI   | Mini International Neuropsychiatric Interview          |
| mITT   | modified intent to treat                               |
| MMRM   | Mixed Effect Model Repeat Measurement                  |
| MRHD   | maximum recommended human dose                         |
| NDA    | new drug application                                   |
| NME    | new molecular entity                                   |
| NNT    | number needed to treat                                 |
| OCS    | Office of Computational Science                        |
| OCPC   | Office of Clinical Pharmacology                        |
| OPQ    | Office of Pharmaceutical Quality                       |
| OSE    | Office of Surveillance and Epidemiology                |
| OSI    | Office of Scientific Investigation                     |
| PANSS  | Positive and Negative Syndrome Scale                   |
| PBO    | placebo  |
| PD     | pharmacodynamics                                       |
| PGIC   | Patient Global Impression of Change                    |
| PI     | prescribing information                                |
| PK     | pharmacokinetics                                       |
| PM     | poor metabolizer                                       |
| PMC    | postmarketing commitment                               |
| PMR    | postmarketing requirement                              |
| PO     | per os (by mouth)                                      |
| PP     | per protocol   |
| PPI    | patient package insert                                 |
| PREA   | Pediatric Research Equity Act                          |
| PRO    | patient reported outcome                               |
| PSP    | Pediatric Study Plan                                   |

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

|       |   |
|-------|---|
| REMS  | risk evaluation and mitigation strategy                                     |
| SAE   | serious adverse event   |
| SAP   | statistical analysis plan   |
| SAS   | Simpson-Angus Scale   |
| SEM   | standard error of the mean  |
| SI/SA | Suicidal ideation/Suicide attempt   |
| SMQ   | Standardized MedDRA Queries   |
| SDTM  | Study Data Tabulation Model   |
| TD    | tardive dyskinesia  |
| TDIS  | Tardive Dyskinesia Impact Scale   |
| TDRS  | Tardive Dyskinesia Rating Scale   |
| TEAE  | treatment emergent adverse event  |
| TQT   | thorough QT   |
| UBACC | University of California, San Diego Brief Assessment of Capacity to Consent |
| VBZ   | valbenazine   |
| VMAT2 | vesicular monoamine transporter 2   |
| YMRS  | Young-Mania Rating Scale  |

## 1 Executive Summary

---

### 1.1. Product Introduction

Valbenazine (developed as NBI-98854; proposed proprietary name: Ingrezza) is a new molecular entity that is being developed by the Applicant for the treatment of tardive dyskinesia (TD). TD is an iatrogenic hyperkinetic movement disorder that can manifest following the sustained use of drugs which block dopaminergic receptors, most notably antipsychotics. TD is distinct from acute extrapyramidal symptoms associated with antipsychotic use, in that its onset is delayed for months to years. Signs and symptoms of TD can include involuntary movements of the orofacial region, trunk, and extremities. These abnormal movements can be disabling and distressing to patients and frequently persist even after tapering or discontinuing antipsychotic medications. There are currently no FDA-indicated treatments for TD.

Valbenazine is an inhibitor of vesicular monoamine transporter 2 (VMAT2), which is an integral membrane transporter that transports monoamines, including dopamine, from the cytosol into synaptic vesicles. Inhibiting VMAT2 decreases the quantity of neurotransmitter molecules released by presynaptic neurons during synaptic transmission. The Applicant hypothesizes that modulating dopaminergic tone in the striatum by inhibiting VMAT2 will reduce the signs and symptoms of TD. The proposed dosage form for valbenazine is a 40 mg capsule, to be titrated to the recommended dose of two capsules (80 mg), by mouth, once daily.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

### 1.2. **Conclusions on the Substantial Evidence of Effectiveness**

The effectiveness of valbenazine for the treatment of tardive dyskinesia was demonstrated in two multi-center randomized controlled trials (Studies 1304 and 1202). The primary endpoint in both studies was the change from baseline to the end of Week 6 on the Abnormal Involuntary Movement Scale (AIMS) total dyskinesia score, which is used in clinical and research settings for rating the severity of involuntary movements across multiple body regions. In the aforementioned studies, the AIMS was scored by central video raters who were blind to study treatment and visit sequence. In the Phase 3 study 1304, valbenazine 80 mg/day (N=79) was found to be significantly superior to placebo (N=76) on the primary endpoint, and its effects appeared to be durable over a 42-week extension period. In the Phase 2 study 1202, flexible-dose valbenazine 25-75 mg/day (N=45, titrated according to efficacy and tolerability) was significantly superior to placebo (N=44) on the primary endpoint, and the majority of subjects were receiving the 75 mg/day dose at the end of treatment. While the primary efficacy endpoint used in the valbenazine development program did not assess functional consequences of dyskinetic movements, it is assumed that a significant reduction in involuntary movements will be clinically meaningful for patients, caregivers, and clinicians.

### 1.3. **Benefit-Risk Assessment**

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Benefit-Risk Summary and Assessment**

Valbenazine (to be marketed as Ingrezza) is a vesicular monoamine transporter 2 (VMAT2) inhibitor developed as a treatment for tardive dyskinesia (TD). TD is characterized by involuntary athetoid or choreiform movements that develop in association with long-term neuroleptic (D<sub>2</sub> dopamine receptor antagonist) use. The intended patient population is adults with TD; given the iatrogenic nature of TD, patients will have current or prior conditions that were treated with neuroleptics (e.g., psychotic disorders, mood disorders, gastric motility disorders, etc.). The purported nature of benefit from valbenazine is a reduction in involuntary movements. From a clinical perspective, it is recommended that valbenazine be approved for this indication.

While TD is not considered to be a life-threatening condition, it can have a significant negative impact on the quality of life of patients. The often-disfiguring involuntary movements can cause a sense of shame and make it difficult for individuals to successfully integrate into the community or workplace. There are currently no FDA-approved treatments indicated for TD. Treatment guidelines generally emphasize prevention, early detection, and modification or discontinuation of the causative neuroleptic agent; this approach is often ineffective or clinically unfeasible. There is limited evidence that off-label treatments for TD are effective.

Evidence from two pivotal studies (1304 and 1202) has demonstrated the effectiveness of valbenazine in reducing the severity of abnormal involuntary movements associated with TD. The primary efficacy endpoint was the change in the Abnormal Involuntary Movement Scale total dyskinesia score from baseline to the end of Week 6, as assessed by central video raters who were blind to treatment and visit sequence. It is anticipated that the majority of individuals with TD who take valbenazine 80 mg/day will experience a reduction in abnormal involuntary movement severity. While evidence from pivotal efficacy studies did not demonstrate whether improvement on the primary efficacy endpoint leads to meaningful improvements in function or quality of life, it is accepted on face that a reduction in involuntary movements will be clinically meaningful to patients.

Evidence from the premarket development demonstrated a clear profile for the following adverse events: somnolence, balance disorders/falls, and akathisia. These events are not life-threatening, generally do not result in hospitalization, and can be mitigated via labeling. Somnolence, which occurs at a rate twice that of placebo and in over 10% of patients, is recommended to be included in the Warnings & Precautions section of the label. Suicidal ideation/behavior and depression did not show a clear association with valbenazine treatment in the development program, as supported by a lack of worsening of instruments measuring suicidality (C-SSRS) and depression (CDSS, MADRS). Minor laboratory abnormalities observed in controlled trials consisted primarily of increased blood glucose and prolactin, with the former additionally appearing

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

as an adverse event. These risks can be mitigated by labeling and a patient package insert.

Overall, considering the condition of TD, available treatment options, and the apparent risks and benefits associated with valbenazine, it is clear that approval should be recommended from a clinical perspective. Because there are no currently-approved treatments for TD, valbenazine will represent the first treatment option for this unmet medical need. Safety findings and assessment of subject disposition in clinical trials suggest valbenazine is reasonably well-tolerated, and the overall benefit-risk profile appears favorable. Important remaining uncertainties (e.g., risk vs. benefit profile of higher doses, assessment of the effect of CYP2D6 inhibition on [+] - $\alpha$ -dihydrotrabenazine exposure, etc.) will be proposed as postmarketing studies.

| Dimension             | Evidence and Uncertainties   | Conclusions and Reasons  |
|-----------------------|--|--|
| Analysis of Condition | Information about the condition of TD was derived from review articles in the medical literature (cited in Section 2.1) as well as clinical experience. TD is characterized by involuntary athetoid or choreiform movements (generally of the tongue, lower face and jaw, extremities, and/or trunk) that develop in association with long term use of D <sub>2</sub> dopamine receptor antagonist medications. Abnormal movements associated with TD can cause functional impairments (i.e., make eating more difficult, impair speech intelligibility, increase fall risk) as well as shame and social isolation for patients, due to their disfiguring appearance. Risk factors for developing TD include older age, the use of first-generation/typical antipsychotics, and the development of acute extrapyramidal symptoms early in neuroleptic treatment. The annual incidence of TD associated with typical antipsychotic exposure is estimated to be ~8.5% and the rate-ratio for atypical vs. typical antipsychotics is estimated to be ~0.68. The point prevalence of TD in the US population in 2013 has been estimated to be ~135,000, though the actual prevalence may be larger as many patients remain | While TD is not considered to be a life-threatening condition, it can have a significant impact on the quality of life of patients experiencing it. The movements can be disfiguring and increase a sense of shame, making it difficult for individuals to successfully integrate into the community or workplace. In some cases, TD can cause functional impairments, such as making eating more difficult and impairing speech intelligibility. The development of TD can impede treatment of the underlying condition (i.e., schizophrenia, bipolar disorder, etc.), as discontinuation or modification of neuroleptic medications could lead to psychiatric destabilization. |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

| Dimension                               | Evidence and Uncertainties   | Conclusions and Reasons  |
|---|--|--|
|   | <p>undiagnosed or misdiagnosed. The clinical course of TD is variable; if identified early and the causative drug is withdrawn, it is often reversible over the course of several months. However, TD is frequently chronic in nature, particularly if continued neuroleptic treatment is necessary for management of the underlying condition. While several pathophysiologic mechanisms for TD have been proposed, a detailed understanding of its biology remains incomplete. There is limited existing knowledge about genetic and other factors that predict the development and clinical course of TD.</p>   |  |
| <p><b>Current Treatment Options</b></p> | <p>There are currently no FDA-approved treatments indicated for TD. The primary treatment recommendations from the medical literature and professional society guidelines consist of early detection and modification of the neuroleptic regimen (e.g., lowering the dose, switching to an antipsychotic with a lower propensity for causing TD such as clozapine, or discontinuing the neuroleptic if clinically feasible). A number of off-label treatments for TD have been evaluated in clinical studies (e.g., benzodiazepines, anticholinergics, calcium channel blockers, GABA agonists, hormones, vitamins, essential fatty acids, herbs, etc.), and there is little evidence supporting these approaches. A small number of controlled studies suggest clonazepam, ginkgo biloba, amantadine, and tetrabenazine might have some benefit on TD symptoms (Table 1); however, these studies have small sample sizes and other methodological issues that limit the strength of evidence. Botulinum toxin administration is occasionally used as a treatment for focal orofacial TD, but evidence supporting this treatment is limited to case series and small open-label studies.</p> | <p>Overall, the current treatment armamentarium is clearly insufficient for meeting the needs of patients with TD. This is evidenced by the lack of FDA-approved treatments for this condition and the very limited body of supportive evidence for off-label treatments. Discontinuing or changing antipsychotic treatments are frequently not feasible clinically and, furthermore, are not considered to be widely effective for resolving TD symptoms.</p> |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

| Dimension | Evidence and Uncertainties  | Conclusions and Reasons  |
|-----------|---|--|
| Benefit   | <p>Evidence for the effectiveness of valbenazine was provided by two pivotal studies. The primary endpoint for both studies was the change from baseline to the end of Week 6 on the Abnormal Involuntary Movement Scale (AIMS) total dyskinesia score. Study 1304 was a Phase 3 trial in which 234 subjects with moderate to severe TD were randomized to receive valbenazine 40 mg/day, 80 mg/day, or placebo. Valbenazine 80 mg/day was found to be significantly superior to placebo, with a least-squares mean difference vs. placebo of -3.1. Study 1202 was a Phase 2 trial in which 102 subjects with moderate to severe TD were randomized to receive flexible-dose valbenazine (25-75 mg/day titrated according to efficacy and tolerability) or placebo. Valbenazine was found to be significantly superior to placebo, with a least-squares mean difference vs. placebo of -2.4.</p> <p>Data from the pivotal efficacy studies were considered to be persuasive for several reasons: 1) the primary endpoint was scored by central video raters who were blind to treatment and visit number; this would reduce the sequence/expectancy bias and inter-rater variability associated with on-site raters at each study center; 2) subjects were generally not allowed to modify or discontinue medications for other psychiatric and medical conditions, so valbenazine effects were unlikely to be confounded by concomitant medications; 3) there was very limited subject attrition during the 6-week placebo-controlled treatment period; and 4) in Study 1304, the 42-week extension period showed a dose-efficacy response for 80 vs. 40 mg/day valbenazine, and TD symptoms appeared to recur following treatment discontinuation. One limitation of the pivotal efficacy data was that Study 1202 used</p> | <p>The evidence submitted with the NDA is assessed as meeting the evidentiary standard for approval. The majority of individuals with TD who take valbenazine 80 mg/day are expected to experience an appreciable reduction in abnormal involuntary movement severity (Figure 9), and a significant minority of individuals are expected to achieve a reduction in TD symptoms to a no more than minimal residual severity (Table 48). There were insufficient numbers of subjects in examined subpopulations to make firm conclusions as to who may experience greater or lesser benefit.</p> <p>Valbenazine will be the first FDA-approved treatment for TD and is expected to be prescribed by psychiatrists, neurologists, and other physicians caring for individuals who have developed the condition of TD. Some patients may have developed TD that is persistent despite changing or discontinuing neuroleptic treatment and other patients may be continuing treatment with the neuroleptic that caused TD as necessary for adequate management of the underlying condition. In any case, patients who are experiencing negative consequences of TD (functional,</p> |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

| Dimension | Evidence and Uncertainties   | Conclusions and Reasons  |
|-----------|--|--|
|           | <p>flexible dosage that did not include the 80 mg/day dose; however, the majority of subjects received 75 mg/day for the two weeks of treatment prior to the primary efficacy endpoint. Overall, the trial design and Applicant analyses were generally consistent with guidance from the Agency (see Section 3.2), and discrepancies did not affect the overall conclusions about benefit.</p> <p>The primary efficacy endpoint was agreed upon by the Division in pre-submission meetings. The AIMS is commonly used in research and clinical settings for the purpose of assessing the presence and severity of TD. One limitation is the lack of consensus as to what would constitute a clinically meaningful change in AIMS score. The Applicant conducted an analysis assessing the concordance of the AIMS change from baseline (CFB) at the end of Week 6 with the Clinical Global Impression-TD (CGI-TD) score; this analysis suggested that the AIMS CFB associated with valbenazine treatment roughly correlated with a global impression of “very much” or “much improved.” While the AIMS measure consists of assessing the severity of involuntary movements across several body regions, it would have also been relevant to assess the functional impact of reducing TD for patients; however, the functional impact is thought to be heterogeneous. At this time it is considered to be acceptable, on face, that a significant reduction of abnormal involuntary movements will be clinically meaningful to patients. The secondary outcome measures did not have a substantial impact on the overall assessment of benefit, as findings were either not replicated or were inadequately controlled for multiple statistical testing.</p> | <p>social, etc.) are anticipated to appreciate the availability of a FDA-approved treatment with substantial evidence of effectiveness.</p> <p>Some uncertainties are recommended to be evaluated in the post-marketing setting. Because there was no clear plateau in the exposure-efficacy response relationship for the studied dose range, it is unclear whether a dose of valbenazine higher than 80 mg/day might confer additional therapeutic benefit. Second, there was some evidence from Study 1304 suggesting certain individuals may not completely return to baseline TD severity after valbenazine is discontinued; assessing the potential for treatment persistency would be a valuable objective for future study. Finally, evidence to date has not clearly demonstrated whether improvement on the AIMS total dyskinesia scale translates into meaningful improvements in function or quality of life; this would represent another important future study objective.</p> |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

| Dimension | Evidence and Uncertainties   | Conclusions and Reasons |
|-----------|--|-------------------------|
|           | <p>An analysis of benefit was conducted by this reviewer in which subjects were categorized as having their TD “well controlled” if there were no body parts with abnormal movement severity greater than “minimal” (corresponding to a score of 1 on the AIMS). Valbenazine treatment (80 mg dose Study 1304 and flexible-dose treatment in Study 1202) was associated with ~34% of subjects meeting this criterion at the end of Week 6, as compared to ~19% of subjects receiving placebo (See Table 48). By this measure, the number needed to treat (NNT), calculated using the change in the proportion of subjects meeting the criterion from baseline to Week 6, is ~4-5. Study 1304 provided some evidence as to the durability of treatment effects, suggesting that efficacy may increase beyond the 6 week primary endpoint and does not appear to lessen over time. After treatment is discontinued, TD symptoms usually returned, though not, on average, to a severity worse than baseline. An analysis of subpopulations was inconclusive given the limited number of subjects in each subgroup; however, there was some suggestion that subjects who continued to use antipsychotics may have a lesser response to valbenazine than subjects no longer using antipsychotics. Overall, there were no subgroups examined that appeared to be unresponsive to valbenazine treatment at the recommended dose (Table 49).</p> <p>The findings from the pivotal efficacy studies are anticipated to be fairly generalizable to the indicated patient population, though the “real world” target population will be more variable in terms of substance use, medical and psychiatric illness severity, and concomitant</p> |                         |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

| Dimension          | Evidence and Uncertainties  | Conclusions and Reasons  |
|--------------------|---|--|
|                    | <p>medication use. The pivotal studies enrolled a reasonable number of subjects in most demographic groups (e.g., sex, race, ethnicity, etc.), though there was a clear underrepresentation of subjects of Asian race as compared to the US population. However, there is no reason to believe valbenazine would be ineffective in races which were not adequately represented in the clinical studies.</p>   |  |
| <p><b>Risk</b></p> | <p>The safety database was adequate and consisted of 613 subjects representing a wide variety of ages, medication use, and concurrent diagnoses. The development program was primarily conducted in the US, allowing for risks to be generalized to the US population. Evidence from the premarket development demonstrated a clear profile for the following adverse events of somnolence (11%), balance disorders/falls (3.8%), and akathisia (2.7%). Suicidal ideation/behavior and depression did not show a clear association with valbenazine treatment in the development program, as supported by a lack of worsening of instruments measuring suicidality (C-SSRS) and depression (CDSS, MADRS). Minor laboratory abnormalities observed in controlled trials consisted primarily of increased blood glucose and prolactin, with the former additionally appearing as an adverse event.</p> <p>Lastly, the QT team identified a dose-response relationship with valbenazine concentration and prolongation of the QT interval. The degree of prolongation was considered only to be potentially clinically significant in patients taking a strong CYP2D6 or CYP3A4 inhibitor, poor metabolizers, or whom otherwise have a cardiac arrhythmia associated with a prolonged QT interval.</p> | <p>These events are not life-threatening, generally do not result in hospitalization, and can be mitigated via labeling. Somnolence, which occurs at a rate twice that of placebo and in over 10% of patients, will be labeled as a Warning &amp; Precaution.</p> <p>To inform clinicians of risks associated with QT prolongation in certain sub-populations, valbenazine will be labeled with a Warning &amp; Precaution, in addition to specific language in labeling directing clinicians to assess the QT interval prior to increases in dosage in sub-populations at increased risk.</p> |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

| Dimension              | Evidence and Uncertainties  | Conclusions and Reasons  |
|------------------------|---|--|
| <b>Risk Management</b> | <p>The product will be labeled to describe adverse reactions and laboratory abnormalities due to valbenazine occurring in pooled, controlled trials and additionally for the single, placebo-controlled, fixed dose study (Study 1304). Additionally, adverse reactions will be summarized in a patient package insert in order to better inform patients.</p> <p>The Applicant did not adequately assess withdrawal, dependence, and tolerance in valbenazine. Therefore, the Agency will require these to be assessed in a PMR, with a recommendation that these assessments be added to ongoing studies.</p> | <p>These risk mitigation strategies will clearly communicate the risks to clinicians and patients.</p> <p>Additionally, a PMR will address undefined risks of withdrawal, dependence, and tolerance.</p> |

## 2 Therapeutic Context

---

### 2.1. Analysis of Condition

Tardive dyskinesia (TD) is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as “involuntary athetoid or choreiform movements (lasting at least a few weeks) generally of the tongue, lower face and jaw, and extremities (but sometimes involving the pharyngeal, diaphragmatic, or trunk muscles) developing in association with the use of a neuroleptic medication for at least a few months” [1]. The “tardive” specifier differentiates these abnormal involuntary movements from other extrapyramidal symptoms (e.g., acute dystonia, parkinsonism, or akathisia) that can present shortly after starting medications that block postsynaptic dopaminergic receptors (neuroleptics). The pathophysiology of TD is not entirely understood but may involve supersensitivity of postsynaptic dopamine receptors following prolonged blockade, an imbalance of dopamine D<sub>1</sub> vs. D<sub>2</sub> receptor-mediated output from the striatum, and/or an excitotoxic loss of striatal interneurons (GABAergic, serotonergic, or peptidergic) which regulate dopaminergic neurons [2, 3].

Clinically, TD typically manifests insidiously as a mixture of oro-buccal-lingual dyskinesias (e.g., tongue twisting and protrusion, lip smacking, puckering, and chewing movements); limb movements (including piano-playing finger movements, grasping, flexion and extension, and foot tapping), and trunk movements (e.g., shoulder shrugging, rocking, and hip rotation or thrusting). Less commonly, irregular breathing rhythms or grunting may emerge as in association with respiratory muscle involvement [3]. The diagnosis of TD is made clinically based on the development of involuntary dyskinesic movements in association with neuroleptic treatment. The DSM-5 specifies “at least a few months” of neuroleptic treatment in the diagnostic criteria but also notes that TD may develop after a shorter period in older persons [1]. When diagnosing TD, other causes of involuntary movements need to be excluded, such as neuroleptic withdrawal-emergent dyskinesia, Huntington or Wilson disease, stereotypic movements associated with the underlying mental illness, other acute extrapyramidal syndromes (EPS) associated with antipsychotic treatment, and other medical illnesses [4].

The development of TD was initially characterized in patients receiving first-generation or “typical” antipsychotics (e.g., haloperidol, chlorpromazine, fluphenazine, etc.). Prospective studies have suggested that the annual incidence of TD associated with typical antipsychotic exposure is ~8.5% [5]. Risk factors found to be predictive of TD development include older age, higher antipsychotic drug dosage, and the development of EPS early in antipsychotic treatment [6]. Subsequently introduced “atypical” antipsychotics (e.g., clozapine, olanzapine, quetiapine, risperidone, etc.) have differences in pharmacological activity from typical antipsychotics that generally confer a lower risk for causing acute EPS as well as TD. However, this risk is non-

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

negligible, as evidenced by a prospective study that followed 352 subjects who were receiving typical or atypical antipsychotics for up to four years and reported an adjusted TD incidence rate-ratio for atypical antipsychotics alone of 0.68, as compared to typical antipsychotics [5]. In addition to drugs used as antipsychotics, the dopamine receptor antagonist metoclopramide, which is used as a treatment for gastrointestinal symptoms, is also a known cause of TD that is reflected as a boxed warning in its product labeling [7].

The clinical course of TD is variable. If identified early and the causative drug is withdrawn, particularly in younger patients, it is often reversible over the course of several months [8]. However, TD is frequently persistent or may improve only partially, in conjunction with changing the neuroleptic medication type or dose [9, 10]. Though a significant proportion of patients with TD may have little to no awareness of their movement disorder [11], its symptoms can be functionally disabling. TD can make eating more difficult, impair speech intelligibility, produce chewing and swallowing difficulties, alter rhythmic breathing patterns, and increase the risk of falls [12]. In addition, the public and societal perception of involuntary movements can lead to shame, depression, and social isolation [13].

Overall, TD is assessed to have a significant impact on patients. Its onset may affect the ability to adequately treat the underlying psychiatric condition (i.e., the discontinuation or modification of antipsychotic medications could lead to psychiatric destabilization). TD can affect the ability of patients to perform activities of daily living as well as make it more difficult for them to engage in the community or workplace, given the visibility of involuntary movements and the unfortunate societal stigma related to mental illness.

## 2.2. Analysis of Current Treatment Options

There are currently no FDA-approved products for the treatment of TD.

General recommendations from the American Psychiatric Association (APA) Work Group on Schizophrenia emphasize early detection and prevention. When TD has been diagnosed, suggested treatment options include switching treatment from a typical to an atypical antipsychotic or reducing the antipsychotic dose [14]. Clozapine is the preferred atypical antipsychotic for patients with TD, given its minimal to lack of propensity for worsening TD [15]. However, clozapine treatment requires frequent blood testing and its use is not always feasible, for tolerability and logistical reasons. The 2004 APA practice guideline lists several treatments that have been studied (e.g., benzodiazepines, anticholinergic agents, calcium channel blockers,  $\gamma$ -amino butyric acid receptor agonists, essential fatty acids, estrogen, and insulin), noting that at the time of publication, there were no convincing data suggesting any of these treatments may be effective [14].

More recently, the American Academy of Neurology published an evidence-based guideline on

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

the treatment of tardive syndromes, including TD [16]. Its conclusions and recommendations were that there is some evidence supporting the use of off-label clonazepam, ginkgo biloba, amantadine, and tetrabenazine for the treatment of TD (see Table 1). There were insufficient data to support or refute either antipsychotic withdrawal or switching from a typical to an atypical antipsychotic as a treatment for TD. There was also insufficient evidence to support or refute the use of the following treatments for TD: acetazolamide, bromocriptine, thiamine, baclofen, vitamin E, vitamin B6, selegiline, clozapine, olanzapine, melatonin, nifedipine, fluperlapine, sulpiride, flupenthixol, thiopropazate, haloperidol, levetiracetam, quetiapine, ziprasidone, sertindole, aripiprazole, buspirone, yi-gan san, biperiden discontinuation, botulinum toxin type A, electroconvulsive therapy,  $\alpha$ -methyldopa, reserpine, and pallidal deep brain stimulation.

Overall, the current treatment armamentarium is clearly insufficient for meeting the needs of patients with TD. This is evidenced by the lack of FDA-approved treatments for this condition and the very limited body of supportive evidence for off-label treatments. Discontinuing or changing antipsychotic treatments is frequently not feasible clinically and, furthermore, is not widely effective for resolving TD symptoms.

APPEARS THIS WAY ON ORIGINAL

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 1: Off-Label Treatments with Limited Supportive Evidence for Treating TD**

| Product Name  | Dosing/<br>Administration   | Efficacy Information  | Comments  | References |
|---------------|---|---|---|------------|
| Clonazepam    | 0.5-4.5 mg PO daily, titrated every 3-4 days according to tolerability and efficacy                   | Maryland Psychiatric Research Center Movement Disorder Scale improvement by ~37%, as compared to placebo, after 4 weeks treatment ( $p < 0.001$ ).                | Single crossover-design study (N=19) with adults with TD and continued antipsychotic treatment.<br><br>In 5 patients who continued open-label clonazepam for up to 9 months, antidyskinetic effects were absent after 5-8 months of treatment, suggesting efficacy may be short-term. | [17]       |
| Ginkgo biloba | EGb-761 (standardized Ginkgo biloba extract) 240 mg PO daily  | AIMS total score significantly improved in EGb-761 group as compared to placebo ( $-2.13 \pm 1.75$ vs. $+0.10 \pm 1.69$ ; $p < 0.0001$ ) at week 12.              | Single randomized, double-blind study (N=157) in China. Subjects were inpatients with schizophrenia and TD.   | [18, 19]   |
| Amantadine    | 100-300 mg PO daily   | AIMS total score significantly improved, as compared to placebo, after 2-7 weeks treatment.   | Two small controlled studies have been conducted (N=22, N=16), as well as several uncontrolled studies and reports.   | [20, 21]   |
| Tetrabenazine | 75-150 mg PO daily; titrated from 12.5 mg daily every few days according to tolerability and efficacy | Measures of TD (AIMS; frequency of oral dyskinesic movements) significantly improved in tetrabenazine groups, as compared to placebo, after 2-14 weeks treatment. | Two small controlled studies have been conducted (N=6, N=24), as well as several uncontrolled studies and reports.  | [22, 23]   |

Source: Reviewer created

## 3 Regulatory Background

### 3.1. U.S. Regulatory Actions and Marketing History

Valbenazine is a new molecular entity (NME) and is not currently marketed in the US or

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

elsewhere. However, its active metabolite NBI-98782 ([+]- $\alpha$ -dihydratotetrabenazine) is an enantiomer of an active metabolite of the VMAT2 inhibitor tetrabenazine, which was approved by the FDA in 2008 (as Xenazine) for the treatment of chorea associated with Huntington's disease.

Xenazine was initially subject to a Risk Evaluation and Mitigation Strategy (REMS), with the goal of informing healthcare professionals of the increased risk of drug-associated depression and suicidality, the proper titration and dosing, and the risk of drug-drug interactions with strong CYP2D6 inhibitors. The REMS requirement was eliminated in 2015 after the Agency determined that the plan had met its goals. The most recent Xenazine label (dated June 3, 2015) contains a boxed warning for depression and suicidality.

### 3.2. Summary of Presubmission/Submission Regulatory Activity

Regulatory activity is presented below in chronological order.

Valbenazine was developed for the treatment of neuroleptic-induced TD under IND 111591, which was submitted on July 19, 2011. The Applicant applied for Fast Track designation on November 22, 2011, which was granted on January 24, 2012. The rationale for granting Fast Track designation was that the condition of TD was serious; the investigational product showed potential to treat TD; the product development program was designed to determine whether it would affect TD; and there are no approved treatments for TD.

#### Type C Guidance Meeting, May 1, 2012

This meeting was held to discuss the nonclinical development program of valbenazine and the initiation of a 12-week Phase 2 clinical study (1201). As documented in the Meeting Minutes:

1. The metabolite NBI-98782 could not be considered the primary analyte for determining acceptable safety margins, as any or all of valbenazine's metabolites (e.g., NBI-98782, NBI-98884, and NBI-136110) may play a role in drug-induced toxicity.
2. Two rodent bioassays are required to assess the carcinogenicity potential of valbenazine.

(b) (4)

#### Type B End of Phase 2 Meeting, June 24, 2014

This meeting was held to discuss the nonclinical and clinical development plans of valbenazine to support a New Drug Application (NDA). As documented in the Meeting Minutes:

1. Because all abundant circulating metabolites in humans are produced in the rat and dog, toxicology studies performed in these two species could provide an adequate

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

qualification of valbenazine and its metabolites.

2. Based on the absence of immune-related adverse signals from toxicity studies conducted to date, additional immunotoxicity studies may not be needed.
3. The data package for the ongoing and completed nonclinical studies appeared sufficient to support the conduct of Phase 3 clinical studies of valbenazine, as well as support NDA submission.
4. The completed, ongoing, and planned drug-drug interaction studies, special populations, and QT studies appeared sufficient to support an NDA filing.
5. It is acceptable to not quantitate the NBI-136110 metabolite in the proposed Phase 3 and open-label safety studies.
6. A single pivotal study to confirm efficacy of valbenazine for the treatment of TD would not be acceptable; two or more studies would be required.
7. The Division believed that study 1202 could potentially provide evidence in support of valbenazine registration for the treatment of TD, but there were concerns about the change in Abnormal Involuntary Movement Scale (AIMS) score descriptors for the evaluation of the study primary outcome. The Division also had concerns that the flexible-dose study did not truly assess the dose-response relationship.
8. The Division recommended that the Applicant conduct a fixed-dose study to evaluate the dose-response relationship; subjects should be maintained on the studied dose for the entire duration of the study unless it was not tolerated. The Division also strongly recommended that a wider range of doses be studied to capture the minimal and maximal effective doses.
9. The Applicant agreed not to include patients with GI disorders and metoclopramide-induced TD in the Phase 3 studies, given concern that this group of patients may represent a different study population from patients with psychiatric disorders. The psychiatric patients in the Phase 3 studies would be stable, with Positive and Negative Syndrome Scale (PANSS) total scores  $\leq 70$ .
10. The use of central raters for AIMS scoring was acceptable, as long as it was prespecified in the protocol and the Statistical Analysis Plan. More frequent AIMS assessments than initially proposed (i.e., baseline, week 4, and week 8) were recommended.
11. The change from baseline on the total score for the first seven items of the AIMS would be acceptable as a primary endpoint for the pivotal trials. The use of modified AIMS descriptors should be justified and pre-specified in the Phase 3 protocols. A proposed key secondary endpoint based on a Clinical Global Impression (CGI) score would be allowed, but the percentage of responders based on CGI scores would not be acceptable.
12. Patients should be assessed for suicidal ideation with an acceptable instrument, such as the Columbia-Suicide Severity Rating Scale (C-SSRS), at baseline and any worsening of the score on any study visit should be reported as an adverse event. The C-SSRS score baseline should be based on a recent history prior to screening (i.e., one month).
13. The proposed open-label studies appeared acceptable to evaluate the safety of longer-

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

term valbenazine use, but the total number of exposed subjects would need to meet the ICH E1 guidelines.

An initial Pediatric Study Plan (iPSP) was submitted on August 22, 2014, which requested a full waiver for trials in pediatric patients (age 0-17 years) for the indication of TD. The Agency agreed with the full waiver because studies would be impossible or highly impractical to conduct. The Applicant applied for Breakthrough Therapy designation on September 5, 2014, which was granted on October 28, 2014, based on the assessment that valbenazine is intended to treat the serious condition of TD, and preliminary evidence indicates it may demonstrate substantial improvement over the currently available therapies.

### Type B Breakthrough Designation Meeting, April 13, 2015

This meeting was held to discuss the clinical development program of valbenazine, reach agreement on the proposed NDA format and content, and discuss the Applicant's upcoming interactions and submissions to the Division. As documented in the Meeting Minutes:

1. Conclusions related to the effect of gene- or drug-induced reductions in CYP2D6 activity on PK and dosing will depend on the adequacy of genotyping and concomitant medication usage data in Phase 2/3 trials and the safety and efficacy profile in CYP2D6 phenotype subgroups. Additional dedicated studies may be needed following the review of results.
2. The statistical analysis plan will include sensitivity analyses to address mechanisms for missing data, specify a multiple comparison control procedure to account for testing the primary and key secondary endpoints at two doses, and the CGI-TD will be included as the key secondary endpoint.
3. The modification of AIMS descriptors appeared adequately supported by provided information. This agreement incorporated input from the Clinical Outcomes Assessment team, who in a consultative review dated April 13, 2015, concluded that the modification of AIMS descriptors was based on a reasonable rationale with intent of improving the measure.
4. The Tardive Dyskinesia Impact Scale (TDIS) is not a pre-specified key secondary endpoint, and labeling claims will not be sought with this instrument.
5. The 2-year rat carcinogenicity study will be available in final form as a post-approval commitment, but a draft report will be submitted as soon as feasible.
6. The ongoing and completed studies with valbenazine appear to meet the requirements for submitting an NDA application. However, it will be essential to demonstrate whether efficacy can be maintained as a post-marketing study.
7. Bone mineral density scans at various time points should be evaluated in longer-term studies, due to the effects of valbenazine on prolactin levels.

### Type B End of Phase 2 Chemistry, Manufacturing, and Controls Meeting, November 9, 2015 (cancelled)

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

This meeting was proposed to discuss the valbenazine drug substance and drug product manufacturing and stability activities and ensure that meaningful data would be generated to support a rolling submission of the NDA. The meeting was cancelled, as the preliminary comments were deemed sufficient.

### Type B Pre-NDA Meeting, February 4, 2016

This meeting was requested to discuss the proposed valbenazine NDA content, analysis plans, and timeline for NDA submission. As documented in the Meeting Minutes:

1. The submitted QT assessment was not adequate, as the proposed plan was not able to rule out small clinically relevant QTc prolongation (10 ms). The Applicant indicated that a forthcoming package would include in vitro data, in vivo safety pharmacology study data, and human Phase 2/3 study data. The Agency indicated that its adequacy would be a matter of review, and if QT prolongation at the clinically relevant exposure could be confirmed with the data and report, a thorough QT (TQT) study would not be needed. ECG waveforms from valbenazine Phase 1 studies should be submitted to the Agency for review.
2. The Applicant will submit an abuse potential assessment, including a comprehensive evaluation of the chemistry, pharmacology, and clinical data. An 8-factor analysis would not be necessary.
3. For an exposure-efficacy analysis, the Agency was concerned that there may not be adequate PK data in each individual to accurately estimate steady-state C<sub>max</sub>. Justification should be provided for the cutoff points which are used to convert safety endpoints to binary outcomes.
4. A pharmacogenomics dataset should be submitted with the NDA, including subject-level CYP2D6 genotype information and a description of genotyping methodologies and quality controls.
5. The proposed Statistical Analysis Plan appeared acceptable, but trial should be included as a factor in analyses of pooled trials, Mixed Effect Model Repeat Measurement (MMRM) methods should be used for analyses of pooled trials if the assessment schedule was common for the three trials, and analyses of primary and key secondary efficacy endpoints should include study center in the model for the individual trials.
6. The conduction of Standardized MedDRA queries (SMQs) for signal detection and risk management for depression and suicide/self-injury were recommended by the Agency.
7. The Division agreed to the Applicant submitting additional long-term data in a 120-Day Safety Update. In this update, the Applicant should include full narratives and case report forms for cases of death, serious adverse events, and discontinuations due to adverse events.

On March 16, 2016, the Applicant requested a rolling submission for the review of NDA 209241, which was granted by the Division on March 29, 2016. On August 11, 2016, the Applicant submitted the Quality and Efficacy modules of the NDA submission and requested a Priority

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Review, based on the fact that its approval would be the first FDA-approved treatment for the unmet medical need of TD. The application was classified as Priority, with a review goal date of April 11, 2017. The 120-Day Safety Update was submitted on November 23, 2016.

### 3.3. Foreign Regulatory Actions and Marketing History

Valbenazine is not currently marketed in any other countries.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

---

### 4.1. Office of Scientific Investigations (OSI)

The OSI was consulted to request clinical inspections. Specifically, the following clinical sites from Studies 1304 and 1202 were to be audited to verify the primary (AIMS dyskinesia total score) and key secondary (CGI-TD) endpoints. These sites were chosen based on enrollment of a relatively large number of study subjects, no prior inspections, and geographic clustering.

1. Kenia Castro, M.D., Reliable Clinical Research, LLC, Hialeah, FL
  - a. Study 1202: 17 subjects
  - b. Study 1304: 12 subjects
2. Julio Castro-Gayol, M.D., Research in Miami, Inc., Hialeah, FL
  - a. Study 1202: 18 subjects
  - b. Study 1304: 12 subjects
3. Dolores Sanchez-Casau, M.D., Sanchez Casau Medical Group, Hialeah, FL
  - a. Study 1304: 14 subjects
4. Cherian Verghese, M.D., Keystone Clinical Studies, LLC, Norristown, PA
  - a. Study 1304: 10 subjects
5. Daniel Mandri, M.D., Biscayne Bay Institute, Hialeah, FL
  - a. Study 1202: 11 subjects
  - b. Study 1304: 11 subjects

As documented in the Clinical Inspection Summary (dated February 14, 2017), four of the clinical investigator inspections were classified as “No Action Indicated,” based on review of the Establishment Inspection Reports. The inspection of Neurocrine Biosciences, Inc. received a preliminary classification as “No Action Indicated.”

The site of Dr. Castro was classified as “Voluntary Action Indicated,” primarily because there was a change in clinical investigator for Study 1202 and Dr. Castro had not received IRB approval as the new clinical investigator prior to study participation. There were several

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

additional findings described from the inspection of Dr. Castro, including 1) subject #215-2011 was enrolled into Study 1202 despite having uncontrolled diabetes mellitus; 2) several subjects had protocol deviations related to concomitant medication use; 3) deviations in the methods for on-site AIMS ratings for four subjects in Study 1202; and 4) deviations in the timing and methods for safety lab collection for three subjects in Study 1202. The OSI reviewer considered most findings from this site to be minor, deemed the corrective actions by Dr. Castro to be acceptable, and concluded that the data generated by this site were acceptable in support of the pursued indication.

The OSI summary commented on the presence of four high-enrolling sites in Hialeah, FL, noting that that subjects were primarily enrolled from community mental health organizations with IRB-approved recruitment pamphlets. Study enrollment logs were compared across the four sites, and no subjects were enrolled at multiple sites for the studies. Overall, the OSI concluded that data submitted in support of the pending application from these five sites were acceptable and the studies were conducted adequately.

### 4.2. Product Quality

Please refer to the Product Quality Team reviews for additional details. The Integrated Quality Assessment recommended approval from a product quality perspective. The drug substance, valbenazine tosylate, is a new molecular entity with four chiral centers; the most (b) (4) form was chosen for development. Two batches of drug substance used in registration trials were from a manufacturer other than that planned for commercial production; however, the substance batches and processes were found to be comparable.

The drug product is a single strength, 40 mg, immediate-release purple/white Size 1 capsule. Each capsule contains 73.0 mg of valbenazine tosylate, with the labeled strength based on the equivalent amount of valbenazine base. Product quality data support a (b) (4) month expiration period rather than the Applicant-proposed (b) (4) month expiration period for capsules. The differences in composition between the product used in Phase 3 studies vs. the proposed commercial product were successfully bridged with a bioequivalence study. Of note, studies 1201 and -1202 used 25 mg and 50 mg valbenazine capsules and the Phase 3 studies 1304 and -1402 used 40 mg capsules. The differences in capsules should not affect the clinical assessment of the product other than the different doses studied in Phase 2 (25-100 mg/day) vs. Phase 3 (40, 80 mg/day) efficacy studies.

### 4.3. Clinical Microbiology

Not applicable for this application.

### 4.4. Nonclinical Pharmacology/Toxicology

CDER Clinical Review Template 2015 Edition

Version date: April 9, 2015 for initial rollout (NME/original BLA reviews)

33

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Please refer to the Pharmacology/Toxicology review for details; this section provides a brief overview of important findings. Valbenazine has been found to bind rat and human VMAT2, with  $K_i \sim 110$  nM and 150 nM, respectively. Three metabolites also bind rat and human VMAT2 with moderate to high affinity:  $[+]\text{-}\alpha\text{-dihydrotetraabenazine}$  (NBI-98782) –  $K_i \sim 2$  nM and 3 nM, respectively; M10b (NBI-679006) –  $K_i \sim 28$  nM and 74 nM, respectively; and M14 (NBI-136110) –  $K_i \sim 160$  nM and 220 nM, respectively.

In vivo radiolabeled mass balance studies conducted in rats, dogs, and humans demonstrated metabolism was qualitatively similar across species, though ester hydrolysis of valbenazine (to form  $[+]\text{-}\alpha\text{-dihydrotetraabenazine}$ ) was significantly greater in rat than dog, mouse, or human. Valbenazine-related radioactivity was found to be highly distributed to the pigmented region of the eye, suggesting extensive melanin binding. However, there were no valbenazine treatment-related eye findings in dog or pigmented mouse, and phototoxicity was not observed in BALB/c 3T3 mouse fibroblasts. Thus, the clinical significance of the extensive eye distribution is unclear.

Safety pharmacology studies found valbenazine moderately inhibits the hERG channel ( $IC_{50} \sim 2$   $\mu$ M) and produces moderate QTc prolongation in dogs at a dose 6 times the maximum recommended human dose (MRHD) of 80 mg/day (based on  $\text{mg}/\text{m}^2$  body surface area). There were no other adverse cardiovascular effects found in dogs at doses up to 12.5 times the MRHD based on  $\text{mg}/\text{m}^2$ .

Pivotal toxicology studies were conducted in Sprague Dawley rats, CD-1 mice, and beagle dogs. The primary target organ of toxicity across nonclinical species was the CNS. Clinical signs consistent with CNS monoamine depletion (e.g., decreased activity, ataxia, trembling, and ptosis) were observed in rats, mice, and dogs. Rodents also exhibited increased activity prior to dosing (when valbenazine levels are at trough) and for around two days following dosing cessation, suggesting a potential withdrawal phenomenon.

Valbenazine administration was associated with tremors and convulsions in rats and dogs. In rats, self-resolving myoclonic jerking or clonic convulsions, generally lasting  $< 1$  minute, were noted at doses approximately equivalent to the MRHD based on  $\text{mg}/\text{m}^2$ . This seizure-like activity required at least two months of dosing, was associated with animal handling, and was not observed following cessation of dosing. There were no CNS lesions noted in neuropathology examinations in these studies. In dogs, tremors and wobbly gait were observed in chronic and chronic studies at doses  $\geq 2$  times the MRHD based on  $\text{mg}/\text{m}^2$ . These effects were related to tremor in proximal muscles (head, neck, shoulders), and there were no associated electroencephalographic abnormalities or neuropathologic lesions. The toxicological significance of these findings was deemed unclear.

Valbenazine was found to be non-genotoxic in the bacterial reverse mutation test, an in vitro mouse lymphoma assay, and an in vivo mouse micronucleus assay. Furthermore, valbenazine

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

was non-carcinogenic and did not induce tumors in rats or mice at doses up to 0.24 times and 4.6 times the MRHD based on  $\text{mg}/\text{m}^2$ , respectively.

In rats and rabbits, valbenazine was found to not produce structural abnormalities, functional impairment, or growth alterations at doses 2 times and 12 times the MRHD based on  $\text{mg}/\text{m}^2$ , respectively. In rats, valbenazine adversely affected male and female fertility; these effects were thought to be due to changes in mating behavior and disruption of estrous cyclicity related to hyperprolactinemia, rather than direct toxicity of valbenazine or metabolites on reproductive organs. An increase in stillbirth incidence and postnatal pup mortality was found associated with valbenazine administration at doses below the MRHD based on  $\text{mg}/\text{m}^2$ . In addition, valbenazine and the metabolites  $[+]-\alpha$ -dihydrotetrabenazine and NBI-136110 were detected in fetuses, as well as in milk and in pups following administration to lactating rats. These data suggest that administering valbenazine to pregnant or breastfeeding women may expose fetuses and infants to valbenazine and metabolites.

### 4.5. Clinical Pharmacology

Please refer to the Clinical Pharmacology discipline reviews for additional details about findings and associated clinical studies; the following sections provide a brief overview of key findings. Key review issues identified by the Office of Clinical Pharmacology (OCP) team were the appropriateness of the dosing instructions in general patients and recommendations in specific patient populations (i.e., CYP2D6 poor metabolizers, severe renal impairment, and patients receiving concomitant medications such as strong CYP2D6 inhibitors).

#### 4.5.1. Mechanism of Action

The exact mechanism of action of valbenazine for the treatment of tardive dyskinesia is unknown. It is believed that upon oral administration, valbenazine is metabolized to  $[+]-\alpha$ -dihydrotetrabenazine, which is ~40-fold more potent than valbenazine. Both valbenazine and  $[+]-\alpha$ -dihydrotetrabenazine are VMAT2 inhibitors, which cause reversible reduction of dopamine release at presynaptic nerve terminals by selectively inhibiting presynaptic VMAT2.

#### 4.5.2. Pharmacodynamics

In Study 1304, PK sampling occurred at Weeks 2, 4, and 6. The Clinical Pharmacology review team conducted an exposure-response analysis for efficacy, using the % change from baseline in the Week 6 AIMS total dyskinesia score as the efficacy measure and the geometric mean concentrations of  $[+]-\alpha$ -dihydrotetrabenazine (NBI-98782) as the exposure variable (Figure 1). This analysis showed an exposure-efficacy response relationship that did not appear to plateau in the tested dose range, which relates to the proposed postmarketing commitment (PMC) of assessing whether a higher dose of valbenazine would confer additional therapeutic benefit for patients with TD (see Section 12). The OCP concluded that substantial evidence of effectiveness

Clinical Review

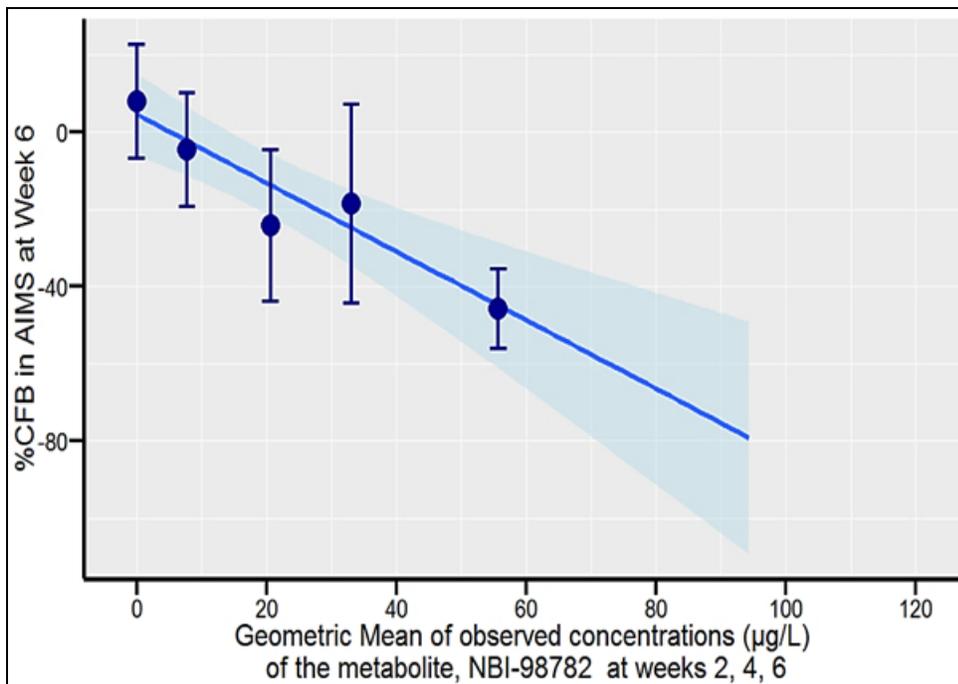
Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

was demonstrated by the registration trials, and a significant dose/exposure-response relationship indicated that higher dose/exposure is associated with higher reduction in the AIMS total score.

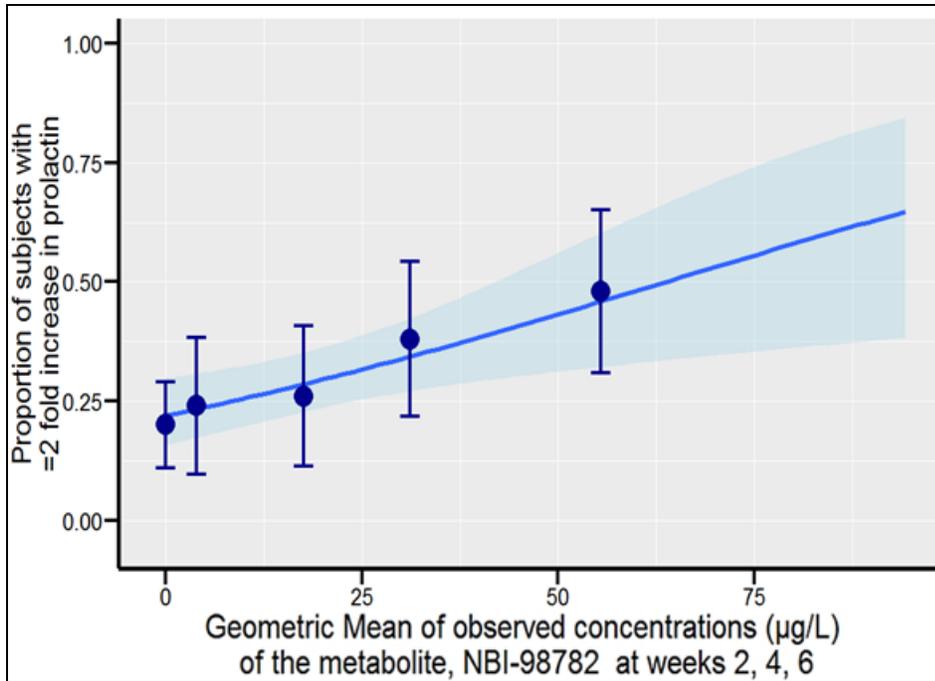
**Figure 1: Exposure-Response Analysis for Efficacy, Study 1304**



Source: Clinical Pharmacology Review Team

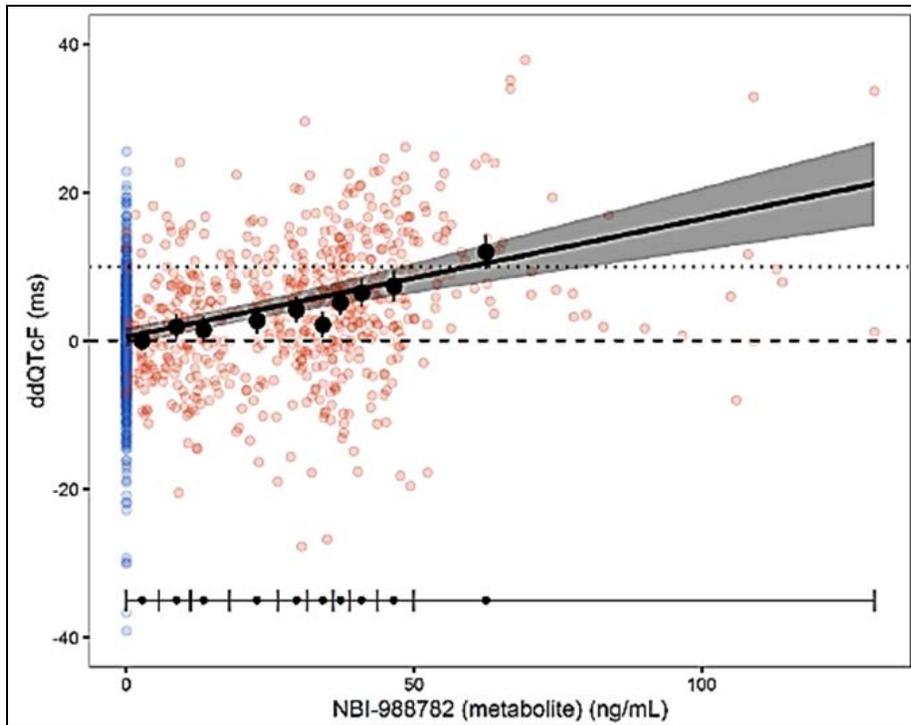
A similar exposure-response analysis was performed for safety, assessing the proportion of subjects with a  $\geq 2$ -fold increase in prolactin levels at Week 6 (Figure 2). This analysis suggests that greater drug exposure confers a greater increase in prolactin levels; this could theoretically be associated with adverse reactions such as oligomenorrhea or galactorrhea. An exposure-response analysis of clinical data from two healthy subject studies revealed a positive correlation in QTc interval with the plasma concentration of  $[+]\text{-}\alpha\text{-dihydrotetraabenzazine}$  (Figure 3); patients taking a 80 mg valbenazine dose may have a mean (95% upper bound) QTc prolongation of 6.7 (8.4) msec, and patients taking an 80 mg dose with increased exposure (e.g., taking a concomitant strong CYP3A4 or CYP2D6 inhibitor) may have a mean QTc prolongation  $> 10$  msec.

**Figure 2: Exposure-Response Analysis for Prolactin Elevation, Study 1304**



Source: Clinical Pharmacology Review Team

**Figure 3: Exposure-Response Analysis for QTc Prolongation**



Source: QT review by Dr. Nan Zheng and Dr. Lars Johannesen

#### 4.5.3. Pharmacokinetics

**Absorption:** The absolute oral bioavailability is estimated to be ~49%. The T<sub>max</sub> following oral administration is 0.5-1.0 hours for valbenazine and 4-8 hours for [+]– $\alpha$ -dihydrotetrabenazine. Ingestion of a high-fat meal decreased valbenazine C<sub>max</sub> by ~47% and AUC by ~13%, as well as [+]– $\alpha$ -dihydrotetrabenazine C<sub>max</sub> by ~18% and AUC by ~6%.

**Exposure:** The AUC<sub>0-24</sub> and C<sub>max</sub> (mean  $\pm$  SD), based on Study 1503 in healthy subjects at the 80 mg daily dose (N=21) on Day 14, were 6150  $\pm$  1510 ng·h/mL and 916  $\pm$  220 ng/mL, respectively for valbenazine; and 694  $\pm$  227 ng·h/mL and 39.4  $\pm$  12.9 ng/mL, respectively for [+]– $\alpha$ -dihydrotetrabenazine. The AUC and C<sub>max</sub> of valbenazine and [+]– $\alpha$ -dihydrotetrabenazine increased approximately proportionally when the valbenazine dose was increased from 40 mg to 300 mg.

**Distribution:** The mean steady state volume of distribution of valbenazine is ~92 L. Plasma protein binding was determined to be >99% for valbenazine and ~64% for [+]– $\alpha$ -dihydrotetrabenazine. The blood to plasma ratio was determined to be 0.75.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*Metabolism:* Please see Figure 4 for a diagram of metabolic pathways for valbenazine (INGREZZA), which illustrates the active metabolite ([+]- $\alpha$ -dihydrotrabenazine/NBI-98782) in common with tetrabenazine (XENAZINE). Valbenazine is primarily metabolized by CYP3A4/5 and ester hydrolysis. The major active metabolite [+]- $\alpha$ -dihydrotrabenazine is metabolized by CYP2D6, CYP3A4/5, and glucuronidation. Increased exposure to [+]- $\alpha$ -dihydrotrabenazine is anticipated in patients with compromised (i.e., poor metabolizers) or inhibited CYP2D6 function.

*Elimination:* Valbenazine has a mean total plasma systemic clearance of 7.2 L/hour. The half-life for valbenazine and the active metabolite [+]- $\alpha$ -dihydrotrabenazine is ~15-22 hours. In a mass balance study, following the administration of a 50 mg oral dose of radiolabeled C-valbenazine, ~60% and ~30% of radioactivity was recovered in the urine and feces, respectively. Less than 2% was excreted as unchanged valbenazine or [+]- $\alpha$ -dihydrotrabenazine in either urine or feces.

APPEARS THIS WAY ON ORIGINAL

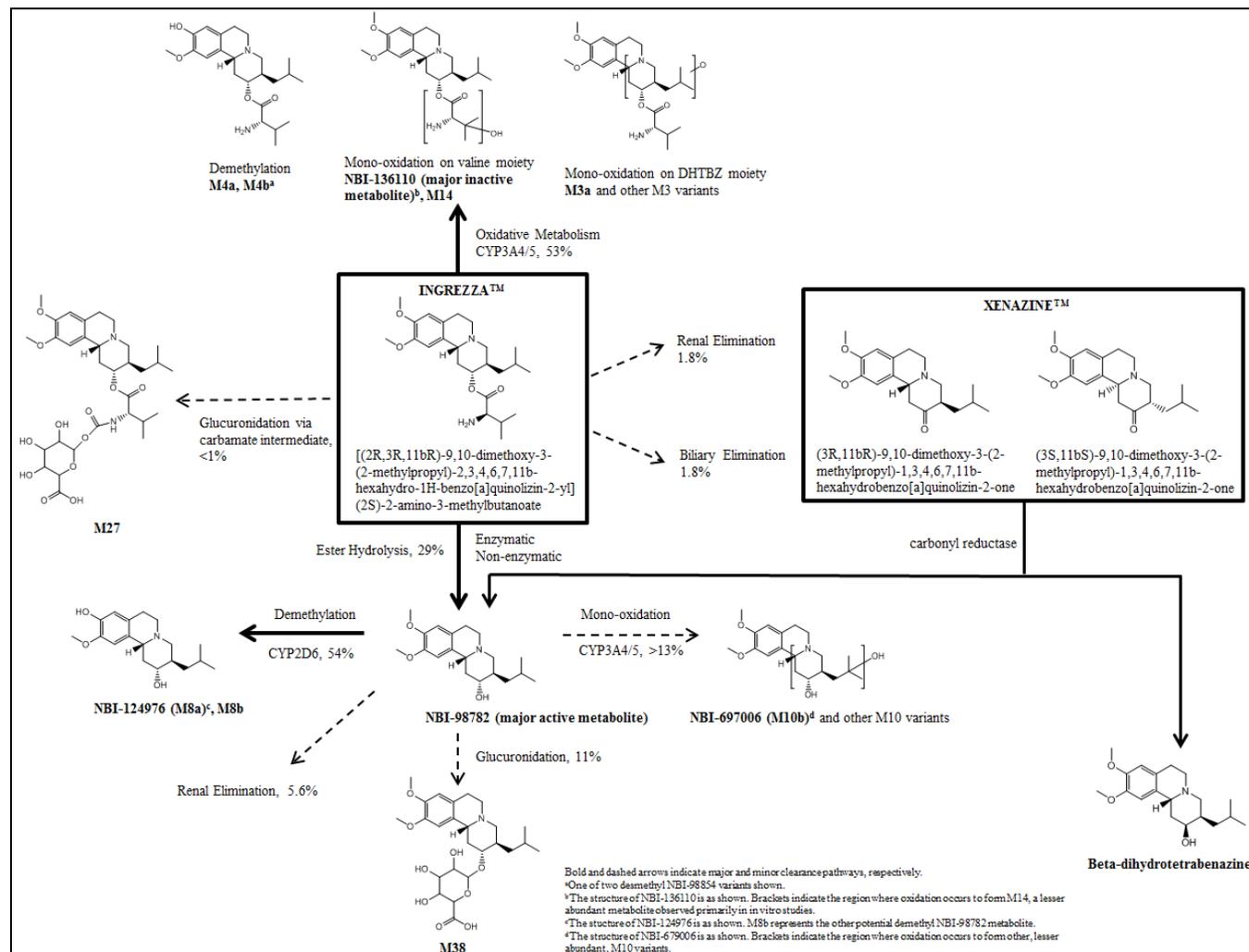
Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Figure 4: Valbenazine Metabolic Pathways



Source: Created by Clinical Pharmacology reviewer Dr. Di Zhou

CDER Clinical Review Template 2015 Edition

Version date: April 9, 2015 for initial rollout (NME/original BLA reviews)

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*Drug Interactions:* Valbenazine and [+]– $\alpha$ -dihydrotrabenzazine are unlikely to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, and CYP3A4/5, or induce CYP1A2, CYP2B6, or CYP3A4/5 at clinically relevant concentrations. The CYP3A4 inhibitor ketoconazole was found to increase the C<sub>max</sub> of valbenazine and [+]– $\alpha$ -dihydrotrabenzazine by ~1.5-fold and the AUC by ~2-fold. The CYP3A4 inducer rifampin was found to decrease the C<sub>max</sub> of valbenazine and [+]– $\alpha$ -dihydrotrabenzazine by 30% and 50%, respectively, and the AUC of valbenazine and [+]– $\alpha$ -dihydrotrabenzazine by 70% and 80%, respectively. In vitro substrate transporter system studies found valbenazine and [+]– $\alpha$ -dihydrotrabenzazine unlikely to inhibit the transporters (BCRP, OAT1, OAT3, OCT2, OATP1B1, or OATP1B3) at clinically relevant concentrations. Valbenazine inhibits intestinal P-glycoprotein, which was found to increase the C<sub>max</sub> and AUC of digoxin by ~1.9-fold and ~1.4-fold, respectively.

The effect of CYP2D6 inhibition (either in individuals with poor metabolizer (PM) status or by concomitant use of strong CYP2D6 inhibitors) has not been adequately characterized. The dataset used for the population PK analyses consisted of a total of only 16 PMs, of which 13 PMs were in studies with sparse sampling (n = 10 in 1304, n=3 in 1202), and only two PMs were administered the therapeutically recommended dose (80 mg). The Applicant also provided exposure data of [+]– $\alpha$ -dihydrotrabenzazine in seven additional PMs (four individuals from phase 1 healthy volunteer studies and three adolescent patients with Tourette's Syndrome). The limited data showed large variability, making it difficult to assess the precise magnitude of differences in [+]– $\alpha$ -dihydrotrabenzazine exposure in PMs vs. non-PMs. Although there was some information about the specific use of CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, duloxetine, sertraline, bupropion), details pertinent to the time of administration were not available, so the lack of obvious [+]– $\alpha$ -dihydrotrabenzazine exposure differences in these subjects was not interpretable.

*Intrinsic and Extrinsic Factors:* Dose adjustment is recommended in patient subgroups based on relevant PK studies, the established exposure-response relationships, and the understanding of the mechanism of drug elimination. Specifically:

- The daily dose should be reduced by half, based on therapeutic response and tolerability, when co-administered with a strong CYP3A4 inhibitor.
- Dose reduction should be considered, based on clinical response, when co-administered with a strong CYP2D6 inhibitor or for a known CYP2D6 poor metabolizer.
- Concomitant use with CYP3A4 inducers is not recommended.
- The daily dose should be reduced to 40 mg/day for patients with moderate or severe hepatic impairment (Child-Pugh score 7 to 15).
- No dose adjustment is necessary for patients with mild to moderate renal impairment.
- Dosing instructions for patients with severe renal impairment and patients receiving concomitant CYP2D6 substrates are pending further investigation in the postmarketing setting.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

- Digoxin concentrations should be monitored when co-administering valbenazine with digoxin. Dosage adjustment of digoxin may be necessary based on digoxin concentration.
- Valbenazine can be taken with or without food.

### 4.6. **Devices and Companion Diagnostic Issues**

Not applicable for this application.

### 4.7. **Consumer Study Reviews**

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed labeling for Ingrezza for areas of vulnerability that may lead to medication errors. There were no human factors studies evaluated for this product. Several recommendations were provided for the Applicant on areas where the container label and professional sample blister pack labeling and packaging could be improved to help facilitate patient handling and viewing of product identifying information. Overall, issues described in the DMEPA review (which are to be communicated with the Applicant) are not anticipated to have a significant impact on the efficacy or safety of valbenazine in the post-market setting.

## **5 Sources of Clinical Data and Review Strategy**

---

### 5.1. **Table of Clinical Studies**

The clinical development program for valbenazine to support the TD indication has consisted of twenty studies: fourteen Phase 1 studies, four Phase 2 studies, and two Phase 3 studies. Of the Phase 1 studies, twelve enrolled healthy subjects, one enrolled subjects with hepatic impairment, and one enrolled children and adolescents with Tourette's Syndrome. Three Phase 1 studies were used for conducting an exposure-QT analysis (see 8.4.9). The Phase 2 and 3 studies included subjects with TD and a clinical diagnosis of schizophrenia, schizoaffective disorder, or mood disorder, with one Phase 2 study also including subjects with gastrointestinal disorders treated with metoclopramide.

The Applicant has indicated that Studies 1304 and 1202 are considered pivotal and Studies 1201 and 1402 are considered supportive for evaluating the efficacy of valbenazine for the treatment of TD. See Table 1 for a description of the six Phase 2/3 studies included with this NDA submission.

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 2: Listing of Phase 2/3 Trials Submitted With NDA 209241**

| <b>Trial Identity<sup>1</sup></b>                               | <b>Trial Design</b>   | <b>Regimen/schedule/route<sup>2</sup></b>   | <b>Study Endpoints<sup>3</sup></b>   | <b>Treatment Duration/Follow Up</b>                   | <b>No. of patients enrolled</b> | <b>Study Population</b>  | <b>No. of Centers and Regions</b>            |
|---|---|---|--|---|---------------------------------|--|--|
| <b><i>Controlled Studies to Support Efficacy and Safety</i></b> |   |   |  |   |                                 |  |  |
| 1101  | Phase 2, randomized, double-blind, placebo-controlled, two-period crossover study   | VBZ 12.5 or 50 mg PO daily or PBO PO daily  | <u>Primary:</u> AIMS dyskinesia total (change from baseline)                                     | 14 days VBZ and 14 days PBO for each treatment period | 37                              | Adults (age 18-65) with neuroleptic-induced tardive dyskinesia and schizophrenia or schizoaffective disorder   | 12 sites in the USA                          |
| 1201  | Phase 2, randomized, double-blind, placebo-controlled, parallel-group study followed by open-label extension                                    | VBZ 100 mg PO daily x 2 weeks, then 50 mg PO daily x 4 weeks, or 50 mg PO daily or PBO x 6 weeks (1:1:2); followed by open-label VBZ 50 mg PO daily | <u>Primary:</u> AIMS dyskinesia total (change from baseline)<br><br><u>Key Secondary:</u> CGI-TD | 6 weeks, followed by 6 week open-label extension      | 109                             | Adults (age 18-65) with neuroleptic-induced tardive dyskinesia and schizophrenia or schizoaffective disorder   | 35 sites in the USA and Puerto Rico          |
| 1202  | Phase 2, randomized, double-blind, placebo-controlled, dose-titration study   | VBZ 25, 50, or 75 mg PO daily (flexible) or PBO PO daily (1:1)  | <u>Primary:</u> AIMS dyskinesia total (change from baseline)                                     | 6 weeks   | 102                             | Adults (age 18-85) with neuroleptic-induced tardive dyskinesia and schizophrenia, schizoaffective disorder, mood disorder, or a gastrointestinal disorder (the latter treated with metoclopramide) | 29 sites in the USA and Puerto Rico          |
| 1304  | Phase 3, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study followed by subject- and investigator-blinded extension | VBZ 40 mg, 80 mg, or PBO PO daily (1:1:1); PBO subjects re-randomized to VBZ 40 mg or 80 mg (1:1) for extension                                     | <u>Primary:</u> AIMS dyskinesia total (change from baseline)<br><br><u>Key Secondary:</u> CGI-TD | 6 weeks, followed by 42 week extension                | 234                             | Adults (age 18-85) with neuroleptic-induced tardive dyskinesia and schizophrenia, schizoaffective disorder, or mood disorder   | 63 sites in the USA, Canada, and Puerto Rico |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

| Trial Identity <sup>1</sup>                           | Trial Design                                     | Regimen/schedule/<br>route <sup>2</sup> | Study Endpoints <sup>3</sup>   | Treatment Duration/<br>Follow Up | No. of patients enrolled | Study Population   | No. of Centers and Regions                   |
|---|--|---|--|----------------------------------|--------------------------|--|--|
| <b>Additional Phase 2/3 Studies to Support Safety</b> |  |   |  |                                  |                          |  |  |
| 1001  | Phase 2, open-label, dose titration study        | VBZ 12.5 mg → 25 mg → 50 mg PO daily    | <u>Safety:</u> AEs, laboratory tests, physical examinations, 12-lead ECGs, BPRS<br><br><u>Efficacy (uncontrolled):</u> AIMS, CGI-TD  | 12 days (4 days of each dose)    | 6                        | Adults (age 18-65) with neuroleptic induced tardive dyskinesia and schizophrenia or schizoaffective disorder                 | 1 (Canada)                                   |
| 1402  | Phase 3, open-label, fixed-dose escalation study | VBZ 40 mg → 80 mg PO daily              | <u>Safety:</u> AEs, laboratory tests, physical examinations, 12-lead ECGs, C-SSRS, BARS, SAS, CDSS, MADRS, PANSS, YMRS<br><br><u>Efficacy (uncontrolled):</u> AIMS, CGI-TD, PGIC, TDIS, AMBMTD | 48 weeks                         | 168                      | Adults (age 18-85) with neuroleptic-induced tardive dyskinesia and schizophrenia, schizoaffective disorder, or mood disorder | 45 sites in the USA, Canada, and Puerto Rico |

<sup>1</sup>All 4-digit identity numbers are prefaced by NBI-98854- for the full trial identifier; <sup>2</sup>VBZ = valbenazine; PO = by mouth; PBO = placebo; <sup>3</sup>AIMS dyskinesia = Abnormal Involuntary Movement Scale Items 1-7; CGI-TD = Clinical Global Impression of Change-Tardive Dyskinesia; ECG = electrocardiogram; BPRS = Brief Psychiatric Rating Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; BARS = Barnes Akathisia Rating Scale; SAS = Simpson-Angus Scale; CDSS = Calgary Depression Scale for Schizophrenia; MADRS = Montgomery-Asberg Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; YMRS = Young-Mania Rating Scale; PGIC = Patient Global Impression of Change; TDIS = Tardive Dyskinesia Impact Scale; AMBMTD = Assessment of Most Bothersome Movement in Tardive Dyskinesia

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

### 5.2. Review Strategy

The review of efficacy focuses primarily on Studies 1304 and 1202. These studies both included six weeks of randomized, double-blind, placebo-controlled treatment of neuroleptic-induced tardive dyskinesia and were considered by the Applicant to be the two pivotal studies for demonstrating efficacy.

Studies 1201 and 1402 were submitted as supportive evidence for efficacy evaluation and are also discussed in this review, albeit with less emphasis given their designs. Study 1201 used on-site AIMS raters for assessing the primary efficacy endpoint, and this was associated with marked scoring variability between sites. The Applicant implemented the use of blinded, central AIMS video raters for assessing the primary efficacy endpoint beginning with Study 1202. Study 1402 was open-label but was analyzed in an exploratory manner, as its 48 weeks of treatment provided limited information about long-term efficacy. Similarly, Studies 1304 and -1201 also included extension phases that were analyzed in an exploratory manner. The Phase 2 studies 1001 and 1101 are not discussed in the efficacy review, because the sample sizes were small (N=6 and N=37) and the treatment durations were short (12 days and 14 days), so the results were less informative.

The efficacy review was based on analyses submitted by the Applicant, supplemented with confirmatory and additional analyses conducted by this reviewer, the Division's Associate Director for Biomedical Informatics Dr. Douglas Warfield, and the Biometrics reviewer Dr. Thomas Birkner. The Clinical Pharmacology team provided input on additional efficacy-related analyses (Section 4.5). The sources of analyses and Table/Figure content are clearly delineated in the text. Analyses were conducted primarily using the software package JMP 12 (SAS Institute).

The review of safety was conducted by Dr. Brian Miller. Prior to commencing the safety review of valbenazine, off-label use in the post-market setting of tetrabenazine (a VMAT2 inhibitor initially approved for the treatment of dyskinesia in Huntington's Disease) was reviewed. This provided additional insight into potential effects of valbenazine. The subsequent pre-market safety review for the product consisted of both re-analysis of the original data submitted by the Sponsor for key safety concerns (e.g. adverse events, concomitant medications and medication interactions, psychiatric scales, etc.), and at times, review of submitted analyses (e.g. vital signs, diagnostic laboratory measurements).

The safety review strategy comprised firstly of a close examination of the placebo controlled periods of Studies 1201 (dose reduction study), 1202 (dose titration study), and 1304 (fixed dose). These controlled studies were examined independently due to the significant differences in dosing regimen. Secondly, in order to increase the power to detect rare events, both the

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

controlled study periods of Studies 1201, 1202, and 1304 were pooled with the open label extensions of Studies 1201 and 1304, and the open label Study 1402. This more extensive safety database was treated as an observational, prospective cohort in which subjects were exposed to varying doses of the drug for different durations. Assistance in reconstructing the drug exposure data for this observational safety database was provided by Dr. Douglas Warfield.

The Applicant's data for adverse events were reviewed in depth, and individual event coding and grouping of preferred terms was performed in order to better evaluate the safety profile of valbenazine. Concomitant medications were reviewed and recoded, as indicated, in order to better examine/attribute class interactions, adverse events, and discontinuations. Psychiatric scale data (e.g. C-SSRS) were examined and analyzed from the submitted datasets. Diagnostic laboratory assessments and vital sign analyses were reviewed and re-analyzed, as needed, from the submitted datasets. Analyses were conducted using JMP 12 (SAS Institute) and Microsoft Excel 2010.

## **6 Review of Relevant Individual Trials Used to Support Efficacy**

---

### **6.1. Study 1304: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel, Fixed-Dose Study to Assess the Efficacy, Safety, and Tolerability of Valbenazine for the Treatment of Tardive Dyskinesia**

#### **6.1.1. Study Design**

##### **Overview and Objective**

The primary objective of this study was to evaluate the efficacy of two doses of valbenazine, administered once daily for up to six weeks, for the treatment of TD. Secondary objectives were to evaluate the efficacy using the Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD) and to evaluate the safety and tolerability of two doses of valbenazine administered for up to 48 weeks.

##### **Trial Design**

*Basic Study Design Summary:* Study 1304 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study designed to evaluate the efficacy, safety, and tolerability of two doses of valbenazine, compared to placebo. This study included a six week double-blind, placebo-controlled, treatment period followed by a 42-week extension period. The study duration for each subject was 52 weeks, including up to 48 weeks of treatment.

## Clinical Review

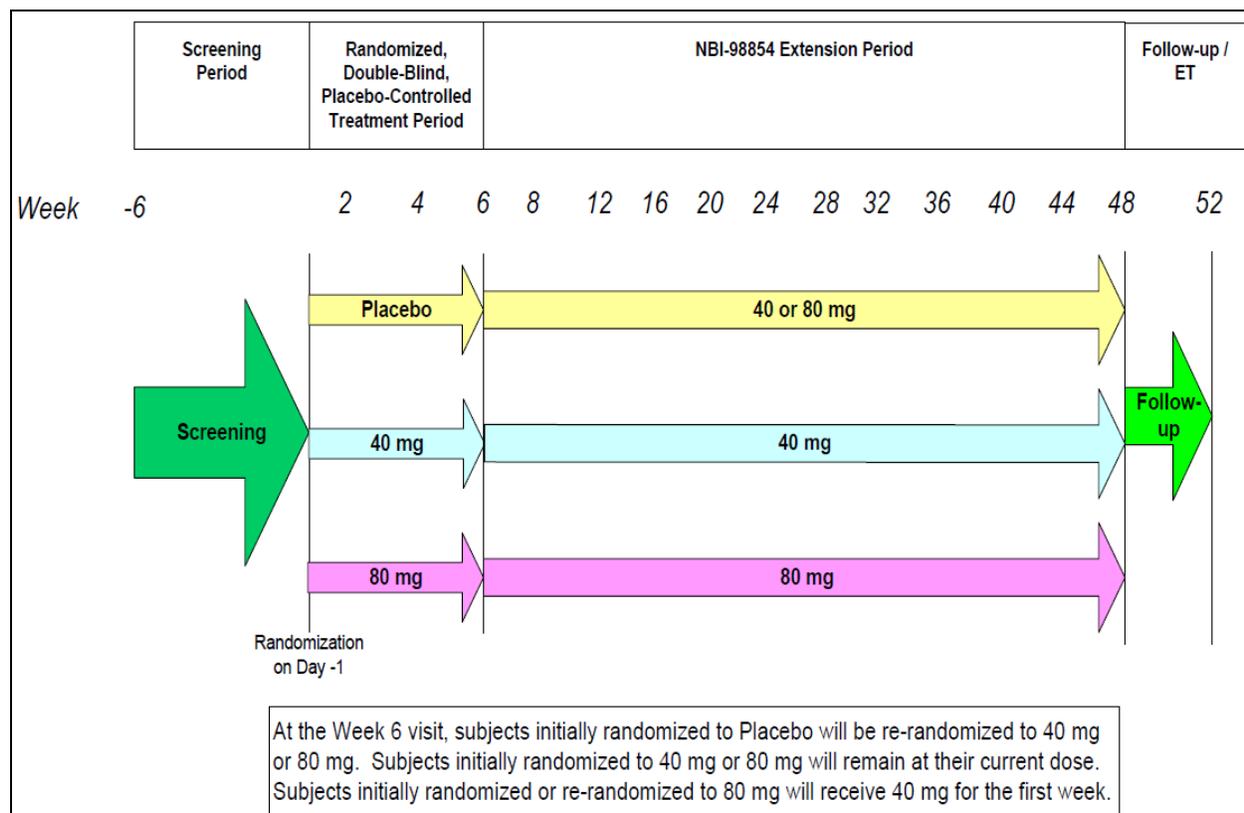
Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Please see Figure 5 for an overview of the design.

**Figure 5: Schematic of 1304 Study Design**



Source: Study 1304 Protocol; April 30, 2015 version; Figure 1 (page 24)

Eligible subjects were initially randomized (1:1:1) to receive valbenazine 40 mg, 80 mg, or placebo by mouth once daily. Subjects who were to receive 80 mg daily were titrated in a blinded manner, receiving 40 mg daily for the first week, following by 80 mg daily. Investigators were permitted to decrease subjects' dose for tolerability reasons one time during the study, and subjects who could not tolerate the adjusted dose were discontinued from the study. To maintain the study blind, subjects who were receiving valbenazine 40 mg daily or placebo were to receive their current dose following a dose "decrease." After six weeks of double-blind treatment, subjects were re-consented to enter the 42-week extension period. During this period, all subjects received valbenazine, though subject and investigator (but not the Applicant) were blinded to the actual dose. Subjects who were initially randomized to receive valbenazine continued their current dose, and those who were initially randomized to receive placebo were re-randomized (1:1) to receive either valbenazine 40 mg or 80 mg daily (with the latter subjects receiving 40 mg daily for the first week). If subjects did not want to continue the study after Week 6, they were asked to return for an early termination visit four weeks later.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*Choice of Control Group:* This study used a placebo control group during the initial 6-week treatment period, which is considered ideal for interpretability. There are no treatments indicated for TD, so an active control was not possible. It would have been ideal from a review perspective to use a placebo control for the 42-week extension period, for optimal interpretability of longer-term efficacy. Nonetheless, the 42-week extension period provided some information regarding the durability and persistence of treatment effect, and the subjects receiving valbenazine 40 mg/day could be considered to be a form of active control to those receiving 80 mg/day.

*Diagnostic Criteria:* Subjects must have met criteria for one of the following DSM-IV clinical diagnoses for at least three months prior to screening: Schizophrenia, Schizoaffective Disorder, or Mood Disorder. The diagnosis was to be confirmed by medical record, reliable self-reported medical history, or evaluation using the Mini International Neuropsychiatric Interview (MINI). Subjects must also have had a clinical diagnosis of neuroleptic-induced TD, as defined by DSM-IV code 333.82, for at least three months prior to screening. The diagnosis was to be confirmed by medical record, physical examination, and reliable self-reported medical history that showed evidence that the involuntary movements associated with dopamine receptor antagonist medication exposure were distinct from other extrapyramidal symptoms. The TD severity needed to be moderate or severe (AIMS item 8  $\geq$  3), as assessed by a blinded, external AIMS video reviewer. These criteria are considered reasonable for the majority of the target population in the US. However, they would exclude subjects who developed TD from neuroleptic use for other conditions, such as gastrointestinal illness (i.e., metoclopramide use) or antipsychotic treatments of other psychiatric illnesses (on- or off-label). This is considered acceptable, as there is no evidence that the pathophysiology of TD differs according to the underlying neuroleptic-treated illness.

### *Key Inclusion/Exclusion Criteria:*

#### Key Inclusion Criteria

1. Be male or female aged 18 to 85 years (inclusive).
2. Meet clinical diagnoses of Schizophrenia, Schizoaffective Disorder, Mood Disorder, and neuroleptic-induced TD for at least 3 months prior to screening, with TD assessed as moderate or severe by AIMS Item 8 (see *Diagnostic Criteria* discussion above).
3. Maintenance medication(s) for schizophrenia or schizoaffective disorder, mood disorders, and other protocol-allowed concurrent medications should be at a stable dose (including no changes to the dose and frequency of ongoing medications and no discontinuation of medications for a minimum of 30 days before screening). Exceptions were allowed if discussed with and approved by study medical monitor or designee prior to randomization. If an exception was approved, the subject must be on a stable dose for 30 days prior to randomization. Benzodiazepines must be at a stable dose for 2

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

weeks before screening.

4. Subjects with a diagnosis of schizophrenia or schizoaffective disorder who are not using antipsychotic medication must have a stable psychiatric status as clinically determined by the investigator. Subjects with a diagnosis of bipolar disorder must be on stable dose of mood stabilizer(s) (e.g., lithium, valproate, olanzapine) for a minimum of 30 days before screening.
5. Have a negative urine drug screen at screening and Day -1, except for any subject receiving a stable dose of benzodiazepine or opiates. Subjects with positive cannabinoid results were allowed to participate in the study provided that the subject was given thorough counseling and agreed to refrain from using cannabinoids for the duration of his/her study participation. Subjects must also have a negative alcohol breath test at screening and Day -1.

### Key Exclusion Criteria

1. Have comorbid abnormal involuntary movement(s) (e.g., parkinsonism, akathisia, truncal dystonia) that is more prominent than TD as assessed by a blinded, external AIMS reviewer using a video recording of the subject's AIMS administration at screening.
2. Have a SAS score  $\geq 3$  on two or more items at screening or Day -1, excluding Items 8 and 10.
3. Have BPRS total score of  $\geq 50$  at screening.
4. Have a significant risk of suicidal or violent behavior. Subjects with any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS in the 3 months prior to screening (using Baseline/Screening version) or Day -1 (using Since Last Visit version) were excluded.
5. Have a known history of neuroleptic malignant syndrome.
6. Have a known history of long QT syndrome or cardiac tachyarrhythmia.
7. Have a screening or Day -1 average triplicate ECG QT interval corrected for heart rate using QTcF of  $>450$  msec (males) or  $>470$  msec (females) or the presence of any clinically significant cardiac abnormality.
8. Subjects with clinical diagnoses of schizophrenia or schizoaffective disorder must not have CDSS total score  $\geq 10$  at screening or Day -1 or PANSS total score  $\geq 70$  at Day -1.
9. Subjects with a clinical diagnosis of mood disorder must not have YMRS total scores  $>10$  at screening or Day -1; been hospitalized for bipolar disorder or major depressive disorder within 6 months prior to screening; have had mood episodes within 2 months prior to screening and Day -1; have history of  $>4$  mood episodes per year; have MADRS total score of  $>13$  at screening or Day -1.

Overall, the eligibility criteria seem to be reasonable for a controlled study population. The "real world" target population is more variable, in terms of substance use and medical and

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

psychiatric illness severity, but the study restrictions were appropriate for assessing efficacy while instituting some control over potential confounders.

*Dose Selection:* The Applicant indicated that the 40 mg and 80 mg doses were selected based on exposure-response analysis that indicated that a steady state  $[+]-\alpha$ -dihydrotrabenazine C<sub>max</sub> of 20-40 ng/mL was an appropriate plasma concentration for efficacy, and that both doses could be administered regardless of CYP2D6 genotype and concomitant medication status. The Applicant noted that doses below 40 mg would be well tolerated but offer dyskinesia reduction comparable to placebo, and that doses above 80 mg afforded little incremental efficacy benefit but would increase the risk of AEs. The dose selection was adequate, but as noted in the End-of-Phase 2 Meeting Minutes, the Division would have preferred an additional dose (e.g., 60 mg daily), as well as a wider range of doses to better capture both the minimal and maximal effective doses.

*Study Treatments:* The study treatments are valbenazine ditosylate 40 mg PO daily, valbenazine ditosylate 80 mg PO daily, and placebo. The placebo capsules appeared identical to the valbenazine capsules. Study treatments were administered in a double-dummy fashion throughout the entire period, with all subjects receiving two capsules for each day of dosing. Subjects randomized to receive valbenazine 80 mg daily were treated with valbenazine 40 mg daily for 7 days for dose titration. Please refer to the Office of Pharmaceutical Quality review for additional information about the product formulation and capsule compositions.

*Assignment to Treatment:* Subjects were randomized by an interactive web response system (IWRS), which occurred on Day -1, after the subjects were confirmed to have met study eligibility criteria. Treatment assignments were made according to a computer-generated randomization schedule. Initial randomization was conducted in a 1:1:1 ratio (valbenazine 40 mg, 80 mg, and placebo), and at Week 6, subjects initially randomized to placebo were re-randomized in a 1:1 ratio to valbenazine 40 mg or 80 mg. Randomization was stratified by underlying disease category (i.e., schizophrenia/schizoaffective disorder and mood disorder) to assure balanced randomization among the three treatment groups. The treatment assignment was adequate, but in this reviewer's opinion it may have been unnecessary to stratify by underlying disease category, as it is not clear that TD pathophysiology differs between psychiatric diagnosis groups; furthermore, the categories are somewhat artificial (i.e., bipolar disorder is categorized as a "mood disorder" but might have more in common neurobiologically with schizoaffective disorder than major depressive disorder).

*Blinding:* As discussed under *Study Treatments*, placebo capsules were identical to valbenazine 40 mg capsules, and treatments were administered in a double-dummy fashion. In the 6-week placebo-controlled treatment period, the subject, investigator, study site personnel, central AIMS video raters, the blinded external AIMS reviewer, and the Applicant were blinded to subject treatment. In the 42-week extension period, the Applicant was unblinded for the

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

purpose of primary efficacy analysis, while all other parties remained blinded to the valbenazine dose. The randomization code was able to be broken for an individual subject only if the subject was pregnant or experienced a Serious Adverse Event that the investigator felt could not be adequately treated without knowing the treatment assignment. The blinding procedures seem generally appropriate, considering the study design.

*Dose Modification and Discontinuation:* Doses could be reduced one time during the study for reason of intolerability. If the new dose was unable to be tolerated, subjects were discontinued from the study. For subjects who were receiving 40 mg daily or placebo, the “reduced” dose would be the current dose, so as to maintain the study blind. This approach for dose modification and discontinuation was reasonable, as there were no other doses available in this study other than valbenazine 40 mg, 80 mg, and placebo.

*Administrative Structure:* The final approved protocol and informed consent form (ICF) documents were reviewed by Institutional Review Boards (IRBs) for each clinical site. Central clinical laboratory tests, prolactin measurements, and CYP2D6 genotyping were performed by (b) (4). The IWRS was conducted by (b) (4). The pharmacokinetics and bioanalysis procedures were performed by (b) (4). The videography data processing was performed by (b) (4). The external AIMS video reviewers and psychiatric scale training procedures were conducted by (b) (4). The electronic data capture system was managed by (b) (4). The study used a Data and Safety Monitoring Board (DSMB) to periodically review ongoing clinical safety data to ensure the safety and well-being of study subjects.

*Procedures and Schedule:* Please refer to Table 3 for a schedule of events during the placebo-controlled period and Table 4 for a schedule of events in the extension period. The primary efficacy assessment measure, the AIMS (described in Study Endpoints), was administered at screening, baseline, Weeks 2, 4, 6, 8, 16, 24, 32, 40, 48, and at the follow-up visit (Week 52 or early termination). The key secondary efficacy measure (CGI-TD), used to rate the overall global improvement of TD since the initiation of study drug dosing, was administered at Weeks 2, 4, 6, 8, 16, 24, 32, 40, 48, and at the follow-up visit (Week 52 or early termination). The schedule for assessing the primary and key secondary efficacy measures seems reasonable for assessing the time course of drug effects.

Clinical Review  
Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH  
NDA 209241  
Ingrezza (valbenazine)

**Table 3: Study 1304 - Schedule of Assessments, Placebo-Controlled Period**

| Procedure   | Screening | Base-<br>line | Randomized, Double-<br>Blind, Placebo-<br>Controlled Period |          |   |   |   |   |
|---|-----------|---------------|---|----------|---|---|---|---|
|   |           |               | Week  | -6 to -1 | 0 | 2 | 4 | 6 |
| <b>Screening assessments:</b> informed consent, UBACC, medical history (update at Baseline), inclusion/exclusion criteria (update at Baseline), serology studies, BPRS, drug and alcohol screening (repeated at Baseline)   | X         |               |   |          |   |   |   |   |
| <b>Safety assessments:</b> physical examination (height at screening only), vital signs, 12-lead ECG, pregnancy test, clinical laboratory tests, serum prolactin (excluding Screening), C-SSRS, BARS (excluding Screening), SAS, AE monitoring, prior and concomitant medications | X         | X             | X   | X        | X | X | X | X |
| <b>Pharmacokinetic sampling</b>   |           |               | X   | X        | X | X | X | X |
| <b>Primary efficacy:</b> AIMS (including video recording)   | X         | X             | X   | X        | X | X | X | X |
| <b>Key secondary efficacy:</b> CGI-TD   |           |               | X   | X        | X | X | X | X |
| <b>Secondary efficacy:</b> TDIS   | X         | X             | X   | X        | X | X | X | X |
| <b>Secondary efficacy:</b> PGIC   |           |               | X   | X        | X | X | X | X |
| <b>Schizophrenia/Schizoaffective Disorder Assessments:</b>  |           |               |   |          |   |   |   |   |
| PANSS   |           | X             | X   | X        | X | X | X | X |
| CDSS  | X         | X             | X   | X        | X | X | X | X |
| <b>Mood Disorder Assessments:</b> MADRS, YMRS   | X         | X             | X   | X        | X | X | X | X |

*Adapted from Study 1304 Protocol; April 30, 2015 version; Tables 1-2 (page 31-34)*

Definitions: AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; BPRS=Brief Psychiatric Rating Scale; CDSS=Calgary Depression Scale for Schizophrenia; CGI-TD=Clinical Global Impression of Tardive Dyskinesia; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; MADRS=Montgomery-Asberg Depression Rating Scale; PANSS=Positive and Negative Syndrome Scale; PGIC=Patient Global Impression of Change; SAS=Simpson-Angus Scale; TDIS=Tardive Dyskinesia Impact Scale; UBACC=University of California, San Diego Brief Assessment of Capacity to Consent; YMRS=Young Mania Rating Scale.

Clinical Review  
Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH  
NDA 209241  
Ingrezza (valbenazine)

**Table 4: Study 1304 - Schedule of Assessments, Extension Period**

| Procedure  | Valbenazine Extension Period |   |    |    |    |    |    |    |    |    |    |    | FU |
|--|------------------------------|---|----|----|----|----|----|----|----|----|----|----|----|
|  | Week                         | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 |    |
| <b>Safety Assessments 1:</b> physical examination, vital signs, 12-lead ECG, pregnancy test, clinical laboratory studies, C-SSRS, AE monitoring, prior and concomitant medications |                              | X | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  |
| <b>Safety Assessments 2:</b> serum prolactin, BARS; SAS  |                              | X |    | X  |    | X  |    | X  |    | X  |    | X  | X  |
| <b>SZ/SAD Assessments</b>  |                              |   |    |    |    |    |    |    |    |    |    |    |    |
| CDSS, PANSS  |                              | X |    | X  |    | X  |    | X  |    | X  |    | X  | X  |
| <b>Mood Disorder Assessments</b>   |                              |   |    |    |    |    |    |    |    |    |    |    |    |
| MADRS, YMRS  |                              | X |    | X  |    | X  |    | X  |    | X  |    | X  | X  |
| <b>Efficacy Assessments</b>  |                              |   |    |    |    |    |    |    |    |    |    |    |    |
| AIMS, TDIS, CGI-TD, PGIC   |                              | X |    | X  |    | X  |    | X  |    | X  |    | X  | X  |
| <b>Pharmacokinetic Sampling</b>  |                              | X |    | X  |    | X  |    | X  |    | X  |    | X  | X  |

*Adapted from Study 1304 Protocol; April 30, 2015 version; Tables 1-2 (page 31-34)*

*FU=Follow-up/Early Termination; SZ=Schizophrenia; SAD=Schizoaffective Disorder; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; CDSS=Calgary Depression Scale for Schizophrenia; CGI-TD=Clinical Global Impression of Change-Tardive Dyskinesia; C-SSRS=Columbia-Suicide Severity Rating Scale; AE=adverse event; ECG=electrocardiogram; PANSS=Positive and Negative Syndrome Scale; PGIC=Patient Global Impression of Change; SAS=Simpson-Angus Scale; TDIS=Tardive Dyskinesia Impact Scale; MADRS=Montgomery-Asberg Depression Rating Scale; YMRS=Young Mania Rating Scale*

**Dietary Restrictions/Instructions:** There were no specific dietary restrictions/instructions except that subjects must limit alcohol use to less than 7 drinks per week during the course of the study; this is reasonable.

**Concurrent Medications:** All coexisting diseases or conditions were to be treated in accordance with prevailing medical practice. No change to the dose, frequency, or discontinuation of medications to treat subjects' psychiatric and medical conditions was allowed for a minimum of 30 days before screening. Exceptions were allowed, if discussed with and approved by the medical monitor prior to randomization. However, subjects must have been on a stable dose of medication for 30 days prior to randomization, and treatment regimens were expected to remain stable during the study. As needed use of over-the-counter and prescription medications was allowed to treat headaches, pain, respiratory symptoms, acute allergic symptoms, and allergies. Medications recommended for as-needed use for insomnia included eszopiclone 7.5 mg, zaleplon 10 mg, zolpidem 5 mg for female subjects and 10 mg for male subjects, and doxepin 3 or 6 mg at night.

The following medications were prohibited from 30 days prior to screening (unless otherwise stated) until the final study visit:

CDER Clinical Review Template 2015 Edition  
Version date: April 9, 2015 for initial rollout (NME/original BLA reviews)

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

1. Antiemetics: Metoclopramide, prochlorperazine, and promethazine.
2. Botulinum toxin: Injections were prohibited starting 90 days prior to screening and during the study.
3. CYP3A4 inducers: Strong inducers of CYP3A4 (e.g., phenytoin, phenobarbital, rifabutin, rifampin, primidone, St. John's Wort). The use of carbamazepine was permitted if approved by the medical monitor prior to randomization.
4. Dopamine agonists and precursors: Dopamine receptor agonists (e.g., ropinirole) and precursors (e.g., carbidopa/levodopa).
5. MAOIs (e.g., isocarboxazid, phenelzine, selegiline, tranylcypromine).
6. Stimulants (e.g., amphetamine, methylphenidate, ephedrine, pseudoephedrine, phenylephrine, and phenylpropanolamine).
7. VMAT2 Inhibitors other than the study drug (e.g., tetrabenazine, reserpine)
8. Drugs known to increase the QT interval: The use of medication known to increase the QT interval was allowed if approved by the Applicant prior to randomization. Baseline QTcF must have been  $\leq 450$  msec for males or  $\leq 470$  msec for females. Specific listed medications that may increase the QT interval were chlorpromazine, thioridazine, citalopram, azithromycin, clarithromycin, erythromycin, moxifloxacin, quinidine, procainamide, amiodarone, and sotalol.
9. As needed use of the following medications: anticholinergics, benzodiazepines, antipsychotics, mood stabilizers, antidepressants, strong CYP3A4 inhibitors and inducers, and strong CYP2D6 inhibitors.

The protocol specifications for concurrent and prohibited medications were generally reasonable. Changes in psychotropic or other dopaminergic medications (e.g., antipsychotics, benzodiazepines, psychostimulants, dopamine receptor agonists and precursors) could confound the efficacy assessment of valbenazine. Botulinum toxin injections, which are sometimes used as an off-label treatment for focal TD movements, could also confound efficacy assessments. It is notable that chronic use of CYP3A4 inhibitors were not prohibited; this could potentially impact efficacy assessment, given the probable importance of valbenazine's major active metabolite ([+]- $\alpha$ -dihydro-tetrabenazine) in mediating drug effects.

*Treatment Compliance:* Subjects were instructed to bring all unused study drug and empty packaging materials to the study center for each visit. Compliance was assessed by counting the capsules returned at each study visit. Subjects were also called weekly by a study center representative to remind them to take the medication daily. In addition, plasma samples were collected at the end of Weeks 2, 4, 6, 8, 16, 24, 32, 40, 48, and the final visit (end of Week 52 or early termination visit) for determination of plasma concentrations of valbenazine and [+]- $\alpha$ -dihydro-tetrabenazine. These methods are deemed adequate and consistent with standard trial practice.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*Rescue Medication:* Not applicable for this protocol.

*Subject Completion, Discontinuation, or Withdrawal:* Subjects who fully completed the study participated in a ≤6 week screening period, a 6-week double-blind, placebo-controlled treatment period, a 42-week blinded valbenazine extension period, and a 4-week follow-up period, with the final study visit approximately four weeks after the last dose of study drug. Subjects were free to discontinue participation at any time. Investigators were required to withdraw subjects if the type, frequency, or severity of any AE became unacceptable or intolerable, if QTcF > 500 msec or a subject had a clinically significant ECG change, if a subject exhibited active suicidal ideation with at least some intent to act, or if the subject was lost to follow-up, confirmed to be pregnant, or was unable to tolerate the treatment dose after a one-time dose reduction. If subjects withdrew prematurely from the study, the reason for withdrawal was recorded and subjects underwent early termination assessments (see *Procedures and Schedule* above). It was considered crucial to obtain follow-up data for subjects withdrawn for safety-related reasons.

## Study Endpoints

The primary efficacy assessment measure was adapted from the AIMS [24]. The original scale, which was designed to assess the severity of TD, included 12 items, with 7 items rating involuntary movements in the orofacial region, extremities, and trunk on a scale from 0 (no dyskinesia) to 4 (severe dyskinesia); 3 items rating global severity, patients awareness, and distress associated with movements; and 2 yes/no items concerning problems with teeth and dentures. In this study, only Items 1-7 were scored by the central video AIMS raters; individual item scores were summed to produce the AIMS dyskinesia total score (range: 0-28, with higher scores reflecting increased severity).

For assessment of efficacy, the AIMS was administered (but not scored) by study investigators and video recorded, as described in *Procedures and Schedule* above. Video recordings for baseline, Weeks 2, 4, 6, 8, 16, 32, 48, and follow-up period were reviewed by central raters who were blinded to the subjects' study visit number and treatment assignments. The central raters were neurologists with movement disorder expertise. Two central raters reviewed each video together and needed to achieve agreement on the score (0 to 4) for AIMS Items 1-7. The central video ratings were performed in two batches: 1) Baseline and Weeks 2, 4, 6, and 2) Weeks 8, 16, 32, 48, and 52. The primary efficacy endpoint was the AIMS dyskinesia total score mean change from baseline to Week 6. As described in Section 3.2, the Division accepted this as the primary endpoint for pivotal efficacy trials, including the Applicant's modification of the original AIMS descriptors to the version used by central AIMS raters (Table 5). Of note, the on-site AIMS examiners were only responsible for videotaping the AIMS assessments in this study and did not score the measure.

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

In this reviewer's opinion, the AIMS was a reasonable choice for a primary efficacy measure. Its validity has been established by comparisons to other similar instruments [25], and it has been widely used in clinical and research settings for the purpose of assessing the presence and severity of TD. Limitations with this measure include the need for a trained and experienced rater [26] (which the Applicant has addressed by using neurologists with movement disorder expertise as central AIMS raters) and the lack of consensus as to what would constitute a meaningful change in AIMS score. The use of consensus central AIMS raters is considered to be strength of this study, because it negated interrater variability and the sequence/expectation bias that can accompany on-site raters.

APPEARS THIS WAY ON ORIGINAL

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 5: Primary Efficacy Assessment - Abnormal Involuntary Movement Scale (AIMS)**

| Score | Descriptors (For items 1-7)  |
|-------|--|
| 0     | No dyskinesia  |
| 1     | Minimal or slight dyskinesia: Low amplitude, present during some but not most of the exam                                  |
| 2     | Mild dyskinesia: Low amplitude and present during most of the exam (or moderate amplitude and present during some of exam) |
| 3     | Moderate dyskinesia: Moderate amplitude and present during most of exam  |
| 4     | Severe dyskinesia: Maximal amplitude and present during most of exam   |

| Facial and Oral Movements  | None | Minimal | Mild | Moderate | Severe |
|--|------|---------|------|----------|--------|
| <b>1. Muscles of Facial Expression</b><br>e.g., movements of forehead, eyebrows, periorbital area, cheeks, include frowning, blinking, smiling, grimacing  | 0    | 1       | 2    | 3        | 4      |
| <b>2. Lips and perioral area</b><br>e.g., puckering, pouting, smacking   | 0    | 1       | 2    | 3        | 4      |
| <b>3. Jaw</b><br>e.g., biting, clenching, chewing, mouth opening, lateral movement   | 0    | 1       | 2    | 3        | 4      |
| <b>4. Tongue</b><br>Rate only increase in movement both in and out of mouth, NOT inability to sustain movement   | 0    | 1       | 2    | 3        | 4      |
| Extremity Movements  |      |         |      |          |        |
| <b>5. Upper (arms, wrists, hands, fingers)</b><br>Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine). DO NOT include tremor (i.e., repetitive, regular, rhythmic) | 0    | 1       | 2    | 3        | 4      |
| <b>6. Lower (legs, knees, ankles, toes)</b><br>e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot  | 0    | 1       | 2    | 3        | 4      |
| Trunk Movements  |      |         |      |          |        |
| <b>7. Neck, shoulders, hips</b><br>e.g., rocking, twisting, squirming, pelvic gyrations  | 0    | 1       | 2    | 3        | 4      |

Source: Study 1304 Clinical Study Protocol Amendment 3 Final Version (4/30/2015)

The Clinical Global Impression of Change – Tardive Dyskinesia (CGI-TD) was used as a key secondary outcome measure. This measure was modified from the Clinical Global Impression (CGI) [27], which was originally developed to provide a global evaluation of improvement over time from the clinician’s perspective. The CGI-TD (Figure 6) was rated by an investigator or qualified clinician designee at Weeks 2, 4, 6, 8, 16, 24, 32, 40, 48, and the follow-up or early termination visit. While it was not mandated, the protocol specified that if possible, the same person should rate the CGI-TD at all time points. Each of the seven CGI-TD responses was assigned a score from 1-7, with 1=very much improved and 7=very much worse. The pre-specified key secondary endpoint was the mean CGI-TD score at Week 6. This was accepted by the Division at the End of Phase 2 meeting; however it was noted that the percentage of

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

responders based on CGI-TD scores would not be acceptable for this purpose. Limitations with this outcome measure include the variability introduced by potentially different raters across visits and the subjective assessment of improvement, which may vary according to training and clinical experience. Furthermore, this comparison-based assessment necessitates an accurate recall of the subjects' baseline presentations. Unlike the AIMS, this measure was not scored by central raters. Overall, this efficacy endpoint is considered to be less useful than the central-rated AIMS change from baseline for assessing efficacy.

### Figure 6: Clinical Global Impression - Tardive Dyskinesia (CGI-TD) Scale

The investigator (or designee) will evaluate the change in the subject's Tardive Dyskinesia (TD) symptoms since initiation of study drug by choosing one of the 7 responses. Since the subject started taking the study medication, his/her TD symptoms are:

- Very Much Improved
- Much Improved
- Minimally Improved
- Not Changed
- Minimally Worse
- Much Worse
- Very Much Worse

Source: Study 1304 Clinical Study Protocol Amendment 3 Final Version (4/30/2015)

Additional efficacy assessments administered in this study were:

1. Patient Global Impression of Change (PGIC) – patient-reported outcome measure in which subjects evaluated the change in their TD symptoms since initiation of study drug by choosing one of seven responses (1=very much improved, 2=much improved, 3=minimally improved, 4=not changed, 5=minimally worse, 6=much worse, and 7=very much worse). This measure was completed by subjects at Weeks 2, 4, 6, 8, 16, 24, 32, 40, 48 and at the follow-up or early termination visit.
2. Tardive Dyskinesia Impact Scale (TDIS) – patient-reported outcome measure, under development by the Applicant, used to assess the impairment and disability associated with dyskinesia. The TDIS consists of 11 questions, each rated on a scale from 0 to 4, where 0 is the least and 4 is the most severe. The questions asked about difficulty speaking, making mouth noises, swallowing, gripping objects, writing or typing, walking, losing balance, pain, unwanted attention from others, embarrassment, and feeling self-conscious due to uncontrollable movements. This measure was completed by subjects at screening, baseline, Weeks 2, 4, 6, 8, 16, 24, 32, 40, 48, and at the follow-up or early

Clinical Review  
 Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH  
 NDA 209241  
 Ingrezza (valbenazine)

termination visit.

Please see Table 6 below for a listing and classification of Applicant-specified study efficacy endpoints.

**Table 6: Summary of Efficacy Endpoints and Classification**

| <b>Efficacy Endpoint</b>  | <b>Endpoint Classification (ITT Analysis Set)</b> |
|---|---|
| AIMS dyskinesia total score mean change from baseline at Week 6         | Primary   |
| CGI-TD mean score at Week 6   | Key secondary                                     |
| Percentage of subjects classified as AIMS responders at Week 6          | Secondary   |
| Percentage of subjects classified as CGI-TD responders at Week 6        | Secondary   |
| PGIC mean score at Week 6   | Secondary   |
| Percentage of subjects classified as PGIC responders at Week 6          | Secondary   |
| TDIS total score mean change from baseline at Week 6                    | Secondary   |
| AIMS dyskinesia total score mean change from baseline at Weeks 2 and 4  | Exploratory                                       |
| CGI-TD mean score at Weeks 2 and 4                                      | Exploratory                                       |
| Percentage of subjects classified as AIMS responders at Weeks 2 and 4   | Exploratory                                       |
| Percentage of subjects classified as CGI-TD responders at Weeks 2 and 4 | Exploratory                                       |
| PGIC mean score at Weeks 2 and 4  | Exploratory                                       |
| Percentage of subjects classified as PGIC responders at Weeks 2 and 4   | Exploratory                                       |
| TDIS total score mean change from baseline at Weeks 2 and 4             | Exploratory                                       |

*Source: 1304 Statistical Analysis Plan, Table 5 (9/3/2015)*

### Statistical Analysis Plan

The Statistical Analysis Plan (SAP) for this study was dated September 3, 2015. The SAP defined three analysis sets for this study:

1. Safety analysis set – included were subjects who were randomized to a treatment group and dispensed study drug, with the following two exclusions: (a) subjects who withdrew from the study and returned all previously dispensed study drug with all doses present, and (b) subjects who had no post-baseline safety data collected.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

2. Intent to treat (ITT) analysis set – included were all subjects in the safety analysis set who had a baseline AIMS dyskinesia total score value and at least one post-randomization AIMS dyskinesia total score value reported during the double-blind, placebo-controlled treatment period. Subjects who discontinued from the study prior to the Week 2 visit would have AIMS data for the early termination visit and were included in the ITT set. The ITT analysis set was used for summaries and analyses of efficacy and PK data. Technically, this is considered to be a modified ITT analysis set, as not all randomized subjects were included in the set.
3. Per protocol (PP) analysis set – included were all subjects in the ITT analysis set who had an AIMS dyskinesia total score value for the Week 6 visit, had no efficacy-related important protocol deviations, and, for subjects receiving valbenazine, had a detectable plasma level of valbenazine at the end of the Week 6 visit. The PP analysis set was used for the Applicant's supportive summaries and analyses of efficacy and PK data.

*Handling of Missing Data:* The SAP indicated that missing values for outcome measures were not replaced with imputed values except for early termination visit data mapped to a scheduled visit for summary and analysis purposes. Imputation of missing AIMS dyskinesia total scores during the double-blind, placebo-controlled treatment period were performed in conjunction with sensitivity analyses of the primary efficacy endpoint. Derived scale total scores (e.g., the YMRS score), which are calculated as the sum of the scores of the individual scale items, were recorded as missing if any of the individual scale item scores were missing. Missing and incomplete dates for AEs and concomitant medications were imputed only for the purposes of estimating the time of the event or medication usage in relationship to the study treatment periods.

*Analysis of Primary Efficacy Endpoint:* The primary efficacy endpoint for the study was the AIMS dyskinesia total score mean change from baseline at Week 6, using the ITT analysis set. The Applicant analyzed this endpoint by Mixed Effect Model Repeat Measurement (MMRM) methods, including the change from baseline at Weeks 2, 4, and 6. The model included the baseline AIMS dyskinesia total score as a covariate, with treatment group, disease category, and visit as fixed effects and subject as a random effect. The model also included the following interaction terms: treatment group x visit and baseline x visit. The Applicant indicated that study site was not included in the model, as there were a large number of sites with most having a small number of subjects, and the AIMS assessments were scored by central raters. The MMRM analysis was implemented with the PROC MIXED procedure of SAS.

*Analysis of the Key Secondary Endpoint:* The CGI-TD mean score at week 6 was analyzed in the ITT analysis set using CGI-TD scores from Weeks 2, 4, and 6, in an MMRM model similar to that of the primary efficacy endpoint but without the baseline AIMS covariate or the baseline x visit interaction term.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*Multiplicity:* The SAP specified that in order to control the family-wise error rate for the primary and key secondary endpoints as well as the two valbenazine dosing group comparisons to placebo, the following fixed-sequence testing procedure was used:

1. Week 6 AIMS dyskinesia total score mean change from baseline: valbenazine 80 mg treatment group vs. placebo treatment group
2. Week 6 CGI-TD mean score: valbenazine 80 mg treatment group vs. placebo treatment group
3. Week 6 AIMS dyskinesia total score mean change from baseline: valbenazine 40 mg treatment group vs. placebo treatment group
4. Week 6 CGI-TD mean score: valbenazine 40 mg treatment group vs. placebo treatment group

In order for a test result in the above list to be considered statistically significant, all of the test results higher in the list must be significant at the  $p=0.05$  level. During the IND phase of development, the Division recommended that the primary endpoint should be tested for both 80 mg and 40 mg prior to testing the key secondary endpoint (CGI-TD), but the Applicant did not implement this recommendation.

*Additional Analyses:* Please see Table 6 for a tabulation of all specified efficacy endpoints and classifications. Additional analyses included the AIMS Responder Analysis (defining that a “responder” is a subject whose AIMS dyskinesia total score is reduced by at least 50% from baseline at the specified post-baseline visit); a CGI-TD Responder Analysis (defining two types of CGI-TD responders: type 1 – score of either 1 (very much improved) or 2 (much improved) and type 2 – score of either 1, 2, or 3 (minimally improved)); and a PGIC Responder Analysis (defining two types of PGIC responders with the same criteria as the CGI-TD).

Please refer to the Biostatistics review for a detailed evaluation of the Applicant’s statistical analyses.

### **Protocol Amendments**

The original protocol was finalized on July 15, 2014. Amendment 1 was finalized on August 12, 2014, and contained the following notable changes:

1. The valbenazine 80 mg dose would be titrated (40 mg daily for the first week, followed by 80 mg daily).
2. The first visit after the start of the double-blind treatment period was changed from 4 weeks to 2 weeks.
3. The use of a valbenazine 80 mg capsule was removed and replaced with a double-dummy design (2 x 40 mg capsules).

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

4. Washout of prohibited medications should occur after signing the Informed Consent Form and 30 days prior to undergoing screening.

Amendment 2 was finalized on November 4, 2014, and contained the following notable changes:

1. The screening visit Calgary Depression Scale for Schizophrenia (CDSS) responses should be based on feelings and experiences during the two weeks prior to the screening visit. At all other time points, the responses should be based on feelings and experiences since the last study visit.
2. The scoring of the Young Mania Rating Scale (YMRS) should be based on the clinical condition over the past 7 days prior to the study visit as well as clinical observations made during the course of the interview.
3. Restrictions to refrain from drinking grapefruit juice and strenuous physical exercise for the study duration were removed.
4. The initially planned statistical analyses were updated to remove the prior sensitivity analyses model, and methods of controlling for multiplicity were revised in the SAP. The TDIS was added as a secondary endpoint for Week 6 analysis.

Amendment 3 was finalized on April 30, 2015, and contained the following notable changes:

1. The 42-week valbenazine treatment period was renamed from “double-blind valbenazine treatment period” to “valbenazine extension period,” so the Applicant could be unblinded for the purpose of primary efficacy analysis after the last subject completed the Week 6 visit.
2. The list of prohibited strong CYP3A4 inducers was amended to add phenytoin.
3. The inclusion criteria were updated to allow a reliable self-reported medical record if the subjects were unable to provide a medical record.
4. The visits from which AIMS videos were to be rated centrally were reduced to baseline and the end of Weeks 2, 4, 6, 8, 16, 32, 48, and 52 (weeks 24 and 40 were removed).
5. The statistical and analytical plan in the study protocol was updated to reflect analyses described in the SAP.

From review of the submitted datasets, the first date of subject randomization was November 5, 2014, which occurred after Protocol Amendment 2 was finalized. The modifications included in the protocol amendments are not expected to significantly impact the integrity of the study or the interpretation of the efficacy results.

### **Data Quality and Integrity: Applicant’s Assurance**

The Applicant indicated that the study was performed in compliance with Good Clinical Practice

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

(GCP) and FDA regulations and guidelines. Throughout the study, the study monitor made frequent contacts with the Investigators by telephone and on-site visits. A 100% source document verification was performed for the first two randomized subjects at each site. All subsequently randomized subjects at each site had the following eCRFs verified: enrollment, inclusion/exclusion, AEs, concomitant medications, AIMS, TDIS, CGI-TD, PGIC, PK blood draw, final visit/end of treatment, study drug accountability, and study drug dosing. Data were collected via an electronic data capture (EDC) system (b) (4). Data were validated using a combination of real time electronic and ongoing manual edit checks. An electronic query was generated for any data discrepancy that required a response and/or data change from the Investigator or other authorized site personnel to resolve the issue. All data changes were tracked using an electronic audit trail. Data from the central AIMS video raters' CRFs were entered into the EDC system by a Sponsor Data Management team member, and the entered data was reviewed by a second team member for accuracy. Upon completion of data entry and review, a team member ran a report of the data entered into the EDC, and the EDC data were compared against the source CRFs for accuracy. Quality assurance audits were performed at 11 clinical study sites, and audit certificates were included with the application. A quality control review of the clinical study report was performed by the Applicant, checking for consistency, clarity, and accuracy. Overall, the data quality and integrity plan appears to have been adequate.

### 6.1.2. Study Results

#### **Compliance with Good Clinical Practices**

The Applicant attested that the study was conducted in accordance with GCP and 21 CFR parts 11, 50, 54, 56, 312, and 314.

#### **Financial Disclosure**

Please see Appendix 13.2 for the financial disclosure review of all covered clinical studies (as defined in 21 CFR 54). There were no disclosable financial interests or arrangements. This information was confirmed by the Applicant in a Response to Information Request received on December 22, 2016. Based on the certification and Applicant verification, there are no concerns about financial conflicts of interest that would affect the interpretation of this study data or the approvability of this application.

#### **Patient Disposition**

Please see Figure 7 for a diagram of subject disposition through Week 6. There were 234 subjects randomized in this study. The ITT sample included 225 subjects; of the nine subjects who were randomized but not included in the efficacy analysis set, two subjects withdrew and returned all study drug and seven subjects had no post-randomization AIMS data. The

## Clinical Review

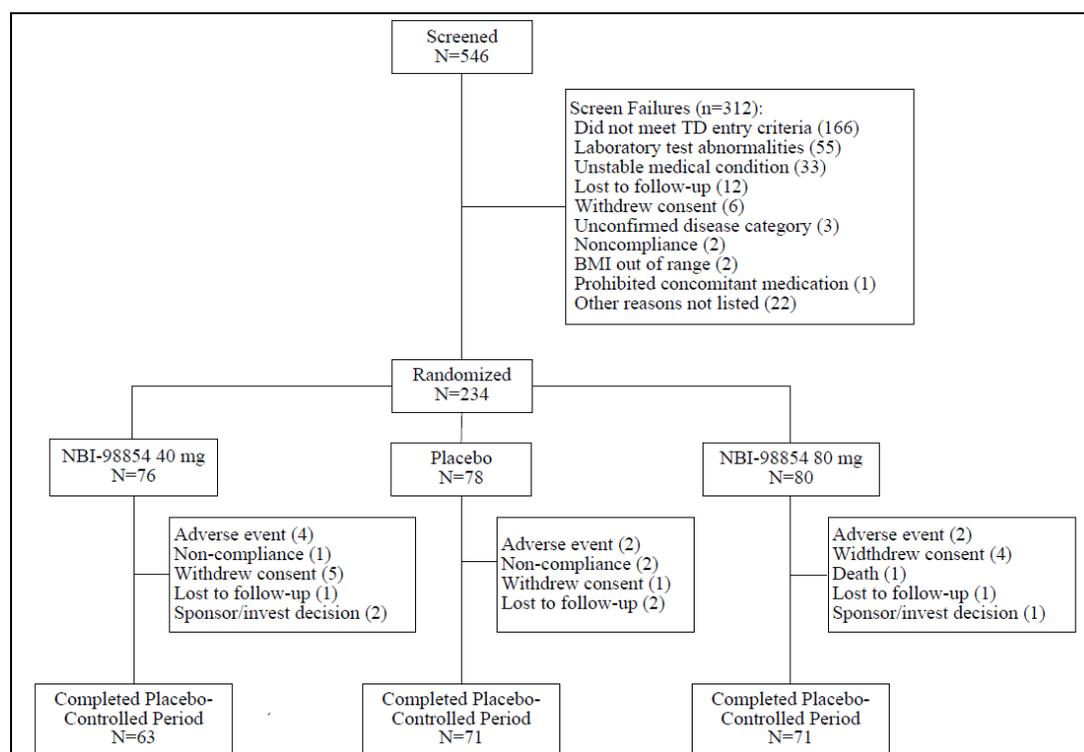
Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

assignments of the nine subjects excluded from the ITT analysis set were placebo (n=2), valbenazine 40 mg (n=6), and valbenazine 80 mg (n=1). Of the 234 randomized subjects, 205 (87.6%) completed the 6-week placebo-controlled period; this included 91% of subjects assigned to placebo, 82.9% of subjects assigned to valbenazine 40 mg, and 88.8% of subjects assigned to valbenazine 80 mg. The lower rate of completion in the valbenazine 40 mg group was mostly attributable to reasons of adverse events and withdrawal of consent.

**Figure 7: Study 1304 - Subject Disposition Through Week 6**



Source: Study 1304 Clinical Study Report, Figure 2, p. 69

The majority of subjects who completed the placebo-controlled 6-week period entered the 42-week extension period (97% of placebo completers, 98% of valbenazine 40 mg completers, and 96% of valbenazine 80 mg completers). Three subjects who were initially randomized to valbenazine 80 mg daily had a dose-reduction during the 6-week period so were included in the valbenazine 40 mg group in the extension period. Please see Table 7 for a summary of patient disposition during the extension period. Overall, the completion rate was not as high in the extension period as the initial 6-week treatment period, but the duration was much longer so this is not unexpected. However, this loss of subjects affects the interpretability of the long-term efficacy results due to attrition bias, as only 121 out of the initial 234 randomized patients (61.1%) completed the entire study. There was no clear relationship of valbenazine dose with

Clinical Review  
 Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH  
 NDA 209241  
 Ingrezza (valbenazine)

whether subjects completed the extension period.

**Table 7: Study 1304 - Subject Disposition in Extension and Post-treatment Periods**

|   | Valbenazine<br>40 mg (N=97) | Valbenazine<br>80 mg (N=101) | Total<br>(N=198) |
|---|-----------------------------|------------------------------|------------------|
| Discontinued during extension period                            | 36 (37.1%)                  | 38 (37.6%)                   | 74 (37.4%)       |
| Completed extension period                                      | 61 (62.9%)                  | 63 (62.4%)                   | 124 (62.6%)      |
| Discontinued during post-treatment period                       | 1 (1.0%)                    | 2 (2.0%)                     | 3 (1.5%)         |
| Completed study   | 60 (61.9%)                  | 61 (60.4%)                   | 121 (61.1%)      |
| <u>Reason for discontinuation during extension period:</u>      |                             |                              |                  |
| Adverse event   | 14 (14.4%)                  | 17 (16.8%)                   | 31 (15.7%)       |
| Protocol deviation  | 0                           | 1 (1.0%)                     | 1 (0.5%)         |
| Non-compliance  | 3 (3.1%)                    | 3 (3.0%)                     | 6 (3.0%)         |
| Withdrawal of consent   | 9 (9.3%)                    | 8 (7.9%)                     | 17 (8.6%)        |
| Death   | 0                           | 1 (1.0%)                     | 1 (0.5%)         |
| Lost to follow-up   | 8 (8.2%)                    | 6 (5.9%)                     | 14 (7.1%)        |
| Sponsor/investigator decision                                   | 2 (2.1%)                    | 2 (2.0%)                     | 4 (2.0%)         |
| <u>Reason for discontinuation during post-treatment period:</u> |                             |                              |                  |
| Adverse event   | 0                           | 1 (1.0%)                     | 1 (0.5%)         |
| Withdrawal of consent   | 1 (1.0%)                    | 0                            | 1 (0.5%)         |
| Lost to follow-up   | 0                           | 1 (1.0%)                     | 1 (0.5%)         |

Source: Adapted from 120-Day Safety Update, Table 14.1.1.2, p. 1575 (November 21, 2016)

### Protocol Violations/Deviations

In the 6-week randomized, placebo-controlled, treatment period, 47 subjects (20.1%) had at least one important protocol deviation identified. The incidence of important protocol deviations was reasonably balanced between treatment groups. Please see Table 8 for a categorization of important protocol deviations by treatment group.

**Table 8: Study 1304 - Important Protocol Deviations, 6-week phase**

|   | Placebo<br>(N=78)<br>n (%) | NBI-98854<br>40 mg<br>(N=76)<br>n (%) | NBI-98854<br>80 mg<br>(N=80)<br>n (%) | All<br>Subjects<br>(N=234)<br>n (%) |
|---|----------------------------|---------------------------------------|---------------------------------------|-------------------------------------|
| <b>Important Protocol Deviations</b>        |                            |                                       |                                       |                                     |
| Subjects with Important Protocol Deviations | 16 (20.5)                  | 12 (15.8)                             | 19 (23.8)                             | 47 (20.1)                           |
| Inclusion or Exclusion Criteria             | 11 (14.1)                  | 9 (11.8)                              | 13 (16.3)                             | 33 (14.1)                           |
| Study Drug Administration or Compliance     | 1 (1.3)                    | 0                                     | 1 (1.3)                               | 2 (0.9)                             |
| Safety Assessments                          | 0                          | 0                                     | 1 (1.3)                               | 1 (0.4)                             |
| Concomitant Medications                     | 5 (6.4)                    | 1 (1.3)                               | 7 (8.8)                               | 13 (5.6)                            |
| Other                                       | 0                          | 2 (2.6)                               | 1 (1.3)                               | 3 (1.3)                             |

Source: 1304 Clinical Study Report, Table 10, p. 73

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

The listing of important protocol deviations was reviewed. The most common category of deviations was Inclusion or Exclusion criteria, which included events such as positive urine toxicology results, the use of various medications for less than 30 days (e.g., antibiotics, antihypertensives, analgesics), and hospitalization for psychiatric disorder within 6 months prior to screening. The second most common category of deviations was Concomitant Medications, which included medications such as levodopa/carbidopa (which led to study discontinuation), haloperidol and lorazepam during a hospitalization (which led to study discontinuation), as-needed benzodiazepines, mixed amphetamine salts for fatigue, as-needed diphenhydramine for allergies, as-needed promethazine for nausea, as-needed phenylephrine for nasal congestion, bromocriptine for hyperprolactinemia, and antibiotics. It is theoretically possible that some of these concomitant medications might affect TD symptoms, but their limited use patterns and low occurrence frequencies suggest that it is unlikely that they would significantly impact the study results.

### **Table of Demographic Characteristics**

Please see Table 9 for a tabulation of demographic characteristics for the ITT sample. Both sexes were reasonably well represented in the sample. The majority of subjects were under 65 years old and the mean and median ages were in the mid-50's across all treatment groups. This is a reasonable approximation of the target population for this drug, as middle-aged to elderly patients would generally have a longer duration of total antipsychotic exposure, as well as exposure to typical antipsychotics, than younger patients. Patients of African-American and Caucasian races, as well as those with Hispanic ethnicity, were well-represented in the study sample. The race that was not represented in the sample was Asian, for reasons that are unclear; however, there is no reason to believe that the response to TD treatment differ between races other than potential differences in drug metabolism. With regards to site location, of the 225 subjects in the ITT sample, three were from sites in Puerto Rico, four were from sites in Canada, and the remaining 218 were from sites in US states; this is reasonable for evaluating a drug to be marketed in the US.

**Table 9: Study 1304 - Baseline Subject Characteristics, 6-week ITT Sample**

| Parameter                                 | Placebo<br>(N=76)<br>n (%) | Valbenazine<br>(N=149)                        |   | Total<br>(N=225)<br>n (%) |
|---|----------------------------|---|---|---------------------------|
|   |                            | Valbenazine<br>40 mg daily<br>(N=70)<br>n (%) | Valbenazine<br>80 mg daily<br>(N=79)<br>n (%) |                           |
| <b>Sex</b>                                |                            |   |   |                           |
| Male                                      | 42 (55.3%)                 | 40 (57.1%)                                    | 39 (49.4%)                                    | 121 (53.8%)               |
| Female                                    | 34 (44.7%)                 | 30 (42.9%)                                    | 40 (50.6%)                                    | 104 (46.2%)               |
| <b>Age</b>                                |                            |   |   |                           |
| Mean years (SD)                           | 57.0 (10.5)                | 55.3 (8.6)                                    | 56.0 (10.0)                                   | 56.1 (9.8)                |
| Median (years)                            | 58                         | 56  | 57  | 57                        |
| Min, max (years)                          | 30, 84                     | 26, 74  | 32, 83  | 26, 84                    |
| <b>Age Group</b>                          |                            |   |   |                           |
| ≥ 17 - < 65 years                         | 60 (78.9%)                 | 62 (88.6%)                                    | 67 (84.8%)                                    | 189 (84.0%)               |
| ≥ 65 years                                | 16 (21.1%)                 | 8 (11.4%)                                     | 12 (15.2%)                                    | 36 (16.0%)                |
| <b>Race</b>                               |                            |   |   |                           |
| Caucasian                                 | 43 (56.6%)                 | 41 (58.6%)                                    | 44 (55.7%)                                    | 128 (56.9%)               |
| Black or African American                 | 29 (38.2%)                 | 25 (35.7%)                                    | 32 (40.5%)                                    | 86 (38.2%)                |
| Asian                                     | 0                          | 0   | 0   | 0                         |
| American Indian or Alaska Native          | 0                          | 1 (1.4%)                                      | 1 (1.3%)                                      | 2 (0.9%)                  |
| Native Hawaiian or Other Pacific Islander | 1 (1.3%)                   | 0   | 0   | 1 (0.4%)                  |
| Other <sup>1</sup>                        | 3 (3.9%)                   | 3 (4.3%)                                      | 2 (2.5%)                                      | 8 (3.6%)                  |
| <b>Ethnicity</b>                          |                            |   |   |                           |
| Hispanic or Latino                        | 23 (30.3%)                 | 22 (31.4%)                                    | 14 (17.7%)                                    | 59 (26.2%)                |
| Not Hispanic or Latino                    | 53 (69.7%)                 | 48 (68.6%)                                    | 65 (82.3%)                                    | 166 (73.8%)               |

<sup>1</sup>Includes identified races "Arabic," "Hispanic," "Mexican," and Mixed

Source: Data derived from 1304 Clinical Study Report (Tables 14.1.6 and 14.1.8) and analysis dataset DM.XPT

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Please see Table 10 for a summary of subject baseline characteristics in the 6-week ITT analysis set. The treatment groups were reasonably well balanced across the examined baseline parameters. However, the valbenazine 40 mg group had higher proportions of subjects with ultra-rapid or poor CYP2D6 activity, which could potentially affect drug concentrations. Since

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

the underlying illness was considered as a potential moderator (and used as a stratification criterion for treatment assignment), it would have been preferable if the diseases were more well-defined; only 80 of the 225 subjects had specific psychiatric diagnoses listed in the MHDIAG.XPT tabulation dataset (DIAGSPEC variable). The number of years since initial TD diagnosis had a wide range but was comparable between treatment groups; this is important in case the duration of TD would moderate the treatment effect. Approximately 85% of study subjects continued to receive an antipsychotic, with the majority of these being of the atypical class. This is important to consider for efficacy assessment, as many if not most of patients with TD will need to continue antipsychotic therapy for underlying mental illnesses. Approximately 1/3 of subjects were receiving anticholinergic drugs (e.g., benztropine, diphenhydramine, trihexyphenidyl); these medications are typically prescribed for prevention of antipsychotic-associated EPS and have not been definitively shown to affect TD symptoms [28]. Overall, the baseline characteristics of the ITT analysis set appear roughly congruent with the expected US target population.

APPEARS THIS WAY ON ORIGINAL

**Table 10: Study 1304 - Baseline Characteristics, ITT Analysis Set**

| Parameter   | Placebo<br>(N=76)<br>n (%) | Valbenazine<br>40 mg daily<br>(N=70)<br>n (%) | Valbenazine<br>80 mg daily<br>(N=79)<br>n (%) | Total<br>(N=225)<br>n (%) |
|---|----------------------------|---|---|---------------------------|
| <b>Body Mass Index</b> (mean kg/m <sup>2</sup> (SD))            | 28.03 (5.44)               | 28.77 (5.45)                                  | 27.78 (5.84)                                  | 28.17 (5.58)              |
| <b>CYP2D6 Genotype Classification</b>                           |                            |   |   |                           |
| Ultra-Rapid Metabolizer   | 1 (1.3)                    | 5 (7.1)                                       | 1 (1.3)                                       | 7 (3.1)                   |
| Extensive or Ultra Rapid Metabolizer                            | 2 (2.6)                    | 2 (2.9)                                       | 1 (1.3)                                       | 5 (2.2)                   |
| Extensive Metabolizer   | 48 (63.2)                  | 31 (44.3)                                     | 46 (58.2)                                     | 125 (55.6)                |
| Intermediate or Extensive Metabolizer                           | 2 (2.6)                    | 1 (1.4)                                       | 1 (1.3)                                       | 4 (1.8)                   |
| Intermediate Metabolizer  | 20 (26.3)                  | 24 (34.3)                                     | 26 (32.9)                                     | 70 (31.1)                 |
| Poor Metabolizer  | 3 (3.9)                    | 7 (10.0)                                      | 3 (3.8)                                       | 13 (5.8)                  |
| Not Reported  | 0                          | 0   | 1 (1.3)                                       | 1 (0.4)                   |
| <b>Disease Category</b>   |                            |   |   |                           |
| Schizophrenia/Schizoaffective Disorder                          | 50 (65.8)                  | 46 (65.7)                                     | 52 (65.8)                                     | 148 (65.8)                |
| Mood Disorder   | 26 (34.2)                  | 24 (34.3)                                     | 27 (34.2)                                     | 77 (34.2)                 |
| <b>TD Duration</b> <sup>1</sup> (years since TD diagnosis (SD)) | 6.5 (6.4)                  | 6.7 (7.9)                                     | 8.2 (10.6)                                    | 7.2 (8.5)                 |
| <b>Baseline AIMS Dyskinesia Total Score</b><br>(mean (SD))      | 9.9 (4.3)                  | 9.8 (4.1)                                     | 10.4 (3.6)                                    | 10.1 (4.0)                |
| <b>Current Antipsychotic Use</b>                                |                            |   |   |                           |
| None  | 13 (17.1)                  | 7 (10)  | 16 (20.3)                                     | 36 (16)                   |
| Atypical Only   | 56 (73.7)                  | 52 (74.3)                                     | 49 (62)                                       | 157 (69.8)                |
| Typical or Combination  | 7 (9.2)                    | 11 (15.7)                                     | 14 (17.7)                                     | 32 (14.2)                 |
| <b>Current Anticholinergic Use</b>                              |                            |   |   |                           |
| Yes   | 22 (29)                    | 27 (38.6)                                     | 31 (39.2)                                     | 80 (35.6)                 |
| No  | 54 (71)                    | 43 (61.4)                                     | 48 (60.8)                                     | 145 (64.4)                |

Source: Reviewer-created, using data from 1304 Clinical Study Report (Table 14.1.8) and ADSL.XPT analysis dataset  
<sup>1</sup>Calculated by subtracting age at TD diagnosis from age at study entry; data available for 161 subjects (N=54 placebo, N=49 valbenazine 40 mg, and N=58 valbenazine 80 mg)

## Treatment Compliance, Concomitant Medications, and Rescue Medication Use

### Treatment Compliance

The Applicant presented treatment compliance data as the estimated number of doses taken divided by the expected number of doses taken in a given time interval, based on returned pill counts. In the 6-week placebo-controlled period, compliance, as assessed by this method, was high and similar between the treatment groups (Table 11). Compliance as assessed by returned pill counts was also high in the valbenazine extension period (Week 6 to Week 48), with 93.8% of subjects receiving valbenazine 40 mg daily and 92.1% of subjects receiving 80 mg daily having ≥80% compliance during this period. Another method of assessing compliance was by examining the plasma concentrations of valbenazine and [+]–α-dihydrotrabenazine. The percentage of subjects who were non-CYP2D6 poor metabolizers, received valbenazine treatment, and had valbenazine and [+]–α-dihydrotrabenazine plasma concentrations above

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

the lower limit of quantification are also displayed in Table 11. From this analysis, it appears there were likely a limited number of subjects who were returning empty pill containers but not ingesting the pills. While this PK-based assessment could not assess placebo noncompliance and provides only a crude measure of whether subjects were taking any medication, it does suggest that there were no major dose-related effects that led to increased noncompliance in subjects receiving the 80 mg valbenazine dose as compared to the 40 mg dose.

**Table 11: Study 1304 - Treatment Compliance, Double-Blind Period, ITT Analysis Set**

|   | Placebo<br>(N=76) | Valbenazine<br>40 mg (N=70) | Valbenazine<br>80 mg (N=79) |
|---|-------------------|-----------------------------|-----------------------------|
| <b>Day 1 through Week 6</b>                   |                   |                             |                             |
| ≥ 80% compliance: n (%)                       | 71 (93.4)         | 66 (94.3)                   | 77 (97.5)                   |
| < 80% compliance: n (%)                       | 5 (6.6)           | 4 (5.7)                     | 2 (2.5)                     |
| <b>Week 2</b>                                 |                   |                             |                             |
| [valbenazine] > LLQ fraction (%)              |                   | 53/62 (85.5)                | 68/72 (94.4)                |
| [[+]-α-dihydrotrabenazine] > LLQ fraction (%) |                   | 56/62 (90.3)                | 67/72 (93.1)                |
| <b>Week 4</b>                                 |                   |                             |                             |
| [valbenazine] > LLQ fraction (%)              |                   | 50/58 (86.2)                | 61/66 (92.4)                |
| [[+]-α-dihydrotrabenazine] > LLQ fraction (%) |                   | 52/58 (89.7)                | 62/66 (93.9)                |
| <b>Week 6</b>                                 |                   |                             |                             |
| [valbenazine] > LLQ fraction (%)              |                   | 51/58 (87.9)                | 57/64 (89.1)                |
| [[+]-α-dihydrotrabenazine] > LLQ fraction (%) |                   | 51/58 (87.9)                | 59/64 (92.2)                |

*Source: Reviewer-created, using data from Study 1304 Clinical Study Report, Table 14.3.5.2.3 (p. 1149) and Table 14.2.5.3 (p. 532). Compliance percentages are based on returned pills at study visits. The PK-based percentages represent the proportion of non-CYP2D6 poor metabolizer subjects who had concentrations > lower limit of quantification (LLQ).*

### Concomitant Medications

The Applicant's tabulation of concomitant medications was reviewed for subjects in the placebo-controlled period (Table 12). The most commonly-used concomitant medications were consistent with those commonly prescribed for patients with schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder (e.g., antidepressants, mood stabilizers, antipsychotics, anxiolytics, hypnotics) as well as medications for common medical comorbidities (antihypertensives, lipid lowering agents, thyroid hormone replacement). There was some variability between treatment groups, but this seems to be most likely random variation and related to the relatively small number of subjects in each group. Concomitant medications were generally required to be administered at stable doses from 30 days prior to randomization for the duration of the study. Medications that hypothetically could affect drug response (described in Section 2) include antipsychotics, benzodiazepines, and medications that might have a pharmacokinetic interaction (i.e., valproic acid). As shown in Table 12, the proportion of patients taking typical vs. atypical antipsychotics was roughly similar between

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

treatment groups. Overall, the differences in stable concomitant medication use between treatment groups are not expected to impact the overall efficacy conclusions of this randomized trial.

APPEARS THIS WAY ON ORIGINAL

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 12: Study 1304 - Concomitant Medications Used by ≥10% of Subjects in Any Treatment Group During Placebo Controlled Period**

| ATC Category/<br>Preferred Name  | Placebo<br>(N=76)<br>n (%) | Valbenazine<br>40 mg<br>(N=72)<br>n (%) | Valbenazine<br>80 mg<br>(N=79)<br>n (%) |
|--|----------------------------|---|---|
| <b>Overall</b>   | <b>76 (100)</b>            | <b>71 (98.6)</b>                        | <b>79 (100)</b>                         |
| <b>Ace inhibitors, plain</b>   | <b>23 (30.3)</b>           | <b>14 (19.4)</b>                        | <b>19 (24.1)</b>                        |
| Lisinopril   | 22 (28.9)                  | 11 (15.3)                               | 15 (19.0)                               |
| <b>Adrenergics, inhalants</b>  | <b>15 (19.7)</b>           | <b>9 (12.5)</b>                         | <b>13 (16.5)</b>                        |
| Salbutamol   | 13 (17.1)                  | 7 (9.7)                                 | 8 (10.1)                                |
| <b>Anticholinergic agents</b>  | <b>22 (28.9)</b>           | <b>30 (41.7)</b>                        | <b>32 (40.5)</b>                        |
| Benzotropine   | 19 (25.0)                  | 30 (41.7)                               | 27 (34.2)                               |
| <b>Antidepressants</b>   | <b>52 (68.4)</b>           | <b>48 (66.7)</b>                        | <b>51 (64.6)</b>                        |
| Citalopram   | 10 (13.2)                  | 10 (13.9)                               | 11 (13.9)                               |
| Fluoxetine   | 10 (13.2)                  | 7 (9.7)                                 | 3 (3.8)                                 |
| Mirtazapine  | 6 (7.9)                    | 8 (11.1)                                | 6 (7.6)                                 |
| Sertraline   | 13 (17.1)                  | 10 (13.9)                               | 9 (11.4)                                |
| Trazodone  | 10 (13.2)                  | 17 (23.6)                               | 17 (21.5)                               |
| <b>Antiepileptics</b>  | <b>25 (32.9)</b>           | <b>21 (29.2)</b>                        | <b>34 (43.0)</b>                        |
| Clonazepam   | 8 (10.5)                   | 5 (6.9)                                 | 15 (19.0)                               |
| Valproate semisodium   | 11 (14.5)                  | 10 (13.9)                               | 7 (8.9)                                 |
| <b>Antiinflammatory and antirheumatic products, non-steroids</b>           | <b>18 (23.7)</b>           | <b>17 (23.6)</b>                        | <b>10 (12.7)</b>                        |
| Ibuprofen  | 8 (10.5)                   | 9 (12.5)                                | 7 (8.9)                                 |
| Naproxen   | 8 (10.5)                   | 5 (6.9)                                 | 1 (1.3)                                 |
| <b>Antipsychotics</b>  | <b>63 (82.9)</b>           | <b>66 (91.7)</b>                        | <b>65 (82.3)</b>                        |
| Aripiprazole   | 10 (13.2)                  | 8 (11.1)                                | 10 (12.7)                               |
| Haloperidol  | 4 (5.3)                    | 13 (18.1)                               | 11 (13.9)                               |
| Olanzapine   | 11 (14.5)                  | 8 (11.1)                                | 8 (10.1)                                |
| Quetiapine   | 18 (23.7)                  | 24 (33.3)                               | 14 (17.7)                               |
| Risperidone  | 14 (18.4)                  | 11 (15.3)                               | 16 (20.3)                               |
| <b>Antithrombotic agents</b>   | <b>16 (21.1)</b>           | <b>10 (13.9)</b>                        | <b>14 (17.7)</b>                        |
| Acetylsalicylic acid   | 15 (19.7)                  | 9 (12.5)                                | 14 (17.7)                               |
| <b>Anxiolytics</b>   | <b>20 (26.3)</b>           | <b>26 (36.1)</b>                        | <b>17 (21.5)</b>                        |
| Alprazolam   | 5 (6.6)                    | 8 (11.1)                                | 1 (1.3)                                 |
| Lorazepam  | 7 (9.2)                    | 7 (9.7)                                 | 9 (11.4)                                |
| <b>Blood glucose lowering drugs, excluding insulins</b>                    | <b>24 (31.6)</b>           | <b>21 (29.2)</b>                        | <b>14 (17.7)</b>                        |
| Metformin  | 23 (30.3)                  | 17 (23.6)                               | 13 (16.5)                               |
| <b>Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)</b> | <b>19 (25.0)</b>           | <b>27 (37.5)</b>                        | <b>25 (31.6)</b>                        |
| Omeprazole   | 13 (17.1)                  | 10 (13.9)                               | 13 (16.5)                               |
| <b>Hypnotics and sedatives</b>   | <b>18 (23.7)</b>           | <b>17 (23.6)</b>                        | <b>19 (24.1)</b>                        |
| Diphenhydramine  | 7 (9.2)                    | 8 (11.1)                                | 5 (6.3)                                 |
| Zolpidem   | 7 (9.2)                    | 5 (6.9)                                 | 9 (11.4)                                |
| <b>Iron preparations</b>   | <b>10 (13.2)</b>           | <b>8 (11.1)</b>                         | <b>1 (1.3)</b>                          |
| Ferrous sulfate  | 8 (10.5)                   | 6 (8.3)                                 | 1 (1.3)                                 |
| <b>Lipid modifying agents, plain</b>                                       | <b>29 (38.2)</b>           | <b>22 (30.6)</b>                        | <b>23 (29.1)</b>                        |
| Atorvastatin   | 6 (7.9)                    | 5 (6.9)                                 | 9 (11.4)                                |
| Simvastatin  | 13 (17.1)                  | 5 (6.9)                                 | 7 (8.9)                                 |
| <b>Selective calcium channel blockers with mainly vascular effects</b>     | <b>9 (11.8)</b>            | <b>8 (11.1)</b>                         | <b>10 (12.7)</b>                        |
| Amlodipine   | 8 (10.5)                   | 6 (8.3)                                 | 10 (12.7)                               |
| <b>Thyroid preparations</b>  | <b>10 (13.2)</b>           | <b>6 (8.3)</b>                          | <b>10 (12.7)</b>                        |
| Levothyroxine  | 10 (13.2)                  | 6 (8.3)                                 | 10 (12.7)                               |

Source: Study 1304 Clinical Study Report, Table 16, p. 79. Includes all subjects in the Safety Analysis Set for the 6-week placebo-controlled period.

CDER Clinical Review Template 2015 Edition

Version date: April 9, 2015 for initial rollout (NME/original BLA reviews)

*Rescue Medications*

There was no role for rescue medications in this study, as there are no current treatments for TD.

**Efficacy Results – Primary Endpoint**

As described in more detail in *Analysis of Primary Efficacy Endpoint* (Section 6.1.1), the primary efficacy endpoint was the mean change from baseline on the AIMS dyskinesia total score from Baseline to the end of Week 6, using the ITT analysis set and analyzed by MMRM methods. As shown in Table 13, valbenazine 80 mg was statistically superior to placebo on the primary efficacy endpoint. While valbenazine 40 mg had a nominally significant p value, it was not considered statistically significant because it was lower in the pre-specified multiple testing sequence than a non-significant statistical test (discussed under *CGI-TD* below).

**Table 13: Study 1304 - Primary Efficacy Endpoint (Applicant Analysis)**

|   | <b>Placebo<br/>(N=76)</b> | <b>Valbenazine<br/>40 mg (N=70)</b> | <b>Valbenazine<br/>80 mg (N=79)</b> |
|---|---------------------------|-------------------------------------|-------------------------------------|
| <b>6-week AIMS CFB: LS mean (SEM)<sup>1</sup></b> | -0.1 (0.4)                | -1.9 (0.4)                          | -3.2 (0.4)                          |
| <b>LS mean difference vs. placebo (SEM)</b>       |                           | -1.8 (0.6)                          | -3.1 (0.6)                          |
| <b>95% confidence interval</b>                    |                           | -3.0, -0.7                          | -4.2, -2.0                          |
| <b>p value<sup>2</sup></b>                        |                           | 0.0021                              | <0.0001                             |

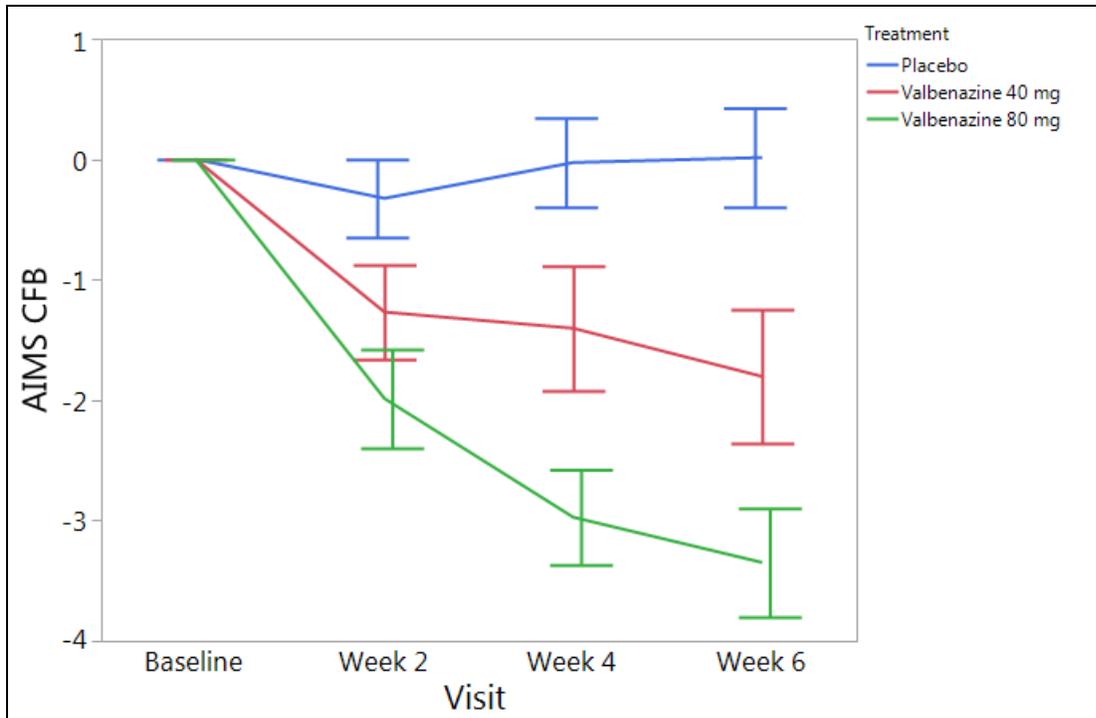
Source: Study 1304 Clinical Study Report, Table 22, p. 86

<sup>1</sup>Least-squares (LS) mean was based on the MMRM model, which included baseline AIMS dyskinesia total score as a covariate and treatment group, primary psychiatric diagnosis, visit, baseline by visit interaction, and treatment group by visit interaction as fixed effects, and subject as a random effect.

<sup>2</sup>p value for test of null hypothesis that difference between the treatment group LS mean is equal to zero

Please refer to Figure 8 for a graph displaying the improvement in AIMS total dyskinesia score over time during the double-blind treatment period. By Week 2, both valbenazine 40 mg and valbenazine 80 mg treatment groups were nominally statistically superior to placebo (p=0.0313 and p=0.0010, respectively, from Applicant analyses), suggesting that onset of therapeutic benefit from valbenazine may occur earlier than 6 weeks.

**Figure 8: Study 1304 - Mean AIMS Change from Baseline, Double-Blind Treatment Period, ITT Analysis Set**

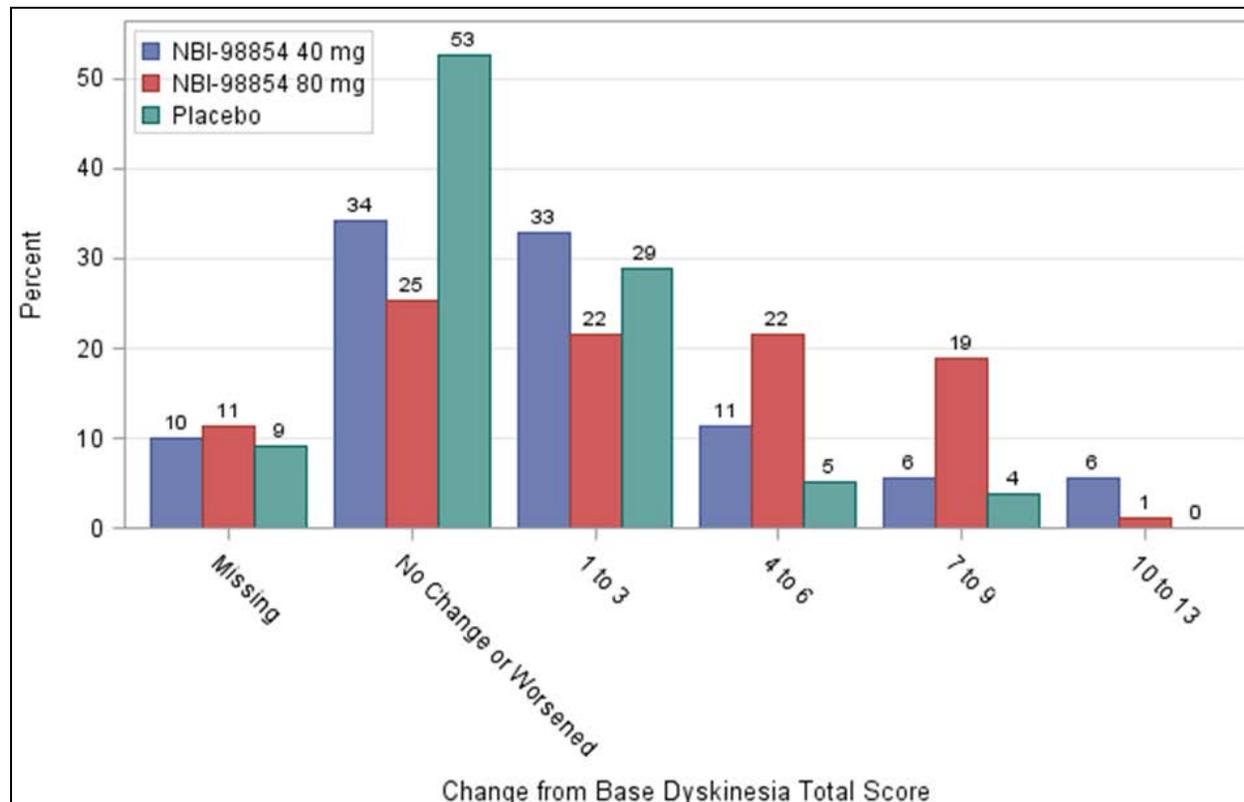


Source: Reviewer-created, using Study 1304 analysis dataset A\_AIMS.XPT. Error bars represent standard error of the mean. CFB = change from baseline.

In order to better visualize the proportion of subjects who achieved various thresholds of AIMS score changes, Biometrics reviewer Dr. Thomas Birkner prepared a response histogram (Figure 9). This analysis shows that at the end of Week 6, 42% of subjects receiving valbenazine 80 mg had  $\geq 4$  reduction on the AIMS total dyskinesia score, as compared to 9% of subjects receiving placebo.

APPEARS THIS WAY ON ORIGINAL

**Figure 9: Study 1304 - Percent of Patients with Specific Magnitude of AIMS Total Score Improvement at Week 6 (ITT Analysis Set)**



Source: created by Biometrics reviewer Dr. Thomas Birkner. NBI-98854=valbenazine.

Since the AIMS total dyskinesia score is comprised of the sum of 7 different body regions, it was important to assess whether the effects of valbenazine were limited to specific regions or if all affected areas improved with treatment. Visual inspection of Figure 10 suggests that, on average, all AIMS component scores improve over time with valbenazine treatment and the drug effects did not appear to be limited to specific muscle groups.

APPEARS THIS WAY ON ORIGINAL

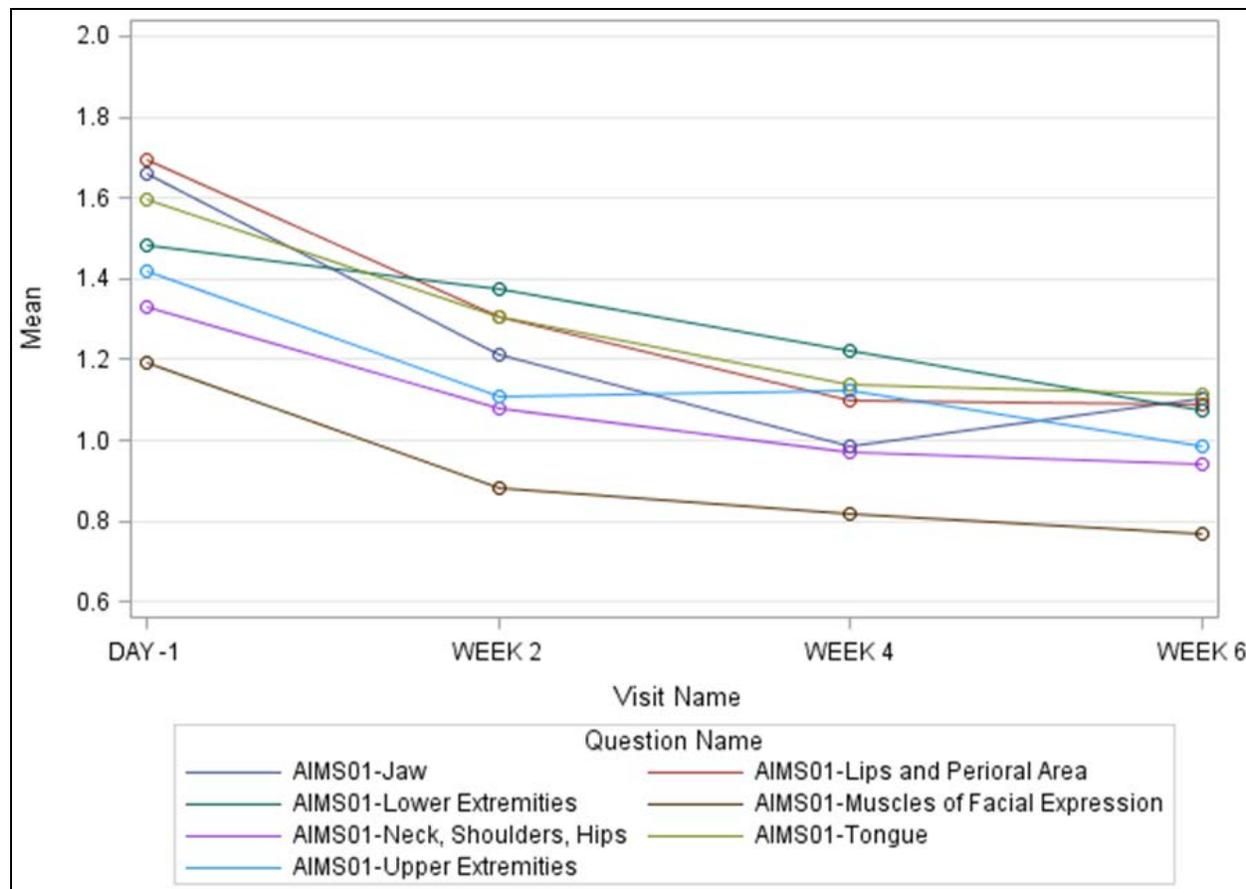
Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Figure 10: Study 1304 - AIMS Component Scores, Valbenazine 80 mg group, ITT Analysis Set**



Source: created by Biometrics reviewer Dr. Thomas Birkner; Day -1=Baseline.

An assessment of effects in demographic subpopulations and by baseline characteristics was performed by this reviewer (Table 14). These analyses are considered exploratory in nature, as the study was not powered to assess subgroup effects and any statistical comparisons would be limited by multiplicity concerns. There were no clear patterns of valbenazine response according to TD duration, ethnicity, antipsychotic type, or the use of anticholinergic medications. There was a modestly less robust valbenazine response in subjects age 65 years or greater, but there were very few subjects in this group. Women appeared to have a modestly better response to valbenazine, particularly with the 40 mg dose. Subjects of black race appeared to have a lesser response to the 40 mg dose, though response to the 80 mg dose appeared equivalent to subjects of white race. Subjects with higher BMIs appeared to have a better response than subjects in the lowest BMI quartile. Subjects who were not using antipsychotic medications appeared to have a better response than those using antipsychotic medications; however, there were a limited number of subjects in the former group. Subjects with schizophrenia or schizoaffective disorder appeared to have a modestly poorer response

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

than those with mood disorders, which might be related to antipsychotic use, as ~70% of subjects with schizophrenia or schizoaffective disorder were taking antipsychotics vs. ~30% of subjects with mood disorders. Altogether, it is difficult to derive any firm conclusions from these subgroup analyses, but all examined groups receiving valbenazine 80 mg/day showed a reduction in AIMS total dyskinesia score at the end of Week 6. Please refer to Section 7.1.3 for subgroup analyses across all efficacy trials.

**Table 14: Study 1304 - Subgroup Efficacy Analysis (6-week AIMS Change from Baseline)**

| Age Group                                 | Treatment |      |         |                   |      |         |                   |      |         |  |
|---|-----------|------|---------|-------------------|------|---------|-------------------|------|---------|--|
|   | Placebo   |      |         | Valbenazine 40 mg |      |         | Valbenazine 80 mg |      |         |  |
|   | N         | Mean | Std Err | N                 | Mean | Std Err | N                 | Mean | Std Err |  |
| <57                                       | 28        | 0.04 | 0.67    | 34                | -1.5 | 0.72    | 33                | -3.2 | 0.71    |  |
| 57-64                                     | 26        | 0.08 | 0.77    | 20                | -2.5 | 1.16    | 26                | -3.8 | 0.74    |  |
| >=65                                      | 15        | -0.1 | 0.58    | 7                 | -1.1 | 0.63    | 10                | -2.6 | 0.78    |  |
| <b>TD Duration</b>                        |           |      |         |                   |      |         |                   |      |         |  |
| >4 years                                  | 29        | -0.5 | 0.67    | 20                | -2.2 | 1.13    | 26                | -3.7 | 0.83    |  |
| 0-4 years                                 | 22        | 0.05 | 0.4     | 25                | -2.1 | 0.76    | 26                | -2.9 | 0.67    |  |
| <b>Sex</b>                                |           |      |         |                   |      |         |                   |      |         |  |
| F   | 32        | -0.9 | 0.58    | 24                | -2.8 | 0.82    | 35                | -3.7 | 0.62    |  |
| M   | 37        | 0.84 | 0.55    | 37                | -1.2 | 0.74    | 34                | -3   | 0.66    |  |
| <b>Race</b>                               |           |      |         |                   |      |         |                   |      |         |  |
| Black                                     | 24        | -0.6 | 0.7     | 23                | -0.7 | 0.99    | 25                | -3.5 | 0.74    |  |
| White                                     | 41        | 0.15 | 0.52    | 34                | -2.5 | 0.72    | 41                | -3.2 | 0.59    |  |
| Other                                     | 4         | 2.25 | 2.14    | 4                 | -2.3 | 0.48    | 3                 | -4.3 | 2.91    |  |
| <b>Ethnicity</b>                          |           |      |         |                   |      |         |                   |      |         |  |
| Hispanic/Latino                           | 21        | 0.38 | 0.74    | 18                | -1.9 | 1.01    | 12                | -2.6 | 1.13    |  |
| Not Hispanic/Latino                       | 48        | -0.1 | 0.5     | 43                | -1.7 | 0.67    | 57                | -3.5 | 0.5     |  |
| <b>BMI</b>                                |           |      |         |                   |      |         |                   |      |         |  |
| 17.4-24.1                                 | 14        | 0.43 | 1.04    | 13                | -0.6 | 1.45    | 25                | -2.2 | 0.7     |  |
| 24.2-27.6                                 | 19        | -1.1 | 0.76    | 16                | -1.8 | 1.2     | 14                | -4.5 | 1       |  |
| 27.7-32.8                                 | 21        | 0.33 | 0.69    | 13                | -2.8 | 0.81    | 15                | -3.9 | 1.11    |  |
| 32.9-46.9                                 | 15        | 0.53 | 0.9     | 19                | -2   | 0.97    | 15                | -3.7 | 0.87    |  |
| <b>Diagnosis Group</b>                    |           |      |         |                   |      |         |                   |      |         |  |
| Schizophrenia or Schizoaffective Disorder | 43        | 0.42 | 0.58    | 40                | -1.4 | 0.76    | 43                | -3.2 | 0.56    |  |
| Mood Disorder                             | 26        | -0.7 | 0.52    | 21                | -2.5 | 0.72    | 26                | -3.6 | 0.77    |  |
| <b>Antipsychotic Use</b>                  |           |      |         |                   |      |         |                   |      |         |  |
| No  | 13        | 0.31 | 0.74    | 6                 | -1.8 | 0.65    | 15                | -4.9 | 0.91    |  |
| Yes                                       | 56        | -0.1 | 0.48    | 55                | -1.8 | 0.61    | 54                | -2.9 | 0.51    |  |
| <b>Antipsychotic Category</b>             |           |      |         |                   |      |         |                   |      |         |  |
| Atypical Only                             | 51        | 0.24 | 0.49    | 45                | -1.8 | 0.57    | 43                | -3   | 0.58    |  |
| Typical or Both                           | 5         | -3   | 1.7     | 10                | -1.7 | 2.3     | 11                | -2.6 | 1.11    |  |
| <b>Anticholinergic Use</b>                |           |      |         |                   |      |         |                   |      |         |  |
| No  | 50        | -0.2 | 0.5     | 37                | -2.2 | 0.58    | 42                | -3   | 0.57    |  |
| Yes                                       | 19        | 0.58 | 0.71    | 24                | -1.2 | 1.1     | 27                | -3.8 | 0.75    |  |

Source: Reviewer-created, using data from analysis dataset ADSL.XPT. Included subjects (N=199) are those in the ITT analysis set with centrally-rated AIMS total dyskinesia score data from

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*Baseline and Week 6.*

The response to valbenazine according to CYP2D6 genotype is displayed in Table 15. There were too few subjects who were poor or ultra-rapid metabolizers from which to draw conclusions.

**Table 15: Study 1304 - CYP2D6 Genotype vs. Week 6 AIMS CFB**

| CYP2D6 Genotype           | Week 6 AIMS CFB |      |         |                   |      |         |                   |      |         |
|---------------------------|-----------------|------|---------|-------------------|------|---------|-------------------|------|---------|
|                           | Placebo         |      |         | Valbenazine 40 mg |      |         | Valbenazine 80 mg |      |         |
|                           | N               | Mean | Std Err | N                 | Mean | Std Err | N                 | Mean | Std Err |
| Poor                      | 3               | 2    | 4.16    | 6                 | -2.2 | 1.83    | 3                 | -6   | 1       |
| Intermediate              | 17              | 0.59 | 0.95    | 22                | -1.3 | 1.01    | 22                | -3.6 | 0.73    |
| Intermediate or Extensive | 2               | 0.5  | 3.5     | 0                 | .    | .       | 1                 | 3    | .       |
| Extensive                 | 44              | -0.3 | 0.45    | 26                | -2.2 | 0.71    | 41                | -3.2 | 0.62    |
| Extensive or Ultra Rapid  | 2               | -0.5 | 1.5     | 2                 | 3.5  | 2.5     | 1                 | -5   | .       |
| Ultra-Rapid               | 1               | -2   | .       | 5                 | -3.8 | 2.52    | 0                 | .    | .       |
| Not Reported              | 0               | .    | .       | 0                 | .    | .       | 1                 | -2   | .       |

*Source: Reviewer-created, using data from analysis dataset ADSL.XPT. Included subjects (N=199) are those in the ITT analysis set with centrally-rated AIMS total dyskinesia score data from Baseline and Week 6.*

A graph was constructed to help visualize whether it appeared that valbenazine was more effective in subjects with TD of greater or lesser baseline severity (Figure 11). The upper panels represent the mean absolute change in AIMS total dyskinesia score from baseline and the lower panels represent the mean percent change in AIMS total dyskinesia score, both according to the baseline AIMS score. From inspection of the graphs, it does not appear that valbenazine is less effective in subjects with more severe baseline TD.

APPEARS THIS WAY ON ORIGINAL

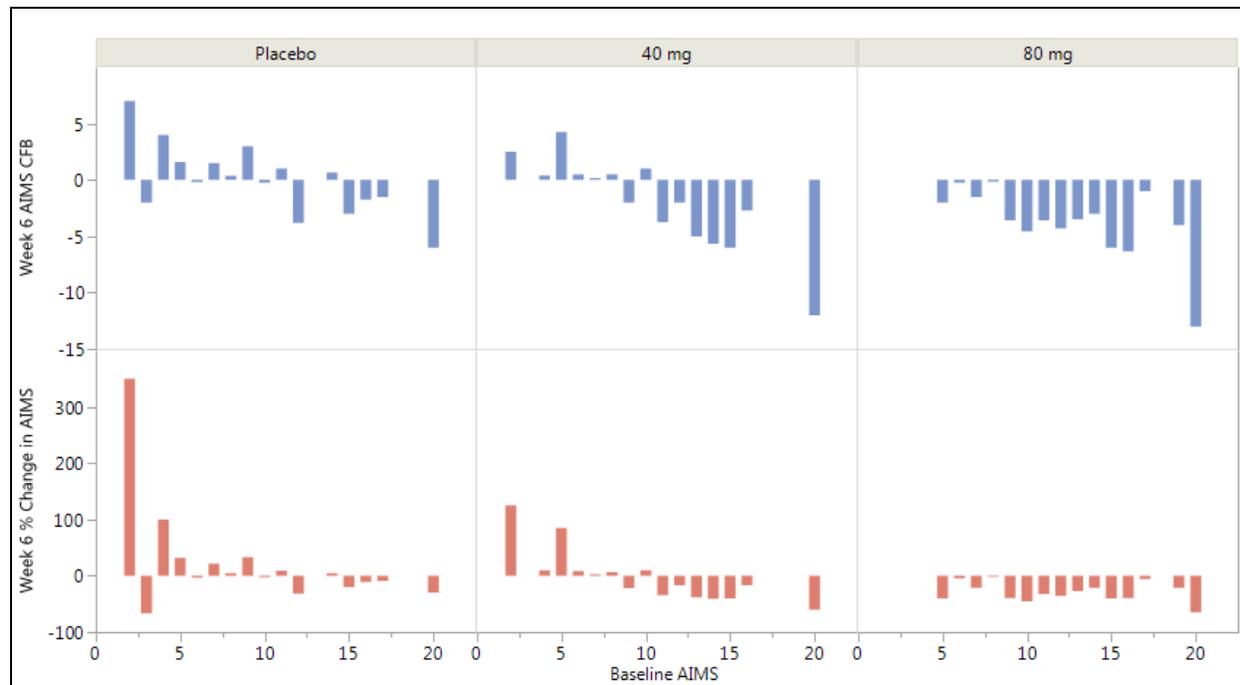
Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

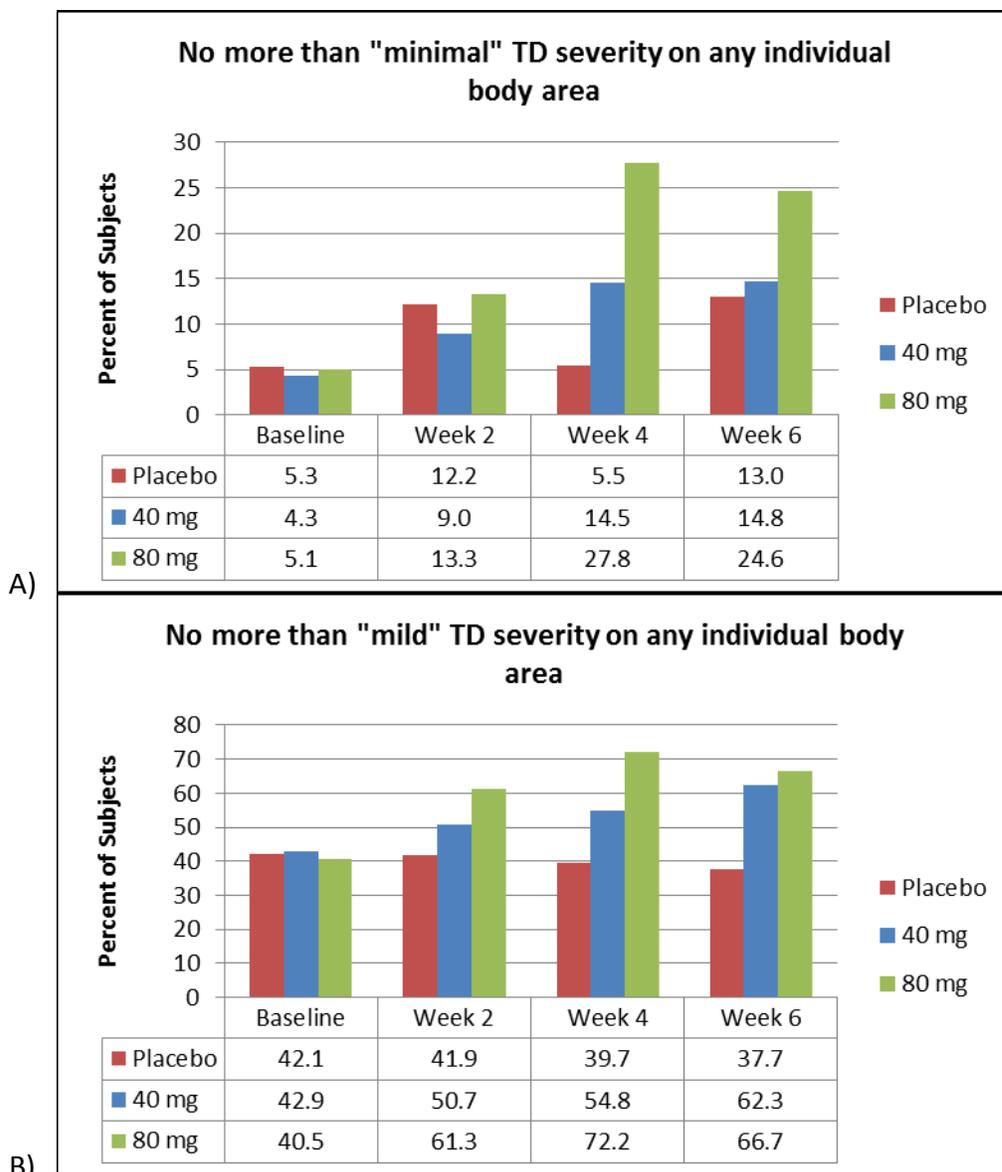
**Figure 11: Study 1304 - Absolute and Relative Change in AIMS at 6 Weeks, by Treatment Arm, According to Baseline AIMS**



Source: Reviewer-created, using data from analysis dataset ADSL.XPT. Included subjects (N=199) are those in the ITT analysis set with centrally-rated AIMS total dyskinesia score data from Baseline and Week 6.

An exploratory analysis on the primary efficacy measure was conducted by Dr. Douglas Warfield, in which subjects were classified according whether they had threshold scores on *any* individual body part item from the AIMS total dyskinesia score (Figure 12). Though there are no widely-used TD remission criteria, a subject that had no more than minimal or mild TD symptoms on any muscle group (see Table 5) might be assessed by a treating clinician as being remitted from TD. In subjects treated with 80 mg valbenazine for six weeks, approximately one quarter reached the more stringent “minimal” criterion for remission and one third met the “mild” criterion for remission; the 80 mg dose of valbenazine appeared more effective than placebo in achieving both exploratory remission criteria.

**Figure 12: Study 1304 - Percentage of Subjects Achieving Exploratory Remission Criteria**



Source: Reviewer-created, using dataset prepared by Dr. Douglas Warfield which included a variable indicating whether subjects had a score of no more than "1" (panel A) or "2" (panel B) on any individual body area comprising AIMS items 1-7.

**Data Quality and Integrity – Reviewers’ Assessment**

An assessment of data quality for this study was performed by Dr. Douglas Warfield. A Mahalanobis distance was computed, using JMP Clinical software, from 1206 variables submitted with the SDTM dataset; this test did not reveal any clear outliers. A site-based analysis of irregularities based on screen failures, deviations, subject discontinuations, and

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

adverse event frequency also did not reveal any clear problematic study sites; however, these analyses were limited by the small number of subjects per site. Visual inspection of enrollment patterns by site did not reveal any obvious irregularities. An analysis of SDTM finding domains (EG, LB, QS, VS, and YG) was performed to help detect screening bias; this analysis also did not reveal any clear instances of screening bias. Please see Section 4.1 for a summary of inspections conducted by the Office of Scientific Investigations, which included several sites from this study.

### Efficacy Results – Secondary and other relevant endpoints

#### CGI-TD

The mean CGI-TD at Week 6 was pre-specified as a key secondary efficacy endpoint. For multiplicity correction, the Applicant pre-specified a fixed sequence of tests (discussed in Statistical Analysis Plan above), with the CGI-TD for the valbenazine 80 mg dose vs. placebo as the second test and the CGI-TD for the valbenazine 40 mg dose vs. placebo as the fourth test. Please see Table 16 for a summary of CGI-TD scores at Weeks 2, 4, and 6 across the three treatment groups. Overall, the mean CGI-TD at all post-baseline visits in all three treatment groups was <4, indicating that on average, all subjects were assessed as having some global improvement over the course of the study. Numerically, both doses of valbenazine were associated with a lower mean CGI-TD score than the placebo group, but the key secondary efficacy endpoint did not reach statistical significance ( $p=0.0560$  for the valbenazine 80 mg group at Week 6 vs. placebo and  $p=0.0742$  for the 40 mg dose). Nominal  $p$  values were <0.05 for both valbenazine dose groups at Week 4.

**Table 16: Study 1304 - CGI-TD, ITT Analysis Set, MMRM Analysis**

|  | Placebo<br>(N=76) | Valbenazine 40 mg<br>(N=70) | Valbenazine 80 mg<br>(N=79) |
|--|-------------------|-----------------------------|-----------------------------|
| <b>Week 2</b>                          |                   |                             |                             |
| N                                      | 76                | 70                          | 77                          |
| LS Mean (SEM)                          | 3.6 (0.1)         | 3.5 (0.1)                   | 3.5 (0.1)                   |
| LS Mean Difference (95% CI)            |                   | -0.1 (-0.3, 0.1)            | -0.1 (-0.4, 0.1)            |
| p value                                |                   | 0.2872                      | 0.1782                      |
| <b>Week 4</b>                          |                   |                             |                             |
| N                                      | 74                | 65                          | 73                          |
| LS Mean (SEM)                          | 3.5 (0.1)         | 3.2 (0.1)                   | 3.1 (0.1)                   |
| LS Mean Difference (95% CI)            |                   | -0.3 (-0.5, -0.1)           | -0.4 (-0.6, -0.1)           |
| p value                                |                   | 0.0180                      | 0.0022                      |
| <b>Week 6 (Key Secondary Endpoint)</b> |                   |                             |                             |
| N                                      | 69                | 63                          | 70                          |
| LS Mean (SEM)                          | 3.2 (0.1)         | 2.9 (0.1)                   | 2.9 (0.1)                   |
| LS Mean Difference (95% CI)            |                   | -0.3 (-0.5, 0)              | -0.3 (-0.5, 0)              |
| p value                                |                   | 0.0742                      | 0.0560                      |

Source: Reviewer-created, using information from 1304 Clinical Study Report, Table 24, p. 89

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

The Applicant performed several post hoc analyses with the CGI-TD measure:

- An ANOVA at Week 6, using the ITT analysis set, with treatment group and primary psychiatric category as fixed effects, found nominal  $p=0.0489$  for the valbenazine 40 mg dose and  $p=0.0352$  for the 80 mg dose.
- An MMRM analysis at Week 6, using the PP analysis set, found nominal  $p=0.0109$  for the valbenazine 40 mg dose and  $0.0109$  for the 80 mg dose.
- CGI-TD responder analysis, defining a response as a CGI-TD score of 1 or 2 (definition 1) or 1-3 (definition 2). At Week 6, by definition 1, 31.4% of the valbenazine 80 mg, 31.7% of the valbenazine 40 mg, and 20.3% of the placebo group met responder criteria. By definition 2, 75.7% of the valbenazine 80 mg, 74.6% of the valbenazine 40 mg, and 62.3% of the placebo group met responder criteria.
- Above analyses by underlying psychiatric diagnosis (schizophrenia/schizoaffective disorder vs. mood disorder), which did not show significant differences in CGI-TD response between disease groups.

Altogether, the prespecified key secondary efficacy endpoint did not reach statistical significance [REDACTED] (b) (4) Exploratory and post hoc analyses, however, did suggest that there might be some clinician-appreciable global clinical benefit in TD symptoms associated with valbenazine treatment. The methods for assessing this measure may not be ideal for detecting global clinical change between treatment groups, because the assessors were not required to be the same individual across all visits and the ratings may have been subject to expectation bias, as evidenced by all treatment groups improving over time in the study. Furthermore, the CGI-TD requires mental comparison to the baseline visit, which may be more unreliable than making a point-in-time global severity assessment (i.e., a CGI-S scale [27]).

### *PGIC*

The PGIC measure was used in several secondary and exploratory endpoints (Table 6) to characterize study subjects' perception of TD symptom changes. Please see Table 17 for a summary of PGIC endpoints for the placebo-controlled period. Numerically, the mean PGIC score at Week 6 was slightly worse in both valbenazine treatment groups as compared to placebo at Week 6, but the differences did not reach nominal statistical significance. The Applicant also conducted a PGIC responder analysis characterizing the proportion of subjects with "much improved" or "very much improved" scores at Week 6. The valbenazine 80 mg group had a lower proportion of PGIC responders than the placebo group which reached nominal statistical significance ( $p=0.0270$ ). The Applicant conducted an exploratory PGIC responder analysis comparing the underlying diagnostic categories, and the difference between valbenazine 80 mg and placebo was driven mainly by subjects with schizophrenia or

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

schizoaffective disorder (nominal  $p=0.0196$ ). The meaning of this is unclear but hypothetically might be related to differences in cognitive processes between disorders [29].

**Table 17: Study 1304 - PGIC Summary, Placebo-Controlled Period, ITT Analysis Set**

|  | Placebo<br>(n=76) | Valbenazine<br>40 mg (n=70) | Valbenazine<br>80 mg (n=79) |
|--|-------------------|-----------------------------|-----------------------------|
| <b>PGIC Week 6 Mean (SEM)</b>                    | 2.7 (0.1)         | 2.9 (0.1)                   | 3.0 (0.1)                   |
| Schizophrenia/Schizoaffective subjects (n=148)   | 2.6 (0.1)         | 2.9 (0.2)                   | 3.0 (0.1)                   |
| Mood Disorder subjects (n=77)                    | 2.7 (0.2)         | 3.0 (0.2)                   | 2.9 (0.2)                   |
| <b>PGIC Week 6 Responders<sup>1</sup> (n, %)</b> | 29 (42.0)         | 20 (31.7)                   | 17 (24.3)                   |
| Schizophrenia/Schizoaffective subjects (n=148)   | 20 (46.5)         | 15 (35.7)                   | 10 (22.7)                   |
| Mood Disorder subjects (n=77)                    | 9 (34.6)          | 5 (23.8)                    | 7 (26.9)                    |

Source: Reviewer created, using data from the 1304 Clinical Study Report (Tables 14.2.3.1, 14.2.3.7, 14.2.3.13, 14.2.3.21, 14.2.3.24, 14.2.3.27)

<sup>1</sup>Subjects were classified as PGIC responders if the assessment was “much improved” or “very much improved.”

Overall, it appears that 6 weeks of blinded valbenazine treatment may not improve subjects' impression of their own TD symptoms, even if their symptoms are decreased by objective clinical assessment. This is consistent with previous findings suggesting patients are frequently unaware of their own dyskinetic movements [30]. It is not clear whether the possible superiority of placebo over valbenazine on the PGIC is a chance finding related to small sample sizes and multiple statistical tests, or whether valbenazine might cause a negative cognitive bias and decrease subjects' appreciation of treatment benefit. The Applicant analyzed PGIC results during the valbenazine extension period and observed a continual decrease in PGIC score (indicating perceived improvement) from Weeks 8 to 48 in both valbenazine treatment groups, which worsened at Week 52, four weeks after subjects had discontinued treatment (data not shown). It is difficult to make conclusions from these findings, however, because there was no placebo group and subjects were aware they were receiving active valbenazine treatment up to Week 48 and stopping treatment before Week 52; this information could likely bias their PGIC assessments. Furthermore, attrition bias could also confound these results, as subjects who did not appreciate clinical benefit might have been more likely to discontinue study participation over the extension period.

### TDIS

The mean change from baseline at Week 6 was specified as a secondary outcome measure and the changes at Weeks 2 and 4 were specified as exploratory. As shown in Table 18, improvement on the TDIS was observed in all treatment groups (including placebo). Both doses of valbenazine were numerically superior to placebo at Weeks 4 and 6, but the differences did not reach statistical significance. The improvements in all treatment groups over time in this

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

patient-reported outcome measure are fairly consistent with the PGIC results, except in this case, valbenazine was numerically superior to placebo (perhaps due to its use of focused questions about TD symptoms as opposed to asking for a global assessment). It is also possible that it would take a longer period of time than six weeks for the impacts of TD symptom improvement to be fully appreciated. Indeed, in the 120-Day Safety Update, TDIS scores continued to improve from Weeks 8 to 48 in both valbenazine treatment groups, though it is difficult to make conclusions from these findings due to the subjects' awareness that they were receiving active treatment and potential attrition bias.

**Table 18: Study 1304 - TDIS Change from Baseline, Placebo-Controlled Period, ITT Analysis Set**

|  | Placebo<br>(n=76) | Valbenazine<br>40 mg<br>(n=70) | Valbenazine<br>80 mg<br>(n=79) |
|--|-------------------|--------------------------------|--------------------------------|
| <b>TDIS Change from Baseline (mean (SEM))</b>        |                   |                                |                                |
| Week 2   | -1.5 (0.7)        | -1.8 (0.7)                     | -1.3 (0.6)                     |
| Week 4   | -3.0 (0.8)        | -3.9 (0.7)                     | -3.3 (0.8)                     |
| Week 6   | -3.7 (0.9)        | -4.1 (0.8)                     | -4.4 (0.8)                     |
| Week 6 p-value vs. placebo (applicant MMRM analysis) |                   | 0.8026                         | 0.4133                         |

Source: Reviewer-created, using data from 1304 Clinical Study Report, Tables 14.2.4.1 and 14.2.4.13

### Dose/Dose Response

Please refer to discussion of efficacy results above for dose-related conclusions. Overall, the 80 mg valbenazine dose was found to be statistically superior to placebo on the primary efficacy endpoint. The 40 mg valbenazine dose did not show statistical significance on the primary efficacy endpoint due to the pre-specified multiple testing sequence. However, the totality of evidence from this study (including the nominal  $p=0.0021$  associated with the 40 mg dose on the primary efficacy endpoint) suggests the 40 mg dose may have an intermediate effect on TD symptoms. Integrated dose response analyses are discussed in Section 7.1.4.

### Durability of Response

As shown in Figure 8, the mean change from baseline in the AIMS total dyskinesia score continued to decrease at each visit during the 6-week placebo-controlled period for both doses of valbenazine, with no evidence of tolerance or a response plateau. Results from the valbenazine extension period are shown in Table 19 and Figure 13, with data for each cohort displayed separately in Table 19 and the re-randomized placebo subjects grouped with the 40 mg and 80 mg treatment groups during the extension period in Figure 13. These data may also suggest modest continued improvement over time, with a maximal AIMS CFB of approximately -5 for the 80 mg valbenazine dose. While the long-term extension period did not include a placebo control, the 40 mg valbenazine dose provided an internal active control to which the 80

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

mg dose could be compared. The use of central video AIMS raters blinded to visit number and treatment dose also strengthens the confidence in these findings. One factor limiting the interpretability of durability findings, however, was the attrition of subjects over the 48-week period (only ~52% of initial randomized subjects remained in the study at Week 48). It is possible that subjects with a less robust response to valbenazine might be more likely to withdraw from the trial, improving the mean scores at later time points due to attrition bias.

**Table 19: Study 1304 - AIMS Change from Baseline, Extension Period, ITT Analysis Set**

| Treatment<br>(initial 6 week/extension) | Week 8 |          |      | Week 16 |          |      | Week 32 |          |      | Week 48 |          |      |
|---|--------|----------|------|---------|----------|------|---------|----------|------|---------|----------|------|
|   | n=     | AIMS CFB |      | n=      | AIMS CFB |      | n=      | AIMS CFB |      | n=      | AIMS CFB |      |
|   |        | Mean     | SE   |         | Mean     | SE   |         | Mean     | SE   |         | Mean     | SE   |
| 80 mg/80 mg                             | 65     | -4.3     | 0.56 | 56      | -4.2     | 0.48 | 49      | -4.9     | 0.59 | 42      | -4.4     | 0.67 |
| 40 mg/40 mg                             | 59     | -2.2     | 0.6  | 47      | -2.4     | 0.61 | 37      | -2.5     | 0.62 | 34      | -3       | 0.75 |
| Placebo/40 mg                           | 31     | -1.3     | 0.52 | 29      | -1.8     | 0.74 | 26      | -2.5     | 0.8  | 24      | -2.9     | 0.79 |
| Placebo/80 mg                           | 32     | -3.5     | 0.72 | 31      | -4.2     | 0.86 | 25      | -5       | 1.13 | 22      | -5.5     | 1.19 |

Source: Reviewer-created, using Study 1304 analysis dataset A\_AIMS.XPT. Data from early termination visits were excluded.

APPEARS THIS WAY ON ORIGINAL

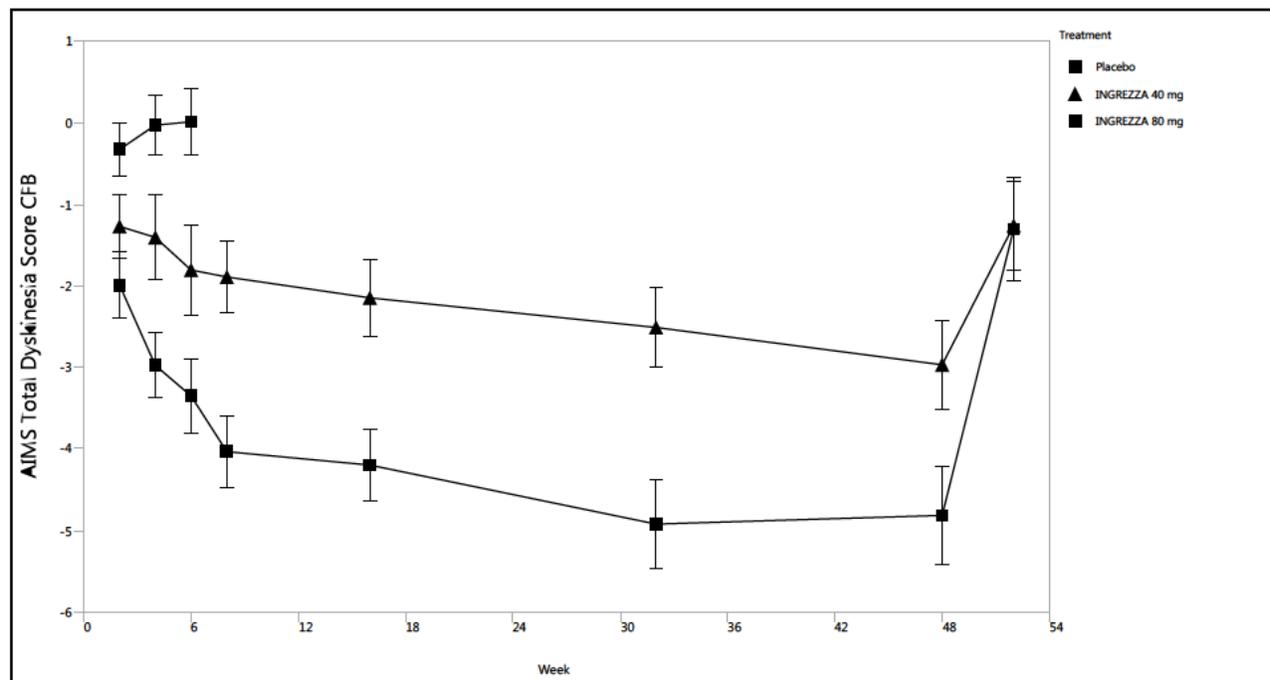
## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Figure 13: Study 1304 - AIMS Change from Baseline by Treatment Group, Entire Study Duration, Central Video Raters**



Source: Reviewer-created, using Study 1304 analysis dataset A\_AIMS.XPT. Subjects who received placebo and were re-randomized to valbenazine after 6 weeks are grouped with the 40 mg and 80 mg treatment groups from Weeks 8-52. Data from early termination visits were excluded. Each error bar is constructed using 1 standard error from the mean.

### Persistence of Effect

Persistence of drug effect was evaluated at the end of the valbenazine extension treatment. At the end of Week 48, subjects were withdrawn from active valbenazine treatment and returned four weeks later for a final assessment. Please see Table 20 for a summary of changes in efficacy measures during this period and Figure 13 for a graphical depiction. Subjects demonstrated a worsening in AIMS score after discontinuing valbenazine treatment but, on average, did not worsen beyond their baseline. This suggests that 42-48 weeks of valbenazine treatment may not worsen the underlying TD process but that continued treatment may be necessary to maintain treatment benefit. The residual mean improvement in AIMS total dyskinesia score at Week 52 (off treatment) raises the question of whether valbenazine might have some benefit on the underlying disease process, as most subjects continued to receive antipsychotic treatment throughout the study. Though extension phase treatment was open-label to subjects (with respect to dose), the use of central AIMS video raters who were blinded to the visit number strengthens the interpretation of these findings. Valbenazine discontinuation was also associated with worsening of CGI-TD scores, but these results are not considered as convincing because the on-site CGI-TD raters were aware that the subjects were

no longer receiving study treatment.

**Table 20: Study 1304 - Assessment of Persistence of Drug Effect**

|                              | <b>Valbenazine<br/>40 mg (N=97)</b> | <b>Valbenazine<br/>80 mg (N=101)</b> |
|------------------------------|-------------------------------------|--------------------------------------|
| Completed study, n (%)       | 60 (61.9)                           | 61 (60.4)                            |
| <b>On Treatment:</b>         |                                     |                                      |
| Week 48 AIMS CFB, mean (SEM) | -3.0 (0.5)                          | -4.8 (0.6)                           |
| Week 48 CGI-TD, mean (SEM)   | 2.4 (0.1)                           | 2.1 (0.1)                            |
| <b>Off Treatment:</b>        |                                     |                                      |
| Week 52 AIMS CFB, mean (SEM) | -1.4 (0.5)                          | -1.2 (0.6)                           |
| Week 52 CGI-TD, mean (SEM)   | 3.1 (0.1)                           | 3.5 (0.2)                            |

*Source: Reviewer-created, using data from 120-Day Safety Update (Tables 20, 21, 23)*

An analysis of subjects who did not return to baseline TD severity following valbenazine discontinuation was conducted by this reviewer, in order to explore whether there were any subpopulation associations with this phenomenon. Of the 121 subjects with AIMS ratings at the end of Week 52 (four weeks off treatment), 20 subjects were scored by blinded central raters as having an AIMS total dyskinesia score at least 5 points below their baseline scores. The 5-point cutoff was selected as it represented the bottom quartile of AIMS CFB values at this time point. A binary logistic regression was performed using JMP 12.1 to assess whether the use of antipsychotics, the duration of TD symptoms, the diagnostic group (mood disorder or schizophrenia/schizoaffective disorder), sex, race, or valbenazine dose might predict whether subjects had AIMS CFB  $\leq$ -5 off treatment. The only factor that reached nominal significance in this analysis ( $p=0.035$ ) was the absence of continued antipsychotic use. This finding is considered highly exploratory, as the number of subjects not taking antipsychotics was very low ( $N=20$ ) and the assessment lacked pre-specification and correction for multiple testing. However, it raises an interesting hypothesis for future consideration.

#### **Additional Analyses Conducted on the Individual Trial**

There were no additional analyses conducted by this reviewer for this trial.

### **6.2. Study 1202: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose Titration Study to Assess the Safety, Tolerability, and Efficacy of Valbenazine for the Treatment of Tardive Dyskinesia**

#### **6.2.1. Study Design**

##### **Overview and Objective**

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

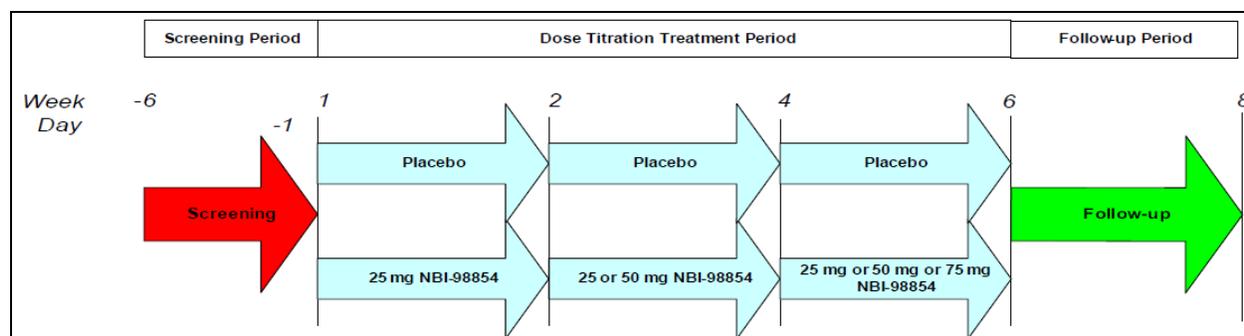
Ingrezza (valbenazine)

The primary objective of this study was to evaluate the efficacy of valbenazine, titrated to optimal dose in the range of 25-75 mg once daily, for the treatment of TD. Secondary objectives were to evaluate the safety and tolerability of valbenazine and evaluate plasma exposure measures of valbenazine, its active metabolite  $[+]\text{-}\alpha\text{-dihydrotrabenazine}$ , and other metabolites.

## Trial Design

*Basic Study Design Summary:* Study 1202 was a Phase 2, randomized, double-blind, placebo-controlled, dose-titration study designed to evaluate the efficacy, safety, and tolerability of valbenazine (titrated to an optimal dose in the range of 25-75 mg daily), as compared to placebo. The study included a total of six weeks of treatment. Please see Figure 14 for an overview of the design.

**Figure 14: Schematic of 1202 Study Design**



Source: Study 1202 Protocol; September 26, 2013 version; Figure 1 (page 29)

Eligible subjects were randomized (1:1) to receive valbenazine or placebo treatment, with randomization stratified by underlying disease category and concomitant use of valproic acid and derivatives. The Applicant noted that the valproic acid stratification was used due to prior observations that valproic acid may reduce exposure to valbenazine and its active metabolite,  $[+]\text{-}\alpha\text{-dihydrotrabenazine}$ . Subjects who were randomized to receive valbenazine received a starting dose of 25 mg by mouth daily. The valbenazine dose could be increased in increments of 25 mg every two weeks to a maximum of 75 mg daily. Subjects who were randomized to receive placebo were also subject to the same dose increase requirements but only received placebo during the treatment period.

The treatment doses were increased based on AIMS scores and the safety and tolerability of the current dose. At the end of Weeks 2 and 4, an independent AIMS rater, who was not involved with other aspects of subject care, notified the physician investigator if a dose escalation was allowed based on AIMS scores (specifically, if any of items 1-7 was scored as  $\geq 2$  (mild, moderate, or severe)). The physician investigator was blinded to the actual AIMS scores.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

The physician investigator assessed whether the dose increase would be acceptable, based on tolerability and safety assessments, and made the decision to increase the dose to the next 25 mg increment, continue the current dose, or reduce the dose to the previous tolerated dose. At any time after Week 2, the dose could be decreased to the previous dose for reason of intolerability. In addition to assessments during the screening and dose titration periods, subjects were assessed at the end of Week 8 (two weeks after the last dose of study drug).

*Choice of Control Group:* This study used a placebo control group, which is considered ideal for interpretability. There are no treatments indicated for TD, so an active control was not possible.

*Diagnostic Criteria:* Subjects must have met criteria for either one of the following DSM-IV clinical diagnoses: Schizophrenia, Schizoaffective Disorder, or Mood Disorder; or gastrointestinal disorder (e.g., gastroparesis, GERD) for at least 3 months prior to screening. The diagnosis needed to be confirmed by medical record, reliable self-reported medical history, or evaluation using the Mini International Neuropsychiatric Interview (MINI) (for psychiatric disorders). Subjects must also have a clinical diagnosis of neuroleptic-induced TD, as defined by DSM-IV code 333.82, for at least 3 months prior to screening. The diagnosis was confirmed by medical record, physical examination, and reliable self-reported medical history that showed evidence that the involuntary movements were distinct from other extrapyramidal symptoms. The overall TD severity needed to be moderate or severe (AIMS item 8  $\geq$  3), as assessed by a blinded, external AIMS video reviewer. These criteria are considered reasonable for the majority of the target population in the US and, unlikely Study 1304, included subjects with gastrointestinal illness and metoclopramide-induced TD.

*Key Inclusion/Exclusion Criteria:*

### Key Inclusion Criteria

1. Be male or female aged 18 to 85 years (inclusive).
2. Meet clinical diagnoses of Schizophrenia, Schizoaffective Disorder, Mood Disorder, or Gastrointestinal Disorder, and neuroleptic-induced TD for at least 3 months prior to screening, with TD assessed as moderate or severe by AIMS Item 8 (see *Diagnostic Criteria* discussion above).
3. Maintenance medication(s) for schizophrenia or schizoaffective disorder, mood disorders, or gastrointestinal disorders (except metoclopramide) must be at a stable dose for  $\geq$ 30 days before screening.
4. Subjects who are not using an antipsychotic medication must have a stable psychiatric status as clinically determined by the investigator. Subjects with a diagnosis of bipolar disorder must be on stable dose of mood stabilizer(s) (e.g., lithium, valproate, olanzapine; carbamazepine was prohibited) for a minimum of 30 days before screening.
5. Have a negative urine drug screen at screening and Day -1, except for any subject receiving a stable dose of benzodiazepine or opiates. Subjects with positive cannabinoid

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

results were allowed to participate in the study provided that the subject was given thorough counseling and agreed to refrain from using cannabinoids for the duration of his/her study participation. Subjects must also have a negative alcohol breath test at screening and Day -1.

### Key Exclusion Criteria

1. Have an active, clinically significant unstable medical condition within 1 month (30 days) prior to screening.
2. Have a SAS score  $\geq 3$  on two or more items at screening or Day -1, excluding Items 8 and 10.
3. Have a significant risk of suicidal or violent behavior. Subjects with any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent), based on the C-SSRS in the 3 months prior to screening, were excluded.
4. Have a known history of neuroleptic malignant syndrome.
5. Have a known history of long QT syndrome or cardiac tachyarrhythmia.
6. Have a screening or Day -1 average triplicate ECG QT interval corrected for heart rate using QTcF of  $>450$  msec (males) or  $>470$  msec (females) or the presence of any clinically significant cardiac abnormality.
7. Subjects with clinical diagnoses of schizophrenia or schizoaffective disorder must not have a CDSS total score  $\geq 10$  at screening or Day -1 or PANSS total score  $\geq 70$  at Day -1.
8. Subjects with a clinical diagnosis of mood disorder must not have a YMRS total score  $>10$  at screening or Day -1; been hospitalized for bipolar disorder or major depressive disorder within 6 months prior to screening; have had mood episodes within 2 months prior to screening and Day -1; have history of  $>4$  mood episodes per year; have MADRS total score of  $>13$  at screening or Day -1.
9. Subjects with a clinical diagnosis of gastrointestinal disorder must not have a symptom score of  $\geq 4$  (severe or very severe) on any of the nine Gastroparesis Cardinal Symptom Index (GCSI) items at screening or Day -1; have a diagnosis of Malabsorption Syndrome; have a history of intractable nausea and vomiting; Use gastric electrical stimulators; or have a MADRS total score of  $>13$  at screening or Day -1.

Overall, the eligibility criteria seem to be reasonable for a controlled study population. The “real world” target population is more variable, in terms of substance use and medical and psychiatric illness severity, but the study restrictions were appropriate for assessing efficacy while controlling for many potential confounders. Unlike Study 1304, this protocol did not explicitly exclude for comorbid prominent abnormal involuntary movements other than TD. This could theoretically confound the assessment of TD symptoms or worsen the overall clinical impression, which could reduce the perceived TD treatment efficacy if non-TD movements remained that were insensitive to valbenazine.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*Dose Selection:* The Applicant indicated that the starting valbenazine dose of 25 mg daily was within the range of well-tolerated doses in earlier studies (Studies 1001 and 1101), including subjects with diminished CYP2D6 metabolism by genotype or concomitant inhibitor use. The titration scheme was thought to allow subjects to potentially receive a dosage that was optimal, based on safety and efficacy, over a 6-week treatment period. The broadness of the dose range is considered acceptable. The flexible dosing scheme is considered to have been reasonable for dose finding and establishing overall efficacy of valbenazine, though it was limited for establishing an accurate correlation between dose and effect and for determining the lowest effective or maximum tolerated dose of valbenazine.

*Study Treatments:* The study treatments were valbenazine free base in 25 mg and 50 mg capsules, or matched placebo capsules. Each morning, subjects administered two capsules by mouth, for a total daily dose of valbenazine 25 mg, 50 mg, 75 mg, or placebo. Please refer to the Office of Pharmaceutical Quality review for additional information about the product formulation and capsule compositions.

*Assignment to Treatment:* Subjects were randomized by an interactive web response system (IWRS), which occurred on Day -1, after the subjects were confirmed to have met study eligibility criteria. Treatment assignments were made according to a computer-generated randomization schedule. Initial randomization to valbenazine or placebo was conducted in a 1:1 ratio, stratified by underlying disease category and by concomitant use of valproic acid and derivatives. The treatment assignment was adequate, but in this reviewer's opinion it may have been unnecessary to stratify by underlying disease category, as it is not clear that TD pathophysiology differs between psychiatric diagnosis groups and gastrointestinal disorders; furthermore, the categories are somewhat artificial (i.e., bipolar disorder is categorized as a "mood disorder" but might have more in common neurobiologically with schizoaffective disorder than major depressive disorder).

*Blinding:* As discussed under *Study Treatments*, placebo capsules were identical to valbenazine capsules, and treatments were administered in two capsules daily. The subject, investigator, independent AIMS rater, central AIMS raters, and study site personnel were all blinded to subject treatment. The randomization code was able to be broken for an individual subject only if the subject was pregnant or experienced a Serious Adverse Event that the investigator felt could not be adequately treated without knowing the treatment assignment. The blinding procedures seem generally appropriate, considering the study design.

*Dose Modification and Discontinuation:* Valbenazine doses could be increased from 25 mg to 50 mg at the end of Week 2 and from 50 mg to 75 mg at the end of Week 4. Dose increases were authorized if the certified independent AIMS rater scored any of AIMS items 1-7  $\geq 2$  (mild, moderate, or severe). The physician investigators were blinded to the actual AIMS scores and assessed whether the dose increase would be acceptable, based on safety and tolerability.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Doses could be decreased to the previous dose at any time for tolerability reasons. Subjects were discontinued if they were unable to tolerate the starting dose or the previous dose following reduction. This dosing approach was generally acceptable, with the caveats of flexible dosing described in *Dose Selection* above. However, the approach for authorizing dose increases for efficacy reasons was somewhat complicated, as the AIMS assessments that informed dose increases were performed by on-site raters (who were not otherwise involved in subject care), and these scores were not necessarily equivalent to the central video raters' AIMS scores used in the primary efficacy measure. Thus, the dose/response information is particularly difficult to interpret.

*Administrative Structure:* The final approved protocol and ICF documents were reviewed by Institutional Review Boards (IRBs) for each clinical site. The Central Clinical Laboratory was

(b) (4). The IWRS was conducted by (b) (4). The Pharmacokinetics and Bioanalysis procedures were performed by (b) (4).

(b) (4) The Videography Data Processing was performed by

(b) (4) The External AIMS Video Review procedures were conducted by

(b) (4) The Electronic Data Capture system was managed by (b) (4)

*Procedures and Schedule:* Please refer to Table 21 for a schedule of events. The primary efficacy assessment measure, the AIMS (described in Study Endpoints), was administered at screening, baseline, Weeks 2, 4, 6, and at the follow-up visit (Week 8 or early termination); however, only baseline and Week 6 AIMS examinations were scored by central video raters.

APPEARS THIS WAY ON ORIGINAL

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 21: Study 1202 - Schedule of Assessments (abridged)**

| Procedure   | Screening | Base-line | Randomized, Dose-Titration Treatment Period |   |   | Follow-Up |
|---|-----------|-----------|---|---|---|-----------|
|   |           |           | Week  | 2 | 4 |           |
| <b>Screening assessments:</b> informed consent, UBACC, medical history (update at Baseline), inclusion/exclusion criteria (update at Baseline), serology studies, BPRS, drug and alcohol screening (repeated at Baseline)   | X         |           |   |   |   |           |
| <b>Safety assessments:</b> physical examination (height at screening only), vital signs, 12-lead ECG, pregnancy test, clinical laboratory tests, serum prolactin (excluding Screening), C-SSRS, BARS (excluding Screening), SAS, AE monitoring, prior and concomitant medications | X         | X         | X   | X | X | X         |
| <b>Pharmacokinetic sampling</b>   |           |           | X   | X | X | X         |
| <b>Primary efficacy:</b> AIMS (including video recording) <sup>1</sup>  | X         | X         | X   | X | X | X         |
| <b>Secondary efficacy:</b> CGI-TD   |           |           | X   |   | X | X         |
| <b>Exploratory efficacy:</b> TDRS   |           | X         | X   |   | X | X         |
| <b>Exploratory efficacy:</b> PGIC   |           |           |   |   | X | X         |
| <b>Schizophrenia/Schizoaffective Disorder Assessments:</b>  |           |           |   |   |   |           |
| PANSS   |           | X         |   |   | X | X         |
| CDSS  | X         | X         |   |   | X | X         |
| <b>Mood Disorder Assessments:</b> MADRS, YMRS   | X         | X         |   |   | X | X         |
| <b>Gastrointestinal Disorder Assessments:</b>   |           |           |   |   |   |           |
| MADRS   | X         | X         |   |   | X | X         |
| GCSI  | X         | X         | X   | X | X | X         |

*Adapted from Study 1202 Protocol; September 26, 2013 version; Table 1 (page 35)*

Definitions: AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; BPRS=Brief Psychiatric Rating Scale; CDSS=Calgary Depression Scale for Schizophrenia; CGI-TD=Clinical Global Impression of Tardive Dyskinesia; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; GCSI=Gastroparesis Cardinal Symptom Index; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C virus antibody; HIV-Ab=human immunodeficiency virus antibody; MADRS=Montgomery-Asberg Depression Rating Scale; PANSS=Positive and Negative Syndrome Scale; PGIC=Patient Global Impression of Change; PK=pharmacokinetic; SAS=Simpson-Angus Scale; TDRS=Tardive Dyskinesia Rating Scale; UBACC=University of California, San Diego Brief Assessment of Capacity to Consent; YMRS=Young Mania Rating Scale.

<sup>1</sup>Blinded central raters scored videos from Baseline and Week 6 only; other visits were scored only by on-site raters.

**Dietary Restrictions/Instructions:** Subjects were instructed to refrain from drinking grapefruit juice from 48 hours prior to Baseline until the completion of study treatment. Alcohol use was limited to <7 drinks per week during the course of the study. These restrictions were reasonable for the study, as inhibiting CYP3A4 could potentially affect valbenazine metabolism.

**Concurrent Medications:** The protocol noted that medications used to treat schizophrenia, schizoaffective disorder, mood disorder, or GI disorders needed to be at stable doses for a minimum of 30 days prior to screening and remain stable during the study. Coexisting diseases

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

or conditions were to be treated in accordance with prevailing medical practice. As needed use of over-the-counter and prescription medications, including dietary and herbal supplements, was generally prohibited after the screening visit without case-by-case permission basis from the medical monitor. However, the following as-needed medications were allowed if approved by the investigator: guaifenesin, milk of magnesia, bisacodyl, bismuth subsalicylate, magnesium hydroxide/aluminum hydroxide /simethicone, acetaminophen, eszopiclone, zaleplon, zolpidem, and doxepin (3 or 6 mg at night).

The following medications were prohibited from 30 days prior to screening until the final study visit:

1. Amantadine (if being used for the treatment of TD).
2. Anticholinergic medications used on an as-needed basis (taking on a regular schedule to treat extrapyramidal symptoms was permitted).
3. Antiemetics: Metoclopramide, prochlorperazine, and promethazine.
4. Benzodiazepines used on an as-needed basis (taking on a regular schedule was permitted).
5. Strong CYP3A4 inducers (e.g., phenobarbital, rifabutin, rifampin, carbamazepine, primidone, St. John's Wort).
6. Strong CYP3A4 inhibitors (e.g., ketoconazole, erythromycin, ritonavir).
7. Dopamine receptor agonists (e.g., ropinirole) and precursors (e.g., carbidopa/levodopa).
8. Stimulants (e.g., amphetamine, methylphenidate, ephedrine, pseudoephedrine, phenylephrine, and phenylpropanolamine).
9. Monoamine oxidase inhibitors (e.g., isocarboxazid, phenelzine, selegiline, tranylcypromine).
10. VMAT2 Inhibitors other than the study drug (e.g., tetrabenazine, reserpine).
11. Drugs known to increase the QT interval, unless approved by the Applicant; baseline QTcF must be  $\leq 450$  msec for males or  $\leq 470$  msec for females.

The protocol specifications for concurrent and prohibited medications were generally reasonable. Changes in psychotropic or other dopaminergic medications (e.g., antipsychotics, benzodiazepines, psychostimulants, dopamine receptor agonists and precursors) or certain as-needed medications (i.e., benzodiazepines) could potentially confound the efficacy assessment of valbenazine. It is notable that regular use of CYP2D6 inhibitors was not prohibited; this could potentially increase exposure to valbenazine's active metabolite  $[+]\text{-}\alpha\text{-dihydrotetrabenazine}$  and confound assessments.

*Treatment Compliance:* Subjects were instructed to bring all unused study drug and empty packaging materials to the study center for each visit. Compliance was assessed by counting the capsules returned at each study visit. In addition, plasma samples were collected at the end of Weeks 2, 4, 6, and approximately two weeks after the last dose of study drug (or early

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

termination) for determination of plasma concentrations of valbenazine, [+]– $\alpha$ -dihydrotetrabenazine, and the NBI-136110 metabolite. These methods are deemed adequate and consistent with standard trial practice.

*Rescue Medication:* Not applicable for this protocol.

*Subject Completion, Discontinuation, or Withdrawal:* Subjects who fully completed the study participated in a  $\leq 6$  week screening period, a 6-week double-blind treatment period, and a 2-week follow up period. Subjects were free to discontinue participation at any time. Investigators were required to withdraw subjects if the type, frequency, or severity of any AE became unacceptable or intolerable; if ALT or AST  $\geq 2.5$  times upper limit of normal (ULN) or GGT  $\geq 3$  times ULN or total bilirubin  $\geq 2$  times ULN or serum creatinine  $\geq 1.5$  times ULN; if QTcF  $> 500$  msec or a subject had a clinically significant ECG change; if a subject exhibited active suicidal ideation with at least some intent to act; if the use of a prohibited medication was required; if compliance with medication dosing was  $< 80\%$ ; if entry criteria were no longer met; if pregnancy was confirmed; or if the initial or reduced dose of study treatment was not tolerated. If subjects withdrew prematurely from the study, the reason for withdrawal was recorded and subjects underwent early termination assessments (see *Procedures and Schedule* above). It was considered crucial to obtain follow-up data for subjects withdrawn for safety-related reasons.

## Study Endpoints

The primary efficacy assessment measure was the AIMS, which is described under Study Endpoints in Section 6.1.1. In this study, the AIMS was administered and scored by an on-site certified, independent AIMS rater who was not involved in other aspects of subject care. The protocol specified that if possible, the independent AIMS rater should administer and score the AIMS for an individual subject at all time points, and the score should be based solely on interactions at the time of examination. The independent rater was blinded to treatment dose adjustments and was not permitted to review prior video recordings of earlier AIMS assessments. The independent raters' scores informed whether a treatment drug titration would be permitted. AIMS examinations were video recorded for external review and blinded central rating. The external reviewer made the determination as to whether the subject had moderate or severe TD at the screening assessment and whether the examinations were being conducted according to the administration manual.

The blinded central raters reviewed AIMS examinations from Baseline and the end of Week 6, scoring only AIMS items 1-7 (the sum of which comprised the AIMS dyskinesia total score). Of note, the plan for central AIMS video raters was implemented mid-study with Protocol Amendment 2 (discussed in Protocol Amendments below) after the Applicant noted inconsistencies with on-site ratings in the prior Phase 2 study 1201. A "triple-blind" review

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

process was used, in which two neurologists who specialized in movement disorders would review AIMS videos, blinded to subject number, treatment assignment, and study visit. The two blinded central raters were required to reach consensus on the scores for Items 1-7, based on the alternative AIMS descriptors shown below in Table 22. The alternative descriptors were recommended by the study's Scientific Advisory Board to improve rating consistency and the ability to detect change in TD severity. The study protocol originally specified that videos from Weeks 2, 4, and 8 (post-treatment) would also be scored by central raters, but the Applicant indicated that this plan was changed because of the large number of video recordings across time points and the flexible-dose nature of the study limited the usefulness of central ratings at intermediate time points.

**Table 22: AIMS Score Descriptors Used by On-Site versus Central Video Raters**

| Score | Descriptors Used by the On-Site Rater  | Descriptors Used by the Central Video Raters  |
|-------|--|---|
| 0     | None   | None: No dyskinesia   |
| 1     | <b>Minimal:</b> Given when there is some movement, but you are not sure that it is TD. May be at upper extreme of normal range | <b>Minimal</b> or slight dyskinesia: Low amplitude, present during some but not most of the exam                                  |
| 2     | <b>Mild:</b> Rated if movements are definitely TD, however slight  | <b>Mild</b> dyskinesia: Low amplitude and present during most of the exam (or moderate amplitude and present during some of exam) |
| 3     | <b>Moderate:</b> Assigned when there is an increase in amplitude and frequency of movements                                    | <b>Moderate</b> dyskinesia: Moderate amplitude and present during most of exam  |
| 4     | <b>Severe:</b> Rated if movements are constant, very noticeable, unsightly. Sharp increase of amplitude and frequency          | <b>Severe</b> dyskinesia: Maximal amplitude and present during most of exam   |

Source: Study 1202 Clinical Study Report, July 7, 2015 version; Table 5 (page 44)

As discussed in Section 3.2, at the End of Phase 2 Meeting, the Agency indicated agreement with the use of central AIMS video raters, as long as it was prespecified in the protocol and the SAP. The Agency also indicated that the change from baseline on the AIMS items 1-7 total score would be acceptable as a primary endpoint. At the subsequent Breakthrough Designation Meeting, the Division agreed, with consultation from the Clinical Outcomes Assessment team, that the modification of AIMS descriptors appeared adequately supported by the provided information.

In this reviewer's opinion, the AIMS was a reasonable choice for a primary efficacy measure. Its validity has been established by comparisons to other similar instruments [25], and it has been widely used in clinical and research settings for the purpose of assessing the presence and severity of TD. Limitations with this measure include the need for a trained and experienced rater [26] and the lack of consensus as to what would constitute a meaningful change in AIMS score. The implementation of central video raters and modification of AIMS anchor points mid-study appears to have been conducted in a reasonable manner to improve scoring consistency; however, changing the anchor points complicates the comparison of results from AIMS

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

measures using other descriptors. The blinding of central raters to visit number is also considered to be beneficial for reducing expectancy bias, which might occur with clinical assessments over the course of a study. It would have preferable to have central video ratings for Weeks 2, 4, and 8, for additional information about the time course to effect and treatment persistence.

The CGI-TD (described in Section 6.1.1 and shown in The Clinical Global Impression of Change – Tardive Dyskinesia (CGI-TD) was used as a key secondary outcome measure. This measure was modified from the Clinical Global Impression (CGI) [27], which was originally developed to provide a global evaluation of improvement over time from the clinician’s perspective. The CGI-TD (Figure 6) was rated by an investigator or qualified clinician designee at Weeks 2, 4, 6, 8, 16, 24, 32, 40, 48, and the follow-up or early termination visit. While it was not mandated, the protocol specified that if possible, the same person should rate the CGI-TD at all time points. Each of the seven CGI-TD responses was assigned a score from 1-7, with 1=very much improved and 7=very much worse. The pre-specified key secondary endpoint was the mean CGI-TD score at Week 6. This was accepted by the Division at the End of Phase 2 meeting; however it was noted that the percentage of responders based on CGI-TD scores would not be acceptable for this purpose. Limitations with this outcome measure include the variability introduced by potentially different raters across visits and the subjective assessment of improvement, which may vary according to training and clinical experience. Furthermore, this comparison-based assessment necessitates an accurate recall of the subjects’ baseline presentations. Unlike the AIMS, this measure was not scored by central raters. Overall, this efficacy endpoint is considered to be less useful than the central-rated AIMS change from baseline for assessing efficacy.

Figure 6) was specified as a secondary outcome measure and assessed by site investigators at the end of Week 2, Week 6, and the follow-up/early termination visit. The protocol specified that, if possible, the same person should administer and rate the scale at all time points. This endpoint is more difficult to interpret, as the investigator rater was not blinded to the independent AIMS raters’ authorization for treatment dose increases, which could bias the assessment of global TD improvement. The potential for different raters across visits would also make this baseline comparison-based measure less meaningful. While the CGI-TD was specified as a secondary measure in the SAP, (b) (4)

Additional exploratory efficacy assessments administered in this study were:

1. Patient Global Impression of Change (PGIC) – patient-reported outcome measure in

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

which subjects evaluated the change in their TD symptoms since initiation of study drug by choosing one of seven responses (very much improved, much improved, minimally improved, not changed, minimally worse, much worse, and very much worse). This measure was completed by subjects at the end of Week 6 and at the follow-up (or early termination) visit.

2. Tardive Dyskinesia Rating Scale (TDRS) –adapted from the Unified Dyskinesia Rating Scale [31], the TDRS consists of 3 parts. Part 1 (Dyskinesia) consists of 12 questions that focus on time spent with dyskinesia and on the impact of dyskinesia on experiences of daily living (e.g., speech, chewing and swallowing, eating, dressing, hygiene, handwriting, hobbies, walking and balance, public and social settings, exciting or emotional settings, and pain). Questions were answered by the subject and/or caregiver. Responses to each question were made on a scale from 0 to 4, with a response ranging from 0=normal to 4=severe. Part 2 (Impairment) and Part 3 (Disability) were assessed by the clinician rater, who observed the subject during four activities of daily living (communication, drinking from a cup, dressing, and walking) and rated the impairment and disability on a similar 0-4 scale. The TDRS was administered by the independent AIMS rater who was otherwise not involved in the subjects' care and only administered the AIMS and the TDRS. This measure was administered at Baseline, the end of Weeks 2 and 6, and at the follow-up or early termination visit.

For the purpose of this efficacy review, I will focus mainly on the AIMS total dyskinesia score for this study, which was pre-specified as the primary outcome measure.

### Statistical Analysis Plan

The SAP for this study was dated October 10, 2013, which occurred prior to the database lock on January 30, 2014. In a response to information request dated March 16, 2017, the Applicant indicated that the SAP was not submitted to the Agency for review prior to database lock and study unblinding. This was not ideal, but Study 1202 was not regarded by the Applicant as a pivotal efficacy trial at that time.

Three analysis sets were used by the Applicant for analyzing study data:

1. Safety analysis set – included all subjects who were randomized to a treatment group and received at least one dose of study drug. The treatment group assignment in this set was based on the treatment actually received.
2. Intent-to-treat (ITT) analysis set – included all subjects in the safety analysis set who had an evaluable blinded, central video rater's AIMS Dyskinesia total score change from baseline (CFB) value at  $\geq 1$  scheduled assessment times during the double-blind treatment period. The treatment group in this set was based on the treatment the subject was randomized to.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

3. Per protocol (PP) analysis set – included all subjects in the ITT set who had an evaluable blinded, central video rater’s AIMS dyskinesia total score CFB at Week 6, a quantifiable [+]– $\alpha$ -dihydrotrabenazine plasma concentration at Week 6, and no efficacy-related important protocol deviations.

*Handling Missing Data:* Missing values for outcome measures were not replaced with imputed values except for early termination visit data assigned to a scheduled visit (for summary and analysis purposes). Derived scale total scores (such as the YMRS) were set equal to missing if any individual scale items were missing. Missing and incomplete dates for AEs and concomitant medications were imputed only for the purpose of estimating the time of the event or medication usage in relationship to study treatment phases. Laboratory data that was missing at Baseline were replaced with screening values, if available.

*Analysis of Primary Efficacy Endpoint:* The prespecified primary efficacy endpoint for the study was the central rated AIMS dyskinesia total score CFB at Week 6 using the PP analysis set. Analysis of covariance (ANCOVA) was performed using a model which included the baseline AIMS total score as a covariate and treatment group and disease category as fixed effects. A linear contrast comparing the least-squares means for the valbenazine and placebo groups was constructed, and the two-sided p-value from this hypothesis test along with a two-sided 95% confidence interval for the difference between treatment group least-square means was reported. The analysis was also performed using the ITT analysis set and with on-site independent AIMS rater scores. The primary efficacy measure itself (AIMS dyskinesia total score Week 6 CFB) is considered appropriate, but it would have been preferable to use the ITT rather than the PP analysis set for the pre-specified primary endpoint of this trial, as using the PP set may introduce an attrition bias if treatment compliance is non-random. Furthermore, even the use of the ITT set is not ideal, as the specified primary analysis method (ANCOVA change from Baseline to the end of Week 6) would essentially make the “ITT” set a completer set, because central AIMS video ratings were only performed at Baseline and the end of Week 6.

*Multiplicity:* There was no specific plan for addressing the issue of multiple testing. The Applicant planned to report nominal two-sided p-values for comparisons between valbenazine and placebo, without any adjustments for multiplicity. This not ideal, particularly for a pivotal efficacy trial, as the Applicant planned to perform inferential statistics on both the AIMS dyskinesia total score CFB and the CGI-TD, and such an analysis plan should contain methods for controlling type I error.

*Interim Analysis:* An analysis of data collected through Week 6 (the end of double-blind treatment) was performed by the Applicant prior to study completion and final database lock. The analysis was conducted to inform the design of future valbenazine studies and did not affect the post-treatment follow-up period for this study. The analysis was performed by an independent, unblinded statistician after all randomized subjects have either completed the

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Week 6 visit or discontinued from the study prior to Week 6. This independent statistician was the only individual with access to individual treatment assignments at the time of the analysis. The interim analysis plan is considered to have been reasonable for this Phase 2 study.

*Additional Analyses:* Additional efficacy analyses discussed in the SAP included: assessing the primary efficacy endpoint with MMRM analysis; conducting an AIMS responder analysis with percent improvement thresholds; conducting a CGI-TD responder analysis using the percentage of subjects achieving CGI-TD score thresholds; assessing PGIC scores and responder rates based on score thresholds; and assessing TDRS scores (Part 1, Part 2-3, and total score).

Please refer to the Biostatistics review for a detailed evaluation of the Applicant's statistical analyses.

### Protocol Amendments

The original protocol was finalized on September 25, 2012. Amendment 1 was finalized on February 4, 2013, which was before the first subject enrolled (February 13, 2013) so would not be expected to affect the integrity of the trial or the interpretation of results. This amendment included the following notable changes:

1. The prohibition on treatment regimen changes in the 30 days prior to screening assessments included the discontinuation of medications during this period.
2. Carbamazepine was prohibited from use during the study, given concern that it may decrease exposure to valbenazine and  $[+]-\alpha$ -dihydrotetrabenazine.

Amendment 2 was finalized on September 26, 2013, which was while the study was being actively conducted. This amendment included the following notable changes:

1. AIMS items 1-7 would be scored by central, blinded central video raters at baseline and all post-dose time points. The primary endpoint (AIMS dyskinesia total score CFB) was changed to be the central raters' score, and the on-site AIMS raters' scores would be used as a secondary efficacy endpoint. The analysis of Week 6 data would not be conducted until the final Week 6 subject visit had occurred.
2. The requirement that no more than 40 subjects in any one of the three disease categories may be randomized in the study was removed.

As discussed in Study Endpoints above, the implementation of central raters mid-study represented a significant change in the study design. However, the rationale (inconsistencies between on-site raters on scoring approaches) was sound and the implementation method was reasonable. The introduced methods for central rating had significant advantages over the

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

initial rating methods, including the raters being blinded to treatment visit sequence and the requirement for two expert raters to reach a consensus on scores.

While Amendment 2 specified that all post-dose time points would be scored by central video raters, only videos from Baseline and Week 6 were scored. In response to an information request received on January 26, 2017, the Applicant confirmed that the other post-dose time points were not scored by central raters because of the large number of video recordings across time points and the flexible-dose nature of the study design. This should have been submitted as an additional protocol amendment. It would have been preferable to perform central video rating for Weeks 2, 4, and 8 for additional information time course and treatment persistence data. However, the collected data is deemed adequate to assess efficacy of valbenazine as indicated by the AIMS change from baseline at Week 6.

### **Data Quality and Integrity: Applicant's Assurance**

The Applicant assured that the study was performed in compliance with GCP and FDA regulations and guidelines. Prior to initiating the study, site initiation visits were conducted and an Investigator's meeting was held to discuss details of the study protocol, data collection procedures, eCRF entry, and regulatory requirements. Data were collected via an EDC (b) (4). Throughout the study, the study monitor made frequent contacts with the Investigator by telephone and on-site visits. At on-site visits, the monitors performed source data verification with the eCRFs, performed drug accountability checks, and monitored for unreported SAEs or discontinuations due to AEs. 100% source document verification was performed for the first two randomized subjects at each site, and subsequent subjects had a subset of key eCRFs verified (including AIMS, CGI-TD, study drug dosing, etc.). All data changes were tracked using an electronic audit trail. Quality assurance audits were performed at four clinical study sites (205, 210, 218, and 224), and audit certificates were included with the application. Quality control review and quality assurance audit of the clinical study report was performed by the Applicant, checking for consistency, clarity, and accuracy. Overall, the data quality and integrity plan appears to have been adequate.

## **6.2.2. Study Results**

### **Compliance with Good Clinical Practices**

The Applicant indicated that the study was conducted in accordance with GCP and 21 CFR parts 11, 50, 54, 56, 312, and 314.

### **Financial Disclosure**

Please see Appendix 13.2 for the financial disclosure review of all covered clinical studies (as defined in 21 CFR 54). There were no disclosable financial interests or arrangements. This

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

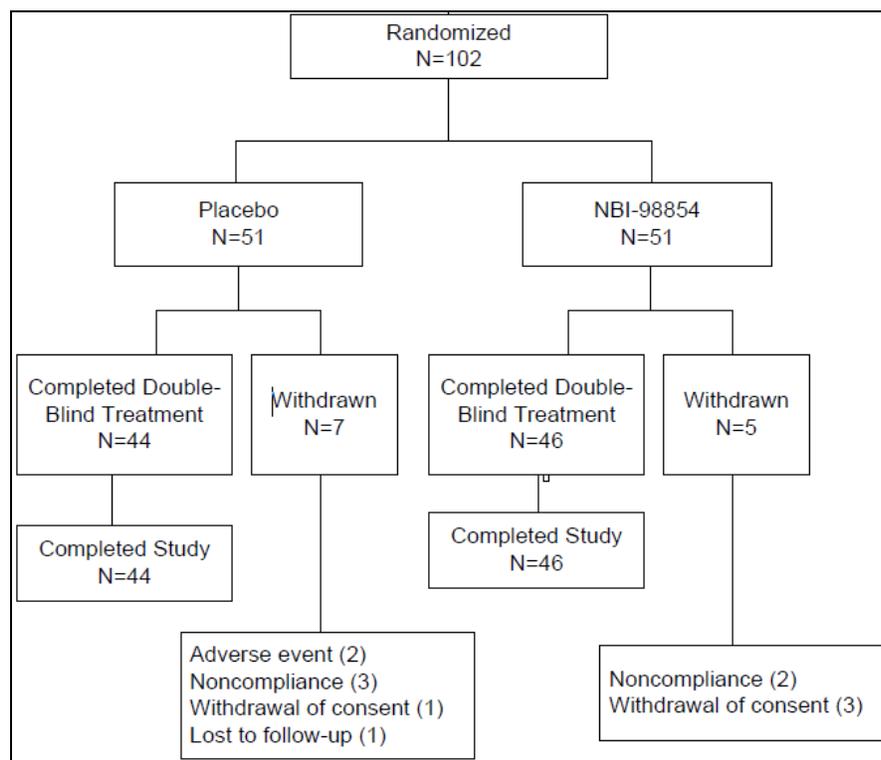
Ingrezza (valbenazine)

information was confirmed by the Applicant in a Response to Information Request received on December 22, 2016. Based on the certification and Applicant verification, there are no concerns about financial conflicts of interest that would affect the interpretation of this study data or the approvability of this application.

### Patient Disposition

Please see Figure 15 for a flow chart of subject disposition. There were 205 subjects screened for the study. Failure to meet AIMS score eligibility criteria was the most common reason for screening failure. The percentage of subjects completing the study was high (88.2% overall) and similar between treatment groups.

**Figure 15: Study 1202 - Subject Disposition**



Source: Study 1202 Clinical Study Report, Figure 3, p. 68

Please see Table 23 for a summary of patients included in each pre-specified analysis set. It is noted that the PP analysis set had substantially more subjects excluded from the valbenazine than the placebo treatment group. This was generally due to 21.6% of subjects having no quantifiable plasma concentration at Week 6. It is possible that a similar number of placebo-treated patients were noncompliant with study treatment, but this was not able to be assessed by plasma measurements. We cannot rule out, however, that there was greater treatment

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

noncompliance in the valbenazine treatment group for reasons of tolerability. Overall, for the purposes of evaluating this Applicant-designated pivotal efficacy study, it is most appropriate to use the ITT analysis set for efficacy analyses.

**Table 23: Study 1202 - Analysis Set Disposition**

| Analysis Set   | Placebo<br>(N=51)<br>n (%) | NBI-98854<br>(N=51)<br>n (%) | All Subjects<br>(N=102)<br>n (%) |
|--|----------------------------|------------------------------|----------------------------------|
| <b>Safety Analysis Set</b>   |                            |                              |                                  |
| Subjects included  | 49 (96.1)                  | 51 (100.0)                   | 100 (98.0)                       |
| Subjects excluded  | 2 (3.9)                    | 0                            | 2 (2.0)                          |
| Reason for exclusion   |                            |                              |                                  |
| Did not receive study drug   | 2 (3.9)                    | 0                            | 2 (2.0)                          |
| <b>Intent-to-Treat Analysis Set</b>  |                            |                              |                                  |
| Subjects included  | 44 (86.3)                  | 45 (88.2)                    | 89 (87.3)                        |
| Subjects excluded  | 7 (13.7)                   | 6 (11.8)                     | 13 (12.7)                        |
| Reason for exclusion:  |                            |                              |                                  |
| Did not have an evaluable central AIMS video raters' CFB AIMS dyskinesia total score during the double-blind treatment | 5 (9.8)                    | 6 (11.8)                     | 11 (10.8)                        |
| Multiple reasons   | 2 (3.9)                    | 0                            | 2 (2.0)                          |
| <b>Per Protocol Analysis Set</b>   |                            |                              |                                  |
| Subjects included  | 44 (86.3)                  | 32 (62.7)                    | 76 (74.5)                        |
| Subjects excluded  | 7 (13.7)                   | 19 (37.3)                    | 26 (25.5)                        |
| Reason for exclusion:  |                            |                              |                                  |
| Important protocol deviation   | 0                          | 1 (2.0)                      | 1 (1.0)                          |
| NBI-98854 treated subject with no quantifiable plasma concentration at Week 6  | 0                          | 11 (21.6)                    | 11 (10.8)                        |
| Multiple reasons   | 7 (13.7)                   | 6 (11.8)                     | 13 (12.7)                        |

Source: Study 1202 Clinical Study Report, Table 7, p. 71; NBI-98854 = valbenazine

## Protocol Violations/Deviations

The applicant defined Important Protocol Deviations (IPDs) as those that could potentially impact the conclusions of the study. They were assessed before unblinding individual subject treatment assignments. A total of four subjects (three receiving valbenazine and one receiving placebo) had IPDs. The one subject randomized to placebo was living in a facility that would not dispense study drug and was discontinued and excluded from all analysis sets. The first subject receiving valbenazine was discontinued due to not taking study drug dispensed during Week 2; she was excluded from PP and ITT analysis sets. The second subject receiving valbenazine discontinued risperidone, lithium, and trazodone four days after her Week 4 visit; this subject completed the study but was excluded from the PP analysis set. In this case, discontinuing risperidone two weeks prior to the final efficacy assessment might worsen TD symptoms and could theoretically reduce the apparent therapeutic effects of valbenazine. The third subject receiving valbenazine used a weight loss supplement after randomization and was discontinued

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

from the study due to noncompliance; this subject was excluded from PP and ITT analysis sets. Overall, protocol violations identified in the study report were infrequent and would not appear to bias the interpretation of results in favor of valbenazine treatment.

### **Table of Demographic Characteristics**

Please see Table 24 for a tabulation of demographic characteristics for the ITT sample. There were a greater proportion of males than females in the overall sample, but the imbalance is not considered large enough to limit study generalizability. The mean and median ages were in the mid-50's across all treatment groups, which is a reasonable approximation of the likely target population for this drug. Patients of African-American and Caucasian races, as well as those with Hispanic ethnicity, were well-represented in the study sample. The race that was substantially underrepresented in the sample as compared to the US population was Asian, for reasons that are unclear. However, there is no reason to believe that the response to TD treatment differs between races, other than potential differences in drug metabolism. With regards to site location, there were three subjects from sites in Puerto Rico and the remaining subjects were from sites in US states; this is reasonable for evaluating a drug to be marketed in the US.

APPEARS THIS WAY ON ORIGINAL

**Table 24: Study 1202 - Demographic Characteristics, ITT Analysis Set**

| Parameter                        | Placebo<br>(N=44)<br>n (%) | Valbenazine<br>(N=45)<br>n (%) | Total<br>(N=89)<br>n (%) |
|----------------------------------|----------------------------|--------------------------------|--------------------------|
| <b>Sex</b>                       |                            |                                |                          |
| Male                             | 25 (56.8)                  | 28 (62.2)                      | 53 (59.6)                |
| Female                           | 19 (43.2)                  | 17 (37.8)                      | 36 (40.4)                |
| <b>Age</b>                       |                            |                                |                          |
| Mean years (SD)                  | 55.3 (1.3)                 | 57.0 (1.5)                     | 55.6 (1.0)               |
| Median (years)                   | 57.0                       | 56.0                           | 56.0                     |
| Min, max (years)                 | 34, 70                     | 32, 78                         | 32, 78                   |
| <b>Race</b>                      |                            |                                |                          |
| Caucasian                        | 25 (56.8)                  | 29 (64.4)                      | 54 (60.7)                |
| Black or African American        | 16 (36.4)                  | 16 (35.6)                      | 32 (36.0)                |
| Asian                            | 0                          | 0                              | 0                        |
| American Indian or Alaska Native | 1 (2.3)                    | 0                              | 1 (1.1)                  |
| Mixed                            | 2 (4.5)                    | 0                              | 2 (2.2)                  |
| <b>Ethnicity</b>                 |                            |                                |                          |
| Hispanic or Latino               | 14 (31.8)                  | 18 (40.0)                      | 25 (32.9)                |
| Not Hispanic or Latino           | 30 (68.2)                  | 27 (60.0)                      | 51 (67.1)                |

Source: Data from 1202 Clinical Study Report (Table 14.4.2), p. 149

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Please see Table 25 for a summary of select subject baseline characteristics in the ITT analysis set. Subjects had a range of CYP2D6 genotypes, with a small number of subjects in each treatment group being classified as ultra-rapid or poor metabolizers. The CYP2D6 phenotype could affect the exposure to valbenazine and its active metabolite [+]–α-dihydrotetrabenazine. The genotypes were reasonably balanced between treatment groups and should not impact overall study interpretability. The underlying diseases were relatively well represented for Schizophrenia/Schizoaffective Disorder and Mood Disorders, but there was only one subject with a Gastrointestinal Disorder. There is no evidence that TD would be differentially responsive between underlying disorders, but there may be a differential need for continuing neuroleptic treatment based the underlying illnesses (i.e., patients with gastroparesis or major depressive disorder have more non-neuroleptic treatment options than patients with schizophrenia, and thus may be more likely to discontinue neuroleptic treatment after developing TD). The proportion of subjects who continued to receive antipsychotics for their underlying illnesses was relatively similar between groups, with the majority of subjects continuing to receive atypical antipsychotics.

**Table 25: Study 1202 - Baseline Characteristics, ITT Analysis Set**

| Parameter   | Placebo<br>(N=44)<br>n (%) | Valbenazine<br>(N=45)<br>n (%) | Total<br>(N=89)<br>n (%) |
|---|----------------------------|--------------------------------|--------------------------|
| <b>BMI (mean (SD))</b>                                  | 28.31 (5.47)               | 28.99 (0.86)                   | 28.65 (0.59)             |
| <b>CYP2D6 Genotype Classification</b>                   |                            |                                |                          |
| Ultra-Rapid Metabolizer                                 | 1 (2.3)                    | 1 (2.2)                        | 2 (2.2)                  |
| Extensive or Ultra Rapid Metabolizer                    | 0                          | 1 (2.2)                        | 1 (1.1)                  |
| Extensive Metabolizer                                   | 29 (65.9)                  | 25 (55.6)                      | 54 (60.7)                |
| Intermediate or Extensive Metabolizer                   | 0                          | 2 (4.4)                        | 2 (2.2)                  |
| Intermediate Metabolizer                                | 11 (25)                    | 12 (26.7)                      | 23 (25.8)                |
| Poor Metabolizer  | 3 (6.8)                    | 3 (6.7)                        | 6 (6.7)                  |
| Not Reported  | 0                          | 1 (2.2)                        | 1 (1.1)                  |
| <b>Disease Category</b>                                 |                            |                                |                          |
| Schizophrenia/Schizoaffective Disorder                  | 27 (61.4)                  | 26 (57.8)                      | 53 (59.6)                |
| Mood Disorder   | 16 (36.4)                  | 19 (42.2)                      | 35 (39.3)                |
| Gastrointestinal Disorder                               | 1 (2.3)                    | 0                              | 1 (1.1)                  |
| <b>Valproic Acid Use: Yes</b>                           | 5 (11.4)                   | 8 (17.8)                       | 13 (14.6)                |
| <b>Baseline AIMS Dyskinesia Total Score (mean (SD))</b> | 7.9 (4.5)                  | 8.0 (3.5)                      | 8.0 (4.0)                |
| <b>Current Antipsychotic Use</b>                        |                            |                                |                          |
| None  | 11 (25.0)                  | 14 (31.1)                      | 25 (28.1)                |
| Atypical Only   | 24 (54.5)                  | 24 (53.3)                      | 48 (53.9)                |
| Typical or Combination                                  | 9 (20.5)                   | 7 (15.6)                       | 16 (18.0)                |

Source: Reviewer-created, using data from the 1202 Clinical Study Report (Table 14.5.2) and the ADSL.XPT analysis dataset

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The applicant defined dosing compliance as the ratio of the estimated number of doses taken to the expected number of doses x 100. Compliance was assessed at each visit by counting the returned capsules. By this method, both placebo and valbenazine groups had a mean compliance of greater than 99% at Weeks 2, 4, and 6. Capsule counting likely overestimated actual compliance, however, as 11 out of 51 subjects (21.6%) randomized to valbenazine treatment had no quantifiable plasma concentration of valbenazine at the end of Week 6 (see Table 23 above). The actual compliance with placebo treatment was not able to be corroborated with PK data.

The most common concomitant medications taken during double-blind treatment were related to the underlying psychiatric illnesses (e.g., anticholinergics such as benztropine for the treatment of EPS, antidepressants, anticonvulsants for mood stabilization, antipsychotics) and medications related to cardiovascular disease (e.g., lipid lowering medications and antihypertensives). From inspection of the tabulation of concomitant medications in the

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Applicant's Clinical Study Report, there were no concerning imbalances between the treatment groups; differences were likely random and related to the relatively small sample size. As shown in Table 25 above, the proportions of subjects taking valproic acid and antipsychotics were relatively similar between treatment groups.

There was no role for rescue medications in this study, given the lack of treatments indicated for TD.

### **Efficacy Results - Primary Endpoint**

The Applicant defined the primary efficacy endpoint as the AIMS dyskinesia total score CFB at Week 6, based on the central raters' assessments, using the PP analysis set. As discussed previously, using a PP analysis set in a pivotal efficacy study is not appropriate, because removing poor compliers could bias the interpretation of efficacy results. This review will focus on the Applicant-defined ITT analysis set, which is modified from a true ITT population in that it excluded subjects who did not receive any study medication or did not have any post-baseline AIMS assessments. This is acceptable but not ideal, as the tendency for subjects to not return for post-baseline AIMS assessments might not be random.

Please see Table 26 for a summary of the Applicant's primary efficacy endpoint analysis, which indicated that subjects who received flexible-dose valbenazine treatment had a significantly greater improvement (decrease) in the AIMS total dyskinesia total score than the placebo group. Of the 45 subjects in the valbenazine group at the end of Week 6 (ITT analysis set), 31 were receiving 75 mg, 9 were receiving 50 mg, and 5 were receiving 25 mg daily (mean dose (SD) = 64.4 (17.3) mg). As expected, the magnitude of the difference between valbenazine and placebo was greater in the PP than the ITT analysis set, but in both cases the difference was statistically significant. See Figure 16 for a histogram, created by Biometrics reviewer Dr. Thomas Birkner, illustrating the distribution of AIMS changes at 6 weeks by treatment group. It was not possible to assess an efficacy time course in this study using blinded central video rater data, as these central ratings were conducted only at Baseline and end of Week 6 visits.

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 26: Study 1202 - Primary Efficacy Endpoint Analysis: PP vs. ITT Analysis Sets (Applicant Analyses)**

| Statistic   | PP Analysis Set   |                   | ITT Analysis Set |                   |
|---|-------------------|-------------------|------------------|-------------------|
|   | Placebo<br>N=44   | NBI-98854<br>N=32 | Placebo<br>N=44  | NBI-98854<br>N=45 |
| Mean (SEM)  | -1.1 (0.6)        | -4.3 (0.6)        | -1.1 (0.6)       | -3.6 (0.5)        |
| SD  | 3.7               | 3.2               | 3.7              | 3.5               |
| Median  | -0.5              | -4.0              | -0.5             | -3.0              |
| Min, max  | -11, 7            | -11, 1            | -11, 7           | -11, 3            |
| LS mean (SEM) <sup>a</sup>                        | -0.3 (1.1)        | -3.4 (1.2)        | -0.2 (1.1)       | -2.6 (1.2)        |
| 95% confidence interval                           | (-2.5, 1.8)       | (-5.7, -1.0)      | (-2.4, 2.0)      | (-4.9, -0.3)      |
| LS mean difference<br>NBI-98854 vs. placebo (SEM) | -3.0 (0.7)        |                   | -2.4 (0.7)       |                   |
| 95% confidence interval                           | (-4.5, -1.6)      |                   | (-3.7, -1.1)     |                   |
| <b>p-value<sup>b</sup></b>                        | <b>&lt;0.0001</b> |                   | <b>0.0005</b>    |                   |

AIMS=Abnormal Involuntary Movement Scale; ITT=intent-to-Treat; LS=least squares; PP=per protocol.

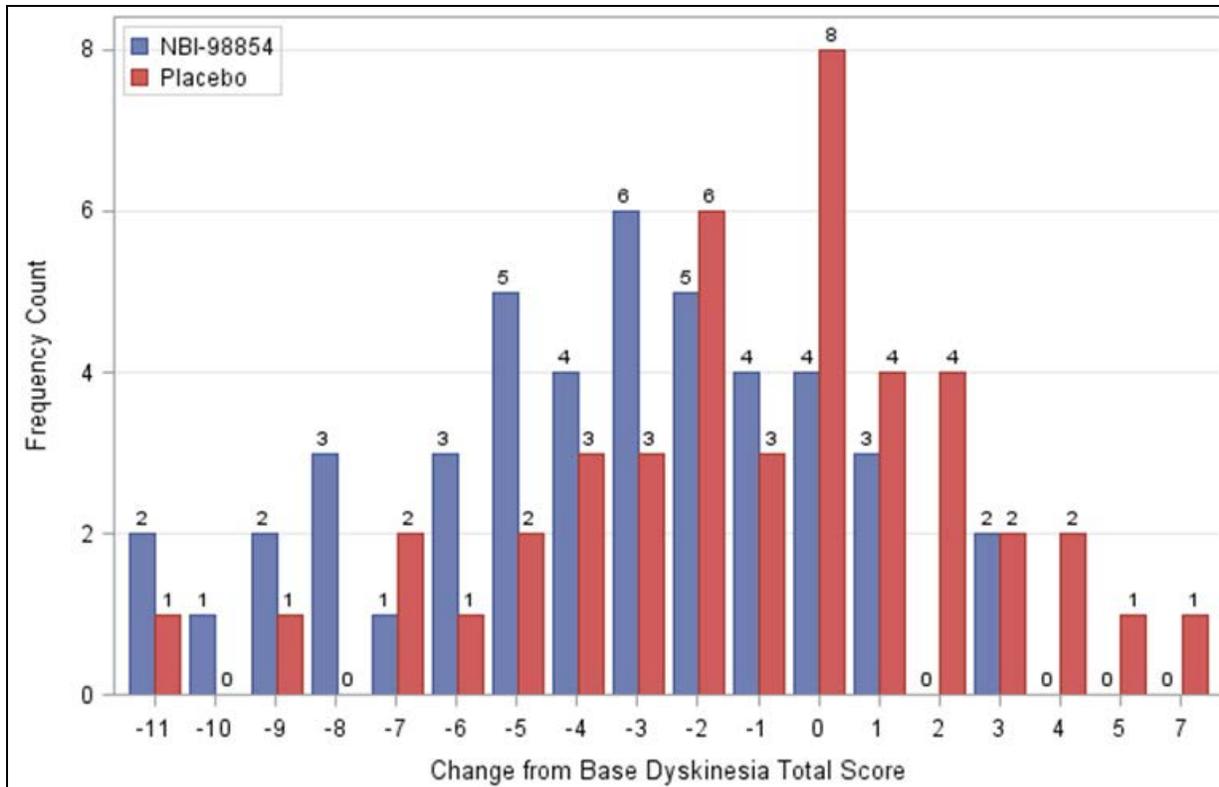
<sup>a</sup> Least-squares mean based on the analysis of covariance (ANCOVA) model, which includes baseline AIMS dyskinesia total score value as a covariate and treatment group and disease category as fixed effects.

<sup>b</sup> p-value for test of null hypothesis that difference between treatment group LS means is equal to zero.

Source: Study NBI-98854-98854-1202 Clinical Study Report, Table 13, p. 82; NBI-98854=valbenazine

APPEARS THIS WAY ON ORIGINAL

**Figure 16: Study 1202 - Frequency of Subjects with Specified AIMS CFB at Week 6**



Source: Created by Biometrics reviewer Dr. Thomas Birkner. Negative change values indicate clinical improvement. NBI-98854=valbenazine. Sample is the ITT analysis set (N=45 valbenazine, N=45 placebo).

To assess whether the change in AIMS total dyskinesia was driven by individual items (corresponding to specific body areas), the mean scores for each item at Baseline and the end of Week 6 were assessed for subjects randomized to valbenazine treatment (Figure 17). While the mean change on Item 7 (Neck, Shoulders, and Hips) was not as large as other body areas (mean change of -0.29), there was a mean numeric decrease in score (indicating improvement) on all AIMS components, suggesting that the drug effects were not limited to specific muscle groups.

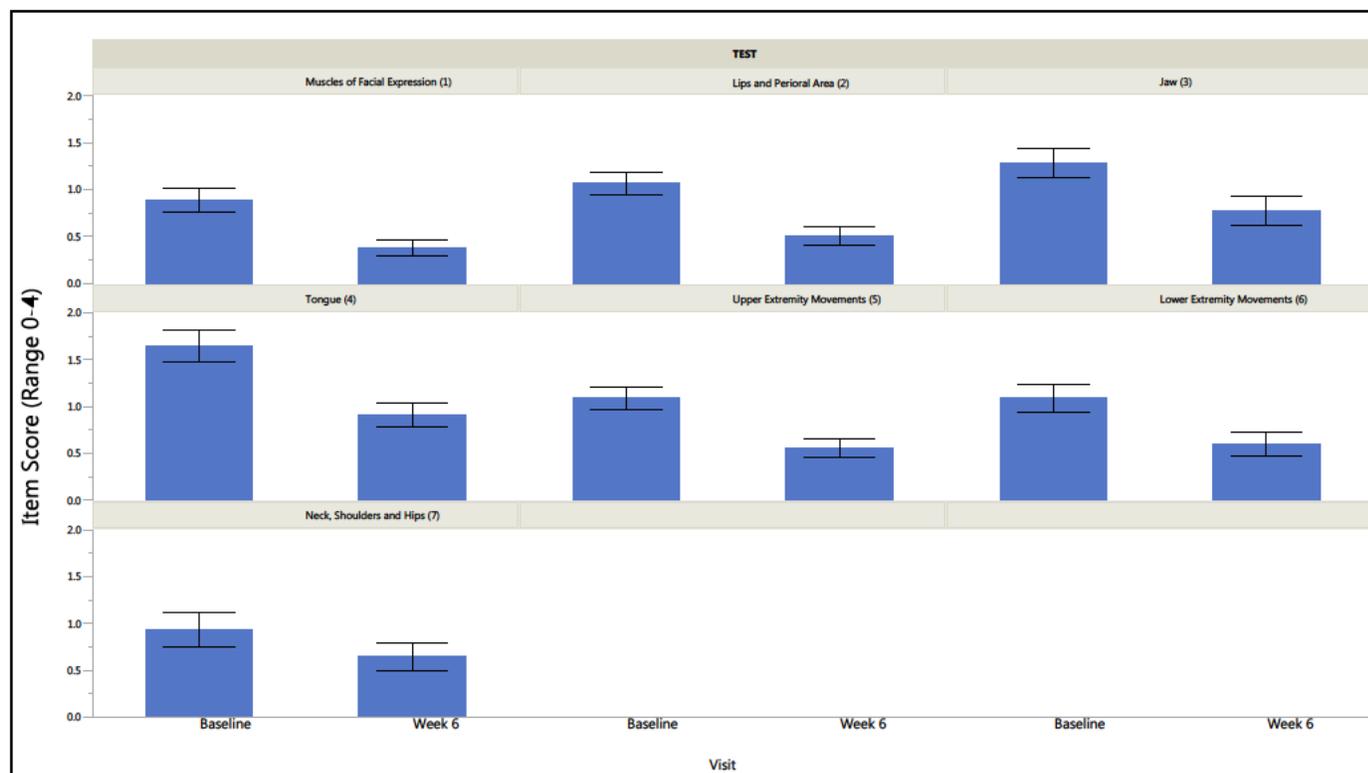
## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Figure 17: Study 1202 - AIMS Component Scores, Valbenazine group, ITT Analysis Set



Source: Reviewer-created using data from Study 1202 analysis dataset AIMS\_CR.XPT. Bars represent mean scores on individual AIMS items, with error bars constructed using 1 standard error from the mean. The sample included in this analysis were those in the ITT analysis set who were randomized to valbenazine treatment (N=45).

An assessment of effects in demographic subpopulations and by baseline characteristics was performed by this reviewer. These analyses are considered exploratory in nature, as the study was not powered to assess subgroup effects and any statistical comparisons would be limited by multiplicity concerns. There was no clear pattern of valbenazine response according to age, TD duration, ethnicity, or anticholinergic medication use. Women appeared to have a modestly better response to valbenazine. Subjects of black race appeared to have a lesser response to valbenazine, though the numeric response was superior to placebo. Subjects in the lowest BMI quartile (17.4-24.1) had a numerically superior response to valbenazine in this study, but the number of subjects in each group was very small. Subjects who were not using antipsychotic medications appeared to have a better response than those using antipsychotic medications; however, there were a limited number of subjects (n=11) in the former group. Subjects with mood disorders appeared to have a modestly better response than those with schizophrenia or schizoaffective disorder, which might be related to antipsychotic use, as ~87% of subjects with schizophrenia or schizoaffective disorder were taking antipsychotics vs. ~51% of subjects with

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

mood disorders. Altogether, it is difficult to derive any conclusions from these subgroup analyses. Please refer to Section 7.1.3 for subgroup analyses across all efficacy trials.

**Table 27: Study 1202 - Subgroup Efficacy Analysis (6-week AIMS Change from Baseline)**

|   | Placebo         |      |         | Valbenazine     |      |         | All             |      |         |
|---|-----------------|------|---------|-----------------|------|---------|-----------------|------|---------|
|   | Week 6 AIMS CFB |      |         | Week 6 AIMS CFB |      |         | Week 6 AIMS CFB |      |         |
| Age Group                                 | N               | Mean | Std Err | N               | Mean | Std Err | N               | Mean | Std Err |
| <57                                       | 21              | -1.8 | 0.86    | 26              | -3.2 | 0.71    | 47              | -2.5 | 0.55    |
| 57-64                                     | 17              | -0.5 | 0.9     | 10              | -4.5 | 1.13    | 27              | -2   | 0.79    |
| >=65                                      | 6               | -0.3 | 0.99    | 9               | -4   | 1.15    | 15              | -2.5 | 0.91    |
| <b>TD Duration</b>                        |                 |      |         |                 |      |         |                 |      |         |
| >4 years                                  | 12              | -0.8 | 0.68    | 15              | -3.5 | 0.94    | 27              | -2.3 | 0.65    |
| 0-4 years                                 | 20              | -1.1 | 0.79    | 18              | -4.3 | 0.82    | 38              | -2.6 | 0.62    |
| <b>Sex</b>                                |                 |      |         |                 |      |         |                 |      |         |
| F   | 19              | -0.8 | 0.88    | 17              | -4.8 | 0.94    | 36              | -2.7 | 0.72    |
| M   | 25              | -1.3 | 0.72    | 28              | -2.9 | 0.6     | 53              | -2.1 | 0.47    |
| <b>Race</b>                               |                 |      |         |                 |      |         |                 |      |         |
| Black                                     | 16              | -1.8 | 0.96    | 16              | -2.4 | 0.78    | 32              | -2.1 | 0.61    |
| White                                     | 25              | -1   | 0.7     | 29              | -4.3 | 0.67    | 54              | -2.8 | 0.53    |
| Other                                     | 3               | 1.67 | 2.4     | 0               | .    | .       | 3               | 1.67 | 2.4     |
| <b>Ethnicity</b>                          |                 |      |         |                 |      |         |                 |      |         |
| Hispanic/Latino                           | 14              | -0.1 | 0.9     | 18              | -3.4 | 0.82    | 32              | -1.9 | 0.67    |
| Not Hispanic/Latino                       | 30              | -1.6 | 0.69    | 27              | -3.8 | 0.7     | 57              | -2.6 | 0.51    |
| <b>BMI Quartile</b>                       |                 |      |         |                 |      |         |                 |      |         |
| 17.4-24.1                                 | 12              | -0.9 | 0.81    | 9               | -5   | 1.03    | 21              | -2.7 | 0.77    |
| 24.2-27.6                                 | 10              | -1.1 | 0.8     | 11              | -3.1 | 0.94    | 21              | -2.1 | 0.64    |
| 27.7-32.8                                 | 12              | -2.1 | 1.59    | 14              | -3.2 | 1.1     | 26              | -2.7 | 0.93    |
| 32.9-46.9                                 | 10              | -0.1 | 0.94    | 11              | -3.5 | 1.11    | 21              | -1.9 | 0.81    |
| <b>Diagnosis Group</b>                    |                 |      |         |                 |      |         |                 |      |         |
| Schizophrenia or Schizoaffective Disorder | 27              | -1   | 0.8     | 26              | -3   | 0.63    | 53              | -2   | 0.53    |
| Mood Disorder                             | 16              | -1.4 | 0.74    | 19              | -4.5 | 0.88    | 35              | -3.1 | 0.63    |
| Gastrointestinal Disorder                 | 1               | 0    | .       | 0               | .    | .       | 1               | 0    | .       |
| <b>Antipsychotic Use</b>                  |                 |      |         |                 |      |         |                 |      |         |
| No  | 11              | 0    | 0.92    | 14              | -5.9 | 0.97    | 25              | -3.3 | 0.89    |
| Yes                                       | 33              | -1.5 | 0.67    | 31              | -2.6 | 0.55    | 64              | -2   | 0.44    |
| <b>Anticholinergic Use</b>                |                 |      |         |                 |      |         |                 |      |         |
| No  | 33              | -1.1 | 0.67    | 34              | -3.8 | 0.64    | 67              | -2.4 | 0.49    |
| Yes                                       | 11              | -1.2 | 1.01    | 11              | -3.2 | 0.86    | 22              | -2.2 | 0.68    |

Source: Reviewer-created, using data from analysis dataset ADSL.XPT. Included subjects (N=89) are those in the ITT analysis set with centrally-rated AIMS total dyskinesia score data from Baseline and Week 6.

The response to valbenazine according to CYP2D6 genotype is displayed in Table 28. There were too few subjects who were poor or ultra-rapid metabolizers from which conclusions could be drawn.

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 28: Study 1202 - CYP2D6 Genotype vs. Week 6 AIMS CFB**

| CYP2D6 Genotype           | Week 6 AIMS CFB |      |         |             |      |         |
|---------------------------|-----------------|------|---------|-------------|------|---------|
|                           | Placebo         |      |         | Valbenazine |      |         |
|                           | N               | Mean | Std Err | N           | Mean | Std Err |
| Poor                      | 3               | -1   | 1.53    | 3           | -9   | 1.15    |
| Intermediate              | 11              | -1.8 | 1.05    | 12          | -2.8 | 0.89    |
| Intermediate or Extensive | 0               | .    | .       | 2           | -5   | 4       |
| Extensive                 | 29              | -0.9 | 0.73    | 25          | -3   | 0.64    |
| Extensive or Ultra Rapid  | 0               | .    | .       | 1           | -3   | .       |
| Ultra-Rapid               | 1               | 2    | .       | 1           | -3   | .       |
| Not Reported              | 0               | .    | .       | 1           | -11  | .       |

*Source: Reviewer-created, using data from analysis dataset ADSL.XPT. Included subjects (N=89) are those in the ITT analysis set with centrally-rated AIMS total dyskinesia score data from Baseline and Week 6.*

A graph was constructed to help visualize whether it appeared that valbenazine was more effective in subjects with TD of greater or lesser severity (Figure 18). The upper panels represent the mean absolute changes in AIMS total dyskinesia score from baseline and the lower panels represent the mean percent change in AIMS total dyskinesia score from baseline, both according to the baseline AIMS score. From inspection of the graphs, it does not appear that valbenazine was less effective in subjects with more severe baseline TD.

APPEARS THIS WAY ON ORIGINAL

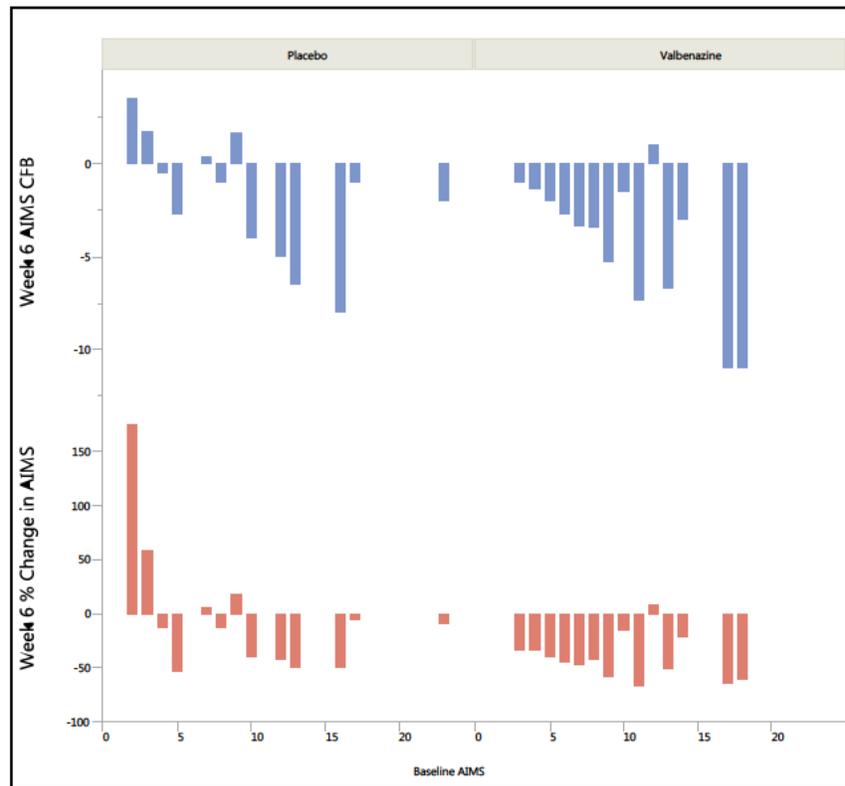
## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

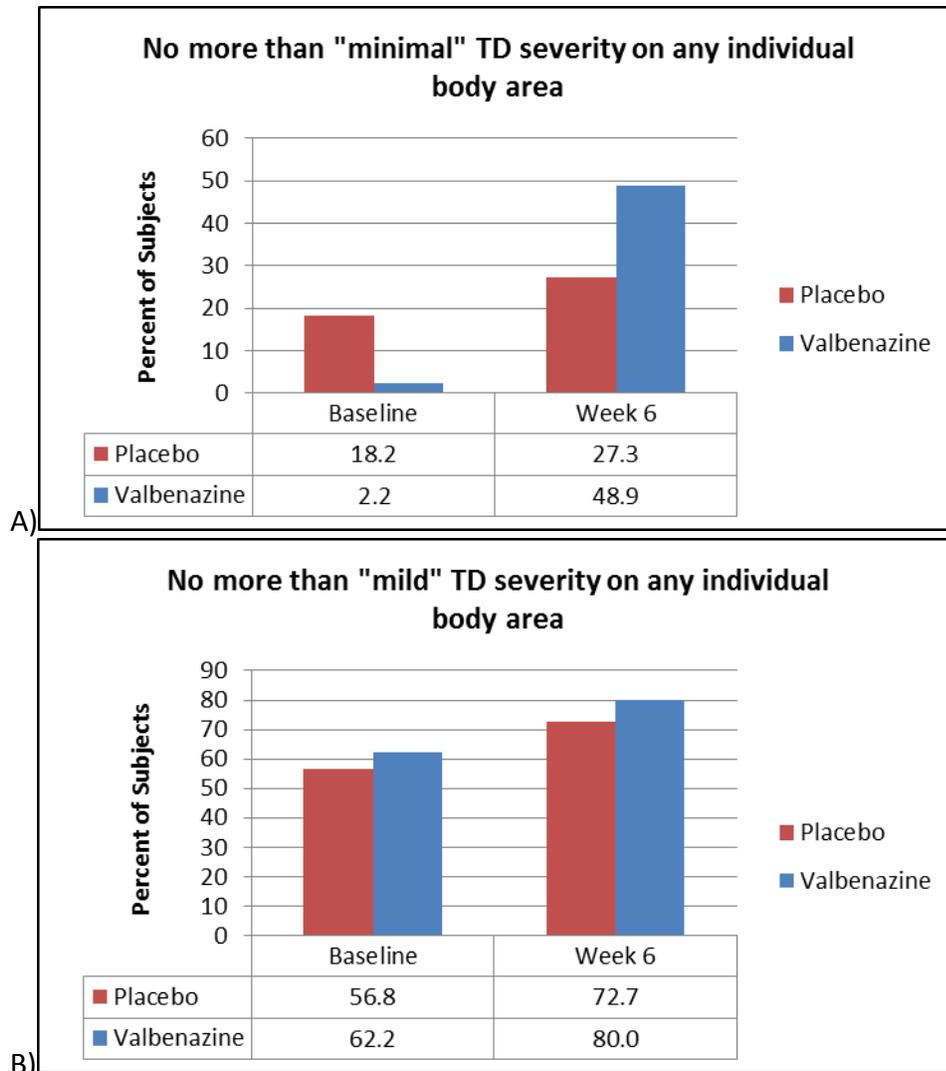
**Figure 18: Study 1202 - Absolute and Relative Change in AIMS at 6 Weeks, by Treatment Arm, According to Baseline AIMS**



*Source: Reviewer-created, using data from analysis dataset ADSL.XPT. Included subjects (N=89) are those in the ITT analysis set with centrally-rated AIMS total dyskinesia score data from Baseline and Week 6.*

An exploratory analysis on the primary efficacy measure was conducted by Dr. Douglas Warfield, in which subjects were classified according whether they had threshold scores on *any* individual body part item from the AIMS total dyskinesia score (Figure 19). Though there are no widely-used TD remission criteria, a subject that had no more than minimal or mild TD symptoms on any muscle group (see Table 5) might be assessed by a treating clinician as being remitted from TD. In subjects treated with flexible dose valbenazine (25-75 mg daily) for six weeks, almost half of the subjects reached the more stringent “minimal” criterion for remission and 80% met the “mild” criterion for remission. While valbenazine was numerically superior to placebo for both criteria, the treatment effect was less apparent for the “mild” criterion, likely because the majority of subjects in both groups had no individual item scores >2, and the dose titration design led to subjects receiving the maximum valbenazine dose (75 mg) for no longer than the last two weeks of treatment.

**Figure 19: Study 1202 - Percentage of Subjects Achieving Exploratory Remission Criteria**



Source: Reviewer-created, using dataset prepared by Dr. Douglas Warfield which included a variable indicating whether subjects had a score of no more than "1" (panel A) or "2" (panel B) on any individual body area comprising AIMS items 1-7.

**Data Quality and Integrity - Reviewers' Assessment**

An assessment of data quality for this study was performed by Dr. Douglas Warfield. A site-based analysis of irregularities based on screen failures, deviations, subject discontinuations, and adverse event frequency also did not reveal any clear problematic study sites; however, these analyses were limited by the small number of subjects per site. Assessment of enrollment patterns by site found only one site with a pattern triggering further review, because it enrolled the most subjects in the study and enrolled five subjects in one day. Further review of data

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

from these subjects revealed no unusual bias or protocol activity. An analysis of SDTM finding domains (EG, LB, QS, VS, and YG) was performed to help detect screening bias; this analysis also did not reveal any clear instances of screening bias. Please see Section 4.1 for a summary of inspections conducted by the Office of Scientific Investigations, which included several sites from this study.

### **Efficacy Results - Secondary and other relevant endpoints**

#### *On-Site AIMS Ratings*

The Applicant analyzed AIMS total dyskinesia scores and changes from baseline at Baseline and Weeks 2, 4, 6, and 8 (the latter being the final visit, when subjects were no longer receiving treatment). The scores, by visit, are presented graphically in Figure 20. While valbenazine treatment appeared graphically to separate from placebo treatment by the end of Week 6, it is notable that the absolute change in AIMS scores were substantially larger in both placebo and valbenazine treatment groups when scored by on-site as compared to blinded central raters. This may be related to visit sequence/expectancy bias as well as the fact that on-site raters in this study used different AIMS item descriptors than those used by central raters (see Table 22). Two weeks after completing treatment (Week 8), the mean AIMS dyskinesia score change from baseline worsened in the valbenazine group and was comparable to the placebo group.

The Applicant conducted supplemental analyses of the AIMS change from baseline at Weeks 2, 4, and 6, based on on-site ratings, using an MMRM approach, and found valbenazine to be superior to placebo at Week 6 (nominal  $p=0.0397$ ).

APPEARS THIS WAY ON ORIGINAL

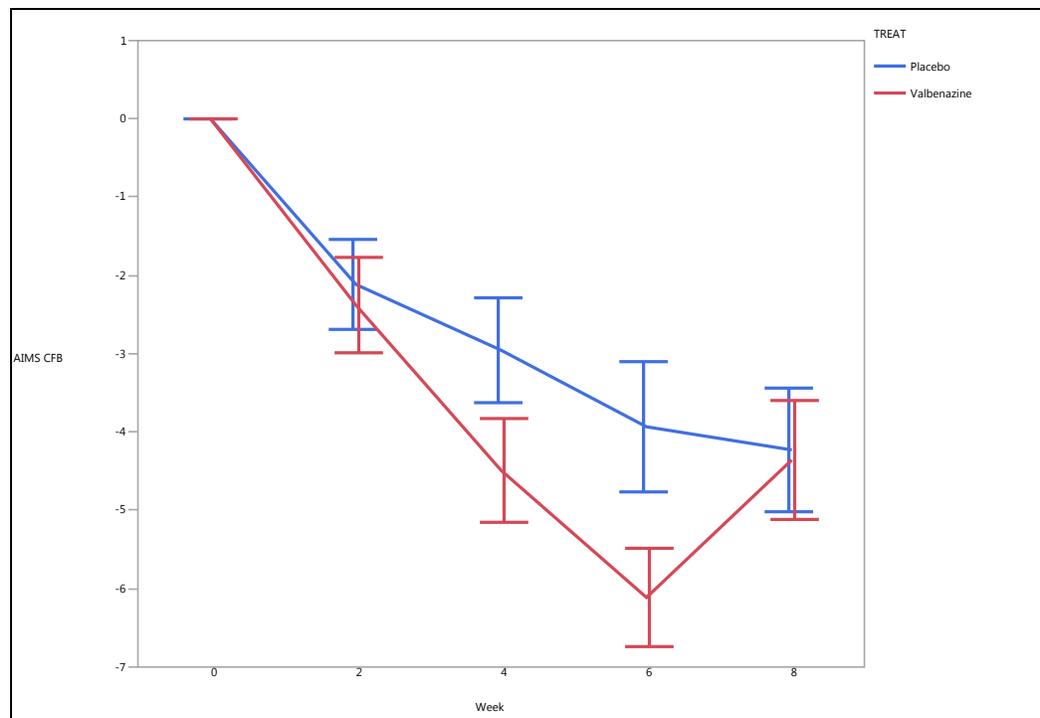
## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Figure 20: Study 1202 - AIMS CFB, On-Site Raters, ITT Analysis Set**



Source: Reviewer-created, using data from analysis dataset A\_AIMS.XPT (on-site raters). Week 0 represents the baseline visit. Subjects were limited to the ITT analysis set (N=89). Error bars represent standard errors of the mean.

### CGI-TD

Please see Table 29 for a summary of CGI-TD scores at the end of Week 6 and statistical analysis submitted by the Applicant. The mean CGI-TD score was lower in subjects receiving valbenazine, suggesting on-site clinician raters may have appreciated greater overall improvement in TD symptoms in this group than those receiving placebo. A greater proportion of subjects receiving valbenazine vs. placebo were categorized as being much or very much improved at the end of Week 6 (67% vs. 16%), and this difference also reached nominal statistical significance according to Applicant analyses ( $p < 0.0001$ , Table 19 in Clinical Study Report). Altogether, these CGI-TD findings provide some support as to the effectiveness of valbenazine. Caveats to this measure include the fact that on-site raters' assessments may have been biased by information from the independent AIMS rater as to whether the treatment dose could be increased at each visit, and that there was no pre-specified plan for controlling for multiple statistical tests.

**Table 29: Study 1202 - CGI-TD Summary and Applicant-Submitted Analysis, Week 6, ITT Analysis Set**

|  | Placebo (N=44) | Valbenazine (N=45) |
|--|----------------|--------------------|
| <b>CGI-TD</b>                          |                |                    |
| Mean (SEM)                             | 3.1 (0.1)      | 2.3 (0.1)          |
| LS mean (SEM) <sup>1</sup>             | 3.1 (0.3)      | 2.2 (0.3)          |
| Difference Valbenazine – Placebo (SEM) | -0.8 (0.2)     |                    |
| Difference 95% Confidence Interval     | (-1.2, -0.5)   |                    |
| p-value <sup>2</sup>                   | <0.0001        |                    |
| <b>CGI-TD Response</b>                 |                |                    |
| Very much improved n= (%)              | 2 (4.5)        | 6 (13.3)           |
| Much improved n= (%)                   | 5 (11.4)       | 24 (53.3)          |
| Minimally improved n= (%)              | 24 (54.5)      | 12 (26.7)          |
| No change n= (%)                       | 13 (29.5)      | 3 (6.7)            |

Source: Adapted from Study 1202 Clinical Study Report, Table 17 (p. 92).

CGI-TD scores: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change.

No subjects had scores >4 at the end of Week 6 in either group.

<sup>1</sup>Least-squares mean based on the ANOVA model which included treatment group and disease category as fixed effects.

<sup>2</sup>p-value for test of null hypothesis that difference between treatment group LS means = 0.

#### PGIC

The PGIC was specified as an exploratory efficacy assessment in this study, with no pre-specified plans for addressing multiplicity. As displayed in Table 30, subjects receiving valbenazine showed a numerically superior response on the PGIC than those receiving placebo. Furthermore, 58% of subjects receiving valbenazine assessed their TD to be very much or much improved as compared to baseline vs. 32% of subjects receiving placebo. This might suggest that patients appreciated an improvement in TD symptoms. However, while subjects were blind to treatment and took two identical capsules each day, it is possible that subjects derived some information from the study physician investigator’s assessment of the tolerability of a given treatment dose (which informed the investigator’s decision whether to escalate the dose to the next level based on safety/tolerability and efficacy).

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 30: Study 1202 - PGIC Summary, Week 6, ITT Analysis Set**

|                           | Placebo (N=44) | Valbenazine (N=45) |
|---------------------------|----------------|--------------------|
| <b>PGIC Mean (SEM)</b>    | 2.9 (0.1)      | 2.2 (0.1)          |
| <b>PGIC Response</b>      |                |                    |
| Very much improved n= (%) | 4 (9.1)        | 11 (24.4)          |
| Much improved n= (%)      | 10 (22.7)      | 15 (33.3)          |
| Minimally improved n= (%) | 15 (34.1)      | 16 (35.6)          |
| No change n= (%)          | 15 (34.1)      | 3 (6.7)            |

Source: Adapted from Study 1202 Clinical Study Report, Table 24 (p. 99).

PGIC scores: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change.

No subjects had scores >4 at the end of Week 6 in either group.

## TDRS

The TDRS was also specified as an exploratory efficacy assessment with no pre-specified plans for addressing multiplicity. On both the subject/caregiver-answered portion (Part 1, Dyskinesia) and the clinician-rated portions (Parts 2 and 3, Impairment and Disability), valbenazine treatment was associated with a numerically superior decrease in total scores to placebo Table 31). However, both drug and placebo groups experienced improvements on all three parts, and the meanings of the differences on this exploratory measure are unclear.

**Table 31: Study 1202 - TDRS Summary at Week 6, ITT Analysis Set**

|   | Placebo (N=44) |            | Valbenazine (N=45) |            | Baseline → Week 6<br>Change, Valbenazine –<br>Placebo Difference |
|---|----------------|------------|--------------------|------------|--|
|   | Baseline       | Week 6     | Baseline           | Week 6     |  |
| <b>TDRS</b>                                 |                |            |                    |            |  |
| Part 1 (Dyskinesia) Total Score (mean, SEM) | 19.2 (1.5)     | 14.5 (1.2) | 22.0 (1.3)         | 14.1 (1.4) | -3.2   |
| Part 2 (Impairment) Total Score (mean, SEM) | 12.6 (1.0)     | 8.7 (0.8)  | 11.8 (0.9)         | 7.3 (0.8)  | -0.6   |
| Part 3 (Disability) Total Score (mean, SEM) | 6.5 (0.5)      | 5.5 (0.4)  | 6.6 (0.5)          | 4.9 (0.4)  | -0.7   |

Source: Adapted from Study 1202 Clinical Study Report, Tables 14.23.13, 14.23.14, and 14.23.15.

Part 1 (Dyskinesia) score range: 0-48, with lower scores representing lesser severity. Parts 2 (Impairment) and 3 (Disability) score ranges: 0-16 each, with lower scores representing lesser severity.

## Dose/Dose Response

This study used flexible dosing, titrated according to efficacy and tolerability. At Week 6, 69% of subjects in the valbenazine group were receiving 75 mg, 20% were receiving 50 mg, and 11% were receiving 25 mg, suggesting that at least a 75 mg dose may be necessary for the majority

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

of subjects to achieve adequate response. Overall analysis of dose response will be addressed in Section 7.1.4.

### **Durability of Response**

This study did not provide adequate information as to the durability of response, given its short duration and its use of flexible dosing. However, there was no evidence that suggested the effect of treatment diminished over time.

### **Persistence of Effect**

From graphical inspection of the AIMS measure as scored by on-site raters (Figure 20), subjects who were receiving valbenazine appeared to show worsening of TD symptoms two weeks after discontinuing treatment (Week 8). The placebo-treated subjects did not exhibit worsening of TD symptoms following discontinuation. On-site raters would have known that all subjects had stopped treatment, but would have been blind to the assigned treatment from Week 1-6, so this suggests that TD symptoms may worsen following valbenazine discontinuation.

### **Additional Analyses Conducted on the Individual Trial**

Biometrics reviewer Dr. Thomas Birkner performed additional analyses related to the primary efficacy measure, based on the fact that there were 12 subjects (five receiving valbenazine and seven receiving placebo) who were randomized but discontinued during the double-blind period. Because they did not have a central AIMS rating at the end of Week 6, they were not included in the "ITT" analysis set. Dr. Birkner performed a tipping point analysis by imputing incrementally worse scores for the excluded valbenazine subjects while imputing either no change or minimal improvement scores for the excluded placebo subjects. The conclusion from this analysis (detailed in the Biostatistics review) was that the excluded valbenazine subjects would have to worsen by 9-10 points on the AIMS total dyskinesia score to overturn the statistical significance of the primary efficacy measure. Observing such a worsening was deemed unlikely, given the highest observed worsening of 3 points among completers who received valbenazine.

## **6.3. Study 1201: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Valbenazine for the Treatment of Tardive Dyskinesia in Subjects with Schizophrenia or Schizoaffective Disorder**

### **6.3.1. Study Design**

#### **Overview and Objective**

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

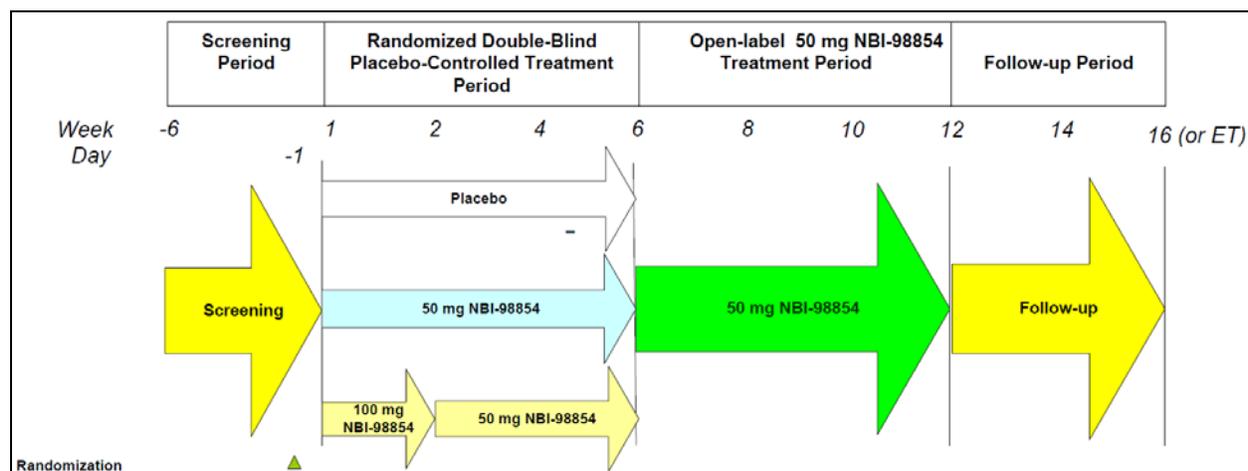
Study 1201 was a Phase 2, multi-center, double-blind, randomized, placebo-controlled, parallel-group study. Its primary objective was to evaluate the efficacy of two doses of valbenazine (50 mg and 100 mg daily) for the treatment of TD in subjects with schizophrenia or schizoaffective disorder. Its secondary objectives were to evaluate the safety and tolerability of valbenazine and evaluate plasma exposure measures of valbenazine, its active metabolite [+] - $\alpha$ -dihydrotetrabenazine, and other metabolites.

This study was submitted as supportive for demonstrating efficacy of valbenazine and will be discussed in this NDA review, albeit with less emphasis than Studies 1304 and 1202, for methodological reasons discussed below.

### Trial Design

**Basic Study Design Summary:** Please see Figure 21 for a schematic providing an overview of the study design. Eligible subjects were randomized (1:1:2) to one of three groups for the first six weeks of dosing: valbenazine 50 mg daily; valbenazine 100 mg for 2 weeks, then 50 mg for 4 weeks; and placebo. After the six weeks of double-blind treatment, subjects were treated with open-label valbenazine 50 mg daily for six additional weeks, as described below. Subjects presented to the study center every two weeks for efficacy, safety, and PK assessments. Follow-up assessments were performed two and four weeks after the last dose of study drug.

**Figure 21: Study 1201 - Study Design Schematic**



Source: Study 1201 Clinical Study Report, Figure 1, p. 16

**Study Eligibility Criteria:** Subjects must have been adults (male or female), age 18-65 years old, with a clinical diagnosis of schizophrenia or schizoaffective disorder and TD (DSM-IV criteria) for at least 3 months prior to screening. The TD needed to be moderate or severe, as indicated by a score on AIMS Item 8 of either 3 or 4 in assessment by a blinded, external video AIMS rater. Antipsychotic medications needed to be at stable dosages for  $\geq 30$  days prior to screening.

CDER Clinical Review Template 2015 Edition

120

Version date: April 9, 2015 for initial rollout (NME/original BLA reviews)

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Subjects were excluded for unstable medical conditions within 30 days prior to screening; substance use disorders (except nicotine and caffeine) within three months prior to baseline; severe underlying psychiatric illness symptoms (as assessed by BPRS  $\geq$ 50 at screening, CDSS  $\geq$ 10 at screening or baseline, or significant risk of suicidal or violent behavior); SAS score  $\geq$ 3 on two or more items at screening or baseline (excluding items 8 and 10); or CYP2D6 poor metabolizer genotype. Overall, the eligibility criteria were relatively similar to Studies 1202 and 1304, except this study did not include subjects with gastrointestinal illness or mood disorder treatment-related TD and had a maximum age cutoff of 65 rather than 85.

*Dose Selection:* The Applicant indicated that the doses were selected based on results from earlier studies. The 50 mg daily dose was well-tolerated in Studies 1001 and 1101, which included subjects with schizophrenia or schizoaffective disorder, and the 100 mg dose had been administered to healthy volunteers for up to eight days (in Study 0901). The Applicant assessed that the 100 mg daily dose would be adequately safe to study for up to two weeks, as subjects who were CYP2D6 poor metabolizers were excluded from participation and concomitant use of strong CYP2D6 inhibitors were prohibited. The dosing paradigm used in this study was reasonable for exploratory purposes, but the treatment group that received 100 mg for two weeks followed by 50 mg daily limited the ability to assess an efficacy dose-response relationship at the 6-week visit (which was used across studies as the primary efficacy endpoint).

*Assignment to Treatment:* Subjects were randomized by an IWRS, which occurred on Day -1, after the subjects were confirmed to have met study eligibility criteria. Treatment assignments were made according to a computer-generated randomization schedule. Randomization was stratified by concomitant use of valproic acid and derivatives, due to prior observations that valproic acid may reduce exposure to valbenazine and [+]– $\alpha$ -dihydrotrabenzazine.

*Blinding:* Placebo capsules were identical to valbenazine capsules, and treatments were administered in two capsules daily. The subject, Applicant, investigator, and study site personnel were blinded to subject treatment for the first six weeks of treatment. The second six weeks of treatment were open-label.

*Procedures and Schedule:* Please refer to Table 32 for a schedule of events from screening to the end of double-blind treatment, which is the focus for this efficacy review. There were five additional visits beyond Week 6 – three during open-label treatment (Weeks 8, 10, and 12), and two follow-up visits after treatment was completed (Weeks 14 and 16). The primary efficacy assessment measure, the AIMS (described in Study Endpoints), was administered at screening, baseline, Weeks 2, 6, 8, 12, and at the final follow-up visit (Week 16 or early termination). The schedule for assessing efficacy measures was generally reasonable; however, it would have been preferable to include an additional AIMS assessment at the end of Week 4 to better characterize the time course (particularly in this study, since one treatment group had the

Clinical Review  
Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH  
NDA 209241  
Ingrezza (valbenazine)

valbenazine dose reduced from 100 mg to 50 mg daily after two weeks).

**Table 32: Study 1201 - Schedule of Assessments, Double-Blind Period (Abridged)**

| Procedure   | Screening | Baseline | Randomized, Double-Blind, Placebo-Controlled Treatment Period |          |   |   |
|---|-----------|----------|---|----------|---|---|
|   |           |          | Week  | -6 to -1 | 0 | 2 |
| <b>Screening assessments:</b> informed consent, UBACC, medical history (update at Baseline), inclusion/exclusion criteria (update at Baseline), serology studies, BPRS, drug and alcohol screening (repeated at Baseline) | X         |          |   |          |   |   |
| <b>Safety assessments 1:</b> vital signs, pregnancy test, serum prolactin (excluding Screening), C-SSRS, AE monitoring, prior and concomitant medications   | X         | X        | X   | X        | X | X |
| <b>Safety assessments 2:</b> physical examination (height at screening only), 12-lead ECG, clinical laboratory tests, serum prolactin (excluding Screening), SAS, BARS (excluding Screening)                              | X         | X        | X   |          |   | X |
| <b>Pharmacokinetic sampling</b>   |           |          | X   |          |   | X |
| <b>Primary efficacy:</b> AIMS (including video recording)   | X         | X        | X   |          |   | X |
| <b>Secondary efficacy:</b> CGI-TD   |           |          | X   |          |   | X |
| <b>Exploratory efficacy:</b> TDRS   |           | X        | X   |          |   | X |
| <b>Exploratory efficacy:</b> PGIC   |           |          | X   |          |   | X |
| <b>Schizophrenia/Schizoaffective Disorder Assessments:</b>  |           |          |   |          |   |   |
| PANSS   |           | X        | X   |          |   | X |
| CDSS  | X         | X        | X   |          |   | X |

*Adapted from Study 1201 Protocol; November 28, 2012; Table 1 (page 32)*

Definitions: AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; BPRS=Brief Psychiatric Rating Scale; CDSS=Calgary Depression Scale for Schizophrenia; CGI-TD=Clinical Global Impression of Tardive Dyskinesia; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; PANSS=Positive and Negative Syndrome Scale; PGIC=Patient Global Impression of Change; SAS=Simpson-Angus Scale; TDRS=Tardive Dyskinesia Rating Scale; UBACC=University of California, San Diego Brief Assessment of Capacity to Consent

**Dietary Restrictions/Instructions:** Subjects were instructed to refrain from drinking grapefruit juice from 48 hours prior to Baseline until the completion of study treatment. Alcohol use was limited to <7 drinks per week during the course of the study. These restrictions were reasonable for the study, as inhibiting CYP3A4 could potentially affect valbenazine metabolism.

**Concurrent Medications:** The protocol noted that allowed concomitant medications needed to be at stable doses for a minimum of 30 days prior to screening and remain stable during the study. Coexisting diseases or conditions were to be treated in accordance with prevailing medical practice. As needed use of over-the-counter and prescription medications, including dietary and herbal supplements, was generally prohibited after the screening visit. However, the following as-needed medications were allowed if approved by the investigator: guaifenesin,

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

milk of magnesia, bisacodyl, bismuth subsalicylate, magnesium hydroxide/aluminum hydroxide /simethicone, acetaminophen, eszopiclone, zaleplon, zolpidem, and doxepin (3 or 6 mg at night).

The following medications were prohibited from 30 days prior to screening until the final study visit:

1. Amantadine (if being used for the treatment of TD).
2. Anticholinergic medications used on an as-needed basis (taking on a regular schedule to treat extrapyramidal symptoms was permitted).
3. Antiemetics: Metoclopramide, prochlorperazine, promethazine, granisetron, and ondansetron.
4. Benzodiazepines used on an as-needed basis (taking on a regular schedule was permitted).
5. Strong CYP3A4 inducers (e.g., phenobarbital, rifabutin, rifampin, carbamazepine, primidone, St. John's Wort).
6. Strong CYP3A4 inhibitors (e.g., ketoconazole, erythromycin, ritonavir).
7. Certain CYP2D6 inhibitors (paroxetine, fluoxetine, duloxetine, quinidine, dronedarone, cinacalcet, terbinafine)
8. Dopamine receptor agonists (e.g., ropinirole) and precursors (e.g., carbidopa/levodopa).
9. Stimulants (e.g., amphetamine, methylphenidate, ephedrine, pseudoephedrine, phenylephrine, and phenylpropanolamine).
10. Monoamine oxidase inhibitors (e.g., isocarboxazid, phenelzine, selegiline, tranylcypromine).
11. VMAT2 Inhibitors other than the study drug (e.g., tetrabenazine, reserpine).
12. Drugs known to increase the QT interval, unless approved by the Applicant; baseline QTcF must be < 450 msec for males or < 470 msec for females.

The protocol specifications for concurrent and prohibited medications were generally reasonable and similar to Studies 1202 and 1304. Changes in psychotropic or other dopaminergic medications (e.g., antipsychotics, benzodiazepines, psychostimulants, dopamine receptor agonists and precursors) or certain as-needed medications (i.e., benzodiazepines) could confound the efficacy assessment of valbenazine. One difference from previously described studies is that certain CYP2D6 inhibitors were excluded; several excluded medications were antidepressants that are frequently used in the drug target population.

### Study Endpoints

The primary efficacy assessment measure was the AIMS, which is described under Study Endpoints in Section 6.1.1. In this study, the AIMS was administered and scored by an on-site certified, independent AIMS rater who was not involved in other aspects of subject care. The

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

protocol specified that if possible, the independent AIMS rater should administer and score the AIMS for an individual subject at all time points, and the score should be based solely on interactions at the time of examination. AIMS examinations were video recorded for external review. The external reviewer made the determination as to whether the subject had moderate or severe TD at the screening assessment and whether the examinations were being conducted according to the administration manual.

Notably, this study was conducted prior to pre-specifying the use of blinded central raters and the modified AIMS scoring anchors (please see Study Endpoints in Section 6.2.1 for details). These methods were changed for subsequent studies based on analyses of topline data from this study which indicated high interrater variability in AIMS scores. Post hoc analyses using central video raters were conducted using videos from this study. It is more difficult to interpret the efficacy findings from this study as compared to the subsequent efficacy trials (i.e., Study 1202 and 1304), given the use of on-site raters and AIMS descriptors prior to revision.

The CGI-TD (described in Section 6.1.1 and shown in The Clinical Global Impression of Change – Tardive Dyskinesia (CGI-TD) was used as a key secondary outcome measure. This measure was modified from the Clinical Global Impression (CGI) [27], which was originally developed to provide a global evaluation of improvement over time from the clinician’s perspective. The CGI-TD (Figure 6) was rated by an investigator or qualified clinician designee at Weeks 2, 4, 6, 8, 16, 24, 32, 40, 48, and the follow-up or early termination visit. While it was not mandated, the protocol specified that if possible, the same person should rate the CGI-TD at all time points. Each of the seven CGI-TD responses was assigned a score from 1-7, with 1=very much improved and 7=very much worse. The pre-specified key secondary endpoint was the mean CGI-TD score at Week 6. This was accepted by the Division at the End of Phase 2 meeting; however it was noted that the percentage of responders based on CGI-TD scores would not be acceptable for this purpose. Limitations with this outcome measure include the variability introduced by potentially different raters across visits and the subjective assessment of improvement, which may vary according to training and clinical experience. Furthermore, this comparison-based assessment necessitates an accurate recall of the subjects’ baseline presentations. Unlike the AIMS, this measure was not scored by central raters. Overall, this efficacy endpoint is considered to be less useful than the central-rated AIMS change from baseline for assessing efficacy.

Figure 6) was used as a secondary efficacy measure in this study. This measure was assessed at the end of Weeks 2 and 6 during double-blind treatment, as well as the end of Weeks 8, 12, and 16 (or the early termination visit). The protocol specified that this measure would be assessed by a physician investigator or other qualified site personnel, and the same person should administer and rate the scale at all time points (if possible). The potential for different raters

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

across visits makes this comparison-to-baseline measure less meaningful than it would be if the same rater was always used.

Additional exploratory efficacy assessments administered in this study were:

1. Patient Global Impression of Change (PGIC) – patient-reported outcome measure in which subjects evaluated the change in their TD symptoms since initiation of study drug by choosing one of seven responses (very much improved, much improved, minimally improved, not changed, minimally worse, much worse, and very much worse). This measure was completed by subjects at the end of Weeks 2, 6, 8, 12, and 16 (or early termination visit).
2. Tardive Dyskinesia Rating Scale (TDRS) – adapted from the Unified Dyskinesia Rating Scale [31], the TDRS consists of 3 parts. Part 1 (Dyskinesia) consists of 12 questions that focus on time spent with dyskinesia and on the impact of dyskinesia on experiences of daily living. Questions are answered by the subject and/or caregiver. Responses to each question are made on a scale from 0 to 4, with a response of 0=normal and 4=severe. Part 2 (Impairment) and Part 3 (Disability) are assessed by the clinician rater, who observes the subject during four activities of daily living (communication, drinking from a cup, dressing, and ambulation) and rates the impairment and disability on a similar 0-4 scale. The TDRS was administered by the independent AIMS rater who was otherwise not involved in the subjects' care and only administered the AIMS and the TDRS. This measure was administered at Baseline and the end of Weeks 2, 6, 12, and 16 (or early termination visit).

## Statistical Analysis Plan

The SAP for this study (Amendment 1 version) was dated August 28, 2013. Three analysis sets were used by the Applicant for analyzing study data:

1. Safety analysis set – included all subjects who were randomized to a treatment group and received at least one dose of study drug. The treatment group assignment in this set was based on the treatment actually received.
2. Intent-to-treat (ITT) analysis set – included all subjects in the safety analysis set who had an evaluable AIMS dyskinesia total score value at either Week 2 or Week 6. The treatment group in this set was based on the treatment the subject was randomized to.
3. Per protocol (PP) analysis sets – separate sets were defined for Week 2 and Week 6 analyses, given the change in dose that occurred at Week 2 in one of the treatment groups. These sets included subjects in the ITT analysis set who had an evaluable AIMS dyskinesia total score at the time point (Week 2 or Week 6), had no efficacy-related important deviations up to the time point, and had quantifiable plasma levels of [+]- $\alpha$ -

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

dihydrotrabenzazine at the time point. The treatment group assignment was based on the treatment actually received.

*Analysis of Primary Efficacy Endpoint:* The prespecified primary efficacy endpoint for the study was the AIMS dyskinesia total score (sum of the scores of items 1-7). The SAP specified that inferential statistics would be calculated for the AIMS dyskinesia total score CFB at Weeks 2 and 6, and nominal two-sided p-values would be reported for all hypothesis tests without adjustments for multiplicity. The analyses would be performed using the ITT analysis set, using an analysis of covariance (ANCOVA) model which included the baseline value as a covariate and the treatment group and valproic acid use as fixed effects. For the Week 6 time point, the primary ANCOVA model would incorporate a last observation carried forward (LOCF) approach to impute values for subjects who had missing Week 6 values.

*Multiplicity:* There was no plan for addressing the issue of multiple testing. The Applicant planned to report nominal two-sided p-values in summary tables. This not an ideal approach, as the Applicant planned to perform inferential statistics on both the AIMS dyskinesia total score CFB and the CGI-TD at multiple time points, and such an analysis plan should contain methods for controlling type I error if the results are intended to be used beyond exploratory purposes.

*Interim Analysis:* An analysis of data collected through Week 6 (the end of double-blind treatment) was performed by the Applicant prior to study completion and final database lock. The analysis was conducted to inform the design of future valbenazine studies and did not affect the post-treatment follow-up period for this study. The analysis was performed by an independent, unblinded statistician after all randomized subjects have either completed the Week 6 visit or discontinued from the study prior to Week 6. This independent statistician was the only individual with access to individual treatment assignments at the time of the analysis. The interim analysis plan is considered to have been reasonable for this Phase 2 study.

*Additional Analyses:* Additional efficacy analyses discussed in the SAP included: conducting an AIMS responder analysis with percent improvement thresholds; conducting a CGI-TD responder analysis using the percentage of subjects achieving CGI-TD score thresholds; assessing PGIC scores and responder rates based on score thresholds; and assessing TDRS scores (Part 1, Part 2-3, and total score).

## Protocol Amendments

The initial version of the protocol was finalized on September 4, 2012. There was one amendment for the protocol, which was finalized on November 28, 2012. Changes incorporated in this amendment included the prohibition of the use of dopamine agonists and precursors as concomitant medications during the study.

## Data Quality and Integrity: Applicant's Assurance

CDER Clinical Review Template 2015 Edition

Version date: April 9, 2015 for initial rollout (NME/original BLA reviews)

126

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

The Applicant assured that the study was performed in compliance with GCP and FDA regulations and guidelines. Prior to initiating the study, site initiation visits were conducted and an Investigator's meeting was held to discuss details of the study protocol, data collection procedures, eCRF entry, and regulatory requirements. Throughout the study, the study monitor made frequent contacts with the Investigator by telephone and on-site visits. At on-site visits, the monitors performed source data verification with the eCRFs, performed drug accountability checks, and monitored for unreported SAEs or discontinuations due to AEs. 100% source document verification was performed for the first two randomized subjects at each site, and subsequent subjects had a subset of key eCRFs verified (including AIMS, CGI-TD, study drug dosing, etc.). All data changes were tracked using an electronic audit trail. Quality assurance audits were performed at seven clinical study sites (118, 127, 128, 139, 140, 145, and 154), and audit certificates were included with the application. Quality control review and quality assurance audit of the clinical study report was performed by the Applicant, checking for consistency, clarity, and accuracy. Overall, the data quality and integrity plan appears to have been adequate.

### 6.3.2. Study Results

#### Compliance with Good Clinical Practices

The Applicant indicated that the study was conducted in accordance with GCP and 21 CFR parts 50, 54, 56, 312, and 314.

#### Financial Disclosure

Please see Appendix 13.2 for the financial disclosure review of all covered clinical studies (as defined in 21 CFR 54). There were no disclosable financial interests or arrangements. This information was confirmed by the Applicant in a Response to Information Request received on December 22, 2016. Based on the certification and Applicant verification, there are no concerns about financial conflicts of interest that would affect the interpretation of this study data or the approvability of this application.

#### Patient Disposition

Please see Figure 22 for a flow chart of subject disposition. The majority of randomized subjects (85.3%) completed double-blind treatment. During the double-blind treatment period, 13% of placebo subjects, 10.7% of subjects in the valbenazine 50 mg group, and 22.2% of subjects in the 100 mg/50 mg group discontinued treatment. It is unclear why a higher proportion of subjects in the latter group discontinued treatment, but it does not appear to be related to 100 mg dose tolerability, as only one subject in this group discontinued treatment during the 100 mg dosing phase.

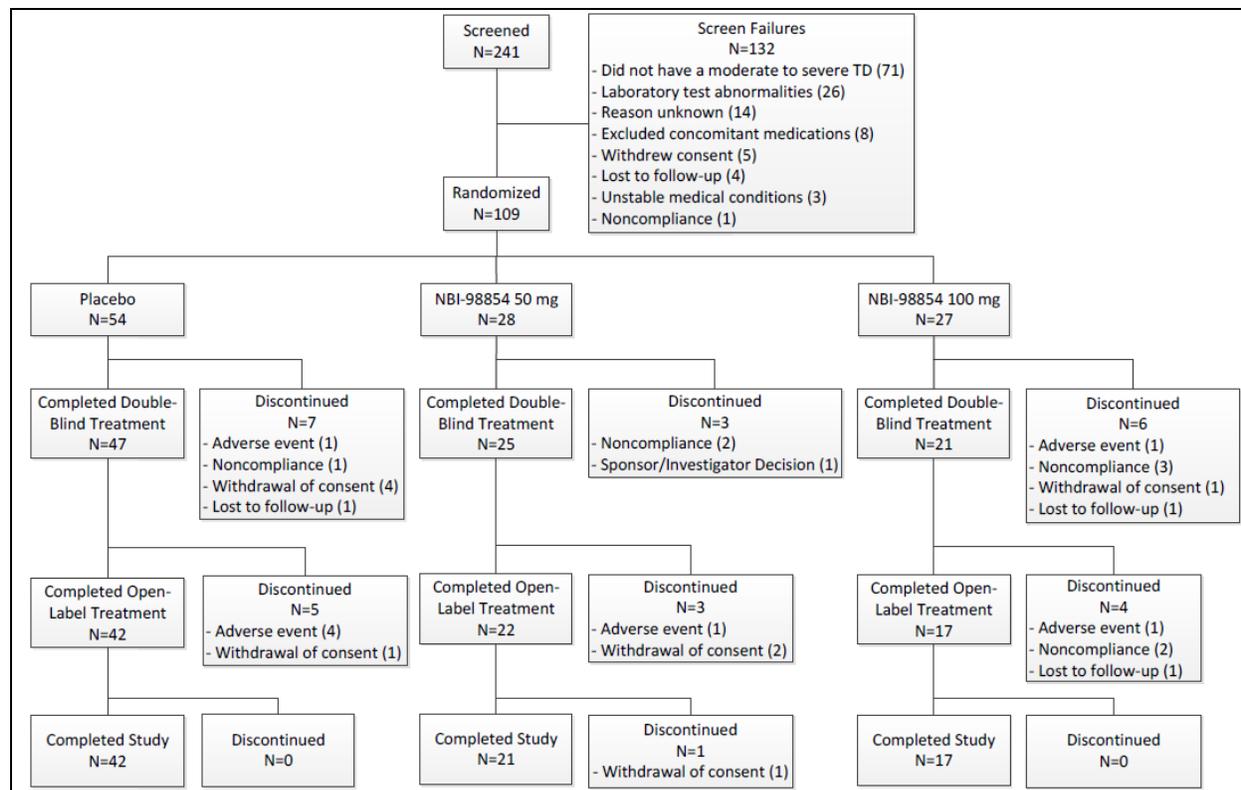
Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Figure 22: Study 1201 - Subject Disposition



Source: Study 1201 Clinical Study Report, Figure 2, p. 52

Please see Table 33 for a tabulation of the number of subjects in each analysis set and the reasons for analysis set exclusion. There were several subjects, mostly from the valbenazine 100 mg/50 mg treatment group, who were excluded from the PP analysis sets due to having undetectable plasma levels of  $[+]-\alpha$ -dihydrotrabenzazine. This raises the possibility that there were tolerability issues with the 100 mg valbenazine dose that led to study treatment noncompliance. However, it was not possible to assess placebo compliance by plasma level monitoring for comparison.

**Table 33: Study 1201 - Summary of Analysis Sets**

| Analysis Set   | Placebo<br>(N=54)<br>n (%) | NBI-98854                |                              | Total<br>(N=109)<br>n (%) |
|--|----------------------------|--------------------------|------------------------------|---------------------------|
|  |                            | 50 mg<br>(N=28)<br>n (%) | 100/50 mg<br>(N=27)<br>n (%) |                           |
| <b>Safety Analysis Set</b>   |                            |                          |                              |                           |
| Subjects included  | 54 (100)                   | 28 (100)                 | 27 (100)                     | 109 (100)                 |
| <b>Intent-to-Treat Analysis Set</b>  |                            |                          |                              |                           |
| Subjects included  | 54 (100)                   | 27 (96.4)                | 26 (96.3)                    | 107 (98.2)                |
| Subjects excluded  | 0                          | 1 (3.6)                  | 1 (3.7)                      | 2 (1.8)                   |
| Reason for exclusion:  |                            |                          |                              |                           |
| Did not have an evaluable AIMS score at Weeks 2 or 6                         | 0                          | 1 (3.6)                  | 1 (3.7)                      | 2 (1.8)                   |
| <b>Per-Protocol Efficacy Week 2 Analysis Set</b>                             |                            |                          |                              |                           |
| Subjects included  | 52 (96.3)                  | 25 (89.3)                | 20 (74.1)                    | 97 (89.0)                 |
| Subjects excluded  | 2 (3.7)                    | 3 (10.7)                 | 7 (25.9)                     | 12 (11.0)                 |
| Reason for exclusions:   |                            |                          |                              |                           |
| Important protocol deviation   | 2 (3.7)                    | 1 (3.6)                  | 2 (7.4)                      | 5 (4.6)                   |
| NBI-98854 treated subject with no quantifiable plasma concentration – Week 2 | 0                          | 1 (3.6)                  | 3 (11.1)                     | 4 (3.7)                   |
| Multiple reasons   | 0                          | 1 (3.6)                  | 2 (7.4)                      | 3 (2.8)                   |
| <b>Per-Protocol Efficacy Week 6 Analysis Set</b>                             |                            |                          |                              |                           |
| Subjects included  | 47 (87.0)                  | 25 (89.3)                | 17 (63.0)                    | 89 (81.7)                 |
| Subjects excluded  | 7 (13.0)                   | 3 (10.7)                 | 10 (37.0)                    | 20 (18.3)                 |
| Reason for exclusions:   |                            |                          |                              |                           |
| Important protocol deviation   | 3 (5.6)                    | 1 (3.6)                  | 2 (7.4)                      | 6 (5.5)                   |
| Did not have an evaluable AIMS score at Week 6                               | 4 (7.4)                    | 0                        | 0                            | 4 (3.7)                   |
| NBI-98854 treated subject with no quantifiable plasma concentration – Week 6 | 0                          | 0                        | 3 (11.1)                     | 3 (2.8)                   |
| Multiple reasons   | 0                          | 2 (7.1)                  | 5 (18.5)                     | 7 (6.4)                   |

Source: 1201 Clinical Study Report, Table 4, p. 55; NBI-98854=valbenazine

### Protocol Violations/Deviations

Please see Table 34 for a tabulation of important protocol deviations (IPDs), which the Applicant defined as those that could potentially impact the conclusions of the study. There were more subjects in the valbenazine 100 mg/50 mg group with such protocol deviations, which included events including taking the study drug twice daily instead of once daily, having less than 10% treatment compliance, and not removing required items of clothing prior to AIMS assessment. Overall, the percentages of subjects with IPDs were relatively low and appear unlikely to significantly impact study conclusions.

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 34: Study 1201 - Protocol Deviations (All Randomized Subjects)**

| Important Protocol Deviations | Placebo<br>(N=54)<br>n (%) | NBI-98854<br>50 mg<br>(N=28)<br>n (%) | NBI-98854<br>100/50 mg<br>(N=27)<br>n (%) | Total<br>(N=109)<br>n (%) |
|-------------------------------|----------------------------|---------------------------------------|---|---------------------------|
| <b>Number of Subjects</b>     | 3 (5.6)                    | 1 (3.6)                               | 4 (14.8)                                  | 8 (7.3)                   |
| Inclusion/exclusion criteria  | 1 (1.9)                    | 0                                     | 1 (3.7)                                   | 2 (1.8)                   |
| Study drug administration     | 0                          | 0                                     | 2 (7.4)                                   | 2 (1.8)                   |
| Concomitant medications       | 1 (1.9)                    | 1 (3.6)                               | 0   | 2 (1.8)                   |
| Efficacy measures             | 0                          | 0                                     | 1 (3.7)                                   | 1 (0.9)                   |
| Other                         | 1 (1.9)                    | 0                                     | 1 (3.7)                                   | 2 (1.8)                   |

Source: 1201 Clinical Study Report, Table 3, p. 54

**Table of Demographic Characteristics**

Please see Table 35 for a summary of subject demographic information. There were approximately twice as many males in this study as females; this imbalance is not ideal for extrapolation of findings to the general population, but there were approximately equal numbers of women in the placebo vs. the valbenazine treatment groups (50 mg and 100/50 mg) for analysis. Patients of African-American and Caucasian races, as well as those with Hispanic ethnicity, were well-represented in the study sample. There were no subjects of Asian race, for reasons that are unclear, but there is no reason to believe that the response to TD treatment would differ between races other than potential differences in drug metabolism.

**Table 35: Study 1201 - Subject Demographics, ITT Analysis Set**

|                                     | Placebo<br>(N=54) | Valbenazine<br>50 mg daily<br>(N=27) | Valbenazine<br>100/50 mg<br>daily (N=26) | All subjects<br>(N=107) |
|-------------------------------------|-------------------|--------------------------------------|--|-------------------------|
| <b>Age (mean, SEM)</b>              | 54.5 (1.5)        | 56.0 (1.7)                           | 55.4 (2.2)                               | 55.1 (1.0)              |
| <b>Gender (n, %)</b>                |                   |                                      |  |                         |
| Male                                | 34 (63.0%)        | 19 (70.4%)                           | 18 (69.2%)                               | 71 (66.4%)              |
| Female                              | 20 (37.0%)        | 8 (29.6%)                            | 8 (30.8%)                                | 36 (33.6%)              |
| <b>Ethnicity (n, %)</b>             |                   |                                      |  |                         |
| Hispanic or Latino                  | 9 (16.7%)         | 9 (33.3%)                            | 8 (30.8%)                                | 26 (24.3%)              |
| Not Hispanic or Latino              | 45 (83.3%)        | 18 (66.7%)                           | 18 (69.2%)                               | 81 (75.7%)              |
| <b>Race (n, %)</b>                  |                   |                                      |  |                         |
| Asian                               | 0                 | 0                                    | 0  | 0                       |
| Black or African American           | 29 (53.7%)        | 11 (40.7%)                           | 6 (23.1%)                                | 46 (43.0%)              |
| Caucasian                           | 23 (42.6%)        | 15 (55.6%)                           | 19 (73.1%)                               | 57 (53.3%)              |
| Native Hawaiian or Pacific Islander | 1 (1.9%)          | 0                                    | 0  | 1 (0.9%)                |
| Other <sup>1</sup>                  | 1 (1.9%)          | 1 (3.7%)                             | 1 (3.8%)                                 | 3 (2.8%)                |

Source: Reviewer-created, with data from Study 1201 Clinical Study Report (Table 14.4.2, p. 120)

<sup>1</sup>Includes subjects with multiple identified races

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

### Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Please refer to Table 36 for a summary of select subject baseline characteristics in the ITT analysis set. There were no CYP2D6 poor metabolizers in this sample. The subjects had a similar mean baseline AIMS dyskinesia total score across groups, which is favorable for comparing changes in the total score at follow-up visits. Approximately 90% of subjects were receiving antipsychotics, with atypical antipsychotics being used by approximately twice as many subjects as typical antipsychotics. This pattern of antipsychotic medication use is expected for subjects with schizophrenia or schizoaffective disorder who are target population for this drug.

**Table 36: Study 1201 - Baseline Characteristics, ITT Analysis Set**

| Parameter   | Placebo<br>(N=54) | Valbenazine<br>50 mg daily<br>(N=27) | Valbenazine<br>100/50 mg<br>daily (N=26) | All subjects<br>(N=107) |
|---|-------------------|--------------------------------------|--|-------------------------|
| <b>BMI</b> (kg/m <sup>2</sup> mean (SD))                | 28.71 (5.68)      | 28.83 (6.00)                         | 26.10 (5.90)                             | 28.10 (5.87)            |
| <b>CYP2D6 Genotype Classification</b> n= (%)            |                   |                                      |  |                         |
| Ultra-Rapid Metabolizer                                 | 4 (7.4%)          | 1 (3.7%)                             | 0  | 5 (4.7%)                |
| Extensive Metabolizer                                   | 27 (50.0%)        | 17 (63.0%)                           | 15 (57.7%)                               | 59 (55.1%)              |
| Intermediate or Extensive Metabolizer                   | 3 (5.6%)          | 1 (3.7%)                             | 1 (3.8%)                                 | 5 (4.7%)                |
| Intermediate Metabolizer                                | 20 (37.0%)        | 8 (29.6%)                            | 10 (38.5%)                               | 38 (35.5%)              |
| Poor Metabolizer  | 0                 | 0                                    | 0  | 0                       |
| <b>Valproic Acid Use:</b> Yes n= (%)                    | 7 (13.0%)         | 5 (18.5%)                            | 2 (7.7%)                                 | 14 (13.1%)              |
| <b>Baseline AIMS Dyskinesia Total Score</b> (mean (SD)) | 15.3 (4.4)        | 14.6 (5.9)                           | 14.6 (4.7)                               | 15.0 (4.8)              |
| <b>Current Antipsychotic Use</b>                        |                   |                                      |  |                         |
| None  | 5 (9.3%)          | 2 (7.4%)                             | 3 (11.5%)                                | 10 (9.4%)               |
| Atypical Only   | 32 (59.3%)        | 16 (59.3%)                           | 19 (73.1%)                               | 67 (62.6%)              |
| Typical or Combination                                  | 17 (31.5%)        | 9 (33.3%)                            | 4 (15.4%)                                | 30 (28.0%)              |

Source: Reviewer-created, using data from the 1201 Clinical Study Report (Table 14.5.2, p. 125) and analysis dataset ADSL.XPT.

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was assessed by the Applicant by counting returned capsules at study visits. By this metric, the estimated cumulative compliance during the double-blind treatment period was 99% for the placebo and valbenazine 50 mg groups and 95% for the valbenazine 100/50 mg group. There was a wider distribution of compliance rate in the highest dose group, with a standard deviation of 19% and a minimum compliance of 3.9%, which might suggest that a small number of subjects did not tolerate starting at the 100 mg dose. Quantification of plasma concentrations of valbenazine at Weeks 2 and Week 6 found three subjects (11%) in the 100/50 mg treatment group had undetectable levels of drug at both visits, as compared to one subject in the 50 mg group at Week 2 (Study 1201 Clinical Study Report, Table 4, p. 55).

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Tabulation of concomitant medications was reviewed in the Clinical Study Report. During the double-blind treatment period, the most common concomitant medications were antipsychotics (used by 90.6% of subjects in the ITT analysis set) and antidepressants (used by 52.3% of subjects). Anticholinergic medications were used by 39.4% of subjects. The differences in the proportion of subjects using specific medications across treatment groups (due to randomization) are not expected to have impacted the overall efficacy conclusions of this study.

There was no role for rescue medications in this study, as there are no current treatments for TD.

### Efficacy Results - Primary Endpoint

The primary efficacy analysis presented by the Applicant was the AIMS dyskinesia total score CFB at Week 6, comparing placebo with the pooled valbenazine treatment groups. The AIMS scores assessed by on-site raters were used in the primary ANCOVA analyses. The mean AIMS CFB was not significantly different between treatment groups. This may be attributable, in part, by the -2.4 change in the placebo group, which is of greater magnitude than the placebo change in Studies 1304 and -1201 which used central video raters who were blinded to study visit number.

**Table 37: Study 1201 - Primary Efficacy Endpoint, ITT Analysis Set**

| AIMS Dyskinesia Total Score Change from Baseline  | Placebo (N=54) | NBI-98854 Pooled 50+100 mg <sup>c</sup> (N=53) |
|---|----------------|--|
| <b>Week 6 – ANCOVA (LOCF)</b>                     | n=54           | n=50   |
| Mean (SEM)  | -2.4 (0.5)     | -3.1 (0.6)                                     |
| LS mean <sup>a</sup> (SEM)                        | -2.5 (0.7)     | -3.3 (0.7)                                     |
| LS mean difference (SEM)<br>NBI-98854 vs. placebo |                | -0.8 (0.8)                                     |
| P value <sup>b</sup>                              |                | 0.2966   |

Source: 1201 Clinical Study Report, Table 7, p. 61

The Sponsor conducted post hoc central video ratings of the AIMS assessments and presented data from a “modified ITT” analysis set, which excluded subjects without AIMS scores at Week 6, with IPDs, or without quantifiable [+-]α-dihydrotetrabenazine plasma levels at Week 6 (in the valbenazine treatment group) (Table 38). This analysis showed a numerically superior response in the valbenazine group than the placebo group which failed to meet nominal statistical significance. The “modified ITT” analysis set was more similar to a PP or an as-treated analysis set, as it did not include subjects without detectable plasma levels of [+-]α-dihydrotetrabenazine. Furthermore, the lack of pre-specification and failure to control for multiplicity limits the usefulness of these analyses for supporting the efficacy of valbenazine.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

While using central raters who were blind to visit number did reduce the magnitude of the placebo response, it also reduced the magnitude of the valbenazine response, even though the consensus raters reportedly used the modified AIMS rating anchors (discussed in Study Endpoints in Section 6.2.1). Comparing the results of this study to 1202 and 1304, the AIMS CFB is comparable to the 40 mg valbenazine dose, which is reasonable because valbenazine-treated subjects in this study were receiving 50 mg/day for the final four weeks of blinded treatment.

**Table 38: Study 1201 - Post Hoc Analyses of Primary Efficacy Measure**

| AIMS Dyskinesia Total Score Change from Baseline | On-Site Rater (ITT) |  | Consensus Video Raters (mITT) |  |
|--|---------------------|--|-------------------------------|--|
|  | Placebo (N=54)      | NBI-98854 Pooled 50+100 mg <sup>c</sup> (N=53) | Placebo (N=47)                | NBI-98854 Pooled 50+100 mg <sup>c</sup> (N=42) |
| <b>Week 6 – ANCOVA</b>                           | n=50                | n=49   | n=46                          | n=40   |
| Mean (SEM)                                       | -2.4 (0.5)          | -3.0 (0.6)                                     | -0.5 (0.4)                    | -1.3 (0.5)                                     |
| LS mean <sup>a</sup> (SEM)                       | -2.3 (0.7)          | -3.0 (0.7)                                     | -0.2 (0.5)                    | -1.2 (0.5)                                     |
| LS mean difference (SEM) NBI-98854 vs. placebo   |                     | -0.7 (0.8)                                     |                               | -1.1 (0.6)                                     |
| P value <sup>b</sup>                             |                     | 0.3795   |                               | <b>0.0663</b>                                  |

Source: Study 1201 Clinical Study Report, Table 8, p. 62

Additional analyses on the primary efficacy endpoint were not conducted for this trial, because success on the primary endpoint was not established.

### Data Quality and Integrity - Reviewers' Assessment

An assessment of data quality for this study was performed by Dr. Douglas Warfield. A site-based analysis of irregularities based on screen failures, deviations, subject discontinuations, and adverse event frequency also did not reveal any clear problematic study sites; however, these analyses were limited by the small number of subjects per site. Assessment of enrollment patterns by site was unremarkable. An analysis of SDTM finding domains (EG, LB, QS, VS, and YG) was performed to help detect screening bias; this analysis also did not reveal any clear instances of screening bias. Please see Section 4.1 for a summary of inspections conducted by the Office of Scientific Investigations.

### Efficacy Results - Secondary and other relevant endpoints

#### CGI-TD

Please see Table 39 below for a summary of CGI-TD data and Applicant analyses at Weeks 2 and 6. While there were no pre-specified plans for handling multiple testing, subjects who received 100 mg for the first two weeks (the 100/50 mg group) had numerically superior CGI-TD scores at the end of Week 2 as compared to subjects receiving placebo; this difference achieved

CDER Clinical Review Template 2015 Edition

133

Version date: April 9, 2015 for initial rollout (NME/original BLA reviews)

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

nominal statistical significance according to Applicant calculations ( $p=0.0277$ ). The valbenazine 50 mg/day (at Week 2) and the pooled valbenazine treatment group (who had all been receiving 50 mg for four weeks) did not achieve nominal statistical superiority over placebo treatment. Acknowledging the caveats of multiple testing, this information might suggest that clinician-appreciable benefit from an adequate dose of valbenazine (100 mg in this case) can occur after as little as two weeks of treatment. Corroborating this result, the Applicant performed a CGI-TD responder analysis using subjects in the ITT analysis set and found 30.8% of subjects receiving 100 mg ( $n=26$ ) were rated as “much improved” or “very much improved” on the CGI-TD after two weeks of treatment, as compared to 7.5% of subjects receiving placebo ( $n=54$ ); this difference also achieved nominal statistical significance ( $p=0.0069$ ).

**Table 39: Study 1201 - CGI-TD, ITT Analysis Set**

|                             | Placebo<br>(N=54) | Valbenazine<br>50 mg (N=27) | Valbenazine<br>100/50 mg (N=26) |
|-----------------------------|-------------------|-----------------------------|---------------------------------|
| <b>Week 2</b>               |                   |                             |                                 |
| N                           | 53                | 27                          | 26                              |
| LS Mean (SEM) <sup>1</sup>  | 3.6 (0.1)         | 3.3 (0.2)                   | 3.2 (0.2)                       |
| LS Mean Difference (SEM)    |                   | -0.3 (0.2)                  | -0.4 (0.2)                      |
| p value <sup>2</sup>        |                   | 0.1151                      | 0.0277                          |
| <b>Week 6</b>               |                   |                             |                                 |
| N                           | 54                |                             | 53 <sup>3</sup>                 |
| LS Mean (SEM)               | 3.2 (0.1)         |                             | 3.3 (0.1)                       |
| LS Mean Difference (95% CI) |                   |                             | 0.1 (0.2)                       |
| p value                     |                   |                             | 0.7430                          |

Source: Reviewer-created, using information from 1201 Clinical Study Report, Tables 13-14 (pp. 67-68)

<sup>1</sup>LS mean based on the Applicant’s ANOVA model, which included randomized treatment group and valproic acid use category as fixed effects.

<sup>2</sup>P value for test of null hypothesis that the differences between treatment group LS means is equal to zero.

<sup>3</sup>Pool of subjects randomized to either valbenazine 50 or 100 mg at baseline.

## PGIC

At the end of Week 6, the mean PGIC scores in all treatment groups were 3.1 (placebo and valbenazine 50 mg groups) or 3.2 (valbenazine 100/50 mg group), suggesting that, on average, subjects did not differ in their appreciation of TD symptom improvement across treatment groups. A PGIC responder analysis found that 30% of subjects receiving placebo at the end of Week 6 ( $n=50$ ) assessed their TD as “much improved” or “very much improved” vs. 24.5% of subjects who were receiving valbenazine 50 mg (including those who received 100 mg for the first two weeks) ( $n=49$ ). This is consistent with findings from Study 1304 that suggested subjects blind to treatment had limited appreciation of therapeutic benefit.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

### TDRS

The TDRS was also specified as an exploratory efficacy assessment with no pre-specified plans for addressing multiplicity. Both drug and placebo groups experienced improvements from Baseline to the end of Week 6 on all three parts (Table 40), and the differences between treatment groups were small. The meanings of the differences on this exploratory measure are unclear.

**Table 40: Study 1201 - TDRS Summary at Week 6, ITT Analysis Set**

|   | Placebo (N=54) |            | Valbenazine 50 mg + 100/50 mg (N=53) |            | Baseline → Week 6 Change, Valbenazine – Placebo Difference |
|---|----------------|------------|--------------------------------------|------------|--|
|   | Baseline       | Week 6     | Baseline                             | Week 6     |  |
| <b>TDRS</b>                                 |                |            |                                      |            |  |
| Part 1 (Dyskinesia) Total Score (mean, SEM) | 21.5 (1.4)     | 19.2 (1.4) | 21.1 (1.5)                           | 17.3 (1.4) | -1.5   |
| Part 2 (Impairment) Total Score (mean, SEM) | 13.8 (0.7)     | 12.0 (0.8) | 12.3 (0.9)                           | 10.7 (1.0) | +0.2   |
| Part 3 (Disability) Total Score (mean, SEM) | 8.6 (0.4)      | 7.0 (0.4)  | 7.1 (0.4)                            | 5.6 (0.5)  | +0.1   |

Source: Adapted from Study 1201 Clinical Study Report, Tables 14.25.13, 14.25.14, and 14.25.15.

Part 1 (Dyskinesia) score range: 0-48, with lower scores representing lesser severity. Parts 2 (Impairment) and 3 (Disability) score ranges: 0-16 each, with lower scores representing lesser severity.

### Dose/Dose Response

This study had limited usefulness for assessing dose/response, as subjects randomized to the 100/50 mg group only received the higher 100 mg dose for the first two weeks of treatment, after which they had their doses decreased to 50 mg daily. At the end of Week 2, CGI-TD data suggested the 100 mg dose might be superior to the 50 mg dose in clinician-appreciable global change in TD symptoms, but this finding was not corroborated by on-site AIMS ratings at the same time point. Please refer to Section 7.1.4 for overall analysis of dose-response information.

### Durability of Response

This study was not designed to assess the durability of treatment response. However, there was no evidence from the study that suggested the effect of drug decreased over time.

### Persistence of Effect

This study provided very limited evidence related to the persistence of treatment effect, because the on-site raters for Weeks 12 and 16 were aware that all subjects had been off study treatment (valbenazine 50 mg daily) for four weeks before the final visit at the end of Week 16.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Nonetheless, the AIMS CFB (mean, SEM) was assessed as -5.9 (0.6) at Week 12 and -4.1 (0.7) at Week 16, suggesting that TD symptoms may have recurred following valbenazine discontinuation.

### **Additional Analyses Conducted on the Individual Trial**

There were no additional analyses conducted by this reviewer for this trial.

## **6.4. Study 1402: A Phase 3, Open-Label, Safety and Tolerability Study of Valbenazine for the Treatment of Tardive Dyskinesia**

### **6.4.1. Study Design**

#### **Overview and Objective**

Study 1402 was a Phase 3, multi-center, open-label, fixed-dose titration study. Its primary stated objectives were to evaluate the safety and tolerability of valbenazine for the treatment of TD for up to 48 weeks.

This study was submitted as supportive for demonstrating efficacy of valbenazine and will be discussed in this efficacy review, albeit with less emphasis than Studies 1304 and 1202 because it had no placebo comparator group. The main information that could be assessed from this study was long-term safety data (to be discussed in Section 8) and uncontrolled data related to durability and persistence of efficacy.

#### **Trial Design**

*Basic Study Design Summary:* Please see Figure 23 for a schematic providing an overview of the study design. Eligible subjects all began open-label treatment with valbenazine 40 mg daily for the first four weeks. At the end of Week 4, the site investigator could increase the dose to 80 mg daily or continue treatment at the current dose. The requirements for increasing the valbenazine dose were that the CGI-TD score was no better than “minimally improved” ( $\geq 3$ ) and the safety and tolerability of the current dose was deemed acceptable by a site physician. Subjects continued the 80 mg daily dose until the end of the treatment period (Week 48). If subjects could not tolerate the 80 mg dose, the dose could be decreased to 40 mg daily until the end of the treatment period. If subjects could not tolerate the 40 mg daily dose of valbenazine, they were discontinued from the study. Subjects presented to the study center every four weeks during the treatment period for assessments, as well as approximately four weeks after the last dose (or early termination).

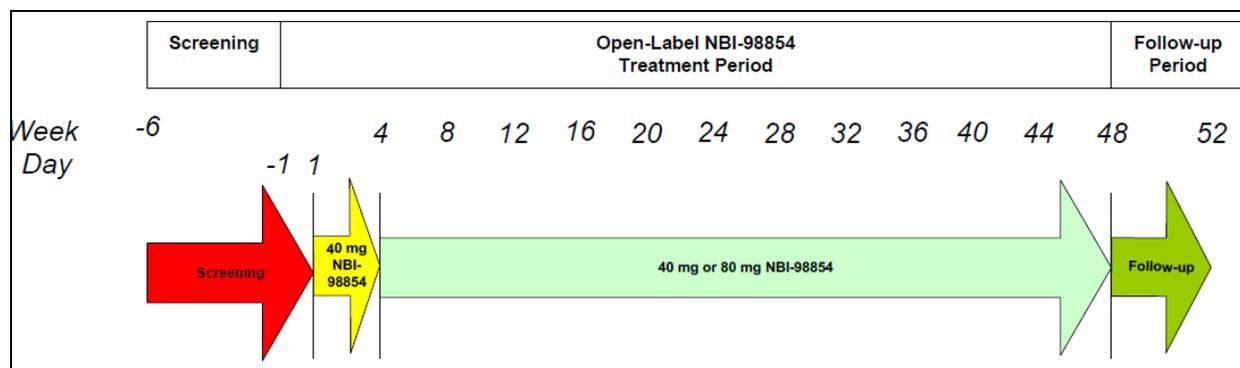
## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Figure 23: Study 1402 - Study Design Schematic**



Source: Study 1402 Clinical Study Report, Figure 1, p. 18

**Study Eligibility Criteria:** Subjects were adults (male or female), age 18-85 years old, with a clinical diagnosis of schizophrenia, schizoaffective disorder, or mood disorder with neuroleptic-induced TD. The TD needed to be moderate or severe, as indicated by a score of  $\geq 3$  on AIMS Item 8 by a blinded, external video AIMS rater. Antipsychotic medications needed to be at stable dosages for  $\geq 30$  days prior to screening. Subjects were excluded for unstable medical conditions within 30 days prior to screening, substance use disorders (except nicotine and caffeine) within three months prior to baseline, severe or unstable underlying psychiatric illness symptoms, or SAS score  $\geq 3$  on two or more items at screening or baseline (excluding items 8 and 10). Overall, the eligibility criteria were relatively similar to Studies 1202 and 1304 and are considered reasonable.

**Dose Selection:** The Applicant indicated that the doses were selected, based on prior studies, to provide a predicted acceptable tolerability and efficacy profile regardless of CYP2D6 genotype and concomitant medication status. The 40 mg and 80 mg daily doses were consistent with those used in the Phase 3 efficacy Study 1304. However, subjects in Study 1304 who were randomized to receive 80 mg valbenazine daily were titrated from 40 mg to 80 mg after one week, and in this study, titration occurred after four weeks according to tolerability and clinical impression of efficacy.

**Treatment Blinding:** Subjects and site staff were not blind to treatment in this open-label study.

**Procedures and Schedule:** Please refer to Table 41 for a schedule of events for this study.

Clinical Review  
Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH  
NDA 209241  
Ingrezza (valbenazine)

**Table 41: Study 1402 - Schedule of Assessments (Abridged)**

| Procedure   | SCN  | BL       | Open-Label Valbenazine Treatment |   |   |    |    |    |    |    |    |    |    |    | FU |    |
|---|------|----------|----------------------------------|---|---|----|----|----|----|----|----|----|----|----|----|----|
|   | Week | -6 to -1 | 0                                | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 |
| <b>Screening Assessments:</b><br>informed consent, UBACC, medical history and inclusion/exclusion criteria (updated at BL), serology studies, BPRS, drug and alcohol screening (repeated at BL)           | X    |          |                                  |   |   |    |    |    |    |    |    |    |    |    |    |    |
| <b>Safety Assessments 1:</b><br>physical examination (height at BL only), vital signs, 12-lead ECG, pregnancy test, clinical laboratory studies, C-SSRS, AE monitoring, prior and concomitant medications | X    | X        | X                                | X | X | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  |
| <b>Safety Assessments 2:</b> serum prolactin, BARS; SAS (also at Screening)   |      | X        | X                                |   | X |    |    | X  |    |    | X  |    |    |    | X  | X  |
| <b>SZ/SAD Assessments</b>   |      |          |                                  |   |   |    |    |    |    |    |    |    |    |    |    |    |
| CDSS  | X    | X        | X                                |   | X |    |    | X  |    |    | X  |    |    |    | X  | X  |
| PANSS   |      | X        | X                                |   | X |    |    | X  |    |    | X  |    |    |    | X  | X  |
| <b>Mood Disorder Assessments</b>  |      |          |                                  |   |   |    |    |    |    |    |    |    |    |    |    |    |
| MADRS, YMRS   | X    | X        | X                                |   | X |    |    | X  |    |    | X  |    |    |    | X  | X  |
| <b>Efficacy Assessments</b>   |      |          |                                  |   |   |    |    |    |    |    |    |    |    |    |    |    |
| AIMS <sup>1</sup> , TDIS, AMBMTD  | X    | X        | X                                | X | X |    |    | X  |    |    | X  |    |    |    | X  | X  |
| CGI-TD, PGIC  |      |          | X                                | X | X |    |    | X  |    |    | X  |    |    |    | X  | X  |
| <b>Pharmacokinetic Sampling</b>   |      |          | X                                | X | X |    |    | X  |    |    | X  |    |    |    | X  | X  |

Source: Adapted from Study 1402 Clinical Study Report, Tables 1-2 (p. 28-31)

SCN=Screening; BL=Baseline; FU=Follow-up/Early Termination; SZ=Schizophrenia; SAD=Schizoaffective Disorder; AIMS=Abnormal Involuntary Movement Scale; AMBMTD=Assessment of Most Bothersome Movement in Tardive Dyskinesia; BARS=Barnes Akathisia Rating Scale; BPRS=Brief Psychiatric Rating Scale; CDSS=Calgary Depression Scale for Schizophrenia; CGI-TD=Clinical Global Impression of Change-Tardive Dyskinesia; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; PANSS=Positive and Negative Syndrome Scale; PGIC=Patient Global Impression of Change; SAS=Simpson-Angus Scale; TDIS=Tardive Dyskinesia Impact Scale; UBACC=University of California, San Diego Brief Assessment of Capacity to Consent; MADRS=Montgomery-Asberg Depression Rating Scale; YMRS=Young Mania Rating Scale

<sup>1</sup>The AIMS was scored by blinded central video raters at Baseline, Week 8, and Week 52 only; AIMS assessments at other visits were scored by on-site raters.

**Concurrent Medications:** Allowed concomitant medications needed to be at stable doses for a minimum of 30 days prior to screening and remain stable during the study. Coexisting diseases or conditions were to be treated in accordance with prevailing medical practice. As needed use of over-the-counter and prescription medications was allowed to treat headaches, pain,

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

respiratory symptoms, and allergy symptoms. Medications recommended for insomnia included eszopiclone, zaleplon, zolpidem, and doxepin (3 or 6 mg at night).

The following medications were prohibited from 30 days prior to screening until the final study visit:

1. Antiemetics: Metoclopramide, prochlorperazine, and promethazine.
2. VMAT2 Inhibitors other than the study drug (e.g., tetrabenazine, reserpine).
3. Botulinum toxin (prohibited starting 90 days prior to screening).
4. Strong CYP3A4 inducers (e.g., phenytoin, phenobarbital, rifabutin, rifampin, primidone, St. John's Wort); carbamazepine permitted if approved by medical monitor prior to Baseline.
5. Dopamine receptor agonists (e.g., ropinirole) and precursors (e.g., carbidopa/levodopa).
6. Monoamine oxidase inhibitors (e.g., isocarboxazid, phenelzine, selegiline, tranylcypromine).
7. Stimulants (e.g., amphetamine, methylphenidate, ephedrine, pseudoephedrine, phenylephrine, and phenylpropanolamine).
8. Drugs known to increase the QT interval, unless approved by the Applicant; baseline QTcF must be < 450 msec for males or < 470 msec for females.
9. As needed use of anticholinergics, benzodiazepines, antipsychotics, mood stabilizers, antidepressants, CYP3A4 inhibitors and inducers, and CYP2D6 inhibitors.

The protocol specifications for concurrent and prohibited medications were generally reasonable and similar to Studies 1202 and 1304. Changes in dosage or as-needed use of psychotropic or other dopaminergic medications (e.g., antipsychotics, benzodiazepines, psychostimulants, dopamine receptor agonists and precursors) could confound the efficacy assessment of valbenazine. Botulinum toxin (which is sometimes used as an off-label treatment of oral TD) could also confound efficacy assessments.

## Study Endpoints

TD severity was assessed using the AIMS, as described in Section 6.1.1. In this study, the AIMS was administered at Screening, Baseline, and the end of Weeks 4, 8, 12, 24, 36, 48, and 52 (or early termination). The AIMS examinations were video recorded at Screening, Baseline, and the end of Weeks 8 and 52 (or early termination). A blinded, external AIMS reviewer evaluated subjects' global TD severity at Screening, as needed for study inclusion. Blinded, central AIMS video raters scored AIMS Items 1-7 at Baseline and the end of Week 8 and 52 (or early termination). The methodology for central AIMS video rating, including the use of modified AIMS scoring anchors, was as described in Study Endpoints in Section 6.2.1. The AIMS dyskinesia total score (defined as the sum of AIMS Items 1-7 as rated by central video raters) was defined as the efficacy variable of primary interest. On-site raters scored AIMS

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

examinations at all time points using the modified AIMS scoring anchors; these ratings were considered exploratory.

This use of central AIMS video raters who were blind to study visit was a positive feature of this study design, as it improved the interpretability of the open-label efficacy data. However, it would have been ideal if the central ratings were performed more frequently over the course of the study for evaluation of treatment durability. It would have been particularly useful to have a Week 48 central rating, as Week 52 occurred four weeks after completing treatment.

Additional efficacy endpoints included:

- Clinical Global Impression of Change – Tardive Dyskinesia (CGI-TD), as described in Section 6.1.1. This measure was rated by an investigator or qualified clinician designee, and the protocol specified that, if possible, the same person should rate the CGI-TD at all time points. Limitations with this outcome measure include the variability introduced by potentially different raters across visits and the subjective assessment of improvement, which may vary according to training, clinical experience, and recall of presentation at baseline. The open-label treatment would also be expected to confound CGI-TD assessment in this study.
- Patient Global Impression of Change (PGIC), as described in Section 6.1.1. The open-label treatment would be expected to confound patients' PGIC ratings.
- Tardive Dyskinesia Impact Scale (TDIS) and Assessment of Most Bothersome Movement in Tardive Dyskinesia (AMBMTD) – patient-reported outcome measures used to assess the impairment, disability, and most bothersome movement associated with dyskinesia.

## Statistical Analysis Plan

The SAP was finalized on April 5, 2016. The only defined analysis set was the Safety analysis set, which included subjects who were enrolled in the study and took at least one dose of study drug and had at least one point of post-baseline data collected.

There were no predefined primary efficacy endpoints in this open-label study, as it had primary objectives related to safety and tolerability. Descriptive statistics were presented for each efficacy variable, with no inferential testing or plans for handling multiplicity. The efficacy variable of primary interest defined in the SAP was the AIMS dyskinesia total score, based on central AIMS video rater assessments. Secondary efficacy variables included the CGI-TD, PGIC, TDIS, and AMBMTD. AIMS scores from on-site raters were considered exploratory.

Additional pre-defined efficacy assessments included an AIMS Responder Analysis (defined as a reduction of  $\geq 50\%$  in AIMS dyskinesia total score from Baseline), CGI-TD Responder Analysis

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

(defined as either scores of 1-2 or 1-3 on the measure at a given visit), and PGIC Responder Analysis (defined as either scores of 1-2 or 1-3 on the measure at a given visit).

## Protocol Amendments

The original protocol was finalized on November 25, 2014. Amendment 1 was finalized on May 21, 2015. This amendment allowed the input of a reliable self-report for the clinical diagnosis of Schizophrenia, Schizoaffective Disorder, and Mood Disorders and updated the statistical and analytical plan to include interim analyses. Amendment 2 was finalized on December 3, 2015. This amendment increased the subject enrollment from 150 to 180 subjects and corrected the design schematic to indicate that the PANSS is not performed at screening. These amendments are not expected to impact the interpretation of study Results.

## Data Quality and Integrity: Applicant's Assurance

The Applicant assured that the study was performed in compliance with GCP and FDA regulations and guidelines. The procedures prior to study initiation and during the conduction of the study were similar to Studies 1304, -1202, and -1201. Quality assurance audits were performed at four clinical study sites (445, 412, 413, and 437).

### 6.4.2. Study Results

#### Compliance with Good Clinical Practices

The Applicant indicated that the study was conducted according to GCP; 21 CFR parts 11, 50, 54, 56, 312, and 314; and the Canadian Guidance for Clinical Trial Sponsors: Clinical Trial Applications.

#### Financial Disclosure

Please see Appendix 13.2 for the financial disclosure review of all covered clinical studies (as defined in 21 CFR 54). There were no disclosable financial interests or arrangements. This information was confirmed by the Applicant in a Response to Information Request received on December 22, 2016. Based on the certification and Applicant verification, there are no concerns about financial conflicts of interest that would affect the interpretation of this study data or the approvability of this application.

#### Patient Disposition

The data cutoff date for this study was August 5, 2016, which was later than the specified cutoff date of March 30, 2016 for the Integrated Summaries of Safety and Efficacy included in the initial NDA. The additional results for Study 1402 were submitted in a 120-Day Safety Update dated November 21, 2016.

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Please see Table 42 below for a tabulation of subject enrollment and disposition up to the data cutoff date. Approximately half of the enrolled subjects remained ongoing at the cutoff date and approximately one fifth of the enrolled subjects had completed the entire 52-week study. Adverse events were the most common reasons for discontinuation, which occurred most often in the 40 mg treatment group. This is expected, as most subjects were increased to the 80 mg dose, and tolerability of the 40 mg dose was a prerequisite for dose increase.

APPEARS THIS WAY ON ORIGINAL

**Table 42: Study 1402 - Subject Disposition as of Data Cutoff Date**

|  | Valbenazine<br>40 mg<br>(N=50) | Valbenazine<br>80 mg<br>(N=107) | Valbenazine<br>80 mg → 40 mg<br>(N=11) | Total<br>(N=168) |
|--|--------------------------------|---------------------------------|--|------------------|
| <b>Completed through at least Week 4</b>   | 41 (82%)                       | 107 (100%)                      | 11 (100%)                              | 159 (94.6%)      |
| <b>Discontinued prior to or at Week 4</b>  | 9 (18%)                        | 0                               | 0                                      | 9 (5.4%)         |
| <b>Reason for DC:</b>                      |                                |                                 |  |                  |
| Adverse event                              | 4 (8%)                         | 0                               | 0                                      | 4 (2.4%)         |
| Protocol deviation                         | 1 (2%)                         | 0                               | 0                                      | 1 (0.6%)         |
| Withdrawal of consent                      | 1 (2%)                         | 0                               | 0                                      | 1 (0.6%)         |
| Lost to follow-up                          | 1 (2%)                         | 0                               | 0                                      | 1 (0.6%)         |
| Sponsor/investigator decision              | 2 (4%)                         | 0                               | 0                                      | 2 (1.2%)         |
|  |                                |                                 |  |                  |
| <b>Completed through at least Week 8</b>   | 34 (68%)                       | 105 (98.1%)                     | 11 (100%)                              | 150 (89.3%)      |
| <b>Discontinued prior to or at Week 8</b>  | 28 (56%)                       | 28 (26.2)                       | 1 (9.1%)                               | 57 (33.9%)       |
| <b>Reason for DC:</b>                      |                                |                                 |  |                  |
| Adverse event                              | 7 (14%)                        | 0                               | 0                                      | 7 (4.2%)         |
| Protocol deviation                         | 1 (2%)                         | 0                               | 0                                      | 1 (0.6%)         |
| Withdrawal of consent                      | 3 (6%)                         | 1 (0.9%)                        | 0                                      | 4 (2.4%)         |
| Death                                      | 0                              | 1 (0.9%)                        | 0                                      | 1 (0.6%)         |
| Lost to follow-up                          | 3 (6%)                         | 0                               | 0                                      | 3 (1.8%)         |
| Sponsor/investigator decision              | 2 (4%)                         | 0                               | 0                                      | 2 (1.2%)         |
|  |                                |                                 |  |                  |
| <b>Completed through at least Week 48</b>  | 7 (14%)                        | 25 (23.4%)                      | 1 (9.1%)                               | 33 (19.6%)       |
| <b>Discontinued prior to or at Week 48</b> | 28 (56%)                       | 28 (26.2%)                      | 1 (9.1%)                               | 57 (33.9%)       |
| <b>Reason for DC:</b>                      |                                |                                 |  |                  |
| Adverse event                              | 15 (30%)                       | 7 (6.5%)                        | 0                                      | 22 (13.1%)       |
| Protocol deviation                         | 1 (2%)                         | 0                               | 0                                      | 1 (0.6%)         |
| Non-compliance                             | 2 (4%)                         | 6 (5.6%)                        | 1 (9.1%)                               | 9 (5.4%)         |
| Withdrawal of consent                      | 4 (8%)                         | 7 (6.5%)                        | 0                                      | 11 (6.5%)        |
| Death                                      | 0                              | 1 (0.9%)                        | 0                                      | 1 (0.6%)         |
| Lost to follow-up                          | 4 (8%)                         | 5 (4.7%)                        | 0                                      | 9 (5.4%)         |
| Sponsor/investigator decision              | 2 (4%)                         | 2 (1.9%)                        | 0                                      | 4 (2.4%)         |
|  |                                |                                 |  |                  |
| <b>Completed through Week 52</b>           | 7 (14%)                        | 22 (20.6%)                      | 1 (9.1%)                               | 30 (17.9%)       |
| <b>Ongoing at Time of Analysis</b>         | 15 (30%)                       | 57 (53.3%)                      | 9 (81.8%)                              | 81 (48.2%)       |

Source: Reviewer-created using data from 120-Day Safety Update, Table 14.1.1

### Protocol Violations/Deviations

In the Interim Clinical Study Report submitted with the NDA, the Applicant summarized the prevalence of Important Protocol Deviations (IPDs), which were defined as deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. Out of a total N=168, 26 subjects (15.5%) had IPDs. The most frequent type was related to inclusion or exclusion criteria. There

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

were no clear patterns to the IPDs by treatment group (i.e., valbenazine 40 mg, 80 mg, or 80 mg → 40 mg), but there were only 7 subjects in the latter treatment group, as compared to 50 in the 40 mg group and 111 in the 80 mg group, at the time of report. The incidence of IPDs was not deemed to be excessive and is roughly comparable with the previously described valbenazine trials. Details about protocol deviations were not included in the 120-Day Safety Update. The occurrences of protocol deviations are assessed as unlikely to affect the interpretation or conclusions from this study.

### Table of Demographic Characteristics

Please see Table 43 for a summary of subject demographic information. Both sexes were reasonably well represented in the sample, and the mean and median ages were in the 55-60 range in all dose groups. Patients of African-American and Caucasian races, as well as those with Hispanic ethnicity, were well-represented in the study sample. The race that was not well-represented in the sample was Asian, for reasons that are unclear. There is no reason to believe that the response to TD treatment differ between races other than potential differences in drug metabolism.

**Table 43: Study 1402 - Subject Demographics, Safety Analysis Set**

|                                     | Valbenazine<br>40 mg<br>(N=46) | Valbenazine<br>80 mg<br>(N=107) | Valbenazine<br>80 mg → 40 mg<br>(N=11) | All subjects<br>(N=164) |
|-------------------------------------|--------------------------------|---------------------------------|--|-------------------------|
| <b>Age (mean, SEM)</b>              | 56.9 (1.6)                     | 57.8 (0.9)                      | 56.3 (2.6)                             | 57.5 (0.7)              |
| <b>Gender (n=, %)</b>               |                                |                                 |  |                         |
| Male                                | 22 (47.8)                      | 59 (55.1)                       | 6 (54.5)                               | 87 (53.0)               |
| Female                              | 24 (52.2)                      | 48 (44.9)                       | 5 (45.5)                               | 77 (47.0)               |
| <b>Ethnicity (n=, %)</b>            |                                |                                 |  |                         |
| Hispanic or Latino                  | 7 (15.2)                       | 48 (44.9)                       | 1 (9.1)                                | 56 (34.1)               |
| Not Hispanic or Latino              | 39 (84.8)                      | 59 (55.1)                       | 10 (90.9)                              | 108 (65.9)              |
| <b>Race (n=, %)</b>                 |                                |                                 |  |                         |
| Asian                               | 1 (2.2)                        | 0                               | 0                                      | 1 (0.6)                 |
| Black or African American           | 17 (37.0)                      | 31 (29.0)                       | 1 (9.1)                                | 49 (29.9)               |
| Caucasian                           | 26 (56.5)                      | 74 (69.2)                       | 10 (90.9)                              | 110 (67.1)              |
| Native Hawaiian or Pacific Islander | 1 (2.2)                        | 1 (0.9)                         | 0                                      | 2 (1.2)                 |
| Other                               | 1 (2.2)                        | 1 (0.9)                         | 0                                      | 2 (1.2)                 |

Source: Reviewer-created, with data from 120-Day Safety Update, Table 14.1.4

### Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline characteristics were reviewed in the Clinical Study Report and the 120-Day Safety Update. The mean BMI (SD) was 28.5 (5.5) kg/m<sup>2</sup> for the total sample, with similar means in each dose group. There were eleven subjects (6.7%) who were classified as CYP2D6 poor metabolizers, and seven (64%) of these subjects ended up taking valbenazine 40 mg daily.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Though the sample size is very small, this might suggest that subjects with poor metabolism of the active metabolite [+]– $\alpha$ -dihydrotetrabenazine may have a better benefit/risk for the lower dose of valbenazine than other subjects. Approximately 73% of the sample had underlying schizophrenia/schizoaffective disorder vs. 27% with an underlying mood disorder. The baseline AIMS dyskinesia total score (mean, SE) for the 40 subjects who had central video rater data at the time of data cutoff was 10.4 (0.7). Overall, from the data available at time of review, the baseline subject characteristics were similar to those in Studies 1304, -1202, and -1201.

### **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Treatment compliance for this study will not be addressed, because at the time of data cutoff, approximately 50% of subjects still remained in the study. The most common concomitant medications used by study subjects, as described in the Clinical Study Report, were antipsychotics (87.6%), antidepressants (65.8%), and lipid modifying agents (40.4%). The use of these medications is not unexpected for the study population of individuals with psychotic and mood disorders whose age was generally in the late 50's. The protocol specified that subjects were expected to continue stable dosages of medications for psychiatric and medical conditions from  $\geq 30$  days prior to screening until the end of the study. There was no role for rescue medications in this study, as there are no current treatments for TD.

### **Efficacy Results - Primary Endpoint**

There was no predefined primary efficacy endpoint in this open-label study with primary objectives related to safety and tolerability. The efficacy-related data collected (up to the data cutoff point) will be discussed below.

### **Data Quality and Integrity - Reviewers' Assessment**

The data set for this study is not yet final, as approximately 50% of subjects were ongoing at the data cutoff date. A limited assessment of data quality for this study was performed by Dr. Douglas Warfield and there were no obvious irregularities. An analysis of SDTM finding domains (EG, LB, QS, VS, and YG) was performed to help detect screening bias; this analysis also did not reveal any clear instances of screening bias.

### **Efficacy Results - Secondary and other relevant endpoints**

This study is currently ongoing as of the data cutoff date. Because the data collection is not yet complete and the study has an open-label design, results will be discussed only briefly due to limited interpretability.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

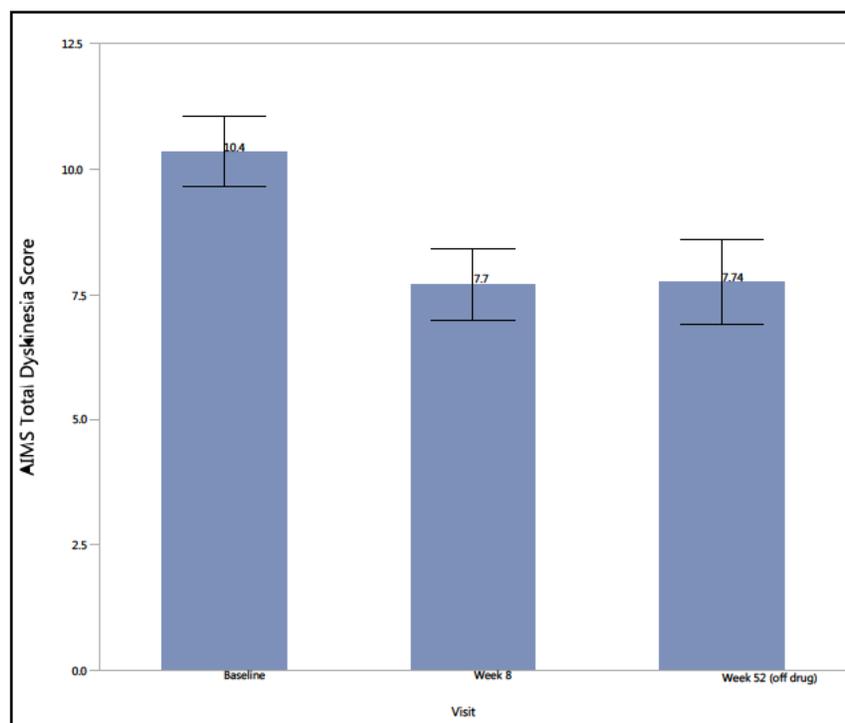
NDA 209241

Ingrezza (valbenazine)

### AIMS

AIMS total dyskinesia scores, as assessed by central video raters who were blind to subject number, treatment, and visit number, are displayed in Figure 24 below. Valbenazine treatment was associated with a mean decrease of ~3 points on the AIMS scale after 8 weeks of treatment. From the data submitted thus far, the therapeutic benefit of valbenazine appeared to persist for four weeks after the treatment was discontinued. This is interpreted with caution because the sample size is very small (n=27 at Week 52). It does, however, support the suggestion from Study 1304 that 48 weeks of valbenazine treatment does not worsen underlying TD disease severity or lead to rebound worsening of TD following discontinuation.

**Figure 24: Study 1402 - AIMS Total Dyskinesia Score, Blinded Central Video Raters**



Source: Reviewer-created using data from the tabulation dataset AIMS\_CR.XPT

All subjects were receiving flexible-dose valbenazine (40 mg or 80 mg daily). N=40 at Baseline and n=27 at Week 8 and Week 52, as study was not complete at the data cutoff date.

Figure 25 depicts the mean change in AIMS dyskinesia score from baseline in all subjects receiving valbenazine, as scored by on-site raters. These AIMS scores are considered less reliable than the central video raters, because the on-site raters were aware of the visit sequence and treatment (i.e., baseline or Week 52 vs. a week when subjects were receiving active treatment). In this study, the on-site and central raters both used the same modified

## Clinical Review

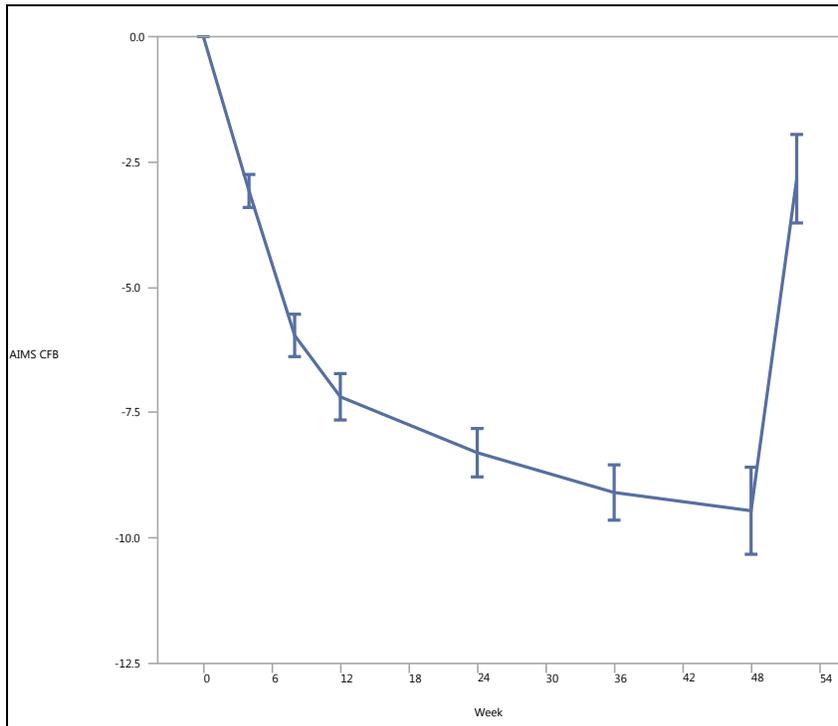
Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

AIMS descriptors. The increased magnitude of AIMS response assessed by on-site raters vs. central raters may represent expectation bias.

**Figure 25: Study 1402 - AIMS Change from Baseline, On-Site Raters**



Source: Reviewer-created using data from analysis dataset AIMS.XPT. Each error bar is constructed using 1 standard error from the mean. N=168 at baseline and N=30 at Week 52; study is not complete.

### CGI-TD

Because treatment was open-label and CGI-TD raters were aware that all subjects were receiving active treatment, CGI-TD scores in this study offer little support for efficacy. After 48 weeks of treatment, 32/33 (97%) of subjects were rated as “much improved” or “very much improved” from baseline on the measure. Following four weeks of treatment discontinuation, 12/30 subjects (40%) remained rated as “much improved” or “very much improved”.

### PGIC

Because treatment was open-label and subjects were aware that they were receiving active treatment, PGIC scores from this study also offer little additional support for efficacy. After 48 weeks of treatment, 31/33 (94%) of patients assessed their TD to be “much improved” or “very much improved”. Following four weeks of treatment discontinuation, 18/30 (60%) of subjects continued to assess their TD as “much improved” or “very much improved”.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

### **Dose/Dose Response**

This open-label flexible-dose study does not provide useful dose/response information. Please refer to Section 7.1.4 for an integrated assessment of dose/response for valbenazine.

### **Durability of Response**

This study does not provide adequate evidence supporting the durability of valbenazine treatment. It has an open-label design and had blinded central rater AIMS scores at only one time point when subjects were receiving treatment (Week 8). The on-site AIMS ratings over the course of the study (Figure 25) do not raise concerns that the valbenazine treatment response lacks durability.

### **Persistence of Effect**

The sample size of subjects with blinded central video AIMS scores at Week 52 (n=27) is too small to support conclusions related to treatment persistence. On-site AIMS ratings (Figure 25) suggest that TD symptoms recur following treatment discontinuation, but this interpretation is limited by the open-label uncontrolled study design.

### **Additional Analyses Conducted on the Individual Trial**

There were no additional analyses conducted by this reviewer on this trial.

## **7 Integrated Review of Effectiveness**

---

### 7.1. Assessment of Efficacy Across Trials

#### 7.1.1. Primary Endpoints

The Applicant indicated that Studies 1304 and 1202 are considered pivotal and Studies 1201 and 1402 are considered supportive for evaluating the efficacy of valbenazine for the treatment of TD. Of these trials, Study 1402 was a long-term open-label study that is not yet complete, so it will not be emphasized in this section. The general primary efficacy endpoint measure was the change from baseline to week 6 on the AIMS dyskinesia total score (sum of AIMS items 1-7). Please see Table 45 for a high-level comparison of methods and efficacy results between the three aforementioned studies.

As discussed in Sections 6.1.1, 6.2.1, and 6.3.1, the use of the AIMS as a primary efficacy measure in Study 1201 had methodological issues that were addressed in the pre-specified analysis plan for subsequent Phase 2/3 studies (1202, -1304, and -1402). These issues included

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

inconsistent AIMS scoring across the large number of on-site raters, AIMS item score descriptors that were less sensitive for detecting change, and sequence/expectancy bias introduced by raters' knowledge of how long subjects had been receiving study treatment.

The Applicant instituted the use of blinded central video AIMS raters and revised the AIMS scoring descriptors (Table 22); the Agency agreed with these changes in pre-submission meetings (Section 3.2). Please refer to Table 44 for a summary of roles for on-site and central AIMS raters at study visits. Notably, on-site examiners video-recorded AIMS assessments in Study 1304 but did not score the examination, and the on-site raters used the revised AIMS item descriptors in Study 1402 and the original AIMS descriptors in Studies 1201 and -1202.

**Table 44: Summary of AIMS Rating Methodology Across Studies 1201, 1202, 1304, and 1402**

| Trial ID <sup>1</sup> | On-site independent AIMS rater (otherwise uninvolved in care) <sup>2</sup>  | Blinded, external AIMS video reviewer                                      | Central blinded AIMS video raters (Items 1-7, using revised score descriptors)                           |
|-----------------------|---|--|--|
| 1201                  | <ul style="list-style-type: none"><li>• Screening</li><li>• Baseline</li><li>• Weeks 2, 6, 8, 12, 16/ET</li></ul>   | Screening: Evaluate global TD severity for study eligibility (AIMS Item 8) | Post hoc: <ul style="list-style-type: none"><li>• Baseline</li><li>• Week 6</li></ul>                    |
| 1202                  | <ul style="list-style-type: none"><li>• Screening</li><li>• Baseline</li><li>• Weeks 2, 4, 6, 8/ET</li></ul>  | Screening: Evaluate global TD severity for study eligibility (AIMS Item 8) | <ul style="list-style-type: none"><li>• Baseline</li><li>• Week 6</li></ul>                              |
| 1304                  | No scoring performed; videotaped examination only: <ul style="list-style-type: none"><li>• Screening</li><li>• Baseline</li><li>• Weeks 2, 4, 6, 8, 16, 24, 32, 40, 48, 52/ET</li></ul> | Screening: Evaluate global TD severity for study eligibility (AIMS Item 8) | <ul style="list-style-type: none"><li>• Baseline</li><li>• Weeks 2, 4, 6, 8, 16, 32, 48, 52/ET</li></ul> |
| 1402                  | <ul style="list-style-type: none"><li>• Screening</li><li>• Baseline</li><li>• Weeks 4, 8, 12, 24, 36, 48, 52/ET</li></ul>  | Screening: Evaluate global TD severity for study eligibility (AIMS Item 8) | <ul style="list-style-type: none"><li>• Baseline</li><li>• Weeks 8, 52/ET</li></ul>                      |

Source: Reviewer-created, using protocols for Studies 1201, -1202, -1304, and -1402

<sup>1</sup>4-digit numbers are prefaced by NBI-98854- for the full trial identifier.

<sup>2</sup>On-site raters used the original AIMS score descriptors for Studies 1201 and -1202 and the revised AIMS score descriptors for Study -1402. In the open-label Study 1402, the on-site rater could be the investigator or designee. Abbreviations: ET=end of treatment

The subject populations were relatively similar between studies. The increase of the maximum age to 85 for Studies 1202 and 1304 did not have a significant effect on the mean and median ages of the study populations, which were in the mid-50's in all three studies. The ineligibility of subjects with gastrointestinal illness for Study 1304 likewise does not have a significant impact, as there was only one subject in this group in the Study 1202 ITT analysis set. Study 1201 did not include subjects with mood disorders and neuroleptic-induced TD, but there was no reason

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

to suspect that the specific underlying psychiatric illness would affect the treatment-sensitivity of neuroleptic-induced TD and there were reasonable proportions of subjects with mood disorders in subsequent Phase 2/3 studies.

Other important differences between the three studies that affect the interpretation of the primary efficacy measure were:

1. Differences in dosing regimens between studies (discussed in Section 7.1.4).
2. Differences in statistical analysis plans (e.g., Study 1202 pre-specified the use of the Per Protocol analysis set for the primary efficacy endpoint; Studies 1201 and -1202 used ANCOVA methods, and Study 1304 used MMRM methods for evaluating statistical significance).
3. Differences in AIMS scoring methods (Study 1201 pre-specified the use of on-site rater AIMS data, which employed AIMS scoring descriptors prior to revision).

APPEARS THIS WAY ON ORIGINAL

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 45: Comparisons Between Controlled Studies Evaluating 6-Week Efficacy Endpoints**

| Trial ID <sup>1</sup> | N=  | Population  | Dosing Regimen  | Pre-specified Primary Efficacy Endpoint  | Pre-specified Analytic Methods  | Notes   |
|-----------------------|-----|---|---|--|---|---|
| 1201                  | 109 | Adults (age 18-65) with Schizophrenia or Schizoaffective Disorder and TD  | 3 groups (1:1:2): valbenazine 50 mg daily; valbenazine 100 mg daily x 2 weeks, then 50 mg daily; and placebo  | AIMS dyskinesia total score Week 6 CFB (on-site AIMS raters), ITT analysis set | Comparison between pooled valbenazine 50+100 mg groups vs. placebo; ANCOVA model                                | Non-significant (p=0.2966); post hoc analysis using central video raters also did not reach significance (p=0.0663)   |
| 1202                  | 102 | Adults (age 18-85) with Schizophrenia, Schizoaffective Disorder, Mood Disorder, or Gastrointestinal Disorder and TD | 2 groups (1:1): valbenazine 25-75 mg daily flexible dose (according to efficacy and tolerability) and placebo | AIMS dyskinesia total score Week 6 CFB (central raters), PP analysis set       | Comparison between valbenazine group and placebo group; ANCOVA model  | Significant (p<0.0001); analysis using ITT analysis set was also significant (p=0.0005)   |
| 1304                  | 234 | Adults (age 18-85) with Schizophrenia, Schizoaffective Disorder, or Mood Disorder and TD                            | 3 groups (1:1:1): valbenazine 40 mg daily, valbenazine 80 mg daily, and placebo                               | AIMS dyskinesia total score Week 6 CFB (central raters), ITT analysis set      | Comparison between valbenazine dose group and placebo group, MMRM analysis; sequential testing for multiplicity | Significant for valbenazine 80 mg dose vs. placebo (p<0.0001). Valbenazine 40 mg dose had nominal p=0.0021 but was non-significant, because previous test in sequence (CGI-TD) was non-significant (p=0.0560) |

<sup>1</sup>4-digit numbers are prefaced by NBI-98854- for the full trial identifier.

mITT = modified intent to treat; PP=per protocol

Source: Reviewer-created, using information from study protocols and statistical analysis plans.

The baseline AIMS total dyskinesia and 6-week CFB scores are summarized in Table 46 below. It is notable that the on-site baseline AIMS scores were significantly higher (in Study 1201) than the centrally rated AIMS baseline scores; this may reflect the impact of the revised AIMS score descriptors as well as the central raters being blind to visit number. It is also notable that the AIMS CFB placebo response was greater with the on-site raters in Study 1201; this may be due

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

to the raters not being blind to visit number (sequence bias) as well as the pre-revision AIMS item descriptors. The mean AIMS CFB at 6 weeks was in the -3 to -4 range in both studies 1202 and 1304 (valbenazine 80 mg treatment group).

**Table 46: Comparison of 6-week AIMS Baseline and Change Scores Across Controlled Studies**

| Study*                     | Treatment Group (N=)                | AIMS Baseline mean (SEM) | AIMS CFB mean (SEM) |
|----------------------------|-------------------------------------|--------------------------|---------------------|
| 1201 on-site <sup>1</sup>  | Placebo (N=54)                      | 15.3 (0.6)               | -2.4 (0.5)          |
| 1201 on-site <sup>1</sup>  | Valbenazine 50+100 mg pooled (N=53) | 14.6 (0.7)               | -3.1 (0.6)          |
| 1201 post hoc <sup>2</sup> | Placebo (N=46)                      | 8.5 (0.7)                | -0.5 (0.4)          |
| 1201 post hoc <sup>2</sup> | Valbenazine 50+100 mg pooled (N=40) | 7.8 (0.6)                | -1.3 (0.5)          |
| 1202                       | Placebo (N=44)                      | 7.9 (0.7)                | -1.1 (0.6)          |
| 1202                       | Valbenazine 25-75 mg pooled (N=45)  | 8.0 (0.5)                | -3.6 (0.5)          |
| 1304                       | Placebo (N=76)                      | 9.9 (0.5)                | 0 (0.4)             |
| 1304                       | Valbenazine 40 mg (N=70)            | 9.8 (0.5)                | -1.8 (0.5)          |
| 1304                       | Valbenazine 80 mg (N=79)            | 10.4 (0.4)               | -3.3 (0.5)          |

Source: Reviewer-created, using data from Clinical Study Reports for Studies 1201, -1202, and -1304 ITT Analysis Sets

AIMS=AIMS total dyskinesia score (sum of Items 1-7); CFB=change from baseline

\*4-digit numbers are prefaced by NBI-98854- for the full study identifier

<sup>1</sup>On-site rater scores using AIMS score descriptors pre-revision

<sup>2</sup>Post hoc central rater scores using modified AIMS descriptors; Applicant's mITT analysis set excluded subjects without AIMS scores or detectable [±]-α-dihydrotrabenzazine plasma levels at Week 6

The Applicant noted that the AIMS total dyskinesia score has a possible range of 0-28, but the scale is based on categorical assessments of seven body regions and most subjects only had dyskinetic movements in 2-4 regions. This is consistent with mean AIMS baseline scores ranging from 7.8-10.4 (central video rated) in the studies listed in Table 46.

While the AIMS is widely used in clinical and research settings for assessing TD, there are no accepted criteria as to what represents a clinically meaningful change in AIMS score. The Applicant conducted an analysis assessing the concordance of the AIMS dyskinesia CFB at 6 weeks with the CGI-TD score, as displayed in Table 47. Subjects who were assessed as being much or very much improved at Week 6 had mean and median changes from baseline of -3.4 and -3.0 on the AIMS dyskinesia total score. This is roughly equivalent to the mean changes associated with valbenazine treatment (either titrated up to 75 mg/day or 80 mg/day fixed dose) as well as the Applicant's "AIMS Responder" definition of a ≥50% decrease in AIMS total dyskinesia score. Overall, this analysis has some limitations, as the on-site CGI-TD raters were not necessarily the same at each visit, were not blinded to visit number, and had additional

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

efficacy-related information in Study 1202 that may have influenced their CGI-TD ratings (authorization to increase study treatment dose by independent AIMS raters). Altogether, however, it seems reasonable that a -3 to -4 decrease in the AIMS total dyskinesia score would represent a clinically meaningful change in TD symptoms.

**Table 47: AIMS Dyskinesia CFB at 6 Weeks by CGI-TD Category (ITT analysis sets, Phase 2/3 controlled studies)**

| Statistic for AIMS Dyskinesia Total Score Change from Baseline at Week 6 | Categorization 1                    |                     | Categorization 2          |                     |
|--|-------------------------------------|---------------------|---------------------------|---------------------|
|  | CGI-TD=1, 2 <sup>a</sup><br>(N=108) | CGI-TD>2<br>(N=265) | CGI-TD=1, 2, 3<br>(N=269) | CGI-TD>3<br>(N=104) |
| Mean (SD)  | -3.4 (4.0)                          | -0.9 (3.4)          | -2.2 (3.8)                | 0.0 (3.1)           |
| SE   | 0.39                                | 0.21                | 0.23                      | 0.31                |
| Median   | -3.0                                | 0.0                 | -2.0                      | 0.0                 |
| Min, max   | -13, 8                              | -12, 8              | -13, 8                    | -8, 8               |

Source: *Integrated Summary of Efficacy, Table 38, p. 82*

The AIMS scores were from blinded, central AIMS video raters and the CGI-TD scores were from on-site investigators who were blind to treatment by not to visit number.

<sup>a</sup>CGI-TD scores: 1="very much improved", 2="much improved", 3="minimally improved", 4="no change", 5="minimally worse", 6="much worse", 7="very much worse".

This reviewer conducted an exploratory analysis of the AIMS in order to further assess the clinical meaningfulness of treatment effects. A clinician might consider a patient's TD symptoms to be well-controlled if there are no body parts with abnormal movement severity greater than "minimal" (corresponding to a score of 1 on the AIMS). As displayed in Table 48, valbenazine treatment (80 mg dose in Study 1304 and flexible-dose treatment in Study 1202) was associated with ~34% of subjects meeting this remission criterion at Week 6, as compared to ~19% of subjects receiving placebo. By this measure, the number needed to treat (NNT), calculated using the change in the proportion of subjects meeting the criterion from baseline to Week 6, is ~4-5. If an adequate treatment response was considered to be having no body parts with abnormal movement severity greater than "mild" (corresponding to a score of 2 on the AIMS), ~72% of subjects receiving valbenazine met this criterion at the end of Week 6 as compared to ~51% of subjects receiving placebo (however, a much larger proportion of subjects met this criterion at baseline).

**Table 48: Studies 1202 and -1304, Exploratory Remission Criteria, ITT Analysis Set**

| Treatment   | Baseline |     |       | Week 6 |     |       |
|-------------|----------|-----|-------|--------|-----|-------|
|             | No       | Yes | % Yes | No     | Yes | % Yes |
| Placebo     | 109      | 13  | 10.7  | 92     | 21  | 18.6  |
| Valbenazine | 120      | 5   | 4.0   | 75     | 39  | 34.2  |

*Source: Reviewer-created, using responder dataset created by Dr. Douglas Warfield in which subjects met responder criteria if they scored no more than “minimal” on any individual body area, as assessed by blinded central video raters. Subjects include those in the ITT analysis set from Studies 1202 (all) and 1304 (placebo and valbenazine 80 mg groups).*

### 7.1.2. Secondary and Other Endpoints

#### CGI-TD

Of the two pivotal studies and two supportive studies submitted by the Applicant, only one secondary endpoint had adequate multiplicity adjustment specified in the SAP. This was the CGI-TD (Figure 6), described in Section 6.1.1. In Study 1304, the mean CGI-TD score at Week 6 in the ITT analysis set was specified as a key secondary endpoint. A fixed-sequence testing procedure was used to control the family-wise error rate, with the Week 6 CGI-TD mean score for valbenazine 80 mg vs. placebo as the second test and the valbenazine 40 mg vs. placebo as the fourth test in the sequence. Both doses of valbenazine treatment were associated with a numerically superior mean CGI-TD improvement at Week 6 than placebo, but statistical significance was not achieved.

In Study 1201, the treatment group receiving valbenazine 100 mg daily (N=26) showed improvement on the CGI-TD at Week 2 as compared to placebo (N=54): LS mean score 3.2 vs. 3.6 (nominal p=0.0277). However, this endpoint was not specified as a key secondary endpoint or adjusted for multiple testing. At the end of Week 6, the difference between placebo and valbenazine treatment groups (pooled 50 mg + 100/50 mg) on the CGI-TD did not achieve nominal statistical significance.

In Study 1202, the treatment group receiving valbenazine 25-75 mg daily (N=45) showed improvement on the CGI-TD at Week 6 as compared to placebo (N=44): LS mean score 2.2 vs. 3.1 (nominal p<0.0001). However, this was also not specified as a key secondary endpoint or adjusted for multiple testing.

(b) (4)  
 (b) (4)

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

There were no other secondary endpoints that were pre-specified as key and had adequate adjustment for multiple testing, but findings from other secondary/exploratory efficacy measures will be summarized briefly.

### *PGIC*

The PGIC measure was used to characterize study subjects' perception of their improvement in TD symptoms. In general, subjects receiving valbenazine (who were blinded to treatment) did not appear to appreciate greater improvement in TD symptoms after six weeks of treatment than subjects receiving placebo, even when TD symptoms were rated as significantly improved by blinded central raters. This finding is consistent with prior literature suggesting patients are frequently unaware of their own dyskinesic movements [30]. It is also possible that subjects' perception of treatment benefit may take a longer time to realize. The PGIC score generally continued to improve with prolonged treatment; however, there was no placebo comparator during long-term open-label treatment, and subject attrition may have also confounded these results.

### *TDIS*

The TDIS was a patient-reported secondary outcome measure designed to assess the impairment and disability associated with TD. In Study 1304, both doses of valbenazine, as well as placebo treatment, were associated with improvement on the TDIS over time. While both doses valbenazine treatment were associated with a numerically superior mean response on the TDIS, the differences did not reach nominal statistical significance. As with the PGIC, it is possible that subjects' perception of treatment benefit may take a longer time to realize.

### *TDRS*

The TDRS was an exploratory mixed patient/caregiver- and clinician-rated measure intended to assess the impact of TD symptoms on daily living. In Study 1202, flexible-dose valbenazine treatment was associated with a numerically superior improvement on all parts of the measure (dyskinesia, impairment, and disability) than placebo at the end of Week 6. In contrast, Study 1201 observed little to no improvement on the TDRS in subjects receiving valbenazine (50 mg for 4-6 weeks) than placebo. It is possible that a higher dose of valbenazine may have been necessary to see a difference between treatment groups, that a longer duration of treatment would be necessary, or that this exploratory measure was not appropriate in achieving its objectives.

### **7.1.3. Subpopulations**

Please refer to Sections 6.1.2 and 6.2.2 for subgroup analyses of the individual pivotal efficacy

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

studies 1304 and -1202. The three 6-week placebo controlled efficacy studies (1304, -1202, and -1201) had differences in study design (patient population, dosing regimen, endpoint assessment and timing) that limit the usefulness of a pooled subpopulation analysis. However, for exploratory purposes, such an analysis was conducted using the following parameters:

1. Include subjects from Studies 1201, -1202, and -1304 who had AIMS ratings scored by blinded central video raters at Baseline and the end of Week 6
2. Divide subjects into three treatment groups: placebo, valbenazine 40-50 mg daily, and valbenazine 75-80 mg daily (caveat: Study 1201 had a dose reduction group and -1202 employed a flexible-dose design).
3. For Study 1201, all valbenazine-treated subjects were grouped as receiving 40-50 mg daily (including subjects who received 100 mg for the first two weeks, followed by 50 mg for the next four weeks).
4. For Study 1202, subjects were grouped according to the dose they were receiving at Week 6. Subjects receiving valbenazine 25 mg daily (n=5) were removed from this analysis.

The resulting subpopulation analysis (total N=371) is displayed in Table 49. Given the limited number of subjects in each subgroup and the differences in study designs, it is not possible to make firm conclusions. Of the variables examined, the lack of continued antipsychotic use appeared to be the strongest examined factor predicting response to a given dose of valbenazine. On face, it seems reasonable that continued antipsychotic use might reduce the effectiveness of a treatment for TD (as assessed by the AIMS change from baseline), either by suppressing TD movements on its own [32] or continuing to propagate the neurobiological processes that resulted in the development of TD.

APPEARS THIS WAY ON ORIGINAL

**Table 49: Exploratory Pooled Subpopulation Analysis**

|   |                     | % of population<br>(N=371) | Week 6 AIMS Change from Baseline |      |     |          |      |     |          |      |     | Mean<br>treatment -<br>placebo Δ |             |
|---|---------------------|----------------------------|----------------------------------|------|-----|----------|------|-----|----------|------|-----|----------------------------------|-------------|
|   |                     |                            | Placebo                          |      |     | 40-50 mg |      |     | 75-80 mg |      |     | 40-50<br>mg                      | 75-80<br>mg |
|   |                     |                            | N=                               | Mean | SEM | N=       | Mean | SEM | N=       | Mean | SEM |                                  |             |
| <b>All Subjects in Pool</b>             |                     | 100                        | 159                              | -0.4 | 0.3 | 113      | -1.9 | 0.4 | 99       | -3.2 | 0.4 | -1.5                             | -2.8        |
| <b>Age Group</b>                        | <60                 | 63.9                       | 101                              | -0.4 | 0.4 | 77       | -1.9 | 0.4 | 59       | -3.1 | 0.5 | -1.5                             | -2.7        |
|   | ≥60                 | 36.1                       | 58                               | -0.5 | 0.4 | 36       | -1.9 | 0.7 | 40       | -3.4 | 0.5 | -1.4                             | -2.9        |
| <b>TD Duration<br/>(when available)</b> | >4 years            | 37.7                       | 62                               | -0.4 | 0.4 | 45       | -1.9 | 0.6 | 33       | -3.6 | 0.7 | -1.5                             | -3.2        |
|   | 0-4 years           | 39.9                       | 61                               | -0.7 | 0.4 | 47       | -2.2 | 0.5 | 40       | -3.1 | 0.5 | -1.5                             | -2.4        |
| <b>Sex</b>                              | F                   | 41.5                       | 69                               | -0.9 | 0.4 | 40       | -3.1 | 0.7 | 45       | -3.4 | 0.5 | -2.2                             | -2.5        |
|   | M                   | 58.5                       | 90                               | -0.1 | 0.4 | 73       | -1.2 | 0.4 | 54       | -3.1 | 0.5 | -1.1                             | -3.0        |
| <b>Race</b>                             | Black               | 38.0                       | 63                               | -1   | 0.4 | 43       | -1   | 0.6 | 35       | -2.9 | 0.6 | 0.0                              | -1.9        |
|   | White               | 57.1                       | 87                               | -0.3 | 0.4 | 64       | -2.5 | 0.5 | 61       | -3.4 | 0.5 | -2.2                             | -3.1        |
|   | Other               | 4.9                        | 9                                | 2.11 | 1.2 | 6        | -2   | 0.5 | 3        | -4.3 | 2.9 | -4.1                             | -6.4        |
| <b>Ethnicity</b>                        | Hispanic/Latino     | 27.2                       | 43                               | -0.1 | 0.5 | 31       | -1.9 | 0.7 | 27       | -3   | 0.7 | -1.8                             | -2.9        |
|   | Not Hispanic/Latino | 72.8                       | 116                              | -0.6 | 0.3 | 82       | -1.9 | 0.4 | 72       | -3.3 | 0.4 | -1.3                             | -2.7        |
| <b>BMI Quartile (kg/m<sup>2</sup>)</b>  | 17.4-24.1           | 25.9                       | 39                               | -0.6 | 0.5 | 24       | -0.4 | 0.9 | 33       | -3   | 0.6 | 0.2                              | -2.4        |
|   | 24.2-27.6           | 24.5                       | 40                               | -0.8 | 0.5 | 32       | -2   | 0.7 | 19       | -3.7 | 0.8 | -1.2                             | -2.9        |
|   | 27.7-32.8           | 25.1                       | 43                               | -0.3 | 0.6 | 26       | -2.7 | 0.7 | 24       | -3.1 | 0.8 | -2.4                             | -2.8        |
|   | 32.9-46.9           | 24.5                       | 37                               | -0.1 | 0.5 | 31       | -2.3 | 0.7 | 23       | -3.3 | 0.6 | -2.2                             | -3.2        |
| <b>Diagnosis Group</b>                  | SZ/Schizoaffective  | 71.2                       | 116                              | -0.3 | 0.3 | 89       | -1.6 | 0.4 | 59       | -3   | 0.5 | -1.3                             | -2.7        |
|   | Mood Disorder       | 28.6                       | 42                               | -0.9 | 0.4 | 24       | -3.1 | 0.7 | 40       | -3.5 | 0.6 | -2.2                             | -2.6        |
| <b>Antipsychotic Use</b>                | No                  | 17.5                       | 29                               | 0    | 0.5 | 12       | -3   | 1.2 | 24       | -4.9 | 0.6 | -3.0                             | -4.9        |
|   | Yes                 | 82.5                       | 130                              | -0.5 | 0.3 | 101      | -1.8 | 0.4 | 75       | -2.7 | 0.4 | -1.3                             | -2.2        |
| <b>Antipsychotic Category</b>           | Atypical Only       | 64.4                       | 102                              | -0.4 | 0.3 | 76       | -1.8 | 0.4 | 61       | -2.6 | 0.5 | -1.4                             | -2.2        |
|   | Typical or Both     | 18.1                       | 28                               | -1.1 | 0.8 | 25       | -1.6 | 1   | 14       | -3   | 0.9 | -0.5                             | -1.9        |
| <b>Anticholinergic Use</b>              | No                  | 66.3                       | 111                              | -0.5 | 0.3 | 70       | -2.3 | 0.4 | 65       | -2.9 | 0.4 | -1.8                             | -2.4        |
|   | Yes                 | 33.7                       | 48                               | -0.3 | 0.5 | 43       | -1.2 | 0.7 | 34       | -3.8 | 0.6 | -0.9                             | -3.5        |

Source: Reviewer-created, as described in text. N=371 in pooled sample. SZ=schizophrenia.

#### 7.1.4. Dose and Dose-Response

Please refer to Section 4.5 for a summary of Clinical Pharmacology information and the OCP team review for additional details related to dose/blood level/response and subpopulation differences. Their review concluded that a significant dose/exposure-response relationship indicated that higher dose/exposure was associated with higher reduction in the AIMS total score.

As displayed in Table 45, the placebo-controlled efficacy studies employed significantly different dosing regimens. Study 1304 provided the most robust dose-response information, as it randomized patients to receive placebo, valbenazine 40 mg, or valbenazine 80 mg daily for the first six weeks, with a one-time dose reduction of 80 mg to 40 mg permitted only for tolerability reasons. Subjects randomized to receive valbenazine 80 mg/day received 40 mg for the first week (for titration). In this study, both valbenazine doses were associated with a greater mean decrease in the AIMS total dyskinesia score than placebo (Table 13 and Figure 8). However, only the 80 mg dose achieved statistical significance on the primary efficacy endpoint. Although the valbenazine 40 mg had a nominally significant p value ( $p=0.0021$ ), this dose was not considered statistically significant because the statistical test was lower in the pre-specified multiple testing sequence than a non-significant statistical test (Week 6 CGI-TD mean change, valbenazine 80 mg group).

Study 1202 employed flexible dosing, in which subjects assigned to valbenazine initiated treatment at 25 mg daily and could increase/decrease the dose (according to efficacy parameters and tolerability) by 25 mg increments every two weeks to a maximum of 75 mg daily. This study design was appropriate for a Phase 2 dose finding study to help establish the overall efficacy of valbenazine, but it was limited in its ability to help establish an accurate correlation between dose and effect and for determining the lowest effective dose of valbenazine. Of the 45 subjects in the valbenazine group at the end of Week 6 (ITT analysis set), 31 were receiving 75 mg, 9 were receiving 50 mg, and 5 were receiving 25 mg daily (mean dose (SD) = 64.4 (17.3) mg). The distribution of doses at the end of Week 6 suggests that 75 mg was a more appropriate treatment dose than 25 or 50 mg daily for the majority of subjects, though a subset of subjects appeared to respond to the lower doses.

Altogether, these findings support the following dosing recommendations:

*The initial dose for valbenazine is 40 mg once daily. After one week, increase the dose to the recommended dose of 80 mg once daily. Continuation of 40 mg once daily may be considered for some patients.*

The OCP team review was in agreement with these dosing recommendations. Additional dose-related conclusions from the OCP review, based on relevant PK studies, the established

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

exposure-response relationships, and the understanding of the mechanism of drug elimination, were:

- No dosage adjustment is necessary based on body weight, age, gender, race, and BMI.
- Valbenazine can be administered with or without food.
- Valbenazine dosage should be reduced by half, based on therapeutic response and tolerability, when co-administered with a strong CYP3A4 inhibitor.
- Dose reduction should be considered, based on clinical response, when co-administered with a strong CYP2D6 inhibitor or for a known CYP2D6 poor metabolizer.
- Concomitant use of valbenazine and strong CYP3A4 inducers should be avoided.
- Valbenazine dosage should be reduced by half for patients with moderate or severe hepatic impairment.
- No dose adjustment is necessary for patients with mild to moderate renal impairment.
- Dosing instructions for patients with severe renal impairment and for patients receiving a CYP2B6 inducer are pending further investigation.

### 7.1.5. Onset, Duration, and Durability of Efficacy Effects

#### *Onset*

As displayed in Table 44, the only placebo-controlled study that collected blinded central video rater AIMS data prior to the end of Week 6 was Study 1304. As shown in Figure 8, there was a numerical separation of the mean AIMS CFB between placebo and the two doses of valbenazine after as early as two weeks of treatment. As a pre-specified exploratory endpoint, the Applicant conducted MMRM analyses using the ITT analysis set, and both 40 mg and 80 mg doses of valbenazine were nominally superior to placebo at the end of Week 2 ( $p=0.001$  for 80 mg and  $p=0.0313$  for 40 mg). While these analyses were uncontrolled for multiplicity, they are suggestive that clinical improvement associated with valbenazine might occur prior to the 6-week efficacy endpoint.

#### *Durability*

The placebo-controlled study best suited for assessing treatment durability was 1304, as it used fixed doses of valbenazine (40 mg and 80 mg) in the 6-week placebo controlled period and randomized subjects who initially received placebo to receive doses of 40 mg or 80 mg for the 42-week extension period. As discussed in Section 6.1.2, there was no evidence suggesting the development of tolerance or a decrease in therapeutic response over the 6-week treatment period. In the 42-week extension period, there was similarly no evidence suggesting that efficacy decreased over time. From visual inspection of the entire study duration in Figure 26, it appears that the maximum effect of treatment (with the 80 mg dose) is reached by ~32-42 weeks. However, the caveat with this interpretation is that subject attrition over the course of

Clinical Review

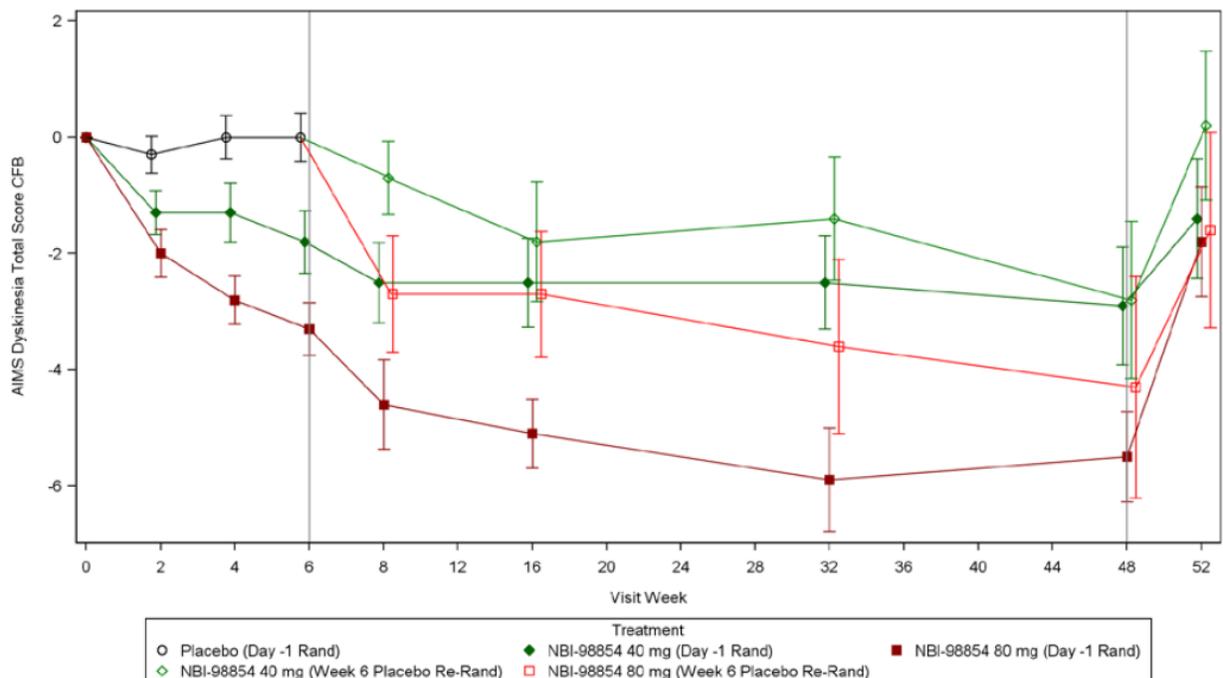
Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

the study may have biased the assessment of drug effect (i.e., if subjects with a more modest treatment response were more likely to discontinue study participation). Study 1402 also included 48 weeks of valbenazine treatment, but it only included blinded central AIMS video ratings at baseline and the end of Weeks 8 and 52 (the latter visit occurring four weeks after treatment discontinuation).

**Figure 26: Study 1304 - AIMS CFB, Entire Study Duration, ITT Analysis Set**



| Treatment Group (n=)        | Visit Week |    |    |    |    |    |    |    |    |
|-----------------------------|------------|----|----|----|----|----|----|----|----|
|                             | 0          | 2  | 4  | 6  | 8  | 16 | 32 | 48 | 52 |
| Placebo                     | 76         | 76 | 73 | 69 |    |    |    |    |    |
| Placebo → Valbenazine 40 mg |            |    |    |    | 32 | 29 | 27 | 24 | 24 |
| Placebo → Valbenazine 80 mg |            |    |    |    | 33 | 31 | 27 | 22 | 22 |
| Valbenazine 40 mg           | 70         | 70 | 64 | 63 | 59 | 50 | 37 | 34 | 34 |
| Valbenazine 80 mg           | 79         | 77 | 73 | 70 | 67 | 58 | 50 | 43 | 41 |

Source: Study 1304 Clinical Study Report, Figure 9 (p. 111). Error bars represent standard errors of the mean. NBI-98854 = valbenazine. Re-Rand refers to the randomization of subjects who received placebo for the first six weeks to valbenazine 40 mg or 80 mg for the remainder of the study. Refer to table above for the number of subjects with AIMS data per visit (including those with early termination data assigned to specific visits).

Persistence

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

The persistence of valbenazine treatment (defined as the effect after treatment is stopped) was best assessed with data from Study 1304. In this study, subjects who were receiving valbenazine 40 or 80 mg daily underwent AIMS central video ratings at the end of Week 48 and the end of Week 52, the final visit occurring four weeks after treatment discontinuation. Since the AIMS raters were blind to visit sequence and treatment and there was very little subject attrition between these visits, it was considered reasonable to assess the effect of treatment discontinuation on TD symptoms. Studies 1201 and -1202 also included follow-up visits 2-4 weeks after treatment discontinuation; however, AIMS ratings at the final visit were performed by on-site raters who were aware that subjects were no longer receiving treatment. Study 1402 did not include blinded AIMS central video ratings at visits between the end of Week 8 and the end of Week 48.

As displayed in Table 50, the mean and median changes from baseline decreased in magnitude from the end of Week 48 to the end of Week 52, suggesting the recurrence of TD symptoms in the absence of continued treatment. It is intriguing that the mean and median changes from baseline at the end of Week 52 remained less than 0; this suggests that either it may take a longer duration without treatment for full reversion to baseline TD severity or that some patients may not fully return to baseline TD severity after discontinuation.

**Table 50: Study 1304 - AIMS CFB Prior to and Following Treatment Discontinuation**

| Valbenazine Dose | AIMS Change from Baseline |      |         |        |         |      |         |        |
|------------------|---------------------------|------|---------|--------|---------|------|---------|--------|
|                  | Week 48                   |      |         |        | Week 52 |      |         |        |
|                  | N                         | Mean | Std Err | Median | N       | Mean | Std Err | Median |
| 40 mg            | 66                        | -3   | 0.52    | -3     | 66      | -1.2 | 0.52    | -0.5   |
| 80 mg            | 56                        | -5   | 0.64    | -6     | 55      | -1.3 | 0.69    | -1     |

*Source: Reviewer-created, using data from the analysis dataset A\_AIMS.XPT. Subjects were grouped according to treatment assignment from Weeks 6-48.*

## 7.2. Additional Efficacy Considerations

### 7.2.1. Considerations on Benefit in the Postmarket Setting

#### *Subpopulations*

Subjects enrolled in efficacy trials needed to have baseline TD severity of moderate or severe, as assessed by a blinded, external AIMS reviewer. This is the expected population who would be treated with valbenazine during post-market use. As displayed in Figure 11 (for Study 1304), valbenazine 80 mg reduced the mean AIMS total dyskinesia score regardless of the baseline severity, and subjects with more severe TD did not appear to have a less robust response to treatment on the primary efficacy measure.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Subpopulations that were under- or unrepresented in the submitted efficacy studies include:

- 1) Individuals who developed TD from the use of dopamine receptor antagonists for conditions other than chronic psychotic and mood disorders (e.g., gastrointestinal illness, certain neurological illnesses, other psychiatric illnesses).
- 2) Individuals with Asian race.
- 3) Individuals with higher psychiatric illness acuity (e.g., unstable symptomatology, active substance use disorders, etc.)
- 4) Individuals taking medications that were excluded in efficacy studies (e.g., strong CYP3A4 inducers, dopaminergic medications, psychostimulants, etc.)

There is no reason, at this time, to expect that TD symptoms would be less sensitive to treatment according to individuals' underlying illness or race, other than factors that could potentially alter drug pharmacokinetics (i.e., genotype of enzymes involved in valbenazine metabolism). It is possible that certain concomitant medications (i.e., dopamine receptor agonists and precursors, MAOIs, other VMAT2 inhibitors, CYP3A4/2D6 inducers or inhibitors) might affect efficacy based on pharmacokinetic or pharmacodynamic interactions, and these are presented in Section 7 (Drug Interactions) in product labeling.

### *Drug Administration and Use*

In the submitted efficacy studies, subjects self-administered valbenazine each morning and were instructed to not take the daily dose later than 6:00 pm. Since somnolence is a potential adverse reaction, it is possible that patients will take valbenazine at night, as is the case with many other psychiatric medications. Since steady state plasma concentrations are reached within one week and the half-lives of valbenazine and [+] - $\alpha$ -dihydrotrabenazine are 15-22 hours, it is not expected that taking the daily dose at a time other than morning would affect efficacy. Treatment compliance does not appear to be a significant concern with valbenazine, as it is judged to be reasonably well tolerated in clinical studies and discontinuations were approximately equal between placebo and valbenazine at the studied dosages.

#### **7.2.2. Other Relevant Benefits**

Valbenazine is proposed to be administered by mouth once daily. The proposed initial dose (40 mg) may be efficacious in a subset of patients but the titrated 80 mg dose has the most robust evidence supporting efficacy. This one-step titration is considered to be uncomplicated and may be considered by patients and providers to be a benefit of this drug. Once daily oral administration is also considered to be a benefit, as more frequent dosing is associated with poorer medication adherence [33]. These administration factors support the overall assessment of drug benefit.

### **7.3. Integrated Assessment of Effectiveness**

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

### *Evidentiary Standard*

The Federal Food, Drug, and Cosmetic Act (the Act) requires that a drug's effectiveness is established by substantial evidence, as defined by Section 505(d) as "evidence consisting of adequate and well-controlled investigations ... on the basis of which it could fairly and responsibly be concluded ... that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling..." As described in the FDA *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (1998), the usual requirement is for more than one adequate and well-controlled investigation.

In the current NDA, Study 1304 is considered to be the strongest evidence for the effectiveness of valbenazine. Assessment of the primary efficacy measure was conducted by central video raters who were blind to visit number, subject identification, and treatment, reducing inter-rater variability and expectancy bias associated with on-site raters. In this study, valbenazine 80 mg daily was statistically superior to placebo on the primary efficacy endpoint of the AIMS total dyskinesia score change from baseline at the end of Week 6 (Table 13). The 42-week valbenazine extension phase, which re-randomized subjects initially treated with placebo to receive either 40 or 80 mg valbenazine, provided additional evidence of continued drug effect, as the 80 mg dose was numerically superior to 40 mg at all time points (Figure 26). Finally, assessment of TD severity four weeks after completing valbenazine treatment found a clear worsening of TD symptoms in the absence of continued treatment.

Study 1202 provides additional evidence of effectiveness. Evidence from this study was considered less robust, however, because central AIMS video ratings occurred only at Baseline and the end of Week 6 (as opposed to visits at the end of Weeks 2 and 4 as in Study 1304). Furthermore, valbenazine was flexibly dosed between 25-75 mg (according to response and tolerability); this does not exactly replicate the assessment of the fixed 80 mg dose from Study 1304. Overall, the study results are considered adequate in supporting the results from Study 1304, as the majority of subjects were receiving the 75 mg dose during weeks 5 and 6 and subjects treated with valbenazine showed significant improvement over placebo on the same primary efficacy endpoint used in Study 1304 (Table 26).

### *Clinical Meaningfulness*

The primary efficacy endpoint was the change from baseline on the AIMS total dyskinesia score at the end of Week 6 (Table 5). The AIMS is widely used and accepted in clinical and research settings for assessing the presence and severity of TD. While there were no primary efficacy endpoints characterizing functional consequences of dyskinesic movements (which might directly answer the question of clinical meaningfulness) it is well-established that TD can be socially stigmatizing as well as adversely affect the ability of patients to perform activities of

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

daily living (Section 2.1). On face, a reduction in dyskinetic movements would be expected to reduce the adverse consequences frequently associated with TD.

As assessed in an exploratory analysis (Table 48), approximately 34% of subjects treated with valbenazine 80 mg daily (Study 1304) or flexible-dose valbenazine 25-75 mg (Study 1202) scored no more than “minimal” on any individual body area affected by TD after six weeks of valbenazine treatment. By this measure, the NNT (calculated using the change in proportion of valbenazine vs. placebo subjects meeting the criterion from baseline to the end of Week 6) was estimated as ~4-5. Evidence from the valbenazine extension phase (Figure 26) suggests that the maximal effect of treatment is not yet reached at the time of the primary efficacy endpoint, and symptoms may continue to improve in subsequent months. Altogether, given that there are no indicated treatments for TD and there is little evidence supporting any off-label treatments, it is expected that patients affected by TD, caregivers, and clinicians will appreciate the availability of this treatment on the market.

### *Presentation of Effectiveness in Labeling*

As discussed in Section 10.1, evidence supporting the effectiveness of valbenazine should be presented by describing the methods and results of Studies 1304 and -1202. The trial designs (duration, randomized treatments, eligibility criteria, endpoint description, etc.) should be communicated to contextualize the results. The study population should be described, including demographic variables and baseline characteristics such as the continued use of antipsychotic medication(s). The absolute change in AIMS total dyskinesia score from Baseline to the end of Week 6 should be presented (including placebo-subtracted differences), as should a histogram indicating the proportion of patients achieving different magnitudes of AIMS changes from baseline (to display the range of results in individuals). Finally, a graphical depiction of the entire Study 1304 results (similar to Figure 26) would be useful for communicating the effectiveness of treatment beyond the initial six weeks and the probable recurrence of TD symptoms in the absence of continued treatment.

## **8 Review of Safety**

---

### **8.1. Safety Review Approach**

The Applicant provided an integrated summary of safety, including detailed safety datasets. The Agency’s approach to the analysis of the safety of valbenazine consisted of a comprehensive review of the Applicant’s approach and results, in conjunction with our own independent analysis of over thirty submitted datasets.

Pre- and post-marketing experience of tetrabenazine (NDA 21894) was also examined. Tetrabenazine is a VMAT2 inhibitor approved for the treatment of chorea in Huntington’s

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

disease (HD). Tetrabenazine is used off-label for the treatment of TD [34]. Tetrabenazine and valbenazine share several active metabolites. Most notably, the active metabolite of valbenazine, [+]– $\alpha$ -dihydrotetrabenazine (also referred to as NBI-98782), is an enantiomer of an active metabolite of tetrabenazine. The metabolism of these two related products is presented in [Section 4.5.3](#).

Based upon the similar mechanism of action and multiple overlapping metabolites of valbenazine and tetrabenazine, here we briefly discuss historical safety concerns with tetrabenazine. Huntington’s disease is a progressive, inherited disorder that results in the progressive deterioration of motor functions and cognitive abilities due to neuronal cell death from mutant huntingtin protein. The decline is associated with a long-term 100% mortality rate and progressive worsening of psychiatric symptoms such as irritability, apathy, anxiety, depression, personality changes, decline in executive functions, and psychosis.

Tetrabenazine was submitted by Prestwick Pharmaceuticals as NDA 21894 for the treatment of chorea in Huntington’s disease. Tetrabenazine was reviewed at an Advisory Committee Meeting on December 6, 2007 and approved on August 16, 2008. The approval was based upon five studies: a 12-week placebo-controlled, randomized dose titration study, a short-term placebo-controlled withdrawal study, two long-term open-label studies (48 and 80 weeks), and a database of 280 patients entitled the “Compassionate Use of Tetrabenazine in the Treatment of Abnormal Movements” (IND (b) (4) at the Baylor College of Medicine in Houston, Texas).

In the examining the development program for the safety profile of the tetrabenazine, a significant baseline rate of adverse events due to progression of HD was expected. The primary pre-market safety analysis consisted of exploring whether there were any differences in effects related to tetrabenazine as compared to placebo. The tetrabenazine safety database consisted of 651 unique individuals who received tetrabenazine (514 subjects in Phase 2/3 controlled and open-label studies). The neurology products safety reviewer found an increased rate of depression (19% of tetrabenazine-treated v. 0% of placebo-treated subjects), which was typically treated with dose reduction. In open-label studies, depression occurred at similar rates in the tetrabenazine and placebo-treated groups, albeit dose reduction was often unsuccessful with one patient committing suicide after dose reduction. Based upon these and other findings, tetrabenazine was given a boxed warning for the risks of depression and suicidality, noting that “patients with active suicidality should not be treated with tetrabenazine, and if depression occurs on tetrabenazine therapy, the dose should be reduced, and consideration should be given to initiating antidepressant treatment. Tetrabenazine should be stopped if depression continues despite these measures.”

Other notable adverse events from the tetrabenazine program included Parkinsonism, anxiety, agitation, akathisia, somnolence, bradykinesia, and dysphagia. QT<sub>c</sub> prolongation was appreciated in QT studies, with an average prolongation of 7.5 msec for the 50 mg

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

tetrabenazine dose, as compared to 12 msec for moxifloxacin.

Post-market experience with tetrabenazine is addressed in detail in [Section 8.9](#). Briefly, it appears that the major post-marketing concerns derived from the off-label use of tetrabenazine are as follows:

- Extrapyrimal symptoms (EPS)
- Dyskinesia
- Fatigue/somnolence
- Depression
- Suicidal ideation

With respect to pre-clinical studies of valbenazine, I reviewed the preliminary findings of Darren Fegley, PhD, in order to shape my review. Briefly, valbenazine, and its major metabolite, NBI-98782 have no activity at the VMAT1 receptor and no appreciable affinity for dopaminergic (including D<sub>2</sub>), serotonergic (including 5-HT<sub>2B</sub>), adrenergic, histaminergic, muscarinic, and NMDA receptors. Valbenazine is metabolized via biotransformation (as opposed to biliary or renal clearance), and its metabolic products bind extensively in the pigmented region of the eye, with a half-life of ~1000 hours and a ratio of tissue to plasma radioactivity of ~4000. Thus, in my pre-market review, I will pay particular attention to visual symptoms, albeit it is likely that pre-market studies will not be powered to detect an effect (i.e. this would likely seen post-market).

Dr. Fegley's review also noted an increased incidence of stillbirth and postnatal mortality<sup>1</sup> at doses below the MRHD of 80 mg/day in rats. Additionally, valbenazine and its metabolites were detected in fetuses, milk, and pups following administration to pregnant or lactating rats. While no pre-market studies were conducted specifically in these populations, this will shape the review of any pregnancies that occur in the development program as well as product labeling.

In conclusion, valbenazine will be reviewed in accordance with standard procedure with particular attention to the agency's pre and post-market findings with tetrabenazine, another VMAT2 inhibitor, in conjunction with pre-clinical valbenazine experience. The safety review will pay particular attention to the following signals:

- Depression and worsening depression
- Suicidal ideation and behavior
- Extrapyrimal symptoms (tremor, dystonia, bradykinesia, hypertonia, etc.)
- Somnolence
- Akathisia, restlessness, etc.

---

<sup>1</sup> In rats, the rate of stillborn pups increased with drug: 14/22 litters had stillborn pups at the 3 mg/kg/day dose as compared to 4/21 litters in the control group. Additionally, at the 10 mg/kg/day dose there were 1720 litters with stillborn pups and 7/20 with total litter loss (no other dose group had total litter loss).

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

- Dysphagia, aspiration pneumonia, and other related symptoms
- Visual symptoms

## 8.2. Review of the Safety Database

### Overall Safety Population

The valbenazine clinical development program included 20 Studies:

- 14 Phase 1 Studies
- 4 Phase 2 Studies
- 2 Phase 3 Studies in patients with schizophrenia or schizoaffective disorder, or mood disorder

### Applicant Study Pooling for Analyses of Controlled Trials

The Applicant grouped studies for safety analyses by clinical trial phase and secondarily by dose. Clinical trial phase grouping was as follows:

**Table 51: Applicant Pooling of Phase 2/3 Controlled Trials for Safety Analyses**

| Trial Identity | Phase   | CTRL/Open | Trial Design   | Regimen/schedule/ route  | Treatment Duration/ Follow Up | Study Population   |
|----------------|---------|-----------|--|--|-------------------------------|--|
| 1201           | Phase 2 | CTRL      | Randomized, double-blind, placebo-controlled, parallel group study             | VBZ 100 mg PO qd x 2 wks, 50 mg PO qd x 4 weeks OR VBZ 50 mg PO qd OR PBO qd (1:1:2) | 6 weeks controlled            | Adults with schizoaffective or schizophrenia and TD  |
| 1202           | Phase 2 | CTRL      | Randomized, double-blind, placebo-controlled, dose titration study             | VBZ 25, 50, or 75 mg PO qd (flexible) or PBO PO qd (1:1)                             | 6 weeks controlled            | Adults with schizoaffective or schizophrenia, mood disorders, or GI disorder (treated with metoclopramide); and TD |
| 1304           | Phase 3 | CTRL      | Randomized, double-blind, placebo-controlled, parallel-group, fixed dose study | VBZ 40 mg, 80 mg, or PBO qd (1:1:1)  | 6 weeks controlled            | Adults with schizoaffective or schizophrenia, mood disorders; and TD   |

Source: Reviewer-created table adapted from Integrated Summary of Safety

VBZ = valbenazine, PBO = placebo, CTRL = controlled, QD = once daily, PO = per os (per mouth)

Notably, four patients with GI disorders and metoclopramide-induced TD from Study 1202 were excluded from this pooling and were analyzed separately.<sup>2</sup> The Applicant stated that this was due to subjects with GI disorders being ineligible for enrollment in Studies 1201 and 1304. However, this exclusion is likely artificial and incorrect as the proposed indication is for the

<sup>2</sup> These four subjects were numbered as follows: 2012001, 2042005, 2072001, and 2372002. One patient (2372002) experienced nausea and vomiting, and another patient (2012001) experienced moderate, increased constipation; diarrhea, dyspepsia, and fell once. These events are unlikely to be due to the study drug and are likely related to underlying, concomitant disease.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

treatment of tardive dyskinesia, not tardive dyskinesia in the setting exclusive of GI disorders.

Upon review, I disagree with the pooling of controlled trials. These trials are distinct in design and pooling is problematic. Namely, Study 1304 is a fixed dose study (placebo, 40 mg, and 80 mg) of 6 weeks duration. Study 1202 is a dose-titration study of 6 weeks duration, wherein subjects received either placebo or were placed on a titration schedule, starting at 25 mg and titrated up 25 mg every two weeks to a maximum of 75 mg. As patients underwent titration instead of being randomized to a fixed dose, a subject who underwent dose escalation achieved an optimal dose as determined by clinical judgment, which is distinct from independent randomization and assignment to a fixed dose.

Lastly, Study 1201 is also distinct from the previous two studies. Subjects were randomized to receive placebo, valbenazine 50 mg, or valbenazine 100 mg. The study was of 6 weeks duration; however, the 100 mg group underwent a scheduled dose reduction after 2 weeks to 50 mg, which was continued for a subsequent 4 weeks. Thus, Study 1201 combines a fixed-dose regimen with a dose-reduction regimen.

In conclusion, these studies cannot be pooled as Study 1304 is a fixed dose randomized, double-blinded, placebo-controlled trial; Study 1202 is a dose-titration study with imperfect blinding, and Study 1201 has a scheduled dose reduction combined with a fixed dose design. Therefore, each of these Studies will be examined independently, and then across controlled trials for consistency of effects (e.g. the adverse event of Parkinsonism was greater in drug v. placebo in one of three studies).

### *Applicant Study Pooling for Analyses for Open-Label Extension Trials*

In order to examine long-term safety, the Applicant pooled all Phase 2/3 open-label extensions. Notably, Study 1304 underwent an extension of a previously controlled trial.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 52: Applicant Pooling of Phase 2/3 Long Term Studies for Safety Analyses**

| Trial Identity | Phase   | CTRL/Open | Trial Design                            | Regimen/schedule/route             | Treatment Duration/ Follow Up | Study Population   |
|----------------|---------|-----------|---|------------------------------------|-------------------------------|--|
| 1201           | Phase 2 | OPEN      | Open-label extension                    | VBZ 50 mg PO qd                    | 6 weeks open label            | Adults with schizoaffective or schizophrenia and TD                  |
| 1304           | Phase 3 | OPEN      | Open-label extension                    | VBZ 40 mg or VBZ 80 mg PO qd (1:1) | 42 weeks                      | Adults with schizoaffective or schizophrenia, mood disorders; and TD |
| 1402           | Phase 3 | OPEN      | Open-label, fixed-dose escalation study | VBZ 40 mg -> 80 mg PO qd           | 48 weeks                      | Adults with schizoaffective or schizophrenia, mood disorders; and TD |

*Source: Reviewer-created table adapted from Integrated Summary of Safety*

*VBZ = valbenazine, PBO = placebo, CTRL = controlled, QD = once daily, PO = per os (per mouth)*

Upon review, I disagree with the Applicant. This pooling assumes that the hazard of adverse events is consistent per unit of time and neither cumulative (i.e. additive) nor multiplicative. As this is a new drug and the function of pre-market clinical trials is to establish safety, one cannot make this assumption.

Additionally, these studies are of vastly different durations. Study 1201 was a 6 week open label extension wherein all subjects received valbenazine 50 mg. Investigators in this open label extension were not required to re-consent study subjects. Study 1304 was a 42 week open-label extension whereby patients were re-randomized (1:1) to receive either valbenazine 40 mg or 80 mg. This study is distinct not just due to differences in duration, but also as patients had to re-consent for the open label extension, which potentially introduces selection bias as the subjects were not treatment-naïve and could decline to enroll in the open-label extension due to previous adverse reactions. Study 1402 was an open-label study lasting 48 weeks. For the initial 4 weeks, all subjects received valbenazine 40 mg. At the end of week 4, if the investigator deemed the subject (via CGI-TD) to be “minimally improved,” “minimally worse,” “much worse,” or “very much worse” and the safety and tolerability of the current dose were acceptable, then the subject could be titrated to an 80 mg dose. This titration introduces bias and is distinct from Study 1304, where subjects were randomized to the extension period dose.

Therefore, I disagree with the Applicant: the three open-label extension studies cannot be directly pooled due to their distinct design, duration, and dosing.

### *Applicant Study Pooling for Analyses for Phase 1 Trials*

The Applicant pooled single-dose arms of Studies 801, 901, 1102, 1203, 1204, 1301, 1401, and 1504 as “studies of healthy adults.” Multiple dose arms were analyzed separately. The Applicant rationalized that patient populations were similar (healthy adults).

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 53: Applicant Pooling of Phase 1 Single-dose Studies for Safety Analyses**

| Trial Identity | Phase   | CTRL/Open | Trial Design   | Regimen/schedule/ route  | Treatment Duration/ Follow Up                                       | Study Population           |
|----------------|---------|-----------|--|--|---|----------------------------|
| 801            | Phase 1 | CTRL      | Randomized, double-blind, placebo controlled, sequential dose escalation, four-period study  | VBZ solution 1, 2, 5, 12.5, 25, 50, 70 mg PO   | 4 single doses  | Healthy men                |
| 901            | Phase 1 | CTRL      | Randomized, double-blind, placebo controlled, sequential dose escalation, three-period study | Single dose: VBZ solution 75, 100, 125, 150 mg PO<br>Multiple ascending dose: VBZ solution 50, 100 mg PO | Single dose: 3 doses (2 active, 1 placebo)<br>Multiple dose: 8 days | Healthy men                |
| 1102           | Phase 1 | CTRL      | Randomized, 3-period crossover   | Solution and capsule: VBZ 25 mg PO   | Adults: 3 single doses at least 7 days apart<br>Elderly: 1 dose     | Healthy adults and elderly |
| 1203           | Phase 1 | CTRL      | Randomized, 2-period crossover   | Solution and capsule: VBZ 100 mg PO  | Single dose x 2   | Healthy adults             |
| 1204           | Phase 1 | OPEN      | Parallel-group, 2 cohorts  | VBZ solution 50 mg PO  | Single dose   | Healthy adult men          |
| 1301           | Phase 1 | CTRL      | Randomized, double-blind, parallel-group, placebo-controlled                                 | VBZ 300 mg PO  | Single dose   | Healthy adults             |
| 1401           | Phase 1 | CTRL      | Randomized, double-blind, 3-period crossover; PBO and moxifloxacin controlled                | VBZ 160 mg PO, Moxifloxacin 400 mg PO  | Single dose   | Healthy adults             |
| 1504           | Phase 1 | CTRL      | Randomized, 2-period crossover   | VBZ 40 mg or 80 mg   | 2 single doses  | Healthy adults             |

*Source: Reviewer-created table adapted from Integrated Summary of Safety*

*VBZ = valbenazine, PBO = placebo, CTRL = controlled, QD = once daily, PO = per os (per mouth)*

Upon review, I disagree with the Applicant’s interpretation of the use of this pool. Phase 1 studies in which subjects received a handful of doses do not provide meaningful safety information about a product which will generally be used for weeks to months, if not years if used as a chronic maintenance drug. Study 1401 is a three-arm, double-blind, controlled, 3-period crossover study to examine the effects of valbenazine on QT (and compare valbenazine to placebo and moxifloxacin). This single-dose study does not provide meaningful information about the long-term safety.

The Applicant analyzed several phase 1 studies separately. The multiple dosing portion of Study 901 was analyzed independently. Studies 1302, 1502, 1503, and 107 were “Drug-Drug Interaction” (DDI) Studies and were analyzed separately. These studies are described in more detail in the following table.

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 54: Applicant Drug-Drug Interaction Studies (Analyzed Independently)**

| Trial Identity | Phase   | Study Type | Trial Design   | Regimen/schedule/ route                  | Treatment Duration/ Follow Up                         | Study Population |
|----------------|---------|------------|----------------|--|---|------------------|
| 1302           | Phase 1 | DDI        | Fixed-sequence | VBZ 50 mg PO, Ketoconazole 200 mg PO BID | VBZ x 2 single doses, Ketoconazole 5 consecutive days | Healthy adults   |
| 1502           | Phase 1 | DDI        | Fixed-sequence | VBZ 80 mg, Rifampin 600 mg PO qd         | VBZ 2 single doses; Rifampin 10 consecutive days qd   | Healthy adults   |
| 1503           | Phase 1 | DDI        | Fixed-sequence | VBZ 80 mg, Digoxin 0.5 mg PO qd          | VBZ 7 multiple doses, Digoxin 2 single doses          | Healthy adults   |
| 1507           | Phase 1 | DDI        | Fixed-sequence | VBZ 80 mg qd, Midazolam syrup 2 mg PO qd | VBZ single dose, Midazolam 2 single doses             | Healthy adults   |

Source: Reviewer-created table adapted from Integrated Summary of Safety

VBZ = valbenazine, DDI = Drug-Drug Interaction, QD = once daily, PO = per os (per mouth)

The Applicant was correct in analyzing these Studies independently. However, the Applicant was incorrect in including these studies in the overall safety population. Study 901 is a multiple ascending dose study lasting only 8 days. These studies are designed to provide meaningful information regarding the short-term interactions between valbenazine and the cross-tested product. For example, Study 1302 was an open-label study in which subjects meeting the eligibility criteria were admitted to the study center for 10 days. Subjects received a single dose of valbenazine 50 mg on days 1 and 6, and on Days 5 through 0 the subjects received ketoconazole 200 mg PO BID. These studies do not provide meaningful safety information about chronic or maintenance use. Therefore, while these studies will be reviewed for relevant drug-drug interactions, they will not be included in the controlled studies safety population or overall safety population for long-term use.

Furthermore, the Applicant indicated several other Phase 1 studies were analyzed separately, including studies involving patients with hepatic impairment (Study 1303) and one study in children and adolescents with Tourette’s Syndrome (Study 1403). These studies represent distinct populations and cannot be pooled in the overall safety database.

**Table 55: Applicant Phase 1 Studies in Special Populations (Analyzed Independently)**

| Trial Identity | Phase   | Study Type | Trial Design   | Regimen/schedule/ route                                    | Treatment Duration/ Follow Up | Study Population   |
|----------------|---------|------------|--|--|-------------------------------|--|
| 1303           | Phase 1 | Hepatic    | Parallel-group, 4 groups; hepatic impairment                                 | VBZ 50 mg PO   | Single dose                   | Adults with mild, moderate, and severe hepatic impairment matched to healthy subjects                      |
| 1403           | Phase 1 | TS         | Parallel-group; 2 cohorts: children and adolescents; multiple ascending dose | VBZ 5, 10 mg PO (children); 10, 25, 50 mg PO (adolescents) | Multiple dose, 14 days qd     | Children with Tourette’s Syndrome (age 6 - 11 years), Adolescents with Tourette’s Syndrome (12 - 18 years) |

Source: Reviewer-created table adapted from Integrated Summary of Safety

VBZ = valbenazine, TS = Tourette’s Syndrome, QD = once daily, PO = per os (per mouth)

These studies were incorrectly included in the safety population. Study 1303 is a single dose, short term study to examine the interaction of valbenazine with ketoconazole. While this Study

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

provides meaningful information regarding single-dose administration in the setting of hepatic impairment, it provides no information regarding the longer-term use of the product.

Lastly, the Applicant analyzed two Phase 2 studies independently due to significant differences in design. Study 1001 was a dose titration study lasting 12 days and Study 1101 was a controlled study of 2 weeks duration. These studies are detailed in the following table.

**Table 56: Applicant Phase 2 Studies of Unique Design (Analyzed Independently)**

| Trial Identity | Phase   | CTRL/Open | Trial Design  | Regimen/schedule/ route              | Treatment Duration/ Follow Up   | Study Population                                    |
|----------------|---------|-----------|---|--------------------------------------|---------------------------------|---|
| 1001           | Phase 2 | OPEN      | Open-label extension, close titration                                     | VBZ 12.5 mg -> 25 mg -> 50 mg PO qd  | 12 days (4 days per dose)       | Adults with schizoaffective or schizophrenia and TD |
| 1101           | Phase 2 | CTRL      | Randomized, double-blind, placebo controlled, two-period cross-over study | VBZ 12.5 or 50 mg PO qd or PBO PO qd | 14 days VBZ and 14 days Placebo | Adults with schizoaffective or schizophrenia and TD |

Source: Reviewer-created table

VBZ = valbenazine, PBO = placebo, CTRL = controlled, QD = once daily, PO = per os (per mouth)

Upon review, I agree that it was appropriate for the Applicant to analyze these studies separately.

## Conclusions

### *Overall Safety Database Population Used for Analysis*

In order to determine the population of subjects who were ever exposed to a therapeutic dose of the study drug, I included Phase 1 trials (Studies 901, 1102, 1203, 1204, 1301, 1302, 1303, 1401, 1502, 1503, 1504, 1507), Phase 2 trials (1001, 1101 – 50 mg dose group only, 1201, 1202), and Phase 3 trials (1304, 1402).

Several Studies were excluded due to inappropriate population selection or a low dose. Study 801, a Phase 1 sequential dose escalation study, was excluded due to the low dose of study drug. Study 1403, a Phase 1 study in children was excluded as the Applicant is not seeking a pediatric indication and the doses were below the proposed therapeutic level. Study 1101, a Phase 2 randomized, double-blind, placebo-controlled, two-period crossover study included placebo and one of two doses of valbenazine (12.5 mg or 50 mg); the lower 12.5 mg dose of valbenazine was excluded. Based upon this, a total of 785 subjects received at least a single therapeutic dose of study drug, as compared to 846 subjects listed as exposed to any dose of drug in the Applicant's ISS.

### *Controlled Safety Population Used for Analysis*

I utilized a different approach to constructing and analyzing a controlled safety population. The three randomized, double-blind, placebo-controlled trials were analyzed independently for the safety profile of valbenazine. These studies were not pooled:

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

- Study 1201: 6 week controlled study comparing placebo, valbenazine 50 mg (fixed dose), and valbenazine 100 mg x 2 weeks followed by valbenazine 50 mg x 4 weeks
- Study 1202: 6 week dose titration study starting at 25 mg, with titration every 2 weeks, to a maximum dose of 75 mg
- Study 1304: 6 week fixed dose study comparing placebo, valbenazine 40 mg, and valbenazine 80 mg

In addition to looking at each of these controlled trials independently, safety profiles across trials will be examined for consistency of effects (albeit not directly pooled, e.g. 1 in 3 trials demonstrated an adverse reaction of Parkinsonism). Datasets utilized for analyzing the above pivotal controlled trials will be sourced from the Applicant's Analysis Dataset (Legacy) for each of the individual trials. Analysis datasets include demographic variables, randomized treatment, first study drug dose date, genotype classification, safety flag, ITT and per-protocol analysis flags

### *Prospective Observational Database Used for Analysis*

In order to increase the power to detect an adverse event or effect in long term use, a larger safety population was constructed. Recognizing the exceptional difficulty of pooling trials with different designs, doses, etc. the following safety database will be treated as an observational, prospective epidemiologic database, comprised of the following studies:

- 6 week controlled Studies 1201, 1202, and 1304 (analyzed as treated)
- Open-label extensions of Studies 1201, 1304, and 1402

This larger safety database was derived from the Data Analysis (ADAM) dataset derived from the 120-Day Safety Update, which the Applicant submitted on November 11, 2016. This updated dataset contained updates from the open-label extension Studies 1304 and 1402. The datasets were further revised to eliminate all Phase 1 studies and the two Phase 2 Studies (1001 and 1101) that I excluded from pooling due to significant differences in study design. This larger safety database, hereafter referred to as the "prospective observational database," will be analyzed as a large observational study (N=613), whereby subjects are exposed to varying doses of a drug for varying periods of time. This database shall be utilized to examine deaths, serious adverse events, dropouts, significant adverse events, and immunogenicity (rare events such as anaphylactic shock or angioedema).

Due to the differing trial designs and exposure data integrity concerns, Douglas Warfield, PhD, reconstructed exposure data on a per subject and per visit basis from the drug accountability data. The submitted Integrated Summary of Safety (ISS) did not represent study date alignment (study week) for individual subject dosing details. The pooled exposures dataset created was subsequently used to calculate the exposure (days) by subject identifier and by dose in order to accurately reflect the dose changes in the included studies. I used this exposure dataset as the basis for my review. Note that while this database includes unique individuals from Studies

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

1201, 1202, 1304, and 1402, that Study 1402 includes 50 subjects who were previously enrolled in the Phase 2 development program. Thus, not all subjects in the prospective observational safety database are valbenazine-naïve upon enrollment. Due to study-designated washout periods, this will likely not affect my analyses as I am primarily interested in events per person-time exposure per dose.

### 8.2.1. Overall Exposure

Per the [ICH E1 guideline](#), it is generally accepted that for drugs used for the long-term treatment of non-life threatening conditions, a clinical development program should include about 1500 subjects exposed to the study drug. To measure longer term exposure, it is expected that 300 – 600 patients be exposed for at least six months and that 100 patients be exposed for a minimum of one year.

Traditional ICH E1 recommended exposure time periods are displayed in the following table, along with additional exposure time points that take into account the clinical trial design in this development program.

**Table 57: Valbenazine Exposure to a Therapeutic Dose (per ICH guidelines & Specific to Development Program) in Safety Database**

*ICH E1 Guideline Exposure Categories*

| Duration of Exposure | Subjects (N) |
|----------------------|--------------|
| ≥1 day               | 785          |
| ≥6 months            | 241          |
| ≥12 months           | 2            |

*Development Program-Specific Exposure Categories*

| Duration of Exposure | Subjects (N) |
|----------------------|--------------|
| ≥36 weeks            | 201          |
| ≥40 weeks            | 185          |
| ≥42 weeks            | 151          |
| ≥44 weeks            | 118          |
| ≥46 weeks            | 109          |
| ≥48 weeks            | 66           |

*Source: Reviewer-created tables derived from exposure dataset*

While this development program does not strictly meet ICH E1 guidelines for single-dose exposure, due to the small overall patient population size (estimated at less than 135,000 patients in the US) within the range of an orphan drug, the long-term exposure population and overall development program are adequate. The safety database decreases in size significantly after 42 weeks due to a number of subjects in Study 1304 who received 6 weeks of placebo and were subsequently re-randomized at week 6 to valbenazine 40 mg or 80 mg. The exposure for pivotal studies was further delineated between controlled trials and open-label extensions, as displayed in the following table.

**Table 58: Safety Population, Size, and Denominators**

| <b>Exposure for Pivotal Studies in Defined Safety Database</b> |   |   |
|--|---|---|
| <b>Clinical Trial Groups</b>                                   | <i>Patients exposed to drug in all controlled trials conducted for TD (N)</i> | <i>Patients exposed to drug in open-label trials conducted for TD (N)</i> |
| Valbenazine  | 262   | 291   |
| Placebo  | 183   |   |

*Source: Reviewer-created table derived from exposure dataset*

This distribution represents adequate short-term controlled exposure complemented by long-term observational exposure in order to increase the power of the development program to detect rare and serious adverse events. The controlled safety database is further characterized as follows by person-years of exposure for the Phase 2/3 development program included in the safety database.

**Table 59: Person-Years Exposure for Controlled Safety Database**

| <b>Group (Placebo or VBZ dose)</b> | <b># of Subjects</b> | <b>Total Person-Years Exposure</b> |
|------------------------------------|----------------------|------------------------------------|
| Placebo                            | 180                  | 19.6                               |
| 25 mg                              | 51                   | 2.4                                |
| 40 mg                              | 387                  | 107.6                              |
| 50 mg                              | 145                  | 16.8                               |
| 75 mg                              | 34                   | 1.3                                |
| 80 mg                              | 215                  | 123.2                              |
| 100 mg                             | 27                   | 1.1                                |
|                                    | VBZ (All Doses)      | 252.4                              |

*Source: Reviewer-created table derived from exposure dataset*

The pivotal, randomized, controlled trials (Studies 1201, 1202, and 1304) will be examined individually for deaths, serious adverse events, dropouts, significant adverse events, treatment emergent adverse events, laboratory findings, vital sign trends, ECG trends, and common signs of immunogenicity (e.g. rash)

**8.2.2. Relevant characteristics of the safety population:**

The demographic features of the study population are displayed in the following table.

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 60: Demographic Features of Safety Database**

|                     |   | <b>Safety Population Characteristic<br/>(N = 613)</b> |
|---------------------|---|---|
| <i>Age</i>          | Mean (years)  | 56.4  |
|                     | Min (years)   | 26.0  |
|                     | Max (years)   | 84.0  |
|                     | Standard deviation (years)  | 10.0  |
|                     | Over 65 years of age (%)  | 16.2%   |
|                     | Over 75 years of age (%)  | 2.4%  |
| <i>Sex</i>          | Men   | 57.1%   |
|                     | Women   | 42.9%   |
| <i>Race</i>         | Caucasian (%)   | 59.9%   |
|                     | Black or African-American (%)   | 36.7%   |
|                     | Native American/Alaskan (%)   | 1.0%  |
|                     | Asian (%)   | 0.3%  |
|                     | Native Hawaiian/Pacific Islander (%)                                  | 0.5%  |
|                     | Other (%)   | 1.6%  |
| <i>Ethnicity</i>    | Hispanic or Latino (%)  | 29.5%   |
|                     | Not Hispanic or Latino (%)  | 70.5%   |
| <i>Weight (lbs)</i> | Mean  | 179.5   |
|                     | Min   | 92.0  |
|                     | Max   | 344.0   |
|                     | S.D.  | 38.6  |
| <i>BMI</i>          | Mean (mg/m <sup>2</sup> )   | 28.3  |
| <i>Diagnosis</i>    | Schizophrenia or schizoaffective disorder with neuroleptic-induced TD | 72.4%   |
|                     | Mood disorder with neuroleptic-induced TD                             | 26.9%   |
|                     | Gastrointestinal disorder with metoclopramide-induced TD              | 0.7%  |
| <i>Geography</i>    | USA   | 97.1%   |
|                     | Canada  | 1.3%  |
|                     | Puerto Rico   | 1.4%  |
|                     |   | N 613   |

*Source: Reviewer-created table from demographics datasets (DM.xpt) for Studies 1201, 1202, 1304, and 1402*

This population includes a wide range of patients with respect to age, gender, and race. Notably, the population represents a typical patient with longstanding schizophrenia, namely, middle-aged or older subjects, a slight preponderance of men, and a mix of Caucasian and African-American subjects. It is worth noting that few to no other groups (e.g. Asians) were included in this study, and that any PMC or PMR should be certain to include this group.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

The subjects represented patients with neuroleptic-induced TD who had either a diagnosis of schizophrenia, schizoaffective disorder, or a mood disorder. The other descriptive characteristics (e.g. BMI, height, weight) are similar to those of the US population in which this product is expected to be used.

Concomitant medications were grouped according to primary and secondary pharmacologic activity. For example, chlorpromazine is a typical antipsychotic with additional recognized, significant anticholinergic activity. Thus, it would be classified as a typical antipsychotic while also counting as an “anticholinergic agent.” These groupings are described in detail in [Section 8.3.1](#), and the results are described in the following table.

**Table 61: Concomitant Medications for Safety Population**

| Concomitant Medication Properties | N   | %     |
|-----------------------------------|-----|-------|
| Anticholinergic agent             | 348 | 56.8% |
| Antihistaminergic agent           | 137 | 22.3% |
| Antipsychotic - Atypical          | 456 | 74.4% |
| Antipsychotic - Typical           | 119 | 19.4% |
| Benzodiazepine                    | 218 | 35.6% |
| Centrally Acting Muscle Relaxant  | 37  | 6.0%  |
| Dopamine agonist                  | 1   | 0.2%  |
| Opioid                            | 78  | 12.7% |
| Psychostimulant                   | 4   | 0.7%  |

*Source: Reviewer-created table from concomitant medications datasets (CM.xpt) for Studies 1201, 1202, 1304, and 1402 (medication properties as classified by the reviewer)*

Notably, almost every patient was on an antipsychotic. Nearly half of the patients were also on a drug with known anticholinergic effects, while one-third were on a benzodiazepine, either long or short-acting. Few patients were on stimulants and only one patient was on a dopamine agonist. Interactions with concomitant medications will be examined later in this review.

Lastly, the geography of the study sites is not considered to be determining factor, as the study sites were all located in the United States, Canada, and Puerto Rico; all of which have a significant compliance presence and surveillance.

### 8.2.3. Adequacy of the safety database:

The clinical safety database for this program does not meet ICH E1 standards; however, the 6 month and 12 month exposures are very close to ICH E1 guidelines with over 241 patients receiving exposure for at least 6 months, 185 patients exposed for at least 40 weeks, 66 patients being exposed for 48 weeks and 2 patients exposed for 52 weeks (1 year). This

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

exposure adequately characterizes long-term use for a study drug which has an estimated population size within the range for an orphan drug. The population over 65 years of age is 16.2%, likely adequately reflecting the patient population in question. The broad distribution of concurrent psychiatric disease is reflective of the TD population (i.e. patients with psychiatric disease necessitating long-term use of antipsychotics).

### 8.3. Adequacy of Applicant's Clinical Safety Assessments

#### 8.3.1. Issues Regarding Data Integrity and Submission Quality

There were multiple concerns regarding the quality of the submission and data, and upon thorough review it is clear that the applicant did not appropriately review their package prior to submission to the agency. First, during a clinical development program, it is expected that patients will experience increased detection of other, unrelated diseases because of clinical surveillance. That is, research subjects undergo close, periodic clinical surveillance in the form of repeated study visits, history and physical (including a lymph node exam) exams, ECG assessments, diagnostic labs, thus increasing the sensitivity of the healthcare system to detect disease.

The thoroughness and completeness of the execution of the Applicant's clinical assessments in their development program is called into question by two events. Subject 413-4012 in Study 1402 successfully completed the 48 week open-label study, and subsequently unexpectedly died three days later from breast cancer. This suggests inadequate clinical surveillance.

Additionally, Subject 1304-328-3002 had a positive urine pregnancy test at Week 20, after receiving valbenazine 80 mg for 14 weeks. The estimated date of conception was approximately 1 week prior to starting the study drug, and the subject had a negative urine pregnancy test at each study visit until Week 20. The subject stopped the study drug, and had an uncomplicated delivery of a normal female infant at 36 weeks of gestation. The hospital records noted the last menstrual period (LMP) as approximately 1 week prior to starting the study drug. This implies that the Applicant's study sites relied solely upon urine pregnancy tests to ascertain pregnancy status, and did not query the patient as to their LMP (or menstrual history) as a low-cost and rapid secondary verification source of pregnancy status. Many urine pregnancy tests rely upon antibodies to hCG to trigger color change signaling pregnancy to the user. These test many be less sensitive than previously believed.[35, 36]

Secondly, in examining the 120-day safety update, there appear to be errors in the ADEX dataset. Study 1304 is a 6 week controlled trial followed by a 42 week open label extension. Thus, maximum drug exposure is 48 weeks, or 336 days. Study 1402 is an open label Study lasting 48 weeks, or 336 days. Multiple subjects in both trials have a listed duration of treatment exceeding this period. For example, Subject ID 382-3002 in Study 1304 has a listed exposure of 356 days and Subject ID 448-4001 in Study 1402 has a listed exposure of 342 days.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

The study protocols specify study windows, for example, for the controlled phase of Study 1304 has a study window of +/- 3 days whereas the open label extension and end of study visits have a visit window of +/- 6 days. The Applicant was queried regarding this discrepancy, and in summary replied that the study windows could be “stacked,” allowing, for example, a maximum of exposure of 408 days in the case of Study 1304. This stacking (as opposed to sticking with the original study clock) was not specified in the original study protocol.

There were numerous issues with the quality and organization of the data submission. A selection of examples follows:

1. The Legacy Analysis Dataset for Study 1201 had the placebo group coded two ways – “Placebo” and “Placebo/50mg.” Upon examination, it became clear that the former included placebo-treated subjects who did not enter the open label extension (i.e. dropped out). The submitted data dictionary did not specify this.
2. The Adverse Event Legacy dataset for Study 1201 has originally reported AE terms that are very similar to MedDRA preferred terms. This is different from other adverse event datasets that the Applicant submitted, wherein the reported AE terms are very different from MedDRA preferred terms.
3. The Adverse Event Legacy dataset for Study 1304 has originally reported AE terms that seem unusually specific for a psychiatric study site investigator, e.g. “intestinal bacterial floral disturbance.”
4. Datasets for controlled and open-label periods were submitted together, as opposed to separately.
5. For multiple psychiatric scales, the datasets submitted varied across studies. For example, for the Barnes Akathisia Scale, the BARS.xpt datasets for Studies 1201 and 1202 lacked a change from baseline; however, the dataset for Study 1304 included a change from baseline computation. The SAS.xpt dataset included ethnicity and race in Study 1201; however, it did not in Study 1202. This disorganization increased the data cleaning and computational work required in the review, and led to questions about the thoroughness and accuracy of the applicant’s ISS.

There were significant issues regarding the classification of concomitant medications. Multiple medications of interest were classified incorrectly; for example, hydroxyzine, an antihistamine, was classified as a benzodiazepine and clonazepam was classified as an anti-epileptic, benzodiazepine, benzodiazepine [*sic*], and as a “benzodiazepines”

Consequently, the concomitant medications legacy datasets for Studies 1201, 1202, 1304, and 1402 were combined and each medication was reviewed for relevance to the safety review, and if necessary, reclassified. Additional pharmacologic activity classifications were created in order to identify possible class interactions. Note that drugs that are classified in multiple classes are counted in both classes in analyses. For example, diphenhydramine is both an anticholinergic and antihistaminergic agent. The antipsychotics are grouped in the following

Clinical Review  
 Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH  
 NDA 209241  
 Ingrezza (valbenazine)

table.

**Table 62: Antipsychotic Product Groupings for Concomitant Medications**

| <b>Agent Properties</b>                              | <b>Product</b>           |
|--|--------------------------|
| <i>Typical Antipsychotic</i>                         | Flupentixol              |
|  | Fluphenazine             |
|  | Haloperidol              |
|  | Haloperidol decanoate    |
|  | Loxapine                 |
|  | Lurasidone hydrochloride |
|  | Perphenazine             |
|  | Promethazine             |
|  | Tiotixene                |
|  | Thioridazine             |
| Trifluoperazine                                      |                          |
| <i>Typical Antipsychotic, Anticholinergic agent</i>  | Chlorpromazine           |
|  | Hydroxyzine embonate     |
| <i>Atypical Antipsychotic</i>                        | Aripiprazole             |
|  | Asenapine                |
|  | Brexpiprazole            |
|  | Iloperidone              |
|  | Lurasidone               |
|  | Olanzapine               |
|  | Paliperidone             |
|  | Quetiapine               |
|  | Risperidone              |
| Ziprasidone  |                          |
| <i>Atypical Antipsychotic, Anticholinergic agent</i> | Clozapine                |

*Source: Reviewer-created table*

Anticholinergic and antihistaminergic products were classified as follows.

Clinical Review  
 Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH  
 NDA 209241  
 Ingrezza (valbenazine)

**Table 63: Grouping of Anticholinergic and Antihistaminergic products for Concomitant Medications**

| <b>Agent Properties</b>                         | <b>Product</b>        |
|---|-----------------------|
| <i>Anticholinergic agent</i>                    | Amitriptyline         |
|   | Benzatropine          |
|   | Benzatropine mesilate |
|   | Clomipramine          |
|   | Desipramine           |
|   | Dicycloverine         |
|   | Doxepin               |
|   | Oxybutynin            |
|   | Procyclidine          |
|   | Tolterodine           |
|   | Trihexyphenidyl       |
| <i>Anticholinergic, Antihistaminergic agent</i> | Benadryl cold and flu |
|   | Cyproheptadine        |
|   | Dimenhydrinate        |
|   | Diphenhydramine       |
|   | Imipramine            |
|   | Meclozine             |
|   | Notriptyline          |
| <i>Antihistaminergic agent</i>                  | Hydroxyzine           |

*Source: Reviewer-created table*

Lastly, other CNS-active drugs (e.g. products with a significant sedation profile, opioids, benzodiazepines, etc.) were grouped as follows in order to examine drug-drug interactions in the AE profiles.

Clinical Review  
 Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH  
 NDA 209241  
 Ingrezza (valbenazine)

**Table 64: Grouping of other CNS Active Drugs for Concomitant Medications**

| <b>Agent Properties</b>                          | <b>Product</b>             |
|--|----------------------------|
| <i>Benzodiazepine</i>                            | Alprazolam                 |
|  | Benzodiazepine derivatives |
|  | Buspirone                  |
|  | Buspirone hydrochloride    |
|  | Chlordiazepoxide           |
|  | Clonazepam                 |
|  | Diazepam                   |
|  | Lorazepam                  |
|  | Oxazepam                   |
| <i>Muscle Relaxants, Centrally Acting Agents</i> | Baclofen                   |
|  | Carisoprodol               |
|  | Cyclobenzaprine            |
|  | Methocarbamol              |
|  | Tizanidine                 |
| <i>Sedating</i>                                  | Fiorinal                   |
|  | Gabapentin                 |
|  | Lithium                    |
|  | Topiramate                 |
|  | Trazodone                  |
|  | Valproate semisodium       |
|  | Valproate semisodium       |
|  | Valproic acid              |
| <i>Opioids</i>                                   | Fentanyl                   |
|  | Hydrocodone                |
|  | Hydrocodone compound       |
|  | Methadone                  |
|  | Morphine                   |
|  | Oxycocet                   |
|  | Oxycodone                  |
|  | Oxymorphone                |
|  | Panadeine co               |
|  | Tramadol                   |
|  | Vicodin                    |
| <i>Dopamine agonist</i>                          | Bromocriptine              |
| <i>Psychostimulants</i>                          | Atomoxetine                |
|  | Caffeine                   |
|  | Modafinil                  |

Source: Reviewer-created table

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

### 8.3.2. Categorization of Adverse Events

The Applicant defined an Adverse Event (AE) in the study protocols as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event was considered drug related. Clinically significant changes in clinical status, ECG, laboratory values (outside of an AE), or physical examinations were additionally classified as AEs. That is, AEs may represent worsening of a condition present at the start of a study (severity, frequency, etc.), deterioration due to the primary illness under investigation, drug interaction, and etc. AEs were evaluated for duration, intensity, frequency, seriousness, outcome, actions taken, and investigator-perceived relationship to the study drug. The study protocols noted that subjects should be questioned in a general way and to avoid asking about the occurrence of any specific symptom. This seems reasonable; albeit more difficult for study investigators to determine a relevant diagnosis (if one exists for the AE in question).

Uniquely, Studies 1304 and 1402 noted that any worsening of the suicidal ideation section of the C-SSRS as compared to the baseline visit (Day -1) will be noted as an AE. This was not explicitly classified as an AE in Studies 1201 and 1202. Notably, all four study protocols note that suicidal ideation or behavior type 4 or 5 is a reportable SAE within 24 hours of occurrence. Examination of the raw data notes differential SI rates across the controlled period of Studies 1201, 1202, and 1304. Since it is unclear if Studies 1201 and 1202 explicitly included SI as an explicit AE, in addition to the AE datasets, the CSSRS data will be relied upon to calculate SI/SA AE event rates in a more precise and accurate fashion.

The Applicant noted, and upon my review I concur, that the following are not considered AEs:

- Continuous persistent disease/symptoms present before drug administration, unless it progresses or increases in severity following drug administration
- Recurrence of signs and symptoms of TD, unless worsened from baseline<sup>3</sup>
- Changes in orthostatic blood pressure or pulse without symptoms<sup>4</sup>
- Pregnancy<sup>5</sup>

The Applicant graded events as follows:

- *Mild*: transient and requiring minimal treatment. Little to no interference with activities of daily living (ADLs)

---

<sup>3</sup> This would be a marker of lack of efficacy, not an AE

<sup>4</sup> Vital sign changes are examined in depth in [Section 8.4.7](#). Please note that this was considered in AE in Study 1201, but not in Study 1202, 1304, and 1402.

<sup>5</sup> Patients were counseled at all visits to use two forms of non-hormonal contraception or hormonal contraception until the end of the follow-up visit. If a subject believed that they were pregnant, they were to discontinue study medications and return to the study site within 24 hours to undergo serum pregnancy tests. All pregnancies were to be followed until resolution (termination or birth).

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

- *Moderate*: alleviated with specific therapeutic intervention, and interfering with ADLs, causing discomfort without significant or permanent risk of harm
- *Severe*: interrupts ADLs, significantly affects clinical status, or may require intensive therapeutic intervention

While not explicitly stated in the study protocols, for the purposes of my analysis I will code the severity as follows: Mild (1), Moderate (2), and Severe (3).

The Applicant defined the relationship of AEs to study drug as follows:

- Definite: a reaction that follows a reasonable temporal sequence from administration, and that is confirmed by stopping or reducing the dosage, and reappearance of the reaction upon repeated exposure
- Possible: an AE in which there is a reasonable possibility that the drug caused the event
- Unlikely: a reaction that follows a reasonable temporal sequence following administration, but could reasonable be explained by known characteristics of the subject's clinical state
- Not related: any event that does not meet the above criteria

Upon my review, I agree with these classifications, albeit will make my own independent determination of whether an AE is related to the study drug.

Serious AEs (including death), pregnancy, events of suicidal behavior or ideation type 4 or 5 (active SI with some intent to act albeit without a plan, or active SI with intent and a specific plan; both based upon the C-SSRS) were to be reported within 24 hours to the medical monitor or Applicant. SAEs were recorded until 30 days after the last dose of study drug. All AEs were followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up. Any resolution of an AE is to be recorded.

The Applicant defined the following as a serious adverse event (SAE):

- Death
- Life-threatening AE (Investigator or Applicant viewed an immediate risk of death)
- Inpatient hospitalization or prolongation of an existing hospitalization (this includes complications that prolong a hospitalization)
- Persistent or significant incapacity or substantial disruption of a subject's ability to perform normal life functions
- Congenital anomaly/birth defect
- Important medical events that do not fall into the above categories but that the Investigator deems to be serious (e.g. bronchospasm requiring intensive treatment in an emergency room)

I agree with the Applicant's inclusion of the above as SAEs. I disagree that emergency room (ER) visits were not included as a SAE, albeit recognize that some of them will fall into the last category of "investigator-determined" SAEs.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Lastly, across all studies, AEs were categorized by MedDRA Version 12.0 system organ class (SOC) and preferred term (PT). I personally reviewed each AE (over 1,500 AEs were audited) for the coding of investigator-reported AEs into MedDRA PT. My findings are as follows:

- For the controlled period and open-label extension of Study 1201, I agree with the Applicant's AE PT coding
- For Study 1202, I agree with the Applicant's AE PT coding
- For the controlled period and open-label extension of Study 1304, I agree with the Applicant's AE PT coding
- For Study 1402, I agree with the Applicant's AE PT coding

Upon review, there were a significant number of foot fractures across Studies, listed in the following table.

**Table 65: Listing of Individually Coded Foot Fractures**

| Subject ID | Study | AE PT                          |
|------------|-------|--------------------------------|
| 139-1009   | 1201  | Foot fracture                  |
| 332-3001   | 1304  | Broken foot, fractured patella |
| 335-3004   | 1304  | Fractured left foot            |
| 354-3003   | 1304  | Broken second left toe         |
| 465-4003   | 1402  | Fractured right foot           |

*Source: Reviewer-created table, sourced from legacy adverse event datasets (AE.xpt) for Studies 1201, 1202, 1304, and 1402*

An Information Request (IR) was sent to the Applicant for additional information. The Applicant's replies are summarized in the following table.

**Table 66: Additional Information from Applicant Regarding Foot Fractures**

| Subject ID | Study | Summarized Sponsor Reply  |
|------------|-------|---|
| 139-1009   | 1201  | The subject stepped on uneven pavement while crossing the street, rolled his ankle, and fractured his foot                          |
| 332-3001   | 1304  | Subject slipped on an icy sidewalk and fractured her foot. The subject was later in a car accident resulting in a fractured patella |
| 335-3004   | 1304  | The subject's foot was run over by a car when crossing the street   |
| 354-3003   | 1304  | No additional information available   |
| 465-4003   | 1402  | The patient slipped on a rug and fractured her foot while getting out of the bathtub  |

*Source: Reviewer-created table based upon response to Information Request sent to applicant on January 27, 2017*

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Upon review, two of the above events will be additionally categorized under the AE grouping “Balance disorders/Falls” (groupings to be described in the following paragraphs). Specifically, the foot fracture in Subject 139-1009 (Study 1201) and in Subject 354-3003 (Study 1304) were deemed likely to be related to a balance disorder, and will be additionally coded as such.

Upon review of the MedDRA terminology for adverse events, it is apparent that the granularity of MedDRA facilitates splitting of some adverse event terms to an extent that may not be clinically useful. Therefore, for the purposes of this review, I grouped AE preferred terms under a common term for calculation of reporting rates in the following manner. Firstly, multiple gastrointestinal, endocrine, and constitutional symptoms were inappropriately split by MedDRA preferred terms. In order to better understand these effects, these terms were grouped for FDA analysis as follows:

**Table 67: FDA Grouping of MedDRA PTs for GI, Endocrine, & Constitutional AEs**

| FDA Grouping       | MedDRA AEPTs                         |
|--------------------|--------------------------------------|
| Abdominal pain     | Abdominal pain                       |
|                    | Abdominal pain lower                 |
|                    | Abdominal pain upper                 |
|                    | Abdominal tenderness                 |
| Decreased appetite | Anorexia                             |
|                    | Decreased appetite                   |
| Diabetes           | Diabetes mellitus                    |
|                    | Diabetes mellitus inadequate control |
| Glycosuria         | Glucose urine present                |
|                    | Glycosuria                           |
| Hyponatremia       | Hyponatraemia                        |
|                    | Hyponatraemia syndrome               |
| Weight Loss        | Abnormal loss of weight              |
|                    | Weight decreased                     |

Source: Reviewer-created table

Additionally, it was noted that many hematologic terms were inappropriately split. For example, anemia was divided into four terms. Hematologic, respiratory, and dermatologic AE patients of note were grouped in the following table.

**Table 68: FDA Grouping of MedDRA PTs for Hematologic, Respiratory, & Dermatologic AEs**

| <b>FDA Grouping</b> | <b>MedDRA AEPTs</b>                   |
|---------------------|---------------------------------------|
| Anemia              | Anaemia                               |
|                     | Haematocrit decreased                 |
|                     | Haemoglobin decreased                 |
|                     | Microcytic anaemia                    |
|                     | Red blood cell count decreased        |
| Bronchospasm        | Asthma                                |
|                     | Chronic obstructive pulmonary disease |
| Leukopenia          | Leukopenia                            |
|                     | Neutropenia                           |
|                     | Agranulocytosis                       |
| Rash                | Rash                                  |
|                     | Rash generalised                      |
|                     | Rash maculo-papular                   |
|                     | Rash papular                          |
|                     | Urticaria                             |
| Sinusitis           | Acute sinusitis                       |
|                     | Allergic sinusitis                    |
|                     | Rhinitis                              |
|                     | Rhinitis allergic                     |
|                     | Sinus congestion                      |
|                     | Sinusitis                             |

*Source: Reviewer-created table*

Given the post-market experience of tetrabenazine, another VMAT2 inhibitor on the market approved for the treatment of chorea in Huntington’s Disorder, we expected a signal for balance/fall, somnolence, and extrapyramidal symptoms. Recent evidence [37] has demonstrated that the SLC18 family is involved in multiple exocytotic releases of neurotransmitters, and that this family includes both vesicular acetylcholine transporter (VACHT), VMAT1, and VMAT2. Therefore, adverse events were also examined for an anticholinergic signal. These neurologic AEs were grouped in my review in the following manner.

**Table 69: FDA Grouping of MedDRA patients for Neurologic AEs<sup>6</sup>**

| <b>FDA Grouping</b>     | <b>MedDRA AEPTs</b>      |
|-------------------------|--------------------------|
| Anticholinergic effects | Urinary retention        |
|                         | Constipation             |
|                         | Diplopia                 |
|                         | Vision blurred           |
|                         | Dry mouth                |
|                         | Disturbance in attention |
|                         | Amnesia                  |
|                         | Delirium                 |
| Balance disorders/Fall  | Balance disorder         |
|                         | Ataxia                   |
|                         | Dizziness                |
|                         | Fall                     |
|                         | Gait disturbance         |
| Drooling                | Drooling                 |
|                         | Salivary Hypersecretion  |
| Dyskinesia              | Dyskinesia               |
|                         | Tardive dyskinesia       |
| EPS - Akathisia         | Akathisia                |
|                         | Restlessness             |
|                         | Restless legs syndrome   |
| EPS - Non-Akathisia     | Dystonia                 |
|                         | Extrapyramidal disorder  |
|                         | Parkinsonism             |
|                         | Muscle rigidity          |
|                         | Tremor                   |
|                         | Muscle spasms            |
|                         | Cogwheel rigidity        |
| Somnolence              | Malaise                  |
|                         | Sedation                 |
|                         | Somnolence               |
|                         | Fatigue                  |

*Source: Reviewer-created table*

Restless legs syndrome was reported originally by the site investigator as an increase in restless legs syndrome, potentially representing akathisia. Lastly, numerous infections were noted, and

<sup>6</sup> In the product labeling, for clarity EPS – Akathisia is referred to as “Akathisia”

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

were grouped as follows. It is worth noting that infections overall (i.e. these categories further combined) will be examined as a whole.

APPEARS THIS WAY ON ORIGINAL

**Table 70: FDA Grouping of MedDRA PTs for Infectious AEs**

| <b>FDA Grouping</b>     | <b>MedDRA AEPTs</b>               |
|-------------------------|-----------------------------------|
| Infection - Respiratory | Bronchitis                        |
|                         | Bronchitis chronic                |
|                         | Influenza                         |
|                         | Nasopharyngitis                   |
|                         | Parainfluenzae virus infection    |
|                         | Pneumonia                         |
|                         | Pneumonia aspiration              |
|                         | Respiratory track congestion      |
|                         | Upper respiratory tract infection |
| Infection - Soft tissue | Abscess limb                      |
|                         | Abscess soft tissue               |
|                         | Cellulitis                        |
|                         | Cellulitis staphylococcal         |
|                         | Furuncle                          |
|                         | Staphylococcal infection          |
|                         | Subcutaneous abscess              |
| Infection - GU          | Dysuria                           |
|                         | Prostatitis                       |
|                         | Pyelonephritis acute              |
|                         | Urinary tract infection           |
|                         | Vulvovaginal mycotic infection    |
| Infection - Other       | Acute tonsillitis                 |
|                         | Pharyngitis                       |
|                         | Body tinea                        |
|                         | Tinea cruris                      |
|                         | Tooth abscess                     |
|                         | Ear infection                     |
|                         | Otitis externa                    |
|                         | Eye infection                     |
|                         | Gingival infection                |
|                         | Onychomycosis                     |
|                         | Oral herpes                       |
|                         | Viral infection                   |
| Infection - GI          | Gastric infection                 |
|                         | Gastroenteritis                   |
|                         | Gastroenteritis viral             |

*Source: Reviewer-created table*

Notably, nasopharyngitis represents MedDRA coding for the “common cold.”

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

### 8.3.3. Routine Clinical Tests

#### *Study 1402*

Per the study protocol, all subjects were screened via a general medical history and psychiatric history upon study entry at Day -1. Specifically, the subject's age at diagnosis of schizophrenia or schizoaffective disorders or mood disorder and the age at TD diagnosis would be gathered. Complete physicals were conducted at each screening visit (end of weeks 4, 8, 16, 20, 24, 28, 32, 36, 40, 44, and 48) and at the follow-up visit (end of week 52) or alternatively, at study termination. Weight was recorded with subjects wearing "ordinary indoor clothing without shoes." With randomization across study group and site, seasonal variation in clothing layers is unlikely to present artificial weight gain or weight loss.

Vital signs were collected via the same schedule (i.e. at study visits) and prior to any scheduled blood sample collection. Measures collected included orthostatic blood pressure (diastolic, systolic), pulse rate, respiratory rate (supine only), and oral body temperature. Pulse was measured for 30 seconds and blood pressure was measured after 5 minutes supine and after 2 minutes standing.

Routine safety labs were analyzed at a central lab and assessed at screening, Day -1, during treatment (end of Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and at the follow-up visit (end of Week 52) or at early termination as applicable. Labs collected at each visit include hematology (e.g. WBC count with differential, hematocrit, hemoglobin, platelet count, etc.), chemistry (standard "Chem 7" labs along with LDH, alkaline phosphatase, AST, ALT, GGT, CK, total bilirubin, total cholesterol, triglycerides, total protein, and glucose), and urinalysis.

ECG 12-lead was collected in triplicate (1 to 3 minutes apart) after the subject had lain supine for at least five minutes. ECG parameters were measured by the machine and were interpreted by the investigator. If deemed necessary by the investigator, the ECGs would be confirmed by a cardiologist or internist. As many site investigators are not internists and ECG machine algorithms are diagnostically inaccurate (albeit they measure intervals appropriately), it would have been appropriate if all ECGs underwent blinded, central review by an internist or cardiologist.

Notably, screening for alcohol (via breathalyzer) and a urine drug screen were conducted at screening and Day -1, in addition to being conducted at random throughout the study. The protocol specified that subjects with a positive cannabinoid result may be allowed to participate in the study presuming that they agree to refrain during study participation. This is less than ideal, as cannabinoids may interfere with study assessments (e.g. of depression) and subject attestation is not the same as continued random testing with subsequent potential removal from the study (this approach is superior to dropping the subjects from the study).

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Subjects who were visibly intoxicated were not allowed to participate.

Serum prolactin was assessed at Day -1, during treatment (end of weeks 4, 12, 24, 36, and 48) and at the follow-up visit (end of week 52) or upon early termination. Pregnancy testing was performed at each study visit in female subjects who had not been postmenopausal for at least 1 year.

Any abnormalities found triggered a repeat analysis until the cause of the abnormality was determined, until the value returned to baseline, or until the investigator deemed the abnormality to be of no clinical significance. Normal values for most lab assessments were defined in the statistical analysis plan. As repeat analysis is also subject to regression to the mean, I will use the first reported abnormal lab value in my analyses (albeit report as needed additional follow-up lab values to show stability, resolution, or other important safety information).

Suicidal ideation and behavior was assessed via the Columbia-Suicide Severity Rating Scale (C-SSRS), a validated scale. Subjects were assessed as per the same schedule as standard labs, starting at screening. Administration was by the site investigator or individuals whom had completed C-SSRS certification. Per the Applicant's study protocol, any worsening from baseline (Day -1) to the SI section will be documented as an AE, and appropriate psychiatry intervention will be taken. This does not take into account that subjects may improve, and subsequently worsen.

The Barnes Akathisia Rating Scale (BARS) was utilized to assess for drug-induced akathisia (subjective and objective items). The Simpson-Angus Scale (SAS) was utilized to evaluate for drug-induced Parkinsonism and other extrapyramidal symptoms. Administration of BARS and SAS by the investigator or other qualified site personnel occurred on Day -1, during the treatment period (end of weeks 4, 12, 24, 36, and 48), and on the follow-up visit (end of week 52) or study termination. It is worth noting that the study protocol did not require the same rater to administer and score the scales at all time points. This is less than optimal as it introduces the problem of interrater reliability.

All patients received the aforementioned safety screens. Population-specific safety assessments are described in the following paragraphs.

For patients with schizophrenia or schizoaffective disorder, the Positive and Negative Syndrome Scale (PANSS), a validated instrument for measuring symptom reduction in patients with schizophrenia, was administered via the same timescale as the BARS. To assess for depression in this group, the Calgary Depression Scale of Schizophrenia (CDSS) was administered on the same time schedule as the BARS. Akin to the BARS administration – and raising the same concerns - the study protocol does not specify that the same rater is required to administer and

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

score the PANSS at all time points. The study protocol suggests that it is advisable that the same rater administer and score the CDSS at all time points.

For patients with mood disorders, the Young Mania Rating Scale (YMRS) was used to assess manic symptoms in patients with mania, and was administered on the same timescale as the BARS. The same concern regarding interrater reliability is raised: the study protocol did not require that the same rater be required to administer and score the psychometric scale at all time points. The Montgomery-Asberg Depression Rating Scale (MADS) using the Structured Interview Guide for the MADRS (SIGMA) was administered on the same timescale as the BARS, and study protocol specified that the same person should administer and score the scale at all time points if possible.

### *Study 1304*

In Study 1304, per the study protocol, all subjects were screened via a general medical history and psychiatric history upon study entry at Day -1. Specifically, the subject's age at diagnosis of schizophrenia or schizoaffective disorders or mood disorder and the age at TD diagnosis would be gathered. Complete physicals were conducted at each screening visit during the controlled Study period (end of weeks 2, 4, 6) and the open-label extension period (end of weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48) and at the follow-up visit (end of week 52) or alternatively, at study termination. Weight was recorded with subjects wearing "ordinary indoor clothing without shoes."

Vital signs were collected via the same schedule (i.e. at study visits) and prior to any scheduled blood sample collection. Measures collected were the same as those in Study 1402. ECGs were collected under the same protocol as per Study 1402. Again, ECG parameters were measured by the machine and were interpreted by the investigator and as investigator-determined, ECGs were confirmed by a cardiologist or internist.

Routine safety labs were analyzed at a central lab and assessed at screening, Day -1, during the controlled study period (end of Weeks 2, 4, 6) and during the open-label extension (end of weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and at the follow-up visit (end of Week 52) or at early termination as applicable. Labs collected at each visit include hematology, chemistry, urinalysis, and other labs as per Study 1402. Additionally, serum prolactin was assessed at Day -1, during treatment (end of weeks 2, 4, 6), during the open-label extension phase (end of weeks 8, 16, 24, 32, 40, and 48) and at the follow-up visit (end of week 52) or upon early termination.

Notably, screening for alcohol (via breathalyzer) and a urine drug screen were conducted at screening and Day -1, in addition to being conducted at random throughout the study. As per Study 1402, the previous entry and exit criteria were applied to cannabinoid and alcohol use. Pregnancy testing was performed at each study visit in female subjects who were not postmenopausal for at least 1 year.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

As in Study 1402, any abnormalities found triggered a repeat analysis until the cause of the abnormality is determined, until the value returns to baseline, or until the investigator deems the abnormality to be of no clinical significance

Suicidal ideation and behavior was assessed via the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects were assessed as per the same schedule as standard labs, starting at screening. Administration is by the site investigator or individuals who have completed SSRS certification. Any worsening from baseline (Day -1) to the SI section will be documented as an AE, and appropriate psychiatry intervention will be taken.

As per Study 1402, the Barnes Akathisia Rating Scale (BARS) was utilized to assess for drug-induced akathisia (subjective and objective items) while the Simpson-Angus Scale (SAS) was utilized to evaluate for drug-induced Parkinsonism and other extrapyramidal symptoms. Administration of BARS and SAS was by the investigator or other qualified site personnel was at Day -1, during the treatment period (end of weeks 2, 4, 6), the open-label extension period (end of weeks 8, 16, 24, 32, 40, and 48), and at the follow-up visit (end of week 52) or study termination. As per Study 1402, the same critiques regarding rater consistency apply.

All patients received the aforementioned safety screens. Population-specific safety assessments are described in the following paragraphs.

For patients with schizophrenia or schizoaffective disorder, the Positive and Negative Syndrome Scale (PANSS), was administered via the same timescale as the BARS. To assess for depression in this group, the Calgary Depression Scale of Schizophrenia (CDSS) was administered on the same time schedule as the BARS. For patients with mood disorders, the Young Mania Rating Scale (YMRS) was used to assess manic symptoms in patients with mania, and was administered on the same timescale as the BARS. The Montgomery-Asberg Depression Rating Scale (MADS) using the Structured Interview Guide for the MADRS (SIGMA) was administered on the same timescale as the BARS.

### *Study 1202*

In Study 1202, per the study protocol, all subjects were screened via a general medical history and psychiatric history upon study entry at Day -1. Specifically, the subject's age at diagnosis of schizophrenia or schizoaffective disorders or mood disorder and the age at TD diagnosis would be gathered. Complete physicals were conducted at each screening visit during the controlled study period (end of weeks 2, 4, 6) and at the follow-up visit (end of week 8) or alternatively, at study termination.

Vital signs were collected via the same schedule (i.e. at study visits) and prior to any scheduled blood sample collection. Measures collected were the same as those in Study 1304. ECGs were

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

collected under the same protocol as per Study 1304. Routine safety labs were analyzed at a central lab and assessed at screening, Day -1, during the controlled study period (end of Weeks 2, 4, 6) and at the follow-up visit (end of Week 8) or at early termination as applicable. Labs collected at each visit include hematology, chemistry, urinalysis, and other labs as per study 1402. Additionally, serum prolactin was assessed at Day -1, during treatment (end of weeks 2, 4, 6) and at the follow-up visit (end of week 8) or upon early termination. As per Study 1402, the previous screening and study entry/exit criteria were applied to cannabinoid and alcohol use. Pregnancy testing was performed at each study visit in female subjects who were not postmenopausal for at least 1 year.

As in Study 1402, any abnormalities found triggered a repeat analysis until the cause of the abnormality is determined, until the value returns to baseline, or until the investigator deems the abnormality to be of no clinical significance.

Suicidal ideation and behavior was assessed via the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects were assessed as per the same schedule as standard labs, starting at screening. The Barnes Akathisia Rating Scale (BARS) was utilized to assess for drug-induced akathisia (subjective and objective items) while the Simpson-Angus Scale (SAS) was utilized to evaluate for drug-induced Parkinsonism and other extrapyramidal symptoms. These scales were administered at screening, Day -1, during treatment (end of weeks 2, 4, 6), and at the study follow-up visit (end of week 8) or early termination.

For patients with schizophrenia or schizoaffective disorder, the Positive and Negative Syndrome Scale (PANSS), was administered at Study Day -1, during treatment (end of week 6), and during follow-up (end of week 8) or at early termination. To assess for depression in this group, the Calgary Depression Scale of Schizophrenia (CDSS) was administered on the same time schedule as the PANSS. For patients with mood disorders, the Young Mania Rating Scale (YMRS) was used to assess manic symptoms in patients with mania, and was administered on the same timescale as the PANSS. The Montgomery-Asberg Depression Rating Scale (MADS) using the Structured Interview Guide for the MADRS (SIGMA) was administered on the same timescale as the PANSS. Lastly, for patients with gastrointestinal disorders, the Gastroparesis Cardinal Symptom Index (GCSI) was utilized to evaluate the severity of gastroparesis at screening, study Day -1, during treatment (end of weeks 2, 4, 6) and during follow-up (end of week 8) or early termination.

### *Study 1201*

In Study 1201, per the study protocol, all subjects were screened via a general medical history and psychiatric history upon study entry at Day -1. Specifically, the subject's age at diagnosis of schizophrenia or schizoaffective disorders or mood disorder and the age at TD diagnosis would be gathered. Complete physicals were conducted at each screening visit during the controlled study period (end of weeks 2, 6, 8, 12) and at the follow-up visit (end of week 16) or

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

alternatively, at study termination.

Vital signs were collected at screening, study Day -1, during treatment (end of weeks 2, 4, 6, 8, 10, 12), and during the follow-up period (end of Weeks 14, 16) or early termination. Measures collected were the same as those in Study 1402. ECGs were collected under the same protocol as per Study 1402 and at the same frequency as physical exams. Routine safety labs were analyzed at a central lab and assessed at screening, Day -1, during the controlled study period (end of Weeks 2, 6, 8, 12) and at the follow-up visit (end of Week 16) or at early termination as applicable. Labs collected at each visit include hematology, chemistry, urinalysis, and other labs as per Study 1402. As per Study 1402, the previous screening and study entry/exit criteria were applied to cannabinoid and alcohol use. Pregnancy testing was performed at each study visit in female subjects who were not postmenopausal for at least 1 year.

As in Study 1402, any abnormalities found triggered a repeat analysis until the cause of the abnormality is determined, until the value returns to baseline, or until the investigator deems the abnormality to be of no clinical significance

Suicidal ideation and behavior was assessed via the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects were assessed as per the same schedule as vital signs, starting at screening. The Barnes Akathisia Rating Scale (BARS) was utilized to assess for drug-induced akathisia (subjective and objective items) while the Simpson-Angus Scale (SAS) was utilized to evaluate for drug-induced Parkinsonism and other extrapyramidal symptoms. These scales were administered at screening, Day -1, during treatment (end of weeks 2, 4, 6), and at the study follow-up visit (end of week 8) or early termination.

For patients with schizophrenia or schizoaffective disorder, the Positive and Negative Syndrome Scale (PANSS), was administered at Study Day -1, during treatment (end of weeks 2, 6, 12), and during follow-up (end of week 16) or at early termination. To assess for depression in this group, the Calgary Depression Scale of Schizophrenia (CDSS) was administered on the same time schedule as the PANSS albeit with an additional screening at the end of week 8.

## 8.4. Safety Results

### 8.4.1. Deaths

There were four deaths in the Study. Upon review, all deaths were deemed not related to the Study drug. The deaths are reviewed as follows:

- Subject 215-2020 in Study 1202 was a 57 year-old Caucasian woman with an 18-year history of schizophrenia/schizoaffective disorder, TD, epilepsy, hypothyroidism, hypopituitary disorder, “hypertensive heart disease” [sic], and heart failure (diagnosed eight months prior to Study enrollment). The patient was a 2 pack per day smoker, and medications included chlorpromazine, hydrocortisone, levetiracetam, levothyroxine,

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

phenytoin, and zolpidem. The patient was randomized to placebo on [REDACTED] (b) (6) and received their first dose the following day. On [REDACTED] (b) (6) the Study experienced a moderate convulsion, but declined hospitalization upon arrival of paramedics. The patient experienced a severe convulsion the following day and was hospitalized. The subject experienced cardiopulmonary arrest secondary to two severe myocardial infarctions and subsequently expired on the same day. These events are not related to the study drug (placebo administration) and are likely a consequence of the patient's inadequately treated seizures and underlying cardiovascular disease.

- Subject 308-3012 in Study 1304 was a 73 year-old African American man with a 40-year history of schizophrenia or schizoaffective disorder and a one-year history of TD. His past medical history was notable for diabetes, hypercholesterolemia, hypertension, and obesity, treated with amlodipine, metformin, metoprolol, simvastatin, and a hydrochlorothiazide/lisinopril fixed dose combination product. The patient received fluphenazine for his psychiatric disorder. At baseline, the patient had sinus bradycardia and a right bundle branch block on EKG. The patient did not complete a placebo-controlled treatment period and was randomized to valbenazine 80 mg. The subject received valbenazine 40 mg for the first week of treatment, followed by valbenazine 80 mg for three weeks. His last dose of Study drug was [REDACTED] (b) (6). The subject died suddenly on [REDACTED] (b) (6) and no autopsy was performed. This sudden death was unlikely related to study drug. Right bundle branch block is often a sign of significant underlying cardiac problem (e.g. cardiomyopathy, ischemic heart disease, etc.) and in combination with the patient's age, medical history, and concomitant medications; it is likely that this patient died of cardiac causes unrelated to the study drug. However, due to the failure to obtain an autopsy, the study drug cannot be definitively ruled out.
- Subject 345-3009 in Study 1304 was a 59 year-old Caucasian man with schizophrenia or schizoaffective disorder (duration unknown) with neuroleptic-induced TD (duration unknown) with a past medical history notable for coronary artery disease, hypertension, diabetes, and asthma. The patient's relevant concurrent medications included haloperidol, risperidone and benztropine for psychiatric disease and metformin, Novolog, and sitagliptin for diabetes. The patient was randomized to valbenazine 80 mg and received valbenazine 40 mg for the first week followed by valbenazine 80 mg. The patient completed the placebo-controlled treatment period and began the open-label extension, continuing valbenazine 80 mg. On day 327, the patient was brought to the ER with altered mental status and right facial swelling. Labs demonstrated hepatic failure (acidosis, markedly increased AST and ALT), and the patient went into cardiopulmonary arrest and died. It is unclear if this drug is related to the study drug as there is not enough information in the pre-hospital medical history surrounding the events of hospitalization and subsequent death.
- Subject 413-4012 in Study 1402 was a 48 year-year old African American woman with a 23 year history of schizophrenia or schizoaffective disorder and a 6 year history of neuroleptic-induced TD. Their past medical history is otherwise notable for asthma,

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

COPD, drug hypersensitivity (unspecified), hypertension, obesity, and tobacco use. Relevant medications include amlodipine, benztropine, and ziprasidone. The patient received 28 days of valbenazine 40 mg, and was subsequently increased to 80 mg for one week. Three days after their last dose of valbenazine, the subject died suddenly. The cause of death listed on the death certificate was listed as breast cancer. This was not likely related to the Study drug.

Review of the 120-day safety update, received and stamped on November 21, 2016 reveals no additional deaths. In conclusion, there are no deaths during the clinical development that are clearly due to the drug.

It is worth noting that the death of Subject 413-4012 raises questions regarding the Applicant's data integrity and standard operating procedures for clinic Study visits. During a clinical development program, it is expected that patients will experience increased detection of other, unrelated diseases due to increased clinical surveillance. That is, if a patient sees a physician more frequently and undergoes a series of standardized exams and laboratory assessments, it is more likely that abnormalities will be found. Thus, if a patient is undergoing close clinical surveillance in the form of repeated Study visits, history and physical (including a lymph node exam), ECG assessment, blood draws for pharmacokinetic assessment and diagnostic labs, completes the Study, and dies three days later from breast cancer, it calls into question the thoroughness of the clinical assessments.

### 8.4.2. Serious Adverse Events

Non-fatal SAEs are defined as AEs that result in life-threatening, hospitalization or prolonged hospitalization, permanent disability, congenital malformations, and/or overdoses. These were reviewed individually for each of the 6-week controlled trials (Studies 1201, 1202, and 1304) in addition to the safety database. I personally reviewed the narratives provided in the Study reports for each SAE. SAEs occurring during the controlled period of Studies are briefly summarized. SAEs occurring in the overall safety database are addressed by incidence and then addressed by likely relation to the Study drug.

#### *Study 1201*

Study 1201 was a controlled trial lasting 6 weeks. Subjects received either placebo, valbenazine 50 mg, or valbenazine 100 mg for 2 weeks followed by valbenazine 50 mg for 4 weeks. Events after 6 weeks (42 days) were not considered in this dataset as they occurred during the open-label extension period, wherein all subjects received the study drug. Serious AEs occurring during this period are listed as follows:

- Subject 118-1015 (fall, 50 mg group): A 66 year-old Caucasian man with a history of schizoaffective disorder or schizophrenia, TD, type 2 diabetes, anxiety, and insomnia on valbenazine 50 mg fell on day 38 while walking and was hospitalized for four days. The patient was also on temazepam, alprazolam, perphenazine, topiramate, and also nightly diphenhydramine and trazodone at the time of the fall. The study report notes that the

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

patient had “a history of attention seeking and frequent hospitalizations” and that no TEAEs were experienced after this hospitalization until Study completion at Day 112.

- Subject 154-1007 (chest pain, 50 mg group): A 69 year-old Caucasian woman, an active smoker, with schizophrenia or schizoaffective disorder, hypertension, and a history of coronary artery disease was hospitalized for chest pain, shortness of breath, headache, and dizziness. Cardiac work-up was negative and the patient was discharged.

These events were deemed to be unlikely related to the study drug.

### *Study 1202*

Study 1202 was an escalating dose study lasting 6 weeks. Subjects received either placebo, or valbenazine. Valbenazine was started at 25 mg for 2 weeks, after which patients could be up titrated as tolerated to 50 mg daily. After an additional 2 weeks, patients could be up-titrated to 75 mg as tolerated or down-titrated to 25 mg as judged necessary by the site investigator. Events occurring during the first week (7 half-lives) of the 2 week follow-up period were included (maximum 42 days), as the half-life of its major active metabolite, [±]-α-dihydrotetrabenazine is ~15-22 hours. No serious AEs occurred in the drug group during this study period.

### *Study 1304*

Study 1304 was a controlled trial lasting 6 weeks. Subjects received either placebo, valbenazine 40 mg, or valbenazine 80 for 6 weeks. Events occurring after 6 weeks (42 days) were not included, as they occurred during the open-label extension period, wherein all subjects received the study drug. Serious AEs occurring this study period are listed as follows:

- Subject 304-3002 (Worsening Schizoaffective disorder, 80 mg group): A 69 year-old African-American woman with multiple medical problems notably anxiety, epilepsy, and depression was hospitalized on study day 14 with worsening schizoaffective disorder and HI. The patient had reportedly stopped taking their regular psychotropic medications.
- Subject 337-3031 (CVA and suicidal ideation, 80 mg): A 51 year-old African-American man with schizophrenia or schizoaffective disorder, coronary artery disease s/p CABG s/p MI, diabetes, CHF, diabetes, and neuropathy. The patient had a stroke immediately prior to enrollment, did not seek treatment and attempted suicide on study day 1 due to the effects of the stroke and was hospitalized.
- Subject 342-3007 (Hostility, 40 mg): A 63 year-old Asian man with schizophrenia or schizoaffective disorder and multiple medical problems who was also receiving benztropine, haloperidol, lithium, and quetiapine who was brought to the ER on Study day 13 due to threatening their roommate and increasing hostility. The subject was hospitalized. During his hospitalization, the subject developed altered mental status.
- Subject 345-3005 (Schizophrenia worsening with suicidal and homicidal ideation, gastroenteritis, 40 mg): A 61 year-old Caucasian man was admitted to the hospital on Day 12 with gastroenteritis and worsening Schizophrenia with SI and HI.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

- Subject 349-3004 (Worsening Schizophrenia, 40 mg): A 54 year-old African American woman with schizophrenia or schizoaffective disorder and multiple other medical problems who was hospitalized on Day 29 for worsening schizophrenia. During the prior month, the patient had missed her psychiatric appointment and her perphenazine prescription was not filled.
- Subject 355-3003 (Pyelonephritis and AE COPD, 40 mg): A 68 year-old Caucasian man with schizophrenia or schizoaffective disorder and COPD, Coronary artery disease, depression, diabetes, current tobacco smoker, and other medical problems was hospitalized with pyelonephritis and COPD.
- Subject 361-3007 (SI/SA: 80 mg): A 41 year-old African-American woman with schizophrenia or schizoaffective disorder, depression, and extrapyramidal disorder who was on citalopram, risperidone, and zolpidem. The patient was hospitalized due to SI (suicidal ideation and positive auditory hallucinations providing instructions to the patient to kill themselves) on day 34. The case report notes that the case manager stated that the subject had not been compliant with her psychiatric medications.
- Subject 369-3004 (Acute hepatitis, 80 mg): A 60 year-old Caucasian man with schizophrenia or schizoaffective disorder and a history of hepatitis C, hepatitis A, and acute hepatitis with jaundice lasting for approximately 6 months as a teenager presented with elevated LFTs (AST, ALT, GGT, LDH) and normal bilirubin on day 40. The subject's medical history is notable for acetaminophen and alcohol use, and concurrent medications include Vicodin 5 / 325.
- Subject 369-3009 (SI, 80 mg): A 50 year-old African American woman with schizophrenia or schizoaffective disorder and a history of SI developed SI on day 10. The patient was hospitalized and was reported as "coming out of a manic episode" and was crashing.

It is unclear if these events were due directly to the Study drug. The absolute risk difference for suicidal ideation/attempt in comparing the drug to placebo group is 2.6% v. 0% (p non-significant, Fisher's exact test, two-tailed). The absolute risk difference for homicidal ideation is 1.3% v. 0% in the drug v. placebo group (non-significant). The incidence of worsening schizoaffective disorder or schizophrenia was similar in the drug and placebo groups (1.3% in each). While these comparisons note no statistically significant difference, it is worth noting that these comparisons were conducted after the fact, and that the pre-market studies were not designed nor powered to detect differences in suicidal ideation/attempts, homicidal ideation, or worsening of schizoaffective disorder or schizophrenia.

### *Summary Observations from Controlled Trials*

There was no discernible pattern of SAEs in Studies 1201 and 1202, and the SAEs were deemed unlikely to be due to the study drug. In the controlled period of Study 1304, nearly all SAEs occurred in subjects receiving the study drug. Upon close examination of the SAEs, it is apparent that they are likely due to pre-existing medical conditions or other events otherwise not attributable to the study drug (e.g. acute hepatitis occurring in a subject who previously had

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

hepatitis A, hepatitis C, acute hepatitis otherwise not specified and who is concurrently taking both acetaminophen and alcohol).

*Pooled Long-Term Observational Safety Database*

This database includes the controlled phases of Studies 1201, 1202, and 1304. The 6 week open-label extension of Study 1201 was also included, wherein all study subjects received valbenazine 50 mg. As previously mentioned, one week of the follow-up period (7 half-lives of the major, active metabolite) were included (i.e. events after 49 days were excluded).

Additionally, this database includes the open-label extension of Study 1304, wherein subjects on valbenazine continued their drug dose for an additional 42 weeks, and placebo subjects were randomized to valbenazine 40 mg or 80 mg for 42 weeks. As previously mentioned, one week of the follow-up period (7 half-lives of the major, active metabolite) were included (i.e. events after 301 days were excluded). Lastly, the open-label Study 1402 was included, lasting 48 weeks. As previously mentioned, one week of the follow-up period (7 half-lives of the major, active metabolite) were included (i.e. events after 342 days were excluded).

In analyzing this database Of 1,552 AEs, 57 AEs were classified as serious. AEs in order of incidence are displayed in the following table.

APPEARS THIS WAY ON ORIGINAL

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 71: Raw Incidence of SAEs in Safety Database**

| FDA AE PT                                      | N  |
|--|----|
| Exacerbation of underlying psychiatric disease | 16 |
| SI/SA  | 14 |
| Syncope  | 4  |
| AMS  | 4  |
| Abdominal pain                                 | 3  |
| TIA  | 3  |
| Chest pain                                     | 2  |
| Fall   | 2  |
| HI   | 2  |
| Foreign body trauma                            | 1  |
| Joint dislocation                              | 1  |
| UTI  | 1  |
| Acute diverticulitis                           | 1  |
| Acute hepatitis                                | 1  |
| ARF  | 1  |
| Bicycle accident                               | 1  |
| Bronchitis                                     | 1  |
| Depression                                     | 1  |
| DJD  | 1  |
| DVT  | 1  |
| Hostility                                      | 1  |
| HTN  | 1  |
| Hyponatremic syndrome                          | 1  |
| Infection - GU                                 | 1  |
| Infection - Soft tissue                        | 1  |
| MVA  | 1  |
| Nephrolithiasis                                | 1  |
| Rash   | 1  |
| SOB  | 1  |
| Spontaneous abortion                           | 1  |
| Traumatic amputation                           | 1  |
| Urinary retention                              | 1  |

*Source: Reviewer-created table derived from adverse event dataset for safety population*

All case narratives were reviewed and nearly all SAEs resulted in hospitalization or prolonged hospitalization. There were no congenital malformations; however, there was one spontaneous abortion in a patient who became pregnant while using condoms as the sole method of birth control. This subject will be discussed in [Section 8.8.2](#). SI/SA and HI occurred concurrently with

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

exacerbation of underlying psychiatric disease in 8 events and 2 events, respectively. There appeared to be no clear trend in time to SAE overall when comparing across dose groups. Additionally, there appeared to be a clear dose-dependent response in the overall rate of SAEs, declining with dose of study drug.

Upon review, most SAEs did not appear to be directly related to study drug. Notably, the exacerbation of underlying psychiatric disease (worsening schizoaffective disorder, schizophrenia, or bipolar), SI/SA, and AMS appeared to be potentially related to the drug based upon case narratives. Several cases of exacerbation of underlying disease appear to be due to the subject discontinuing their antipsychotic. While it is possible that this is the normal course of disease, it is equally possible that effects of the study drug increase the rate of discontinuation of antipsychotic medications. While these pre-market studies are likely underpowered to detect such an effect, this is an outcome of interest in the post-market setting.

Examining the incidence across dose group for the SAEs of interest reveals an apparent dose-dependent response (improvement) for exacerbation of underlying psychiatric disease or AMS. However, there does not appear to be a dose-dependent response for SI/SA. These relationships are displayed in the table below.

**Table 72: Incidence of SAEs in Safety Database**

| Dose       | Incidence (Events per 100 Person-Years)        |         |       |         |     |         |
|------------|--|---------|-------|---------|-----|---------|
|            | Exacerbation of Underlying Psychiatric Disease |         | SI/SA |         | AMS |         |
|            | N  | Density | N     | Density | N   | Density |
| Placebo    | 3  | 15.3    | 0     | 0.0     | 1   | 5.1     |
| 40 - 50 mg | 6  | 4.7     | 6     | 4.7     | 1.0 | 1.3     |
| 80 mg      | 3  | 2.4     | 3     | 2.4     | 1   | 0.8     |

Source: Reviewer-created table derived from adverse event dataset for safety population

This trend in SI/SA will be correlated in the review with other analyses (e.g. TEAEs, C-SSRS scores, etc.). The dose-dependent improvement in AMS as an SAE is neither expected nor unexpected, and could be due to interactions with other concomitant psychiatric medications. The number of events is too small to conduct a meaningful analysis of such a potential interaction. The dose-dependent improvement in SAEs resulting in hospitalization from exacerbation of psychiatric disease will be compared to disease-specific scale assessments (e.g. PANSS, MADRS, etc.) later in this review. Notably, all but one of these subjects were on an antipsychotic, typical or atypical.

### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

All studies specify withdrawal criteria. In Study 1201, according to the study protocol, the investigator or Applicant may withdraw a subject at any time if the subject experiences any of the following:

- Type, frequency, or severity of any AE becomes intolerable
- ALT, AST, or GGT  $\geq 3.0x$  upper limit of normal, total bilirubin  $> 2.0x$  upper limit of normal or the serum creatinine value  $> 1.5x$  upper limit of normal
- QTcF  $> 500$  msec or if the subject has a “clinically significant” ECG change (definition of the latter not specified)
- If the subject exhibits suicidal behavior or ideation type 4 (active SI with some intent to act without a specific plan) or type 5 (active SI with specific plan and intent) based on the C-SSRS
- Subject requires a medication that is prohibited by the protocol
- Does not follow guidelines specific in the protocol (Applicant did not specify which guidelines)
- Subject is non-compliant with the dosing regimen ( $<80\%$  dosing compliance) as verified by drug accountability
- Is lost to follow-up
- Does not continue to meet entry criteria
- Confirmed pregnancy

The investigator must record the reason for withdrawal on the Study CRF. Per the Study protocol, the Applicant may at any point discontinue the Study at any point.

Study 1202 has exactly the same withdrawal criteria. The study protocol for Study 1202 additionally specifies that during the dose titration period that any subject who is unable to tolerate the starting dose or resumption of the previous dose will be discontinued from the study. Tolerability is defined as the “subject’s reports of signs and symptoms and the physician investigator’s assessments.”

In Study 1304, the requirements changed slightly, with the Applicant differentiating between mandatory and optional withdrawal requirements in the study protocol. Specifically, the site investigator was required to withdraw the subject if any of the following occur:

- Type, frequency, or severity of any AE becomes intolerable (not specified as intolerable in the judgment of the investigator and/or the opinion of the subject)
- QTcF  $> 500$  msec or if the subject has a “clinically significant” ECG change (definition of the latter not specified)
- If the subject exhibits suicidal behavior or ideation type 4 (active SI with some intent to act without a specific plan) or type 5 (active SI with specific plan and intent) based on the C-SSRS
- Subject lost to follow-up
- Subject is pregnant

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

- Subject is unable to tolerate drug dose after a dose reduction (investigators may only reduce a dose once during a Study)

The investigator or Applicant may withdraw the subject from the Study for additional reasons as listed below (these criteria may bias the study). However, these cases must be discussed with the Applicant medical monitor prior to subject withdrawal:

- ALT, AST, or GGT  $\geq 3.0x$  upper limit of normal, total bilirubin  $> 2.0x$  upper limit of normal or the serum creatinine value  $> 1.5x$  upper limit of normal
- Subject requires a medication that is prohibited by the protocol
- Subject is non-compliant with the dosing regimen ( $<80\%$  dosing compliance) as verified by drug accountability

Study 1402 had similar withdrawal criteria to Study 1304, albeit with the following differences noted:

- The subject must be withdrawn if they are unable to tolerate the starting dose
- The subject must be withdrawn if they do not follow guidelines specified in the protocol
- The investigator or Applicant may withdraw the subject if the ALT or AST  $\geq 2.5x$  upper limit of normal or if the GGT  $\geq 3.0x$  upper limit of normal. This is contrast to Study 1304, where the AST and ALT triggered withdrawal criteria if they were  $\geq 3.0x$  upper limit of normal.

Overall, the withdrawal criteria across Studies in the development program exhibit normal variation, demonstrating the natural evolution of the Applicant's understanding of the product. It would have been more efficient to start with mandatory and optional withdrawal criteria from Study 1201 onwards.

Next, we address the dropouts due to adverse events. Recognizing that the Applicant's classification of the rationale for dropouts may differ, I personally reviewed every classification for dropout/discontinuation in Studies 1201, 1202, 1304, and 1402. Dropouts/discontinuations due to deaths were accounted for in [Section 8.4.1](#).

In the overall safety database, discontinuations due to noncompliance were observed at a similar rate in both groups, with 6/129 placebo-treated subjects (4.7%) discontinuing due to noncompliance as compared to 25/484 drug-treated subjects (5.2%). The most common reasons for non-compliance were positive urine drug screen (cocaine) or failure to take the study medication. Amongst patients lost to follow-up, 7/129 (5.4%) were in the placebo-treated group as compared to 21/484 (4.3%) in the drug-treated group. Notably, amongst patients lost to follow-up, discontinuation in the drug group was on average after 162 days as compared to 176 days in the placebo-treated group. Only 2 drug-treated patients dropped out due to protocol deviations. Withdrawal of consent accounted for 11/129 (8.5%) placebo-treated subject discontinuations as compared to 37/484 (7.6%) drug-treated subject discontinuations.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Applicant/Investigator decision resulted in termination of 11 subjects, all of whom were on study drug. Notably, 2 subjects became pregnant, 1 subject was withdrawn due to family request, 1 subject was withdrawn due to an unstable living situation, 5 subjects were withdrawn due to site non-compliance (failure of integrity of pharmacokinetic assays and site tampering), and 1 subject was withdrawn due to enrolling at 2 sites. With respect to non-compliance, 1 subject was removed due to investigator suspicion. 6 other subjects were terminated due to Applicant discretion.

### *Study 1201*

Discontinuations due to adverse events occurred in 8 subjects, 3 of whom were on drug in both the controlled and open-label extensions, and 5 of whom were on placebo during the controlled phase and then drug during the open label extension. During the controlled period, one subject on placebo discontinued due to worsening of Schizophrenia, and one subject on drug (100 mg) discontinued due to a UTI and concurrent syncope. During the open label extension, one subject each in the placebo/50 mg group discontinued due to depression, urticaria, SI, exacerbation of schizoaffective disorder, sedation, and an increase in hepatic enzymes. There was no apparent clear trend of discontinuation due to drug or placebo during the controlled phase, nor a distinct pattern of AEs resulting in discontinuation during the open-label extension.

### *Study 1202*

In Study 1202, only two subjects – both in the placebo group – discontinued due to an AE. One subject discontinued after 13 days due to a myocardial infarction. A second subject discontinued after 55 days due to urinary retention; this subject was also on benztropine, an anticholinergic agent.

### *Study 1304*

In Study 1304, 44/234 (18.8%) dropped out due to adverse events. Of note, 7 subjects dropped out during the controlled period (2/80 or 2.5% of subjects on placebo, 5/154 or 3.2% of subjects on drug) and notably neither a significant difference in the dropout rates between placebo and drug nor a dose-dependent dropout response were observed. During open-label extensions, 37 subjects dropped out due to AEs, and dropout rates due to AEs were similar between the 40 mg and 80 mg groups (15/97 or 15.4% in the 40 mg group versus 19/101 or 18.8% in the 80 mg group).

The most frequent AEs resulting in discontinuation during the controlled period were SI/SA (1/234 subjects or <1%), somnolence (4/234 subjects or 1.7%), exacerbation of underlying schizoaffective disorder, psychosis, or Tourette's symptoms (4/234 or 1.7%); EPS, altered mental status, and rash (2/234 or 0.9%).

Notably, discontinuation due to exacerbation of underlying psychiatric disease appeared to

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

occur at similar rates in both placebo and drug-treated groups and with no apparent clear time course. SI/SA resulting in discontinuation appeared to occur only after four weeks, suggesting that this is not due to study drug initiation. Notably, SA only occurred in the higher dose group and not in the lower dose group, which exhibited only SI. While there is no placebo group in the open-label extension, thus making comparison to a background rate difficult, there is potentially a dose-dependent response. SI/SA primarily occurred in patients with schizophrenia or schizoaffective disorder (5 subjects) as compared to those with mood disorder (2 subjects). Somnolence, EPS (non-Akathisia), and rash resulted in discontinuation only during the open label extension.

Other notable AEs of note leading to discontinuation include acute hepatitis (Subject 3693004), acute renal failure (Subject 3743003), and TIA (Subject 3553006 and 3083007). Discussion of these events was covered in [Section 8.4.2](#).

### *Safety Database – Observational Prospective Cohort*

The dropouts due to AEs for the controlled period of Studies 1201, 1202, and 1304 were combined with the open-label extensions of Studies 1201 and 1304, and the open-label Study 1402. The AEs triggering dropout were grouped using the AE PT groupings previously described. Additionally, for this database, exacerbation of schizoaffective disorder and exacerbation of schizophrenia were grouped together in order to better to understand if the Study drug caused dropouts due to worsening of the patient's underlying disease. Upon review of the dropouts due to AEs in this database, the AEs of greatest incidence and clinical significance causing Study discontinuation are akathisia, AMS, depression, elevated liver function tests, EPS (non-akathisia), exacerbation of underlying psychiatric disease, rash, SI/SA, and somnolence. Of note, there was no significant difference in time to event between placebo and drug groups. In order to better examine differential rates of events, incidence for the AEs leading to discontinuation was calculated by dose. The 50 mg dose exposure group and events were pooled with the 40 mg dose exposure group and events for the purposes of analysis.

**Table 73: Incidence of AEs Resulting in Study Discontinuation, by Dose**

| AE   | Incidence (Events per 100 Person-Years) |            |       |
|--|---|------------|-------|
|  | Placebo                                 | 40 - 50 mg | 80 mg |
| Akathisia                                      | -                                       | 1.6        | -     |
| AMS  | -                                       | 2.4        | -     |
| Depression                                     | -                                       | 1.6        | -     |
| Elevated LFTs                                  | -                                       | 2.4        | -     |
| EPS - Non-Akathisia                            | -                                       | 0.8        | 0.8   |
| Exacerbation of Underlying Psychiatric Disease | 10.2                                    | 2.4        | 1.6   |
| Rash   | 1.1                                     | 4.8        | -     |
| SI/SA  | -                                       | 4.0        | 4.9   |
| Somnolence                                     | -                                       | 1.6        | 2.4   |

Source: Reviewer-created table, derived from adverse event and exposure safety population datasets

Notably, exacerbation of underlying psychiatric disease (schizophrenia, schizoaffective disorder) and somnolence showed a clear dose-response relationship. Notably, the relationship between exposure to the Study drug and:

- Somnolence are established later in this review as having a clear dose-dependent response as a TEAE (see [Section 8.4.5](#))
- Exacerbation of underlying psychiatric disease is consistent with the same trend seen in SAEs. This will be examined through multiple psychiatric scales (PANSS, SAS, etc.)

#### 8.4.4. Significant Adverse Events

Significant adverse events will be defined as non-serious but important events (e.g. worsening of schizophrenia resulting in an ER visit but not hospitalization) relevant to the population or events resulting in the administration of concomitant medications.

Events that result in death, dropouts or discontinuations, or are otherwise classified as an SAE are not classified as significant adverse events. Neither are significant laboratory abnormalities, which will be analyzed in [Section 8.4.6](#). Events registered on psychiatric scales (e.g. suicidality reported only on the C-SSRS questionnaire and not as a specific AE) are not considered to be significant adverse events; these scales will be examined in [Section 8.5](#).

##### Study 1201

In Study 1201, an AE resulting in an ER or outpatient visit (but not a hospitalization) occurred at a similar rate across all three groups – placebo, valbenazine 50 mg, and valbenazine 100/50 mg. No dose-dependent response was observed.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 74: Rate of ER or Outpatient Visits in Study 1201**

|              | # of Events | Group Size (N) | Rate |
|--------------|-------------|----------------|------|
| Placebo      | 3           | 54             | 5.6% |
| 50 mg        | 2           | 28             | 7.1% |
| 100 mg/50 mg | 2           | 27             | 7.4% |

Source: Reviewer-created table, derived from Study 1201 Adverse event dataset (AE.xpt)

AEs resulting in the administration of new concomitant medications were similar across groups, with both 14.8% placebo and valbenazine 100 mg / 50 mg subjects experiencing an AE resulting in the administration of a concomitant medication, as opposed to 21.4% of valbenazine 50 mg Study subjects (not statistically significant, chi-squared test). There was no specific AE that resulted in administration of concomitant medications that either a dose-dependent response or an event rate statistically significantly different from that of placebo (analysis not shown).

### Study 1202

In Study 1202, two subjects experienced an AE that resulted in an ER or outpatient visit – both subjects received placebo. For AEs resulting in the administration of concomitant medications, approximately 21.6% of valbenazine subjects (all doses), as opposed to 13.7% of placebo-treated subjects, experienced an AE resulting from the administration of a concomitant medication (p-value not significant, Fisher's exact test). No specific AE resulted in a statistically significant difference in administration of a concomitant medication.

### Study 1304

In Study 1304, there was a trend towards a statistically significant difference in the incidence of AEs triggering an ER or outpatient visit in the valbenazine v. placebo group. The dose-specific trend is shown below (p-value not significant, chi-squared test).

**Table 75: AEs Resulting in ER or Outpatient Visit in Study 1304**

|                   | # of Events | Group Size (N) | Rate  |
|-------------------|-------------|----------------|-------|
| Placebo           | 5           | 78             | 6.4%  |
| Valbenazine 40 mg | 10          | 76             | 13.2% |
| Valbenazine 80 mg | 13          | 80             | 16.3% |

Source: Reviewer-created table, derived from Study 1304 Adverse event dataset (AE.xpt)

There was no specific AE that accounted for these effects. AEs resulting in the administration of new concomitant medications were similar across groups, with 21.3% placebo-treated, 21.1% of valbenazine 40 mg-treated, and 26.9% of valbenazine 80 mg-treated subjects experiencing an AE resulting in the administration of a concomitant medication (not statistically significant, chi-squared test).

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

### *Conclusions*

There was no consistent trend of the study drug valbenazine, as compared to placebo, resulting in an increased risk of AEs triggering an ER or outpatient visit, or AEs that required the administration of concomitant medications. Specific treatment emergent AEs will be reviewed in greater detail in the following section.

#### **8.4.5. Treatment Emergent Adverse Events and Adverse Reactions**

Treatment Emergent Adverse Events (TEAEs) and Adverse Reactions (ARs) were reviewed for the 6-week controlled trial periods of Studies 1201 (dose reduction), 1202 (dose titration), and 1304 (fixed dose). For the purposes of this in-depth analysis, the Studies were not pooled due to differences in Study design and variance in randomization. AE PT groupings were previously described in [Section 8.3.2](#).

##### *Study 1201*

Study 1201 was a controlled trial lasting 6 weeks wherein subjects received either placebo or valbenazine (100 mg x 2 weeks followed by 50 mg x 4 weeks or a fixed dose of 50 mg). Events after 6 weeks (42 days) were not considered in this dataset as they occurred during the open-label extension period, wherein all subjects received the Study drug.

Out of 109 subjects in this study, TEAEs were reported by 41 subjects (37.6%) overall, or specifically more placebo-treated subjects (22 or 40.7% of 54 subjects) as compared to drug-treated subjects (19 or 34.5% of 55 subjects). TEAEs reported by  $\geq 5\%$  of subjects in any drug arm were Infection (Respiratory), Arthralgia, Anticholinergic effects, Balance disorders/Fall, and Somnolence. TEAEs reported at  $\geq 5\%$  and consistently more than twice the rate of placebo were somnolence, which is a noted TEAE from tetrabenazine, a previously approved product in the same pharmacologic class for HD-related chorea. Other TEAEs reported such as anticholinergic effects and balance disorders/fall are consistent with the pharmacologic mechanism of the product. TEAEs occurring at  $\geq 2\%$  are displayed in the following table.

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 76: TEAEs from Study 1201 occurring at ≥2% in any arm**

| AE PT  | Placebo |      | VBZ 50 mg |      | VBZ 100 mg / 50 mg |       | VBZ (All doses) |      |
|--|---------|------|-----------|------|--------------------|-------|-----------------|------|
|  | N       | %    | N         | %    | N                  | %     | N               | %    |
| <b>Endocrine Disorders</b>                             |         |      |           |      |                    |       |                 |      |
| Blood triglycerides increased                          | 0       | 0.0% | 0         | 0.0% | 1                  | 3.7%  | 1               | 1.8% |
| Chest pain   | 0       | 0.0% | 1         | 3.6% | 0                  | 0.0%  | 1               | 1.8% |
| <b>Gastrointestinal Disorders</b>                      |         |      |           |      |                    |       |                 |      |
| Abdominal pain   | 0       | 0.0% | 1         | 3.6% | 0                  | 0.0%  | 1               | 1.8% |
| Vomiting   | 1       | 1.9% | 1         | 3.6% | 0                  | 0.0%  | 1               | 1.8% |
| <b>General Disorders</b>                               |         |      |           |      |                    |       |                 |      |
| Syncope  | 0       | 0.0% | 0         | 0.0% | 1                  | 3.7%  | 1               | 1.8% |
| <b>Infectious Disorders</b>                            |         |      |           |      |                    |       |                 |      |
| Infection - GU   | 2       | 3.7% | 0         | 0.0% | 1                  | 3.7%  | 1               | 1.8% |
| Infection - Respiratory                                | 2       | 3.7% | 0         | 0.0% | 2                  | 7.4%  | 2               | 3.6% |
| Infection - Soft tissue                                | 0       | 0.0% | 1         | 3.6% | 0                  | 0.0%  | 1               | 1.8% |
| Sinusitis  | 0       | 0.0% | 1         | 3.6% | 0                  | 0.0%  | 1               | 1.8% |
| <b>Musculoskeletal and Connective Tissue Disorders</b> |         |      |           |      |                    |       |                 |      |
| Arthralgia   | 0       | 0.0% | 2         | 7.1% | 0                  | 0.0%  | 2               | 3.6% |
| Muscle strain  | 0       | 0.0% | 1         | 3.6% | 0                  | 0.0%  | 1               | 1.8% |
| Muscular weakness                                      | 0       | 0.0% | 1         | 3.6% | 0                  | 0.0%  | 1               | 1.8% |
| <b>Neurologic Disorders</b>                            |         |      |           |      |                    |       |                 |      |
| Anticholinergic effects                                | 2       | 3.7% | 1         | 3.6% | 2                  | 7.4%  | 3               | 5.5% |
| Balance disorders/Fall                                 | 2       | 3.7% | 2         | 7.1% | 1                  | 3.7%  | 3               | 5.5% |
| Headache   | 0       | 0.0% | 0         | 0.0% | 1                  | 3.7%  | 1               | 1.8% |
| Oral dysaesthesia                                      | 0       | 0.0% | 1         | 3.6% | 0                  | 0.0%  | 1               | 1.8% |
| Salivary hypersecretion                                | 0       | 0.0% | 0         | 0.0% | 1                  | 3.7%  | 1               | 1.8% |
| Somnolence   | 0       | 0.0% | 2         | 7.1% | 3                  | 11.1% | 5               | 9.1% |
| <b>Pulmonary Disorders</b>                             |         |      |           |      |                    |       |                 |      |
| Chronic obstructive pulmonary disease                  | 0       | 0.0% | 0         | 0.0% | 1                  | 3.7%  | 1               | 1.8% |

Source: Reviewer-created table derived from Study 1201 adverse event file (AE.xpt)

**Study 1202**

Study 1202 was a controlled trial lasting 6 weeks wherein subjects received either placebo or valbenazine on a dose titration schedule starting at 25 mg, with up-titration every 2 weeks by 25 mg as tolerated. Events after 6 weeks (42 days) were not considered in this dataset as they occurred during the open-label extension period, wherein all subjects received the study drug.

Out of 102 subjects in this Study, TEAEs were reported by subjects (35.3%) overall, or specifically more placebo-treated subjects (15 or 29.4% of 51 subjects) as compared to drug-treated subjects (21 or 41.2% of 51 subjects). TEAEs reported by ≥5% of subjects in any drug arm were decreased appetite, nausea, vomiting, headache, anticholinergic effects, and somnolence. TEAEs reported at ≥5% and consistently more than twice the rate of placebo were decreased appetite, vomiting, and somnolence. TEAEs occurring at ≥2% are displayed in the following table.

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

APPEARS THIS WAY ON ORIGINAL

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 77: TEAEs from Study 1202 occurring at ≥2% in any arm**

| AE PT  | Placebo |      | VBZ (Any Dose) |       |
|--|---------|------|----------------|-------|
|  | N       | %    | N              | %     |
| <b>Infectious Disorders</b>                            |         |      |                |       |
| Infection - GU   | 2       | 3.9% | 2              | 3.9%  |
| Infection - Respiratory                                | 1       | 2.0% | 1              | 2.0%  |
| <b>Dermatologic Disorders</b>                          |         |      |                |       |
| Livedo reticularis                                     | 0       | 0.0% | 1              | 2.0%  |
| <b>Gastrointestinal Disorders</b>                      |         |      |                |       |
| Decreased appetite                                     | 0       | 0.0% | 4              | 7.8%  |
| Dyspepsia  | 1       | 2.0% | 1              | 2.0%  |
| Dysphagia  | 0       | 0.0% | 1              | 2.0%  |
| Nausea   | 2       | 3.9% | 3              | 5.9%  |
| Vomiting   | 0       | 0.0% | 3              | 5.9%  |
| <b>Musculoskeletal and Connective Tissue Disorders</b> |         |      |                |       |
| Muscular weakness                                      | 0       | 0.0% | 1              | 2.0%  |
| Gamma-glutamyltransferase increased                    | 1       | 2.0% | 1              | 2.0%  |
| Headache   | 2       | 3.9% | 4              | 7.8%  |
| Hot flush  | 1       | 2.0% | 1              | 2.0%  |
| Hypoaesthesia  | 1       | 2.0% | 1              | 2.0%  |
| Increased appetite                                     | 0       | 0.0% | 1              | 2.0%  |
| Limb discomfort  | 0       | 0.0% | 1              | 2.0%  |
| Temporomandibular joint syndrome                       | 0       | 0.0% | 1              | 2.0%  |
| Tension  | 0       | 0.0% | 1              | 2.0%  |
| <b>Neurologic Disorders</b>                            |         |      |                |       |
| Anticholinergic effects                                | 4       | 7.8% | 5              | 9.8%  |
| Asthenopia   | 0       | 0.0% | 1              | 2.0%  |
| Back pain  | 0       | 0.0% | 2              | 3.9%  |
| Balance disorders/Fall                                 | 1       | 2.0% | 2              | 3.9%  |
| Blood glucose increased                                | 0       | 0.0% | 1              | 2.0%  |
| Bradycardia  | 0       | 0.0% | 1              | 2.0%  |
| Bruxism  | 0       | 0.0% | 1              | 2.0%  |
| EPS - Akathisia  | 0       | 0.0% | 2              | 3.9%  |
| Insomnia   | 0       | 0.0% | 1              | 2.0%  |
| Irritability   | 0       | 0.0% | 1              | 2.0%  |
| Pain   | 0       | 0.0% | 1              | 2.0%  |
| Panic attack   | 0       | 0.0% | 1              | 2.0%  |
| Poor quality sleep                                     | 0       | 0.0% | 1              | 2.0%  |
| Psychomotor retardation                                | 0       | 0.0% | 1              | 2.0%  |
| Somnolence   | 4       | 7.8% | 10             | 19.6% |

Source: Reviewer-created table derived from Study 1202 adverse event file (AE.xpt)

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*Study 1304*

Study 1304 was a controlled trial lasting 6 weeks wherein subjects received either placebo or valbenazine 40 mg or 80 mg. Events after 6 weeks (42 days) were not considered in this dataset as they occurred during the open-label extension period, wherein all subjects received the Study drug.

Out of 234 subjects in this Study, TEAEs were reported by subjects (29.9%) overall, or specifically more placebo-treated subjects (32 or 41.0% of 78 subjects) as compared to drug-treated subjects, which exhibited a dose dependent response when the dose was increased from 40 mg (29 or 38.2% of 76 subjects) to 80 mg (41 or 51.3% of 80 subjects). TEAEs reported by  $\geq 5\%$  of subjects in any drug arm were anticholinergic effects, drooling, infection (overall), and somnolence. TEAEs reported at  $\geq 5\%$  and consistently more than twice the rate of placebo were anticholinergic effects, drooling, infection (overall), and somnolence. TEAEs occurring at  $\geq 2\%$  are displayed in the following table.

APPEARS THIS WAY ON ORIGINAL

**Table 78: TEAEs for Study 1304 occurring at ≥2% in any arm**

| AE PT  | Placebo |      | VBZ 40 mg |      | VBZ 80 mg |      | VBZ (All Doses) |      |
|--|---------|------|-----------|------|-----------|------|-----------------|------|
|  | N       | %    | N         | %    | N         | %    | N               | %    |
| <b>Endocrine Disorders</b>                             |         |      |           |      |           |      |                 |      |
| Weight increased                                       | 0       | 0.0% | 1         | 1.3% | 2         | 2.5% | 3               | 1.9% |
| <b>Gastrointestinal Disorders</b>                      |         |      |           |      |           |      |                 |      |
| Blood glucose increased                                | 0       | 0.0% | 0         | 0.0% | 2         | 2.5% | 2               | 1.3% |
| Vomiting   | 0       | 0.0% | 0         | 0.0% | 3         | 3.8% | 3               | 1.9% |
| <b>Infectious Disorders</b>                            |         |      |           |      |           |      |                 |      |
| Infection - Overall                                    | 6       | 7.7% | 7         | 9.2% | 1         | 1.3% | 8               | 5.1% |
| <b>Musculoskeletal and Connective Tissue Disorders</b> |         |      |           |      |           |      |                 |      |
| Arthralgia   | 1       | 1.3% | 1         | 1.3% | 3         | 3.8% | 4               | 2.6% |
| <b>Neurologic Disorders</b>                            |         |      |           |      |           |      |                 |      |
| Anticholinergic effects                                | 3       | 3.8% | 6         | 7.9% | 0         | 0    | 6               | 3.8% |
| Balance disorders/Fall                                 | 1       | 1.3% | 3         | 3.9% | 2         | 2.5% | 5               | 3.2% |
| Droling  | 0       | 0.0% | 0         | 0.0% | 4         | 5.0% | 4               | 2.6% |
| Dyskinesia   | 1       | 1.3% | 0         | 0.0% | 3         | 3.8% | 3               | 1.9% |
| EPS - Akathisia  | 1       | 1.3% | 3         | 3.9% | 2         | 2.5% | 5               | 3.2% |
| EPS - Non-Akathisia                                    | 0       | 0.0% | 0         | 0.0% | 3         | 3.8% | 3               | 1.9% |
| Somnolence   | 4       | 5.1% | 6         | 7.9% | 7         | 8.8% | 13              | 8.3% |
| <b>Psychiatric Disorders</b>                           |         |      |           |      |           |      |                 |      |
| Anxiety  | 0       | 0.0% | 1         | 1.3% | 2         | 2.5% | 3               | 1.9% |
| Insomnia   | 1       | 1.3% | 1         | 1.3% | 2         | 2.5% | 3               | 1.9% |

Source: Reviewer-created table derived from Study 1202 adverse event file (AE.xpt)

### Conclusions

Recognizing the constraints of product labeling, the Deputy Director for Safety (Marc B. Stone, MD) used a random effects logit model to account for the differences in randomization across the (3) 6-week controlled trials in order to derive a summary AE profile for labeling for TEAEs occurring at an incidence of ≥2% and greater than placebo. This is discussed in-depth in [Section 10.1](#) and is displayed in the following table.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 79: TEAEs Across (3) Controlled-Trial Periods**

| Adverse Reaction                  | Placebo (%) | VBZ (%) |
|-----------------------------------|-------------|---------|
| <b>Nervous System Disorders</b>   |             |         |
| Anticholinergic effects           | 4.9%        | 5.5%    |
| Balance disorders/fall            | 2.2%        | 3.8%    |
| Akathisia                         | 0.5%        | 2.7%    |
| Headache                          | 2.1%        | 3.4%    |
| <b>General Disorders</b>          |             |         |
| Somnolence                        | 4.2%        | 11.0%   |
| <b>Gastrointestinal Disorders</b> |             |         |
| Nausea                            | 2.1%        | 2.3%    |
| Vomiting                          | 0.5%        | 2.7%    |
| <b>Musculoskeletal Disorders</b>  |             |         |
| Arthralgia                        | 0.5%        | 2.3%    |

Source: Reviewer-created table, derived from adverse event files for Studies 1201, 1202, and 1304 (AE.xpt)

Additional TEAEs occurring at a rate  $\geq 1\%$  and greater than placebo include increased blood glucose, increase in weight, respiratory infections, drooling, dyskinesia, extrapyramidal symptoms (non-akathisia), anxiety, and insomnia.

### 8.4.6. Laboratory Findings

In Studies 1201, 1202, and 1304, labs were assessed during both the controlled and open-label extensions (as applicable). My analysis will focus on the controlled period assessments (Study day -1 and end of weeks 2, 6). Routine safety labs collected at each Study visit included a full hematology panel (complete blood count with differential), a full chemistry panel, liver enzymes and other associated tests (AST, ALT, GGT, total bilirubin, total protein, total cholesterol, triglycerides, creatine kinase, albumin, alkaline phosphatase, lactate dehydrogenase), urinalysis, and serum prolactin. Other tests were conducted per protocol (e.g. screening for hepatitis and HIV serologies)

Specific lab-related abnormalities during the controlled period of Studies 1201, 1202, and 1304 are described briefly by subject as follows:

- Subject 112-1005 in Study 1201 in the 100 mg/50 mg group, and on day 42 experienced a TEAE of increased blood triglycerides (3.20 v. 1.64 mmol/L at baseline,) that had resolved by day 56.
- Subject 224-2007 in Study 1202 in the valbenazine group had a GGT of 189 U/L at week 6 (day 41) while receiving 75 mg of Study group. By an unscheduled visit on day 48, this had resolved. The patient had no other associated symptoms.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

- Subject 224-2008 in Study 1202 had an elevated GGT of 141 U/L at day 14 while receiving placebo. This resolved by day 28.
- Subject 2335-2002 in Study 1202 in the valbenazine group had an elevated glucose of 12.3 mmol/L (upper-limit of normal 7.6 mmol/L) while receiving 50 mg of Study drug. This resolved by day 61. The patient had a history of type 2 diabetes and exhibited no other symptoms.
- Subject 345-3009 in Study 1304 in the 80 mg experience a TEAE of hyperkalemia, albeit this occurred in the setting of cardiac and hepatic failure. This subject expired and their case is discussion in [Section 8.4.1](#). This lab event was not study-related.

One subject (369-3004 in Study 1304) experienced an episode of acute hepatitis; however, this was complicated by multiple medical conditions, and is discussed in [Section 8.4.2](#). This case is unlikely to have been caused by the Study drug.

Mean drug effects on lab parameters for Studies 1201, 1202, and 1304 were analyzed during the controlled period via a mixed-effects logistic regression by the Deputy Director for Safety, Marc Stone, M.D. Based upon this, signals for increased blood glucose, decrease hemoglobin A1C, and increased prolactin were found. In the following table, displayed are the incidence of and the odds of an abnormally high (as defined in the Study protocol) result for drug relative to no drug, all with statistically significant p-values.

**Table 80: Laboratory Parameters Significantly affected by Valbenazine**

| Lab Parameter  | Incidence |         | Odds Ratio |             |          |
|----------------|-----------|---------|------------|-------------|----------|
|                | Drug      | No drug | Ratio      | 95% CI      | P-value  |
| Glucose        | 3.50%     | 2.00%   | 1.77       | 1.33 - 2.38 | < 0.0005 |
| Hemoglobin A1C | 31.20%    | 39.60%  | 0.69       | 0.53 - 0.90 | 0.007    |
| Prolactin      | 6.00%     | 2.00%   | 3.17       | 2.24 - 4.47 | < 0.0005 |

Source: Reviewer-generated table

Notably, increased blood glucose appeared as a TEAE, which suggests that this signal is clinically meaningful. The meaning of the decrease in the hemoglobin A1C within this context is unclear. Given the strong signal for prolactin, it was examined specifically across studies, and was found to increase in a dose-dependent manner. No prolactin-related TEAEs were observed (e.g. galactorrhea).

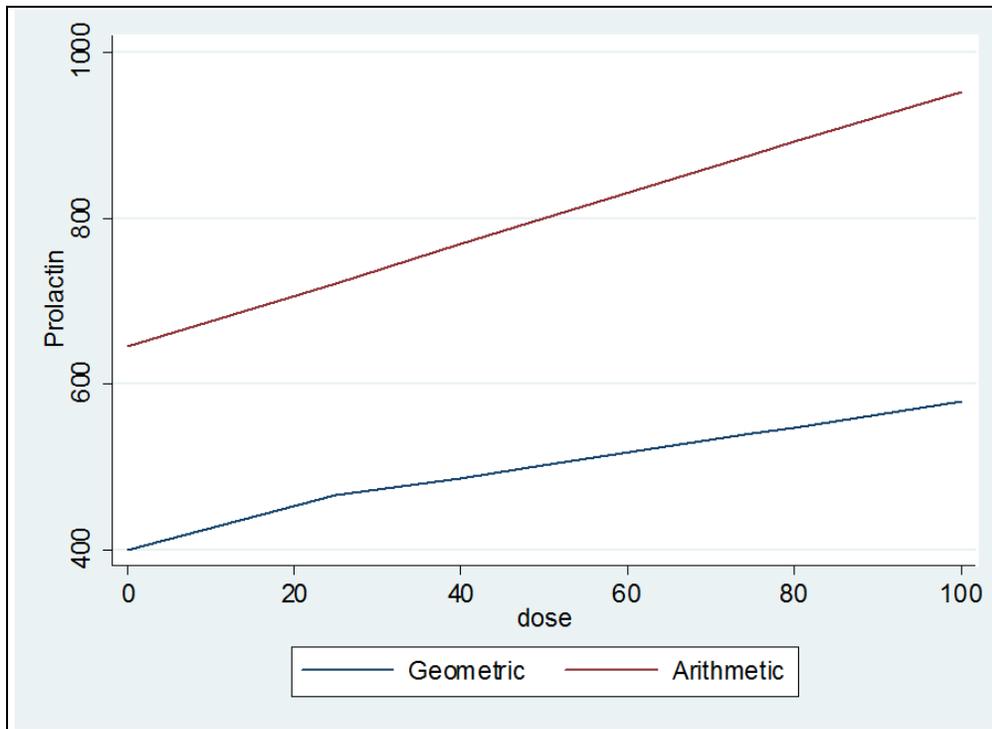
Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Figure 27: Geometric & Arithmetic Mean Trends Relative to Dosage for Prolactin across Controlled Studies 1201, 1202, and 1304**



Source: Created by Marc Stone, M.D., demonstrating Prolactin (pmol/L) (v. Valbenazine dose (mg))

It is worth noting that the majority of subjects were on atypical antipsychotics (74.4%) or typical antipsychotics (19.4%), which are well-established products that raise prolactin. In practice, many patients with neuroleptic-induced TD will continue to take multiple medications that can raise prolactin levels, and with a dose-response effect of valbenazine on prolactin, valbenazine should as increasing prolactin.

Given the potential signal for cholestasis from TEAEs of increased GGT, the relationship between bilirubin and alkaline phosphatase was further examined, demonstrating a potential signal for cholestasis below.

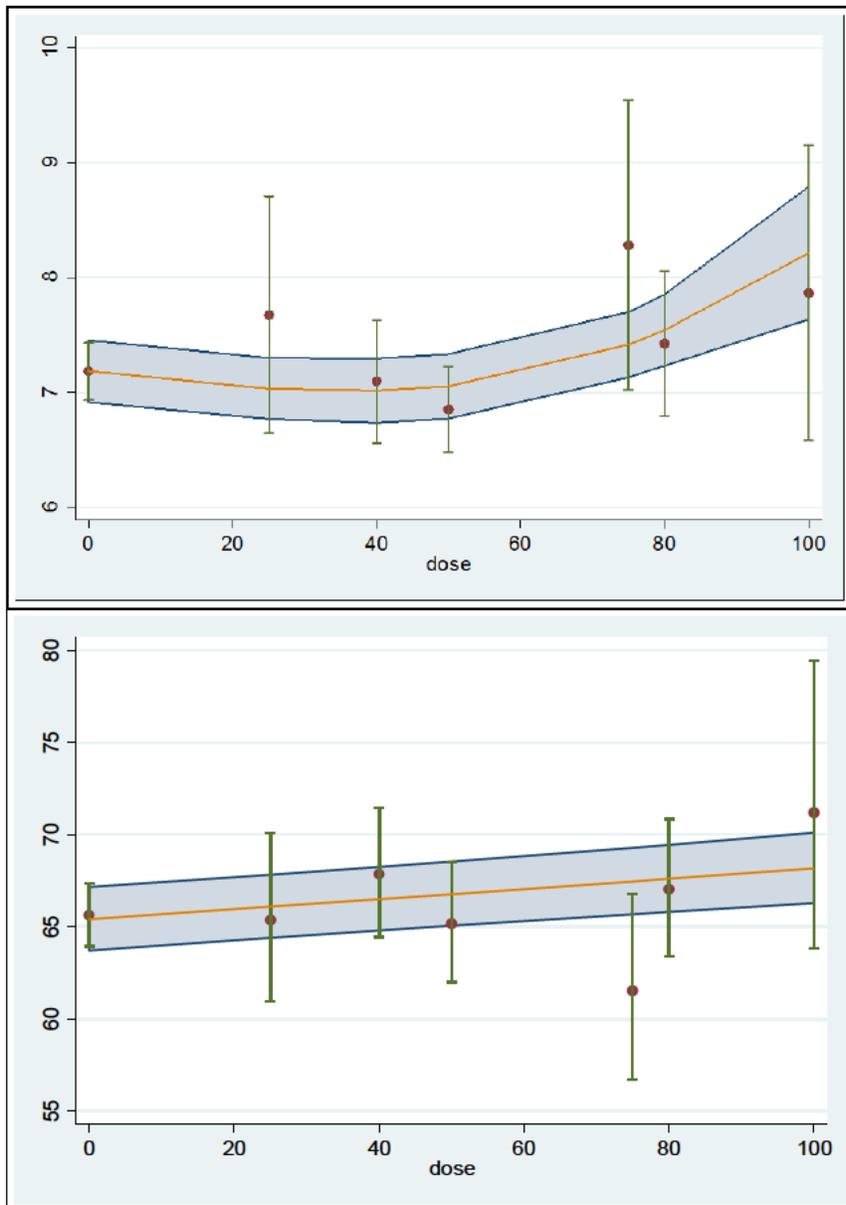
Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Figure 28: Trends in Bilirubin & Alkaline Phosphatase by Dosage across Controlled Studies 1201, 1202, and 1304**



Source: Created by Marc Stone, M.D. The first graph depicts the geometric mean of Alkaline Phosphatase (IU/L), whereas the second depicts the geometric mean of Total Bilirubin (IU/L). The error bars represent the 95% confidence interval.

While there were no TEAEs appreciated specific to cholestasis (i.e. abdominal pain is a vague complaint and exhibited no dose-response), this effect is worth noting in the label.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

### *Treatment Emergent Adverse Events due to Laboratory Abnormalities*

Several subjects had events that qualified as treatment emergent adverse events during the 6-week controlled period in valbenazine-treated subjects. These are briefly described as follows for Study 1201:

- Subject 112-1005 (Study 1201): A 62 year-old woman (100 mg / 50 mg group) with a history of hyperlipidemia developed elevated triglycerides (3.20 mmol/L as compared to baseline of 1.64 mmol/L on day 42. This resolved by day 56 with a value of 2.11 mmol/L. It is unclear if this is due to the study drug.

Additional treatment emergent adverse events due to lab abnormalities were observed during the controlled period of Study 1202:

- Subject 210-2003 (Study 1202): A 46 year-old man experienced an elevated AST of 1127 U/L and ALT of 1257 U/L on day 61 at the follow-up visit approximately 2 weeks after the final dose of study drug. They concurrently had an elevated total bilirubin of 27.4  $\mu$ mol/L and a GGT of 447 U/L. These down trended on day 61 (AST, ALT, and GGT were 152, 446, and 353 U/L, respectively) and resolved on day 71 (AST, ALT, and GGT were 39, 82, 177 U/L, respectively). As this occurred two weeks after his last dose of study drug, it is unlikely to be due to study drug.
- Subject 224-2007 (Study 1202): A 56 year-old woman experienced an elevated GGT of 189 U/L at day 41, with their most recent dose of valbenazine reported as 75 mg. At an unscheduled follow-up visit on day 48, this had resolved with a GGT of 12 U/L. The subject had no additional lab abnormalities and no relevant clinical findings of jaundice, tiredness, nausea, or vomiting. The subject completed the study without further events. It is unclear if this is due to the study drug.
- Subject 235-2002 (Study 1202): A 50 year-old woman experienced an elevated blood glucose of 12.3 mmol/L on day 40, with their most recent dose of valbenazine reported as 50 mg. This resolved on day 61, with a blood glucose level reported at 9.1 mmol/L. This patient had a history of type 2 diabetes. As VMAT2 receptors are expressed in the pancreas (discussed previously in this review), it is likely that this is due to the study drug.

Lastly, in the valbenazine 40 mg and 80 mg groups, the following treatment emergent adverse events due to lab abnormalities were observed:

- Subject 304-3001 (Study 1304, 40 mg group): A 60 year-old woman experienced an elevated BUN of 12.1 mmol/L on day 17, increased from their baseline of 5.4 mmol/L. This resolved on day 45, when the subject discontinued from the study due to body tinea. It is unclear if this is due to the study drug.
- Subject 311-3005 (Study 1304, 80 mg group): A 42 year-old Caucasian man with an elevated GGT of 101 U/L at baseline experienced an increase of GGT to 160 U/L at Day 28 (Week 4). The subject had no other elevated diagnostic labs associated with the liver or biliary tract, which resolved at week 6 to normal levels, below baseline. It is unclear if

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

this is due to the study drug.

- Subject 318-3011 (Study 1304, 40 mg): A 57 year-old African American woman with a history of hypertension, hyperlipidemia, COPD, and multiple other medical problems had an elevated BN of 10.4 mmol/L and creatinine 185.6  $\mu\text{mol/L}$  at Day 45 (Week 6). This resolved on Day 91 (unscheduled visit), when the subject was discontinued due to noncompliance (positive urine dip stick result for cocaine). This is not likely related to the study drug.
- Subject 319-3001 (Study 1304, 80 mg): A 40 year-old Caucasian man with a history of continuing urinary retention on multiple medications – sertraline, topiramate, olanzapine, benztropine, aripiprazole, lorazepam, valproate, and desmopressin – developed an isolated increase in AST and CK on Day 28 (Week 4), which were reported at 157 and 2,751 U/L, respectively. These had both resolved within the normal range at a one-week unscheduled follow-up visit on Day 35. It is unclear if this is due to the study drug.
- Subject 330-3002 (Study 1304, 40 mg): A 63 year-old Caucasian man with a history of multiple medical problems, most notably dementia, cardiomyopathy, coronary artery disease, and chronic bronchitis, on multiple medications had an elevated creatinine of 79.6  $\mu\text{mol/L}$  on Day 28 (Week 4), which had resolved by a subsequent study visit on Day 45 (Week 6). This event is unlikely due to the study drug, as the subject has extensive chronic disease known to be associated with chronic (microvascular) renal disease. Additionally, the subject reported no additional related adverse events in association with this lab abnormality.
- Subject 330-3003 (Study 1304, 40 mg): A 67 year-old Caucasian man with a history of multiple medical problems most notably hypertension, hyperlipidemia, fluid retention, and hypothyroidism and on multiple medications including enalapril, potassium, and diclofenac developed a creatinine at the upper limit of normal on Day 42 (Week 6) of 114.9  $\mu\text{mol/L}$ , which had resolved by Day 143. This event is unlikely due to the study drug, as the subject has extensive chronic disease known to be associated with chronic (microvascular) renal disease. Additionally, the subject reported no additional related adverse events in association with this lab abnormality.
- Subject 337-3020 (Study 1304, 80 mg): A 60 year-old African-American man with a history of multiple medical problems most notable for anemia, hypertension, blindness, chronic pain (generalized, back, jaw, eye, and extremity) and taking benztropine, paracetamol, and multiple other medications developed an isolated increase in BUN on Day 41 (Week 6) of 12.1 mmol/L and an associated elevated creatinine of 282.9  $\mu\text{mol/L}$ . This resolved at the subsequent study visit. It is unclear if this is related to the study drug.
- Subject 350-3004 (Study 1304, 80 mg): A 55 year-old African-American woman who had multiple medical problems most notably atrioventricular block, a tooth abscess, and was on multiple medications most notable for amoxicillin and acetylsalicylic acid. The patient had an isolated drop in their absolutely neutrophils count on Day 28 (week 4) from 2.6

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

(within normal limits) to  $1.1 \times 10^9/L$ , increasing back to within normal limits (2.1) at the subsequent unscheduled study visit on Day 49. This may be associated with the tooth abscess, as infections may manifest as either an increase or decrease in neutrophils. While the temporality is not provided, this is likely related to the abscess, and not to the study drug.

- Subject 361-3005 (Study 1304, 40 mg): A 49 year-old Caucasian man with a history of psoriasis, upper limb fracture, hydrocele, and hypersensitivity on diphenhydramine, omeprazole, olanzapine, and other medications who developed intermittent neutropenia without clinical symptoms (0.9 on Day 14, 7.1 on Day 17, 1.1 on Day 28, and 9.0 on Day 31). The sporadic nature and lack of associated symptoms and other diagnostic findings suggest that this finding was not clinically significant. The patient's history of unspecified hypersensitivity and psoriasis further conflates the immunologic picture. Therefore, this event is unlikely to be related to the study drug.
- Subject 362-3001 (Study 1304, 40 mg): A 49 year-old African-American woman with a history of hypertension, seasonal allergy, and back who was on valproate, enalapril, trazadone, and ibuprofen developed sporadic mild neutropenia with other subjects while on the drug. With a normal baseline absolute neutrophil count (ANC) of 2.5, the subject subsequently developed neutropenia to ANC count of 0.7 on Day 14 (Week 2), which had increased back to approximately baseline of 2.4 on Day 24 (Unscheduled visit). The subject had no other adverse events related to neutropenia or infection. It is unclear if this is due to the study drug.
- Subject 365-3003 (Study 1304, 80 mg): A 64 year-old African-American woman with a past medical history notable most for hypertension and hepatitis C on clonidine, amlodipine, lisinopril, hydrochlorothiazide, and other medications had a normal baseline creatinine which increased to  $176.8 \mu\text{mol/L}$  on Day 15 (Week 2). At the next study visit the value returned to baseline. There were no associated symptomatic adverse events. It is unclear if this is due to the study drug.
- Subject 369-3004 (Study 1304, 80 mg): A 60 year-old Caucasian man with a history of hepatitis C, hepatitis A, acute hepatitis with jaundice lasting for approximately six months as a teenager, acetaminophen use, and alcohol use was taking multiple medications, most notably Vicodin 5/325 mg BID, and on the last visit of the controlled period (Day 40 or Week 6), was found to have elevated AST (586 IU/L), ALT (626 IU/L), GGT (281 IU/L), and a normal total bilirubin (1.1 mg/dL). At screening, the subject had an undetectable hepatitis C viral load and was found to have a normal AST, ALT, GGT, and bilirubin. This event was reported as an SAE of acute hepatitis. The patient admitted to consuming alcohol. The patient was later hospitalized due to worsening labs. During a 14-day hospital stay, the patient was found to have a significant viral load, with a hepatitis C quantitative value of 3,485,870. While the site investigator assessed this event as likely due to the study drug. I disagree. The subject had active hepatitis C, a history of hepatitis A, a history of acute hepatitis with jaundice, was regularly taking an acetaminophen-containing product, and admitted to alcohol use. This combination of

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

multiple factors accounts for this SAE and laboratory abnormalities.

In conclusion, there is no clear pattern of lab abnormalities outside of the normal range that were considered a treatment emergent adverse event that can be clearly attributed to the drug.

### *Other Observed Lab Abnormalities*

All lab abnormalities during the 6-week placebo-controlled period of Studies 1201, 1202, and 1304 that were outside of the reference ranges and flagged as low, high, or abnormal were individually reviewed. This includes a review of 7,399 abnormal lab results, broken down as follows:

- 1,258 abnormal lab results for Study 1201
- 1,502 abnormal lab results for Study 1202
- 4,639 abnormal lab results for Study 1304

Many lab abnormalities clearly correlated with already described AEs; for example, urine WBCs seen on a urinalysis with a patient who had an AE of a UTI. Many of the abnormalities appear to represent noise (e.g. a single reading of an elevated WBC count of 11.4 in an otherwise series of normal values in a patient), and overall there was no consistent pattern observed in differences between placebo and valbenazine. However, premarket studies are limited as they are not powered to detect differences in laboratory measures for safety analyses.

### 8.4.7. **Vital Signs**

During the 6-week controlled period of Studies 1201, 1202, and 1304 there was no clinically significant difference in the mean change in vital signs -- blood pressure (systolic and diastolic), heart rate, respiratory rate, body temperature, and body weight -- between the valbenazine and placebo-treated groups. In examining shift tables of vital signs, there was no clinically or statistically significant difference between valbenazine and placebo groups for the following changes:

- Systolic blood pressure
  - Low: <90 mmHg and decrease from baseline  $\geq$  20 mmHg
  - High: >180 mmHg and increase from baseline  $\geq$  20 mmHg
- Diastolic blood pressure
  - Low: <50 mmHg and decrease from baseline  $\geq$  10 mmHg
  - High: >105 mmHg and increase from baseline  $\geq$  10 mmHg
- Heart rate
  - Low: < 50 bpm and increase from baseline  $\geq$  15 bpm
  - High: > 120 bpm and increase from baseline  $\geq$  15 bpm
- Orthostatic systolic blood pressure
  - Low: decrease of  $\geq$  20 mmHg

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

- High: increase of  $\geq 20$  mmHg
- Orthostatic diastolic blood pressure
  - Low: decrease of  $\geq 10$  mmHg
  - High: increase of  $\geq 20$  mmHg
- Orthostatic heart rate
  - Low: decrease of  $\geq 15$  bpm
  - High: increase of  $\geq 15$  bpm

In exploratory analyses, pooling of the controlled studies showed a trend to increased high orthostatic diastolic blood pressure ( $>10$  mmHg increase) albeit the results were not statistically significant.

### 8.4.8. Electrocardiograms (ECGs)

Analysis of EKG effects will be derived from the controlled periods of Studies 1201, 1202, and 1304. Specifically, I will examine trends in heart rate (HR), the PR interval, the QRS duration, and the  $QT_cF$ . Note that [Section 8.4.9](#) will further evaluate effects of the Study drug on QT. Of note, the Sponsor did not provide a clear standardized submission or summary of waveform abnormalities, and thus I am unable to comment on waveform abnormalities.

#### *Study 1201*

In Study 1201, subjects underwent at standard 12-lead EKG in triplicate (1 – 3 minutes apart) after the subject had rested supine for a minimum of 5 minutes. This was conducted at screening, Study Day -1, and during treatment (end of Weeks 2, 6, 8, and 12) and during the follow-up period (end of week 16). My analysis will focus on the controlled period, namely the measurements at Study Day -1, and the end of Weeks 2, 6.

With respect to conduction, there appeared to be a dose-dependent decrease in the QRS and PR intervals at week 6, albeit this effect was not observed at week 2. The maximum difference in the QRS duration between placebo and drug was observed in the 100 mg / 50 mg group, which was a mean change from the previous Study visit of -0.7 msec. However, this effect is likely below the minimum precision of a standard EKG machine used in clinical practice. The maximum difference in PR interval observed was similarly between the 100 mg / 50 mg and placebo groups, was -3.2 msec. That this effect was not observed in the 50 mg group suggests either a cumulative dose effect or that this is artifact.

There is no consistent, dose-dependent effect on HR at week 6. In contrast,  $QT_cF$  at week 6 in highest dose group showed a mean increase from baseline (Day -1) of 3.6 msec as compared to no change from baseline in the placebo group; this effect appeared to be more pronounced for CYP2D6 extensive metabolizers v. intermediate metabolizers (6.3 v. 1.1 msec). The 50 mg group showed no statistically significant change in  $QT_cF$  from baseline.

In comparing early terminators to those who remained enrolled, the only difference

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

appreciated was that early terminators were more likely to have to have a longer corrected QT interval at week 6 (449 v. 401 msec). This difference was statistically significant (via two-tailed t-test, unpaired,  $P < 0.05$ ). In contrast, at any point during the Study, drug-treated v. placebo-treated subjects were no more likely to experience a  $QT_cF > 450$  msec.

Overall, during the controlled period, no subjects had a change in  $QT_cF$  from baseline  $> 50$  msec. Only one subject had an average  $QT_cF$  exceed 500 msec, 1201-1271006, who received placebo and registered at their week 2 visit a  $QT_cF$  of 504 and 513 msec. This returned to under 500 msec at the next Study visit.

In conclusion, while minor abnormalities were observed, there was no consistent effect (i.e. dose-dependent) on EKG due to the Study drug, except for a weak signal of prolonged QT at the highest doses at the end of the controlled period.

### *Study 1202*

In Study 1202, subjects underwent at standard 12-lead EKG in triplicate (1 – 3 minutes apart) after the subject had rested supine for a minimum of 5 minutes. This was conducted at screening, Study Day -1, and during treatment (end of Weeks 2, 6) and during the follow-up period (end of week 8) or early termination.

Analysis of the data by Study visit and dose revealed:

- No significant dose-dependent response in HR or change from baseline in HR
- No significant dose-dependent response in PR interval or change from baseline in PR interval
- No significant dose-dependent response in QRS duration or change from baseline in QRS duration
- No significant dose-dependent response in  $QT_cF$  or change from baseline in  $QT_cF$

Notably, no subject experienced a  $QT_cF > 500$  msec during Study 1202 and only one subject (placebo-treated) experienced a change from baseline in  $QT_cF > 50$  msec. Of the subjects who exhibited a  $QT_cF > 450$  msec at any point in the Study, only one was a placebo-treated subject (1/51 subjects or 1.9%) whereas 12 drug-treated subjects (12/51 or 21.8%) did. This difference was statistically significant (Fisher's exact test, two-tailed,  $P = 0.0002$ ).

In conclusion, the only consistent effect is that drug-treated subjects are more likely to experience a  $QT_cF > 450$  msec as compared to placebo-treated subjects.

### *Study 1304*

In Study 1304, subjects underwent at standard 12-lead EKG in triplicate (1 – 3 minutes apart) after the subject had rested supine for a minimum of 5 minutes. This was conducted at screening, Study Day -1, and during treatment (end of Weeks 2, 4, and 6) and during the open-label extension period or early termination. My analysis will consist of the controlled period.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Analysis of the data by Study visit and dose revealed:

- No significant dose-dependent response in HR or change from baseline in HR
- No significant dose-dependent response in PR interval or change from baseline in PR interval
- No significant dose-dependent response in QRS duration or change from baseline in QRS duration
- No significant dose-dependent response in QT<sub>c</sub>F or change from baseline in QT<sub>c</sub>F

Of subjects experiencing a change from baseline in QT<sub>c</sub>F > 50 msec, there was one subject each in the placebo, valbenazine 40 mg, and valbenazine 80 mg groups. These results are not statistically significant (chi-squared test,  $p > 0.05$ ). No subjects experienced a QT<sub>c</sub>F > 500 msec, and the distribution of subjects who experienced a QT<sub>c</sub>F > 450 msec at any point in the Study was similar across groups (8/78 or 10% in placebo, 10/76 or 13% in 40 mg, 7/80 or 9% in 80 mg) and not statistically significant (chi-squared test,  $p > 0.05$ ).

### *Summary of EKG Changes*

Throughout the controlled trials in the safety database for valbenazine, only one placebo-treated subject and no drug-treated subjects experienced a QT<sub>c</sub>F > 500 msec. In one of three Studies, drug-treated subjects as compared to placebo-treated subjects were more likely to experience a QT<sub>c</sub>F > 450 msec. In no Studies was there a clear dose-response effect on the proportion of subjects who experienced a change in baseline of QT<sub>c</sub>F > 50 msec. There were no significant, dose-dependent, and consistent changes in HR, PR interval, or QRS duration. QT effects will be examined in greater detail in the next section.

### 8.4.9. QT

For further evaluation of potential QT<sub>c</sub> prolongation, the Division of Psychiatry Products consulted the QT team. The Applicant conducted Study 1401 in order to examine the effects of a high dose of valbenazine in healthy volunteers. Specifically, the Study sought to examine whether a single dose of valbenazine 160 mg affected the QT in healthy volunteers. Secondary objects were as follows:

- Measuring the effects on heart rate, PR interval, QRS duration, and the QT interval
- Assessing the relationship between plasma concentrations of valbenazine, its major metabolites NBI-98782 (active metabolite, resulting from ester hydrolysis) and NBI-136110 (inactive metabolite, resulting from oxidative metabolism via CYP3A4), and any effect on the QT<sub>c</sub>
- Assess the effect of a positive control, moxifloxacin, on QT<sub>c</sub> and compare it to the effects (if any) of valbenazine and its major metabolites

Study 1401 was a three-way crossover Study, whereby subjects received placebo, moxifloxacin,

## Clinical Review

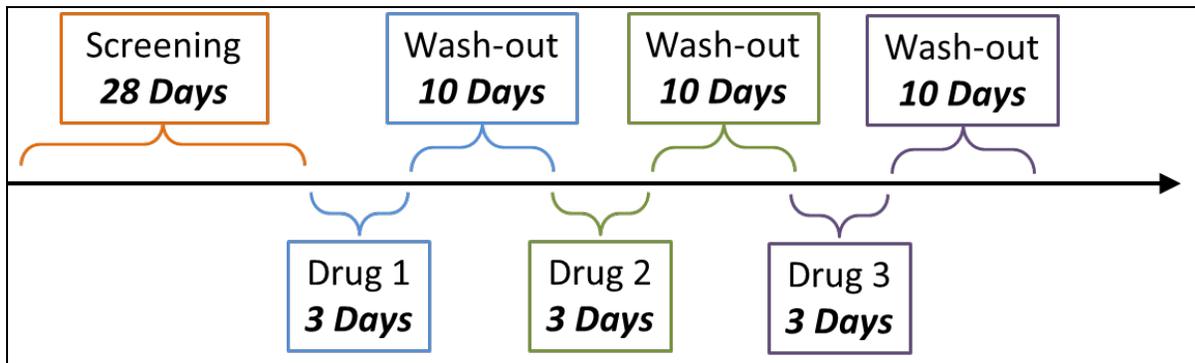
Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

and valbenazine. A total of 48 healthy subjects (1:1 men: women) enrolled, and 46 subjects completed the Study. The expected duration was 8 weeks: 28 days of screening, 3 days of Study drug dosing, 10 day wash-out, and a final Study visit 10 days later.

**Figure 29: Study 1401 Diagram**



Source: Reviewer-created study diagram

The treatment arms were as follows:

- Treatment A: (4) x 40 mg valbenazine capsules + 1 moxifloxacin placebo tablet
- Treatment B: (4) x placebo capsules + 1 x 400 mg moxifloxacin tablet
- Treatment C: (4) x placebo capsules + 1 placebo tablet

The valbenazine 160 mg dose was chosen as its projected steady-state C<sub>max</sub> was similar to that of the projected steady-state C<sub>max</sub> in individuals with severe hepatic impairment taking the maximum proposed therapeutic dose of 80 mg. The 160 mg dose was also projected to result in exposure to active metabolite NBI-98782 at a concentration that would be similar to the steady state peak plasma concentration following an 80 mg daily dose in CYP2D6 extensive metabolizers. EKG monitoring was conducted during each treatment period from 1.5 hours pre-dose until 48 hours post dose. EKGs (in triplicate) and blood samples for pharmacokinetic studies were assessed at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post dose.

In order to determine the best QT correction methodology, the QT team computed the mean sum of the squared slopes (MSSS) for different QT-RR correction methods (QT<sub>cB</sub>, QT<sub>cF</sub>, and QT<sub>cI</sub>)<sup>7</sup> for Study 1401. These values are displayed in the following table.

<sup>7</sup> Bazett's formula:  $QT_{cB} = QT / \sqrt{RR}$   
Fridericia's formula:  $QT_{cF} = QT / \sqrt[3]{RR}$   
QT<sub>cI</sub> = QT<sub>c</sub> Individually corrected

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 81: Mean of Sum of Squared Slopes for Different QT-RR correction methods (Study 1401)**

| Treatment Group     | QTcB |         | QTcF |         | QTcI |         |
|---------------------|------|---------|------|---------|------|---------|
|                     | N    | MSSS    | N    | MSSS    | N    | MSSS    |
| Placebo             | 46   | 0.00617 | 46   | 0.00270 | 46   | 0.00061 |
| Moxifloxacin 400 mg | 48   | 0.00588 | 48   | 0.00283 | 48   | 0.00349 |
| NBI-98854 160 mg    | 46   | 0.00454 | 46   | 0.00156 | 46   | 0.00156 |
| All                 | 48   | 0.00524 | 48   | 0.00145 | 48   | 0.00165 |

Source: Reviewer-created table (adapted from QT team) for corrected QT interval

Thus, QTcF was used for the primary statistical analysis. Initially, the statistical reviewer used a mixed model in order to analyze the  $\Delta QT_cF$  effect, with treatment as a fixed effect and the baseline value as a covariate. Adjustment was via the Bonferroni method.

**Table 82: Study 1401, Analysis of QTcF for Valbenazine 160 mg and Moxifloxacin 400 mg**

| Time (h) | Placebo       | Moxifloxacin 400 mg |         |                     |             |              | NBI-98854 160 mg |         |                     |              |
|----------|---------------|---------------------|---------|---------------------|-------------|--------------|------------------|---------|---------------------|--------------|
|          | $\Delta QTcF$ | $\Delta QTcF$       |         | $\Delta\Delta QTcF$ |             |              | $\Delta QTcF$    |         | $\Delta\Delta QTcF$ |              |
|          | LS Mean       | N                   | LS Mean | LS Mean             | 90% CI      | *Adj. 90% CI | N                | LS Mean | LS Mean             | 90% CI       |
| 0.5      | -1.9          | 48                  | 3.7     | 5.6                 | (3.5, 7.7)  | (2.7, 8.4)   | 46               | -2.7    | -0.8                | (-2.9, 1.3)  |
| 1        | -0.2          | 48                  | 9.9     | 10.1                | (8.2, 11.9) | (7.5, 12.6)  | 46               | -2.2    | -2.0                | (-4.0, -0.1) |
| 2        | 0.0           | 48                  | 11.9    | 11.8                | (9.8, 13.9) | (9.0, 14.7)  | 46               | 2.6     | 2.6                 | (0.5, 4.7)   |
| 3        | 2.8           | 48                  | 11.2    | 8.4                 | (5.8, 11.0) | (4.9, 11.9)  | 46               | 6.0     | 3.2                 | (0.6, 5.8)   |
| 4        | -1.8          | 48                  | 7.7     | 9.4                 | (6.4, 12.4) | (5.3, 13.5)  | 46               | 1.3     | 3.0                 | (0.0, 6.1)   |
| 5        | -3.3          | 47                  | 4.5     | 7.8                 | (4.6, 10.9) | (3.5, 12.0)  | 45               | 2.2     | 5.5                 | (2.4, 8.6)   |
| 6        | -3.1          | 47                  | 6.2     | 9.3                 | (6.2, 12.4) | (5.1, 13.5)  | 45               | 1.9     | 5.0                 | (1.9, 8.1)   |
| 8        | -4.2          | 47                  | 6.4     | 10.6                | (7.8, 13.3) | (6.8, 14.3)  | 44               | 4.7     | 8.9                 | (6.1, 11.7)  |
| 12       | -4.1          | 47                  | 3.2     | 7.3                 | (4.6, 10.0) | (3.6, 11.1)  | 45               | 4.2     | 8.3                 | (5.6, 11.1)  |
| 24       | -7.2          | 47                  | -2.3    | 4.9                 | (2.1, 7.7)  | (1.1, 8.7)   | 44               | -1.0    | 6.1                 | (3.3, 8.9)   |
| 36       | -5.3          | 47                  | -1.4    | 3.9                 | (1.0, 6.8)  | (-0.0, 7.9)  | 46               | -2.1    | 3.2                 | (0.2, 6.1)   |
| 48       | -6.5          | 47                  | -3.5    | 3.0                 | (-0.1, 6.1) | (-1.2, 7.3)  | 46               | -1.3    | 5.2                 | (2.1, 8.3)   |

Source: Reviewer-created table (adapted from QT team) of corrected QT interval based upon time from dose

Notably, the highest upper bound for the 90% confidence interval above is 11.7 ms (8.9 ms at 8 hours, 90% CI 6.1 – 11.7 ms), exceeding the regulatory concern described in the ICH E14 guidelines (10 ms ceiling). The reviewer examined the individual values for each Study, noting that for both Study 1401 and Study 1301, no QTcF values above 480 ms were observed. Furthermore, no  $\Delta QTcF$  values for either Study were above 60 ms for valbenazine 160 mg or 300 mg doses.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

The QT team felt that the suprathreshold dose examined in Study 1401 was inadequate, and examined additional Studies for the purposes of pooling. The Studies analyzed by the QT team are as follows:

**Table 83: Summary of Studies for QT review**

|                | Study Design   | Dose: Subject #   | PK/ECG Sampling Schedule   |
|----------------|--|---|--|
| NBI-98854-1401 | Thorough QT/QTc study: single-dose, double-blind, 3-way cross-over, double-dummy, placebo- | 160 mg single dose: 48;<br>Poor CYP metabolizer not eligible  | PK/Continuous 12-lead Holter monitoring: 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48 hrs post-dose   |
| NBI-98854-1301 | Double-blind, placebo-controlled, parallel study   | Placebo: 3<br>150 mg single dose: 6<br>300 mg single dose: 6<br>Poor CYP metabolizer not eligible   | PK: 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 96, and 168 hrs post-dose<br>Standard 12-lead ECG: screening, Day-2, and final study visit<br>Continuous 12-lead Holter monitoring: 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hrs postdose  |
| NBI-98854-0901 | Double-blind, placebo-controlled, cross-over/parallel, single dose/multiple dose           | Placebo: 10<br>50 mg QD: 1<br>Poor CYP metabolizer, 6<br>Intermediate CYP metabolizer, 7<br>Extensive CYP metabolizer<br>100 mg QD: 4 Extensive CYP metabolizer; 4 Intermediate CYP metabolizer | PK: 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24 hrs after Day 1 and Day 8 dose<br>Standard 12-lead ECG: screening; Day -1; Day 3-5 pre-dose; 24 hrs after Day 8 dose; final visit<br>Holter monitoring: 0, 2, 4, 8, 10, 24 hrs after Day 8 dose and 5 matching time points on Day -1 |

Source: Reviewer-created table

Briefly, Study 901 was not included due to failure to show an appropriate and consistent dose-response curve in the concentration of the major active metabolite, NBI-988782. Thus, Studies 1301 and 1401 were pooled. Based upon this analysis, the predicted mean value and 90% confidence interval (CI) for valbenazine 80 mg doses in healthy volunteers was 6.7 msec (5.1 – 8.4 msec) as compared to 11.7 msec (8.8 – 14.7 msec) in CYP2D6 poor metabolizers.

For further details regarding this analysis, please refer to the QT team review.

### 8.4.10. Immunogenicity

Hypersensitivity and overall immunogenicity is of interest in any new molecular entity. In order to assess the immunogenicity of valbenazine, the three randomized, controlled trials (Studies 1201, 1202, and 1304) and the prospective observational safety database (613 subjects experiencing 1,552 AEs) were examined to look for AEs that could represent hypersensitivity reactions or immunogenicity. Specifically, the controlled period of Studies 1201, 1202, and 1304 were examined for more common hypersensitivity reactions such as pruritus, urticaria, rash, wheezing, edema, or laryngospasm. The prospective observational safety database was additionally examined for rare hypersensitivity reactions such as angioedema, anaphylactic shock, and asthma exacerbation.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

### *Experience in Controlled Trials*

In Studies 1201 and 1202 during the controlled period, no subject reported a TEAE of wheezing, edema, rash, urticarial, laryngospasm, hypersensitivity reaction, or a related term. Two subjects in Study 1201 receiving placebo reported pruritus

Notably, none of the aforementioned AEs were experienced in controlled period Study 1304 except the following:

- In Study 1304, three subjects experienced peripheral edema, one subject was receiving placebo and two subjects were receiving valbenazine 40 mg (p-value not significant, Fisher's exact test, two-tailed)
- Two subjects in Study 1304, one on placebo and another receiving valbenazine 80 mg, experienced rash (p-value not significant, Fisher's exact test, two-tailed)

No subjects discontinued during the controlled period of Studies 1201, 1202, or 1304 due to these events.

### *Experience in Prospective, Observational Safety Database*

The prospective, observational safety database has been previously described. In this AE database comprising 613 subjects and 1,552 AEs, there were no reported AEs of angioedema or anaphylactic shock. Of note, four unique subjects experienced an AE of bronchospasm, one subject receiving valbenazine 40 mg and three subjects receiving valbenazine 80 mg. The incidence per 100 Person-Years exposure is 0.9 events v. 2.4 events for the 40 mg and 80 mg groups, respectively (a rate ratio of 2.6). The rates for pruritis and rash did not demonstrate any drug effect (i.e. no increase in drug v. placebo or a dose-dependent response) in the prospective observational safety database.

## 8.5. Analysis of Submission-Specific Safety Issues

With the extensive baseline burden of psychiatric disease in the patient population and the extensive use of psychiatric concomitant medications (antipsychotics, antidepressants, benzodiazepines, etc.), additional assessments are necessary to measure psychiatric symptoms.

Specifically,

- In order assess suicidal ideation and behavior, the Applicant utilized the Columbia-Suicide Severity Rating Scale (C-SSRS)
- In order to assess akathisia and extrapyramidal symptoms, the Applicant used the Barnes Akathisia Rating Scale (BARS) and the Simpson-Angus Scale (SAS)
- In order to assess for the worsening or improvement of symptoms of schizophrenia or schizoaffective disorder, the Applicant used the Positive and Negative Syndrome Scale for Schizophrenia (PANSS)
- In order to assess for depressive symptoms in the setting of schizophrenia or

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

schizoaffective disorder, the Applicant used the Calgary Depression Scale (CDS)

- In order to assess for symptoms of mania, the Applicant utilized the Young Mania Rating Scale (YMRS)
- In order to assess for changes in the severity of depressive symptoms in the setting of mood disorder(s), the Applicant utilized the Montgomery-Asberg Depression Rating Scale (MADRS)

Each of these assessments, their schedule of administration in the controlled Studies (1201, 1202, 1304), and an analysis of their results will be addressed in the following sections. It is important to note that these instruments are deployed in the development program as measures of depression, suicidality, mania, etc. as measures of adverse events for the Study drug, not as measures of improvement of the underlying disease.

### 8.5.1. Suicidal Ideation and Behavior

The C-SSRS is a validated instrument used to prospectively assess suicidality ideation and behavior. It is used as screening (Baseline/Screening version), Baseline or Day -1, and scheduled visits throughout the Study (since last visit version). All versions include standard screening questions related to suicidal ideation and behavior. A subject response of “yes” to one or more questions will prompt the investigator to ask additional questions to evaluate the frequency and intensity of the suicidal ideation or behavior. If at any point after the baseline visit, a subject’s response to the SI section of the C-SSRS was worse than baseline, it was document as an AE. All suicidal behaviors were automatically documented as AEs. The complete C-SSRS questionnaire is available in [Section 13.2](#).

In Study 1201, the C-SSRS was administered at screening, Study Day -1, and during the treatment period visits (end of Weeks 2, 4, 6, 8, 10, and 12) and at follow-up visits 2 and 4 weeks after the last dose of the Study drug or at early termination. The “screening/baseline” version was used to evaluate subject eligibility and baseline, while the “since last visit” version was used at all other times. In Study 1202, the C-SSRS was administered on the same schedule, except that the last treatment period visit occurs at the end of week 6, with the follow-up period visit occurring at the end of week 8. In Study 1304, investigators administered the C-SSRS at screening, Day -1, during the controlled period (end of weeks 2, 4, and 6), during the extension period (end of weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48) and at the follow-up visit (end of week 52) or at early termination.

My analysis of Studies 1201, 1202, and 1304 will focus on examining the controlled periods. As the absolute event rate for ideation and behavior is very small and overall C-SSRS scores are low, I will compare the incidence of specific C-SSRS items and the cumulative rate of ideation or behavior. In Study 1201, a dose-reduction Study, the rate of suicidal ideation or behavior during the controlled period was higher in the placebo group (not statistically significant,  $p > 0.05$ , Fisher’s exact test, two-tailed).

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 84: C-SSRS data for Study 1201**

|                             | Item   | Placebo |      | VBZ (50 - 100 mg) |      |
|-----------------------------|--|---------|------|-------------------|------|
|                             |  | N       | %    | N                 | %    |
| <b>Suicidal Ideation</b>    | Wish to be Dead  | 2       | 3.7% | 1                 | 1.8% |
|                             | Non-Specific Active Suicidal Thoughts                  | 2       | 3.7% | 0                 | 0.0% |
|                             | Active Suicidal Ideation without Intent                | 0       | 0.0% | 0                 | 0.0% |
|                             | Active Suicidal Ideation with Some Intent              | 0       | 0.0% | 0                 | 0.0% |
|                             | Active Suicidal Ideation with Specific Plan and Intent | 0       | 0.0% | 0                 | 0.0% |
| <b>Suicidal Behavior</b>    | Preparatory Acts or Behavior                           | 0       | 0.0% | 0                 | 0.0% |
|                             | Aborted attempt  | 0       | 0.0% | 0                 | 0.0% |
|                             | Interrupted attempt                                    | 0       | 0.0% | 0                 | 0.0% |
|                             | Non-fatal suicide attempt                              | 0       | 0.0% | 0                 | 0.0% |
|                             | Completed suicide                                      | 0       | 0.0% | 0                 | 0.0% |
| <b>Ideation or Behavior</b> |  | 2       | 3.7% | 1                 | 1.8% |
| N                           |  | 54      |      | 55                |      |

Source: Reviewer-created table for Study 1201, adapted from Study 1201 Study Report

In comparison, Study 1202 was a dose-titration Study, wherein subjects were titrated from 25 mg to up to 75 mg during the 6-week controlled period. No suicidal ideation or behavior occurred in the placebo group, whereas 5.9% of subjects in the valbenazine group (varying doses) experienced suicidal ideation, and no subjects exhibited suicidal behavior. This trend is not statistically significant (Fisher’s exact test,  $p > 0.05$ , two-tailed).

**Table 85: C-SSRS data for Study 1202**

|                             | Item   | Placebo |      | VBZ (25 - 75 mg) |      |
|-----------------------------|--|---------|------|------------------|------|
|                             |  | N       | %    | N                | %    |
| <b>Suicidal Ideation</b>    | Wish to be Dead  | 0       | 0.0% | 3                | 5.9% |
|                             | Non-Specific Active Suicidal Thoughts                  | 0       | 0.0% | 1                | 2.0% |
|                             | Active Suicidal Ideation without Intent                | 0       | 0.0% | 1                | 2.0% |
|                             | Active Suicidal Ideation with Some Intent              | 0       | 0.0% | 1                | 2.0% |
|                             | Active Suicidal Ideation with Specific Plan and Intent | 0       | 0.0% | 0                | 0.0% |
| <b>Suicidal Behavior</b>    | Preparatory Acts or Behavior                           | 0       | 0.0% | 0                | 0.0% |
|                             | Aborted attempt  | 0       | 0.0% | 0                | 0.0% |
|                             | Interrupted attempt                                    | 0       | 0.0% | 0                | 0.0% |
|                             | Non-fatal suicide attempt                              | 0       | 0.0% | 0                | 0.0% |
|                             | Completed suicide                                      | 0       | 0.0% | 0                | 0.0% |
| <b>Ideation or Behavior</b> |  | 0       | 0.0% | 3                | 5.9% |
| N                           |  | 49      |      | 51               |      |

Source: Reviewer-created table for Study 1202, adapted from Study 1202 Study Report

Lastly, suicidal ideation and behavior was examined in Study 1304, a placebo-controlled, fixed dose Study which demonstrated no clear drug effect or dose-response.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table 86: C-SSRS data for Study 1304**

|                             | Item   | Placebo |      | VBZ 40 mg |      | VBZ 80 mg |      |
|-----------------------------|--|---------|------|-----------|------|-----------|------|
|                             |  | N       | %    | N         | %    | N         | %    |
| <b>Suicidal Ideation</b>    | Wish to be Dead  | 3       | 3.9% | 4         | 5.6% | 2         | 2.8% |
|                             | Non-Specific Active Suicidal Thoughts                  | 3       | 3.9% | 0         | 0.0% | 2         | 2.8% |
|                             | Active Suicidal Ideation without Intent                | 1       | 1.3% | 0         | 0.0% | 1         | 1.4% |
|                             | Active Suicidal Ideation with Some Intent              | 0       | 0.0% | 0         | 0.0% | 1         | 1.4% |
|                             | Active Suicidal Ideation with Specific Plan and Intent | 0       | 0.0% | 0         | 0.0% | 1         | 1.4% |
| <b>Suicidal Behavior</b>    | Preparatory Acts or Behavior                           | 0       | 0.0% | 0         | 0.0% | 1         | 1.4% |
|                             | Aborted attempt  | 0       | 0.0% | 0         | 0.0% | 0         | 0.0% |
|                             | Interrupted attempt                                    | 0       | 0.0% | 0         | 0.0% | 0         | 0.0% |
|                             | Non-fatal suicide attempt                              | 0       | 0.0% | 0         | 0.0% | 1         | 1.4% |
|                             | Completed suicide                                      | 0       | 0.0% | 0         | 0.0% | 0         | 0.0% |
| <b>Ideation or Behavior</b> |  | 4       | 5.3% | 4         | 5.6% | 2         | 2.8% |
| N                           |  | 76      |      | 71        |      | 79        |      |

Source: Reviewer-created table for Study 1304, adapted from Study 1304 Study Report

A systematic review of 51 Studies estimated the lifetime risk of suicide at 5% in schizophrenics. [38] These trial results are consistent with baseline rate of suicide in schizophrenics and patients with schizoaffective disorder, suggesting no increased risk from valbenazine in the premarket setting.

### 8.5.2. Akathisia and Extrapyrimal Symptoms

The Barnes Akathisia Scale (BARS) and Simpson-Angus Scale (SAS) were utilized to assess the presence and severity of drug-induced akathisia. The BARS is a validated, [39] four-item scale that includes objective and subject items (each rated on a scale of 0 to 3), which are summed for a total score ranging from 0 to 9. Additionally, there is a global assessment item, which is rated on a scale of 0 to 5 (0 = absent, 1 = questionable, 2 = mild akathisia, 3 = moderate akathisia, 4 = moderate akathisia, 5 = severe akathisia).

The SAS is a validated [40] 10-item scale focusing on clinician-assessed rigidity. Each item is rated on a scale of 0 to 4 of increasing severity with definitions for each anchor point. The SAS is calculated by adding all items together, and dividing by 10. The complete BARS and SAS questionnaires are available in [Section 13.2](#).

In Studies 1201, the investigator administered the BARS and SAS at Screening, Study Day -1, during treatment (end of weeks 2, 6, and 12), and at the end of the follow-up period (end of week 16) or at early termination. In Study 1202, the BARS and SAS were administered on a similar schedule, except that treatment period visits were more frequent (end of weeks 2, 4, and 6), with the follow-up period visit occurring at the end of week 8. In Study 1304, investigators administered the BARS and SAS at screening, Day -1, during the controlled period

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

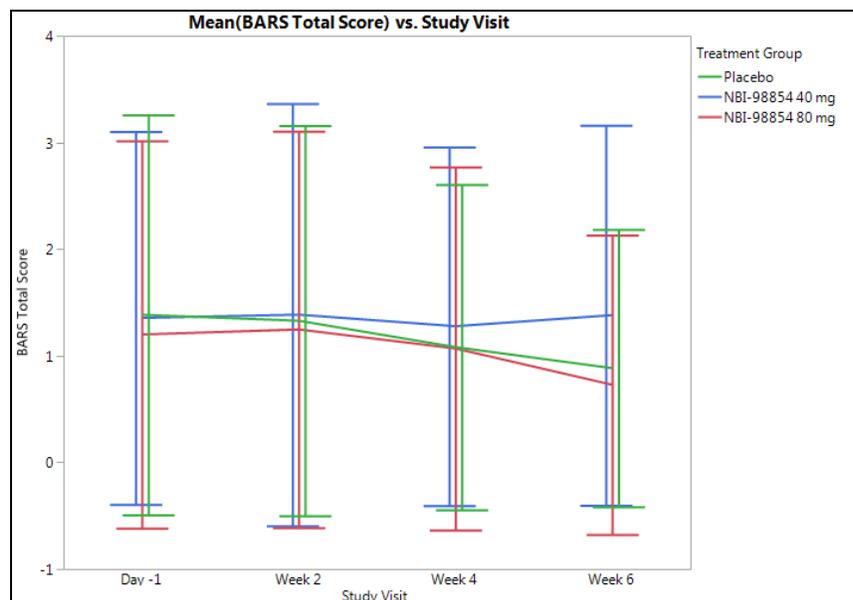
Ingrezza (valbenazine)

(end of weeks 2, 4, and 6), during the extension period (end of weeks 8, 16, 24, 32, 40, and 48) and at the follow-up visit (end of week 52) or at early termination.

### *Barnes Akathisia Scale (BARS)*

In Studies 1201, 1202, and 1304, the BARS was assessed at Study Day -1, end of week 2, and the end of week 6 (end of treatment period). I examined the absolute value and CFB in BARS Item #4 - the global clinical assessment (score range 0 – 5) - and in the BARS total score (sum of BARS Items 1 – 3, range total score 0 – 9). In all Studies, the population had low group mean Item #4 and mean group Total scores at baseline and throughout the 6-week controlled trial period. There was no effect of the drug on the overall mean BARS Total Score or mean Item #4 score. I conducted exploratory analyses in order to assess for the role of gender, age, ethnicity, race, genotype (CYP2D6 metabolizer status), diagnosis, and early termination, and found no significant differences amongst sub-groups (analyses not shown). The following figure demonstrates the BARS Total Score for Study 1304 (errors bars represent +/- 1 S.E.).

**Figure 30: Mean BARS Total Score v. Study Visit in Study 1304**



Source: Reviewer-created chart from derived from BARS dataset (BARS.xpt) for Study 1304. Error bars represent +/- 1 S.E.M.

The BARS Total Score demonstrated minimal drug-induced akathisia (maximum score of 9) and showed no statistically significant change over time or between groups, demonstrating no consistent dose-response drug effect. This was confirmed by a similar trend seen in the BARS Item #4, the global clinical assessment of akathisia.

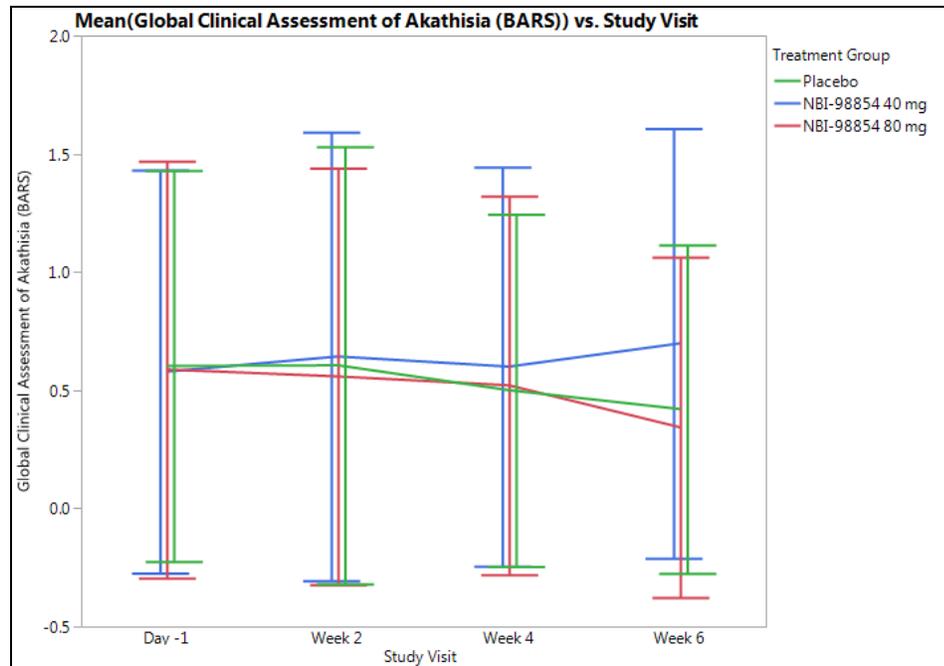
## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Figure 31: Mean BARS Item #4 (Global Clinical Assessment of Akathisia) v. Study Visit in Study 1304**



Source: Reviewer-created chart from derived from BARS dataset (BARS.xpt) for Study 1304. Error bars represent +/- 1 S.E.M.

### Simpson-Angus Scale (SAS)

In Studies 1201, 1202, and 1304, the SAS was assessed at Study Day -1, end of week 2, and the end of week 6 (end of treatment period). I examined the absolute value and CFB in SAS Global Score (score range 0 – 4). In all Studies, the population had low SAS Global scores at baseline and throughout the 6-week controlled trial period. There was no effect of the drug on the overall SAS Total Score and no dose-response observed. I conducted exploratory analyses in order to assess for the role of gender, age, ethnicity, race, genotype (CYP2D6 metabolizer status), diagnosis, and early termination, and found no significant differences amongst sub-groups (analyses not shown). The following figure demonstrates the SAS Global Score for Study 1304 (errors bars represent +/- 1 S.E.).

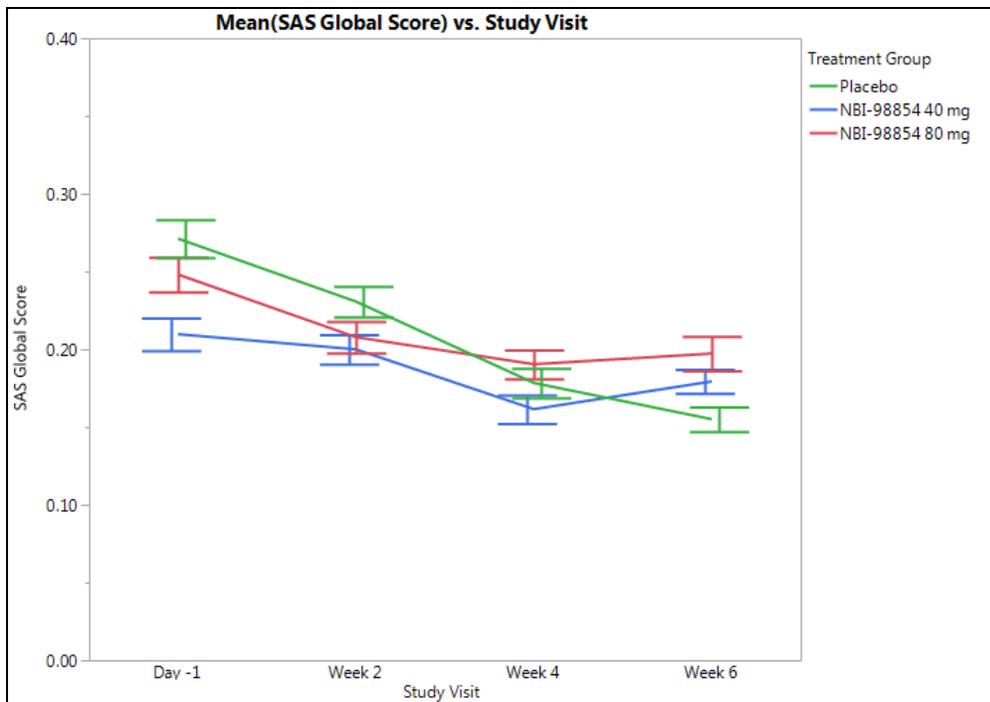
## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Figure 32: Mean SAS Global Score v. Study Visit (Study 1304)**



Source: Reviewer-created chart from derived from SAS dataset (SAS.xpt) for Study 1304. Error bars represent +/- 1 S.E.M.

### Conclusions: Akathisia and Extrapyramidal Symptoms

Based upon the assessment of akathisia and extrapyramidal symptoms via the BARS and SAS instruments during the controlled period of Studies 1201, 1202, and 1304, there was no significant drug effect resulting in worsening of akathisia or other extrapyramidal symptoms. This is consistent with the weak signal in the TEAE data for akathisia and extrapyramidal symptoms observed during controlled trials.

### 8.5.3. Exacerbation of Symptoms of Schizophrenia or Schizoaffective Disorder

The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia is validated [41] instrument used to assess symptoms in schizophrenia patients. The scale is divided into three sections with 7 items to evaluate positive symptoms, 7 items to evaluate negative symptoms, and 16 items to assess general psychopathology. Each item is scored on a 7-point severity scale<sup>8</sup> (0 = absent, 1 = minimal, 2 = mild, 3 = moderate, 4 = moderate severe, 5 = severe, 6 =

<sup>8</sup> Note that the Applicant used PANSS anchors of 0 – 6 whereas 1 – 7 is typical.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

extreme), with a total maximum score of 180. A composite scale expresses the direction and magnitude of the difference between positive and negative symptoms. The complete PANSS questionnaire is available in [Section 13.2](#).

In Study 1201, investigators administered the PANSS at study Day -1, during treatment (end of weeks 2, 6, and 12), and during the follow-up (end of week 16) or at early termination. In Study 1202, investigators administered the PANSS at Study Day -1, during treatment (end of week 6), and during the follow-up period (end of week 8). In Study 1304, investigators administered the PANSS at screening, Day -1, during the controlled period (end of weeks 2, 4, and 6), during the extension period (end of weeks 8, 16, 24, 32, 40, and 48) and at the follow-up visit (end of week 52) or at early termination.

My analysis will consist of examining the total positive, negative, and general psychopathology scores for each trial, in addition to the composite scale. In Studies 1201, 1202, and 1304, the PANSS was assessed at study Day -1, end of week 2, and the end of week 6 (end of treatment period). I examined the absolute value and CFB for the positive score (range 0 - 42), negative score (range 0 - 42), general psychopathology (range 0 – 96), and composite score (range -42 to +42). Overall, across Studies, there was no consistent drug effect or dose-response in either the score or CFB for each of the four PANSS categories. I conducted exploratory analyses in order to assess for the role of gender, age, ethnicity, race, genotype (CYP2D6 metabolizer status), diagnosis, and early termination, and found no significant differences amongst sub-groups (analyses not shown). The following figure demonstrates the mean total Positive and Negative Symptom Scores for Study 1304 (errors bars represent +/- 1 S.E.).

APPEARS THIS WAY ON ORIGINAL

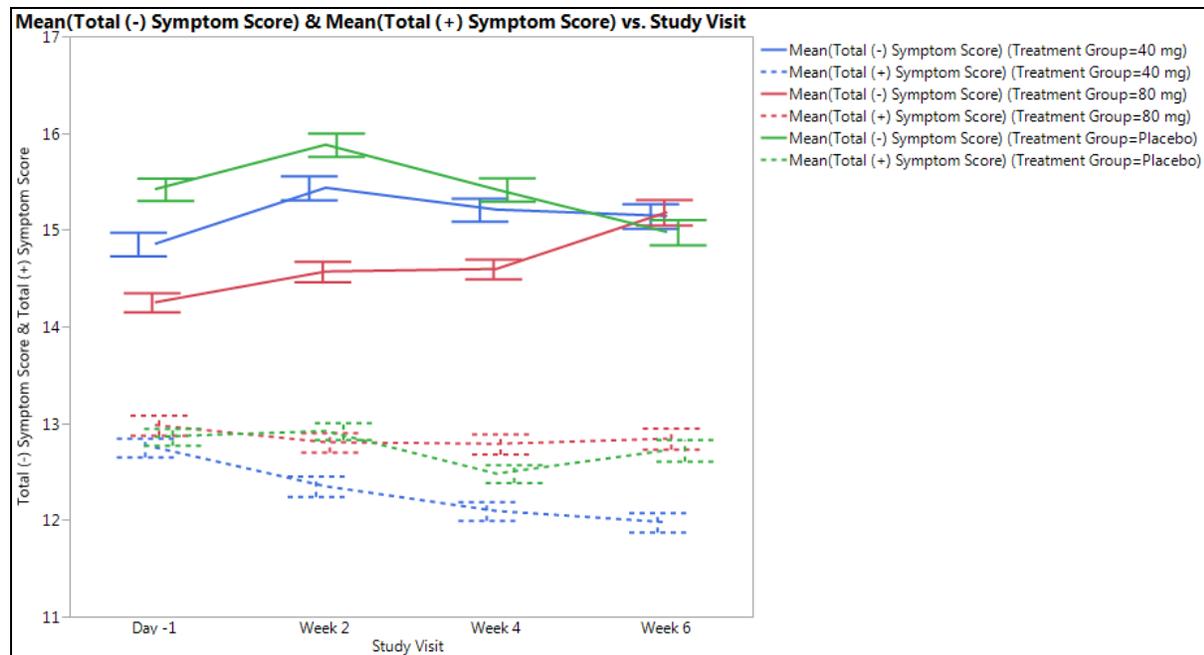
Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Figure 33: Mean Total Negative & Positive Symptom Scores from PANSS in Study 1304**



Source: Reviewer-created chart from derived from PANSS dataset (PANSS.xpt) for Study 1304. Error bars represent +/- 1 S.E.M.

The trend in composite scale score is not shown, but is similar. Notably, there was no significant increase relative to placebo in the mean total psychopathology score across groups.

APPEARS THIS WAY ON ORIGINAL

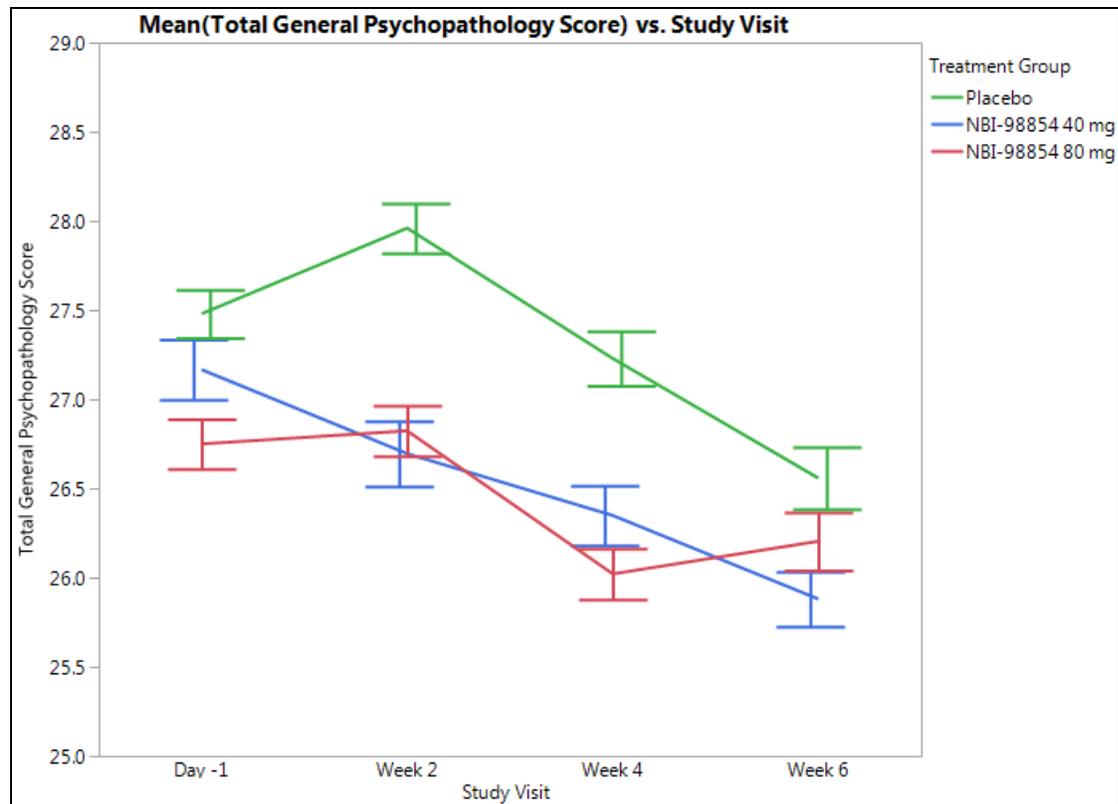
Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Figure 34: Mean Total General Psychopathology Score (by PANSS) in Study 1304**

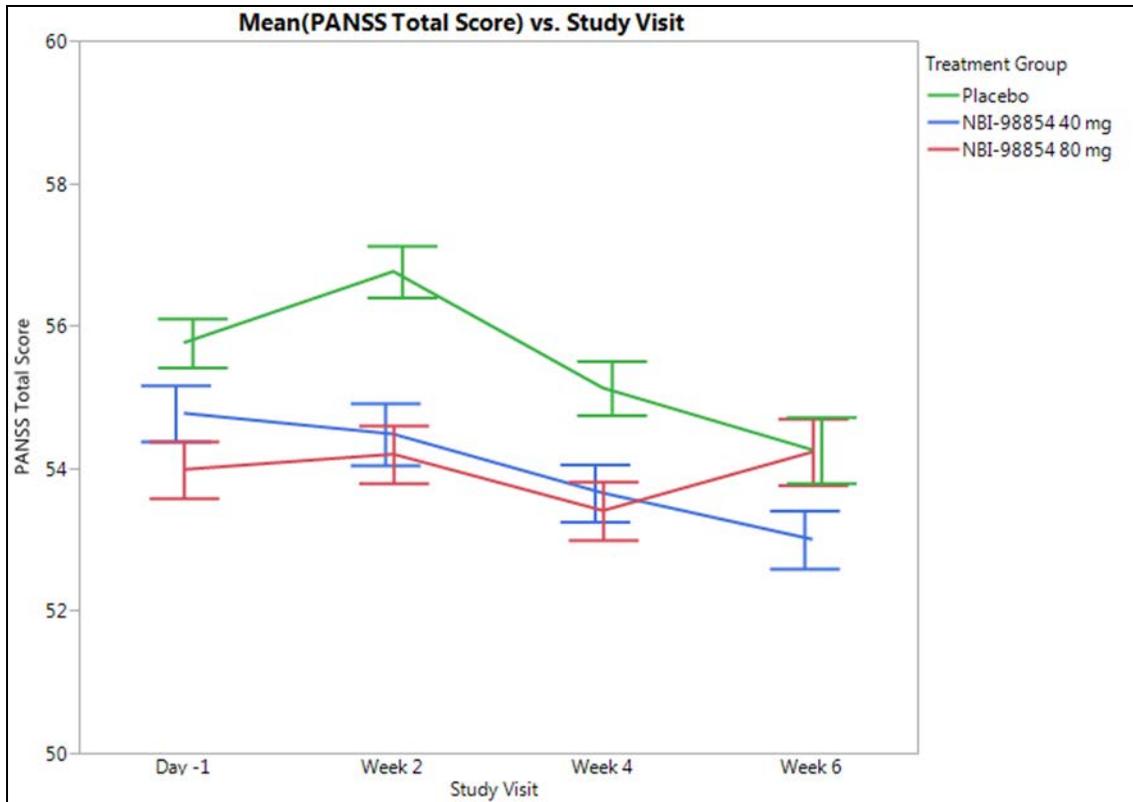


Source: Reviewer-created chart from derived from PANSS dataset (PANSS.xpt) for Study 1304. Error bars represent +/- 1 S.E.M.

These findings were confirmed, in that there was no drug effect or dose-dependent increase in the mean PANSS Total Score, as demonstrated in the following figure. Notably, the differences in total change for the mean PANSS Total Score between groups approached the minimum measurement unit of the scale (i.e. one point).

APPEARS THIS WAY ON ORIGINAL

**Figure 35: Mean PANSS Total Score in Study 1304**



Source: Reviewer-created chart from derived from PANSS dataset (PANSS.xpt) for Study 1304. Error bars represent +/- 1 S.E.M.

These trends correspond with the TEAE data, which noted no effect of valbenazine on the worsening of underlying schizophrenia or schizoaffective disorder.

#### 8.5.4. Exacerbation of Depression in the Setting of Schizophrenia or Schizoaffective Disorder

The Calgary Depression Scale for Schizophrenia (CDSS) is a validated,[42] nine-item scaled used to assess depression in patients with schizophrenia. Each item is scored on a scale of 0 to 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe) and the total score is the CDSS depression score. The complete CDSS questionnaire is available in [Section 13.2](#).

In Study 1201, the CDSS was administered at screening, study Day -1, during treatment end of Weeks 2, 6, 8, and 12) and during the follow-up period (end of Week 16) or at early termination. In Study 1202, investigators administered the CDSS at screening, study day -1, during treatment (end of week 6), and during the follow-up period (end of week 8) or early termination. In Study 1304, investigators administered CDSS at screening, Day -1, during the

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

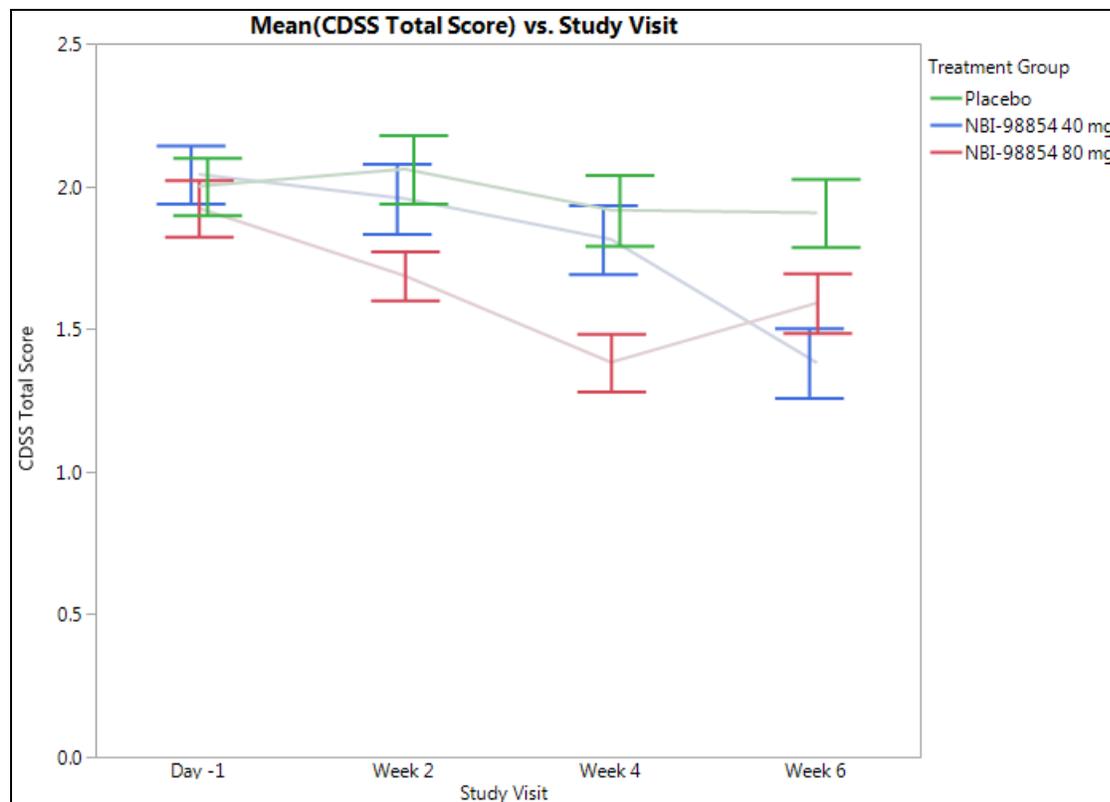
NDA 209241

Ingrezza (valbenazine)

controlled period (end of weeks 2, 4, and 6), during the extension period (end of weeks 8, 16, 24, 32, 40, and 48) and at the follow-up visit (end of week 52) or at early termination. Subjects were to respond based upon their feelings and experiences during the previous two weeks.

My analysis consisted of examining the mean Total CDSS score and CFB in mean total score during the controlled period in Studies 1201, 1202, and 1304. No worsening of depression as measured by CDSS was observed consistently across subjects in either measure. Additionally, I conducted exploratory analyses in order to assess for the role of gender, age, ethnicity, race, genotype (CYP2D6 metabolizer status), diagnosis, and early termination, and found no significant differences amongst sub-groups (analyses not shown). In conclusion, for the indication that the applicant is seeking, it is worth noting that valbenazine does not appear to worsen depression in patients with schizoaffective disorder or schizophrenia. The results for Study 1304 are displayed in the following figure.

**Figure 36: Mean CDSS Total Score in Study 1304**



Source: Reviewer-created chart from derived from CDSS dataset (CDSS.xpt) for Study 1304. Error bars represent +/- 1 S.E.M.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

### 8.5.5. Manic Symptoms

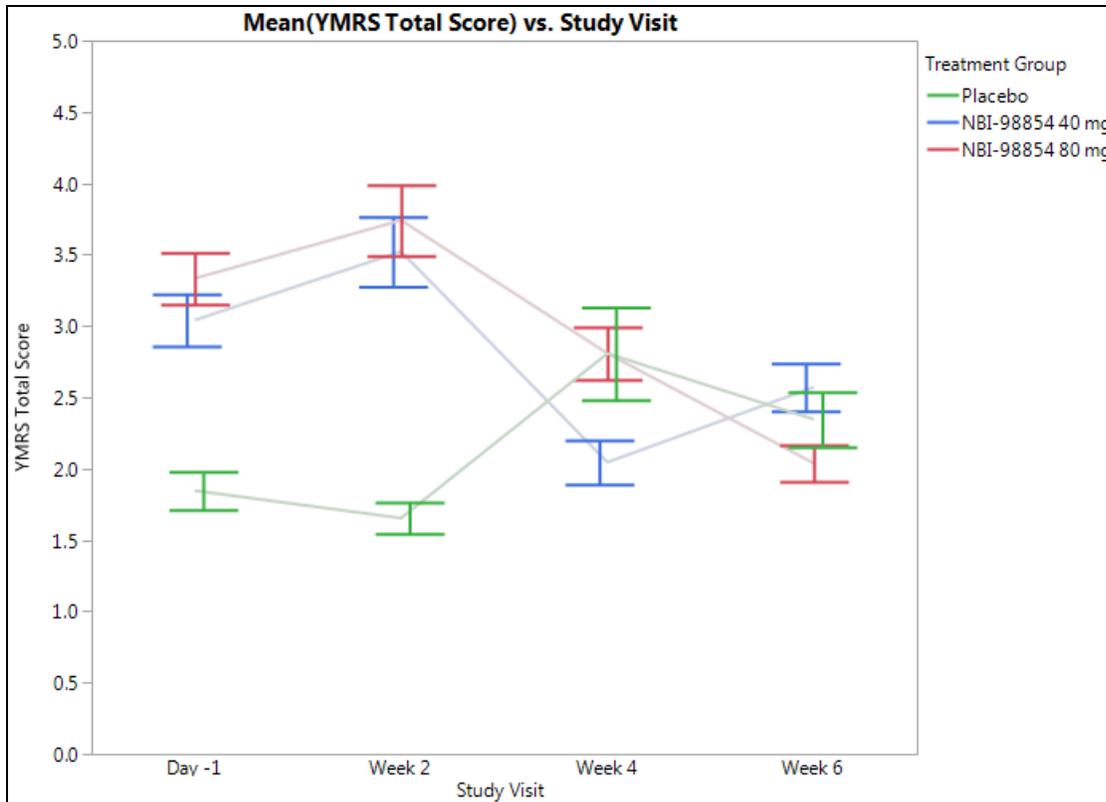
The Young Mania Rating Scale (YMRS) is a validated [43] scale used to assess mania symptoms. The scale consists of 11 items. Seven are scored on a 5-point scale (0 to 4) and four items are graded on a nine-point scale (0 to 8). Each point has anchors, and across items, increasing number score indicates increasing severity of the described abnormality. The scale permits the scoring of half points. Scoring is based upon the subject's self-report of their condition over the previous 48 hours and the interviewer's assessment during the interview. The complete YMRS questionnaire is available in [Section 13.2](#).

In Study 1202, investigators administered the YMRS at screening, study day -1, during treatment (end of week 6), and during follow-up (end of week 8) or at early termination. In Study 1304, investigators administered the YMRS at screening, Day -1, during the controlled period (end of weeks 2, 4, and 6), during the extension period (end of weeks 8, 16, 24, 32, 40, and 48) and at the follow-up visit (end of week 52) or at early termination.

My analysis consisted of examining the total YMRS and CFB in the total YMRS in Studies 1202 and 1304 during the controlled period. There was no effect of the drug on the overall mean YMRS Total Score in either study. I conducted exploratory analyses in order to assess for the role of gender, age, ethnicity, race, genotype (CYP2D6 metabolizer status), diagnosis, and early termination, and found no significant differences amongst sub-groups (analyses not shown). Overall, there was neither an overall nor a dose-response effect for valbenazine in symptoms of mania in Studies 1202 and 1304. The trend for Study 1304, a placebo-controlled fixed dose Study, is shown in the following figure.

APPEARS THIS WAY ON ORIGINAL

**Figure 37: YMRS Total Score in Study 1304**



Source: Reviewer-created chart derived from YMRS dataset (YMRS.xpt) for Study 1304. Error bars represent +/- 1 S.E.M.

### 8.5.6. Depression in Patients with Underlying Mood Disorders

The Montgomery-Asberg Depression Rating Scale (MADRS) using the Structured Interview Guide for the MADRS (SIGMA) was utilized to assess the severity of depressive symptoms. The MADRS is a validated [44] scale consisting of 10 items scored on a 7-point scale (0-6) with increasing number value indicating increasing severity. Anchor points occur at two-point intervals and the maximum total score is 60. The complete MADRS questionnaire is available in [Section 13.2](#).

In Study 1202, investigators administer the MADRS (SIGMA) at screening, Study day -1, during treatment (end of week 6), and during follow-up (end of week 8) or at early termination. In Study 1304, investigators administered the MADRS (SIGMA) at screening, Day -1, during the controlled period (end of weeks 2, 4, and 6), during the extension period (end of weeks 8, 16, 24, 32, 40, and 48) and at the follow-up visit (end of week 52) or at early termination. In both Studies 1202 and 1304, subjects were instructed to respond based upon feelings and experiences from the previous seven days.

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

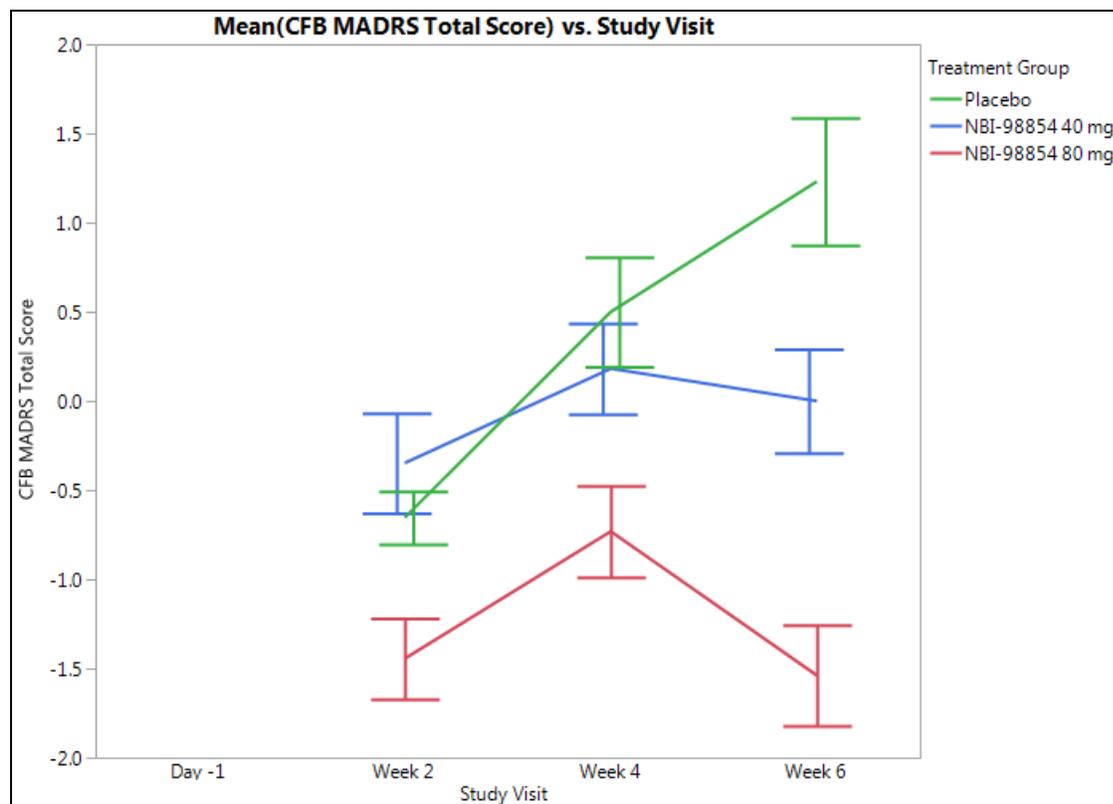
NDA 209241

Ingrezza (valbenazine)

My analysis consisted of examining the mean Total MADRS score and CFB in mean total score during the controlled period in Studies 1202 and 1304. No difference was observed in Study 1202, a dose titration study. However, statistically significant improvement in the CFB MADRS Total Score was observed in Study 1304, a fixed-dose study. This highlights a potential future area of research, as it is unclear if the improvement in depression is due to either improvement in a subject's TD and hence decreased social isolation or an underlying pharmacologic mechanism.

Additionally, I conducted exploratory analyses in order to assess for the role of gender, age, ethnicity, race, genotype (CYP2D6 metabolizer status), diagnosis, and early termination, and found no significant differences amongst sub-groups (analyses not shown). In conclusion, for the indication that the applicant is seeking, it is worth noting that valbenazine does not appear to worsen depression in patients with underlying mood disorders.

**Figure 38: CFB MADRS Total Score in Study 1304**



Source: Reviewer-created chart derived from MADRS dataset (MADRS.xpt) for Study 1304. Error bars represent +/- 1 S.E.M.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

### 8.6. Safety Analyses by Demographic Subgroups

Safety analyses by demographic sub-groups were conducted, as able, in each section of this review. Generally, across measurements (e.g. vital signs, diagnostic labs, etc.) there were no specific demographic sub-groups that consistently had a significantly different safety profile as compared to the safety population.

### 8.7. Specific Safety Studies/Clinical Trials

There were no additional critical safety studies in the valbenazine development program.

### 8.8. Additional Safety Explorations

#### 8.8.1. Human Carcinogenicity or Tumor Development

In animal Studies, valbenazine was not carcinogenic and did not induce tumors in rats at doses up to 4.6 the MRHD of 80 mg. For further details, please see the nonclinical review. The human development program was not designed to detect small, long-term differential risks in increased cancer risk. However, there appears no additional significant risk of cancer observed in the prospective observational database of 613 subjects. No additional AEs of cancer or neoplasm were observed in the Applicant's submitted ISS, which also included all Phase 1 and Phase 2 trials.

Direct AEs of cancer were as follows:

- Breast cancer occurred in Study 1402 in one subject (413-4012) who was receiving valbenazine. This case was discussed in [Section 8.4.1](#) and is unlikely related to valbenazine
- Lung neoplasm occurred in Study 1402 in one subject (435-4006) at study day 157. The subject had a long history of tobacco use, COPD and multiple other medical problems. This event is unlikely related to valbenazine.

These events were deemed to be unlikely to be related to the study drug. Additionally, recognizing that carcinogenesis is a long-term process (and that cancer represents a wide spectrum of diseases), the prospective observational database was examined for AEs of cysts, polyps, adenomas, and nodules of undetermined significance (i.e. potential precursor lesions). The events noted were as follows:

- Subject 318-3012 in Study 1304 received placebo followed by valbenazine 80 mg during the controlled and open-label extension periods, respectively, and experienced an AE of "6mm left thyroid nodule" on study day 74. This was an incidental finding on a diagnostic test while the patient was hospitalized after a motor vehicle accident. It is unclear if this event is related to valbenazine.
- Subject 349-3004 in Study 1304 received valbenazine 40 mg during the controlled

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

period and open-label extension. They experienced an AE of “worsened left mid kidney cyst” and also “multiple pulmonary nodules” (baseline chest x-ray unknown). This patient had a complex history with multiple medical problems (notably a history of hepatitis C, hepatomegaly, pituitary tumor, hyperprolactinemia, tuberculosis, etc.), multiple hospitalizations, and a history of a renal cyst. It is unlikely that the study drug contributed to these AEs.

- Subject 313-3019 in Study 1304 received valbenazine 40 mg and is noted to have experienced an AE of “left adrenal adenoma” on Study day 166. The patient had been hospitalized for gastritis and this finding occurred on a diagnostic test. This event is unlikely to be related to valbenazine.
- Subject 337-3023 in Study 1304 received placebo and subsequently valbenazine 40 mg in the controlled and open-label extension, respectively, and experienced an AE of “multiple adenomatous colon polyps” on Study day 164. No additional information is provided. It is unclear if this is related to the Study drug.
- Subject 355-3022 in Study 1304 received valbenazine 40 mg and experienced an AE of “colon polyp” on Study day 43. No additional information is provided. It is unclear if this is related to the Study drug.

There were no Study discontinuations due solely due cysts or polyps. As these events do not demonstrate a clear positive dose-response relationship (i.e. incidence in person-years) this effect is not significant and may represent surveillance bias.

### 8.8.2. Human Reproduction and Pregnancy

There were no human Studies in pregnancy in the valbenazine development program. The protocols for Studies 1201, 1202, 1304, and 1402 specified that subjects of childbearing potential must agree to use hormonal or two forms of non-hormonal contraception (dual contraception) during the screening, treatment, and follow-up periods of the Study.

Two subjects became pregnant during the development program. Subject 1304-328-3002 had a positive urine pregnancy test at Week 20, after receiving valbenazine 80 mg for 14 weeks. The estimated date of conception was approximately 1 week prior to starting the Study drug, and the subject had a negative urine pregnancy test at each Study visit until Week 20. The subject stopped the Study drug, and delivered a normal, female infant without complication at 36 weeks of gestation.

Subject 1402-496-4001 became pregnant and experienced an SAE of spontaneous abortion. This was a 32 year-old African-American female with schizophrenia and schizoaffective disorder, TD, and hypertension who was taking bupropion, lorazepam, lurasidone, and propranolol. The subject received valbenazine 80 mg and on Study day 84 had a positive urine pregnancy test, confirmed by a positive serum pregnancy test. Four days later on Study day 88

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

the patient presented to the ER with 7 days of vaginal bleeding, and ultrasound revealed no evidence of an intrauterine pregnancy. This was classified as an SAE and the patient was discharged. The subject reported using condoms without a secondary method of birth control, in violation of Study protocol. It is unclear if this spontaneous abortion is due to the Study drug, concomitant medications, or is otherwise simply an untoward medical event.

Please refer to the non-clinical section of the review for Studies of drug effects in the setting of pregnancy in animals.

### 8.8.3. Pediatrics and Assessment of Effects on Growth

There were no Phase 2 or Phase 3 studies involving valbenazine in pediatric patients. A single Phase 1 study (Study 1403) was conducted to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of valbenazine in pediatric patients with Tourette Syndrome. However, the Sponsor is applying for an indication for the treatment of Tardive Dyskinesia, not Tourette Syndrome.

Thus, the Applicant applied for a full waiver of pediatric studies. In the Applicant's justification for the waiver, the Applicant cited demographic projections. Specifically, the Applicant partnered with (b) (4) to Study longitudinal patient-level data from the commercial, Medicare supplement, and Medicaid populations, a database which includes 180 million unique patients. The Applicant sorted the dataset for an ICD-9 code of "subacute dyskinesia due to drugs" (333.85) or "orofacial dyskinesia" (333.82). Notably, this is the narrowest coding definition of TD, and excludes less specific ICD-9 codes that may include subjects with TD, such as "other fragments of torsion dystonia" (333.89).

From the Applicant's definition of the two identified disease codes, they calculated a 7-year point-prevalence rate of 0.019 - 0.024% and a pediatric (age 5 – 19 years of age) prevalence of 2.9 – 5.2% of this population. Using U.S. Census Bureau data (June 2013), the Applicant estimated a TD population of 135,000 population and a pediatric sub-population of 4,000 – 7,000. Literature supports this estimate, with annual TD incidence rates in adolescents estimated at 0.3%. [45] Notably, the Applicant did not assess the population size of children under 5 years of age, as antipsychotics are not approved for use in this population, and estimates of use for this population would be difficult to ascertain in a precise and accurate fashion. The Applicant did note that infants with gastroesophageal reflux (GER) could be at risk for developing TD due to prolonged use of metoclopramide; however, the Applicant noted that after the box warning issued in 2009 that the prescribing rate for metoclopramide declined significantly. The Applicant did not cite specific trends in metoclopramide prescribing, or rates categorized by age.

The Division of Psychiatry Products reviewed this request for a full waiver of pediatric Studies and agreed with the Applicant on February 17, 2015. The FDA Pediatric Review Committee

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

(PeRC) reviewed this request under IND 111591 and agreed with the Division of Psychiatry Products and Applicant, granting a full waiver of pediatric Studies on February 23, 2015.

### 8.8.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

The Applicant did not conduct specific trials (animal or human) to assess dependence, withdrawal, or abuse potential. There was a single overdose event that occurred during the valbenazine development program. In Study 1201, Subject 153-1001 was randomized to 100 mg once daily, albeit the patient's caregiver accidentally administered it twice daily. On Day 8, the subject experienced syncope and was evaluated at a local ER, where they were found to have a UTI. This event was not likely related to the Study drug.

The CSS reviewer, Alicja Lerner, MD, PhD, concluded that abuse potential Studies are not required as:

- Valbenazine has a similar chemical structure to tetrabenazine, which is not known to be a drug of abuse
- Valbenazine selectively binds VMAT2 and valbenazine and its metabolites do not bind receptors of abuse (benzodiazepine, mu opioid, and other receptors)
- The AE profile seen in the clinical development program and the post-market experience of tetrabenazine do not suggest a signal of abuse potential

I agree with Dr. Lerner's assessment, and that valbenazine does not demonstrate significant abuse potential, and therefore scheduling is not necessary.

Notably, valbenazine did demonstrate some suggestion of a dose-dependent withdrawal syndrome in animals. However, dependence and withdrawal were not systematically evaluated in Phase 2/3 trials, and study visits were not frequent enough to capture withdrawal symptoms for valbenazine (i.e. a 2-week interval for study visits would miss withdrawal symptoms for a drug with a half-life of 20 hours). Additionally, no withdrawal questionnaires were administered.

The CSS reviewer noted, and I agree, that as valbenazine inhibits VMAT2 transporters and thus decreases the levels of dopamine, serotonin, and norepinephrine, that rapid reversal of long standing inhibition (i.e. cessation of therapy) may cause an acute withdrawal syndrome. In the premarket review of tetrabenazine (dated 3/17/2008), Katherine Bonson, a CSS pharmacologist, noted that tetrabenazine did not produce a withdrawal syndrome in the HD population. As previously discussed, the HD and TD populations are distinct, and therefore while no dependence and withdrawal effects were seen in the human development program, I agree with the CSS reviewer that the Applicant should evaluate clinical dependence and withdrawal as a PMR. Clinical dependence and withdrawal could be evaluated at the completion of on-going Studies 1304 and 1402. Withdrawal scales (e.g. Physician Withdrawal Checklist, Hamilton Anxiety Scale, etc.), disease-specific scales (e.g. AIMS, CGI-TD, MADRS,

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

CDSS, etc.), AEs, and vital signs should be assessed on the last day of treatment, day 1 off-treatment, every other day thereafter for the first week, and then 2 – 3 times weekly for two additional weeks.

Additionally, in order to better ascertain dependence, withdrawal, tolerance, and overdose in the post-market setting, the Applicant should undertake expedited reporting of “Events of Interest” based upon the following MedDRA preferred terms (standardized MedDRA Query for “Drug Abuse, Dependence, and Withdrawal”):

*Drug administered at inappropriate site, Drug administration error, Incorrect dose administered, Incorrect route of drug administration, Wrong technique in drug usage process, Intentional drug misuse, Accidental exposure, Accidental overdose, Intentional overdose, Multiple drug overdose, Multiple drug overdose accidental, Multiple drug overdose intentional, Overdose, Drug abuser, Substance abuser, Dependence, Drug dependence, Drug tolerance, Drug tolerance decreased, Drug tolerance increased.*

Additionally, the Applicant should review data from the Drug Abuse Warning Network (DAWN) and the Toxic Exposure Surveillance System (TESS) reports prepared by the National Poison Data System, and submit analysis of this information in their quarterly periodic report and annual reports, with analysis based on both individual cases and aggregate analysis.

## 8.9. Safety in the Postmarket Setting

### 8.9.1. Safety Concerns Identified Through Postmarket Experience

Pre-market experience of tetrabenazine (NDA 21894) was examined in [Section 8.2](#); post-marketing experience will be examined in this section. Tetrabenazine is a VMAT2 inhibitor approved for and used primarily for the treatment of chorea in Huntington’s disease. It is used off-label for the treatment of TD. Tetrabenazine and valbenazine share several active metabolites, most notably alpha-dihydratetrabenazine (NBI-98782), which is an active metabolite of valbenazine that is also an enantiomer of an active metabolite of tetrabenazine. The metabolism of these two related products is reviewed in [Section 4.5.3](#). Consequently, the post-market experience of tetrabenazine is relevant in determining the post-market expectations for valbenazine.

Historically, the Division of Neurology Products (DNP) and the OSE completed a pharmacovigilance and drug utilization review on February 25, 2015 in response to postmarketing reports of pediatric deaths (tetrabenazine was not studied or approved for use in pediatric populations). Briefly, examining a five-year period (2009 – 2014) of prescription

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

claims<sup>9</sup>, reviewers found that 5.7% of prescriptions were to patients aged 16 years or younger (335 patients). Further screening by associated ICD-9 diagnoses codes revealed 58 patients with Tourette's syndrome, 2 patients with tardive dyskinesia, and 5 patients with drug-induced dyskinesia. Of the patients with tardive dyskinesia, no patients died.

In addition to reviewing previous post-market reviews, DPP consulted the Office of Surveillance and Epidemiology (OSE) for a substantive review of the post-market experience of tetrabenazine. Ofir Noah Nevo, PharmD, completed the review for OSE on January 5, 2017, and the following is my interpretation of his review.

The FDA Adverse Event Reporting System (FAERS) was queried in order to conduct a review of adverse events associated with off-label use of tetrabenazine. Specifically, cases were defined as follows:

- Serious outcome: death, life-threatening, hospitalization, disability, required intervention, congenital anomaly, or other serious medical events
- Product used to treat TD or subacute dyskinesia
- Product had a probable or possible cause

The time window searched was January 1, 2010 through December 8, 2016, yielding N = 3,152 reports. Sorting for "reported reasons for use" (with N≥5 reports) and serious<sup>10</sup> outcomes yielded 3,014 reports. Upon further review, cases with reported reasons for use as "Huntington's Disease," "Huntington's Chorea," or "Not reported / product used for unknown indication" were eliminated. Sorting to eliminate these indications and increasing the threshold to N≥10 reports yielded 1,023 reports. This approximates post-marketing reports of off-label use, noting that some of these post-marketing reports may involve patients with unreported Huntington's Disease.<sup>11</sup> Off-label use may include multiple rationales for the use of tetrabenazine, including the use of tetrabenazine to treat TD.

Within this universe of off-label case reports, filtering to MedDRA preferred terms with to N≥10 serious outcomes resulted in a variety of events; after review of the original medical officer review of tetrabenazine and discussion with reviewer Michael C. Davis, MD, PhD; the events of relevant interest given tetrabenazine's pharmacology (VMAT2 inhibitor) are displayed in the following table.

---

<sup>9</sup> Symphony Health Solutions Integrated Dataverse, including claims from U.S commercial, Medicare Part D, Cash, and Medicaid plans

<sup>10</sup> Serious is defined as an event resulting in the following: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious events.

<sup>11</sup> As reporters are more likely to report rare and unusual disorders such as HD, it is likely that HD is not underreported.

**Table 87: Grouping of Terms for Post-marketing Reports for the Off-Label Use of Tetrabenazine**

| MedRA Preferred Term      | # of FAERS reports | Grouped Terms* |
|---------------------------|--------------------|----------------|
| Depression                | 81                 | Depression     |
| Suicidal ideation         | 64                 |                |
| Parkinsonism              | 33                 | EPS            |
| Tremor                    | 28                 |                |
| Musculoskeletal stiffness | 19                 |                |
| Dystonia                  | 16                 |                |
| Movement disorder         | 16                 |                |
| Restlessness              | 16                 |                |
| Asthenia                  | 13                 |                |
| Muscle spasms             | 12                 |                |
| Dizziness                 | 26                 | Balance        |
| Gait disturbance          | 30                 |                |
| Balance disorder          | 14                 |                |
| Fall                      | 50                 |                |
| Dyckinesia                | 28                 | Dyskinesia     |
| Tardive dyskinesia        | 14                 |                |
| Somnolence                | 42                 | Fatigue        |
| Fatigue                   | 28                 |                |
| Malaise                   | 14                 |                |

\*Re-coded

*Source: Reviewer-created table derived from Office of Surveillance and Epidemiology (OSE) consult*

This suggests a potential signal for depression, EPS, balance difficulties/falls, dyskinesia, and fatigue. The cases reporting TD as a post-market event were examined in detail. Of the 14, 4 were miscoded, 2 were due to neuroleptic or metoclopramide exposure, and 3 were worsening TD after a patient’s tetrabenazine dose was decreased. The 4 other cases were due to chorea not elsewhere classified, orofacial dyskinesia, Tourette’s syndrome, and dystonia. These four cases had limited clinical information. Three fatal case reports were coded with TD; however, upon review I agree with the OSE that these cases were not attributable to tetrabenazine.

Alternatively, examining the 16 cases of off-label use for the treatment of TD that reported an SAE yields a slightly different picture. Two patients experienced Parkinsonism or akathisia, four patients experienced depression, and three suicidal behaviors. Limited information is available.

Lastly, the OSE queried the European Medicines Agency (EMA), which submitted a written response. I reviewed this response with OSE Staff (Noah Ofir Nevo and Vicky Chan). Upon review, the EMA had no clinical trial data from the use of tetrabenazine in TD patients. The

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

EMA noted a periodic safety update report (PSUR) that cited two small, blinded trials in TD, one in 24 hospitalized psychotic patients from 1972 and another open-label Study in 19 TD patients treated with tetrabenazine for 20 weeks. Prominent SAEs noted were drowsiness, Parkinsonism, akathisia, and depression with SI; all were noted especially in elderly subjects. Off-label use was noted to primarily represent that of the US, albeit the EMA had collected 2,112 cases of off label use from 2008. The EMA reviewer noted that there were three deaths specifically associated with tetrabenazine use in TD and that these, along with reported AEs associated with generic off-label use were “in line with the known safety profile of tetrabenazine.” Additionally, the EMA reviewer noted two cases of worsening TD associated with tetrabenazine use; however, information regarding medical history and concomitant medications were not available. Lastly, the European pre and post-market experience with tetrabenazine was reviewed at the periodic Pharmacovigilance Cluster Call with the EMA, Health Canada, and the Pharmaceuticals and Medical Devices Agency (PMDA, Japan). No additional information was found.

Other countries provided additional post-market experience. HealthCanada noted 17 case reports of adverse reactions associated with tetrabenazine, 4 of which were associated with off-label use for TD. Relevant adverse reaction terms reported included fatigue, gait disturbance, balance disorder, fall, reduced facial expression, chills, restlessness, and insomnia. The Therapeutic Goods Administration (TGA) of Australia provided an adverse event profile for tetrabenazine, but did not have the data reporting structure to approximate off-label use. MedSafe New Zealand reported 9 cases of adverse reactions; all but 2 of the cases are prior to 1990. One of these two cases involves infantile cerebral palsy, and the diagnoses in the second case are unclear. The Health Sciences Authority of Singapore reported that the product license for tetrabenazine has expired, albeit historically one adverse reaction involving Stevens Johnson Syndrome in a 68 year-old female who was on quetiapine and tetrabenazine was reported (indications for product use not available).

Based upon this review, it appears that the major post-marketing concerns derived from the off-label use of tetrabenazine are as follows:

- Extrapyramidal symptoms (EPS)
- Dyskinesia
- Fatigue/somnolence
- Depression
- Suicidal ideation

### 8.9.2. Expectations on Safety in the Postmarket Setting

The previous product in the reversible VMAT2 inhibitor class<sup>12</sup> – tetrabenazine – was approved

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

for the treatment of chorea in Huntington's Disease. The Office of Surveillance and Epidemiology assessed off-label use in the US of this product, which includes use for the treatment of tardive dyskinesia, and found a post-market signal for extrapyramidal symptoms (EPS), dyskinesia, fatigue/somnolence, depression, and suicidal ideation. In the premarket valbenazine development program, depression and suicidality were not appreciated to occur at a rate significantly different from that of placebo-treated subjects. Psychiatric instrument-based assessment of depression (CDSS, MADRS) and suicidality (C-SSRS) supported these findings. EPS and somnolence were appreciated as adverse reactions in the valbenazine development program.

During the valbenazine development program, analysis of laboratory parameters for the controlled periods of Studies 1201, 1202, and 1304 revealed increased blood glucose, supported by TEAEs. In the post-market setting, one may expect to see this manifest by reports of increased blood glucose, worsening type 2 diabetes, or other events (most likely to occur in an outpatient setting). An additional signal for cholestasis was observed in increases in alkaline phosphatase and bilirubin, which may manifest as increased AEs of cholestasis in susceptible populations (e.g. morbidly obese, those with underlying gallbladder disease, etc.) in the post-market setting. An increase in cholestatic events, associated with valbenazine use, was not appreciated in the pre-market setting.

With respect to AEs, in the post-market setting, I would expect to see a significant signal for balance disorders/falls, as this was appreciated in the pre-market setting. This may be due to patients' conscious or unconscious adjustment (or failure thereof) to changes in their TD symptoms.

Critically, the development program did not include a formal assessment of dependence, tolerance, or withdrawal. I concur with the CSS review team that this will need to be addressed as a PMR. Consequently, I cannot comment on whether withdrawal symptoms will be expected in the post-market setting.

Lastly, the applicant did not include an appreciable number of subjects of Asian race in the development program (they represented 0.3% of the Study population). As Asians may differ in enzymes involved in drug metabolism, this subpopulation would be important group to assess in the post-market setting.

### 8.10. Additional Safety Issues From Other Disciplines

Please refer to [Sections 4.4](#) and [4.5](#) for summaries of Nonclinical Pharmacology/Toxicology and

---

<sup>12</sup> Note that reserpine, a non-selective VMAT inhibitor that irreversibly binds the receptor, may also be used off-label.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Clinical Pharmacology reviews, which relate to safety issues discussed in Section 8.

### 8.11. Integrated Assessment of Safety

Valbenazine was evaluated for its safety in the treatment of tardive dyskinesia. The discussion here will be focused on the AE profile, psychiatric instrument measure profile, laboratory study profile, and other related findings from this review.

With respect to AEs in the development program, a clear signal for balance disorders/falls was observed in controlled safety population. This may be due to patients adjusting (or failing to adjust) to changes in their TD symptoms. Additional signals for akathisia and somnolence were observed, which correlated with those associated with off-label use of tetrabenazine in the post-marketing period. The somnolence rate was significant (11.0% v. 4.2% in placebo), necessitating a warning in product labeling. Akathisia, headache, and anticholinergic symptoms were also appreciated as adverse reactions, with akathisia resulting in dropouts/discontinuation. Depression and suicidal ideation/behavior were observed in the premarket development program, with both depression and SI resulting in several dropouts in the prospective observational database. In examining psychiatric instruments for the assessment of depression (CDSS, MADRS) and suicidality (C-SSRS), there was neither worsening due to drug effect nor a dose-response, and suicidality consisted primarily of ideation, at a rate comparable to the background rate for the patient population. The development program was not powered to detect suicidal behavior. In examination of other instruments which assessed symptoms of mania (YMRS), schizophrenia (PANSS), and EPS/Akathisia (BARS, SAS), there was no signal for worsening associated with the study drug.

With respect to laboratory findings, a consistent increase in prolactin was observed on diagnostic labs; however, no treatment-related AEs were associated with increased prolactin. Thus, labeling for prolactin was recommended in order to recognize this risk and inform clinicians, should a prolactin-related event occur in the post-market setting. Additional laboratory findings of increased blood glucose and a potential signal for cholestasis were also observed and labeled accordingly.

## 9 Advisory Committee Meeting and Other External Consultations

---

On January 4, 2017, the review division determined that this NDA did not require a public discussion, so the application was not taken to an Advisory Committee. The rationale for this decision was that while valbenazine is a new molecular entity, it has a similar mechanism to the previously-approved VMAT2 inhibitor tetrabenazine. Furthermore, while there are no currently-approved treatments for TD, the primary efficacy endpoint (Abnormal Involuntary Movement Scale) is a widely-used clinical and research measure for assessing tardive

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

dyskinesia. Finally, the application review did not identify any major safety issues that would bring into question the benefit/risk assessment for the intended use (which has no other approved treatments).

## 10 Labeling Recommendations

---

### 10.1. Prescribing Information

The tetrabenazine label was briefly reviewed by the division. While it initially served as a comparator, many of the sections were deemed to not be relevant due to the significant differences of the patient population studied (Huntington's Disease). Thus, the valbenazine label was reviewed independently. Our recommendations are as follows:

- **2.1 Dosing and Administration:**
  - Revisions are being proposed to specify the titration schedule (i.e., initiate treatment at 40 mg once daily, then increase the dose to the recommended dose of 80 mg after one week). The schedule was based on that used in Study 1304.
  - A sentence is also being proposed that continuation of 40 mg once daily may be considered for some patients. While valbenazine 40 mg daily did not achieve statistical significance on the pre-specified primary efficacy measure, a subset of patients may find that this dose provides an adequate benefit-risk profile. For example, approximately one third of subjects receiving valbenazine in Study 1202 were receiving less than 75 mg/day at the primary efficacy endpoint; 11 subjects had dose reductions from 80 mg to 40 mg/day in Study 1304 due to treatment-emergent adverse events; and the 40 mg/day dose is being recommended for some patient groups, such as those with severe hepatic impairment or who are also receiving a strong CYP3A4 inhibitor.
- **2. (b) (4) Dosing Recommendations for Concomitant Use with Strong CYP3A4 or CYP2D6 Inhibitors, or CYP3A4 Inducers:** Revisions are being proposed to specify that dosage should be 40 mg/day when valbenazine is co-administered with a strong CYP3A4 inhibitor. Dose reduction should be considered, based on tolerability, when valbenazine is co-administered with a strong CYP2D6 inhibitor. Concomitant use of valbenazine with strong CYP3A4 inducers is not recommended. These revisions were recommended by the OCP review team based on review findings.
- **4 Contraindications:** Revisions are being proposed to remove (b) (4)  
(b) (4)

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

[Redacted] (b) (4)

- **5.2 QT Prolongation:** Revisions are being proposed to more clearly describe the relationship between valbenazine and prolongation of the QT interval. Specifically, language was added noting that in patients taking a strong CYP2D6 or CYP3A4 inhibitor or who are poor metabolizers, valbenazine concentrations may be higher, resulting in clinically significant QT prolongation, and a dose reduction may be necessary. In order to mitigate this risk, language instructing clinicians to assess the QT interval prior to increasing the valbenazine dose was added.

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

- **6 Adverse reactions:** This section was extensively revised to include the following:
  - The clinical trial experience section was modified to describe the pooling of the three pivotal controlled Studies used to support the agency’s labeling recommendations and the associated characteristics of the patient population (i.e., age, diagnoses, ethnicity, race, concomitant medications)
  - An adverse reaction table for the pooled Studies was inserted, as below:

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Table (b) (4) Adverse Reactions in 3 Placebo-Controlled Studies of 6-weeks Treatment Duration (b) (4)  $\geq 2\%$  (b) (4) and >Placebo**

| Adverse Reaction                  | Placebo<br>(n = (b) (4) ) (%) | INGREZZA<br>(n = (b) (4) ) (%) |
|-----------------------------------|-------------------------------|--------------------------------|
| <b>General Disorders</b>          |                               |                                |
| Somnolence                        | 4.2%                          | 10.9%                          |
| <b>Nervous System Disorders</b>   |                               |                                |
| Anticholinergic effects           | 4.9%                          | 5.4%                           |
| Balance disorders/fall            | 2.2%                          | 4.1%                           |
| Headache                          | 2.7%                          | 3.4%                           |
| Akathisia                         | 0.5%                          | 2.7%                           |
| <b>Gastrointestinal Disorders</b> |                               |                                |
| Vomiting                          | 0.6%                          | 2.6%                           |
| Nausea                            | 2.1%                          | 2.3%                           |
| <b>Musculoskeletal Disorders</b>  |                               |                                |
| Arthralgia                        | 0.5%                          | 2.3%                           |

Source: Reviewer-created table (adapted from analysis by Dr. Marc Stone)

- Adverse reactions occurring at  $\geq 1\%$  incidence and greater than placebo were also listed.
- A sentence was added describing a dose-related increase in prolactin observed during controlled trials.
- A sentence was added describing a dose-related increase in alkaline phosphatase and bilirubin.
- **7 Drug Interactions:** Revisions are being proposed to add monoamine oxidase inhibitors, as this section can include predicted drug interactions.
- **10 Overdose:** This section was revised to eliminate (b) (4)
- **12.2 Pharmacodynamics:** The language was updated for the cardiac electrophysiology section to reflect the two healthy volunteer studies, which demonstrated a positive correlation of the QTc interval with the plasma concentration of the active metabolite (b) (4). Language was added to reflect the mean (double-sided (b) (4) % confidence interval) QT prolongation associated with healthy volunteers as compared to those taking a strong CYP3A4 or CYP2D6 inhibitor.
- **14 Clinical Studies:** The following revisions are being proposed:

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

- Addition of a sentence specifying that subjects were ineligible for study participation if they were assessed as having a significant risk for suicidal or violent behavior or if their underlying psychiatric illness symptoms were unstable. This was recommended to contextualize the study findings; for example, there was no clear signal for suicidal ideation or behavior in the valbenazine studies, as compared to studies of the VMAT2 inhibitor tetrabenazine for the treatment of Huntington's disease.
- Descriptors for AIMS scores (0-4) were added, with the rationale that this may be helpful for clinicians to interpret study data (who may be familiar with descriptors from other versions of the AIMS).
- Language was added that the AIMS was scored by central video raters who were blind to the subject identification, treatment, and visit number.
- Information about the number of subjects enrolled, completed, and discontinued from the described study (Study 1304) was incorporated.
- Information was added that that subgroup analysis by gender, age, racial subgroup, underlying psychiatric diagnostic category, and concomitant antipsychotic medication did not suggest any clear evidence of differential responsiveness.
- Language was added describing the Study 1304 extension phase, including the finding that the mean AIMS dyskinesia total worsened following valbenazine discontinuation.
- The Applicant's (b) (4) was removed, (b) (4)
- A histogram indicating the percent of patients with specified magnitude of AIMS total score improvement at the end of Week 6 was being proposed to replace the (b) (4)
- A graph of the efficacy results for the entire Study 1304 duration was proposed to replace the (b) (4)  
This graph, incorporating AIMS change from baseline at Weeks 2, 4, 6, 8, 16, 32, 48, and 52, illustrates findings from the extension period (Weeks 7-48) as well as the AIMS score changes four weeks after treatment discontinuation (Week 48 → 52). The number of subjects at each time point was provided to help contextualize the results (considering subject attrition). Overall, this graph (Figure 41) is considered to provide useful clinical information for prescribers about long-term treatment and discontinuation, in addition to the response pattern in the initial 6-week double-blind placebo-controlled period.
- (b) (4) was removed (b) (4) (b) (4)  
(b) (4) The results from Study 1 were assessed as sufficient to describe the efficacy of the recommended

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

dosage regimen in labeling. The regulatory basis for removing

(b) (4)

(b) (4)

(b) (4)

**Figure 39: Proposed Labeling Figure - Study 1304 - Percent of Patients with Specified Magnitude of AIMS Total Score Improvement at Week 6**

(b) (4)

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**Figure 40: Proposed Labeling Figure - Study 1304 - AIMS Dyskinesia Total Score Mean Change from Baseline - Entire Study Duration (Arithmetic Mean)**



**10.2. Patient Labeling**

The Applicant submitted a Medication Guide. Our review has indicated that a Medication Guide is not necessary. In accordance with the recommendations of Kimberly Updegraff, PharmD, the Associate Director for Labeling, the Medication Guide was converted into a Patient Package Insert (PPI). The PPI will describe common adverse reactions and when patients should bring them to the attention of their physician.

**10.3. Non-Prescription Labeling**

Not applicable.

## **11 Risk Evaluation and Mitigation Strategies (REMS)**

---

The safety issues identified in the review of this product do not merit a REMS. Adverse reactions identified in this review can be addressed through labeling. The observed laboratory abnormalities that are likely due to the drug (increased blood glucose, increased prolactin, and a potential signal for cholestasis) can also be addressed through labeling. These effects are non-serious and can be managed by drug discontinuation or symptomatic treatment on a non-urgent basis in an outpatient setting.

These risks can be described a patient package insert and do not require a medication guide, restricted distribution, physician training, or other risk evaluation and mitigation strategies or elements to assure safe use.

### **11.1. Safety Issue(s) that Warrant Consideration of a REMS**

There are no significant safety issues the warrant a REMS.

### **11.2. Conditions of Use to Address Safety Issue(s)**

Not applicable.

### **11.3. Recommendations on REMS**

In conclusion, as there are no serious safety issues, a REMS is not required.

## **12 Postmarketing Requirements and Commitments**

---

The following postmarketing commitments will be proposed to the Applicant based on findings from this clinical review. Please refer to reviews from other disciplines for descriptions and rationales for additional proposed postmarketing studies.

1. To better determine the maximal effective dose of valbenazine for the treatment of TD, perform a randomized controlled trial to assess whether a higher dose would confer additional therapeutic benefit. You may consider a design in which subjects with an inadequate response to valbenazine 80 mg are randomized to continue the 80 mg dose or receive a higher dose.
2. To better assess the persistence of valbenazine treatment for TD, perform a study in which subjects who have demonstrated an adequate response to valbenazine are

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

randomized to receive placebo or continue their current dose. Subjects should be stratified based on whether they are continuing to take an antipsychotic. A significant proportion of subjects should no longer be taking antipsychotics in order to assess the potential for differential persistency.

3. To provide evidence as to whether improvement on the AIMS total dyskinesia scale translates into long-term functional improvements, perform a study to address this question. Given the functional heterogeneity of patients with TD, it will be important to select an appropriate patient population and outcome measures. As discussed at the late-cycle meeting, one potential measure could assess social isolation.

The following postmarketing requirement will also be proposed to the Applicant based on findings from this clinical review. Please refer to reviews from other disciplines (i.e., Controlled Substance Staff) for additional rationale for the proposed study:

1. To evaluate for clinical dependence and withdrawal [REDACTED] (b) (4) [REDACTED] please administer withdrawal scales [REDACTED] (b) (4) [REDACTED], assess for withdrawal-related AEs, and monitor vital signs on the last day of treatment, day 1 off-treatment, every other day thereafter for the first week, and then 2-3 times weekly for two additional weeks.

## 13 Appendices

---

### 13.1. References

1. Association, A.P., *Diagnostic and statistical manual of mental disorders (DSM-5®)*. 2013: American Psychiatric Pub.
2. Trugman, J.M.M.D., *TARDIVE DYSKINESIA: DIAGNOSIS, PATHOGENESIS, AND MANAGEMENT*. *Neurologist*, 1998. **4**(4): p. 180-187.
3. Aquino, C.C. and A.E. Lang, *Tardive dyskinesia syndromes: current concepts*. *Parkinsonism Relat Disord*, 2014. **20 Suppl 1**: p. S113-7.
4. Waln, O. and J. Jankovic, *An update on tardive dyskinesia: from phenomenology to treatment*. *Tremor and Other Hyperkinetic Movements*, 2013.
5. Woods, S.W., et al., *Incidence of tardive dyskinesia with atypical versus conventional antipsychotic medications: a prospective cohort study*. *J Clin Psychiatry*, 2010. **71**(4): p. 463-74.
6. Glazer, W.M., *Review of incidence studies of tardive dyskinesia associated with typical antipsychotics*. *J Clin Psychiatry*, 2000. **61 Suppl 4**: p. 15-20.

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

7. Rao, A.S. and M. Camilleri, *Review article: metoclopramide and tardive dyskinesia*. *Aliment Pharmacol Ther*, 2010. **31**(1): p. 11-9.
8. Tarsy, D. and R.J. Baldessarini, *Tardive dyskinesia*. *Annu Rev Med*, 1984. **35**: p. 605-23.
9. Gardos, G., et al., *Ten-year outcome of tardive dyskinesia*. *Am J Psychiatry*, 1994. **151**(6): p. 836-41.
10. Fernandez, H.H., B. Krupp, and J.H. Friedman, *The course of tardive dyskinesia and parkinsonism in psychiatric inpatients: 14-year follow-up*. *Neurology*, 2001. **56**(6): p. 805-7.
11. Emsley, R., et al., *Subjective awareness of tardive dyskinesia and insight in schizophrenia*. *Eur Psychiatry*, 2011. **26**(5): p. 293-6.
12. Cloud, L.J., D. Zutshi, and S.A. Factor, *Tardive dyskinesia: therapeutic options for an increasingly common disorder*. *Neurotherapeutics*, 2014. **11**(1): p. 166-76.
13. Margolese, H.C., et al., *Tardive dyskinesia in the era of typical and atypical antipsychotics. Part 1: pathophysiology and mechanisms of induction*. *Can J Psychiatry*, 2005. **50**(9): p. 541-7.
14. Lehman, A.F., et al., *Practice guideline for the treatment of patients with schizophrenia*. *American Journal of psychiatry*, 2004. **161**(2 SUPPL.).
15. Hazari, N., N. Kate, and S. Grover, *Clozapine and tardive movement disorders: a review*. *Asian J Psychiatr*, 2013. **6**(6): p. 439-51.
16. Bhidayasiri, R., et al., *Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology*. *Neurology*, 2013. **81**(5): p. 463-9.
17. Thaker, G.K., et al., *Clonazepam treatment of tardive dyskinesia: a practical GABA-mimetic strategy*. *Am J Psychiatry*, 1990. **147**(4): p. 445-51.
18. Zhang, W.F., et al., *Extract of Ginkgo biloba treatment for tardive dyskinesia in schizophrenia: a randomized, double-blind, placebo-controlled trial*. *J Clin Psychiatry*, 2011. **72**(5): p. 615-21.
19. Zhang, X.Y., et al., *Brain-derived neurotrophic factor levels and its Val66Met gene polymorphism predict tardive dyskinesia treatment response to Ginkgo biloba*. *Biol Psychiatry*, 2012. **72**(8): p. 700-6.
20. Angus, S., et al., *A controlled trial of amantadine hydrochloride and neuroleptics in the treatment of tardive dyskinesia*. *J Clin Psychopharmacol*, 1997. **17**(2): p. 88-91.
21. Pappa, S., et al., *Effects of amantadine on tardive dyskinesia: a randomized, double-blind, placebo-controlled study*. *Clin Neuropharmacol*, 2010. **33**(6): p. 271-5.
22. Godwin-Austen, R.B. and T. Clark, *Persistent phenothiazine dyskinesia treated with tetrabenazine*. *Br Med J*, 1971. **4**(5778): p. 25-6.
23. Kazamatsuri, H., C. Chien, and J.O. Cole, *Treatment of tardive dyskinesia. I. Clinical efficacy of a dopamine-depleting agent, tetrabenazine*. *Arch Gen Psychiatry*, 1972. **27**(1): p. 95-9.
24. Guy, W., *Abnormal involuntary movement scale (AIMS)*. ECDEU assessment manual for psychopharmacology, 1976. **338**: p. 534-537.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

25. Gharabawi, G.M., et al., *Abnormal Involuntary Movement Scale (AIMS) and Extrapyrmidal Symptom Rating Scale (ESRS): cross-scale comparison in assessing tardive dyskinesia*. Schizophr Res, 2005. **77**(2-3): p. 119-28.
26. Taksh, U., *A critical review of rating scales in the assessment of movement disorders in schizophrenia*. Curr Drug Targets, 2006. **7**(9): p. 1225-9.
27. Guy, W., *Clinical global impression scale*. The ECDEU Assessment Manual for Psychopharmacology-Revised Volume DHEW Publ No ADM, 1976. **76**(338): p. 218-22.
28. Soares, K.V. and J.J. McGrath, *Anticholinergic medication for neuroleptic-induced tardive dyskinesia*. Cochrane Database Syst Rev, 2000(2): p. CD000204.
29. Barch, D.M., *Neuropsychological Abnormalities in Schizophrenia and Major Mood Disorders: Similarities and Differences*. Current psychiatry reports, 2009. **11**(4): p. 313-319.
30. Arango, C., et al., *Relationship of awareness of dyskinesia in schizophrenia to insight into mental illness*. American Journal of Psychiatry, 1999.
31. Goetz, C.G., J.G. Nutt, and G.T. Stebbins, *The unified dyskinesia rating scale: presentation and clinimetric profile*. Movement Disorders, 2008. **23**(16): p. 2398-2403.
32. Jeste, D.V. and R. Jed Wyatt, *Therapeutic strategies against tardive dyskinesia: Two decades of experience*. Archives of General Psychiatry, 1982. **39**(7): p. 803-816.
33. Srivastava, K., et al., *Impact of reducing dosing frequency on adherence to oral therapies: a literature review and meta-analysis*. Patient Prefer Adherence, 2013. **7**: p. 419-34.
34. Waln, O. and J. Jankovic, *An update on tardive dyskinesia: from phenomenology to treatment*. Tremor Other Hyperkinet Mov (N Y), 2013. **3**.
35. Gnoth, C. and S. Johnson, *Strips of Hope: Accuracy of Home Pregnancy Tests and New Developments*. Geburtshilfe Frauenheilkd, 2014. **74**(7): p. 661-669.
36. Cole, L.A., et al., *Accuracy of home pregnancy tests at the time of missed menses*. Am J Obstet Gynecol, 2004. **190**(1): p. 100-5.
37. Lawal, H.O. and D.E. Krantz, *SLC18: Vesicular neurotransmitter transporters for monoamines and acetylcholine*. Mol Aspects Med, 2013. **34**(2-3): p. 360-72.
38. Hor, K. and M. Taylor, *Suicide and schizophrenia: a systematic review of rates and risk factors*. J Psychopharmacol, 2010. **24**(4 Suppl): p. 81-90.
39. Barnes, T.R., *A rating scale for drug-induced akathisia*. Br J Psychiatry, 1989. **154**: p. 672-6.
40. Simpson, G.M. and J.W. Angus, *A rating scale for extrapyramidal side effects*. Acta Psychiatr Scand Suppl, 1970. **212**: p. 11-9.
41. Kay, S.R., A. Fiszbein, and L.A. Opler, *The positive and negative syndrome scale (PANSS) for schizophrenia*. Schizophr Bull, 1987. **13**(2): p. 261-76.
42. Addington, D., J. Addington, and B. Schissel, *A depression rating scale for schizophrenics*. Schizophr Res, 1990. **3**(4): p. 247-51.
43. Young, R.C., et al., *A rating scale for mania: reliability, validity and sensitivity*. Br J Psychiatry, 1978. **133**: p. 429-35.

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

44. Montgomery, S.A. and M. Asberg, *A new depression scale designed to be sensitive to change*. Br J Psychiatry, 1979. **134**: p. 382-9.
45. Correll, C.U. and J.M. Kane, *One-year incidence rates of tardive dyskinesia in children and adolescents treated with second-generation antipsychotics: a systematic review*. J Child Adolesc Psychopharmacol, 2007. **17**(5): p. 647-56.

### 13.2. Psychiatric Instruments

Psychiatric standardized questionnaires are listed as follows:

1. Columbia-Suicide Severity Rating Scale (C-SSRS)
2. Barnes Akathisia Rating Scale (BARS)
3. Simpson-Angus Extrapyramidal Side Effects Scale (SAS)
4. Positive and Negative Syndrome Scale (PANSS)
5. Calgary Depression Scale for Schizophrenia (CDSS)
6. Young Mania Rating Scale (YMRS)
7. Montgomery-Asberg Depression Rating Scale (MADRS)

APPEARS THIS WAY ON ORIGINAL

### 13.2.1. Columbia-Suicide Severity Rating Scale (C-SSRS)

#### Baseline Screening Questionnaire

| <b>SUICIDAL IDEATION</b>  |   |  |
|---|---|--|
| <i>Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.</i>  |   |  |
| <b>1. Wish to be Dead</b><br>Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.<br><i>Have you wished you were dead or wished you could go to sleep and not wake up?</i>   | Lifetime: Time He/She Felt Most Suicidal<br>Yes No<br><input type="checkbox"/> <input type="checkbox"/> | Past 3 Months<br>Yes No<br><input type="checkbox"/> <input type="checkbox"/> |
| If yes, describe:<br><b>2. Non-Specific Active Suicidal Thoughts</b><br>General non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.<br><i>Have you actually had any thoughts of killing yourself?</i>  | Yes No<br><input type="checkbox"/> <input type="checkbox"/>   | Yes No<br><input type="checkbox"/> <input type="checkbox"/>                  |
| If yes, describe:<br><b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b><br>Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."<br><i>Have you been thinking about how you might do this?</i>   | Yes No<br><input type="checkbox"/> <input type="checkbox"/>   | Yes No<br><input type="checkbox"/> <input type="checkbox"/>                  |
| If yes, describe:<br><b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b><br>Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u> , as opposed to "I have the thoughts but I definitely will not do anything about them."<br><i>Have you had these thoughts and had some intention of acting on them?</i>   | Yes No<br><input type="checkbox"/> <input type="checkbox"/>   | Yes No<br><input type="checkbox"/> <input type="checkbox"/>                  |
| If yes, describe:<br><b>5. Active Suicidal Ideation with Specific Plan and Intent</b><br>Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.<br><i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i>  | Yes No<br><input type="checkbox"/> <input type="checkbox"/>   | Yes No<br><input type="checkbox"/> <input type="checkbox"/>                  |
| <b>INTENSITY OF IDEATION</b>  |   |  |
| <i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.</i>  |   |  |
| <b>Lifetime - Most Severe Ideation:</b><br>Type * (1-5) _____<br>Description of Ideation _____  | Most Severe   | Most Severe  |
| <b>Past X Months - Most Severe Ideation:</b><br>Type * (1-5) _____<br>Description of Ideation _____   |   |  |
| <b>Frequency</b><br><i>How many times have you had these thoughts?</i><br>(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day   | —   | —  |
| <b>Duration</b><br><i>When you have the thoughts how long do they last?</i><br>(1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day<br>(2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous<br>(3) 1-4 hours/a lot of time   | —   | —  |
| <b>Controllability</b><br><i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i><br>(1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty<br>(2) Can control thoughts with little difficulty (5) Unable to control thoughts<br>(3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts  | —   | —  |
| <b>Deterrents</b><br><i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i><br>(1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you<br>(2) Deterrents probably stopped you (5) Deterrents definitely did not stop you<br>(3) Uncertain that deterrents stopped you (0) Does not apply  | —   | —  |
| <b>Reasons for Ideation</b><br><i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i><br>(1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (0) Does not apply | —   | —  |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

| <b>SUICIDAL BEHAVIOR</b><br><i>(Check all that apply, so long as these are separate events; must ask about all types)</i>   | <b>Lifetime</b>                 |                                | <b>Past ___ Years</b>           |                                |
|---|---------------------------------|--------------------------------|---------------------------------|--------------------------------|
| <b>Actual Attempt:</b><br>A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i> . Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <i>any</i> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <i>There does not have to be any injury or harm</i> , just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.<br>Inferring Intent: Even if an individual <i>claims</i> intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone <i>claims</i> intent to die, but they thought that what they did could be lethal, intent may be inferred.<br>Have you made a suicide attempt?<br>Have you done anything to harm yourself?<br>Have you done anything dangerous where you could have died?<br>What did you do?<br>Did you _____ as a way to end your life?<br>Did you want to die (even a little) when you _____?<br>Were you trying to end your life when you _____?<br>Or Did you think it was possible you could have died from _____?<br>Or did you do it purely for other reasons / without <i>ANY</i> intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent)<br>If yes, describe: | Yes<br><input type="checkbox"/> | No<br><input type="checkbox"/> | Yes<br><input type="checkbox"/> | No<br><input type="checkbox"/> |
| Total # of Attempts<br>_____<br>Total # of Attempts<br>_____  |                                 |                                |                                 |                                |
| Has subject engaged in Non-Suicidal Self-Injurious Behavior?<br>Yes <input type="checkbox"/> No <input type="checkbox"/>  |                                 |                                |                                 |                                |
| <b>Interrupted Attempt:</b><br>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act ( <i>if not for that, actual attempt would have occurred</i> ).<br>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.<br>Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?<br>If yes, describe:  | Yes<br><input type="checkbox"/> | No<br><input type="checkbox"/> | Yes<br><input type="checkbox"/> | No<br><input type="checkbox"/> |
| Total # of interrupted<br>_____<br>Total # of interrupted<br>_____  |                                 |                                |                                 |                                |
| <b>Aborted Attempt:</b><br>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.<br>Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?<br>If yes, describe:   | Yes<br><input type="checkbox"/> | No<br><input type="checkbox"/> | Yes<br><input type="checkbox"/> | No<br><input type="checkbox"/> |
| Total # of aborted<br>_____<br>Total # of aborted<br>_____  |                                 |                                |                                 |                                |
| <b>Preparatory Acts or Behavior:</b><br>Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).<br>Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?<br>If yes, describe:   | Yes<br><input type="checkbox"/> | No<br><input type="checkbox"/> | Yes<br><input type="checkbox"/> | No<br><input type="checkbox"/> |
| <b>Suicidal Behavior:</b><br>Suicidal behavior was present during the assessment period?<br>Yes <input type="checkbox"/> No <input type="checkbox"/>  |                                 |                                |                                 |                                |
| <b>Answer for Actual Attempts Only</b>  | Most Recent Attempt Date:       | Most Lethal Attempt Date:      | Initial/First Attempt Date:     |                                |
| <b>Actual Lethality/Medical Damage:</b><br>0. No physical damage or very minor physical damage (e.g., surface scratches).<br>1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).<br>2. Moderate physical damage, medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).<br>3. Moderately severe physical damage, medical/hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).<br>4. Severe physical damage, medical/hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).<br>5. Death   | Enter Code<br>_____             | Enter Code<br>_____            | Enter Code<br>_____             |                                |
| <b>Potential Lethality: Only Answer if Actual Lethality=0</b><br>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).<br>0 = Behavior not likely to result in injury<br>1 = Behavior likely to result in injury but not likely to cause death<br>2 = Behavior likely to result in death despite available medical care  | Enter Code<br>_____             | Enter Code<br>_____            | Enter Code<br>_____             |                                |

Since Last Visit Questionnaire

| <b>SUICIDAL IDEATION</b>  |   | Since Last Visit |
|---|---|------------------|
| <i>Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.</i>  |   |                  |
| <b>1. Wish to be Dead</b><br>Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.<br><i>Have you wished you were dead or wished you could go to sleep and not wake up?</i><br><br>If yes, describe:  | Yes No<br><input type="checkbox"/> <input type="checkbox"/> |                  |
| <b>2. Non-Specific Active Suicidal Thoughts</b><br>General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.<br><i>Have you actually had any thoughts of killing yourself?</i><br><br>If yes, describe:   | Yes No<br><input type="checkbox"/> <input type="checkbox"/> |                  |
| <b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b><br>Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."<br><i>Have you been thinking about how you might do this?</i><br><br>If yes, describe:  | Yes No<br><input type="checkbox"/> <input type="checkbox"/> |                  |
| <b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b><br>Active suicidal thoughts of killing oneself and subject reports having <b>some intent to act on such thoughts</b> , as opposed to "I have the thoughts but I definitely will not do anything about them."<br><i>Have you had these thoughts and had some intention of acting on them?</i><br><br>If yes, describe:   | Yes No<br><input type="checkbox"/> <input type="checkbox"/> |                  |
| <b>5. Active Suicidal Ideation with Specific Plan and Intent</b><br>Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.<br><i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i><br><br>If yes, describe:  | Yes No<br><input type="checkbox"/> <input type="checkbox"/> |                  |
| <b>INTENSITY OF IDEATION</b>  |   | Most Severe      |
| <i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).</i>   |   |                  |
| Most Severe Ideation: _____<br><div style="display: flex; justify-content: space-between;"> <span>Type # (1-5)</span> <span>Description of Ideation</span> </div>   |   |                  |
| <b>Frequency</b><br><i>How many times have you had these thoughts?</i><br>(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day   |   | _____            |
| <b>Duration</b><br><i>When you have the thoughts, how long do they last?</i><br>(1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day<br>(2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous<br>(3) 1-4 hours/a lot of time  |   | _____            |
| <b>Controllability</b><br><i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i><br>(1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty<br>(2) Can control thoughts with little difficulty (5) Unable to control thoughts<br>(3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts  |   | _____            |
| <b>Deterrents</b><br><i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i><br>(1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you<br>(2) Deterrents probably stopped you (5) Deterrents definitely did not stop you<br>(3) Uncertain that deterrents stopped you (0) Does not apply  |   | _____            |
| <b>Reasons for Ideation</b><br><i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i><br>(1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (0) Does not apply |   | _____            |

Version 1/14/09

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

| <b>SUICIDAL BEHAVIOR</b><br><i>(Check all that apply, so long as these are separate events; must ask about all types)</i>  |  | Since Last Visit |
|--|--|------------------|
| <p><b>Actual Attempt:</b><br/>A potentially self-injurious act committed with at least some wish to die, as a result of act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <i>There does not have to be any injury or harm</i>, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.<br/>Inferring intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.<br/><i>Have you made a suicide attempt?</i><br/><i>Have you done anything to harm yourself?</i><br/><i>Have you done anything dangerous where you could have died?</i><br/><i>What did you do?</i><br/><i>Did you _____ as a way to end your life?</i><br/><i>Did you want to die (even a little) when you _____?</i><br/><i>Were you trying to end your life when you _____?</i><br/><i>Or did you think it was possible you could have died from _____?</i><br/><i>Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?</i> (Self-Injurious Behavior without suicidal intent)<br/>If yes, describe:</p> | <p>Yes No<br/><input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of Attempts<br/>_____</p> <p>Yes No<br/><input type="checkbox"/> <input type="checkbox"/></p> |                  |
| <p><b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b></p> <p><b>Interrupted Attempt:</b><br/>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>).<br/>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt.<br/>Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.<br/><i>Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?</i><br/>If yes, describe:</p>  | <p>Yes No<br/><input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of interrupted<br/>_____</p>  |                  |
| <p><b>Aborted Attempt:</b><br/>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.<br/><i>Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?</i><br/>If yes, describe:</p>   | <p>Yes No<br/><input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of aborted<br/>_____</p>  |                  |
| <p><b>Preparatory Acts or Behavior:</b><br/>Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).<br/><i>Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?</i><br/>If yes, describe:</p>   | <p>Yes No<br/><input type="checkbox"/> <input type="checkbox"/></p>  |                  |
| <p><b>Suicidal Behavior:</b><br/>Suicidal behavior was present during the assessment period?</p>   | <p>Yes No<br/><input type="checkbox"/> <input type="checkbox"/></p>  |                  |
| <p><b>Suicide:</b></p>   | <p>Yes No<br/><input type="checkbox"/> <input type="checkbox"/></p>  |                  |
| <p><b>Answer for Actual Attempts Only</b></p>  | <p>Most Lethal Attempt Date:<br/>_____</p>   |                  |
| <p><b>Actual Lethality/Medical Damage:</b><br/>0. No physical damage or very minor physical damage (e.g., surface scratches).<br/>1. Minor physical damage (e.g., lethargic speech, first-degree burns, mild bleeding, sprains).<br/>2. Moderate physical damage, medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).<br/>3. Moderately severe physical damage, medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact, third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).<br/>4. Severe physical damage, medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).<br/>5. Death</p>   | <p>Enter Code<br/>_____</p>  |                  |
| <p><b>Potential Lethality: Only Answer if Actual Lethality=0</b><br/>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; lying on train tracks with oncoming train but pulled away before run over).<br/>0 = Behavior not likely to result in injury<br/>1 = Behavior likely to result in injury but not likely to cause death<br/>2 = Behavior likely to result in death despite available medical care</p>   | <p>Enter Code<br/>_____</p>  |                  |

Source: Study 1304 Protocol

### 13.2.2. Barnes Akathisia Rating Scale (BARS)

| Barnes Akathisia Rating Scale (BARS)  |   |
|---|---|
| <b>Instructions:</b> Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning. |   |
| <b>Objective</b>  |   |
| 0   | Normal, occasional fidgety movements of the limbs   |
| 1   | Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, <i>and/or</i> rocking from foot to foot or "walking on the spot" when standing, but movements present for less than half the time observed |
| 2   | Observed phenomena, as described in (1) above, which are present for at least half the observation period   |
| 3   | Patient is constantly engaged in characteristic restless movements, <i>and/or</i> has the inability to remain seated or standing without walking or pacing, during the time observed  |
| <b>Subjective</b>   |   |
| <i>Awareness of restlessness</i>  |   |
| 0   | Absence of inner restlessness   |
| 1   | Non-specific sense of inner restlessness  |
| 2   | The patient is aware of an inability to keep the legs still, or a desire to move the legs, <i>and/or</i> complains of inner restlessness aggravated specifically by being required to stand still   |
| 3   | Awareness of intense compulsion to move most of the time <i>and/or</i> reports strong desire to walk or pace most of the time   |
| <i>Distress related to restlessness</i>   |   |
| 0   | No distress   |
| 1   | Mild  |
| 2   | Moderate  |
| 3   | Severe  |
| <b>Global Clinical Assessment of Akathisia</b>  |   |
| 0   | <i>Absent.</i> No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia                           |
| 1   | <i>Questionable.</i> Non-specific inner tension and fidgety movements   |
| 2   | <i>Mild akathisia.</i> Awareness of restlessness in the legs <i>and/or</i> inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress. |
| 3   | <i>Moderate akathisia.</i> Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing  |
| 4   | <i>Marked akathisia.</i> Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing.   |
| 5   | <i>Severe akathisia.</i> The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia.                                       |

Source: Study 1304 Protocol

## Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

### 13.2.3. Simpson-Angus Extrapyramidal Side Effects Scale (SAS)

| SIMPSON-ANGUS EXTRAPYRAMIDAL SIDE EFFECTS SCALE  |  |
|--|--|
| <p>The exam should be conducted in a room where the subject can walk a sufficient distance to allow him/her to get into a natural rhythm (e.g. 15 paces). Each side of the body should be examined. If one side shows more pronounced pathology than the other, this score should be noted and this taken. Cogwheel rigidity may be palpated when the examination is carried out for items 3, 4, 5, and 6. It is not rated separately and is merely another way to detect rigidity. It would indicate that a minimum score of 1 would be mandatory.</p>  |  |
| <p>1. <b>Gait:</b> The patient is examined as he walks into the examining room, his gait, the swing of his arms, his general posture, all form the basis for an overall score for this item. This is rated as follows:</p> <p>0 Normal<br/>1 Diminution in swing while the patient is walking<br/>2 Marked diminution in swing with obvious rigidity in the arm<br/>3 Stiff gait with arms held rigidly before the abdomen<br/>4 Stopped shuffling gait with propulsion and retropulsion</p>   | <p>6. <b>Leg Pendulousness:</b> The patient sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially extended. It is then allowed to fall. The resistance to falling and the lack of swinging form the basis for the score on this item:</p> <p>0 The legs swing freely<br/>1 Slight diminution in the swing of the legs<br/>2 Moderate resistance to swing<br/>3 Marked resistance and damping of swing<br/>4 Complete absence of swing</p>  |
| <p>2. <b>Arm Dropping:</b> The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject, a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly:</p> <p>0 Normal, free fall with loud slap and rebound<br/>1 Fall slowed slightly with less audible contact and little rebound<br/>2 Fall slowed, no rebound<br/>3 Marked slowing, no slap at all<br/>4 Arms fall as though against resistance; as though through glue</p>  | <p>7. <b>Head Dropping:</b> The patient lies on a well-padded examining table and his head is raised by the examiner's hand. The hand is then withdrawn and the head allowed to drop. In the normal subject the head will fall upon the table. The movement is delayed in extrapyramidal system disorder, and in extreme parkinsonism it is absent. The neck muscles are rigid and the head does not reach the examining table. Scoring is as follows:</p> <p>0 The head falls completely with a good thump as it hits the table<br/>1 Slight slowing in fall, mainly noted by lack of slap as head meets the table<br/>2 Moderate slowing in the fall quite noticeable to the eye<br/>3 Head falls stiffly and slowly<br/>4 Head does not reach the examining table</p> |
| <p>3. <b>Shoulder Shaking:</b> The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:</p> <p>0 Normal<br/>1 Slight stiffness and resistance<br/>2 Moderate stiffness and resistance<br/>3 Marked rigidity with difficulty in passive movement<br/>4 Extreme stiffness and rigidity with almost a frozen shoulder</p> | <p>8. <b>Glabella Tap:</b> Subject is told to open eyes wide and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:</p> <p>0 0-5 blinks<br/>1 6-10 blinks<br/>2 11-15 blinks<br/>3 16-20 blinks<br/>4 21 and more blinks</p>   |
| <p>4. <b>Elbow Rigidity:</b> The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.)</p> <p>0 Normal<br/>1 Slight stiffness and resistance<br/>2 Moderate stiffness and resistance<br/>3 Marked rigidity with difficulty in passive movement<br/>4 Extreme stiffness and rigidity with almost a frozen elbow</p>   | <p>9. <b>Tremor:</b> Patient is observed walking into examining room and is then reexamined for this item:</p> <p>0 Normal<br/>1 Mild finger tremor, obvious to sight and touch<br/>2 Tremor of hand or arm occurring spasmodically<br/>3 Persistent tremor of one or more limbs<br/>4 Whole body tremor</p>   |
| <p>5. <b>Wrist Rigidity or Fixation of Position:</b> The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, flexion and ulnar and radial deviation:</p> <p>0 Normal<br/>1 Slight stiffness and resistance<br/>2 Moderate stiffness and resistance<br/>3 Marked rigidity with difficulty in passive movement<br/>4 Extreme stiffness and rigidity with almost frozen wrist</p>   | <p>10. <b>Salivation:</b> Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:</p> <p>0 Normal<br/>1 Excess salivation to the extent that pooling takes place if the mouth is open and the tongue raised<br/>2 When excess salivation is present and might occasionally result in difficulty speaking<br/>3 Speaking with difficulty because of excess salivation<br/>4 Frank drooling</p>  |

Source: Study 1304 Protocol

**13.2.4. Positive and Negative Syndrome Scale (PANSS)**

*Positive Scale (P)*

*P1. Delusions.* Beliefs which are unfounded, unrealistic, and idiosyncratic. *Basis for rating:* thought content expressed in the interview and its influence on social relations and behavior as reported by primary care workers or family.

| Rating            | Criteria  |
|-------------------|---|
| 1 Absent          | Definition does not apply.  |
| 2 Minimal         | Questionable pathology; may be at the upper extreme of normal limits.   |
| 3 Mild            | Presence of one or two delusions, which are vague, uncrystallized, and not tenaciously held. Delusions do not interfere with thinking, social relations, or behavior.   |
| 4 Moderate        | Presence of either a kaleidoscopic array of poorly formed, unstable delusions or a few well-formed delusions that occasionally interfere with thinking, social relations, or behavior.  |
| 5 Moderate Severe | Presence of numerous well-formed delusions that are tenaciously held and occasionally interfere with thinking, social relations, or behavior.   |
| 6 Severe          | Presence of a stable set of delusions which are crystallized, possibly systematized, tenaciously held, and clearly interfere with thinking, social relations, and behavior.   |
| 7 Extreme         | Presence of a stable set of delusions which are either highly systematized or very numerous, and which dominate major facets of the patient's life. This frequently results in inappropriate and irresponsible action, which may even jeopardize the safety of the patient or others. |

*Positive Scale (P)*

*P2. Conceptual disorganization.* Disorganized process of thinking characterized by disruption of goal-directed sequencing, e.g., circumstantiality, tangentiality, loose associations, non-sequiturs, gross illogicality, or thought block. *Basis for rating:* cognitive-verbal processes observed during the course of interview.

| Rating            | Criteria   |
|-------------------|--|
| 1 Absent          | Definition does not apply.   |
| 2 Minimal         | Questionable pathology; may be at the upper extreme of normal limits.  |
| 3 Mild            | Thinking is circumstantial, tangential, or paralogical. There is some difficulty in directing thoughts toward a goal, and some loosening of associations may be evidenced under pressure.      |
| 4 Moderate        | Able to focus thoughts when communications are brief and structured, but becomes loose or irrelevant when dealing with more complex communications or when under minimal pressure.             |
| 5 Moderate Severe | Generally has difficulty in organizing thoughts, as evidenced by frequent irrelevancies, disconnectedness, or loosening of associations even when not under pressure.                          |
| 6 Severe          | Thinking is seriously derailed and internally inconsistent, resulting in gross irrelevancies and disruption of thought processes, which occur almost constantly.                               |
| 7 Extreme         | Thoughts are disrupted to the point where the patient is incoherent. There is marked loosening of associations, which results in total failure of communication, e.g., "word salad" or mutism. |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*Positive Scale (P)*

**P3. Hallucinatory behavior.** Verbal report or behavior indicating perceptions which are not generated by external stimuli. These may occur in the auditory, visual, olfactory, or somatic realms. *Basis for rating:* verbal report and physical manifestations during the course of interview as well as reports of behavior by primary care workers or family.

|   | Rating          | Criteria   |
|---|-----------------|--|
| 1 | Absent          | Definition does not apply.   |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.  |
| 3 | Mild            | One or two clearly formed but infrequent hallucinations, or else a number of vague abnormal perceptions, which do not result in distortions of thinking or behavior.   |
| 4 | Moderate        | Hallucinations occur frequently but not continuously, and the patient's thinking and behavior are affected only to a minor extent.   |
| 5 | Moderate Severe | Hallucinations are frequent, may involve more than one sensory modality, and tend to distort thinking and/or disrupt behavior. Patient may have delusional interpretation of these experiences and respond to them emotionally and, on occasion, verbally as well.   |
| 6 | Severe          | Hallucinations are present almost continuously, causing major disruption of thinking and behavior. Patient treats these as real perceptions, and functioning is impeded by frequent emotional and verbal responses to them.  |
| 7 | Extreme         | Patient is almost totally preoccupied with hallucinations, which virtually dominate thinking and behavior. Hallucinations are provided a rigid delusional interpretation and provoke verbal and behavioral responses, including obedience to command hallucinations. |

*Positive Scale (P)*

**P4. Excitement.** Hyperactivity as reflected in accelerated motor behavior, heightened responsivity to stimuli, hypervigilance, or excessive mood lability. *Basis for rating:* behavioral manifestations during the course of interview as well as reports of behavior by primary care workers or family.

|   | Rating          | Criteria   |
|---|-----------------|--|
| 1 | Absent          | Definition does not apply.   |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.  |
| 3 | Mild            | Tends to be slightly agitated, hypervigilant, or mildly overaroused throughout the interview, but without distinct episodes of excitement or marked mood lability. Speech may be slightly pressured.         |
| 4 | Moderate        | Agitation or overarousal is clearly evident throughout the interview, affecting speech and general mobility, or episodic outbursts occur sporadically.   |
| 5 | Moderate Severe | Significant hyperactivity or frequent outbursts of motor activity are observed, making it difficult for the patient to sit still for longer than several minutes at any given time.                          |
| 6 | Severe          | Marked excitement dominates the interview, delimits attention, and to some extent affects personal functions such as eating and sleeping.  |
| 7 | Extreme         | Marked excitement seriously interferes in eating and sleeping and makes interpersonal interactions virtually impossible. Acceleration of speech and motor activity may result in incoherence and exhaustion. |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*Positive Scale (P)*

*P5. Grandiosity.* Exaggerated self-opinion and unrealistic convictions of superiority, including delusions of extraordinary abilities, wealth, knowledge, fame, power, and moral righteousness. *Basis for rating:* thought content expressed in the interview and its influence on behavior as reported by primary care workers or family.

|   | Rating          | Criteria  |
|---|-----------------|---|
| 1 | Absent          | Definition does not apply.  |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.   |
| 3 | Mild            | Some expansiveness or boastfulness is evident, but without clear-cut grandiose delusions.   |
| 4 | Moderate        | Feels distinctly and unrealistically superior to others. Some poorly formed delusions about special status or abilities may be present but are not acted upon.                          |
| 5 | Moderate Severe | Clear-cut delusions concerning remarkable abilities, status, or power are expressed and influence attitude but not behavior.  |
| 6 | Severe          | Clear-cut delusions of remarkable superiority involving more than one parameter (wealth, knowledge, fame, etc.) are expressed, notably influence interactions, and may be acted upon.   |
| 7 | Extreme         | Thinking, interactions, and behavior are dominated by multiple delusions of amazing ability, wealth, knowledge, fame, power, and/or moral stature, which may take on a bizarre quality. |

*Positive Scale (P)*

*P6. Suspiciousness/persecution.* Unrealistic or exaggerated ideas of persecution, as reflected in guardedness, a distrustful attitude, suspicious hypervigilance, or frank delusions that others mean one harm. *Basis for rating:* thought content expressed in the interview and its influence on behavior as reported by primary care workers or family.

|   | Rating          | Criteria  |
|---|-----------------|---|
| 1 | Absent          | Definition does not apply.  |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.   |
| 3 | Mild            | Presents a guarded or even openly distrustful attitude, but thoughts, interactions, and behavior are minimally affected.  |
| 4 | Moderate        | Distrustfulness is clearly evident and intrudes on the interview and/or behavior, but there is no evidence of persecutory delusions. Alternatively, there may be indication of loosely formed persecutory delusions, but these do not seem to affect the patient's attitude or interpersonal relations. |
| 5 | Moderate Severe | Patient shows marked distrustfulness, leading to major disruption of interpersonal relations, or else there are clear-cut persecutory delusions that have limited impact on interpersonal relations and behavior.   |
| 6 | Severe          | Clear-cut pervasive delusions of persecution which may be systematized and significantly interfere in interpersonal relations.  |
| 7 | Extreme         | A network of systematized persecutory delusions dominates the patient's thinking, social relations, and behavior.   |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*Positive Scale (P)*

**P7. Hostility.** Verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behavior, verbal abuse, and assaultiveness. *Basis for rating:* interpersonal behavior observed during the interview and reports by primary care workers or family.

|   | Rating          | Criteria   |
|---|-----------------|--|
| 1 | Absent          | Definition does not apply.   |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.  |
| 3 | Mild            | Indirect or restrained communication of anger, such as sarcasm, disrespect, hostile expressions, and occasional irritability.  |
| 4 | Moderate        | Presents an overtly hostile attitude, showing frequent irritability and direct expression of anger or resentment.  |
| 5 | Moderate Severe | Patient is highly irritable and occasionally verbally abusive or threatening.  |
| 6 | Severe          | Uncooperativeness and verbal abuse or threats notably influence the interview and seriously impact upon social relations. Patient may be violent and destructive but is not physically assaultive toward others. |
| 7 | Extreme         | Marked anger results in extreme uncooperativeness, precluding other interactions, or in episode(s) of physical assault toward others.  |

*Negative Scale (N)*

**N1. Blunted affect.** Diminished emotional responsiveness as characterized by a reduction in facial expression, modulation of feelings, and communicative gestures. *Basis for rating:* observation of physical manifestations of affective tone and emotional responsiveness during the course of interview.

|   | Rating          | Criteria  |
|---|-----------------|---|
| 1 | Absent          | Definition does not apply.  |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.   |
| 3 | Mild            | Changes in facial expression and communicative gestures seem to be stilted, forced, artificial, or lacking in modulation.   |
| 4 | Moderate        | Reduced range of facial expression and few expressive gestures result in a dull appearance.   |
| 5 | Moderate Severe | Affect is generally "flat," with only occasional changes in facial expression and a paucity of communicative gestures.  |
| 6 | Severe          | Marked flatness and deficiency of emotions exhibited most of the time. There may be unmodulated extreme affective discharges, such as excitement, rage, or inappropriate uncontrolled laughter. |
| 7 | Extreme         | Changes in facial expression and evidence of communicative gestures are virtually absent. Patient seems constantly to show a barren or "wooden" expression.                                     |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*Negative Scale (N)*

*N2. Emotional withdrawal.* Lack of interest in, involvement with, and affective commitment to life's events. *Basis for rating:* reports of functioning from primary care workers or family and observation of interpersonal behavior during the course of interview.

|   | Rating          | Criteria   |
|---|-----------------|--|
| 1 | Absent          | Definition does not apply.   |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.  |
| 3 | Mild            | Usually lacks initiative and occasionally may show deficient interest in surrounding events.   |
| 4 | Moderate        | Patient is generally distanced emotionally from the milieu and its challenges but, with encouragement, can be engaged.   |
| 5 | Moderate Severe | Patient is clearly detached emotionally from persons and events in the milieu, resisting all efforts at engagement. Patient appears distant, docile, and purposeless but can be involved in communication at least briefly and tends to personal needs, sometimes with assistance. |
| 6 | Severe          | Marked deficiency of interest and emotional commitment results in limited conversation with others and frequent neglect of personal functions, for which the patient requires supervision.   |
| 7 | Extreme         | Patient is almost totally withdrawn, uncommunicative, and neglectful of personal needs as a result of profound lack of interest and emotional commitment.  |

*Negative Scale (N)*

*N3. Poor rapport.* Lack of interpersonal empathy, openness in conversation, and sense of closeness, interest, or involvement with the interviewer. This is evidenced by interpersonal distancing and reduced verbal and nonverbal communication. *Basis for rating:* interpersonal behavior during the course of interview.

|   | Rating          | Criteria  |
|---|-----------------|---|
| 1 | Absent          | Definition does not apply.  |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.   |
| 3 | Mild            | Conversation is characterized by a stilted, strained, or artificial tone. It may lack emotional depth or tend to remain on an impersonal, intellectual plane.                                   |
| 4 | Moderate        | Patient typically is aloof, with interpersonal distance quite evident. Patient may answer questions mechanically, act bored, or express disinterest.  |
| 5 | Moderate Severe | Disinvolvement is obvious and clearly impedes the productivity of the interview. Patient may tend to avoid eye or face contact.   |
| 6 | Severe          | Patient is highly indifferent, with marked interpersonal distance. Answers are perfunctory, and there is little nonverbal evidence of involvement. Eye and face contact are frequently avoided. |
| 7 | Extreme         | Patient is totally uninvolved with the interviewer. Patient appears to be completely indifferent and consistently avoids verbal and nonverbal interactions during the interview.                |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*Negative Scale (N)*

*N4. Passive/apathetic social withdrawal.* Diminished interest and initiative in social interactions due to passivity, apathy, anergy, or avolition. This leads to reduced interpersonal involvements and neglect of activities of daily living. *Basis for rating:* reports on social behavior from primary care workers or family.

|   | Rating          | Criteria   |
|---|-----------------|--|
| 1 | Absent          | Definition does not apply.   |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.  |
| 3 | Mild            | Shows occasional interest in social activities but poor initiative. Usually engages with others only when approached first by them.                                      |
| 4 | Moderate        | Passively goes along with most social activities but in a disinterested or mechanical way. Tends to recede into the background.  |
| 5 | Moderate Severe | Passively participates in only a minority of activities and shows virtually no interest or initiative. Generally spends little time with others.                         |
| 6 | Severe          | Tends to be apathetic and isolated, participating very rarely in social activities and occasionally neglecting personal needs. Has very few spontaneous social contacts. |
| 7 | Extreme         | Profoundly apathetic, socially isolated, and personally neglectful.  |

*Negative Scale (N)*

*N5. Difficulty in abstract thinking.* Impairment in the use of the abstract-symbolic mode of thinking, as evidenced by difficulty in classification, forming generalizations, and proceeding beyond concrete or egocentric thinking in problem-solving tasks. *Basis for rating:* responses to questions on similarities and proverb interpretation, and use of concrete vs. abstract mode during the course of the interview.

|   | Rating          | Criteria  |
|---|-----------------|---|
| 1 | Absent          | Definition does not apply.  |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.   |
| 3 | Mild            | Tends to give literal or personalized interpretations to the more difficult proverbs and may have some problems with concepts that are fairly abstract or remotely related.   |
| 4 | Moderate        | Often utilizes a concrete mode. Has difficulty with most proverbs and some categories. Tends to be distracted by functional aspects and salient features.   |
| 5 | Moderate Severe | Deals primarily in a concrete mode, exhibiting difficulty with most proverbs and many categories.   |
| 6 | Severe          | Unable to grasp the abstract meaning of any proverbs or figurative expressions and can formulate classifications for only the most simple of similarities. Thinking is either vacuous or locked into functional aspects, salient features, and idiosyncratic interpretations.   |
| 7 | Extreme         | Can use only concrete modes of thinking. Shows no comprehension of proverbs, common metaphors or similes, and simple categories. Even salient and functional attributes do not serve as a basis for classification. This rating may apply to those who cannot interact even minimally with the examiner due to marked cognitive impairment. |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*Negative Scale (N)*

*N6. Lack of spontaneity and flow of conversation.* Reduction in the normal flow of communication associated with apathy, avolition, defensiveness, or cognitive deficit. This is manifested by diminished fluidity and productivity of the verbal-interactive process. *Basis for rating:* cognitive-verbal processes observed during the course of interview.

|   | Rating          | Criteria  |
|---|-----------------|---|
| 1 | Absent          | Definition does not apply.  |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.   |
| 3 | Mild            | Conversation shows little initiative. Patient's answers tend to be brief and unembellished, requiring direct and leading questions by the interviewer.  |
| 4 | Moderate        | Conversation lacks free flow and appears uneven or halting. Leading questions are frequently needed to elicit adequate responses and proceed with conversation.   |
| 5 | Moderate Severe | Patient shows a marked lack of spontaneity and openness, replying to the interviewer's questions with only one or two brief sentences.  |
| 6 | Severe          | Patient's responses are limited mainly to a few words or short phrases intended to avoid or curtail communication. (E.g., "I don't know," "I'm not at liberty to say.") Conversation is seriously impaired as a result, and the interview is highly unproductive. |
| 7 | Extreme         | Verbal output is restricted to, at most, an occasional utterance, making conversation impossible.   |

*Negative Scale (N)*

*N7. Stereotyped thinking.* Decreased fluidity, spontaneity, and flexibility of thinking, as evidenced in rigid, repetitious, or barren thought content. *Basis for rating:* cognitive-verbal processes observed during the interview.

|   | Rating          | Criteria   |
|---|-----------------|--|
| 1 | Absent          | Definition does not apply.   |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.  |
| 3 | Mild            | Some rigidity shown in attitudes or beliefs. Patient may refuse to consider alternative positions or have difficulty in shifting from one idea to another.   |
| 4 | Moderate        | Conversation revolves around a recurrent theme, resulting in difficulty in shifting to a new topic.  |
| 5 | Moderate Severe | Thinking is rigid and repetitious to the point that, despite the interviewer's efforts, conversation is limited to only two or three dominating topics.  |
| 6 | Severe          | Uncontrolled repetition of demands, statements, ideas, or questions which severely impairs conversation.   |
| 7 | Extreme         | Thinking, behavior, and conversation are dominated by constant repetition of fixed ideas or limited phrases, leading to gross rigidity, inappropriateness, and restrictiveness of patient's communication. |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*General Psychopathology Scale (G)*

*G1. Somatic concern.* Physical complaints or beliefs about bodily illness or malfunctions. This may range from a vague sense of ill being to clear-cut delusions of catastrophic physical disease. *Basis for rating:* thought content expressed in the interview.

|   | Rating          | Criteria  |
|---|-----------------|---|
| 1 | Absent          | Definition does not apply.  |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.   |
| 3 | Mild            | Distinctly concerned about health or somatic issues, as evidenced by occasional questions and desire for reassurance.   |
| 4 | Moderate        | Complains about poor health or bodily malfunction, but there is no delusional conviction, and over-concern can be allayed by reassurance.   |
| 5 | Moderate Severe | Patient expresses numerous or frequent complaints about physical illness or bodily malfunction, or else patient reveals one or two clear-cut delusions involving these themes but is not preoccupied by them.                 |
| 6 | Severe          | Patient is preoccupied by one or a few clear-cut delusions about physical disease or organic malfunction, but affect is not fully immersed in these themes, and thoughts can be diverted by the interviewer with some effort. |
| 7 | Extreme         | Numerous and frequently reported somatic delusions, or only a few somatic delusions of a catastrophic nature, which totally dominate the patient's affect and thinking.   |

*General Psychopathology Scale (G)*

*G2. Anxiety.* Subjective experience of nervousness, worry, apprehension, or restlessness, ranging from excessive concern about the present or future to feelings of panic. *Basis for rating:* verbal report during the course of interview and corresponding physical manifestations.

|   | Rating          | Criteria   |
|---|-----------------|--|
| 1 | Absent          | Definition does not apply.   |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.  |
| 3 | Mild            | Expresses some worry, over-concern, or subjective restlessness, but no somatic and behavioral consequences are reported or evidenced.  |
| 4 | Moderate        | Patient reports distinct symptoms of nervousness, which are reflected in mild physical manifestations such as fine hand tremor and excessive perspiration.                             |
| 5 | Moderate Severe | Patient reports serious problems of anxiety, which have significant physical and behavioral consequences, such as marked tension, poor concentration, palpitations, or impaired sleep. |
| 6 | Severe          | Subjective state of almost constant fear associated with phobias, marked restlessness, or numerous somatic manifestations.   |
| 7 | Extreme         | Patient's life is seriously disrupted by anxiety, which is present almost constantly and, at times, reaches panic proportion or is manifested in actual panic attacks.                 |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*General Psychopathology Scale (G)*

**G3. Guilt feelings.** Sense of remorse or self-blame for real or imagined misdeeds in the past. *Basis for rating:* verbal report of guilt feelings during the course of interview and the influence on attitudes and thoughts.

|   | Rating          | Criteria   |
|---|-----------------|--|
| 1 | Absent          | Definition does not apply.   |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.  |
| 3 | Mild            | Questioning elicits a vague sense of guilt or self-blame for a minor incident, but the patient clearly is not overly concerned.  |
| 4 | Moderate        | Patient expresses distinct concern over his or her responsibility for a real incident in his or her life but is not preoccupied with it, and attitude and behavior are essentially unaffected.   |
| 5 | Moderate Severe | Patient expresses a strong sense of guilt associated with self-deprecation or the belief that he or she deserves punishment. The guilt feelings may have a delusional basis, may be volunteered spontaneously, may be a source of preoccupation and/or depressed mood, and cannot be allayed readily by the interviewer. |
| 6 | Severe          | Strong ideas of guilt take on a delusional quality and lead to an attitude of hopelessness or worthlessness. The patient believes he or she should receive harsh sanctions for the misdeeds and may even regard his or her current life situation as such punishment.  |
| 7 | Extreme         | Patient's life is dominated by unstable delusions of guilt, for which he or she feels deserving of drastic punishment, such as life imprisonment, torture, or death. There may be associated suicidal thoughts or attribution of others' problems to one's own past misdeeds.  |

*General Psychopathology Scale (G)*

**G4. Tension.** Overt physical manifestations of fear, anxiety, and agitation, such as stiffness, tremor, profuse sweating, and restlessness. *Basis for rating:* verbal report attesting to anxiety and, thereupon, the severity of physical manifestations of tension observed during the interview.

|   | Rating          | Criteria  |
|---|-----------------|---|
| 1 | Absent          | Definition does not apply.  |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.   |
| 3 | Mild            | Posture and movements indicate slight apprehensiveness, such as minor rigidity, occasional restlessness, shifting of position, or fine rapid hand tremor.   |
| 4 | Moderate        | A clearly nervous appearance emerges from various manifestations, such as fidgety behavior, obvious hand tremor, excessive perspiration, or nervous mannerisms.   |
| 5 | Moderate Severe | Pronounced tension is evidenced by numerous manifestations, such as nervous shaking, profuse sweating, and restlessness, but conduct in the interview is not significantly affected.                                |
| 6 | Severe          | Pronounced tension to the point that interpersonal interactions are disrupted. The patient, for example, may be constantly fidgeting, unable to sit still for long, or show hyperventilation.                       |
| 7 | Extreme         | Marked tension is manifested by signs of panic or gross motor acceleration, such as rapid restless pacing and inability to remain seated for longer than a minute, which makes sustained conversation not possible. |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*General Psychopathology Scale (G)*

**G5. Mannerisms and posturing.** Unnatural movements or posture as characterized by an awkward, stilted, disorganized, or bizarre appearance. *Basis for rating:* observation of physical manifestations during the course of interview as well as reports from primary care workers or family.

|   | Rating          | Criteria  |
|---|-----------------|---|
| 1 | Absent          | Definition does not apply.  |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.   |
| 3 | Mild            | Slight awkwardness in movements or minor rigidity of posture.   |
| 4 | Moderate        | Movements are notably awkward or disjointed, or an unnatural posture is maintained for brief periods.   |
| 5 | Moderate Severe | Occasional bizarre rituals or contorted posture are observed, or an abnormal position is sustained for extended periods.  |
| 6 | Severe          | Frequent repetition of bizarre rituals, mannerisms, or stereotyped movements, or a contorted posture is sustained for extended periods.   |
| 7 | Extreme         | Functioning is seriously impaired by virtually constant involvement in ritualistic, manneristic, or stereotyped movements or by an unnatural fixed posture which is sustained most of the time. |

*General Psychopathology Scale (G)*

**G6. Depression.** Feelings of sadness, discouragement, helplessness, and pessimism. *Basis for rating:* verbal report of depressed mood during the course of interview and its observed influence on attitude and behavior as reported by primary care workers or family.

|   | Rating          | Criteria  |
|---|-----------------|---|
| 1 | Absent          | Definition does not apply.  |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.   |
| 3 | Mild            | Expresses some sadness or discouragement only on questioning, but there is no evidence of depression in general attitude or demeanor.   |
| 4 | Moderate        | Distinct feelings of sadness or hopelessness, which may be spontaneously divulged, but depressed mood has no major impact on behavior or social functioning, and the patient usually can be cheered up.   |
| 5 | Moderate Severe | Distinctly depressed mood is associated with obvious sadness, pessimism, loss of social interest, psychomotor retardation, and some interference in appetite and sleep. The patient cannot be easily cheered up.  |
| 6 | Severe          | Markedly depressed mood is associated with sustained feelings of misery, occasional crying, hopelessness, and worthlessness. In addition, there is major interference in appetite and/or sleep as well as in normal motor and social functions, with possible signs of self-neglect.                                    |
| 7 | Extreme         | Depressive feelings seriously interfere in most major functions. The manifestations include frequent crying, pronounced somatic symptoms, impaired concentration, psychomotor retardation, social disinterest, self-neglect, possible depressive or nihilistic delusions, and/or possible suicidal thoughts or actions. |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**General Psychopathology Scale (G)**

**G7. Motor retardation.** Reduction in motor activity as reflected in slowing or lessening of movements and speech, diminished responsiveness to stimuli, and reduced body tone. *Basis for rating:* manifestations during the course of interview as well as reports by primary care workers or family.

|   | Rating          | Criteria  |
|---|-----------------|---|
| 1 | Absent          | Definition does not apply.  |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.   |
| 3 | Mild            | Slight but noticeable diminution in rate of movements and speech. Patient may be somewhat underproductive in conversation and gestures.   |
| 4 | Moderate        | Patient is clearly slow in movements, and speech may be characterized by poor productivity, including long response latency, extended pauses, or slow pace.                                       |
| 5 | Moderate Severe | A marked reduction in motor activity renders communication highly unproductive or delimits functioning in social and occupational situations. Patient can usually be found sitting or lying down. |
| 6 | Severe          | Movements are extremely slow, resulting in a minimum of activity and speech. Essentially the day is spent sitting idly or lying down.   |
| 7 | Extreme         | Patient is almost completely immobile and virtually unresponsive to external stimuli.   |

**General Psychopathology Scale (G)**

**G8. Uncooperativeness.** Active refusal to comply with the will of significant others, including the interviewer, hospital staff, or family, which may be associated with distrust, defensiveness, stubbornness, negativism, rejection of authority, hostility, or belligerence. *Basis for rating:* interpersonal behavior observed during the course of interview as well as reports by primary care workers or family.

|   | Rating          | Criteria   |
|---|-----------------|--|
| 1 | Absent          | Definition does not apply.   |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.  |
| 3 | Mild            | Complies with an attitude of resentment, impatience, or sarcasm. May inoffensively object to sensitive probing during the interview.   |
| 4 | Moderate        | Occasional outright refusal to comply with normal social demands, such as making own bed, attending scheduled programs, etc. The patient may project a hostile, defensive, or negative attitude but usually can be worked with.  |
| 5 | Moderate Severe | Patient frequently is in compliant with the demands of his or her milieu and may be characterized by others as an "outcast" or having "a serious attitude problem." Uncooperativeness is reflected in obvious defensiveness or irritability with the interviewer and possible unwillingness to address many questions. |
| 6 | Severe          | Patient is highly uncooperative, negativistic, and possibly also belligerent. Refuses to comply with most social demands and may be unwilling to initiate or conclude the full interview.  |
| 7 | Extreme         | Active resistance seriously impacts on virtually all major areas of functioning. Patient may refuse to join in any social activities, tend to personal hygiene, converse with family or staff, and participate even briefly in an interview.   |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*General Psychopathology Scale (G)*

*G9. Unusual thought content.* Thinking characterized by strange, fantastic, or bizarre ideas, ranging from those, which are remote or atypical to those which are distorted, illogical, and patently absurd. *Basis for rating:* thought content expressed during the course of interview.

|   | Rating             | Criteria   |
|---|--------------------|--|
| 1 | Absent             | Definition does not apply.   |
| 2 | Minimal            | Questionable pathology; may be at the upper extreme of normal limits.  |
| 3 | Mild               | Thought content is somewhat peculiar or idiosyncratic, or familiar ideas are framed in an odd context.   |
| 4 | Moderate           | Ideas are frequently distorted and occasionally seem quite bizarre.  |
| 5 | Moderate<br>Severe | Patient expresses many strange and fantastic thoughts (e.g., being the adopted son of a king, being an escapee from death row) or some which are patently absurd (e.g., having hundreds of children, receiving radio messages from outer space through a tooth filling). |
| 6 | Severe             | Patient expresses many illogical or absurd ideas or some, which have a distinctly bizarre quality (e.g., having three heads, being a visitor from another planet).   |
| 7 | Extreme            | Thinking is replete with absurd, bizarre, and grotesque ideas.   |

*General Psychopathology Scale (G)*

*G10. Disorientation.* Lack of awareness of one's relationship to the milieu, including persons, place, and time, which may be due to confusion or withdrawal. *Basis for rating:* responses to interview questions on orientation.

|   | Rating             | Criteria   |
|---|--------------------|--|
| 1 | Absent             | Definition does not apply.   |
| 2 | Minimal            | Questionable pathology; may be at the upper extreme of normal limits.  |
| 3 | Mild               | General orientation is adequate but there is some difficulty with specifics. For example, patient knows his or her location but not the street address; knows hospital staff names but not their functions; knows the month but confuses the day of week with an adjacent day; or errs in the date by more than two days. There may be narrowing of interest evidenced by familiarity with the immediate but not extended milieu, such as ability to identify staff but not the Mayor, Governor, or President. |
| 4 | Moderate           | Only partial success in recognizing persons, places, and time. For example, patient knows he or she is in a hospital but not its name; knows the name of his or her city but not the borough or district, knows the name of his or her primary therapist but not many other direct care workers; knows the year and season but is not sure of the month.   |
| 5 | Moderate<br>Severe | Considerable failure in recognizing persons, place, and time. Patient has only a vague notion of where he or she is and seems unfamiliar with most people in his or her milieu. He or she may identify the year correctly or nearly so but not know the current month, day of week, or even the season.  |
| 6 | Severe             | Marked failure in recognizing persons, place, and time. For example, patient has no knowledge of his or her whereabouts; confuses the date by more than one year; can name only one or two individuals in his or her current life.   |
| 7 | Extreme            | Patient appears completely disoriented with regard to persons, place, and time. There is gross confusion or total ignorance about one's location, the current year, and even the most familiar people, such as parents, spouse, friends, and primary therapist.  |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*General Psychopathology Scale (G)*

*G11. Poor attention.* Failure in focused alertness manifested by poor concentration, distractibility from internal and external stimuli, and difficulty in harnessing, sustaining, or shifting focus to new stimuli. *Basis for rating:* manifestations during the course of interview.

|   | Rating          | Criteria   |
|---|-----------------|--|
| 1 | Absent          | Definition does not apply.   |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.  |
| 3 | Mild            | Limited concentration evidenced by occasional vulnerability to distraction or faltering attention toward the end of the interview.   |
| 4 | Moderate        | Conversation is affected by the tendency to be easily distracted, difficulty in long sustaining concentration on a given topic, or problems in shifting attention to new topics. |
| 5 | Moderate Severe | Conversation is seriously hampered by poor concentration, distractibility, and difficulty in shifting focus appropriately.   |
| 6 | Severe          | Patient's attention can be harnessed for only brief moments or with great effort, due to marked distraction by internal or external stimuli.                                     |
| 7 | Extreme         | Attention is so disrupted that even brief conversation is not possible.  |

*General Psychopathology Scale (G)*

*G12. Lack of judgment and insight.* Impaired awareness or understanding of one's own psychiatric condition and life situation. This is evidenced by failure to recognize past or present psychiatric illness or symptoms, denial of need for psychiatric hospitalization or treatment, decisions characterized by poor anticipation of consequences, and unrealistic short-term and long-range planning. *Basis for rating:* thought content expressed during the interview.

|   | Rating          | Criteria  |
|---|-----------------|---|
| 1 | Absent          | Definition does not apply.  |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.   |
| 3 | Mild            | Recognizes having a psychiatric disorder but clearly underestimates its seriousness, the implications for treatment, or the importance of taking measures to avoid relapse. Future planning may be poorly conceived.  |
| 4 | Moderate        | Patient shows only a vague or shallow recognition of illness. There may be fluctuations in acknowledgment of being ill or little awareness of major symptoms, which are present, such as delusions, disorganized thinking, suspiciousness, and social withdrawal. The patient may rationalize the need for treatment in terms of its relieving lesser symptoms, such as anxiety, tension, and sleep difficulty. |
| 5 | Moderate Severe | Acknowledges past but not present psychiatric disorder. If challenged, the patient may concede the presence of some unrelated or insignificant symptoms, which tend to be explained away by gross misinterpretation or delusional thinking. The need for psychiatric treatment similarly goes unrecognized.   |
| 6 | Severe          | Patient denies ever having had a psychiatric disorder. He or she disavows the presence of any psychiatric symptoms in the past or present and, though compliant, denies the need for treatment and hospitalization.   |
| 7 | Extreme         | Emphatic denial of past and present psychiatric illness. Current hospitalization and treatment are given a delusional interpretation (e.g., as punishment for misdeeds, as persecution by tormentors, etc.), and the patient may thus refuse to cooperate with therapists, medication, or other aspects of treatment.   |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

**General Psychopathology Scale (G)**

**G13. Disturbance of volition.** Disturbance in the willful initiation, sustenance, and control of one's thoughts, behavior, movements, and speech. *Basis for rating:* thought content and behavior manifested in the course of interview.

|   | Rating          | Criteria  |
|---|-----------------|---|
| 1 | Absent          | Definition does not apply.  |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.   |
| 3 | Mild            | There is evidence of some indecisiveness in conversation and thinking, which may impede verbal and cognitive processes to a minor extent.   |
| 4 | Moderate        | Patient is often ambivalent and shows clear difficulty in reaching decisions. Conversation may be marred by alteration in thinking, and in consequence verbal and cognitive functioning are clearly impaired.                           |
| 5 | Moderate Severe | Disturbance of volition interferes in thinking as well as behavior. Patient shows pronounced indecision that impedes the initiation and continuation of social and motor activities, and which also may be evidenced in halting speech. |
| 6 | Severe          | Disturbance of volition interferes in the execution of simple, automatic motor functions, such as dressing and grooming, and markedly affects speech.   |
| 7 | Extreme         | Almost complete failure of volition is manifested by gross inhibition of movement and speech, resulting in immobility and/or mutism.  |

**General Psychopathology Scale (G)**

**G14. Poor impulse control.** Disordered regulation and control of action on inner urges, resulting in sudden, unmodulated, arbitrary, or misdirected discharge of tension and emotions without concern about consequences. *Basis for rating:* behavior during the course of interview and reported by primary care workers or family.

|   | Rating          | Criteria   |
|---|-----------------|--|
| 1 | Absent          | Definition does not apply.   |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.  |
| 3 | Mild            | Patient tends to be easily angered and frustrated when facing stress or denied gratification but rarely acts on impulse.   |
| 4 | Moderate        | Patient gets angered and verbally abusive with minimal provocation. May be occasionally threatening, destructive, or have one or two episodes involving physical confrontation or a minor brawl.   |
| 5 | Moderate Severe | Patient exhibits repeated impulsive episodes involving verbal abuse, destruction of property, or physical threats. There may be one or two episodes involving serious assault, for which the patient requires isolation, physical restraint, or p.r.n. sedation.     |
| 6 | Severe          | Patient frequently is impulsively aggressive, threatening, demanding, and destructive, without any apparent consideration of consequences. Shows assaultive behavior and may also be sexually offensive and possibly respond behaviorally to hallucinatory commands. |
| 7 | Extreme         | Patient exhibits homicidal attacks, sexual assaults, repeated brutality, or self-destructive behavior. Requires constant direct supervision or external constraints because of inability to control dangerous impulses.  |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

*General Psychopathology Scale (G)*

*G15. Preoccupation.* Absorption with internally generated thoughts and feelings and with autistic experiences to the detriment of reality orientation and adaptive behavior. *Basis for rating:* interpersonal behavior observed during the course of interview.

|   | Rating          | Criteria  |
|---|-----------------|---|
| 1 | Absent          | Definition does not apply.  |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.   |
| 3 | Mild            | Excessive involvement with personal needs or problems, such that conversation veers back to egocentric themes and there is diminished concern exhibited toward others.  |
| 4 | Moderate        | Patient occasionally appears self-absorbed, as if daydreaming or involved with internal experiences, which interferes with communication to a minor extent.   |
| 5 | Moderate Severe | Patient often appears to be engaged in autistic experiences, as evidenced by behaviors that significantly intrude on social and communicational functions, such as the presence of a vacant stare, muttering or talking to oneself, or involvement with stereotyped motor patterns. |
| 6 | Severe          | Marked preoccupation with autistic experiences, which seriously delimits concentration, ability to converse, and orientation to the milieu. The patient frequently may be observed smiling, laughing, muttering, talking, or shouting to himself or herself.                        |
| 7 | Extreme         | Gross absorption with autistic experiences, which profoundly affects all major realms of behavior. The patient constantly may be responding verbally and behaviorally to hallucinations and show little awareness of other people or the external milieu.                           |

*General Psychopathology Scale (G)*

*G16. Active social avoidance.* Diminished social involvement associated with unwarranted fear, hostility, or distrust. *Basis for rating:* reports of social functioning by primary care workers or family.

|   | Rating          | Criteria   |
|---|-----------------|--|
| 1 | Absent          | Definition does not apply.   |
| 2 | Minimal         | Questionable pathology; may be at the upper extreme of normal limits.  |
| 3 | Mild            | Patient seems ill at ease in the presence of others and prefers to spend time alone, although he or she participates in social functions when required.  |
| 4 | Moderate        | Patient grudgingly attends all or most social activities but may need to be persuaded or may terminate prematurely on account of anxiety, suspiciousness, or hostility.  |
| 5 | Moderate Severe | Patient fearfully or angrily keeps away from many social interactions despite others' efforts to engage him. Tends to spend unstructured time alone.   |
| 6 | Severe          | Patient participates in very few social activities because of fear, hostility, or distrust. When approached, the patient shows a strong tendency to break off interactions, and generally he or she appears to isolate himself or herself from others. |
| 7 | Extreme         | Patient cannot be engaged in social activities because of pronounced fears, hostility, or persecutory delusions. To the extent possible, he or she avoids all interactions and remains isolated from others.   |

Source: Study 1304 Protocol

### 13.2.5. Calgary Depression Scale for Schizophrenia (CDSS)

**Interviewer:** Ask the first question as written. Use follow up probes or qualifiers at your discretion. Time frame refers to last two weeks unless stipulated. N.B. The last item, #9, is based on observations of the entire interview.

**1. DEPRESSION:** How would you describe your mood over the last two weeks? Do you keep reasonably cheerful or have you been very depressed or low spirited recently? In the last two weeks how often have you (own words) every day? All day?

- 0. Absent
- 1. Mild Expresses some sadness or discouragement on questioning.
- 2. Moderate Distinct depressed mood persisting up to half the time over last 2 weeks: present daily.
- 3. Severe Markedly depressed mood persisting daily over half the time interfering with normal motor and social functioning.

**2. HOPELESSNESS:** How do you see the future for yourself? Can you see any future? - or has life seemed quite hopeless? Have you given up or does there still seem some reason for trying?

- 0. Absent
- 1. Mild Has at times felt hopeless over the last two weeks but still has some degree of hope for the future.
- 2. Moderate Persistent, moderate sense of hopelessness over last week. Can be persuaded to acknowledge possibility of things being better.
- 3. Severe Persisting and distressing sense of hopelessness.

**3. SELF DEPRECIATION:** What is your opinion of your self compared to other people? Do you feel better, not as good, or about the same as others? Do you feel inferior or even worthless?

- 0. Absent
- 1. Mild Some inferiority; not amounting to feeling of worthlessness.
- 2. Moderate Subject feels worthless, but less than 50% of the time.
- 3. Severe Subject feels worthless more than 50% of the time. May be challenged to acknowledge otherwise.

**4. GUILTY IDEAS OF REFERENCE:** Do you have the feeling that you are being blamed for something or even wrongly accused? What about? (Do not include justifiable blame or accusation. Exclude delusions of guilt.)

- 0. Absent
- 1. Mild Subject feels blamed but not accused less than 50% of the time.
- 2. Moderate Persisting sense of being blamed, and/or occasional sense of being accused.
- 3. Severe Persistent sense of being accused. When challenged, acknowledges that it is not so.

**5. PATHOLOGICAL GUILT:** Do you tend to blame yourself for little things you may have done in the past? Do you think that you deserve to be so concerned about this?

- 0. Absent
- 1. Mild Subject sometimes feels over guilty about some minor peccadillo, but less than 50% of time.
- 2. Moderate Subject usually (over 50% of time) feels guilty about past actions the significance of which he exaggerates.
- 3. Severe Subject usually feels s/he is to blame for everything that has gone wrong, even when not his/her fault.

**6. MORNING DEPRESSION:** When you have felt depressed over the last 2 weeks have you noticed the depression being worse at any particular time of day?

- 0. Absent No depression.
- 1. Mild Depression present but no diurnal variation.
- 2. Moderate Depression spontaneously mentioned to be worse in a.m.
- 3. Severe Depression markedly worse in a.m., with impaired functioning which improves in p.m.

**7. EARLY WAKENING:** Do you wake earlier in the morning than is normal for you? How many times a week does this happen?

- 0. Absent No early wakening.
- 1. Mild Occasionally wakes (up to twice weekly) 1 hour or more before normal time to wake or alarm time.
- 2. Moderate Often wakes early (up to 5 times weekly) 1 hour or more before normal time to wake or alarm.
- 3. Severe Daily wakes 1 hour or more before normal time.

**8. SUICIDE:** Have you felt that life wasn't worth living? Did you ever feel like ending it all? What did you think you might do? Did you actually try?

- 0. Absent
- 1. Mild Frequent thoughts of being better off dead, or occasional thoughts of suicide.
- 2. Moderate Deliberately considered suicide with a plan, but made no attempt.
- 3. Severe Suicidal attempt apparently designed to end in death (i.e.: accidental discovery or inefficient means).

**9. OBSERVED DEPRESSION:** Based on interviewer's observations during the entire interview. The question "Do you feel like crying?" used at appropriate points in the interview, may elicit information useful to this observation.

- 0. Absent
- 1. Mild Subject appears sad and mournful even during parts of the interview, involving affectively neutral discussion.
- 2. Moderate Subject appears sad and mournful throughout the interview, with gloomy monotonous voice and is tearful or close to tears at times.
- 3. Severe Subject chokes on distressing topics, frequently sighs deeply and cries openly, or is persistently in a state of frozen misery if examiner is sure that this is present.

© Dr. Donald Addington and Dr. Jean Addington.

Source: Study 1304 Protocol

### 13.2.6. Young Mania Rating Scale (YMRS)

#### **Young Mania Rating Scale (YMRS)**

##### **Guide for scoring items**

The purpose of each item is to rate the severity of that abnormality in the patient. When several keys are given for a particular grade of severity, the presence of only one is required to qualify for that rating.

The keys provided are guides. One can ignore the keys if that is necessary to indicate severity, although this should be the exception rather than the rule.

Scoring between the points given (whole or half points) is possible and encouraged after experience with the scale is acquired. This is particularly useful when severity of a particular item in a patient does not follow the progression indicated by the keys.

##### **1. Elevated Mood**

- 0 Absent
- 1 Mildly or possibly increased on questioning
- 2 Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
- 3 Elevated, inappropriate to content; humorous
- 4 Euphoric; inappropriate laughter; singing

##### **2. Increased Motor Activity/Energy**

- 0 Absent
- 1 Subjectively increased
- 2 Animated; gestures increased
- 3 Excessive energy; hyperactive at times; restless (can be calmed)
- 4 Motor excitement; continuous hyperactivity (cannot be calmed)

##### **3. Sexual Interest**

- 0 Normal; not increased
- 1 Mildly or possibly increased
- 2 Definite subjective increase on questioning
- 3 Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
- 4 Overt sexual acts (toward patients, staff, or interviewer)

##### **4. Sleep**

- 0 Reports no decrease in sleep
- 1 Sleeping less than normal amount by up to one hour
- 2 Sleeping less than normal by more than one hour

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

- 3 Reports decreased need for sleep
- 4 Denies need for sleep

**5. Irritability**

- 0 Absent
- 2 Subjectively increased
- 4 Irritable at times during interview; recent episodes of anger or annoyance on ward
- 6 Frequently irritable during interview; short or curt throughout
- 8 Hostile, uncooperative; interview impossible

**6. Speech (rate and amount)**

- 0 No increase
- 2 Feels talkative
- 4 Increased rate or amount at times, verbose at times
- 6 Push; consistently increased rate and amount; difficult to interrupt
- 8 Pressured; uninterruptible, continuous speech

**7. Language/Thought Disorder**

- 0 Absent
- 1 Circumstantial; mild distractibility; quick thoughts
- 2 Distractible; loses goal of thought; changes topics frequently; racing thoughts
- 3 Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia
- 4 Incoherent; communication impossible

**8. Content**

- 0 Normal
- 2 Questionable plans; new interests
- 4 Special project(s); hyperreligious
- 6 Grandiose or paranoid ideas; ideas of reference
- 8 Delusions; hallucinations

**9. Disruptive/Aggressive Behaviour**

- 0 Absent, cooperative
- 2 Sarcastic; loud at times, guarded
- 4 Demanding; threats on ward
- 6 Threatens interviewer; shouting; interview difficult
- 8 Assaultive; destructive; interview impossible

**10. Appearance**

- 0 Appropriate dress and grooming

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

- |   |  |
|---|--|
| 1 | Minimally unkempt                                  |
| 2 | Poorly groomed; moderately disheveled; overdressed |
| 3 | Disheveled; partly clothed; garish makeup          |
| 4 | Completely unkempt; decorated; bizarre garb        |
- 
- |                    |   |
|--------------------|---|
| <b>11. Insight</b> |   |
| 0                  | Present; admits illness; agrees with need for treatment |
| 1                  | Possibly ill  |
| 2                  | Admits behaviour change, but denies illness             |
| 3                  | Admits possible change in behaviour, but denies illness |
| 4                  | Denies any behaviour change                             |

Source: Study 1304 Protocol

APPEARS THIS WAY ON ORIGINAL

### 13.2.7. Montgomery-Asberg Depression Rating Scale (MADRS)

| <b>STRUCTURED INTERVIEW GUIDE FOR THE<br/>           MONTGOMERY AND ASBERG DEPRESSION RATING SCALE (SIGMA)</b>  |   |
|---|---|
| PT'S INITIALS: _____ PT'S ID: _____   | TIME BEGAN SIGMA: _____ AM / PM   |
| INTERVIEWER: _____  | DATE: _____   |
| <b>OVERVIEW:</b><br>I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF WEEK)?<br>IF OUTPATIENT: Have you been working? (What kind of work do you do? Have you been able to work your normal hours?) IF NOT WORKING OR WORKING LESS, CLARIFY WHY.  |   |
| <p><b>In the past week, have you been feeling sad or unhappy?</b> (Depressed at all?) IF YES: Can you describe what this has been like for you? (IF UNKNOWN: How bad has that been?)</p> <p>IF DEPRESSED: Does the feeling lift at all if something good happens? How much does your mood lift? Does the feeling ever go away completely? (How often have you had lifts in your mood this week? What things have made you feel better?)</p> <p>How often did you feel (depressed/OWN EQUIVALENT) this past week? (IF UNKNOWN: How many days this week did you feel that way? How much of each day?)</p> <p><b>In the past week, how have you been feeling about the future?</b> (Have you been discouraged or pessimistic?) What have your thoughts been? How (discouraged or pessimistic) have you been? How often have you felt that way? Do you think things will ever get better for you?</p> <p><b>ESTABLISH EUTHYMIC BASELINE:</b> When was the last time you were well, not depressed at all, for at least 2 months?</p> | <p><b>1. REPORTED SADNESS.</b> Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.</p> <p>0 - Occasional sadness in keeping with the circumstances.<br/>           1 -<br/>           2 - Sad or low but brightens up without difficulty.<br/>           3 -<br/>           4 - Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.<br/>           5 -<br/>           6 - Continuous or unvarying sadness, misery, or despondency.</p> |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

| SIGMA 2011, v. 1  |  |
|---|--|
| <p><b>RATING BASED ON OBSERVATION DURING INTERVIEW AND THE FOLLOWING QUESTIONS.</b></p> <p><b>In the past week, do you think you have looked sad or depressed to other people? Did anyone say you looked sad or down?</b></p> <p><b>How about when you've looked in the mirror; did you look gloomy or depressed?</b></p> <p><b>IF YES:</b> How sad or depressed do you think you have looked? How much of the time over the past week do you think you have looked depressed or down?</p> <p><b>Has it been hard for you to laugh or smile in the past week?</b></p>   | <p><b>2. APPARENT SADNESS.</b> Representing despondency, gloom and despair. (More than just ordinary transient low spirits) reflected in speech, facial expressions, and posture. Rate by depth and inability to brighten up.</p> <p>0 - No sadness<br/>1 -<br/>2 - Looks dispirited but does brighten up without difficulty.<br/>3 -<br/>4 - Appears sad and unhappy most of the time.<br/>5 -<br/>6 - Looks miserable all the time. Extremely despondent.</p>  |
| <p><b>Have you felt tense or edgy in the last week? Have you felt anxious or nervous?</b></p> <p><b>IF YES:</b> Can you describe what that has been like for you? How bad has it been?</p> <p><b>What about feeling fearful that something bad is about to happen?</b></p> <p><b>How much of the time have you felt (anxious/tense/OWN EQUIVALENT) over the past week?</b></p> <p><b>Have you felt panicky in the past week? IF YES:</b> Can you describe this feeling? How often have you felt this way?</p> <p><b>IF YES TO ANY TENSION SYMPTOM:</b> How hard has it been to control these feelings? (What has it taken to help you feel calmer? Has anything worked to calm you down?)</p> | <p><b>3. INNER TENSION.</b> Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.</p> <p>0 - Placid. Only fleeting inner tension.<br/>1 -<br/>2 - Occasional feelings of edginess and ill-defined discomfort.<br/>3 -<br/>4 - Continuous feelings of inner tension or intermittent panic which the patient can master with some difficulty.<br/>5 -<br/>6 - Unrelenting dread or anguish. Overwhelming panic.</p> |
| <p><b>How has your sleeping been in the last week? (How many hours have you been sleeping, compared to usual?)</b></p> <p><b>Have you had trouble falling asleep? (How long has it been taking you to fall asleep this past week? How many nights?)</b></p> <p><b>Have you been able to stay asleep through the night? (Have you been waking up at all in the middle of the night? How long does it take you to fall back to sleep? How many nights?)</b></p> <p><b>Have there been any mornings this past week when you have awakened earlier than (EUTHYMIC BASELINE)?</b></p> <p><b>IF UNKNOWN:</b> Has your sleeping been restless or disturbed?</p>                                      | <p><b>4. REDUCED SLEEP.</b> Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.</p> <p>0 - Sleeps as usual.<br/>1 -<br/>2 - Slight difficulty dropping off to sleep or slightly reduced, light, or fitful sleep.<br/>3 -<br/>4 - Sleep reduced or broken by at least 2 hours.<br/>5 -<br/>6 - Less than 2 or 3 hours sleep.</p>  |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

| SIGMA 2011, v. 1   |  |
|--|--|
| <p>How has your appetite been this past week? (What about compared to your usual appetite?)</p> <p>IF NOT REDUCED: Have you been less interested in food? (How much less?)</p> <p>Does food taste as good as usual? IF LESS: How much less? Does it have any taste at all?</p> <p>(Have you had to push yourself to eat or have other people had to urge you to eat?)</p>  | <p><b>5. REDUCED APPETITE.</b> Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.</p> <p>0 - Normal or increased appetite.<br/>1 -<br/>2 - Slightly reduced appetite.<br/>3 -<br/>4 - No appetite. Food is tasteless.<br/>5 -<br/>6 - Needs persuasion to eat at all.</p>  |
| <p>Have you had trouble concentrating or collecting your thoughts in the past week? (How about at home or at work?) IF YES: Can you give me some examples? (Have you been able to concentrate on reading a book or on the computer? Do you need to read things over and over again? Are you able to follow movies or television?)</p> <p>How often has that happened in the past week? Has this caused any problems for you?</p> <p>Have you had any trouble following a conversation? (IF YES: How bad has that been? How often has that happened this past week?)</p> <p><b>NOTE: ALSO CONSIDER BEHAVIOR DURING INTERVIEW.</b></p>       | <p><b>6. CONCENTRATION DIFFICULTIES.</b> Representing difficulties in collecting one's thoughts amounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.</p> <p>0 - No difficulties in concentration.<br/>1 -<br/>2 - Occasional difficulties in collecting one's thoughts.<br/>3 -<br/>4 - Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.<br/>5 -<br/>6 - Unable to read or converse without great difficulty.</p> |
| <p>Have you had any trouble getting started at things in the past week? IF YES: What things? How bad has that been? Have you had difficulty getting started at simple routine everyday things (like getting dressed, brushing your teeth, showering)?</p> <p>Are you OK once you get started at things or is it still more of an effort to get something done?</p> <p>Has there been anything that you needed to do that you were unable to do? Have you needed help to do things? IF YES: What things? How often?</p> <p>Have you done everyday things more slowly than usual? IF YES: Like what, for example? How bad has that been?</p> | <p><b>7. LASSITUDE.</b> Representing a difficulty getting started, or slowness initiating and performing everyday activities.</p> <p>0 - Hardly any difficulty in getting started. No sluggishness.<br/>1 -<br/>2 - Difficulties in starting activities.<br/>3 -<br/>4 - Difficulties in simple routine activities, which are carried out with effort.<br/>5 -<br/>6 - Complete lassitude. Unable to do anything without help.</p>   |

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

|  |   |
|--|---|
| SIGMA 2011, v. 1   |   |
| <p>Have you been less interested in things around you, or in activities you used to enjoy? IF YES: What things? How much less interested in (those things) are you now compared to (EUTHYMIC BASELINE)?</p> <p>What things have you enjoyed this week? How much did you enjoy them?</p> <p>Has there been any change in your ability to feel emotions? (Do you feel things less intensely than you used to, things like anger, grief, pleasure?) IF YES: Can you tell me more about that? (IF UNKNOWN: Are you able to feel any emotions at all?)</p> <p>Have your feelings towards family and friends changed at all? IF YES: Do you feel less towards them than you used to?</p> | <p><b>8. INABILITY TO FEEL.</b> Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.</p> <p>0 - Normal interest in the surroundings and in other people.<br/>                 1 -<br/>                 2 - Reduced ability to enjoy usual interests.<br/>                 3 -<br/>                 4 - Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.<br/>                 5 -<br/>                 6 - The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure, and a complete or even painful failure to feel for close relatives and friends.</p> |
| <p>Have you been putting yourself down, or feeling that you're a failure in some way, over the past week? (Have you been blaming yourself for things that you've done, or not done?) IF YES: What have your thoughts been? How often have you felt that way?</p> <p>In the past week have you been feeling guilty about anything? What about feeling as if you have done something bad or sinful? IF YES: What have your thoughts been? How often have you felt that way?</p> <p>ALSO CONSIDER RESPONSES TO QUESTIONS ABOUT PESSIMISM FROM ITEM 1.</p>   | <p><b>9. PESSIMISTIC THOUGHTS.</b> Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin.</p> <p>0 - No pessimistic thoughts.<br/>                 1 -<br/>                 2 - Fluctuating ideas of failure, self-reproach, or self-deprecation.<br/>                 3 -<br/>                 4 - Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.<br/>                 5 -<br/>                 6 - Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakeable.</p>   |
| <p>This past week, have you felt like life isn't worth living? (IF NO: What about feeling as if you're tired of living?) IF YES: Tell me about that. How often have you felt that way?</p> <p>This week, have you thought that you would be better off dead? IF YES: Tell me about that. How often have you felt that way?</p> <p>Have you had thoughts of hurting or even killing yourself this past week? IF YES: What have you thought about? How often have you had these thoughts? How long have they lasted? Have you actually made plans? IF YES: What are these plans? Have you made any preparations to carry out these plans? (Have you told anyone about it?)</p>       | <p><b>10. SUICIDAL THOUGHTS.</b> Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparation for suicide. Suicidal attempts should not in themselves influence this rating.</p> <p>0 - Enjoys life or takes it as it comes.<br/>                 1 -<br/>                 2 - Weary of life. Only fleeting suicidal thoughts.<br/>                 3 -<br/>                 4 - Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.<br/>                 5 -<br/>                 6 - Explicit plans for suicide when there is an opportunity. Active preparations for suicide.</p>                              |
| <p><b>TIME ENDED SIGMA:</b></p>  | <p>_____ AM / PM</p>  |
| <p><b>TOTAL MADRS SCALE SCORE:</b></p>   | <p>_____</p>  |

Source: Study 1304 Protocol

### 13.3. Financial Disclosure

The Applicant provided a list of clinical investigators for Studies NBI-98854-0801, NBI-98854-0901, NBI-98854-1101, NBI-98854-1102, 1201, 1202, NBI-98854-1203, NBI-98854-1204, NBI-98854-1301, NBI-98854-1302, NBI-98854-1303, 1304, NBI-98854-1401, 1402, NBI-98854-1403, NBI-98854-1502, 1503, NBI-98854-1504, NBI-98854-1507. There were a total of 157 Principal

Clinical Review

Michael C. Davis, MD, PhD and Brian J. Miller, MD, MBA, MPH

NDA 209241

Ingrezza (valbenazine)

Investigators and 917 Sub-Investigators listed in the Applicant's certification of financial interests and arrangements of clinical investigators (Form 3454).

There were no investigators who were Applicant employees or who had disclosable financial interests or arrangements. There were no clinical investigators from which the Applicant was unable to obtain disclosures. This information was confirmed by the Applicant in a Response to Information Request received on December 22, 2016. Based on the certification and Applicant verification, there are no concerns about financial conflicts of interest that would affect the interpretation of study data or the approvability of this application.

APPEARS THIS WAY ON ORIGINAL

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

MICHAEL C DAVIS  
04/04/2017

BRIAN J MILLER  
04/04/2017

MARC B STONE  
04/04/2017

JAVIER A MUNIZ  
04/04/2017