

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213586Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2)
Application Number(s)	NDA 213586
Priority or Standard	Resubmission – Class 2
Submit Date(s)	October 28, 2022
Received Date(s)	October 28, 2022
PDUFA Goal Date	April 28, 2023
Division/Office	Division of Psychiatry/Office of Neuroscience
Review Completion Date	April 28, 2023
Established/Proper Name	Risperidone extended-release
(Proposed) Trade Name	Uzedy
Pharmacologic Class	Antipsychotics/Schizophrenia
Code name	2020200
Applicant	Teva Neuroscience Inc.
Dosage form	Prefilled syringes - Injectable suspension
Applicant proposed Dosing Regimen	50 mg, 75 mg, 100 mg, 125 mg one injection once monthly or 100 mg, 150 mg, 200 mg, 250 mg once every two months
Applicant Proposed Indication(s)/Population(s)	Treatment of schizophrenia
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	58214004 Schizophrenia (Disorder)
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	Adults with schizophrenia
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	58214004 Schizophrenia (disorder)
Recommended Dosing Regimen	50 mg, 75 mg, 100 mg, 125 mg one injection once monthly or 100 mg, 150 mg, 200 mg, 250 mg once every two months

Table of Contents

Table of Tables	4
Table of Figures	6
Reviewers of Multi-Disciplinary Review and Evaluation	7
Signatures	8
Glossary	9
1 Executive Summary	10
1.1. Product Introduction	10
1.2. Conclusions on the Substantial Evidence of Effectiveness	10
1.3. Benefit-Risk Assessment	12
1.4. Patient Experience Data	18
2 Therapeutic Context	19
2.1. Analysis of Condition	19
2.2. Analysis of Current Treatment Options	19
3 Regulatory Background	22
3.1. U.S. Regulatory Actions and Marketing History	22
3.2. Summary of Presubmission/Submission Regulatory Activity	22
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety	24
4.1. Office of Scientific Investigations (OSI)	24
4.2. Product Quality	24
4.3. Clinical Microbiology	24
4.4. Devices and Companion Diagnostic Issues	24
5 Nonclinical Pharmacology/Toxicology	25
6 Clinical Pharmacology	26
6.1. Executive Summary	26
7 Sources of Clinical Data and Review Strategy	27
7.1. Table of Clinical Studies	27
7.2. Review Strategy	30
8 Statistical and Clinical and Evaluation	31
8.1. Review of Relevant Individual Trials Used to Support Efficacy	31
8.1.1. Study Results of TV-46000-CNS-30072	31
8.1.2. Study Results	33
8.1.3. Assessment of Efficacy Across Trials	44

8.1.4. Integrated Assessment of Effectiveness	44
8.2. Review of Safety	44
8.2.1. Safety Review Approach	44
8.2.2. Review of the Safety Database	45
8.2.3. Adequacy of the Safety Database	46
8.2.4. Adequacy of Applicant’s Clinical Safety Assessments	46
8.2.5. Safety Results	46
8.2.6. Analysis of Submission-Specific Safety Issues.....	56
8.2.7. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability.....	56
8.2.8. Safety Analyses by Demographic Subgroups.....	56
8.2.9. Specific Safety Studies/Clinical Trials.....	56
8.2.10. Additional Safety Explorations	56
8.2.11. Safety in the Postmarket Setting.....	57
8.2.12. Integrated Assessment of Safety.....	57
8.3. Statistical Issues	57
8.4. Conclusions and Recommendations	57
9 Advisory Committee Meeting and Other External Consultations.....	59
10 Pediatrics	60
11 Labeling Recommendations	61
11.1. Prescription Drug Labeling	61
12 Risk Evaluation and Mitigation Strategies (REMS)	64
13 Postmarketing Requirements and Commitment	65
14 Signatory (Deputy Division Director) Comments	66
15 Appendices	67
15.1. References.....	67
15.2. Financial Disclosure	67
15.3. Nonclinical Pharmacology/Toxicology	67
15.4. Clinical Pharmacology	67
15.4.1. Pharmacometrics Review	67
15.5. Additional Clinical Outcome Assessment Analyses.....	79

Table of Tables

Table 1. Summary of Long-Acting Injectable Antipsychotics Currently Available in the United States.....	19
Table 2. Listing of Completed Clinical Trials Submitted with NDA 213586 Resubmission	28
Table 3. Definition of Terms for Sensitivity Analyses	32
Table 4. Patient Disposition in the Sensitivity Analysis Subgroups (Excluding Dually- and Triply-Enrolled Patients) Compared to That in the Study 30072 CSR (ITT Analysis Set)	33
Table 5. Dosing Errors per Patient and Visits by Treatment Arm (Dually-and Triply-enrolled Patients Included) in Study 30072 (ITT Analysis Set).....	35
Table 6. Patients and Visits with Lack of Documentation by Treatment Arm (Dually and Triply Enrolled Patients Included) in Study 30072 (ITT Analysis Set)	36
Table 7. Dosing-related Deviations per Patient by Treatment Arm (Dually- and Triply-enrolled Patients Included) in Study 30072 (ITT Analysis Set).....	36
Table 8. Subjects Disposition for the Sensitivity Analyses (ITT Analysis Set)	37
Table 9. Demographic Characteristics in the Analysis Subgroups (Excluding Dually- and Triply-enrolled Patients) Compared to Those in the Study 30072 CSR (ITT Analysis Set)	38
Table 10. Other Baseline Characteristics in the Analysis Subgroups (Excluding Dually- and Triply-enrolled Patients) Compared to Those in the Study 30072 CSR (ITT Analysis Set)	39
Table 11. Sensitivity Analyses of Primary Endpoint: Time to Relapse (Weeks) by Treatment Group for Subsets—Log Rank Test and Cox Proportional Hazards Model (ITT Analysis Set)	41
Table 12. Sensitivity Analyses for Primary Endpoint: Time to Impending Relapse (Weeks) by Treatment Group Including Patients with Dosing Error, with Lack of Documentation, or with Dosing-related Deviations Censored at the First Occurrence of Error Dosing (ITT Analysis Set (Excluding Duplicate and Triplicate Patients))	43
Table 13. Total Exposure to Study Drug in Study TV46000-CNS-30078 by Treatment Group and Source of Patients	45
Table 14. Serious adverse events (completed Study 30078, adult population).....	46
Table 15. Discontinuations due to adverse events (completed Study 30078, adult population) 47	
Table 16. Most Common TEAEs (≥2%) (completed Study 30078, adult population)	47
Table 17. Sensitivity Analysis without Dually- and Triply-enrolled Subjects - Serious Adverse Events (Completed Study 30078, Adult Population)	49
Table 18. Sensitivity Analysis without Dually- and Triply-enrolled Subjects - Discontinuations Due to Adverse Events (Completed Study 30078, Adult Population)	50

Table 19. Sensitivity Analysis without Dually- and Triply-enrolled Subjects – Most Common TEAEs ($\geq 2\%$) (Completed Study 30078, Adult Population)	50
Table 20. Sensitivity Analysis without Dually- and Triply-enrolled Subjects – Most Common TEAEs ($\geq 2\%$, TV-46000>Placebo) (Study 30072, adult population)	53
Table 21. Overall Summary of Adverse Events—Sensitivity Analyses (Excluding Dually- and Triply-enrolled Patients) and Original CSR Results for Study 30072	54
Table 22. Overall Summary of Adverse Events—Sensitivity Analyses (Excluding Dually- and Triply-enrolled Patients) and Final CSR Results for Study 30078	55
Table 23. Definition of Terms for Sensitivity Analysis of Investigational Product Dosing Data in Phase 3 Studies	68
Table 24. Data in the Original Dataset and Number of Errors and Stratification for Subjects Administered with TV-46000	69
Table 25. Summary of Subjects and Pharmacokinetic Measurements Included in the Population Pharmacokinetic Analysis for Subjects Administered with TV-46000	69
Table 26. Comparison of Key Primary Parameters of the Parent Population Pharmacokinetic Model Based on the Original and Updated Datasets	70
Table 27. The %Difference between 3 Subsets Compared to the Originally Reported Primary Estimates	71
Table 28. Model Parameter Estimates for TV-46000 Parent PK – Subset II	71
Table 29. Comparison of Key Primary Parameters of the Metabolite Population Pharmacokinetic Model Based on the Original and Updated Datasets	72
Table 30. Subset Comparison for the % Difference from Original Metabolite Model to the Updated Model	72
Table 31. Model Parameter Estimates for TV-46000 Metabolite PK – Subset II	73
Table 32. Summary Statistics of Total Active Moiety Metrics Based on Final PopPK Models per Exposure Quartiles for Original and Updated Datasets for Subset II	73
Table 33. Analysis Data Sets	75

Table of Figures

Figure 1. Hazard Ratio of TV-46000 q1m vs Placebo	42
Figure 2. Hazard Ratio of TV-46000 q2m vs Placebo	42
Figure 3. Kaplan-Meier Plots for Occurrence of Impending Relapse up to 2 Years, Comparing Placebo and Exposure Quartiles for Cavg,ss, Ctrough,ss and Cmax,ss in Subset II	74
Figure 4. Impact of Early or Late TV-46000 Administration of the Next Dose on Total Active Moiety Concentrations in Subset II	77
Figure 5. Kaplan-Meier Plots for Occurrence of Impending Relapse up to 2 Years, Comparing Placebo and Different Doses Levels in Subset II (Top Panel: Q1m, Bottom Panel: Q2m)	78

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Signatures

See archived signatory memos for each discipline.

Glossary

CRL	Complete Response Letter
CRO	Clinical research organization
EPS	extrapyramidal symptoms
E-R	exposure-response
IM	intramuscular
IP	Investigational Product
ITT	intent-to-treat
LD	listed drug
NDA	new drug application
OCF	Office of Clinical Pharmacology
OSI	Office of Scientific Investigations
PANSS	Positive and Negative Syndrome Scale
PI	prescribing information
popPK	population pharmacokinetics
q1m	once monthly
q2m	every two months
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
TEAEs	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The Applicant has developed risperidone extended-release injectable suspension for subcutaneous (sc) use (TV-46000) for the treatment of schizophrenia in adults. It is an atypical antipsychotic designed to be an alternative to current oral and parenteral formulations of risperidone with a once-monthly or once every 2-month dosing interval. The first risperidone product was approved in 1993 for the treatment of schizophrenia in adults; risperidone products are currently available in the United States and internationally in multiple dosage forms. The proposed dosage strengths for the once-monthly injection are 50 mg, 75 mg, 100 mg, and 125 mg; the proposed dosage strengths for the once every 2-month injection are 100 mg, 150 mg, 200 mg, and 250 mg. The TV-46000 dosage form is an extended-release injectable suspension in a single-dose prefilled syringe.

1.2. Conclusions on the Substantial Evidence of Effectiveness

On June 21, 2021, Teva Pharmaceuticals (Teva) submitted new drug application (NDA) 213586 to support the safety and efficacy of risperidone extended-release suspension TV-46000 for the treatment of schizophrenia. This submission included two phase 3 studies, TV46000-CNS-30072 (hereafter Study 30072), the pivotal efficacy study, and TV46000-CNS-30078 (hereafter Study 30078), the long-term safety study. Four clinical investigator inspections and an inspection of the clinical research organization (CRO), (b) (4) were conducted during that review cycle. Those inspections identified protocol deviations related to investigational product (IP) dosing errors, lack of documentation of IP administration, duplicate subject enrollment at different clinical sites, and potential unblinding at one clinical site (see the Clinical Inspection Summary, archived on March 18, 2022). As a result, data from the two phase 3 studies could not be relied upon and a complete response action was taken on April 15, 2022. The Agency recommended that the Applicant commission an independent third-party audit or post-study monitoring by the Sponsor/Clinical Research Organization (CRO) for all sites and all subjects to establish the extent of IP dosing errors and lack of IP dose documentation and to determine what study data can be relied upon for regulatory decision making. In addition, the Agency recommended that the Applicant submit relevant updated analyses and dosing datasets based on the audit findings.

This Class 2 resubmission includes the results of the third-party audit and updated analyses, but no new studies. Based on the information provided in this Class 2 resubmission, the Agency determined that the structured database was adequate to conduct further analyses. The updated analyses were verified, and they confirmed the findings of the original NDA analyses (see the NDA Multi-disciplinary Review and Evaluation for NDA 213586 archived on April 15, 2022).

Substantial evidence of effectiveness for the treatment of schizophrenia is provided by the

following:

- An adequate scientific bridge was established to rely, in part, on the previous Agency's prior findings of efficacy for the listed drug (LD) risperidone oral tablets (Risperdal, NDA 20272)
- Study 30072, a randomized, double-blind, placebo-controlled relapse-prevention study in 543 subjects, which met its prespecified primary endpoint for both the TV-46000 once-monthly (q1m) and once every 2 months (q2m) dosing regimens (i.e., the Study demonstrated a favorable, statistically significant difference in the time to impending relapse in subjects treated with TV-46000 compared to placebo).
- Results of the sensitivity analyses that was conducted to assess the impact of dosing errors, lack of dosing documentation, and duplicated subjects, which confirmed the findings of the primary efficacy analysis of Study 30072.

Therefore, the Applicant has provided substantial evidence of effectiveness to support product approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Applicant has developed risperidone extended-release injectable suspension for subcutaneous (sc) use (TV-46000, proposed trade name: Uzedyl) for the treatment of schizophrenia in adults. The proposed dosage strengths for the once-monthly injection are 50 mg, 75 mg, 100 mg, and 125 mg; the proposed dosage strengths for the once every 2-month injection are 100 mg, 150 mg, 200 mg, and 250 mg. TV-46000 dosage form is an extended-release injectable suspension in a single-dose prefilled syringe.

Schizophrenia is a serious chronic mental illness characterized by a constellation of symptoms that may include positive symptoms (e.g., delusions, hallucinations, disorganized speech), negative symptoms (e.g., social withdrawal, avolition, blunted affect) and cognitive deficits (e.g., impaired attention, executive function, and working memory). Symptomatic exacerbations of schizophrenia, which are associated with nonadherence to antipsychotic medications, can severely impact patients' functioning and necessitate psychiatric hospitalization. Antipsychotic medications are the first-line pharmacotherapy for schizophrenia and are recommended to be used for the treatment of schizophrenia exacerbations as well as on a continuing basis to reduce the risk of relapse. Long-acting injectable antipsychotics may reduce the risk of schizophrenia exacerbation in patients who are nonadherent to oral antipsychotics. Although there are a number of approved antipsychotics (oral and long-acting injectable formulations) for schizophrenia, an individual patient may require several trials with different antipsychotic drugs before an effective and reasonably tolerated treatment is identified, therefore alternative to current oral and parenteral formulations are needed.

On June 21, 2021, the Applicant submitted NDA 213586 to support the safety and efficacy of TV-46000 for the treatment of schizophrenia. While the application relied in part on the Agency's previous findings of safety and effectiveness for risperidone oral tablets (Risperdal, NDA 20272) based on pharmacokinetic data, an efficacy study with TV-46000 was necessary to inform labeling regarding dosage and administration and inter-dose interval. An initial NDA review found that an adequate scientific bridge was established; however, due to protocol deviations identified during the Office of Scientific Investigations (OSI) inspections for studies 30072 and 30078, the Agency took a complete response action because dosing data and dosing regimen could not be relied upon. The Applicant executed a third-party audit and provided a quantification of the extent of IP dosing errors, lack of IP dosing source documentation, and the extent of the dually- and triply-enrolled patients. This Class 2 resubmission includes sensitivity analyses for the primary efficacy analysis of Study 30072 along with some descriptive summaries of patients' characteristics, using data obtained and/or verified from the third-party audit. Efficacy of TV-46000 was evaluated in a randomized, double-blind, placebo-controlled relapse prevention study (Study 30072) in 543 subjects. The study met its prespecified primary

endpoint for both the TV-46000 once-monthly and once every 2 months dosing regimens and demonstrated statistically significant improvement in the time to impending relapse in subjects treated with TV-46000 compared to placebo. Results of the sensitivity analyses evaluating the effect of dosing errors and/or lack of dosing documentation are consistent with the results and conclusions of the original primary efficacy analysis.

The safety profile of TV-46000 is similar to the known safety profile of risperidone. TV-46000 was associated with weight gain, dyslipidemia, hyperglycemia, increased prolactin, sedation/somnolence, and extrapyramidal symptoms. Some subjects experienced injection site reactions, but these reactions are not appreciably worse than other long-acting injectable formulations. Results of sensitivity analyses evaluating the effect of dosing errors, lack of dosing documentation and duplicated subjects, confirmed the conclusions of the original safety analyses.

The benefit-risk profile of TV-46000 does not appreciably differ from the LD. This product has a smaller needle size, lower injection volume, and does not require reconstitution compared to existing risperidone products. Its anticipated benefit to the target population is a reduction in symptoms of schizophrenia, such as delusions and hallucinations and presents an alternative to currently approved risperidone products. Accordingly, TV-46000 will be approved for the treatment of schizophrenia via the 505(b)(2) regulatory pathway.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Schizophrenia is a serious mental illness characterized by chronic or recurrent psychosis (e.g., delusions, hallucinations, and thought disorganization). - Schizophrenia is also frequently associated with negative symptoms (e.g., social withdrawal, avolition, blunted affect) and cognitive deficits (e.g., attention, executive function, working memory, and social cognition). - Individuals with schizophrenia experience significant impairments in social and occupational functioning and, on average, have a life expectancy around 15 years less than individuals without schizophrenia. - The worldwide prevalence of schizophrenia is approximately 0.5 to 1%, and schizophrenia is one of the leading causes of years lost due	Schizophrenia is a serious condition, associated with significant disability and a shortened life expectancy. Evidence informing the analysis of the condition of schizophrenia is from published literature and psychiatric textbooks, as well as clinical experience with this population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	to disability worldwide. - Approximately 50% of individuals with schizophrenia experience a relapse/exacerbation in psychotic symptoms within one year after their last episode; most relapses occur in the context of medication nonadherence. - Medication nonadherence or partial adherence is common, affecting the average patient with schizophrenia.	
<u>Current Treatment Options</u>	- Antipsychotics are the first-line medication therapy for schizophrenia; current practice guidelines recommend that antipsychotics should be initiated as soon as possible in an acute schizophrenia exacerbation and continued indefinitely to reduce the risk of relapse. - Antipsychotics have been shown to be effective for reducing positive symptoms of schizophrenia (e.g., delusions, hallucinations, disorganized thinking and behavior). Negative symptoms and cognitive deficits of schizophrenia generally show little to no improvement from antipsychotic treatment. - Antipsychotics are broadly categorized as first-generation/typical antipsychotics (e.g., chlorpromazine, fluphenazine, haloperidol, etc.), second-generation/atypical antipsychotics (e.g., clozapine, risperidone, olanzapine, quetiapine), and third-generation antipsychotics (aripiprazole, cariprazine, brexpiprazole, and lumateperone). In general, first-generation antipsychotics have a higher risk for causing extrapyramidal side effects than second- and third-generation antipsychotics. - Adverse reactions from antipsychotics vary between drugs but may include weight gain, extrapyramidal side effects, increased prolactin, sedation, and QT prolongation.	Antipsychotics reduce the severity of positive symptoms of schizophrenia and the risk of psychosis exacerbations. Nonadherence to daily oral antipsychotics is common in individuals with schizophrenia and can lead to psychiatric hospitalization and other adverse outcomes. Long-acting injectable antipsychotics may reduce the risk of schizophrenia exacerbations in patients who are nonadherent to oral antipsychotics. Patients may also prefer long-acting medications over taking oral medications daily. Risperidone is currently available in two intramuscular injection formulations that are administered every 14 days and a subcutaneous injection formulation that is administered once per month.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Nonadherence to daily oral antipsychotic treatment is very common in individuals with schizophrenia. The consequences of medication nonadherence can include acute psychosis exacerbation, occupational and social problems, danger to self or others, and psychiatric hospitalization. • Long-acting injectable antipsychotic medications maintain therapeutic blood levels of antipsychotics for extended periods (weeks to months) and may reduce the risk of schizophrenia exacerbation in patients who are nonadherent to oral antipsychotics. • In addition to antipsychotic medications, patients with schizophrenia are frequently treated with adjunctive medications to target depression, anxiety, obsessions and compulsions, and side effects of antipsychotics (e.g., dystonia, parkinsonism, tardive dyskinesia, and akathisia). • When integrated with pharmacotherapy, psychosocial interventions have been shown to improve the course of schizophrenia. These interventions include cognitive behavioral therapy, assertive community treatment, supported employment, and social skills therapy.	The dosing schedule for TV-46000 injection (every 1 to 2 months) offers an additional choice for patients and providers.
<u>Benefit</u>	• The Applicant submitted Study TV-46000-CNS-30072, a randomized, double-blind, multicenter, parallel-group, placebo-controlled, relapse prevention study, which evaluated the efficacy, safety, and tolerability of TV-46000 in 543 patients with schizophrenia at dose of 50 to 125 mg sc q1m or at dose of 100 to 250 mg sc q2m. • The primary efficacy endpoint was time to impending relapse. The definition of impending relapse, was acceptable and clinically	In Study 30072, The Applicant has demonstrated that the proportion of patients with impending relapse was lower in the group treated with TV-46000 as compared to placebo. Despite dosing errors, lack of dosing documentation and duplicated subjects,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	driven by positive symptoms and included worsening of symptoms as assessed by the positive and negative syndrome scale (PANSS), hospitalization for psychotic symptoms, violent behavior and suicidal ideation and behavior. • The primary efficacy variable, the time to impending relapse, showed statistically significant differences from placebo in favor of study drug for both TV-46000 q1m and TV-46000 q2m. The proportion of patients with impending relapse was lower in the TV-46000 group [13 (7%) patients in the TV-46000 q1m group and 23 (13%) patients in the TV-46000 q2m group] compared to the placebo group [53 (29%) patients]. • The primary efficacy variable, time to impending relapse, was re-analyzed in the ITT analysis set excluding dually and triply enrolled patients, and in each of the analysis subsets (patients without dosing-related deviations, patients without dosing errors, patients without significant dosing errors, and patients without lack of documentation). The results of the sensitivity analyses of the primary endpoint in all the analysis subsets based on the stratified log-rank test were consistent with the originally reported results, showing improved time to relapse for both q1m and q2m over placebo. • Pharmacokinetic (PK) data established a scientific bridge between risperidone oral tablets and TV-46000. • The range of strengths planned for marketing corresponds to 2 to 5 mg of daily oral risperidone based on the PK data. This is not the full approved dose range of oral risperidone for the treatment of schizophrenia, which starts at 2 mg for initial dose and goes up to 16 mg.	sensitivity analyses accounting for these factors were consistent with the primary analysis and confirmed effectiveness. In addition, pharmacokinetic studies demonstrated that the doses of TV-46000 yield daily plasma concentrations of risperidone that are equivalent to doses of oral risperidone with previously established efficacy (2 to 5 mg daily doses). Therefore, the Applicant has provided substantial evidence of effectiveness to support product approval. It is anticipated that this product will fit into the therapeutic armamentarium as a long-acting injectable antipsychotic option that may require less frequent injections than the other risperidone product on the market. This fact, in addition to the use of a smaller needle size, lower injection volume, and the lack of reconstitution compared to other existing products, are anticipated benefits to patients, caregivers, and healthcare providers.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• TV-46000 was associated with weight gain, dyslipidemia, hyperglycemia, increased prolactin, sedation/somnolence, and extrapyramidal symptoms. • Twenty-one percent of subjects had injection site reactions (one severe) and 2% of patients discontinued treatment due to injection site reactions in the TV-46000 groups. • The full dose range for oral risperidone is not covered by the strengths proposed for marketing based on the PK data and prescribers could use more than one injection to achieve higher daily dose equivalents, which has not been studied. • There were safety data submitted in the age 13 to 17 pediatric population for only four subjects, one in the Study 30072 and three in Study 30078, a long-term safety study, which the Applicant states was due to enrollment difficulties. • The results of the sensitivity safety analyses accounting for dosing errors, lack of documentation, and duplicated subjects did not show differences with the original NDA safety analyses.	The assessment of safety findings from the TV-46000 development program did not reveal any unexpected safety signals when compared to other formulations of risperidone. Formulation-specific injection site reactions were observed, but do not significantly affect the benefit-risk balance of this product. Potential risks related to administration of this product will be described in labeling. Labeling will include language instructing prescribers not to administer more than one dose of TV-46000 per dosing interval. There are insufficient safety data to complete a pediatric assessment for patients with schizophrenia 13 to 17 years of age due to the small number of subjects enrolled. There were no safety issues that would preclude approval of this NDA.

1.4. **Patient Experience Data**

See NDA Multi-disciplinary Review and Evaluation NDA 213586 Uzedy (risperidone extended release injection) archived on April 15, 2022.

2 Therapeutic Context

2.1. Analysis of Condition

See the NDA Multi-disciplinary Review and Evaluation NDA 213586 Uzedly (risperidone extended release injection) archived on April 15, 2022.

2.2. Analysis of Current Treatment Options

See the NDA Multi-disciplinary Review and Evaluation NDA 213586 Uzedly (risperidone extended release injection) archived on April 15, 2022, and updated Table 1 below.

Table 1. Summary of Long-Acting Injectable Antipsychotics Currently Available in the United States

Product Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Important Differentiating Safety and Tolerability Issues	Other Comments
Aripiprazole monohydrate (Abilify Maintena)	Schizophrenia in adults. <i>Also indicated for the maintenance treatment as monotherapy of bipolar I disorder in adults</i>	2013	IM in deltoid or gluteal, monthly	N/A	In conjunction with first dose, need to continue oral antipsychotic for 14 days
Aripiprazole lauroxil (Aristada)	Schizophrenia in adults	2015	IM in deltoid or gluteal, every 1 or 2 months, or every 6 weeks	N/A	In conjunction with first dose, need to continue oral aripiprazole for 3 weeks
Aripiprazole lauroxil (Aristada Initio)	Schizophrenia in adults	2018	IM deltoid or gluteal, one time injection	N/A	To be used as one-time loading dose with a one-time oral aripiprazole loading dose at time of Aristada initiation
Fluphenazine decanoate	Schizophrenia in adults	1972	IM or SC, every 2 to 4 weeks	First generation antipsychotic – higher EPS liability	Need to continue oral fluphenazine until effective decanoate dosage is established
Haloperidol decanoate	Schizophrenia in adults	1986	IM, monthly	First generation antipsychotic – Higher EPS liability	Depending on initiation dose, may need to

NDA/BLA Multi-disciplinary Review and Evaluation
NDA 213586: Risperidone extended-release injectable suspension

					continue oral haloperidol for up to 3 months.
Olanzapine pamoate (Zyprexa Relprevv)	Schizophrenia in adults	2009	IM in gluteal muscle, every 2 or 4 weeks	Risk of post injection delirium/sedation syndrome: drug available only through restricted distribution program; requires 3 hours monitoring post-injection	No overlap period needed with oral antipsychotic
Paliperidone palmitate (Invega Sustenna)	Schizophrenia in adults, <i>also indicated for the treatment of schizoaffective disorder</i>	2009	IM in deltoid or gluteal muscle; monthly after loading doses (two loading doses 1 week apart)	N/A	No overlap period needed with oral paliperidone
Paliperidone palmitate (Invega Trinza)	Schizophrenia in adults	2015	IM in deltoid or gluteal muscle; every 3 months	N/A	Can only be used if patient has received monthly injections of Invega Sustenna for ≥4 months
Paliperidone palmitate (Invega Hafyera)	Schizophrenia in adults	2021	IM in gluteal muscle; every 6 months	N/A	Can only be used if patient has received monthly injections of Invega Sustenna for ≥4 months or Invega Trinza for ≥1 three month cycle
Risperidone microspheres (Risperdal Consta)	Schizophrenia in adults, <i>also indicated for the maintenance treatment as monotherapy or adjunctive with lithium or valproate of bipolar I disorder in adults</i>	2003	IM in deltoid or gluteal muscle, every 2 weeks	N/A	In conjunction with first dose, need to continue oral antipsychotic for 3 weeks
Risperidone for extended release injectable suspension (Perseris)	Schizophrenia in adults	2018	SC injection in abdomen every 4 weeks	N/A	No overlap period needed with oral risperidone

NDA/BLA Multi-disciplinary Review and Evaluation
NDA 213586: Risperidone extended-release injectable suspension

Risperidone for extended release injectable suspension (Rykindo)	Schizophrenia in adults, <i>also indicated for the maintenance treatment as monotherapy or adjunctive with lithium or valproate of bipolar I disorder in adults</i>	2023	IM in gluteal muscle, every 2 weeks	N/A	In conjunction with first dose, need to continue oral risperidone for 1 week
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Abbreviations: EPS = extrapyramidal symptoms; IM = intramuscular; N/A = not applicable; SC = subcutaneous

Source: Clinical reviewer-generated.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

TV-46000 (risperidone extended-release injectable suspension for subcutaneous use) has not been approved or marketed in the United States. Risperidone was first approved in 1993 as tablets for oral administration for the treatment of schizophrenia in adults (NDA 020272). Currently, there are multiple additional dosage forms available for risperidone including: two injectable suspensions for intramuscular use (NDA 21346: Risperdal Consta; NDA 212849: Rykindo), an oral solution (NDA (b) (4) : Risperdal), an orally disintegrating tablet (NDA 021444: Risperdal MTab), and an injectable suspension for subcutaneous use (NDA 210655: Perseris).

3.2. Summary of Presubmission/Submission Regulatory Activity

Teva Branded Pharmaceutical Products R&D, Inc. has developed TV-46000 (proposed name Uzedy), an extended-release injectable sc formulation of the atypical antipsychotic risperidone, for the treatment of schizophrenia.

The Applicant submitted NDA 213586 on June 17, 2021, via the 505(b)2 regulatory pathway, referencing risperidone oral tablets (Risperdal, NDA 20272) as the LD.

Following an OSI inspection, it was found that data from clinical studies 30072 and 30078, could not be relied upon because of IP dosing errors, lack of documentation of IP administration, duplicate subject enrollment at different clinical sites. The Agency sent a Complete Response Letter (CRL) on April 15, 2022.

The Division requested the Applicant to submit results of an independent third party audit or post-study monitoring by the Sponsor/CRO for all sites and all subjects to establish the extent of IP dosing errors and lack of IP dose documentation and to determine what study data can be relied upon for regulatory decision making. In addition, the Applicant was requested to submit relevant updated analyses and dosing datasets based on the audit findings. Alternatively, the Applicant could have submitted a new adequate and well-controlled clinical efficacy and safety study to establish an adequate scientific bridge to rely in part on the previous Agency's finding of efficacy for the listed drug (LD) Risperdal.

Following the CRL, the Applicant submitted a Type A meeting request to review the Agency's concerns outlined in the CRL and to obtain the Agency's feedback and concurrence on the Applicant's plan to address those deficiencies in support of a resubmission.

June 15, 2022: Type A meeting

The Applicant proposed 1) to conduct a third party audit of the IP dosing source documentation from Studies 30072 and 30078; 2) to provide a quantification of the extent of IP dosing errors

and lack of IP dosing source documentation; 3) to audit and report the extent of the dually and triply enrolled patients; and 4) to provide sensitivity analyses for the primary efficacy analysis along with some descriptive summaries, using data obtained and/or verified from the third-party audit.

The Agency confirmed the Applicant's proposal was acceptable. Additionally, the Agency confirmed that the data package appeared to be generally adequate for a NDA resubmission and stated that the information to be communicated in labeling would have been a matter of review.

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

4.1. Office of Scientific Investigations (OSI)

Based on the information provided in this Class 2 resubmission, OSI agreed that the structured database submitted by the Applicant could be used for further analyses by the review division and biometrics.

See the OSI Memo for this resubmission, archived on February 27, 2023.

4.2. Product Quality

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

4.3. Clinical Microbiology

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

4.4. Devices and Companion Diagnostic Issues

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

5 Nonclinical Pharmacology/Toxicology

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022. No additional nonclinical data were submitted with this Class 2 resubmission.

6 Clinical Pharmacology

6.1. Executive Summary

During OSI inspections of the original NDA, dosing errors were found in the phase 3 studies. Given the results of the phase 3 studies were not reliable, the Agency took a Complete Response action. However, the clinical pharmacology information submitted in the original review cycle were acceptable. The Office of Clinical Pharmacology (OCP) review was completed in the previous cycle; see the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

In this resubmission, the Applicant submitted results of an independent third-party audit for all sites and all subjects to determine if IP dosing errors and lack of IP dose documentation affected the results of Study 30072. The Applicant conducted sensitivity analyses to assess the impact of dosing errors on the robustness of the population pharmacokinetics (popPK) model and subsequently on the safety and efficacy exposure-response (E-R) analysis. Overall, the sensitivity analyses indicate that the primary parameters were comparable between the original and updated datasets. The E-R analysis using updated subset II from the phase 3 studies (Study 30072 and Study 30078) demonstrated comparable outcome to the original analyses. Therefore, the findings from popPK and E-R analyses performed in the original review are acceptable. See Section 19.1 for additional information.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant did not submit new studies. This resubmission includes:

- Sensitivity analyses for studies 30072 and 30078, to account for dosing errors, lack of dosing documentation, and dually and triply enrolled patients.
- Additional safety data from Study 30078, which was ongoing at the time of the original submission and completed at the time of the resubmission.

For a description of Study 30072, see the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedy (risperidone extended release injection), archived on April 15, 2022. An updated description of Study 30078 is presented in Table 2.

Table 2. Listing of Completed Clinical Trials Submitted with NDA 213586 Resubmission

Study Identifier (Type of Study) Total Number of Centers with Enrolled Subjects Country(ies)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects/Patients: Enrolled (M/F) Treated (M/F) Completed Study Age Range (y)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
TV46000-CNS- 30078 (Safety and Tolerability) Phase 3 60 centers US and Bulgaria TV46000-CNS- 30078 CSR addendum 01	The primary objective of the study was to evaluate the long-term safety and tolerability of TV-46000 administered in adult and adolescent^a patients with schizophrenia. There were no secondary study objectives.	Multicenter, double-blind, parallel-group, uncontrolled ^h study	TV-46000 administered q1m at doses of 50 mg, 75 mg, 100 mg, and 125 mg, or q2m at doses of 100 mg, 150 mg, 200 mg, and 250 mg sc (comparable to 2 to 5 mg/day of oral risperidone), per the oral dose on which the patient was stabilized in Stage 1.	Enrolled^e: 150 (de novo) Not randomized: 41 patients (de novo) 29M/12F Randomized: 336 patients (109 de-novo and 227 rollover patients) 216M/120F Treated: 334 patients 214M/120F Completed treatment^g: 235 patients (70%) Age Range (Enrolled): Not randomized: (16^a, 64) Randomized: (16^a, 64)	New patients with schizophrenia AND Patients with schizophrenia who completed Study TV-46000-CNS-30072 without important protocol deviations	For new patients: 12 weeks of the oral conversion/stabilization stage (Stage 1)ⁱ and a double-blind maintenance stage (Stage 2) of up to 56 weeks. For roll-over patients: Double blind maintenance stage (Stage 2) of up to 56 weeks.	Completed; Final Full CSR (dated 24 April 2022) CSR addendum 01 – sensitivity analysis (dated 19 October 2022)

^aDespite the Applicant's efforts to recruit adolescents, the safety data collected in these studies are not sufficient to evaluate safety in the adolescent patient population. Thus,

NDA/BLA Multi-disciplinary Review and Evaluation

NDA 213586: Risperidone extended-release injectable suspension

efficacy and safety analyses in the review are limited to the adult population only.

^e The term "enrolled" refers to the number of patients who entered Stage 1 of the study. The numbers shown are of the enrolled patients set.

^g The number of treatment completers is shown, since study completers include both patients who completed treatment and discontinued treatment.

^h There was no placebo arm in this study. TV-46000 Placebo was administered in this study in an alternating manner to patients in the TV-46000 q2m treatment group in order to maintain the blind.

ⁱ Oral risperidone was mandated for use in Stage 1 of this study; however, for the purposes of this study, it was not considered an investigational medicinal product.

CSR=clinical study report; F=females; M=males; q1m=once-monthly; q2m=once every 2 months; sc=subcutaneous(ly); US=United States.

Source: Adapted from Applicant's Listing of Clinical Studies, in Synopses of Individual Studies (DARRTS SDN 41, Section 2.7.6, page 6).

7.2. Review Strategy

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022. In the original NDA submission, the Applicant submitted two studies: Study 30072 was a randomized, double-blind, placebo-controlled relapse prevention study in 543 subjects, and Study 30078 was a 56-week, randomized, uncontrolled safety and tolerability study, which was still ongoing at the time of the original NDA submission.

Study 30072 study met its prespecified primary endpoint for both the TV-46000 once-monthly (q1m) and every 2 months (q2m) dosing regimens and demonstrated statistically significant improvement in the time to impending relapse in subjects treated with TV-46000 compared to placebo. With this resubmission, the Applicant conducted sensitivity analyses of Study 30072 to assess the impact of dosing errors, lack of IP dose documentation, and duplicate patients on the primary efficacy analysis. These analyses were replicated by the statistical reviewer and compared with those submitted by the Applicant. The Applicant also submitted sensitivity safety analyses of Study 30078; these were verified by the clinical team and compared to data and analyses conducted by the third-party audit and reported by the Applicant. Additionally, the Applicant submitted new safety data from completed Study 30078 and the clinical reviewer conducted additional safety analyses on the completed dataset.

Despite the Applicant's efforts to recruit adolescents, only four adolescents were recruited in the two phase 3 studies; the size of the pediatric population is not sufficient to evaluate either efficacy or safety. Thus, efficacy and safety analyses in the review are limited to the adult population with schizophrenia.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study Results of TV-46000-CNS-30072

Trial Design

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

Study Endpoints

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

Statistical Analysis Plan

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022, for the original statistical analysis plan. Below is the summary of the sensitivity analyses the Applicant performed based on the third-party audit of specific protocol deviations for Study 30072.

The primary efficacy endpoint of Study 30072 was time to impending relapse. It was originally calculated as the earliest date the patient met ≥ 1 of the impending relapse criteria minus the randomization date plus 1. Data from patients who did not relapse were censored at the End-of-Treatment/Early Termination visit. As defined in the Study 30072 statistical analysis plan (SAP), the time to impending relapse for TV-46000 q1m and TV-46000 q2m was compared versus placebo using the stratified log-rank test. This test was accompanied by hazard ratios based on the stratified Cox proportional hazard model.

In order to evaluate the impact of dosing errors and/or lack of IP dosing source data documentation on study efficacy results, the primary endpoint was re-analyzed in the following subset:

- Patients with no documented dosing error (i.e., received intended dose or treatment (active or placebo] provided)
- Patients with complete source documentation at all visits
- Patients with complete dose documentation at all visits and no dosing errors at any visit

The primary efficacy endpoint was also re-analyzed censoring at the first occurrence of either a dosing error or lack of source documentation on administered IP dose, as described below:

- Time-to-relapse for all patients with dosing error (i.e., too high, too low, and wrong treatment regimen) censored at the first occurrence of error dosing
- Time-to-relapse for all patients with lack of IP dose source documentation censored at the first occurrence of lack of IP dose source documentation

Additionally, the primary efficacy endpoint was re-analyzed excluding only subjects with significant dosing errors as described below:

- Patients with no significant dosing error
- Patients with complete dose documentation at all visits and no significant dosing errors

Duplicate (dually- and triply-enrolled) patients were excluded from all the sensitivity analyses of efficacy.

The following table summarized the definitions of terms used for sensitivity analyses.

Table 3. Definition of Terms for Sensitivity Analyses

Term	Definition
Original	All randomized and treated
Duplicate	Dually and triply enrolled patients
Dosing Error	Injections in which the documented administered dose of IP is confirmed to be incorrect relative to protocol-intended treatment, including high volume, low volume, and/or IP dosing error due to mistakes in oral risperidone stabilization dose.
Significant Dosing Error	Injections in which the administered dose of IP differs from the protocol-specified dose by >10% while participating in the study and - Provided too high a dose volume on active treatment or - Provided too low a dose volume on active treatment or Any error in which a patient received the incorrect treatment (active treatment instead of placebo or vice-versa)
Lack of Documentation	Injection events lacking any essential documentation elements, including missing fields on any of dosing volume, stabilization dose, IP kit number and date of IP administration. Data from sites from which reliable data could not be obtained were included in this category.
Dose Related Deviation	Refers to all injections in which any dosing error or lack of documentation is confirmed: incorrect treatment, high or low volume relative to the planned dose, or IP dosing error due to mistakes in oral risperidone stabilization dose, or lack of documentation. Dosing-related deviations included all the dosing errors and cases of lack of documentation. Thus, patients without dosing-related deviations comprised the "cleanest" subgroup of patients with no errors.

Source: Table 1 of Study 30072 Clinical Study Report Addendum 02.

Protocol Amendments

There were no changes in the conduct of Study 30072. The addendum only reports the results of the safety analyses for efficacy and safety in response to the CRL.

8.1.2. Study Results

Compliance with Good Clinical Practices

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

Financial Disclosure

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

Patient Disposition

In the original SAP, the intent-to-treat (ITT) analysis set was defined as all adult patients randomized to the double-blind maintenance stage (relapse prevention period), regardless of whether they received treatment or not. In this addendum, the ITT analysis set included all adult patients randomized to the relapse prevention period, excluding dually- and triply-enrolled patients. Safety analysis set included all adult patients who were randomized to the relapse prevention period and treated with at least one dose of IP. As seen in the table below, there were no apparent differences in the reasons for discontinuation across the analysis subgroups.

Table 4. Patient Disposition in the Sensitivity Analysis Subgroups (Excluding Dually- and Triply-Enrolled Patients) Compared to That in the Study 30072 CSR (ITT Analysis Set)

Analysis subgroup, Analysis set, n (%)	Study 30072 CSR ITT analysis set (overall) N=543	ITT analysis set (and excluding dually and triply enrolled patients) N=534	Patients without any dosing-related deviation ^a N=330	Patients without dosing error N=460	Patients without significant dosing error ^b N=517	Patients without lack of documentation N=380
Randomized, not treated	2 (<1)	2 (<1)	2 (<1)	2 (<1)	2 (<1)	2 (<1)
Safety analysis set	541 (>99)	532 (>99)	328 (>99)	458 (>99)	515 (>99)	378 (>99)
Completed treatment	338 (62)	331 (62)	212 (64)	280 (61)	320 (62)	247 (65)
Discontinued treatment	205 (38)	203 (38)	118 (36)	180 (39)	197 (38)	133 (35)
– Death	5 (<1)	5 (<1)	3 (<1)	4 (<1)	4 (<1)	4 (1)
– Adverse event	45 (8)	44 (8)	29 (9)	41 (9)	43 (8)	31 (8)
– Withdrawal by patient	70 (13)	70 (13)	39 (12)	63 (14)	67 (13)	43 (11)

NDA/BLA Multi-disciplinary Review and Evaluation
NDA 213586: Risperidone extended-release injectable suspension

– Non-compliance with study drug	8 (1)	8 (1)	6 (2)	7 (2)	8 (2)	6 (2)
– Protocol deviation	17 (3)	17 (3)	11 (3)	15 (3)	17 (3)	13 (3)
– Pregnancy	0	0	0	0	0	0
– Lost to follow-up	31 (6)	30 (6)	14 (4)	26 (6)	30 (6)	17 (4)
– Lack of efficacy	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)
– Other	28 (5)	28 (5)	15 (5)	23 (5)	27 (5)	18 (5)
Completed study	425 (78)	417 (78)	267 (81)	358 (78)	403 (78)	306 (81)
Discontinued study	118 (22)	117 (22)	63 (19)	102 (22)	115 (22)	74 (19)
• Death	5 (<1)	5 (<1)	3 (<1)	4 (<1)	4 (<1)	4 (1)
• Adverse event	9 (2)	9 (2)	7 (2)	9 (2)	9 (2)	7 (2)
• Withdrawal by patient	45 (8)	45 (8)	25 (8)	41 (9)	44 (8)	28 (7)
• Non-compliance with study drug	0	0	0	0	0	0
• Protocol deviation	8 (1)	8 (1)	6 (2)	6 (1)	8 (2)	8 (2)
• Pregnancy	0	0	0	0	0	0
• Lost to follow-up	44 (8)	43 (8)	20 (6)	37 (8)	43 (8)	24 (6)
• Lack of efficacy	0	0	0	0	0	0
• Other	7 (1)	7 (1)	2 (<1)	5 (1)	7 (1)	3 (<1)

^a Dosing error and/or lack of documentation.

^b For definition of significant dosing errors, see Table X

^c ITT analysis set included all the adult patients, randomized to the relapse prevention period. One adolescent patient was excluded from the eITT. eITT=extended intent-to-treat; ITT=intent-to-treat; n=number of patients in each category.

Note: The denominator for calculating the percentages is the number of patients in the eITT analysis set excluding duplicate and triplicate patients.

Source: Table 3 of Study 30072 Clinical Study Report Addendum 02 and Statistical Reviewer's Summary Based on dataset ADSL.xpt.

Protocol Violations/Deviations

Dually- and Triply-enrolled Patients

Analyses to identify patients dually- or triply-enrolled were undertaken separately and jointly for Study 30072 and Study 30078. Based on the third-party audit, a total of 10 patients dually-enrolled and 1 patient triply-enrolled were identified across both studies. Among these 10 subjects, 4 (2%) were treated in the placebo arm, 4 (2%) in the q1m arm, and 1 (<1%) in the q2m, and 2 received oral risperidone only.

Dosing Errors

Various types of dosing errors are presented in the following table, they include:

- Low volume administered relative to the protocol-specified dose
- High volume administered relative to the protocol-specified dose
- Incorrect treatment (TV-46000 treatment instead of placebo and vice-versa) significant dosing error (defined as any error which occurred at >10% of a patient's IP administrations while participating in the study and provided too high or provided too low a dose volume on active treatment or any error in which a patient received the incorrect treatment)
- IP dosing error which occurred due to a mistake in the oral risperidone stabilization dose

According to the Applicant, this significant dosing error subgroup was defined to identify patients for whom a dosing error could potentially result in a clinically significant impact.

Table 5. Dosing Errors per Patient and Visits by Treatment Arm (Dually-and Triply-enrolled Patients Included) in Study 30072 (ITT Analysis Set)

Dosing-related deviation type	Placebo (N=181)	TV-46000 q1m (N=183)	TV-46000 q2m ^a (N=179)	Total (N=543)
All randomized patients	181	183	179	543
At least 1 dosing error ^b , n (%)	19 (10)	5 (3)	50 (28)	74 (14)
Volume too low ^c , n (%)	15 (8)	2 (1)	21 (12)	38 (7)
Volume too high ^d , n (%)	6 (3)	2 (1)	35 (20)	43 (8)
Incorrect treatment, n (%)	0	1 (<1)	1 (<1)	2 (<1)
Significant dosing error, n (%)	0	4 (2)	13 (7)	17 (3)
IP dosing error based on oral stabilization dose ^e , n (%)	0	1 (<1)	4 (2)	5 (<1)

N=number of patients; n=number of patients/visits; q1m=once every month; q2m=once every 2 months.

^a Due to study design, a patient randomized to q2m arm was counted under both TV-46000 and placebo. Patients who withdrew or relapsed in the first month are counted only under TV-46000 and not under placebo.

^b Incorrect treatment and/or high volume and /or low volume relative to the planned dose.

^c At least one low volume relative to the planned dose.

^d At least one high volume relative to the planned dose.

^e Significant dosing errors were determined at a patient level while accounting for multiple TV 46000 injections.

^f Patients counted in this category are also counted in volume too low or volume too high. For patients (b) (6) error in the volume due to the wrong stabilization dose could not have been ruled out and hence included in the category.

Source: Table 7 of Study 30072 Clinical Study Report Addendum 02 and Statistical Reviewer's Summary based on dataset ADSL.xpt.

Lack of Documentation

Distribution of injection administrations with lack of documentation, is presented in the following table. In total, there were 155 (29%) patients with at least one injection administration with lack of documentation: 51 (28%) in the placebo arm, 51 (28%) in the q1m arm, and 53 (30%) in the q2m arm. The vast majority of cases of lack of documentation (92% of patients with lack of documentation) were identified for cases where the volume of the IP administered was missing in the source documents.

Table 6. Patients and Visits with Lack of Documentation by Treatment Arm (Dually and Triply Enrolled Patients Included) in Study 30072 (ITT Analysis Set)

Dosing-related deviation type	Placebo (N=181)	TV-46000 q1m (N=183)	TV-46000 q2m ^a (N=179)	Total (N=543)
All randomized patients	181	183	179	543
At least 1 lack of documentation, n (%)	51 (28)	51 (28)	53 (30)	155 (29)
Volume is missing, n (%)	48 (27)	48 (26)	47 (26)	143 (26)
Oral stabilization dose is missing, n (%)	1 (<1)	0	1 (<1)	2 (<1)
No record received, n (%)	2 (1)	1 (<1)	4 (2)	7 (1)
Other ^b , n (%)	1 (<1)	2 (1)	4 (2)	7 (1)

N=number of patients; n=number of patients/visits; q1m=once every month; q2m=once every 2 months.

^a Due to study design, a patient randomized to q2m arm was counted under both TV-46000 and placebo. Patients who withdrew or relapsed in the first month are counted only under TV-46000 and not under placebo.

^b Other include missing IP kit number or date of IP administration.

Source: Table 8 of Study 30072 Clinical Study Report Addendum 02 and Statistical Reviewer's Summary based on dataset ADSL.xpt.

Dosing-Related Deviations

Distribution of dosing-related deviations identified in Study 30072 for patients and visits are presented in the following table, where dosing-related deviations included all the dosing errors and cases of lack of documentation listed above. Thus, patients without dosing-related deviations comprised the "cleanest" subgroup of patients with no errors.

In total, out of 543 patients randomized to the relapse prevention period and treated with at least one dose of IP, 205 (38%) patients had at least one dosing-related deviation. These included 66 (36%) patients of the placebo arm, 53 (29%) patients administered q1m treatment, and 86 (48%) patients administered q2m treatment.

Table 7. Dosing-related Deviations per Patient by Treatment Arm (Dually- and Triply-enrolled Patients Included) in Study 30072 (ITT Analysis Set)

Dosing-related deviation type	Placebo (N=181)	TV-46000 q1m (N=183)	TV-46000 q2m (N=179)	Total (N=543)
All randomized	181	183	179	543
Patients with no dosing-related deviation ^a , n (%)	115 (64)	130 (71)	93 (52)	338 (62)
Patients with at least 1 dosing-related deviation ^a , n (%)	66 (36)	53 (29)	86 (48)	205 (38)

N=number of patients; n=number of patients/visits; q1m=once every month; q2m=once every 2 months.

^a Other include missing IP kit number or date of IP administration.

Source: Statistical Reviewer's Summary based on dataset ADSL.xpt.

In summary, the following table presents the subjects disposition in each of the sensitivity analyses subset.

Table 8. Subjects Disposition for the Sensitivity Analyses (ITT Analysis Set)

Term	Placebo (N=181)	TV-46000 q1m (N=183)	TV-46000 q2m (N=179)
Original, n (%)	181 (100)	183 (100)	179 (100)
Without Duplicate, n (%)	177 (98)	179 (98)	178 (99)
Without Dosing Error, n (%)	158 (87)	174 (95)	128 (72)
Without Significant Dosing Error, n (%)	177 (98)	175 (96)	165 (92)
Without Lack of Documentation, n (%)	126 (70)	129 (70)	125 (70)
Without Dose-related Deviation, n (%)	111 (61)	127 (69)	92 (51)

Source: Statistical Reviewer's Summary based on dataset ADSL.xpt.

Table of Demographic Characteristics

The demographic characteristics of patients did not notably differ across the analysis subsets (ITT analysis set, excluding dually- and triply-enrolled patients), patients without any dosing related deviation, patients without dosing error, patients without significant dosing error, and patients without lack of documentation) and as compared to the demographic characteristics presented for the ITT analysis set; see the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

Table 9. Demographic Characteristics in the Analysis Subgroups (Excluding Dually- and Triply-enrolled Patients) Compared to Those in the Study 30072 CSR (ITT Analysis Set)

Analysis Subgroups Demographic Variables	Study 30072 CSR ITT Analysis Set (N=543)	ITT Analysis Set (Excluding Dually- and Triply-enrolled Patients) (N=534)	Patients without Dosing-related Deviations ^a (N=330)	Patients without Dosing Error (N=460)	Patients without Significant Dosing Errors ^b (N=517)	Patients without Lack of Documentation (N=380)
Age, years						
n	543	534	330	460	517	380
Mean	49.3	49.2	49.3	49.5	49.2	49.0
SD	10.89	10.91	11.02	10.91	10.91	11.05
Sex, n (%)						
Male	332 (61)	325 (61)	203 (62)	281 (61)	316 (61)	233 (61)
Race, n (%)						
White	206 (38)	203 (38)	137 (42)	174 (38)	198 (38)	160 (42)
Black or African American	322 (59)	316 (59)	186 (56)	272 (59)	304 (59)	212 (56)
Asian	7 (1)	7 (1)	2 (<1)	6 (1)	7 (1)	3 (<1)
American Indian or Alaska Native	0	0	0	0	0	0
Native Hawaiian or other Pacific Islander	2 (<1)	2 (<1)	1 (<1)	2 (<1)	2 (<1)	1 (<1)
Not reported	3 (<1)	3 (<1)	1 (<1)	3 (<1)	3 (<1)	1 (<1)
Other	3 (<1)	3 (<1)	3 (<1)	3 (<1)	3 (<1)	3 (<1)
Ethnicity, n (%)						
Not Hispanic or Latino	427 (78)	423 (79)	248 (75)	355 (77)	407 (79)	294 (77)
Hispanic or Latino	116 (22)	111 (21)	82 (25)	105 (23)	110 (21)	86 (23)
BMI, kg/m²						
n	541	532	328	458	515	378
Mean	29.34	29.32	29.34	29.33	29.32	29.33
SD	5.064	5.069	4.858	5.015	5.095	4.982

BMI=body mass index; cm=centimeters; eITT= extended intent-to-treat; ITT=intent-to-treat; kg=kilogram; m=meter; n/N=number of patients; SD=standard deviation.

^a Dosing error and/or lack of documentation.

^b For definition of significant dosing errors, see Table X

Source: Table 4 of Study 30072 Clinical Study Report Addendum 02 and Statistical Reviewer's Summary Based on dataset ADSL.xpt.

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

There were no apparent differences in other baseline characteristics across the analysis subgroups (table below) and as compared to the corresponding baseline characteristics

presented for the eITT analysis set in the original NDA review for Study 30072; see the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

Table 10. Other Baseline Characteristics in the Analysis Subgroups (Excluding Dually- and Triply-enrolled Patients) Compared to Those in the Study 30072 CSR (ITT Analysis Set)

Analysis Subgroups Demographic variables	Study 30072 CSR ITT Analysis Set (N=543)	ITT Analysis Set (Excluding Dually- and Triply-enrolled Patients) (N=534)	Patients without Dosing-related Deviations ^a (N=330)	Patients without Dosing Errors (N=460)	Patients without Significant Dosing Errors ^b (N=517)	Patients without Lack of Documentation (N=380)
Oral risperidone at randomization, n (%)						
2 mg	167 (31)	166 (31)	108 (33)	143 (31)	160 (31)	124 (33)
3 mg	108 (20)	108 (20)	66 (20)	97 (21)	104 (20)	70 (18)
4 mg	203 (37)	198 (37)	124 (38)	167 (36)	192 (37)	148 (39)
5 mg	65 (12)	63 (12)	32 (10)	53 (12)	61 (12)	38 (10)
Disease length (years)						
n	543	534	330	460	517	380
Mean	20.8	20.8	20.9	21.2	20.8	20.6
SD	12.21	12.12	12.26	12.01	12.12	12.33
Time since the most recent relapse (months)						
n	542	533	330	460	516	379
Mean	10.2	10.0	10.3	10.0	10.1	10.4
SD	6.98	6.88	7.06	6.93	6.92	7.01
Injection site, n (%)						
Arm	172 (32)	170 (32)	103 (31)	154 (33)	168 (33)	107 (28)
Abdomen	369 (68)	362 (68)	225 (68)	304 (66)	347 (67)	271 (71)
Missing	2 (<1)	2 (<1)	2 (<1)	2 (<1)	2 (<1)	2 (<1)

ITT=intent-to-treat; kg=kilogram; m=meter; n/N =number of patients; SD=standard deviation.

^a Dosing error and/or lack of documentation.

^b For definition of significant dosing errors, see Table X

Source: Table 5 of Study 30072 Clinical Study Report Addendum 02 and Statistical Reviewer's Summary Based on dataset ADSL.xpt.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

Efficacy Results – Primary Endpoint

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

Data Quality and Integrity

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

Efficacy Results – Secondary and other relevant endpoints

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

Dose/Dose Response

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

Durability of Response

Not Applicable

Persistence of Effect

Not Applicable

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

Additional Analyses Conducted on the Individual Trial

The primary efficacy variable, time to impending relapse, was re-analyzed in the ITT analysis set excluding dually- and triply-enrolled patients, and in each of the analysis subsets (patients without dosing-related deviations, patients without dosing errors, patients without significant dosing errors, and patients without lack of documentation).

The results of the sensitivity analyses of the primary endpoint in all the analysis subsets based on the stratified log-rank test were consistent with the originally reported results, showing improved time to relapse for both q1m and q2m over placebo.

Table 11. Sensitivity Analyses of Primary Endpoint: Time to Relapse (Weeks) by Treatment Group for Subsets—Log Rank Test and Cox Proportional Hazards Model (ITT Analysis Set)

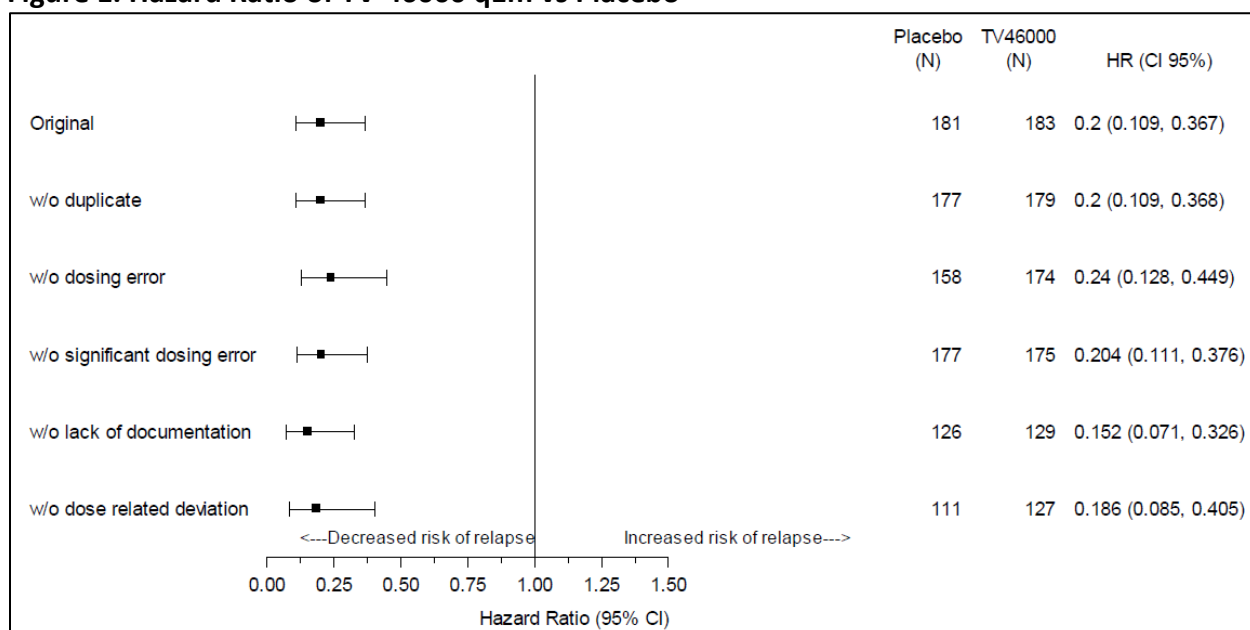
	Placebo	TV-46000 q1m	TV-46000 q2m
Original			
N	181	183	179
Patients with impending relapse, n (%)	53 (29)	13 (7)	23 (13)
Log-rank test p-value	-	<0.0001	<0.0001
Hazard ratio (95% CI) ^a	-	0.200 (0.109, 0.367)	0.375 (0.227, 0.618)
Proportional hazards test p-value ^b	0.7251	-	-
Excluding dually and triple enrolled patients			
N	177	179	178
Patients with impending relapse, n (%)	52 (29)	13 (7)	23 (13)
Log-rank test p-value	-	<0.0001	<0.0001
Hazard ratio (95% CI) ^a	-	0.200 (0.109, 0.368)	0.370 (0.224, 0.610)
Proportional hazards test p-value ^b	0.7429	-	-
Patients without dosing error			
N	158	174	128
Patients with impending relapse, n (%)	41 (26)	13 (7)	21 (16)
Log-rank test p-value	-	<0.0001	0.011
Hazard ratio (95% CI) ^a	-	0.240 (0.128, 0.449)	0.597 (0.348, 1.023)
Proportional hazards test p-value ^b	0.8336	-	-
Patients without significant dosing error			
N	177	175	165
Patients with impending relapse, n (%)	52 (29)	13 (7)	22 (13)
Log-rank test p-value	-	<0.0001	<0.0001
Hazard ratio (95% CI) ^a	-	0.204 (0.111, 0.376)	0.378 (0.227, 0.630)
Proportional hazards test p-value ^b	0.7573	-	-
Patients without lack of documentation			
N	126	129	125
Patients with impending relapse, n (%)	36 (29)	9 (7)	16 (13)
Log-rank test p-value	-	<0.0001	0.0001
Hazard ratio (95% CI) ^a	-	0.152 (0.071, 0.326)	0.337 (0.182, 0.625)
Proportional hazards test p-value ^b	0.5154	-	-
Patients without dosing-related deviation			
N	111	127	92
Patients with impending relapse, n (%)	28 (25)	9 (7)	14 (15)
Log-rank test p-value	-	<0.0001	0.0142
Hazard ratio (95% CI) ^a	-	0.186 (0.085, 0.405)	0.520 (0.265, 1.023)
Proportional hazards test p-value ^b	0.5333	-	-

^a The hazard ratio (95% CI) coming from the stratified Cox proportional hazard model, with treatment (placebo, TV-46000 q1m and TV-46000 q2m, or placebo and TV-46000 overall (including q1m and q2m)) as exploratory variable and sex-dose as a stratification factor, and the stratified log-rank test p-value (sex-dose as a stratification factor) refer to TV-46000/placebo comparison.

^b The proportional hazards test p-value tests the overall proportional hazard assumption for the primary model.

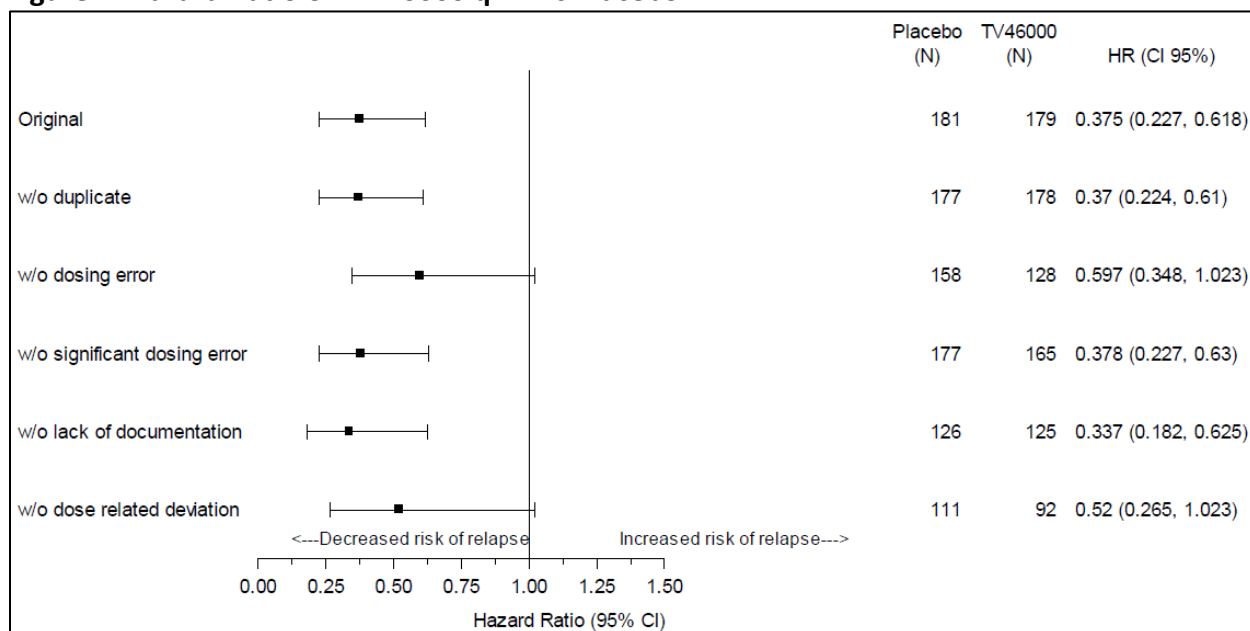
Source: Summaries 4.1, 4.2, 4.3, 4.4, and 4.7 of Study TV46000-CNS-30072 Clinical Study Report Addendum 02.

Figure 1. Hazard Ratio of TV-46000 q1m vs Placebo



CI=confidence interval; ITT=intention-to-treat; q1m=once monthly; q2m=once every 2 months.
Source: Figure 8 of Study 30072 Clinical Study Report Addendum 02.

Figure 2. Hazard Ratio of TV-46000 q2m vs Placebo



CI=confidence interval; ITT=intention-to-treat; q1m=once monthly; q2m=once every 2 months.
Source: Figure 9 of Study 30072 Clinical Study Report Addendum 02.

The Applicant also re-analyzed the primary endpoint where patients with dosing errors, with lack of documentation, or with dosing-related deviations were censored at the first occurrence of the error, rather than being completely removed from the dataset. The results of these sensitivity analyses were also consistent with the originally-reported results.

Table 12. Sensitivity Analyses for Primary Endpoint: Time to Impending Relapse (Weeks) by Treatment Group Including Patients with Dosing Error, with Lack of Documentation, or with Dosing-related Deviations Censored at the First Occurrence of Error Dosing (ITT Analysis Set (Excluding Duplicate and Triplicate Patients))

	Placebo	TV-46000 q1m	TV-46000 q2m
Original			
N	181	183	179
Patients with impending relapse, n (%)	53 (29)	13 (7)	23 (13)
Log-rank test p-value	-	<0.0001	<0.0001
Hazard ratio (95% CI) ^a	-	0.200 (0.109, 0.367)	0.375 (0.227, 0.618)
Proportional hazards test p-value ^b	0.7251	-	-
Patients with dosing error censored			
N	177	179	178
Patients with impending relapse, n (%)	41 (23)	13 (7)	21 (12)
Log-rank test p-value	-	<0.0001	0.0034
Hazard ratio (95% CI) ^a	-	0.238 (0.127, 0.446)	0.524 (0.306, 0.898)
Proportional hazards test p-value ^b	0.9094	-	-
Patients with lack of documentation censored			
N	177	179	178
Patients with impending relapse, n (%)	36 (20)	9 (5)	16 (9)
Log-rank test p-value	-	<0.0001	<0.0001
Hazard ratio (95% CI) ^a	-	0.148 (0.070, 0.316)	0.313 (0.169, 0.581)
Proportional hazards test p-value ^b	0.5051	-	-
Patients with dosing-related deviation censored			
N	177	179	178
Patients with impending relapse, n (%)	28 (16)	9 (5)	14 (8)
Log-rank test p-value	-	<0.0001	0.0059
Hazard ratio (95% CI) ^a	-	0.181 (0.083, 0.394)	0.461 (0.235, 0.907)
Proportional hazards test p-value ^b	0.7030	-	-

^a The hazard ratio (95% CI) coming from the stratified Cox proportional hazard model, with treatment (placebo, TV-46000 q1m and TV-46000 q2m, or placebo and TV-46000 overall (including q1m and q2m)) as exploratory variable and sex-dose as a stratification factor, and the stratified log-rank test p-value (sex-dose as a stratification factor) refer to TV-46000/placebo comparison.

^b The proportional hazards test p-value tests the overall proportional hazard assumption for the primary model.

Source: Summaries 4.5, 4.6, and 4.9 of Study 30072 Clinical Study Report Addendum 02.

Additionally, per the clinical reviewer's request, the statistical reviewer performed subgroup analysis of the time to impending relapse based on oral risperidone dose at randomization for the original primary analysis population, the results are consistent with those seen for the overall population.

Integrated Review of Effectiveness

Based on results of the sensitivity analyses evaluating the effect of dosing errors and/or lack of dosing documentation in Study 30072 identified, the treatment effect of TV-46000 (q1m and

q2m) over placebo is robust to the identified deviations and is consistent with the results and conclusions of the original primary efficacy endpoint analysis.

8.1.3. **Assessment of Efficacy Across Trials**

Not Applicable

8.1.4. **Integrated Assessment of Effectiveness**

Not Applicable

8.2. **Review of Safety**

8.2.1. **Safety Review Approach**

Risperdal oral tablet was approved in the United States in 2003 and its safety profile is well-characterized. The initial NDA review found that safety findings were similar to that seen with the oral formulation, with the exception of injection site adverse reactions, which are expected for a long-acting injection formulation (see the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedy (risperidone extended release injection), archived on April 15, 2022). However, due to protocol deviations identified during the OSI inspections data from studies 30072 and 30078, it failed to meet the quality standard necessary to assure data integrity to conduct a clinical safety review with conclusive results.

The following are included in this clinical review for safety:

- Safety analyses of completed long-term safety Study 30078 including all adult participants who completed the study (ongoing at time of the original submission). Deaths, serious adverse events (SAEs), adverse events leading to treatment discontinuation, and common treatment emergent adverse events (TEAEs) events were reviewed and compared with the original NDA analysis.
- Safety sensitivity analyses for Studies 30078 and 30072. Based on the third-party audit findings and the Agency's recommendations following the complete response action, the Applicant conducted five sensitivity analyses:
 - Safety analysis without duplicate and triplicate subjects
 - Safety analysis without duplicate and triplicate subjects and without dosing errors
 - Safety analysis without duplicate and triplicate subjects and without significant dosing errors

- o Safety analysis without duplicate and triplicate subjects and without lack of documentation
- o Safety analysis without duplicate and triplicate subjects and without dose related deviation
- Deaths, SAEs, adverse events leading to discontinuation, and TEAEs in subgroups of patients without dosing-related deviations, patients without dosing errors and patients without lack of documentation were reviewed for both Study 30072 and 30078 and compared with the original NDA safety analyses. In the subgroups used to conduct the sensitivity analyses, we excluded dually- and triply-enrolled patients.

Despite the Applicant's efforts to recruit adolescents, only four adolescent patients were randomized. The safety data collected in these studies are not sufficient to evaluate safety in the adolescent patient population. Thus, the following safety analysis is limited to the adult population with schizophrenia.

8.2.2. Review of the Safety Database

Overall Exposure

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022, for the exposure table for Study 30072. Updated exposure data for Study 30078 are reported in Table 13.

Table 13. Total Exposure to Study Drug in Study TV46000-CNS-30078 by Treatment Group and Source of Patients

Weeks Treated, n (%)			
Roll-Over Patients	TV-46000 q1m (N=171)	TV-46000 q2m (N=108)	Total (N=225)
<=13 weeks	11 (9)	6 (6)	17 (8)
>13 to <=26 weeks	13 (11)	12 (11)	25 (11)
>26 to <=39 weeks	93 (79)	90 (83)	183 (81)
>39 to <=52 weeks	0	0	0
>52 to <=56 weeks	0	0	0
>56 weeks	0	0	0
New patients	TV-46000 q1m (N=54)	TV-46000 q2m (N=52)	Total (N=106)
<=13 weeks	0	0	0
>13 to <=26 weeks	16 (30)	9 (17)	25 (24)
>26 to <=39 weeks	2 (4)	7 (13)	9 (8)
>39 to <=52 weeks	9 (17)	7 (13)	16 (15)
>52 to <=56 weeks	4 (7)	3 (6)	7 (7)
>56 weeks	23 (43)	26 (50)	49 (46)

Source: Applicant response to IR dated February 9, 2023 (eCTD 0042) - Summary Table 15.15.3a and Summary Table 15.15.2.2a of Summary-Safety-Table-Adults of Study 30078.

8.2.3. Adequacy of the Safety Database

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

8.2.4. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

See the Memo-To-File compiled by the Division of Clinical Compliance Evaluation dated February 27, 2023. The Division of Clinical Compliance Evaluation did not identify new discrepancies and concluded that the structured database could be used for analyses for review purposes.

Categorization of Adverse Events

Not applicable

Routine Clinical Tests

Not applicable

8.2.5. Safety Results

Safety analyses on completed dataset of Study 30078

Deaths

There were no new deaths reported during the interval time between the original submission and the resubmission. See the original NDA review archived in DARRTS on April 15, 2022.

Serious Adverse Events

Table 14. Serious adverse events (completed Study 30078, adult population)

Preferred Term	TV-46000 q1m (N = 171) n (%)	TV-46000 q2m (N = 160) n (%)
Patients with at least one SAE	8 (5)	10 (6)
Acute myocardial infarction	0	1 (<1)
Anemia	0	1 (<1)
Angina pectoris	0	1 (<1)
Atrial fibrillation	1 (<1)	0
Cerebrovascular accident	1 (<1)	0
Chronic obstructive pulmonary disease	0	1 (<1)
Deep vein thrombosis	1 (<1)	0

NDA/BLA Multi-disciplinary Review and Evaluation
NDA 213586: Risperidone extended-release injectable suspension

Hyperglycemia	1 (<1)	1 (<1)
Major depression	1 (<1)	0
Myocardial infarction	1 (<1)	0
Panic attack	0	1 (<1)
Psychotic disorder	0	1 (<1)
Schizophrenia	1 (<1)	2 (1)
Self-injurious ideation	0	1 (<1)
Substance-induced psychotic disorder	1 (<1)	0

Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) on adult population of final Study 30078 (deaths and schizophrenia relapses were included). Similar to Applicant's Table 23 in Clinical Study Report of final Study 30078 (page 134), but without adolescent population. Of note, deaths and schizophrenia relapses included (excluded in Table 28, Serious Adverse Events, Study 30078, page 28, reported in the original review dated April 15, 2022).

Dropouts and/or Discontinuations Due to Adverse Effects

Table 15. Discontinuations due to adverse events (completed Study 30078, adult population)

System Organ Class (Preferred Term)	TV-46000 q1m (N =171) n (%)	TV-46000 q2m (N=160) n (%)
Cardiac disorders (Acute myocardial infarction, Myocardial infarction)	1 (<1)	1 (<1)
General disorders and administration site conditions (Injection site nodule, Fatigue)	1 (<1)	1 (<1)
Investigations (Blood pressure increased)	0	1 (<1)
Nervous system disorders (Cerebrovascular accident, Tremor)	1 (<1)	1 (<1)
Psychiatric disorders (psychotic disorder)	0	1 (<1)

Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) on adult population of final Study 30078. Similar to Applicant's Table 25 in Clinical Study Report of final Study 30078 (page 136-137), but without adolescent population.

Treatment Emergent Adverse Events and Adverse Reactions

Table 16. Most Common TEAEs (≥2%) (completed Study 30078, adult population)

System Organ Class Preferred Term	TV-46000 q1m N=171 n (%)	TV-46000 q2m N=160 n (%)
General disorders and administration site conditions	18 (11)	17 (11)
Injection site nodule	4 (2)	9 (6)
Injection site pain	9 (5)	7 (4)
Injection site pruritus	3 (2)	2 (1)

NDA/BLA Multi-disciplinary Review and Evaluation
NDA 213586: Risperidone extended-release injectable suspension

Nervous system disorders	14 (8)	11 (7)
Headache	1 (<1)	3 (2)
Akathisia	4 (2)	1 (<1)
Tremor	1 (<1)	5 (3)
Sedation	3 (2)	0
Somnolence	3 (2)	1 (<1)
Gastrointestinal disorders	5 (3)	3 (2)
Constipation	1 (<1)	1 (<1)
Flatulence	0	1 (<1)
Nausea	2 (1)	0
Dry mouth	0	1 (<1)
Salivary hypersecretion	2 (1)	0
Metabolism and nutrition disorders	4 (2)	4 (3)
Increased appetite	3 (2)	1 (<1)
Hyponatremia	0	1 (<1)
Hyperglycemia	1 (<1)	1 (<1)
Hyperlipidemia	0	1 (<1)
Psychiatric disorders	4 (2)	1 (<1)
Confusional state	0	1 (<1)
Depression	1 (<1)	0
Insomnia	2 (1)	0
Abnormal dreams	1 (<1)	0
Investigations	4 (2)	1 (<1)

NDA/BLA Multi-disciplinary Review and Evaluation
NDA 213586: Risperidone extended-release injectable suspension

Weight increased	4 (2)	1 (<1)
Reproductive system and breast disorders	3 (2)	0
Breast discharge	1 (<1)	0
Ejaculation disorder	1 (<1)	0
Priapism	1 (<1)	0

Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) on adult population of final Study 30078. Similar to Applicant's Table 18 in Clinical Study Report of final Study 30078 (page 124-125), but without adolescent population. Patients are counted only once in each preferred term category, and only once in each system organ class category. For No. of cases, multiple records with the same PT and AE onset date for the same patient are counted only once, selecting the adverse event with the highest severity and seriousness.

***Clinical Reviewer's Comment:** Safety analyses were conducted for Study 30078 including all adult participants who completed the study (the study was ongoing at time of the original submission). These updated safety tables were compared with the original NDA safety tables, with a particular focus on key safety endpoints, such as deaths, serious adverse events, adverse events leading to treatment discontinuation, and common adverse events. The differences identified in the key safety endpoints following the inclusion of all adult participants who completed the study were negligible and have no impact on the results and their interpretation.*

Sensitivity analyses for safety without dually- and triply-enrolled subjects

Study 30078

Deaths

There are no differences in the number of deaths when excluding dually and triply enrolled patients from the completed dataset. See the original NDA review archived in DARRTS on April 15, 2022, for details on death events.

Serious Adverse Events

Table 17. Sensitivity Analysis without Dually- and Triply-enrolled Subjects - Serious Adverse Events (Completed Study 30078, Adult Population)

Preferred Term	TV-46000 q1m (N=163) n (%)	TV-46000 q2m (N=154) n (%)
Acute myocardial infarction	0	1 (<1)
Anemia	0	1 (<1)
Angina pectoris	0	1 (<1)
Atrial fibrillation	1 (<1)	0
Cerebrovascular accident	1 (<1)	0

Chronic obstructive pulmonary disease	0	1 (<1)
Deep vein thrombosis	1 (<1)	0
Hyperglycemia	0	1 (<1)
Major depression	1 (<1)	0
Myocardial infarction	1 (<1)	0
Panic attack	0	1 (<1)
Psychotic disorder	0	1 (<1)
Schizophrenia	1 (<1)	2 (1)
Self-injurious ideation	0	1 (<1)
Substance-induced psychotic disorder	1 (<1)	0

Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) on adult population of final Study 30078 excluding dually- and triply-enrolled patients. Of note, deaths and schizophrenia relapses included (excluded in Table 28, Serious Adverse Events, Study 30078, page 28, reported in the original review dated April 15, 2022).

Dropouts and/or Discontinuations Due to Adverse Effects

Table 18. Sensitivity Analysis without Dually- and Triply-enrolled Subjects - Discontinuations Due to Adverse Events (Completed Study 30078, Adult Population)

Preferred Term	TV-46000 q1m (N=163) n (%)	TV-46000 q2m (N=154) n (%)
Acute myocardial infarction	0	1 (<1)
Blood pressure increased	0	1 (<1)
Cerebrovascular accident	1 (<1)	0
Fatigue	1 (<1)	0
Injection site nodule	0	1 (<1)
Myocardial infarction	1	0
Psychotic disorder	0	1 (<1)
Tremor	0	1 (<1)

Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) on adult population of final Study 30078 excluding dually- and triply-enrolled patients.

Treatment Emergent Adverse Events and Adverse Reactions

Table 19. Sensitivity Analysis without Dually- and Triply-enrolled Subjects – Most Common TEAEs (≥2%) (Completed Study 30078, Adult Population)

System Organ Class Preferred Term	TV-46000 q1m (N=163) n (%)	TV-46000 q2m (N=154) n (%)
Gastrointestinal disorders	4 (2.5)	3 (2)
Constipation	1 (<1)	1 (<1)
Flatulence	0	1 (<1)

NDA/BLA Multi-disciplinary Review and Evaluation
NDA 213586: Risperidone extended-release injectable suspension

Nausea	1 (<1)	0
Dry mouth	0	1 (<1)
Salivary hypersecretion	2 (1)	0
General disorders and administration site conditions	17 (10)	17 (11)
Injection site erythema	1 (<1)	1 (<1)
Injection site hemorrhage	1 (<1)	0
Injection site induration	2 (1)	1 (<1)
Injection site mass	1 (<1)	2 (1)
Injection site nodule	4 (2.5)	9 (6)
Injection site pain	9 (6)	7 (5)
Injection site pruritus	2 (1)	2 (1)
Injection site swelling	1 (<1)	0
Pyrexia	0	1 (<1)
Fatigue	0	2 (1)
Chills	0	1 (<1)
Investigations	3 (2)	1 (<1)
Weight increased	3 (2)	1 (<1)
Metabolism and nutrition disorders	3 (2)	4 (3)
Increased appetite	2 (1)	1 (<1)
Hyponatremia	0	1 (<1)
Hyperglycemia	1 (<1)	1 (<1)
Hyperlipidemia	0	1 (<1)
Nervous system disorders	12 (7)	11 (7)
Headache	1 (<1)	3 (2)
Akathisia	4 (2.5)	1 (<1)
Dyskinesia	0	1 (<1)
Extrapyramidal disorder	0	1 (<1)
Dystonia	1 (<1)	1 (<1)
Parkinsonism	0	1 (<1)

NDA/BLA Multi-disciplinary Review and Evaluation
NDA 213586: Risperidone extended-release injectable suspension

Tremor	1 (<1)	5 (3)
Sedation	3 (2)	0
Somnolence	3 (2)	1 (<1)
Dizziness	1 (<1)	0
Psychiatric disorders	4 (2.5)	1 (<1)
Confusional state	0	1 (<1)
Depression	1 (<1)	0
Insomnia	2 (2)	0
Abnormal dreams	1 (<1)	0
Reproductive system and breast disorders	3 (2)	0
Breast discharge	1 (<1)	0
Ejaculation disorder	1 (<1)	0
Priapism	1 (<1)	0

Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) on adult population of final Study 30078 excluding dually- and triply-enrolled patients. Patients are counted only once in each preferred term category, and only once in each system organ class category. For No. of cases, multiple records with the same PT and AE onset date for the same patient are counted only once, selecting the adverse event with the highest severity and seriousness.

***Clinical Reviewer's Comment:** The sensitivity analyses for safety in Study 30078, excluding dually- and triply-enrolled patients, did not identify significant differences in the key safety endpoints (such as deaths, serious adverse events, adverse events leading to treatment discontinuation, and common adverse events) when compared to the safety analyses of the completed dataset and also to the safety analyses of the original NDA (see previous review archived on April 15, 2022).*

Study 30072

Sensitivity analyses for deaths, serious adverse events, adverse events leading to treatment discontinuation, and common adverse events were conducted excluding dually- and triply-enrolled patients. Only the table of common adverse events is reported in this review for Study 30072, to illustrate and confirm that EPS and injection site AEs are still present even when removing dually- and triply-enrolled subjects who may have been exposed to higher doses of the IP and more likely to present those TEAEs (Table 20).

Table 20. Sensitivity Analysis without Dually- and Triply-enrolled Subjects – Most Common TEAEs (≥2%, TV-46000>Placebo) (Study 30072, adult population)

System Organ Class Preferred Term	Placebo (N=175) n (%)	TV-46000 q1m (N=179) n (%)	TV-46000 q2m (N=178) n (%)
General disorders and administration site conditions	24 (14)	37 (21)	37 (21)
Injection site erythema	2 (1)	6 (3)	8 (5)
Injection site mass	1 (<1)	3 (2)	6 (3)
Injection site nodule	6 (3)	11 (6)	13 (7)
Injection site pain	11 (6)	9 (5)	12 (7)
Injection site pruritus	4 (2)	8 (5)	6 (3)
Injection site swelling	0	2 (1)	3 (2)
Investigations	5 (3)	10 (6)	11 (6)
Weight increased	4 (2)	7 (4)	10 (6)
Nervous system disorders	9 (5)	29 (16)	30 (17)
Akathisia	5 (3)	7 (4)	6 (3)
Extrapyramidal disorder	0	9 (5)	6 (3)
Tremor	0	2 (1)	3 (2)
Sedation	1 (<1)	3 (2)	1 (<1)
Somnolence	1 (<1)	5 (3)	7 (4)
Dizziness	0	3 (2)	4 (2)
Droping	0	0	3 (2)
Reproductive system and breast disorders	0	4 (2)	5 (3)

Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) on adult population of Study 30072, excluding dually- and triply-enrolled patients. Patients are counted only once in each preferred term category, and only once in each system organ class category. For No. of cases, multiple records with the same PT and AE onset date for the same patient are counted only once, selecting the adverse event with the highest severity and seriousness. Only AE ≥2% in TV-46000 more than placebo are reported.

***Clinical Reviewer's Comment:** The sensitivity safety analyses for Study 30072, excluding dually- and triply-enrolled patients did not identify significant differences in the key safety endpoints when compared to the safety analyses of the original NDA (see original review archived on April 15, 2022). Most common TEAEs include injection site TEAEs and extrapyramidal symptoms (EPS) even after excluding duplicate and triplicate subjects, confirming that these TEAEs are associated with administration of regular doses of risperidone injection, and not only with higher doses.*

Other sensitivity safety analyses

See the Division of Clinical Compliance Evaluation's Memo-To-File for details on the numbers of dose-related deviations, dosing errors, and lack of documentation.

The following sensitivity analyses were conducted by the Applicant for both Study 30072 and 30078:

- Sensitivity safety analysis without dosing-related deviations (and without duplicate and triplicate subjects)

- Sensitivity safety analysis without significant dosing errors (and without duplicate and triplicate subjects)
- Sensitivity safety analysis without lack of documentation (and without duplicate and triplicate subjects)

Table 21 and Table 22 summarize TEAEs by treatment arm for the three sensitivity analyses in each study.

Table 21. Overall Summary of Adverse Events—Sensitivity Analyses (Excluding Dually- and Triply-enrolled Patients) and Original CSR Results for Study 30072

	Placebo	TV-46000 q1m	TV-46000 q1m
Study 30072 CSR N	N=179	N=183	N=179
Patients without dosing-related deviations N	N=109	N=127	N=92
Patients without dosing errors N	N=156	N=174	N=129
Patients without lack of documentation N	N=124	N=129	N=125
Patients with at least 1 adverse event, n (%)			
Study 30072 CSR	92 (51)	111 (61)	121 (67)
Patients without dosing-related deviations	55 (50)	70 (55)	61 (66)
Patients without dosing errors	82 (53)	103 (59)	86 (67)
Patients without lack of documentation	62 (50)	72 (56)	82 (66)
Patients with any serious adverse event, n (%)			
Study 30072 CSR	14 (8)	8 (4)	10 (6)
Patients without dosing-related deviations	7 (6)	5 (4)	5 (5)
Patients without dosing errors	11 (7)	8 (5)	7 (5)
Patients without lack of documentation	10 (8)	5 (4)	7 (6)
Patients with any adverse event leading to discontinuation from treatment, n (%)			
Study 30072 CSR	10 (6)	21 (11)	14 (8)
Patients without dosing-related deviations	12 (11)	13 (10)	13 (14)
Patients without dosing errors	18 (12)	22 (13)	20 (16)

NDA/BLA Multi-disciplinary Review and Evaluation
NDA 213586: Risperidone extended-release injectable suspension

Patients without lack of documentation	14 (11)	14 (11)	14 (11)
Patients with any adverse event leading to death			
Study 30072 CSR	1 (<1)	0	4 (2)
Patients without dosing-related deviations	1 (<1)	0	2 (2)
Patients without dosing errors	1 (<1)	0	3 (2)
Patients without lack of documentation	1 (<1)	0	3 (2)

Source: Modified (excluding adolescent participant) from Applicant's Summary, Clinical Study Report Addendum 02 – Report Body, Table 14, pages 59-60.

Table 22. Overall Summary of Adverse Events—Sensitivity Analyses (Excluding Dually- and Triply-enrolled Patients) and Final CSR Results for Study 30078

Parameter	TV-46000 q1m	TV-46000 q2m
Study 30078 final CSR N	N=171	N=160
Patients without dosing-related deviations N	N=152	N=85
Patients without dosing errors N	N=163	N=97
Patients without lack of documentation N	N=153	N=139
Patients with at least 1 adverse event, n (%)		
Study 30078 final CSR	64 (37)	72 (45)
Patients without dosing-related deviations ^a	51 (34)	39 (46)
Patients without dosing errors	59 (36)	50 (52)
Patients without lack of documentation	51 (33)	59 (42)
Patients with any other serious adverse event, n (%)		
Study 30078 final CSR	8 (5)	10 (6)
Patients without dosing-related deviations ^a	7 (5)	7 (8)
Patients without dosing errors	7 (4)	8 (8)
Patients without lack of documentation	7 (5)	10 (7)
Patients with any adverse event leading to discontinuation from treatment, n (%)		
Study 30078 final CSR	3 (2)	5 (3)
Patients without dosing-related deviations ^a	3 (2)	3 (4)
Patients without dosing errors	3 (2)	5 (5)

NDA/BLA Multi-disciplinary Review and Evaluation
NDA 213586: Risperidone extended-release injectable suspension

Patients without lack of documentation	3 (2)	4 (3)
Patients with any adverse event leading to death		
Study 30078 final CSR	2 (1)	1 (<1)
Patients without dosing-related deviations ^a	2 (1)	1 (1)
Patients without dosing errors	2 (1)	1 (1)
Patients without lack of documentation	2 (1)	1 (<1)

Source: Applicant's Summary, Clinical Study Report Addendum 01 – Report Body, Table 13, pages 52, and Applicant's Summary of Safety Tables Adults (SDN 42, eCTD 0042) in response to the Agency's IR dated February 02, 2023.

***Clinical Reviewer's Comment:** When comparing deaths, SAEs, adverse events leading to discontinuation, and AEs in subgroups of patients without dosing-related deviations, patients without dosing errors and patients without lack of documentation, there are no notable differences with the corresponding findings presented of the original NDA safety review of Study 30072. Similarly, there are no differences when comparing with the safety analyses of the complete dataset for Study 30078.*

8.2.6. Analysis of Submission-Specific Safety Issues

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

8.2.7. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

8.2.8. Safety Analyses by Demographic Subgroups

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

8.2.9. Specific Safety Studies/Clinical Trials

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

8.2.10. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

Human Reproduction and Pregnancy

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

Pediatrics and Assessment of Effects on Growth

The pediatric population was not included in the safety analysis.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

8.2.11. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

Expectations on Safety in the Postmarket Setting

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

8.2.12. Integrated Assessment of Safety

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

8.3. Statistical Issues

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022.

There was no major statistical issue identified for this NDA submission.

8.4. Conclusions and Recommendations

Study 30072 was a randomized, double-blind, placebo-controlled relapse prevention study in 543 subjects. The primary efficacy variable, time to impending relapse, was re-analyzed in the ITT analysis set excluding dually- and triply-enrolled patients, and in each of the analysis subsets (patients without dosing-related deviations, patients without dosing errors, patients without significant dosing errors, and patients without lack of documentation). The results of the sensitivity analyses of the primary endpoint in all the analysis subsets based on the stratified

log-rank test were consistent with the originally reported results, showing improved time to relapse for both q1m and q2m over placebo.

The safety of TV-46000 is informed by the LD Risperdal oral tablet. The initial NDA review found that safety findings were similar to that seen with the oral formulation, with the exception of injection site adverse reactions, which are expected for a long-acting injection formulation. Analyses of safety based on the completed dataset for Study 30078 and the audited database demonstrated that the safety profile of TV-46000 was unchanged relative to the profile described in the original NDA review.

We recommend approval for this application.

9 Advisory Committee Meeting and Other External Consultations

The Agency did not refer this marketing application to an advisory committee for review. This drug is not first in its class. Evaluation of the data did not raise significant, unexpected safety or efficacy issues. Therefore, the Agency concluded that outside expertise was not necessary.

10 Pediatrics

As per agreed the iPSP and initial NDA submission, the Applicant had planned to include adolescent patients with schizophrenia 13 to 17 years of age in Studies 30072 and 30078 and requested a partial waiver of PREA requirements for ages birth to 12 years because of the low prevalence of schizophrenia in that age group.

Despite efforts to recruit adolescents to the two phase 3 studies, only four adolescent patients were randomized to receive TV-46000 (three patients were randomized prior to the data cutoff date for the 120-Day Safety Update and one patient was randomized after the data cutoff date). Data collected in adolescents are deemed inadequate to support a pediatric assessment due to the small number of patients enrolled. At the time of the original NDA review, a final determination about granting a full waiver was deferred because the Agency took a complete response action on the application. (For additional information see Section 10 of the original NDA review archived on April 15, 2022.) The Division recommended a full waiver of PREA requirements to PeRC as further studies in adolescents would be unlikely to be successful given the effort the Applicant has made to enroll adolescents (i.e., enrollment of an adequate number of adolescents to support an assessment is not feasible). The PeRC agreed to grant full waiver for pediatrics birth to younger than 18 years of age because necessary studies are impossible or highly impracticable.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

See the following summary of labeling:
HIGHLIGHTS OF PRESCRIBING INFORMATION

- ADVERSE REACTIONS. (b) (4) and replaced with safety data reported in the currently approved label for the LD, except for injection site adverse reactions. The following sentence was added:
“The most common injection site reactions with UZEDY (≥5% and greater than placebo) were pruritus and nodule. (6.1).”

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

UZEDY is indicated for the treatment of schizophrenia in adults. (b) (4)

2 DOSAGE AND ADMINISTRATION

- (b) (4) was removed from the text, given that it was already reported in the (b) (4)
- “Prior to initiating (b) (4) UZEDY” was added to clarify when to establish the tolerability to oral risperidone
- (b) (4) was added for clarity
- “Do not administer more frequently than recommended” was added for clarity.
- The language in the section for dose adjustment for hepatic and renal impairment was modified to be consistent with the LD PI and other risperidone product PI.

3 DOSAGE FORMS AND STRENGTHS

The language in the section was modified to be consistent with the LD PI and other risperidone product PI.

5 WARNINGS AND PRECAUTIONS

- The language in Warning and Precautions was modified to be consistent with the LD PI and other antipsychotic PIs.

- Priapism was added as identified in postmarketing use of other risperidone products. The priapism case from Study 30072 was included.
- Metabolic Changes (Section 5.5), Leukopenia, Neutropenia, and Agranulocytosis (Section 5.9), Potential for Cognitive and Motor Impairment (Section 5.10): (b) (4)
(b) (4)
(b) (4) replaced with safety data reported in the currently approved label for the LD.
- Dysphagia. “Aspiration (b) (4)” was modified to “aspiration” to include all potential pathological conditions and be consistent with more recent second and third generation antipsychotic labels.

6 ADVERSE REACTIONS

- (b) (4)
(b) (4) replaced with the same section of the label for the LD, with the exception of the injection site ARs. This was decided because, in consideration of the (b) (4)
(b) (4)
(b) (4) When reporting frequencies of injection site ARs, we removed adolescents and dually and triply enrolled patients from the safety population.

7 DRUG INTERACTIONS

Language was modified to be consistent with the LD PI and other risperidone products.

8 USE IN SPECIFIC POPULATIONS

- (b) (4)
- Juvenile animal nonclinical data from the LD PI were included.

12 CLINICAL PHARMACOLOGY

(b) (4)

14 CLINICAL STUDIES

NDA/BLA Multi-disciplinary Review and Evaluation
NDA 213586: Risperidone extended-release injectable suspension

- A sentence was added for clarification to explain that efficacy data are based on results obtained from the LD as well as from Study 30072. Efficacy data from Study 30072 were retained in the labeling, (b) (4), to demonstrate effectiveness of UZEDY as compared to placebo.
- The following sentence was removed because it did not describe disposition in detail and can be confusing (b) (4)
(b) (4)
- Figure 1 was revised to clarify Study 30072 results.
- (b) (4)

12 Risk Evaluation and Mitigation Strategies (REMS)

Based on the clinical review, the use of a risk evaluation and mitigation strategy (REMS) does not appear to be necessary. Favorable benefit-risk balance will be maintained through appropriate labeling.

13 Postmarketing Requirements and Commitment

Postmarketing requirements or commitments were not deemed necessary for this product.

14 Signatory (Deputy Division Director) Comments

This review reflects my edits and feedback. I agree with the findings as described by the review team and concur with the approval decision.

15 Appendices

15.1. References

Not applicable

15.2. Financial Disclosure

See the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedry (risperidone extended release injection), archived on April 15, 2022.

15.3. Nonclinical Pharmacology/Toxicology

Not Applicable

15.4. Clinical Pharmacology

15.4.1. Pharmacometrics Review

Applicant's Analysis

The Applicant conducted sensitivity analyses to assess the impact of dosing errors on the robustness of the population pharmacokinetics (popPK) model and subsequently on the safety and efficacy exposure-response (E-R) analysis. PopPK and E-R analyses were performed on the updated datasets which included data flags for dosing errors.

With the sensitivity flags for dosing errors added to the dataset for TV-46000, three subsets of subjects were created (Table 23):

- Subjects with correctly assigned dose and complete dose documentation (subset I)
- Subset I + subjects with corrected erroneous doses (subset II)
- Subset II + subjects with undocumented dosing (subset III)

Table 23. Definition of Terms for Sensitivity Analysis of Investigational Product Dosing Data in Phase 3 Studies

Statistical Analysis Term	Definition	Included in subset		
		I	II	III
No dosing related deviations	No dosing errors or lack of documentation	X	X	X
Dosing related deviations^a				
1. Dosing error	Incorrect treatment and/or high volume and/or low volume relative to the planned dose			
– High volume/dose relative to the planned dose	In Study 30072: if the volume drawn from vials is above the intended volume per stabilization dose In Study 30078: if patient received volume of IP above the intended volume per stabilization dose according to kit number		X	X
– Low volume/dose relative to the planned dose	In Study 30072: if the volume drawn from vials is below the intended volume per stabilization dose In Study 30078: if patient received volume of IP below the intended volume per stabilization dose according to kit number		X	X
– Incorrect treatment	When the actual treatment is different from intended treatment based on randomization (ie, active instead of placebo, placebo instead of active)			X
2. Lack of documentation	In Study 30072, any of the following missing fields: dosing volume, IP kit number, or date of IP administration In Study 30078, any of the following missing fields : kit number for PFS dispensed or missing date of IP administration			X

^a The term significant dosing error, presented in Section 9.7 of the CSR addenda for studies 30072 and 30078, is not applicable to the popPK sensitivity analysis as doses in the popPK analysis were flagged for low/high volume and adjusted based on information provided.

CSR=clinical study report; IP = investigational product; PFS = prefilled syringe; popPK=population pharmacokinetics

Source: *The Applicant's Summary of Clinical Pharmacology, Table 2.*

Sensitivity Analysis

For the sensitivity analyses, subset II was selected as the representative dataset because it had the most complete and accurate dosing information. To identify any clinically meaningful difference between the original and updated popPK models, the primary parameter value estimates, CL and V, of the updated parent and metabolite popPK models were compared to those originally reported.

For the E-R analyses, a predefined threshold of $\pm 20\%$ change in the log-transformed space of the typical value for apparent clearance of parent (CL), apparent clearance of metabolite (CLMO), apparent volume of distribution of parent (V), or apparent volume of distribution of metabolite (VMO) was established as a clinically significant difference in the popPK model. The popPK model was evaluated in a sequential manner. Initially, the parameter estimates for the parent model were compared to the original values, and after fitting the parent popPK model, the metabolite model was updated using the new post-hoc parameters of the parent model. Finally, the resulting parameter estimates for the metabolite model were compared to the values in the original report.

After applying the updated sequential parent-metabolite model, individual exposure estimates for the derived parameters of $C_{avg,ss}$, $C_{max,ss}$, and $C_{trough,ss}$ were computed and then compared to the values in the original report.

Analysis of dosing related deviations

Dosing-related deviations were summarized by treatment group (Table 24). A summary of subjects and pk measurements included in the popPK analysis are provided in Table 25.

Table 24. Data in the Original Dataset and Number of Errors and Stratification for Subjects Administered with TV-46000

STUDY	Total subjects n	Total doses ^a n	Confirmed doses with no errors ^b n	Erroneous doses corrected ^c n	Doses unconfirmed ^d n	% erroneous doses corrected	% doses unconfirmed
TV46000-SAD-10055	97	139	139	0	0	0	0
RISPE1ZG15EU	50	50	50	0	0	0	0
Study 30072	353 ^e	2695	2190	72	433	2.7	16.1
Study 30078	74 ^{fg}	300	263	4	33	1.3	11.0
TV46000-BA-10148	120	120	120	0	0	0	0
Overall	694	3304	2762	76	466	2.3	14.1

^a Total dosing administrations.

^b Confirmed doses are the same as doses with complete documentation.

^c Doses flagged as having either a too low or too high volume administered were corrected.

^d Unconfirmed doses are the same as undocumented doses.

^e SUBJID (b) (6) had only below the lower assay limit of quantification (BLQ) observations and no concentrations above lower limit of quantification (LLOQ).

^f SUBJID (b) (6) had only BLQ observations and no concentrations above LLOQ.

^g Of the total number of patients enrolled to 30078, 74 patients are presented here to match the number presented in the original NDA submission at which time Study 30078 was still ongoing.

n=number.

Source: The Applicant's popPK report addendum, Table 3, Table 4 and Table 5.

Table 25. Summary of Subjects and Pharmacokinetic Measurements Included in the Population Pharmacokinetic Analysis for Subjects Administered with TV-46000

Analysis	Subjects ^a	Subjects from Phase 3 ^b	Observations Risperidone	Observations 9-OH risperidone
Original	692 ^c	425	12,452	12,468
Subset I	583	316	11,375	11,393
Subset II	611	344	11,525	11,542
Subset III	690	423	12,423	12,441

^a Duplicate and triplicate patients were excluded from the original data base.

NDA/BLA Multi-disciplinary Review and Evaluation
NDA 213586: Risperidone extended-release injectable suspension

^b the number of patients from phase 3 studies was calculated as (total number of enrolled subjects)-(total number of phase 1 enrolled subjects). The total of phase 1 enrolled patients is 267.

^c SUBJID (b) (6) and SUBJID (b) (6) had only BLQ observations and no concentrations above LLOQ and were therefore not included in this summary.

Source: The Applicant's popPK report addendum, Table 6.

PopPK Analysis

The final popPK analysis dataset included 12830 measurable PK parent observations and 12810 measurable PK metabolite observations from 694 subjects. In the popPK analysis of subset II, 11566 PK parent observations and 11589 PK metabolite observations from 646 subjects were analyzed. A nonlinear mixed effects modeling approach with the first-order conditional estimation with interaction (FOCEI) method in NONMEM, version 7.4.3. (b) (4) was used for the PopPK analysis.

PopPK Analysis for Parent Drug

The popPK model was rerun with the updated TV-46000 dataset. Comparison of key primary parameter estimates between the originally reported parent model and the rerun of the updated dataset based on the identified dosing errors for all three subsets are presented Table 26.

Table 26. Comparison of Key Primary Parameters of the Parent Population Pharmacokinetic Model Based on the Original and Updated Datasets

Key primary parameters	Parameter	Original dataset	Estimates based on updated dataset		
			Subset I	Subset II	Subset III
CL (L/h)	Estimate (%RSE)	14.3 (2.9)	14.2 (3.5)	14.2 (3.6)	14.3 (3.0)
	95% CI	13.4-15.1	13.3-15.2	13.2-15.2	13.4-15.1
V (L)	Estimate (%RSE)	66.3 (4.4)	66.2 (4.3)	66.2 (4.8)	66.3 (4.4)
	95% CI	60.6-71.9	60.7-71.8	60.0-72.3	60.6-72.0

CI=confidence interval; CL=apparent clearance; RSE=relative standard error; V=apparent volume of distribution parent.

Source: The Applicant's popPK report addendum, Table 14, Table 26 and Table 28.

Table 27 displays a comparison of the percent difference of primary estimates between originally reported and their re-run values for three subsets. The popPK model was re-run on these subsets, and the resulting differences for CL and V were up to 0.23% and up to 0.03%, respectively.

Table 27. The %Difference between 3 Subsets Compared to the Originally Reported Primary Estimates

Parameter	Original parameter value	Subset I difference ^a	Subset II difference	Subset III difference
CL	14.26	-0.09%	-0.23%	0.08%
V	66.26	-0.02%	-0.03%	0.01%

CL=apparent clearance parent; V=apparent volume of distribution.

^a Difference (for all subsets) is calculated using the following equation: difference=100-(log(original parameter value)/log(subset parameter value))x100.

Source: The Applicant's popPK report addendum, Table 17.

Table 28 presents a comparison between the parameter estimates of the parent model as originally reported and the updated parameter estimates obtained from a re-run with the adjusted dataset. The adjustments were made based on the dosing-related deviations identified for subset II.

Table 28. Model Parameter Estimates for TV-46000 Parent PK – Subset II

Parameter	Originally Reported Parameter Estimates			Updated Parameter Estimates (Subset II)		
	Estimates	%RSE	95%CI	Estimates	%RSE	95%CI
CL [L/h]	14.3	2.9	13.4-15.1	14.2	3.6	13.2-15.2
V [L]	66.3	4.4	60.6-71.9	66.2	4.8	60.0-72.3
KA2 [1/h]	0.000408	9.9	0.000329-0.000486	0.000395	5.4	0.000354-0.000437
KTR [1/h]	0.0252	4.8	0.0228-0.0275	0.0252	4.5	0.0230-0.0274
KA1 [1/h]	0.000632	3.6	0.000588-0.000676	0.000635	2.9	0.000599-0.000671
KA1ADMSITE1	0.331	34.2	0.109-0.553	0.328	30.7	0.131-0.525
KA1BMI1	-1.1	16.6	-1.46;-0.745	-1.26	9.4	-1.49;-1.03
KA1INJV1	-0.384	11.3	-0.469;-0.298	-0.372	13.2	-0.468;-0.276
KA2BMI1	1.7	21.3	0.992-2.41	1.8	7.2	1.54-2.05
Random effects	Estimates (%CV)	%RSE [%Shrinkage]	95%CI	Estimates (%CV)	%RSE [%Shrinkage]	95%CI
IIV on KA2 [%]	254.2	5.2 [25.8]	198.8-320.1	268.8	4.5 [25.6]	215.4-330.8
Correlation IIV KA2 and KA1 [%]	42.8	14.7		40.1	16.5	
IIV on KA1 [%]	51.0	6.0 [32.7]	44.0-57.5	50.0	5.7 [30.5]	43.6-56.0
IIV on CL [%]	82.3	3.3 [6.6]	75.3-89.3	82.1	3.6 [6.3]	74.7-89.5
Residual error	Estimates	%RSE [%Shrinkage]		Estimates	%RSE [%Shrinkage]	
EP [%]	40.5	2.3 [5.8]		38.2	4.5 [5.6]	

KA1ADMSITE1 = administration site effect on KA1; KA1BMI1 = body mass index effect on KA1; KA2BMI1 = body mass index effect on KA2; CI = confidence interval; CL = apparent clearance; CV = coefficient of variation; EP = proportional residual error; IIV = inter-individual variability; KA1INJV1 = injection volume effect on KA1; KA1 = absorption rate constant 1; KA2 = absorption rate constant 2; KTR = transit rate constant; RSE = relative standard error; V = apparent volume of distribution parent.

Note: CV was calculated as $CV = \sqrt{e^{\omega^2} - 1}$.

Source: The Applicant's popPK report, Table 19 and popPK report addendum, Table 15.

PopPK Analysis for Metabolite

The popPK model for metabolite was re-run with the updated TV-46000 dataset. Comparison of key primary parameter estimates between the originally reported metabolite model and the re-run of the updated dataset based on the identified dosing errors for all three subsets are presented in Table 29.

Table 29. Comparison of Key Primary Parameters of the Metabolite Population Pharmacokinetic Model Based on the Original and Updated Datasets

Key primary parameters	parameters	Originally reported model	Updated dataset with different subset scenario		
			Subset I	Subset II	Subset III
CLMO (L/h)	Estimate (%RSE)	5.78 (2.3)	5.73 (2.5)	5.73 (2.5)	5.77(2.3)
	95% CI	5.5-6.0	5.5-6.0	5.5-6.0	5.5-6.0
VMO (L)	Estimate (%RSE)	95.7 (3.8)	96.1 (3.8)	96.1 (3.8)	95.7 (3.8)
	95% CI	88.5-103.0	89.0-103.0	89.0-103.0	88.6-103.0

CI=confidence interval; CLMO=apparent clearance metabolite; RSE=relative standard error; VMO= apparent volume of distribution of metabolite.

Source: The Applicant's popPK report addendum, Table 16, Table 27 and Table 29.

Table 30 displays a comparison of the %difference of primary estimates between originally reported and their rerun values for three subsets. The popPK model was re-run on these subsets, and the resulting differences for CLMO and VMO were up to -0.49% and up to 0.10%, respectively.

Table 30. Subset Comparison for the % Difference from Original Metabolite Model to the Updated Model

Parameter	Original parameter value	Subset I difference ^a	Subset II difference	Subset III difference
CLMO	5.78	-0.49%	-0.47%	-0.13%
VMO	95.71	0.10%	0.08%	0.01%

^a Difference for all subsets is calculated using the following equation: difference=100-(log(original parameter value)/log(subset parameter value))x100. CLMO=apparent clearance metabolite; popPK=population pharmacokinetics; VMO=apparent volume of distribution metabolite.

Source: The Applicant's popPK report addendum, Table 17.

Table 31 presents a comparison between the parameter estimates of the metabolite model as originally reported and the updated parameter estimates obtained from a re-run with the adjusted dataset. The adjustments were made based on the dosing-related deviations identified for subset II.

Table 31. Model Parameter Estimates for TV-46000 Metabolite PK – Subset II

Originally Reported Parameter Estimates				Updated Parameter Estimates (Subset II)		
Parameter	Estimates	%RSE	95%CI	Estimates	%RSE	95%CI
CLMO [L/h]	5.78	2.322	5.52-6.04	5.73	2.5	5.46-6.01
VMO [L]	95.7	3.822	88.5-103	96.1	3.8	89.0-103.0
Random effects	Estimates (%CV)	%RSE [%Shrinkage]	95%CI	Estimates (%CV)	%RSE [%Shrinkage]	95%CI
IIV on CLMO [%]	65.1	4.0 [5.5]	58.9-71.1	65.2	4.4 [5.3]	58.5-71.7
Residual error	Estimates	%RSE [%Shrinkage]		Estimates	%RSE [%Shrinkage]	
EP [%]	38.3	2.0 [2.7]		36.9	4.3 [2.4]	

CI = confidence interval; CL = apparent clearance; CV = coefficient of variation; EP = proportional residual error; IIV = inter-individual variability; PK = pharmacokinetic; RSE = relative standard error; VMO = apparent volume of distribution.

Note: CV was calculated as $CV = \sqrt{e^{\omega^2} - 1}$.

Source: The Applicant's popPK report, Table 21 and popPK report addendum, Table 17.

Exposure-Response Analysis

The Applicant updated E-R analysis using exposure metrics derived from subset II. This analysis incorporated a total of 523 subjects, comprising 179 who received a placebo and 344 who received TV-46000 treatment. In comparison, the original analysis included 604 subjects, with 179 receiving a placebo and 425 receiving TV-46000 treatment.

The exposure parameters utilized are $C_{avg,ss}$, $C_{max,ss}$, and $C_{trough,ss}$ in the updated E-R analysis. The exposure levels were split into four quartiles of equal size based on the distribution of the metric for the exploratory analysis (Table 32).

Table 32. Summary Statistics of Total Active Moiety Metrics Based on Final PopPK Models per Exposure Quartiles for Original and Updated Datasets for Subset II

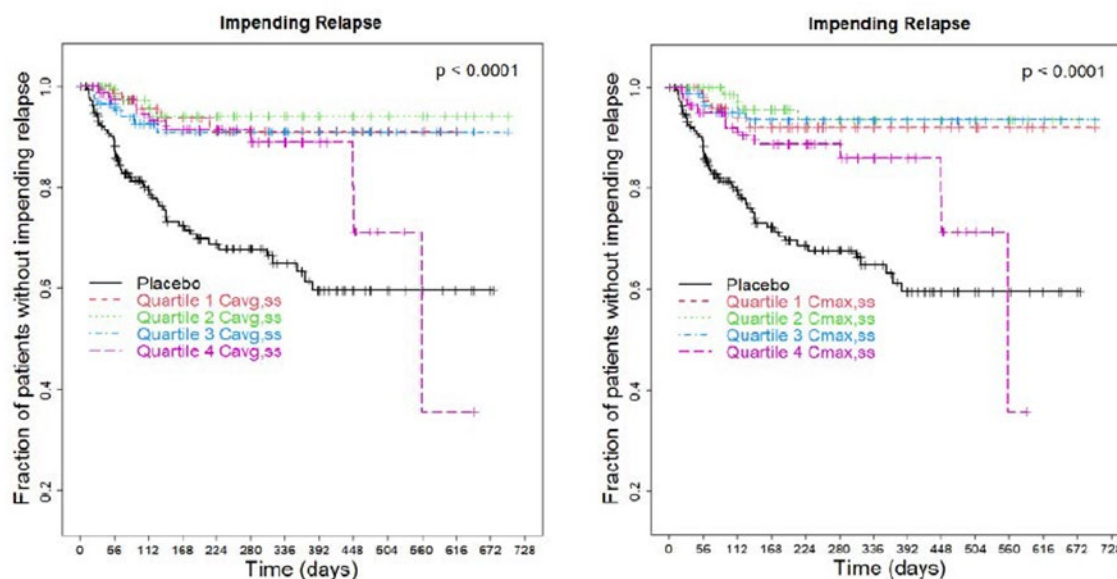
Median [Min, Max]				
Quartile	Dataset (N)	$C_{avg,ss}$ (ng/mL)	$C_{max,ss}$ (ng/mL)	$C_{trough,ss}$ (ng/mL)
1	Original (107)	15.4 [3.6-20.3]	20.3 [5.0-27.3]	5.7 [0.3-10.1]
	Updated (86)	15.3 [3.4-20.0]	20.0 [4.9-27.1]	5.7 [0.3-10.1]
2	Original (106)	25.4 [20.3-30.9]	34.2 [27.4-42.1]	13.3 [10.2-16.7]
	Updated (86)	25.3 [20.1-30.2]	34.1 [27.4-41.4]	13.3 [10.2-16.4]
3	Original (106)	38.0 [31.0-45.7]	51.4 [42.1-63.1]	22.4 [16.9-29.0]
	Updated (86)	38.2 [30.3-45.6]	50.3 [41.6-62.0]	22.6 [16.5-28.8]
4	Original (106)	62.4 [46.3-168]	89.7 [63.2-308.0]	39.6 [29.1-140.0]
	Updated (86)	61.3 [46.3-169]	92.5 [62.0-314.0]	40.5 [29.0-142.0]

NDA/BLA Multi-disciplinary Review and Evaluation
NDA 213586: Risperidone extended-release injectable suspension

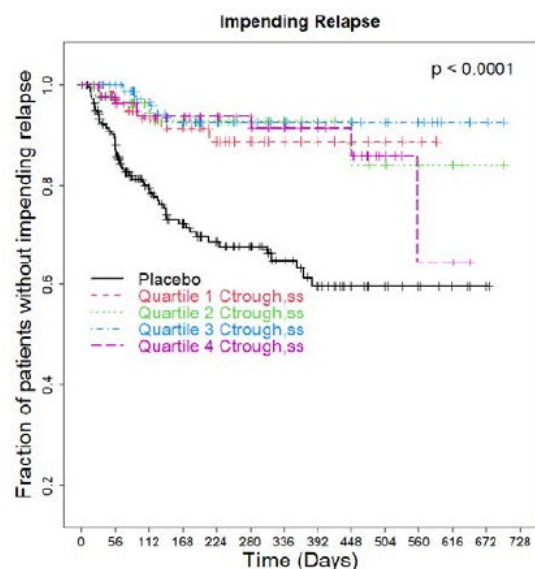
Cavg,ss=average plasma drug concentration during the dosing interval at steady state; Cmax,ss=maximum plasma drug concentration at steady state; Ctrough,ss=trough plasma drug concentration; E-R=exposure-response; Max=maximum; Min=minimum; N=number; PopPK=population pharmacokinetics; TAM=total active moiety.
Source: The Applicant's E-R addendum, Table 2 and Table 3.

To explore the impending relapse E-R trends, the Applicant generated Kaplan-Meier plots stratified by TV-46000 treatment, treatment frequency and total active moiety exposure parameters. Similar to the original analysis, a notable difference in the impending relapse rate was observed for patients treated with TV-46000 (q1m and q2m) compared to placebo (Figure 3) using the updated datasets. No trend was observed within the different quartiles stratified by TV-46000 exposure parameters, Cavg,ss, Cmax,ss and Ctrough,ss. In general, all quartiles of TV-46000 exposure overlapped throughout the observation period.

Figure 3. Kaplan-Meier Plots for Occurrence of Impending Relapse up to 2 Years, Comparing Placebo and Exposure Quartiles for Cavg,ss, Ctrough,ss and Cmax,ss in Subset II



NDA/BLA Multi-disciplinary Review and Evaluation
NDA 213586: Risperidone extended-release injectable suspension



Cavg,ss=average observed plasma drug concentration at steady state; Cmax,ss=maximum observed plasma drug concentration at steady state; Ctrough,ss=trough plasma drug concentration at steady state; E-R=exposure-response; p=significance value.

Source: The Applicant's E-R addendum, Figure 7.

OCP Reviewer's Comment: Overall, the Applicant's sensitivity analyses indicate that the primary parameters were comparable between the original and updated datasets. The E-R analysis using updated subset II from the Phase 3 studies (Study 30072 and Study 30078) demonstrated comparable outcome to the original analyses. Since the sensitivity analysis of the popPK and E-R did not reveal any noteworthy disparities, it can be inferred that the original review (the NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022) is still applicable.

Reviewer's Analysis

Methods

Data sets used are summarized in Table 33.

Table 33.34 Analysis Data Sets

Study	Name	Link to EDR
TV46000-SAD-10055; RISPE1ZG15EU; CNS-30072; CNS-30078; BA-10148	tv46000poppk20220819-outlier-run006-run014.csv	\\CDSESUB1\EVSPROD\nda213586\0044\m5\datasets\cp-18-11-subset-ii\legacy\datasets\tv46000poppk20220819-outlier-run006-run014.csv
	tv46000poppk20220819-ph-run020-outlier-051-054.csv	\\CDSESUB1\EVSPROD\nda213586\0044\m5\datasets\cp-18-11-subset-ii\legacy\datasets\tv46000poppk20220819-ph-run020-outlier-051-054.csv

Software

Population PK model fitting was performed in NONMEM 7.4.3 and Pirana 2.9.9. Primary analysis and plotting were performed in R 4.1.2.

Results

The reviewer was able to replicate the Applicant's popPK results using NONMEM, and no significant inconsistencies were observed.

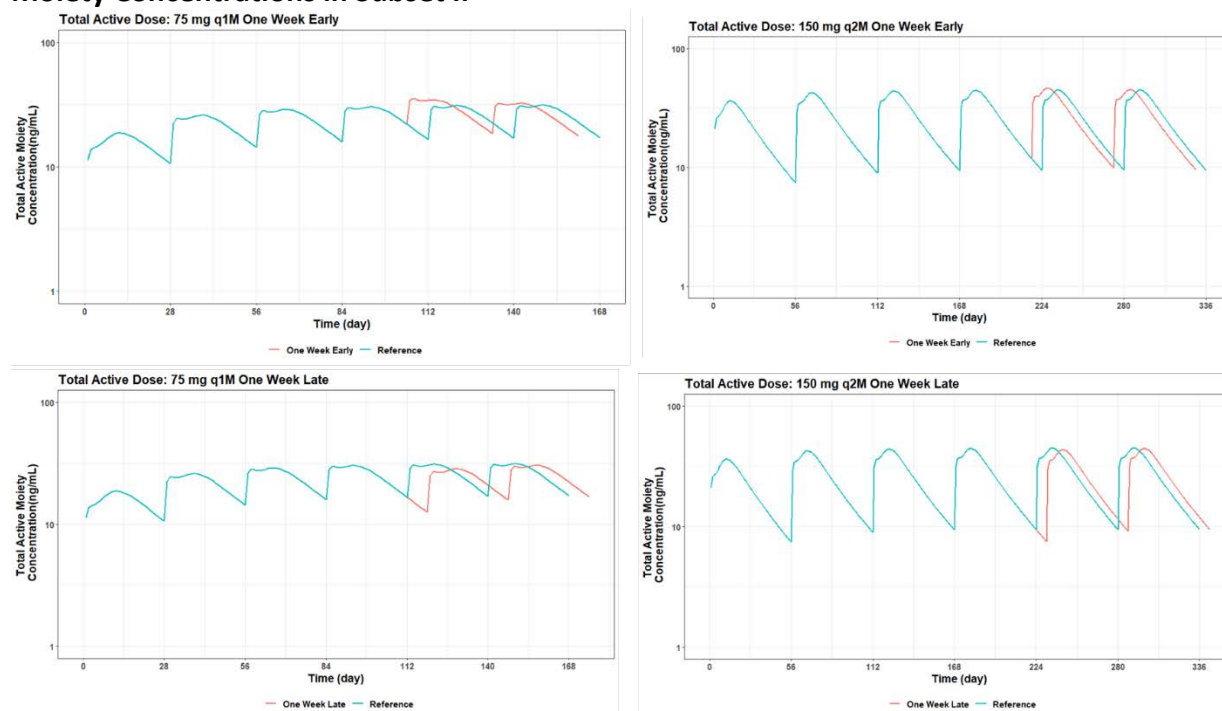
Switchability between Q1M and Q2M

Given no significant discrepancies were found in the sensitivity analysis of the popPK, refer to original Clinical Pharm review (NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022) for additional information.

Early or Late Dose Evaluation

The reviewer conducted a simulation to evaluate the impact of early or late dosing using the updated dataset. Based on simulation results, deviations from the defined dosing interval can be managed with flexibility, as the impact on total active moiety exposure due to administering the subsequent dose early or late (within ± 1 week for q1m and q2m) is anticipated to be negligible (Figure 4). The conclusion is in accordance with the previous evaluation (NDA Multi-disciplinary Review and Evaluation for NDA 213586, Uzedly (risperidone extended release injection), archived on April 15, 2022: Section 6.3.1).

Figure 4. Impact of Early or Late TV-46000 Administration of the Next Dose on Total Active Moiety Concentrations in Subset II



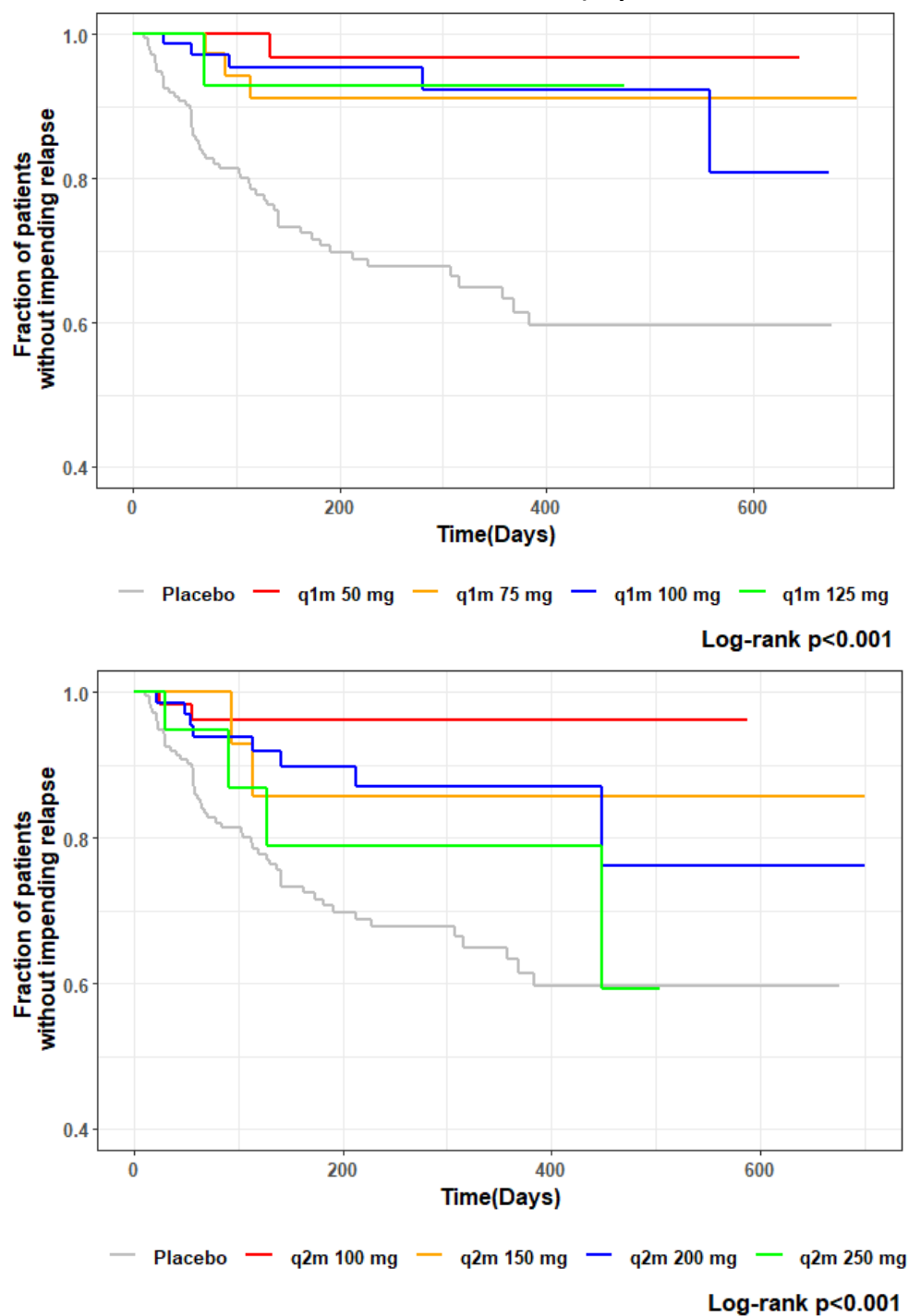
q1m = once monthly; q2m = once every 2 months.

Source: Reviewer's Analysis.

Dose Response Analysis

The reviewer performed a dose-response analysis to confirm the Applicant's analysis on impending relapse E-R trends (Figure 5).

Figure 5. Kaplan-Meier Plots for Occurrence of Impending Relapse up to 2 Years, Comparing Placebo and Different Doses Levels in Subset II (Top Panel: Q1m, Bottom Panel: Q2m)



Source: Reviewer's Analysis.

Listing of Analyses Codes and Output Files

File Name	Description	Location
Risperidone LAI pk analysis. R	PK and popPK analysis file	\\NDA213586 Risperidone LAI\FDA Review\PK\Rscript

15.5. Additional Clinical Outcome Assessment Analyses

Not Applicable

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BERNARD A FISCHER
04/28/2023 01:10:46 PM

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
 Uzedy (risperidone extended release injection)

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2) NDA
Application Number(s)	213586
Priority or Standard	Standard
Submit Date(s)	June 17, 2021
Received Date(s)	June 17, 2021
PDUFA Goal Date	April 17, 2022
Division/Office	Division of Psychiatry / Office of Neuroscience
Review Completion Date	4/15/2022
Established/Proper Name	Risperidone Extended Release, Injection
(Proposed) Trade Name	Uzedy
Pharmacologic Class	Atypical Antipsychotic
Code name	TV-46000
Applicant	Teva Neuroscience Inc.
Dosage form	Prefilled syringes
Applicant proposed Dosing Regimen	50 mg, 75 mg, 100 mg, 125 mg one injection once monthly or 100 mg, 150 mg, 200 mg, 250 mg once every two months
Applicant Proposed Indication(s)/Population(s)	Schizophrenia
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	58214004 Schizophrenia (disorder)
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	N/A
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	N/A
Recommended Dosing Regimen	N/A

Table of Contents

Table of Tables	5
Table of Figures	7
Reviewers of Multi-Disciplinary Review and Evaluation	8
Glossary	9
1 Executive Summary	11
1.1. Product Introduction	11
1.2. Conclusions on the Substantial Evidence of Effectiveness	11
1.3. Benefit-Risk Assessment	12
1.4. Patient Experience Data	18
2 Therapeutic Context	21
2.1. Analysis of Condition	21
2.2. Analysis of Current Treatment Options	22
3 Regulatory Background	25
3.1. U.S. Regulatory Actions and Marketing History	25
3.2. Summary of Presubmission/Submission Regulatory Activity	25
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety	28
4.1. Office of Scientific Investigations (OSI)	28
4.2. Product Quality	28
4.3. Clinical Microbiology	29
4.4. Devices and Companion Diagnostic Issues	29
5 Nonclinical Pharmacology/Toxicology	30
5.1. Executive Summary	30
5.2. Referenced NDAs	33
5.3. Pharmacology	33
5.4. ADME/PK	34
5.5. Toxicology	36
5.5.1. General Toxicology	37
5.5.2. Genetic Toxicology	51
5.5.3. Carcinogenicity	52
5.5.4. Reproductive and Developmental Toxicology	52
5.5.5. Other Toxicology Studies	52
5.5.6. Qualification of the inactive ingredients	54
6 Clinical Pharmacology	56

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
 Uzedy (risperidone extended release injection)

6.1.	Executive Summary	56
6.2.	Summary of Clinical Pharmacology Assessment.....	57
6.2.1.	Pharmacology and Clinical Pharmacokinetics.....	58
6.2.2.	General Dosing and Therapeutic Individualization	61
6.3.	Comprehensive Clinical Pharmacology Review.....	63
6.3.1.	Clinical Pharmacology Questions.....	63
7	Sources of Clinical Data and Review Strategy	75
7.1.	Table of Clinical Studies	75
7.2.	Review Strategy	82
8	Statistical and Clinical and Evaluation	83
8.1.	Review of Relevant Individual Trials Used to Support Efficacy	83
8.1.1.	Study TV-46000-CNS-30072	83
8.1.2.	Study Results of TV-46000-CNS-30072	95
8.1.3.	Assessment of Efficacy Across Trials.....	110
8.1.4.	Integrated Assessment of Effectiveness	110
8.2.	Review of Safety	110
8.2.1.	Safety Review Approach.....	110
8.2.2.	Review of the Safety Database	112
8.2.3.	Adequacy of Applicant’s Clinical Safety Assessments	113
8.2.4.	Safety Results	115
8.2.5.	Analysis of Submission-Specific Safety Issues	125
8.2.6.	Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability	127
8.2.7.	Safety Analyses by Demographic Subgroups	127
8.2.8.	Specific Safety Studies/Clinical Trials.....	128
8.2.9.	Additional Safety Explorations.....	128
8.2.10.	Safety in the Postmarket Setting.....	129
8.2.11.	Integrated Assessment of Safety.....	129
8.3.	Statistical Issues.....	130
8.4.	Conclusions and Recommendations	130
9	Advisory Committee Meeting and Other External Consultations	131
10	Pediatrics	132
11	Labeling Recommendations.....	134
11.1.	Prescription Drug Labeling	134
12	Risk Evaluation and Mitigation Strategies (REMS)	135
13	Postmarketing Requirements and Commitment	136

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586

Uzedy (risperidone extended release injection)

14	Division Director (Clinical) Comments.....	137
15	Appendices	138
15.1.	References	138
15.2.	Financial Disclosure.....	140
15.3.	OCP Appendices (Technical documents supporting OCP recommendations)	141
15.3.1.	Bioanalytical Method Validation	141
15.3.2.	Summary of clinical pharmacology studies	143
15.3.3.	Pharmacometric Review	158

Table of Tables

Table 1. Summary of Long-Acting Injectable Antipsychotics Currently Available in the United States	23
Table 2. Composition of the drug product and vehicle batches used in the nonclinical toxicology studies in comparison to the clinical/commercial batches	37
Table 3. Pharmacokinetics Parameter Values (Mean [CV%]) for Total Active Moiety Following a Single Subcutaneous Administration of TV-46000 at 50 mg/minipig	49
Table 4: TV-46000 Dosage Selection Guide	61
Table 5: Summary of Pharmacokinetic Parameters for Multiple Doses of TV-46000 75 mg and 150 mg Versus Oral Risperidone 3 mg and 5 mg.....	63
Table 6: Median Total Active Moiety Pharmacokinetic Parameters for TV-46000 (Model Predicted) and for Oral Risperidone (Observed, Simulated, and Literature Reported Values) ...	64
Table 7: Comparison of Total Active Moiety Pharmacokinetic Parameters by Subcutaneous Injection Site	65
Table 8: Relative Bioavailability of TV-46000 PFS as Compared to TV-46000 Vial	69
Table 9: Median Total Active Moiety Pharmacokinetic Parameters for TV-46000 Dosing Regimens (Model Simulated)	71
Table 10: Number of Patients and Incidence of Efficacy Endpoints by Study and Treatment Group for Patients Included in the Efficacy Exposure-Response Analysis	71
Table 11: Comparison of Injection Site Manipulation on Total Active Moiety Exposure Following a Single Subcutaneous Dose of TV-46000 (Study RISPE1ZG15EU)	74
Table 12. Listing of Clinical Trials for TV-46000	75
Table 13. Conversion Table Between Oral Risperidone and TV-46000 Doses	86
Table 14. Schedule of Assessments for Study TV-46000-CNS-30072	88
Table 15. Summary of Analysis Sets (All Subjects)	96
Table 16. Disposition of Subjects (ITT Analysis Set).....	96
Table 17. Demographic characteristics of the ITT analysis set	99
Table 18. Baseline Disease Characteristics (e.g., disease characteristics, important concomitant drugs, ITT analysis set)	100
Table 19. Therapeutic Classification of Concomitant Medications – Stage 2 (ITT Analysis Set)	101
Table 20. Primary Efficacy Results: Time to Impending Relapse (Study TV-46000-CNS-30072, ITT analysis set).....	104
Table 21. Statistical Reviewer’s Supplementary Analyses	106
Table 22. Secondary/Exploratory Endpoints (ITT Analysis Set)	107
Table 23. Subgroup analysis.....	108
Table 24. Safety Population for TV-46000 Development	112
Table 25.Exposure to TV-46000 (Study TV-46000-CNS-30072)	113
Table 26. Exposure to TV-46000 (Study TV-46000-CNS-30078)	113
Table 27. Serious adverse events (Study TV-46000-CNS-30072).....	117
Table 28.Serious adverse events (Study TV-46000-CNS-30078).....	118
Table 29.Discontinuations due to adverse events (Study TV-46000-CNS-30072)	119
Table 30. Most common TEAEs (>2%, TV-46000>Placebo) (Study TV-46000-CNS-30072)	120

Table 31. Shift in prolactin level (Study TV-46000-CNS-30072).....	122
Table 32. Injection Site Adverse Events (Study TV-46000-CNS-30072)	125
Table 33. Adverse Events Of Special Interest (Only >2% Reported) (Study TV-46000-CNS-30072)	126
Table 34. Proportion of Patients with Fasting Triglycerides <150 mg/dL and Shifts to ≥200 mg/dL by Treatment Group (Study TV-46000-CNS-30072)	127
Table 35. Proportion of Adult Patients with Fasting Glucose <100 mg/dL and Shifts to ≥126 mg/dL by Treatment Group (Study TV-46000-CNS-30072)	127
Table 36. Dose-dependent analysis of adverse reactions (Study TV-46000-CNS-30072 and Study TV-46000-CNS-20078).....	128
Table 37. Overview of Validated Bioanalytical Assays Used in TV-46000 Clinical Studies.....	141
Table 38. Summary of Method Validation for Analysis of Risperidone and 9-OH-Risperidone by RP-LC-MS/MS in Human K2EDTA Plasma	142
Table 39: Geometric Mean (%CV) Total Active Moiety Plasma Pharmacokinetic Parameters from Cohorts C to G, Following a Single 12.5 mg or 25 mg Subcutaneous Dose of TV-46000	143
Table 40: Study 10055 Treatment Allocation Scheme.....	145
Table 41: Geometric Mean (%CV) Total Active Moiety Plasma Pharmacokinetic Parameters for Oral Risperidone (Study 10055)	146
Table 42: Geometric Mean (%CV) Total Active Moiety Plasma Pharmacokinetic Parameters by Dose Following a Single Subcutaneous TV-46000 Dose	148
Table 43: Geometric Mean (%CV) Total Active Moiety Plasma Pharmacokinetic Parameters by Dose Following Multiple TV-46000 75 mg and 150 mg Subcutaneous Doses	150
Table 44: Comparison of Systemic Exposure by TV-46000 Dosing Interval	151
Table 45: Summary of Pharmacokinetic Parameters for Multiple Doses of TV-46000 75 mg and 150 mg Versus Oral Risperidone 3 mg and 5 mg.....	151
Table 46: Geometric Mean (%CV) Total Active Moiety Plasma Pharmacokinetic Parameters by Treatment Group (TV-46000 PFS, TV-46000 Vial) for Pharmacokinetic Evaluable Patients (Primary Analysis Dataset)	153
Table 47: Geometric Mean (%CV) Total Active Moiety Plasma Pharmacokinetic Parameters by Treatment Group (TV-46000 PFS, TV-46000 Vial) for Pharmacokinetic Evaluable Patients (Ad- hoc Analysis Dataset)	154
Table 48: Selected Pharmacokinetic Parameters of TV-46000 by Treatment Group Compared to Oral Risperidone Tablets for the Primary and Ad-hoc Datasets	157
Table 49: Summary of studies included in the population PK analysis.....	158
Table 50: Summary of Demographics in the Population PK Development Dataset.....	160
Table 51: Summary of Laboratory Parameters in the Population PK Development Dataset.....	161
Table 52: Final Model Parameter Estimates for TV-46000 Parent PK.....	168
Table 53: Final Model Parameter Estimates for TV-46000 Metabolite PK	168
Table 54: Analysis Data Sets.....	170

Table of Figures

Figure 1: Risperidone (Parent) and 9-OH-Risperidone (Metabolite) - Apparent Clearance Stratified by Poor and Non-Poor CYP2D6 Metabolizer Status.....	61
Figure 2: Risperidone Final Model - Stratified by Administration Site.....	66
Figure 3: Comparison of Injection Site on Total Active Moiety Exposure.....	66
Figure 4: Scatter Plot of TV-46000 PFS and TV-46000 Vial Total Active Moiety AUC _{0-84d} (Primary Dataset and Ad-hoc Dataset).....	68
Figure 5: Impact of Early or Late TV-46000 Administration of the Next Dose on Total Active Moiety Concentrations	70
Figure 6: Impact of interchange of q1m and q2m dosing regimen on the Total Active Moiety Exposure	72
Figure 7 : Mean ($\pm$ SD) Plasma Total Active Moiety Concentrations (ng/mL) for Cohort C (TV-46000 12.5 mg; no rubbing) and Cohort G (TV-46000 12.5 mg; rubbing) Presented on a Linear Scale.....	74
Figure 8. Study Schema	85
Figure 9. Kaplan-Meier Estimation of Percent of Impending Relapse by Treatment Group (ITT Analysis Set)	105
Figure 10: Mean ($\pm$ SD) Plasma Total Active Moiety Concentrations (ng/mL) Following TV-46000 Single Subcutaneous Dose Administration.....	147
Figure 11: Box Plot of TV-46000 Vial, TV-46000 PFS, TV-46000 Vial + PFS for AUC _{0-∞} and of Oral Risperidone for AUC _{0-28d} , calculated (Total Active Moiety) for Primary and Ad-hoc datasets...	156
Figure 12: Final PopPK Model Schematic for Risperidone.....	162
Figure 13: Final PopPK Model Schematic for Metabolite (9-OH Risperidone).....	163
Figure 14: Goodness-of-fit plots for Final PopPK Model for Risperidone	164
Figure 15: Goodness-of-fit plots for Final PopPK Model for 9OH-Risperidone.....	165
Figure 16: Prediction-corrected Visual Predictive Check per Study for the Final Parent Model	166
Figure 17: Prediction-corrected Visual Predictive Check per Study for the Final Metabolite Model.....	167
Figure 18: Dose-Normalized Risperidone Concentration Versus Time After Dose by Study	171
Figure 19 : Dose-Normalized 9-OH Risperidone Concentration Versus Time After Dose by Study	172
Figure 20: Individual Random Effects versus Weight, BMI and Age for Final PopPK Models	172
Figure 21 : Individual Random Effects versus Sex, Race, CYP2D6 Metabolizer Status and for Final PopPK Models	173

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OSE/DRISK	N/A

OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
APA	American Psychiatric Association
AR	adverse reaction
BMI	Body mass index
BP	Blood pressure
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CGI-SS	Clinical Global Impression-Severity of Suicidality
CMC	chemistry, manufacturing, and controls
COPD	chronic obstructive pulmonary disease
CRO	clinical research organization
CSR	clinical study report
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCTD	electronic common technical document
eITT	extended intent-to-treat
EoT	End of Treatment
ET	early termination
FDA	Food and Drug Administration
GCP	good clinical practice
HR	hazard ratio
ICF	Informed Consent Form
IM	intramuscular
IND	Investigational New Drug
IP	Investigational Product
ITT	intent to treat
LD	listed drug
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NDA	new drug application
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PANSS	Positive and Negative Syndrome Scale
PD	pharmacodynamics

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
Uzedy (risperidone extended release injection)

PFS	prefilled syringes
PH	proportional hazard
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per-protocol
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	Preferred Term
q1m	one monthly
q2m	once every two months
q3m	once every three months
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
sc	subcutaneous
SCID-5	Structured Clinical Interview for DSM-5
TAM	total active moiety
TEAE	treatment emergent adverse event
ULN	upper limit of the normal range

1 Executive Summary

1.1. Product Introduction

The Applicant has developed risperidone extended-release injectable suspension for subcutaneous (sc) use (TV-46000) for the treatment of schizophrenia in adults. It is an atypical antipsychotic designed to be an alternative to current oral and parenteral formulations of risperidone with a once monthly or once every two month dosing interval. The first risperidone product was approved in 1993 for the treatment of schizophrenia in adults; risperidone products are currently available in the United States and internationally in multiple dosage forms. The proposed dosage strengths are 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 200 mg, and 250 mg of risperidone, each provided in a single-dose prefilled syringe.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness was not demonstrated. An adequate scientific bridge was established to rely in part on the previous Agency finding of efficacy for the listed drug (LD) Risperdal. However, a clinical efficacy study is necessary to demonstrate the efficacy of TV-46000, and the data from clinical study TV-46000-CNS-30072 in patients with schizophrenia, which evaluated the efficacy of the q1 month and q2 month dosing regimens compared to placebo, cannot be relied upon because the dosing data could not be verified. In order to determine whether the data from this study can be relied upon, the Applicant needs to submit results of an independent third party audit or post-study monitoring by the sponsor/ Clinical Research Organization (CRO) for all sites and all subjects to determine the extent of investigational product (IP) dosing errors and lack of IP dose documentation. Alternatively, a new clinical efficacy study may be submitted to demonstrate product efficacy and establish the effective dose range of the product.

1.3. **Benefit-Risk Assessment**

[Do not insert text here. Use the table]

Benefit-Risk Summary and Assessment

TV-46000 is proposed for marketing in 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 200 mg, and 250 mg strengths, each provided in a single-dose prefilled syringe. It is intended to be administered to adults with schizophrenia, and its anticipated benefit to the target population is a reduction in symptoms of schizophrenia, such as delusions and hallucinations. Based on the clinical review and input from the multidisciplinary review team, I recommend a complete response.

Schizophrenia is a serious and disabling mental illness characterized by chronic or recurrent psychosis and frequently associated with negative symptoms (e.g., social withdrawal, avolition, blunted affect) and cognitive deficits (e.g., impaired attention, executive function, working memory, and social cognition). Symptomatic exacerbations of schizophrenia, which are associated with nonadherence to antipsychotic medications, can severely impact patients' functioning and necessitate psychiatric hospitalization. Antipsychotic medications are the first-line pharmacotherapy for schizophrenia and are recommended to be used for the treatment of acute schizophrenia exacerbations as well as on a continuing basis to reduce the risk of relapse. Long-acting injectable antipsychotics maintain therapeutic blood levels for extended periods and may reduce the risk of schizophrenia exacerbation in patients who are nonadherent to oral antipsychotics.

This application relies in part on the Agency's previous findings of safety and effectiveness for risperidone oral tablets (Risperdal, new drug application [NDA] 20272) based on pharmacokinetic data that establish a scientific bridge between oral risperidone and TV-46000. Although TV-46000 had comparable bioavailability to the LD at steady state, the route of administration and intended duration of effect are quite different. Thus, an efficacy study with TV-46000 was necessary to inform labeling regarding dosage and administration and interdose interval. Efficacy of TV-46000 was evaluated in a randomized, double-blind, placebo-controlled study (TV-46000-CNS-30072) that evaluated relapse in 543 subjects, but the dosing data cannot be relied upon and the effective dose range of this new formulation cannot be evaluated.

The safety profile of TV-46000 is generally like other formulations of risperidone. TV-46000 was associated with weight gain, dyslipidemia, hyperglycemia, increased prolactin, sedation/somnolence, and extrapyramidal symptoms. Some subjects experienced injection site reactions, but these reactions are not appreciably worse than other long-acting injectable formulations. This additional formulation-specific risk is counterbalanced by the potential advantage of adding an additional long-acting injectable formulation with a once monthly or once every two month dosing interval to the current armamentarium. However, because the dosing data cannot be relied upon, the dose-response relationship for the safety findings, including formulation-specific adverse reactions, cannot be evaluated.

The Applicant has not provided substantial evidence of effectiveness to support approval. Although the scientific bridge supports partial reliance on the previous Agency findings for Risperdal tablets, an adequate and well-controlled study of TV-46000 is also necessary. The dosing data from study TV-46000-CNS-30072, which was submitted to meet the requirement for a positive adequate and well-controlled efficacy study, cannot be relied upon for regulatory decision making based on the available information. To determine whether the data from this study can be relied upon, the Applicant needs to submit results of an independent third party audit or post-study monitoring by the sponsor/Clinical Research Organization (CRO) for all sites and all subjects to determine the extent of investigational product (IP) dosing errors and lack of IP dose documentation. Alternatively, a new clinical efficacy study may be submitted to demonstrate product efficacy and establish the effective dose range of the product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Schizophrenia is a serious mental illness characterized by chronic or recurrent psychosis (e.g., delusions, hallucinations, and thought disorganization). - Schizophrenia is also frequently associated with negative symptoms (e.g., social withdrawal, avolition, blunted affect) and cognitive deficits (e.g., attention, executive function, working memory, and social cognition). - Individuals with schizophrenia experience significant impairments in social and occupational functioning and, on average, have a life expectancy around 15 years less than individuals without schizophrenia. - Approximately 50% of individuals with schizophrenia experience a relapse/ exacerbation in psychotic symptoms within one year after their last episode; most relapses occur in the context of medication nonadherence.	Schizophrenia is a serious condition associated with significant disability and a shortened life expectancy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The worldwide prevalence of schizophrenia is approximately 0.5 to 1%, and schizophrenia is one of the leading causes of years lost due to disability worldwide.	
<u>Current Treatment Options</u>	- Antipsychotics are the first-line medication therapy for schizophrenia; current practice guidelines recommend that antipsychotics should be initiated as soon as possible in an acute schizophrenia exacerbation and continued indefinitely to reduce the risk of relapse. - Antipsychotics have been shown to be effective for reducing positive symptoms of schizophrenia (e.g., delusions, hallucinations, disorganized thinking and behavior). Negative symptoms and cognitive deficits of schizophrenia generally show little to no improvement from antipsychotic treatment. - Antipsychotics are broadly categorized as first-generation/typical antipsychotics (e.g., chlorpromazine, fluphenazine, haloperidol, etc.) and second-generation/atypical antipsychotics (e.g., clozapine, risperidone, olanzapine, quetiapine, and aripiprazole). - In general, first-generation antipsychotics have a higher risk for causing extrapyramidal side effects than second-generation antipsychotics. - Adverse reactions from antipsychotics vary between drugs but may include weight gain, dyslipidemia, hyperglycemia, extrapyramidal side effects, increased prolactin, sedation, and QT prolongation. - Nonadherence to daily oral antipsychotic treatment is very common in individuals with schizophrenia.	- Antipsychotics reduce the severity of positive symptoms of schizophrenia and the risk of psychosis exacerbations. - Nonadherence to daily oral antipsychotics is common in individuals with schizophrenia and can lead to psychiatric hospitalization and other adverse outcomes. - Long-acting injectable antipsychotics may reduce the risk of schizophrenia exacerbations in patients who are nonadherent to oral antipsychotics. - Risperidone is currently available in an intramuscular injection formulation that is administered every 14 days and a subcutaneous injection formulation that is administered once a month. - Overall, this patient population's needs are being only partially met by currently available therapies. - Most patients do not achieve full remission of schizophrenia symptoms, and current

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The consequences of medication nonadherence can include acute psychosis exacerbation, occupational and social problems, danger to self or others, and psychiatric hospitalization. • Long-acting injectable antipsychotic medications maintain therapeutic blood levels for extended periods (weeks to months) and may reduce the risk of schizophrenia exacerbation in patients who are nonadherent to oral antipsychotics. • In addition to antipsychotic medications, patients with schizophrenia are frequently treated with adjunctive medications to target depression, anxiety, obsessions and compulsions, and side effects of antipsychotics (e.g., dystonia, parkinsonism, tardive dyskinesia, and akathisia). • When integrated with pharmacotherapy, psychosocial interventions have been shown to improve the course of schizophrenia. These interventions include cognitive behavioral therapy, assertive community treatment, supported employment, and social skills therapy.	medications are generally ineffective for negative symptoms and cognitive deficits of schizophrenia. • Additional treatment options are needed that target unmet clinical needs and promote improved adherence.
Benefit	• The Applicant submitted study TV-46000-CNS-30072, a randomized, double-blind, placebo-controlled study that evaluated relapse in 543 subjects. • Consistent with the design of other schizophrenia clinical trials that have supported product registration, the definition of relapse, which was the primary efficacy outcome measure, was mainly driven by positive symptoms and included worsening of symptoms as assessed	• Substantial evidence of effectiveness has not been provided because dosing data from the one positive adequate and well-controlled study could not be verified and the effective dose range of TV-46000, a product with a unique PK profile compared to the LD Risperdal tablets, has not been established.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	by the POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS), hospitalization for psychotic symptoms, violent behavior and suicidal ideation and behavior. • The study population appears to be suitable to generalize the results to the target patient population of adults with schizophrenia. • The primary efficacy analysis demonstrated superiority but due to lack of IP dose documentation of undetermined extent and dosing errors of undetermined extent, the results cannot be confirmed with respect to actual IP received and cannot be used to determine the effective dose range of TV-46000. • Pharmacokinetic (PK) data established a scientific bridge between risperidone oral tablets and TV-46000. • The range of strengths planned for marketing corresponds to 2 to 5 mg of daily oral risperidone based on the PK data. This is not the full approved dose range of oral risperidone for the treatment of schizophrenia, which starts at 2 mg for initial dose and goes up to 16 mg. • The effective dose range of TV-46000 could not be evaluated due to lack of IP documentation and dosing errors, the extent of which could not be determined. • All the subgroup analysis results for gender, age, race, and baseline PANSS scores were consistent with those seen for the overall population.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• TV-46000 was associated with weight gain, dyslipidemia, hyperglycemia, increased prolactin, sedation/somnolence, and extrapyramidal symptoms. • Twenty-one percent of subjects had injection site reactions (one severe) and 2% of patients discontinued treatment due to injection site reactions in the TV-46000 groups. • The full dose range for oral risperidone is not covered by the strengths proposed for marketing based on the PK data and prescribers could use more than one injection to achieve higher daily dose equivalents, which has not been studied. • The dose-response relationship for the safety findings could not be evaluated because the IP dosing data cannot be relied upon. • There were safety data submitted in the age 13-17 pediatric population for only four subjects, one in the study TV-46000-CNS-30072 and three in study TV-46000-CNS-30078, a long-term safety study, which the Applicant states was due to enrollment difficulties.	• The safety profile of TV-46000 is generally like other formulations of risperidone, but there is inadequate information about exposure to TV-46000 and dose-response in the clinical efficacy and safety studies due to lack of IP dosing documentation and IP dosing errors. • Formulation-specific injection site reactions do not significantly affect the benefit-risk balance of this product. • If the Applicant is able to address the application deficiencies in a subsequent review cycle such that the submitted data can be relied upon, injection site reaction incidence should be communicated in the product label and labeling should include language instructing prescribers not to administer more than one dose of TV-46000 per dosing interval • There are insufficient safety data to complete a pediatric assessment for the 13-17 year-old age group due to the small number of subjects enrolled.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

The patient experience data that were submitted as part of the application include:		Section of clinical study report where discussed, if applicable	
	☒	Clinical outcome assessment (COA) data, such as	
	☒	Patient reported outcome (PRO)	
		5-Level EuroQol Five Dimensions Questionnaire (EQ-5D-5L)	TV-46000-CNS-30072 CSR: Sections 9.5.1.1.3, 11.4.1.3.2 TV-46000-CNS-30078 Interim CSR: Sections 9.5.1.1.3, 11.4.1.2
		Schizophrenia Quality of Life Scale (SQLS)	TV-46000-CNS-30072 CSR: Sections 9.5.1.1.2.7, 9.7.1.3.2.7, 11.4.1.2.7 TV-46000-CNS-30078 Interim CSR: Sections 9.5.1.1.3, 11.4.1.2
		Drug Attitudes Inventory 10-item version (DAI-10)	TV-46000-CNS-30072 CSR: Sections 9.5.1.1.2.6, 9.7.1.3.2.6, 11.4.1.2.6 TV-46000-CNS-30078 Interim CSR: Sections 9.5.1.1.3, 11.4.1.2
		Healthcare Resource Utilization	TV-46000-CNS-30072 CSR: Sections 9.5.1.1.3, 11.4.1.3.3 TV-46000-CNS-30078 Interim CSR: Sections 9.5.1.1.3, 11.4.1.2
	☐	Observer reported outcome (ObsRO)	
	☒	Clinician reported outcome (ClinRO)	
		Positive and Negative Syndrome Scale (PANSS)	TV-46000-CNS-30072 CSR: Sections 9.5.1.1.3, 11.4.1.3.4 TV-46000-CNS-30078 Interim CSR: Sections 9.5.1.1.3, 11.4.1.2 TV-46000-SAD-10055 CSR: Sections 9.5.1.3.10.1, 9.7.1.5.12, 12.5.4.5 TV-46000-BA-10148 CSR: Sections 9.5.1.4.11.1, 9.7.1.5.10.1, 12.5.4.5
		Extrapyramidal Syndrome Rating Scale (ESRS)	RISPE1ZG15EU CSR: Sections 9.5.2.11, 12.2.5.4, 13.1.1 TV-46000-SAD-10055 CSR: Sections 9.5.1.3.10.2, 9.7.1.5.13, 12.5.4.3 TV-46000-BA-10148 CSR: Sections 9.5.1.4.11.2, 9.7.1.5.10.2, 12.5.4.4
		Calgary Depression Scale for Schizophrenia (CDSS)	TV-46000-CNS-30072 CSR: Sections 9.5.12.7, , 9.7.1.5.7.5, 12.5.4.5 TV-46000-CNS-30078 Interim CSR:

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
Uzedy (risperidone extended release injection)

		Clinical Global Impression-Severity (CGI-S)	TV-46000-CNS-30072 CSR: Sections 9.5.1.12.8, , 9.7.1.5.7.7, 12.5.4.8 TV-46000-CNS-30078 Interim CSR: Sections 9.5.1.12.8, 9.7.1.5.7.8, 12.5.4.8 TV-46000-SAD-10055 CSR: Sections 9.5.1.3.10.3, 9.7.1.5.14, 12.5.4.4 TV-46000-BA-10148 CSR: Sections 9.5.1.4.11.3, 9.7.1.5.10.3, 12.5.4.6
		Personal and Social Performance Scale (PSP)	TV-46000-CNS-30072 CSR: Sections 9.5.1.1.3, 11.4.1.3.6 TV-46000-CNS-30078 Interim CSR: Sections 9.5.1.1.3, 11.4.1.2
		Clinical Global Impression-Improvement (CGI-I)	TV-46000-CNS-30072 CSR: Sections 9.5.1.1.3, 11.4.1.3.5 TV-46000-CNS-30078 Interim CSR: Sections 9.5.1.1.3, 11.4.1.2
		Abnormal Involuntary Movement Scale (AIMS)	TV-46000-CNS-30072 CSR: Sections 9.5.12.4, 9.7.1.5.7.2, 12.5.4.3 TV-46000-CNS-30078 Interim CSR: Sections 9.5.1.12.3, 9.7.1.5.7.3, 12.5.4.3
		Simpson-Angus Scale (SAS)	TV-46000-CNS-30072 CSR: Sections 9.5.12.6, , 9.7.1.5.7.3, 12.5.4.4 TV-46000-CNS-30078 Interim CSR: Sections 9.5.1.12.4, 9.7.1.5.7.4, 12.5.4.4

	The patient experience data that were submitted as part of the application include:		Section of clinical study report where discussed, if applicable
	☐	Barnes Akathisia Rating Scale (BARS)	TV-46000-CNS-30072 CSR: Sections 9.5.12.5, 9.7.1.5.7.4, 12.5.4.6 TV-46000-CNS-30078 Interim CSR: Sections 9.5.1.12.5, 9.7.1.5.7.5, 12.5.4.6
	☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify):	

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
 Uzedy (risperidone extended release injection)

☐	Patient experience data that were not submitted in the application but were considered:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☐	Patient experience data was not submitted as part of this application.	

Source: TV-46000-CNS-30072 CSR, TV-46000-CNS-30078 CSR, RISPE1ZG15EU CSR, TV-46000-SAD-10055 CSR, TV-46000-BA-10148 CSR

CSR=clinical study report

2 Therapeutic Context

2.1. Analysis of Condition

Schizophrenia is a serious psychiatric disorder affecting approximately 1% of the population worldwide. Schizophrenia is a severe, chronic condition with significant morbidity and mortality. The disorder is characterized by a constellation of symptoms that may include delusions, hallucinations, disorganized speech, grossly disorganized behavior, diminished emotional expression, and avolition (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5, American Psychiatric Association – APA - 2013). Although cognitive symptoms are not included in the diagnostic criteria of schizophrenia, impairments in processing speed, attention, working memory, and social cognition are frequent and disabling manifestations. Mood and anxiety symptoms are also common in individuals with schizophrenia.

The pathogenesis of schizophrenia is poorly understood. Schizophrenia is a heterogeneous syndrome likely caused by a complex group of diseases resulting from interactions between genes and environment. Rare cases arise from an abnormality in a single genetic locus (e.g., 22q11 deletion syndrome). However, for most people with schizophrenia, multiple genes are involved, each contributing a small amount to the overall condition. Environmental risk factors associated with schizophrenia are equally diverse and include prenatal maternal infections, nutritional deficiencies, obstetrical complications, adverse childhood events, and urbanicity (Wahbeh and Avramopoulos 2021). The underlying neurobiology of schizophrenia has not been clearly established; there is no recognized central pathophysiology or disease mechanism (Rasetti and Weinberger 2011). Hypothetical neurochemical models of schizophrenia include excessive mesolimbic dopaminergic activity, hypoactivity of N-methyl-D-aspartate (NMDA) glutamate receptors, and dysfunctional gamma-amino-butyric acid (GABA)-mediated modulation of pyramidal neurons (Birnbaum and Weinberger 2017).

The onset of schizophrenia is typically in early adulthood, occurring 5 to 7 years later in women than in men. The course of illness is heterogeneous, with many experiencing multiple acute symptom exacerbations and remissions within a chronic and disabling illness. On average, women tend to have better premorbid functioning and less prominent negative symptoms (e.g., affective flattening, alogia, anhedonia, and avolition) and a higher severity of affective symptoms (Giordano et al, 2021).

Schizophrenia is associated with significant impairments in social and occupational functioning and is among the 20 leading causes of disability worldwide (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Individuals with schizophrenia experience premature mortality compared with the general population, with an average of 14.5 years of potential life lost (Hjorthøj, Stürup et al. 2017). About 4% to 10% of persons with schizophrenia die by suicide, with rates that are highest among males in the early course of the disorder (Sher

and Kahn 2019). Overall, schizophrenia is a serious condition, associated with significant disability and a shortened life expectancy.

2.2. Analysis of Current Treatment Options

The most recent APA practice guideline for the treatment of schizophrenia recommends that patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects (Keepers et al, 2020). Antipsychotic treatment should be initiated in an acute schizophrenia exacerbation to reduce acute symptoms, with the aim of returning the individual to his or her baseline level of functioning. Later, maintenance treatment will aim to prevent recurrence of symptoms and maximize functioning and quality of life.

The mechanism by which antipsychotics improve psychotic symptoms is not completely understood but may involve antagonism of dopamine D2 receptors and/or serotonin 5-HT_{2A} receptors. Binding to other neurotransmitter receptors (e.g., α ₁-adrenergic, muscarinic, and histaminergic receptors) generally corresponds to the adverse reaction profile for a given drug (Correll and Kane, 2014). First-generation or typical antipsychotics are dopamine antagonists and second-generation or atypical antipsychotics, including risperidone, are serotonin and dopamine antagonists.

Some of the relevant class-based safety issues for antipsychotics include extrapyramidal symptoms (EPS) and tardive dyskinesia, neuroleptic malignant syndrome, hyperprolactinemia, orthostatic hypotension, metabolic effects including dyslipidemia, hyperglycemia, and weight gain, QT interval prolongation, seizures, blood dyscrasias, sedation, and an increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis. In general, risperidone and other second generation antipsychotics have been associated with more weight gain, hyperglycemia, and hyperlipidemia compared to the first-generation antipsychotics.

Several antipsychotics are available in long-acting injectable (LAI) formulations (Table 1). The primary clinical benefit of LAIs is that they maintain therapeutic blood levels of antipsychotics for extended periods (weeks to months) and may reduce the risk of schizophrenia exacerbation in patients who are nonadherent to oral medications (Kishimoto et al. 2018). Potential disadvantages of LAIs include a longer time to achieve steady state blood levels, delayed resolution of adverse reactions (AR), injection site reactions, and more frequent appointments for drug administration (Brissos et al. 2014).

Although there are a number of approved treatments for schizophrenia, an individual patient may require several trials with different antipsychotic drugs before an effective and reasonably-tolerated treatment is identified. Additionally, most available medications predominantly affect positive symptoms but do not appear to meaningfully impact negative symptoms or cognitive impairment.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
 Uzedly (risperidone extended release injection)

Table 1. Summary of Long-Acting Injectable Antipsychotics Currently Available in the United States

Product Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Important Differentiating Safety and Tolerability Issues	Other Comments
Aripiprazole monohydrate (Abilify Maintena)	Schizophrenia in adults, <i>Also indicated for the maintenance treatment of bipolar I disorder in adults</i>	2013	IM in deltoid or gluteal, monthly	N/A	In conjunction with first dose, need to continue oral antipsychotic for 14 days
Aripiprazole lauroxil (Aristada)	Schizophrenia in adults	2015	IM in deltoid or gluteal, every 1 or 2 months, or every 6 weeks	N/A	In conjunction with first dose, need to continue oral aripiprazole for 3 weeks
Aripiprazole lauroxil (Aristada Initio)	Schizophrenia in adults	2018	IM deltoid or gluteal, once	N/A	To be used as one-time loading dose with a one-time oral aripiprazole loading dose at time of Aristada initiation
Fluphenazine decanoate	Schizophrenia in adults	1972	IM or SC, every 2 to 4 weeks	First generation antipsychotic – higher EPS liability	Need to continue oral fluphenazine until effective decanoate dosage is established
Haloperidol decanoate	Schizophrenia in adults	1986	IM, monthly	First generation antipsychotic – Higher EPS liability	Depending on initiation dose, may need to continue oral haloperidol for up to 3 months.
Olanzapine pamoate (Zyprexa Relprevv)	Schizophrenia in adults	2009	IM in gluteal muscle, every 2 or 4 weeks	Risk of post injection delirium/sedation syndrome: drug available only through restricted distribution program; requires 3 hours monitoring post injection	No overlap period needed with oral antipsychotic
Paliperidone palmitate (Invega Sustenna)	Schizophrenia in adults, <i>also indicated for the treatment of schizoaffective disorder</i>	2009	IM in deltoid or gluteal muscle; monthly after loading doses (two loading doses 1 week apart)	N/A	No overlap period needed with oral Paliperidone
Paliperidone palmitate (Invega Trinza)	Schizophrenia in adults	2015	IM in deltoid or gluteal muscle; every 3 months	N/A	Can only be used if patient has received monthly injections of Invega Sustenna for ≥4 months
Paliperidone palmitate (Invega Hafyera)	Schizophrenia in adults	2021	IM in gluteal muscle; every 6 months	N/A	Can only be used if patient has received monthly injections of Invega Sustenna for ≥4 months or Invega Trinza for ≥1 three month cycle
Risperidone microspheres (Risperdal Consta)	Schizophrenia in adults, <i>also indicated for the maintenance</i>	2003	IM in deltoid or gluteal muscle, every 2 weeks	N/A	In conjunction with first dose, need to continue oral antipsychotic for 3 weeks

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
 Uzedry (risperidone extended release injection)

	<i>treatment of bipolar I disorder in adults</i>				
Risperidone for extended release Injectable suspension (Perseris)	Schizophrenia in adults	2018	SC injection in abdomen every 4 weeks	N/A	No overlap period needed with oral risperidone

Source: Clinical reviewer-generated

Abbreviations: EPS = extrapyramidal symptoms; IM = intramuscular; SC = subcutaneous

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

TV-46000 (risperidone extended-release injectable suspension for sc use) has not been approved or marketed in the United States. Risperdal (risperidone), the LD, was first approved in 1993 as tablets for oral administration for the treatment of schizophrenia in adults (NDA 20272). Currently, there are multiple additional dosage forms available for risperidone including: an injectable suspension for intramuscular use (NDA 21346; Risperdal Consta), (b) (4) oral solution (NDA (b) (4) Risperdal), an orally disintegrating tablet (NDA 021444; Risperdal M-Tab), and an injectable suspension for subcutaneous use (NDA 210655; Perseris).

3.2. Summary of Presubmission/Submission Regulatory Activity

On October 15, 2015, the Division met with the Sponsor for a pre-IND meeting. At that time, the Sponsor proposed to conduct a pharmacokinetic (PK) study to provide a scientific bridge to the proposed listed drug, Risperdal tablets (NDA 20272) and a phase 3 placebo-controlled efficacy study in patients with schizophrenia with a plan to submit a 505(b)(2) application. The Division agreed with the overall development plan, but stated that the proposed primary efficacy endpoint was not acceptable for the phase 3 efficacy study and the Sponsor agreed to use an endpoint of time to impending relapse.

The Sponsor opened Investigational New Drug (IND) application 124384 (TV-46000) on May 20, 2016, with the PK study TV-46000-SAD-10055.

The Division met with the Sponsor in May 2017 for a Type C meeting to discuss changes to the phase 3 development plan and a plan to change the product presentation from a vial to a prefilled syringe (PFS). The Division agreed with the plan for a phase 3 efficacy study and open-label extension safety study and provided advice on conducting a comprehensive use-related risk analysis to inform the need for human factors studies.

At an end-of-phase 1 meeting in December 2017, the Sponsor informed the Division that, based on the results of study TV-46000-SAD-10055, they planned to use a once monthly (q1m) regimen and change the planned once every three months (q3m) regimen to a once every two months (q2m) regimen in the planned efficacy study TV-46000-CNS-30072. The Division noted that, scientifically, matching peak and trough concentrations for a long-acting injection to those from an oral formulation to determine product dosing may not be a good strategy because it could result in trough levels lasting a few days or weeks that could confer a different risk of relapse. The Sponsor indicated their plan to continue the phase 3 study with the selected dosing regimens and committed to documenting and analyzing the timing of adverse events and relapse within the dosing interval. The Division agreed with the Sponsor's proposal to conduct a dedicated relative bioavailability study to demonstrate comparability in the PK of the

vial and PFS. The Division also agreed that the Sponsor can introduce the new PFS presentation in the phase 3 program.

The Sponsor submitted an Initial Pediatric Study Plan (iPSP) on March 8, 2018, requesting a full waiver of requirements for studies in the pediatric population (aged 0 to 17 years). The Division sent a Written Response to the iPSP on May 24, 2018, agreeing to the plan for a partial waiver for pediatric patients 0 to 12 years of age but not for patients 13 to 17 years of age. The Sponsor and Division reached agreement on a revised iPSP planning a partial waiver for patients aged 0 to 12 years and open enrollment for patients aged 13 to 17 in phase 3 studies.

On August 8, 2018, the Division sent Written Responses to the Sponsor clarifying plans for the proposed relative bioavailability study (i.e., TV-46000-BA-10148) to provide bridging between their product and Risperdal, the LD. The Division recommended that statistical analysis be performed for the key pharmacokinetic parameters (C_{max} and AUC) comparing each presentation of the Sponsor's product separately and combined to the LD.

In an advice letter sent May 21, 2020, the Division communicated that

(b) (4)

These endpoints are listed in Section 8 of the review.

The Sponsor submitted a proprietary name request for "Uzedy" on October 21, 2021, which was conditionally accepted.

The Sponsor submitted a Fast-Track designation request on September 1, 2020. This was denied due to an inadequate development plan. As designed, the planned study did not allow for an independent determination of efficacy in the adolescent population to address an unmet medical need in this population.

On March 31, 2021, the Division and Sponsor held a Pre-NDA meeting. In the agreed initial pediatric study plan, the Sponsor described their intent to recruit adolescent patients with schizophrenia in their proposed phase 3 studies because of the lack of pediatric data in long-acting injectable schizophrenia trials. However, due to the anticipated challenges in enrolling adolescents, there was no target number for enrollment.

(b) (4)

(b) (4)

The Applicant submitted the NDA on June 17, 2021; it was filed on August 27, 2021, with a standard review priority.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
Uzedy (risperidone extended release injection)

On Friday March 25, 2022, the Division issued a clinical discipline review (DR) letter communicating deficiencies identified during the Office of Scientific Investigations (OSI) inspections for studies TV46000-CNS-30072 and TV46000-CNS-30078.

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

4.1. Office of Scientific Investigations (OSI)

Refer to the OSI discipline review for details about their evaluation. Four clinical investigators and (b) (4) CRO were inspected in support of this NDA, covering the pivotal efficacy study, TV-46000-CNS-30072, and the long-term safety study, TV-46000-CNS-30078. The clinical sites (Site # 14771, #14865, #14787, and #14810) were chosen primarily based on risk ranking in the site selection tool, numbers of enrolled subjects, site efficacy, protocol deviations, and prior inspectional history.

The inspections identified protocol deviations related to IP dosing errors, lack of documentation of IP administration, duplicate subject enrollment at different clinical sites, and potential unblinding at one clinical site. Although no discrepancies in primary efficacy endpoint data were identified, based on these inspections and related information requests, the extent of the IP dosing errors cannot be determined. Additionally, the extent of the lack of IP dose documentation, which precludes IP dose verification, is not known.

OSI recommends that an independent third party audit or post-study monitoring by the sponsor/CRO be conducted for all sites and all subjects to determine the extent of IP dosing errors and lack of IP dose documentation.

Clinical reviewer's comment: The OSI inspection indicated that the data obtained in the efficacy study, Study TV-46000-CNS-30072, and the long-term safety study, Study TV-46000-CNS-30078, failed to meet the quality standard necessary to assure data integrity to conduct a clinical review with conclusive results. Specifically, deficiencies pertaining to IP dosing errors, lack of documentation of IP administration, duplicate and triplicate subject enrollment at different clinical sites, and potential unblinding at a site could have affected data integrity, leaving the results of the clinical review inconclusive. I agree with the OSI recommendation that the Applicant needs to submit results of an independent third party audit or post-study monitoring by the sponsor/CRO for all sites and all subjects to determine the extent of IP dosing errors and lack of IP dose documentation.

The Applicant submitted a response to the March 25, 2022 clinical DR letter on March 31, 2022. The response stated that audits have been conducted on roughly half the study sites and around two thirds of the subjects enrolled. It did not contain audit results of all sites and was on face inadequate to address the deficiencies identified. Because review of this submission would not have the potential to result in an approval action, the review clock was not extended.

4.2. Product Quality

Refer to the Office of Product Quality (OPQ) Integrated Quality Assessment and the incorporated OPQ discipline reviews for details about their evaluations. Chemistry,

Uzedy (risperidone extended release injection)

manufacturing, and controls (CMC) recommends approval of the application with the following post-marketing commitments (PMCs):

(b) (4)

Biopharmaceutics PMC:

Biopharmaceutics identified deficiencies in the IVIVC report and accepts the Applicant's dissolution method and acceptance criteria on an interim basis. Biopharmaceutics will make a final decision on the dissolution method and acceptance criterion once the Applicant submits a IVIVC modeling summary report and supporting documentation within six months post-action. Finalization of the dissolution method and acceptance criteria will be made upon review of these documents within one year post-action.

4.3. Clinical Microbiology

Risperidone extended-release injectable suspension (50, 75, 100, 125, 150, 200, 250 mg/ PFS) involve (b) (4)

(b) (4)

The drug substance and drug product microbiology assessment concluded that the application is adequate.

4.4. Devices and Companion Diagnostic Issues

Prior to conducting the phase 3 studies using PFS under IND 124384, the Division requested a Center for Device and Radiological Health (CDRH) consult. CDRH reviewed the essential device requirement, risk analysis, and shipping/transportation studies and found them to be adequate.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

TV-46000 is an extended-release injectable formulation of the atypical antipsychotic risperidone for administration once every one month or once every two months via the subcutaneous (SC) route. The TV-46000 drug product contains the active pharmaceutical ingredient (risperidone) and two biodegradable copolymer excipients (methoxy-poly(ethylene glycol)-co-poly(D,L-lactide) and poly(D,L-lactide)-co-poly(ethylene glycol)-co-poly(D,L-lactide)) suspended in dimethyl sulfoxide (DMSO). The Applicant submitted a 505(b)(2) NDA in which they are relying in part on the Agency's previous finding of safety of risperidone from risperidone tablets (Risperdal) as the listed drug, and published literature. The Applicant conducted several nonclinical pharmacokinetic and toxicity studies to support the TV-46000 clinical formulation, including the copolymer excipients, and conducted a safety assessment of the excipients based on information from published literature.

Pharmacokinetic (PK) studies with the final clinical formulation of TV-46000 were conducted in rats and subsequently in dogs – a species that allowed application of clinically relevant dose volumes of TV-46000 and covered all expected human circulating metabolites based on in vitro assessment using liver microsomes. The effect of extrinsic heating and massaging of the injection site on TV-46000 PK, as well as depot imaging and excision, was further evaluated in minipigs as their skin is considered the most suitable representation of the human skin for dermal procedures.

Given that both risperidone and its active metabolite, 9-OH-risperidone, have similar pharmacological activity, the combined exposure to these two entities was used throughout the submission and in this review to represent the overall total active moiety (TAM).

Plasma kinetics of risperidone, 9-OH risperidone, and TAM following SC administration of TV-46000 in rats, dogs, and minipigs, showed a similar PK profile in all tested animal species, characterized by extended release of the parent drug from the SC depot over a duration of at least one month. In all tested species, TV-46000 showed rapid initial increase in TAM plasma levels, with initial peak 3 to 6 h post dose, an additional, more prominent peak around 3 to 14 days post dose, and an extended exposure with TAM $t_{1/2}$ of about 6 to 10 days. Average TAM plasma concentrations were similar to those measured at equivalent doses of intramuscular (IM) Risperdal Consta or at equivalent doses of oral Risperdal. Fluctuation in plasma levels over the same duration were markedly lower for TV-46000 than those observed for the oral or IM products. The PK profile of TV-46000 shows two advantages over the oral and IM comparator drugs: 1) evading peak to trough fluctuation seen after oral dosing, and 2) evading the lag phase (10 to 14 days) seen after IM administration of Risperdal Consta.

Plasma exposure (AUC) to TAM in dogs and rats increased, in general, dose proportionally over the tested dose range. No accumulation of TAM was observed in dogs after three repeated SC

monthly administrations of TV-46000 at dose levels of 5 and 7 mg/kg; however, higher doses of 20 and 50 mg/kg resulted in an increase in exposure with an accumulation ratio ranging from 1.36 to 2.58. Male dogs had up to 1.7-fold higher TAM exposure compared to females, with high inter-individual variability.

A decline in TAM concentrations with apparent plasma $t_{1/2}$ of less than 2 days was observed in dogs following the removal of the TV-46000 SC depot four days post injection with a nearly complete release of risperidone from the SC depot .

Heating of the injection site in minipigs had no effect on the overall TAM PK profile or the release of risperidone from the SC depot. Massaging/rubbing studies in dogs and minipigs indicated that rubbing of the SC injection site after the depot formation (≥ 0.5 hr post SC injection) had no effect on TAM exposure, while rubbing immediately post injection resulted in an increased TAM exposure vs. exposure without injection site rubbing, although it allowed the depot formation. There was no evidence of dose dumping following site of injection manipulation in these studies. Evaluation of the effect of obesity on TV-46000 PK showed that SC injection of TV-46000 into fat-rich tissue in dogs resulted in a delayed t_{max} and almost doubled AUC value relative to injection into non-fat tissue. The same study showed that TAM PK profile is not affected by the location of the SC injection site (lumbar vs interscapular region) in non-obese dogs. Variations in risperidone particle size and needle gauge and size also had little or no effect on the PK characteristics TV-46000 TAM in dogs. A change in the needle gauge (21G vs. 23G) and/or syringe size (1 mL vs. 250 μ L) for SC injection of TV-46000 had little or no effect on the overall TAM PK profile in dogs.

No in vivo distribution, metabolism and excretion studies were conducted with TV-46000, as these parameters, as well as drug-drug interaction potential for risperidone, are expected to be similar for all routes of administration and literature data are available. In vitro metabolism of risperidone was studied in liver microsomes from minipigs, dogs, and humans; the results confirmed the selection of the dog as a suitable toxicological species, presenting all expected human circulating metabolites.

Toxicology: The toxicological evaluation of TV-46000 included single- and repeat- dose SC toxicity studies in the most appropriate species, with the clinically relevant TV-46000 formulation, using the clinical route of administration for a period sufficient to assess the entire duration of the extended release. Genotoxicity, carcinogenicity, and reproductive and developmental toxicology studies were not conducted because relevant nonclinical data are included in the label for the listed drug (Risperdal) and this information will be included in the label for TV-46000. This approach is in line with the FDA's 2015 guidance: Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route.

Systemic and local toxicity of TV-46000 were evaluated in GLP single-dose SC toxicity studies in rats and dogs, followed by a GLP 13-week repeat-dose SC toxicity study in dogs with three once

monthly SC injections of TV-46000 (corresponding to the highest administration frequency in humans).

Systemic and local toxicity: In a GLP single-dose study in Wistar rats with TV-46000 SC administration at dose levels of 20, 40, 100, and 140 mg/kg, systemic effects attributed to the pharmacology of risperidone were observed at all dose levels (microscopic changes in the male and female reproductive organs related to the hyperprolactinemic effects of risperidone, with partial recovery). Locally, TV-46000 was well tolerated up to the HD of 140 mg/kg. Local findings at the injection sites consisted of an expected, vehicle-related non-adverse foreign body granulomatous reaction with a surrounding fibrous capsule in both vehicle and TV-46000 treated animals, with a partial recovery at the end of the study. In a GLP single-dose study conducted in Beagle dogs with TV-46000 SC administration at dose levels of 7, 14, 50, and 100 mg/kg, effects in reproductive organs related to the antidopaminergic pharmacological effect of risperidone were observed at all dose levels (e.g., lower epididymis weight and hypo-spermatogenesis). Locally, TV-46000 was well tolerated up to the HD of 100 mg/kg. Vehicle-related non-adverse injection site reactions, similar to those observed in rats, were also observed in dogs with evidence of partial recovery. The NOAEL for local toxicity was the highest dose tested, 140 and 100 mg/kg in rats and dogs, respectively.

A GLP 13-week SC repeat-dose toxicology study with a 12-week recovery period was conducted in Beagle dogs with three once-a-month TV-46000 SC injections at dose levels of 7, 20, and 50 mg/kg, and vehicle and saline control groups. Toxicity related to the pharmacology of risperidone was observed in reproductive organs (prostate, epididymis, testes, ovaries, and uterus) in all TV-46000 dose groups with little or no reversibility observed. Local findings at the injection sites (erythema, edema, and hematoma during the first 2 months post injection, and nodules and induration from the end of first month through the end of the study) were present in the vehicle control and all TV-46000-treated groups. These local findings were transient, showed no dose dependency, and were related to the vehicle because similar findings were not observed in the saline-treated controls. Microscopically, the findings at the injection sites were consistent with an expected foreign body reaction toward the SC injected polymers. This foreign body granulomatous reaction showed a trend for a progressive, time-related recovery. A marked reduction in the size of the drug depot occurred by day 172 post-injection. Minimal to moderate vacuolation in axillary lymph nodes was observed at a higher incidence and/or severity in animals treated with the vehicle or TV-46000 compared to saline controls. This finding was related to the drainage of subcutaneously injected polymers (vehicle) by these lymph nodes and its incidence and severity correlated with the volume of injected vehicle; the finding was partially reversible. A NOAEL for systemic toxicity was not determined because of the drug effects at all doses on the reproductive parameters related to risperidone pharmacology. The NOAEL for local toxicity was the highest dose of 50 mg/kg, with systemic TAM exposure after the third injection on Day 57 of: C_{max} of 636 and 456 ng/mL and AUC_{0-648h} of 311000 and 258000 ng·h/mL (for males and females, respectively), compared to the human C_{max} of 110.5 ng/mL and AUC of 78622 ng·h/mL at steady state.

Manipulation of TV-46000 injection site by heating, massage, and rubbing had no effect on local and systemic tolerability in a dedicated local tolerance study in minipigs, as well as in studies in minipigs and dogs.

The safety assessment of the copolymer excipients in the TV-46000 drug product included: a vehicle-alone group in each of the toxicity studies, an Ames test to evaluate the potential mutagenicity of the copolymers, and two single-dose intravenous toxicity studies in rats to assess the acute toxicity and PK of potential degradation products of the copolymers. No adverse local, systemic toxicity, or genotoxicity was identified in these studies.

The totality of nonclinical safety data included in the NDA submission for TV-46000, including risperidone and the copolymer excipients, support the approval of TV-46000.

5.2. Referenced NDAs

NDA 20272, Risperdal - Risperidone oral tablet - Listed Drug

5.3. Pharmacology

Risperidone is a monoaminergic antagonist with high affinity (K_i of 0.12 to 7.3 nM) for the 5-HT₂, D₂, α_1 and α_2 adrenergic, and H₁ histaminergic receptors. Risperidone showed low to moderate affinity (K_i of 47 to 253 nM) for the 5-HT_{1C}, 5-HT_{1D}, and 5-HT_{1A} receptors, weak affinity (K_i of 620 to 800 nM) for the D₁ and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations > 10⁻⁵ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors. (Excerpted from approved label for listed drug, Risperdal).

No pharmacology studies were conducted with TV-46000, as all pertinent pharmacology information for risperidone is included in the approved label for the listed drug, Risperdal. A summary of literature data on key pharmacology findings was provided in the application. Based on the approved label for Risperdal, the mechanism of action of risperidone in schizophrenia is unclear. The drug's therapeutic activity in schizophrenia could be mediated through a combination of dopamine Type 2 (D₂) and serotonin Type 2 (5-HT₂) receptor antagonism. The clinical effect results from the combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone (paliperidone).

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
<i>Study # DS-2014-043:</i> TV-46000: One-Month and Three-Month Single Subcutaneous Injection Toxicology Study in Wistar Rats with a Recovery Period. <i>Study # DP-2014-146:</i> Pharmacokinetic and local tolerability study of MedinGel-based risperidone formulations after a single subcutaneous administration compared to Risperdal Consta® repeated intramuscular administrations in dogs <i>Study # DP-2014-156:</i> Pharmacokinetic and local tolerance study of F1M-17* and F3M-36 MedinGel-based risperidone formulations after a single subcutaneous administration compared to a repeated intramuscular administration of Risperdal Consta® in male Beagle dogs. <i>Study # DS-2014-041:</i> One- and Three-Month Single SC Injection Toxicology Study in Beagle Dogs with a Recovery Period. <i>Study # DS-2014-039:</i> TEV-90102 - Single SC Injection Dose-Range-Finding Study in Beagle Dogs with a 7-Day Observation Period <i>Study # DS-2014-096:</i> MedinGel-Based Risperidone Single Dose Subcutaneous Tolerability and TK Study in Minipigs	Plasma concentrations of TV-46000 total active moiety (the sum of risperidone and metabolite 9-OH-risperidone) (TAM) in rats, dogs and minipigs show rapid initial increase, with initial peak 3 to 6 h post-dose, and additional, more prominent peak around 3-14 days post dose, with sustained concentration-time profile and extended exposure, with TAM $t_{1/2}$ of 6-10 days. Average plasma concentrations similar to equivalent dose of oral risperidone or of the IM extended-release Risperdal Consta for 1 and 3 months, while fluctuation in plasma levels over the same duration were markedly lower for TV-46000 compared to risperidone oral or IM products (<i>Studies # DP-2914-146, DP-2014-156, DS-2014-096</i>). Plasma exposure (AUC) to TAM in dogs and rats increased dose proportionally over the tested dose range (7- 100 mg/kg and 20-140 mg/kg TV-46000 in dogs and rats, respectively) (<i>Studies # DS-2014-041 and DS-2014-043</i>).
<i>Study # DS-2014-050:</i> A Pharmacokinetic Study Following Repeated Subcutaneous Injections (Days 1, 31 and 61) in Female Dogs.	No accumulation was found in a PK study in female dogs, following 3 repeated monthly SC injections at the same high dose of 50 mg/kg, with TAM plasma exposure similar after single or repeated dosing.
<i>Study # DP-2014-153:</i> Pharmacokinetic and local tolerance study of F1M-17 MedinGel-based risperidone formulation after a single subcutaneous administration in male Beagle dogs)	Upon removal of TV-46000 SC depot (50 mg in 140 μl) 4 days post SC injection in dogs, a systemic decline in TAM concentrations occurred with plasma $t_{1/2}$ of less than 2 days
<i>Study # DP-2014-157:</i> Analysis of Excised Depots - in vivo PK study A144746 in dog. Analysis of RisperMed Q3M explants obtained at the end of the PK study A144746 in dogs after subcutaneous injection of Q3M formulation candidate	Excision and analysis of injection sites in dogs 4 days post TV-46000 injection showed a nearly complete release of risperidone, with less than 0.4% of risperidone dose left in the depots.
<i>Study # DP-2016-004:</i> Risperidone extended-release injectable suspension (TV-46000) Single Dose PK Study in Minipigs by Subcutaneous Route	Heating of the injection site in minipigs (40-42°C for 20 min) from 2 h to 7 days post injection did not affect the overall TAM PK profile or the release of risperidone from the SC depot.
<i>Study # DP-2018-931:</i> Effect of Rubbing Site of Injection on PK after Single Dose SC administration of Risperidone Formulation TV-46000 to Beagle Dogs. <i>Study # DP-2014-158:</i> MedinGel-Based Risperidone PK Study in Minipigs by Subcutaneous Route	Massaging/ rubbing studies in dogs and minipigs indicated that rubbing of the TV-46000 SC injection site after the depot formation (≥ 0.5 h post SC injection) had no effect on TAM exposure, while rubbing immediately post injection resulted in an increased TAM exposure vs. exposure without injection site rubbing. There was no evidence of dose dumping following the injection site manipulation in these studies.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586

Uzedy (risperidone extended release injection)

<i>Study # DP-2015-080: Pharmacokinetic Study Following Single Subcutaneous Injection of F1M-17 (TV-46000) in Beagle dogs</i>	PK effect of obesity: SC injection of TV-46000 into fat-rich tissue resulted in a delayed t_{max} and doubled the AUC value relative to non-fat tissue. PK was not affected by the location of the SC injection site (lumbar vs interscapular region)
<i>Study # DP-2015-117: Pharmacokinetic Study of TV-46000 formulation following a single subcutaneous administration using different dosing devices</i>	A change in the needle gauge (21G vs. 23G) and syringe size (1 mL vs. 250 μ L) for SC injection of TV-46000 to dogs had little or no effect on the overall TAM PK profile.
<i>Study # DP-2019-0817: Variations of risperidone particle size on PK characteristics of TV-46000 in dogs</i> <i>Study # DP-2019-0818: Variations of copolymers molecular weights on PK characteristics of TV-46000 in dogs</i>	Variations of risperidone particle size (D90 17-96 μ m) and copolymers molecular weights (Mn 8500-12000 Da, <i>Study DP-2019-0818</i>) had no effect on the PK characteristics of TV-46000 TAM in dogs.
Distribution	Distribution studies were not performed with TV-46000.
Metabolism	
<i>Study# DP-2014-150: Inter-species Comparison for Metabolite Profiles of Risperidone in Minipig, Dog and Human Liver</i>	<i>In vitro</i> metabolism study in liver microsomes from minipigs, dogs, and humans showed a higher metabolic rate in the minipig compared to dogs and humans, with $t_{1/2}$ of 3.4 minutes compared to 20.5 and 44.4 minutes in dogs and humans, respectively. Two major mono-hydroxylated metabolites (M7, M4) were formed by minipig, dog, and human microsomes. M7 was the most abundant metabolite in all 3 tested species. M4 was more abundant in the minipig. These results confirmed the selection of the dog as a suitable toxicological species, presenting all expected human circulating metabolites. <i>In vivo</i> metabolism studies were not conducted with TV-46000, as the metabolism of risperidone is well documented in the literature and the metabolic pathway is expected to be similar for all routes of administration.
Excretion	Excretion studies were not performed with TV-46000.
TK data from general toxicology studies	
TV-46000: One-month and Three-month Single Subcutaneous Injection Toxicology Study in Wistar Rats with a Recovery Period <i>Study# DS-2014-043</i>	TV-46000 doses: 0, 20, 40, 100, 140 mg/kg $T_{1/2}$ for total active moiety: 441h (M) and 338 h (F) C_{max} of risperidone and TAM reached 1 to 6 h post-dose <i>Dose proportionality:</i> C_{max} and AUC_{0-t} for risperidone, its metabolite 9-OH risperidone and TAM increased with dose from 20 to 100 mg/kg; from 100 to 140 mg/kg less than dose-proportional.

Uzedy (risperidone extended release injection)

5/14-Week Single Subcutaneous Injection Toxicology Study in Beagle Dogs with a Recovery Period <i>Study# DS-2014-041</i>	TV-46000 doses: 7, 14, 50, 100 mg/kg $T_{1/2}$ for TAM: 292-649 h (M); 433-833 h (F) Rapid initial absorption with median T_{max} for TAM 24h post dose. A slower and milder increase in plasma levels peaking at 7 days post injection with a gradual decline in concentrations thereafter. <i>Dose proportionality:</i> TAM plasma exposure parameters increased approximately dose proportionally; the increase in C_{max} slightly less than dose proportional at HD.
TV-46000: 13-Week Repeated Dose Subcutaneous Toxicology Study with 12-Week Recovery Period in Beagle Dogs <i>Study# DS-2015-049</i>	TV-46000 (3 once-a-month repeat doses): 7, 20, 50 mg/kg $T_{1/2}$ for TAM (range): 204-347 h at LD, 202-406 h at MD, and 125 to 888 h at HD. Median T_{max} (range): (F): 6 -144 h, 24 -480 h, 6 -312 h (M): 24- 144 h, 6-312 h, and 24- 480 h for LD, MD, and HD, respectively. Increase in TAM exposure generally dose-proportional; slightly less than dose-proportional between LD and MD in males only. Accumulation of TAM was observed after 3 repeated SC monthly administrations of TV-46000 at 20 and 50 mg/kg. Increased exposure to TAM (AUC_{0-648h}) after the 2nd and 3rd injections vs 1st injection; exposure ratios ranged from 1.2 to 2.4 after 2nd dose and from 1.4 to 2.6 after 3rd dose. <i>Sex differences:</i> Up to 1.7-fold higher exposure to TAM ($AUC_{(0-648h)}$) was observed in males vs. females on all sampling days at 7 and 50mg/kg, with high inter-individual variability.

TAM = total active moiety (risperidone+9-OH-risperidone), (M= male, F = female, LD = low dose, MD = mid dose, HD = high dose, *= TV-46000 was previously referred to as F1M-17 and TEV-90102

5.5. Toxicology

The composition of the drug product and vehicle used in the nonclinical toxicology studies is the same as the composition of the drug product and vehicle used in the clinical/commercial batches, as shown in the following table.

Table 2. Composition of the drug product and vehicle batches used in the nonclinical toxicology studies in comparison to the clinical/commercial batches

Study title/ number	TV-46000, supplied as ready to use dosage form (prefilled vial)		TV-46000 Vehicle (Non-API control formulation), supplied as Ready to use dosage form (prefilled vial)	
	Batch Number	Composition	Batch Number	Composition
TV-46000: One-month and Three-month Single Subcutaneous Injection Toxicology Study in Wistar Rats with a Recovery Period /DS-2014-043	36482084	Same as clinical/ commercial composition: Risperidone - (b) (4)	36481084	Same as clinical placebo composition:
TV-46000: 1 and 3-Month Subcutaneous Injection Toxicology Study in Beagle Dogs with a Recovery Period/DS-2014-041	36482084		36481084	Triblock PDL-PEG-PDL Copolymer - (b) (4)
TV-46000: 13-Week Repeated Dose Subcutaneous Toxicology Study with 12-Week Recovery Period in Beagle Dogs/ DS-2015-049	36532115		36531115	Diblock mPEG-PDL Copolymer - (b) (4)
MedinGel-Based Risperidone Single Dose Subcutaneous Tolerability and Toxicokinetic Study in Minipig/DS-2014-096	F1M 17 20140106-1		PL1M 17 20140106-1	Dimethyl Sulfoxide (b) (4)
TV-46000 Pharmacokinetic Study in Minipigs by Subcutaneous Route: Effect of Heat Application on Site of Injection /DP-2016-004	36532115		Not applicable	Not applicable
TV-46000 Pharmacokinetic Study in Minipigs by Subcutaneous Route: Effect of Massage After Injection/ DP-2014-158	30-030-01-F1M1701-ARE-190314			
Effect of Rubbing Site of Injection on Pharmacokinetic After Single Dose Subcutaneous Administration of Risperidone Formulation TV46000 to Beagle Dogs/ DP-2018-931	S-RIS-136			

Source: Applicant's response to Division's Information request (NDA 213586 SDN 33, 03/15/2022)

5.5.1. General Toxicology

Study title/ number: TV-46000: One-month and Three-month Single Subcutaneous Injection Toxicology Study in Wistar Rats with a Recovery Period /DS-2014-043

Key Study Findings: TV-46000 single-dose SC administration at 20, 40, 100, and 140 mg/kg resulted in the following local and drug pharmacology-related systemic effects:

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586

Uzedy (risperidone extended release injection)

- Systemic clinical signs attributable to risperidone: half-closed eyes and dyspnea at all dose levels; transient hypoactivity and hunched posture at 140 mg/kg. Transient, dose-related reduction in body weight gain during the 1st month at all doses.
- Microscopic changes in the prostate and mammary gland at all doses, suggestive of hyperprolactinemia attributable to risperidone, with complete recovery by the end of recovery period at 20 and 40 mg/kg, and partial recovery at higher doses. Statistically significant decrease in ovarian weight at 140 mg/kg without corresponding histopathology.
- At injection sites, non-adverse and partially reversible local findings in vehicle control and all TV-46000 treated groups: vehicle-related foreign body granulomatous reaction with a surrounding fibrous capsule.
- No NOAEL for systemic toxicity identified due to systemic effects attributed to risperidone at all tested dose levels. The NOAEL for local toxicity at the injection site is the highest dose tested: 140 mg/kg with plasma exposure for total active moiety: C_{max}: 297 and 459 ng/mL; AUC_{0-t}: 48570 and 62427 ng*h/mL in M and F, respectively.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 20, 40, 100, 140 mg/kg (single dose)

TV-46000 Batch N 36482084 (Dose volume 0.056, 0.111, 0.278 and 0.390 mL/kg)

Route of administration:	SC
Formulation/Vehicle:	Solution /TV-46000 –Non-API control formulation, Batch # 36481084 Dose volume: 0.195 and 0.273 mL/kg (b) (4) of the volume injected to HD groups, as TV-46000 consists of (b) (4) weight of API and (b) (4) of non-API
Species/Strain:	Rat/Wistar Han
Number/Sex/Group:	15; Additional satellite animals for TK: 3/sex/group
Age:	8-9 weeks
Unique design:	Two control groups (1 and 2) received injection volumes of 0.195 and 0.273 mL/kg, respectively; each group received two consecutive SC injections (vehicle at injection site 1 followed immediately by 0.9% NaCl at injection site 2, approximately 2 cm apart in the interscapular region). Volumes of injection for the vehicle and 0.9% NaCl were (b) (4) of the volume injected to the HD groups (TV-46000 0.278 and 0.390 mL/kg) Prior to the SC injection of TV-46000, all animals, including controls, were pre-treated for 7 days with oral risperidone (0.2 mg/kg/day) in order to be in-line with the clinical regimen of the

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
Uzedy (risperidone extended release injection)

	drug product and to acclimatize the TV-46000 groups to the active drug. Recovery period duration: 3 months
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	Half-closed eyes in all dose groups with a dose-related incidence and duration; at ≥ 100 mg/kg: transient, risperidone-related signs (hunched posture, hypoactivity, chromodacryorrhea, dyspnea, bilateral myosis) during the 1 st week post injection.
Body Weights	Transient, dose-related reduction in body weight gain during the first 4 weeks (in males at all dose levels and in both sexes at HD), correlating with lower food consumption at HD. No differences from controls in the final body weights on completion of recovery period.
Hematology	No changes of toxicological importance
Clinical Chemistry	No changes of toxicological importance.
Gross Pathology	Macroscopic white masses at injection sites in vehicle control and all dose groups
Organ Weights	Decrease in ovarian weights (-10% vs control) at 140 mg/kg, A relationship to the test item could not be excluded in view of the resting aspect of the uterus at histology which is also described with risperidone. Moderate decrease in absolute and relative thymus weight (up to -23%) in males at 20 and 100 mg/kg (statistically significant at LD only), correlating microscopically with marginal increase in the incidence of lymphoid atrophy in males.
Histopathology Adequate battery: Yes	Microscopic changes in prostate and mammary gland at all doses, suggestive of hyperprolactinemia, characterized by inflammation of the lateral lobes of the prostate, female aspect (tubulo-alveolar arrangement) of the male mammary gland and lobuloalveolar hyperplasia of the female mammary gland. At ≥ 100 mg/kg, female reproductive tract had a resting aspect characterized by mucification of vagina, atrophy of the vaginal epithelium and/or uterus, increased interstitial gland in ovaries, and lower ovarian weights. These changes are associated with the pharmacological properties of risperidone and recovered completely by the end of the recovery period at 20 and 40 mg/kg, and partially in the higher dose groups. Injection site: Macroscopic white masses correlated microscopically with empty cavities surrounded by chronic granulomatous inflammation with fibrosis. These effects, characterized as an expected foreign body reaction, were present with similar incidence and severity in all groups, including vehicle controls, and were related to the vehicle. No local reactions were observed in the saline control group. At HD, there was a slight increase in the severity/incidence of granulomatous inflammation vs vehicle controls, attributable to the higher volume of formulation injected. At the end of recovery period, there was partial recovery of the granulomatous inflammation and fibrosis in all groups including controls, and there were no significant differences between groups.

TK		Toxicokinetic parameters of total active moiety (sum of risperidone and 9-OH-risperidone) following single SC administration of TV-46000 in rats* [Mean $\pm$ SD (CV) Median for T _{max} (min-max)]							
Group		3		4		5		6	
Dose-level (mg/kg)		20		40		100		140	
Sex		M	F	M	F	M	F	M	F
T _{max}	h	3 [3-504]	1 [1-6]	3 [1-3]	3 [3-3]	3 [1-3]	3 [1-6]	3 [3-6]	6 [3-6]
C _{max}	ng/mL	77.0 $\pm$ 32.6 (42)	221 $\pm$ 97 (44)	238 $\pm$ 53 (22)	275 $\pm$ 317 (115)	423 $\pm$ 156 (37)	685 $\pm$ 199 (29)	297 $\pm$ 135 (46)	459 $\pm$ 197 (43)
AUC _{0-t}	ng $\cdot$ h/mL	6473 $\pm$ 2556 (39)	10576 $\pm$ 4514 (43)	15920 $\pm$ 3389 (21)	16461 $\pm$ 15639 (95)	54727 $\pm$ 28868 (53)	67741 $\pm$ 13978 (21)	48570 $\pm$ 20534 (42)	62427 $\pm$ 19230 (31)
AUC _{0-720h}	ng $\cdot$ h/mL	9249 $\pm$ 2089 (23)	10654 $\pm$ 4518 (42)	na	na	54727 $\pm$ 28868 (53)	67741 $\pm$ 13978 (21)	na	na
AUC _{0-1440h}	ng $\cdot$ h/mL	na	na	16405 $\pm$ 3331 (20)	16483 $\pm$ 15609 (95)	na	na	48570 $\pm$ 20534 (42)	62427 $\pm$ 19230 (31)
AUC _{0-∞}	ng $\cdot$ h/mL	9343 ^a	10983 $\pm$ 4967 (45)	16697 $\pm$ 3054 (18)	16746 $\pm$ 16007 (96)	95557 ^a	69392 $\pm$ 15512 (22)	52712 $\pm$ 22456 (43)	66089 $\pm$ 18494 (28)
t _{1/2}	h	243.0 ^a	114.1 $\pm$ 72.2 (63)	135.2 $\pm$ 17.7 (13)	162.1 $\pm$ 96.7 (60)	179.7 ^a	112.5 $\pm$ 12.0 (11)	441.0 $\pm$ 63.1 (14)	337.9 $\pm$ 196.9 (58)
λ_z	1/h	0.0029 ^a	0.0078 $\pm$ 0.0042 (54)	0.0052 $\pm$ 0.0007 (14)	0.0056 $\pm$ 0.0037 (65)	0.0039 ^a	0.0062 $\pm$ 0.0006 (10)	0.0016 $\pm$ 0.0002 (15)	0.0031 $\pm$ 0.0027 (88)

M: Male; F: Female, na: not applicable.
^a: value obtained from one animal.
In italic: values measured with a low-level of confidence

Study title/ number: TV-46000: 1 and 3-Month Subcutaneous Injection Toxicology Study in Beagle Dogs with a Recovery Period/DS-2014-041

Key Study Findings: TV-46000 single-dose SC administration at 7, 14, 50 and 100 mg/kg resulted in the following local and drug pharmacology-related systemic effects:

- Systemic effects in reproductive organs at all dose levels (lower epididymis weight and hypo-spermatogenesis) related to the pharmacological effect of risperidone.
- At injection sites, non-adverse, partially reversible local findings in vehicle control and all TV-46000 treated groups: vehicle-related foreign body granulomatous reaction with a surrounding fibrous capsule, with similar incidence and severity in all groups. The severity of reactions was not dose (or volume) dependent.
- No NOAEL for systemic toxicity identified due to systemic effects attributed to risperidone pharmacology at all dose levels. The NOAEL for local toxicity at injection site is the highest dose tested (100 mg/kg) with plasma exposure for total active moiety: C_{max}: 647 and 653 ng/mL; AUC_{0-t}: 611379 and 433716 ng $\cdot$ h/mL for M and F, respectively.

Conducting laboratory and location: (b) (4)
 GLP compliance: Yes

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586

Uzedly (risperidone extended release injection)

Methods

Dose and frequency of dosing: 7, 14, 50, 100 mg/kg, single dose

TV-46000 Batch N 36482084 (Dose volume 0.019, 0.039, 0.139 and 0.278 mL/kg)

Route of administration:	SC
Formulation/Vehicle:	Solution /TV-46000 –Non-API control formulation Batch # 36481084 Dose volume 0.097 and 0.195 mL/kg (b) (4) of the volume injected to HD groups, as TV-46000 consists of (b) (4) weight of API and (b) (4) of non-API
Species/Strain:	Dog/Beagle
Number/Sex/Group:	6 (4 main + 2 recovery); Satellite animals for TK: 3/sex/group
Age:	7-9 months
Unique design:	Prior to TV-46000 SC injection, all animals, including controls were pre-treated for 7 days by oral risperidone (0.2 mg/kg/day) to be in-line with the clinical regimen of the drug product and to acclimatize the TV-46000 groups to the active drug. Two control groups (1 and 2) received injection volumes of 0.097 and 0.195 mL/kg, respectively. Each control group received two consecutive SC injections (vehicle at injection site 1 followed immediately by 0.9% NaCl at injection site 2, approximately 3 cm apart in the interscapular region). Volumes of injection for the vehicle and 0.9% NaCl were (b) (4) of the volume injected to the HD groups (0.139 and 0.278 mL/kg) as TV-46000 consists of (b) (4) weight of API and (b) (4) of non-API. Vehicle and saline control injections: administered by 2 consecutive SC injections in 2 sites approximately 3 cm apart in the inter-scapular region. Observation period: Main groups: 31 days for 7- and 50 mg/kg and 91 days for 14- and 100 mg/kg groups. Recovery period: 129 days for 7- and 50 mg/kg groups; 149 days for 14- and 100 mg/kg groups
Deviation from study protocol:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	Hypoactivity, hypersalivation (males only) and tremors observed transiently at 50 mg/kg (males) and 100 mg/kg. Half-closed eyes at all dose levels, up to Day 2 or 3 (at 7 to 50 mg/kg), and up to Day 5 in males and even until Day 31-day in females at 100 mg/kg. These clinical signs are of risperidone-related pharmacological origin. No signs related to pain at the injection site were observed.
Body Weights	Statistically significant transient body weight loss in males at 100 mg/kg vs. controls (-0.4 kg over 29 days, p<0.01)
Hematology	Decrease in WBC count in females at 50 and 100 mg/kg (reversible)
Clinical Chemistry	Changes in clinical pathology parameters compared to controls mainly at 100 mg/kg (decrease in potassium, inorganic phosphorus in males, increase in cholesterol levels in females). These changes were reversible. All changes (except for phosphorus) are known pharmacological effects of risperidone. Due to the lack of dose-response, reduction in phosphorus levels considered not adverse.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586

Uzedy (risperidone extended release injection)

Gross Pathology	Higher incidence of small uterus and small prostate at 100 mg/kg compared to controls. At injection sites, macroscopic white masses in vehicle control and all dose groups; no edema or hematoma. At the end of the recovery periods: thickening, and white, yellow, or black masses in all groups. These findings were related to the vehicle.																																																																																																																			
Organ Weights	Risperidone-related lower epididymis weights at ≥ 14 mg/kg and lower testis and ovary weights at 100 mg/kg, partially reversible after recovery period. Decreased thymus weights at all doses correlating microscopically with increase in the incidence of thymus lymphoid atrophy in males (likely attributable to non-specific stress effect due to injection). Increased adrenal gland weights in females at all dose levels without corresponding microscopic findings (likely stress-related).																																																																																																																			
Histopathology Adequate battery: Yes	Changes in the male and female reproductive organs attributable to risperidone pharmacology: In males, increased incidence and severity of acinar cell atrophy in prostate at 100 mg/kg, hypo-spermatogenesis in testes at ≥ 14 mg/kg and sloughed cells in the lumen from epididymis tubules secondary to hypo-spermatogenesis at 100 mg/kg. Hypo-spermatogenesis also observed at the end of the recovery period, with minimally increased severity/incidence vs. controls, indicating partial reversibility. In females, at 100 mg/kg, immaturity of genital tract in 3/4 females (absence of <i>corpora lutea</i> in ovaries, immature uterus and vagina), resting appearance of reproductive system in 1/4 females (atrophy of the uterus and vagina) suggestive of a delayed estrus. The findings in females were completely reversible at the end of the recovery period. Injection site: Macroscopic white masses correlated microscopically with empty cavities surrounded by chronic granulomatous inflammation with fibrosis. These effects, characterized as an expected foreign body reaction, were present with similar incidence and severity in all groups, including vehicle control, (but not saline control) and were related to the vehicle. In recovery samples there was a trend for a progressive, time-related healing of these findings, without any suggestion of aggravation and no indication for time-related increase in incidence or severity.																																																																																																																			
TK*	<table border="1"> <thead> <tr> <th>Group</th><th colspan="2">Group 3, 20mg/kg</th><th colspan="2">Group 4, 40mg/kg</th><th colspan="2">Group 5, 100mg/kg</th><th colspan="2">Group 6, 140mg/kg</th></tr> <tr> <th>PK Parameters: Mean$\pm$SD (CV)</th><th>Male</th><th>Female</th><th>Male</th><th>Female</th><th>Male</th><th>Female</th><th>Male</th><th>Female</th></tr> </thead> <tbody> <tr> <td colspan="9">Total Active Moiety</td></tr> <tr> <td>t_{max} (h)^a</td><td>24 [3-168]</td><td>24 [24-24]</td><td>24 [6-336]</td><td>24 [3-24]</td><td>3 [3-24]</td><td>24 [6-336]</td><td>528 [24-1800]</td><td>6 [3-168]</td></tr> <tr> <td>C_{max} (ng/mL)</td><td>111$\pm$45 (40)</td><td>84.3$\pm$ 19.0 (23)</td><td>164$\pm$85 (52)</td><td>140$\pm$46 (33)</td><td>360$\pm$100 (28)</td><td>469$\pm$195 (42)</td><td>647$\pm$266 (41)</td><td>653$\pm$255 (39)</td></tr> <tr> <td>AUC_{0-4} (ng·h/mL)</td><td>33806$\pm$13024 (39)</td><td>25927$\pm$8400 (32)</td><td>99353$\pm$20201 (20)</td><td>62563$\pm$15671 (25)</td><td>93853$\pm$ 37820 (40)</td><td>179596$\pm$ 48085 (27)</td><td>611379$\pm$ 192962 (32)</td><td>433716$\pm$183925 (42)</td></tr> <tr> <td>$AUC_{0-\infty}$ (ng·h/mL)</td><td>NR</td><td>NR</td><td>113925^b</td><td>54457^b</td><td>107079^b</td><td>181619^c</td><td>709619$\pm$ 243155 (34)</td><td>NR</td></tr> <tr> <td>$t_{1/2}$ (h)</td><td>478.6$\pm$146.8 (31)</td><td>542.7$\pm$227.1 (42)</td><td>225.8^c</td><td>832.9$\pm$687.0 (82)</td><td>649.0$\pm$ 649.4 (100)</td><td>433.2^b</td><td>291.9$\pm$119.7 (41)</td><td>NR</td></tr> <tr> <td colspan="9">Additional Information: All animals received an oral pretreatment of risperidone (0.2 mg/kg/day) from days -7 to -1 prior to the sc injection to simulate the clinical dosing regimen.</td></tr> <tr> <td colspan="9">^a Median [minimum-maximum].</td></tr> <tr> <td colspan="9">^b no SD and CV were calculated, as the mean value was obtained from two reliable data.</td></tr> <tr> <td colspan="9">^c Value obtained from 1 animal.</td></tr> </tbody> </table> Source: Study report Sponsor Reference Number: DS-2014-041, p. 1096 * TK data discussion in Section 5.4. ADME/PK of this review								Group	Group 3, 20mg/kg		Group 4, 40mg/kg		Group 5, 100mg/kg		Group 6, 140mg/kg		PK Parameters: Mean $\pm$ SD (CV)	Male	Female	Male	Female	Male	Female	Male	Female	Total Active Moiety									t_{max} (h) ^a	24 [3-168]	24 [24-24]	24 [6-336]	24 [3-24]	3 [3-24]	24 [6-336]	528 [24-1800]	6 [3-168]	C_{max} (ng/mL)	111 $\pm$ 45 (40)	84.3 $\pm$ 19.0 (23)	164 $\pm$ 85 (52)	140 $\pm$ 46 (33)	360 $\pm$ 100 (28)	469 $\pm$ 195 (42)	647 $\pm$ 266 (41)	653 $\pm$ 255 (39)	AUC_{0-4} (ng·h/mL)	33806 $\pm$ 13024 (39)	25927 $\pm$ 8400 (32)	99353 $\pm$ 20201 (20)	62563 $\pm$ 15671 (25)	93853 $\pm$ 37820 (40)	179596 $\pm$ 48085 (27)	611379 $\pm$ 192962 (32)	433716 $\pm$ 183925 (42)	$AUC_{0-\infty}$ (ng·h/mL)	NR	NR	113925 ^b	54457 ^b	107079 ^b	181619 ^c	709619 $\pm$ 243155 (34)	NR	$t_{1/2}$ (h)	478.6 $\pm$ 146.8 (31)	542.7 $\pm$ 227.1 (42)	225.8 ^c	832.9 $\pm$ 687.0 (82)	649.0 $\pm$ 649.4 (100)	433.2 ^b	291.9 $\pm$ 119.7 (41)	NR	Additional Information: All animals received an oral pretreatment of risperidone (0.2 mg/kg/day) from days -7 to -1 prior to the sc injection to simulate the clinical dosing regimen.									^a Median [minimum-maximum].									^b no SD and CV were calculated, as the mean value was obtained from two reliable data.									^c Value obtained from 1 animal.								
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LD: low dose; MD: mid dose; HD: high dose. -: indicates reduction in parameters compared to control.

Study title/number: TV-46000: 13-Week Repeated Dose Subcutaneous Toxicology Study with 12-Week Recovery Period in Beagle Dogs/ DS-2015-049

Key Study Findings: TV-46000 repeat-dose SC administration in dogs at 7, 20, and 50 mg/kg resulted in the following local and drug pharmacology-related systemic effects:

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586

Uzedy (risperidone extended release injection)

- Systemic effects related to known properties of risperidone: Transient clinical sign of half-closed eyes at all doses with dose-dependent incidence. Decreased weight of male and female reproductive organs (prostate, epididymis, testes, ovaries, and uterus), without correlating histopathology, in all TV-46000-treated groups, persisting through the end of recovery period for prostate (at all dose levels), and for ovaries and uterus (at HD).
- At injection sites, non-adverse local findings in vehicle control and all TV-46000 treated groups: vehicle-related foreign body granulomatous reaction with a surrounding fibrous capsule, with similar incidence and severity in all groups and partial recovery at the end of the study. No local reactions in the saline control group.
- No NOAEL for systemic toxicity identified due to systemic effects on reproductive organs at all tested dose levels, attributable to the pharmacological effect of risperidone. The NOAEL for local toxicity at injection site is the highest dose of 50 mg/kg with plasma exposure for total active moiety: Cmax: 636 and 496 ng/mL; AUC_{0-648h}: 311000 and 258000 ng*h/mL in M and F, respectively.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 7, 20, 50 mg/kg/ once a month for 3 months

TV-46000 Batch N 36532115 (Dose volume 0.019, 0.056, 0.139 mL/kg)

Route of administration:	SC
Formulation/Vehicle:	Solution /TV-46000–Non-API control formulation, Batch # 36531115 Dose volume 0.097 mL/kg (b) (4) of the volume injected to HD group as TV-46000 consists of (b) (4) weight of API and (b) (4) of non-API).
Species/Strain:	Dog/Beagle
Number/Sex/Group:	5 (3 main + 2 recovery); Satellite animals for TK: 3/sex/group
Age:	6-7 months
Unique design:	Preloading with oral Risperidone (0.2 mg/kg/day) for all animals, including controls for 7 consecutive days (Days -7 to -1). Two control groups: Vehicle control and Saline (0.9% NaCl) control, dose volume 0.097 mL/kg each (b) (4) of the volume injected to the HD group (0.139 mL/kg) as TV-46000 consists of (b) (4) weight of API and (b) (4) of non-API). On Days 1, 29 and 57, the animals received one single SC injection of the dose formulation, vehicle, or saline, administered at 3 different sites per dog separated by approximately 3 cm in the interscapular region. On day 85, all main groups were sacrificed; recovery animals were kept for a recovery period of 56 days (sacrificed on Day 141).
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	Half-closed eyes at all dose levels, with dose-dependent incidence (6/ 10, 8/10 and 10/10 animals at LD, MD and HD, respectively). This sign was transient and observed from Day 7 on, for 2-3 months, until the middle phase of the study.
Body Weights	No consistent drug-related changes in body weight and food consumption
Hematology	No drug-related changes
Clinical Chemistry	No changes were of toxicological concern
Gross Pathology	Local reactions at injection sites: slight erythema and/or edema, and hematoma from day 2 to day 60. Nodules and induration in all TV-46000-treated and vehicle control groups from day 29 to end of the recovery period, but not in the saline control. The depot size was reduced from a diameter of approximately 13 mm (on day 83) to approximately 5 mm (on day 172) post-injection.
Organ Weights	Decrease in the weight of reproductive organs (prostate, epididymis, testes, ovaries, and uterus) in all TV-46000-treated groups. Smaller prostate size at all dose levels in correlation with the low prostate weights. At the end of recovery period, the values were still lower than controls for prostate (at all dose levels), and for ovaries and uterus (at HD). These changes in the male and female reproductive systems are related to the known properties of risperidone.
Histopathology Adequate battery: Yes	Minimal to moderate vacuolation in axillary lymph nodes with higher incidence and/or severity in vehicle- or the drug-treated groups vs. saline control, particularly at MD and HD. This finding was related to drainage of subcutaneously injected polymers (vehicle) by these lymph nodes. The incidence/severity of the finding correlated with the volume of injected vehicle. At the end of the recovery period, the finding was still present, but at lower severity, in all vehicle and drug treated groups. Injection site: Nodules, observed microscopically in all vehicle and drug-treated groups (but not in the saline control), related to the vehicle (polymers) and consisting of cavities in the subcutaneous space associated with granulomatous inflammation, fibrosis, lymphoid cell infiltrates, and granulocytes in the lumen. This is an expected foreign body reaction toward the SC injected polymers. At the end of recovery period, there was partial recovery of the granulomatous inflammation and fibrosis in all groups including vehicle control, and there were no significant differences between groups.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
Uzedy (risperidone extended release injection)

TK

Systemic Exposure to Total Active Moiety after repeat SC Administration of TV-46000 to Dogs* (Study DS-2015-049)

Treatment	Study day	Gender	n	Nominal dose (mg/kg)	C _{max} ^b (ng/mL)	AUC _{0-648h} ^b (ng·h/mL)
LOW	1 (1 st injection)	Male	5	7	163 (47.4)	51500 (39.2)
		Female	5	7	84.4 (47.5)	29500 (48.8)
	29 (2 nd injection)	Male	5	7	196 (37.7)	62900 (47.1)
		Female	5	7	108 (54.1)	40300 (61.3)
	57 (3 rd injection)	Male	5	7	174 (39.9)	68400 (38.5)
		Female	5	7	92.8 (61.9)	40100 (55.9)
MID	1 (1 st injection)	Male	5	20	164 (54.2)	59900 (48.2)
		Female	5	20	170 (34.4)	55900 (29.3)
	29 (2 nd injection)	Male	5	20	209 (42.5)	91300 (40.4)
		Female	5	20	297 (27.8)	125000 (26.2)
	57 (3 rd injection)	Male	5	20	218 (35.3)	115000 (35.5)
		Female	5	20	280 (31.7)	137000 (43.6)
HIGH	1 (1 st injection)	Male	5	50	541 (69.1)	159000 (45.7)
		Female	5	50	262 (16.5)	100000 (10.3)
	29 (2 nd injection)	Male	5	50	576 (62.3)	244000 (75.0)
		Female	5	50	496 (38.5)	237000 (40.5)
	57 (3 rd injection)	Male	5	50	636 (64.9)	311000 (62.4)
		Female	5	50	456 (32.9)	258000 (39.1)

^a median (minimum-maximum)

^b mean (CV%)

AUC_{0-648h}=area under the plasma concentration-time curve from time 0 to 648 hours after study drug administration;

C_{max}=maximum observed plasma drug concentration.

Source: 2.6.6 Toxicology Written Summary, Table 10, p. 31

* TK data discussion in Section 5.4. ADME/PK of this review

LD: low dose; MD: mid dose; HD: high dose. -: indicates reduction in parameters compared to control.

5.5.1.1. General toxicology; additional studies

Local tolerability was evaluated as part of the general toxicology studies in rats and dogs described above. In addition, local tolerability was evaluated in a dedicated study in minipigs, as well as in studies assessing the effect of application of heat, massage or rubbing on TV-46000 tolerability and PK in minipigs and dogs, as described below.

Study title /number: MedinGel-Based Risperidone Single Dose Subcutaneous Tolerability and Toxicokinetic Study in Minipig/DS-2014-096

Key Study Findings: TV-46000 was well tolerated in male minipigs over a 45-day period after a single SC administration at 50 mg/animal.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586

Uzedy (risperidone extended release injection)

- Systemic effects: There were no mortalities, clinical signs, or body weights changes during the study.
- At injection sites, there were no signs of irritation, edema, erythema, or pain, and no macroscopic or microscopic treatment-related changes.

Conducting laboratory and location: (b) (4)

GLP compliance: No

Methods

Dose and frequency of dosing: 50 mg/animal, single SC dose

TV-46000 (F1M-17) Batch N F1M_17 20140106-1 (Dose volume 0.14 mL/animal)

Route of administration:	SC
Formulation/Vehicle:	Solution / ready to use dosage form (prefilled vial), Batch N PL1M_17 20140106-1. Dose volume 0.14 mL/animal
Species/Strain:	Minipig
Number/Sex/Group:	3/M/group
Age:	4-5 months (9-11kg)
Unique design:	Each animal received TV-46000 by a single SC injection plus 2 additional subsequent SC injections (of vehicle and saline) at the same dose volume, for a total of 3 subsequent SC injections per animal at 3 different sites: the inter-scapular region for TV-46000, the right and left flank regions for vehicle and saline, respectively. Each animal served as its own control. Animals were sacrificed after 6 h, 24 h, and 7, 14, 30, and 45days post injection. Assessments included Injection sites histopathology and TK plasma levels of risperidone, 9-OH-risperidone and total active moiety (at 1, 3, and 6 h post-dose on day 1, and on days 2, 8, 15, 31 and 46).
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

TV-46000 was well tolerated, there were no mortalities, clinical signs, or changes in body weights during the study. At injection sites, there were no signs of irritation, edema, erythema, or pain, and no macroscopic or microscopic treatment-related changes.

TK: Rapid absorption with median T_{max} of 3 h and 168 h for risperidone and 9-OH-risperidone, respectively. Low initial increase in plasma levels, with a mean C_{max} of 13.4 ng/mL for total active moiety. The initial absorption phase was followed by a slow decrease in plasma concentrations with no quantifiable levels of risperidone or 9-OH-risperidone on day 30. The mean exposure to total active moiety (AUC0-t) ranged between 4135 and 3535 ng·h/mL.

Study title /number: TV-46000 Pharmacokinetic Study in Minipigs by Subcutaneous**Route: Effect of Heat Application on Site of Injection /DP-2016-004**

Key Study Findings: Heating the injection site did not result in any differences in local or systemic tolerability vs. animals not subjected to heating. Release of risperidone and its related PK profile was not affected by heating.

Conducting laboratory and location:

(b) (4)

GLP compliance: No

Methods

Dose and frequency of dosing: 50 mg/animal, single SC dose

TV-46000 Batch N 36532115 (Dose volume 0.14 mL/animal)

Route of administration:	SC
Formulation/Vehicle:	Solution / ready to use dosage form (prefilled vial)
Species/Strain:	Minipig
Number/Sex/Group:	8/M/group
Age:	4-5 months (9-11kg)
Unique design:	Two groups received TV-46000 360 mg/mL by a single SC injection of 50 mg/animal using a dose volume of 0.14 mL/animal, at the right side of the spine. Group 1 was subjected to 20-min heating sessions at 40° C to 42° C, directly on the injection site, 2 h post-dosing on day 1 and on days 2, 4, 6, and 8 post injection. No heating of the injection site was applied to animals in group 2. Injection sites of all animals were observed for induration and swelling, pain at palpation, presence of depot, inflammation (erythema, cutaneous heat, swelling, hardening and itching) from day 1 until sacrifice on day 31 post-injection. Upon sacrifice, injection sites were retrieved for histopathology examination. TK: Plasma levels of risperidone, 9-OH-risperidone and total active moiety were determined in blood samples collected from pre-dose through 30 days post-injection, prior to and at 0.5, 1, 3, 6 h after each heating session.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Clinical signs: Risperidone-related decreased activity, incoordination, reduced food intake, tremors during the 1st week of the study, with higher incidence and duration in animals from the heated group. Body weights were unaffected by treatment.

Injection site: Group 1 (heat): slight swelling and induration due to the presence of depot in the majority of animals from the day of dosing up to day 28. Slight erythema in individual animals, recovering by day 9. Group 2 (control): slight swelling due to the presence of depot in majority of animals from the day of

Uzedy (risperidone extended release injection)

dosing up to day 31. Slight induration of the treated site in 5/8 animals from day 4, with incomplete recovery. Increased cutaneous thickness in 2/8 animals on day 31. Microscopically, typical foreign-body reaction at the injection sites was observed in both groups. No substantial differences in local tolerability were observed between animals subjected to heating at the injection site and animals that did not receive heat at the injection site.

TK: Release of risperidone and its related PK profile was not affected by heating. TAM peak concentration was observed at 2 h post-injections for both groups, before heating sessions were conducted. Plasma concentration of TAM at 6 h after each heating session indicated that heating had no effect on risperidone release when compared to preheating values. The values up to 6 h post heating were similar to control values (group 2). A similar concentration-time profile was achieved from both groups showing similar exposure.

**Study title /number: TV-46000 Pharmacokinetic Study in Minipigs by Subcutaneous
Route: Effect of Massage After Injection/ DP-2014-158**

Key Study Findings:

- No substantial differences in the systemic and local tolerability due to massage at the injection site. TV-46000 was locally and systemically well tolerated after a single SC injection of 50 mg/animal. Transient clinical signs related to the pharmacological action of risperidone were observed in all animals after injection.
- No differences in exposure (C_{max} and AUC_{0-t}) to risperidone and 9-OH-risperidone due to massage at the injection site. No spike in concentrations was observed when comparing the pre- and post-massage plasma samples. No residual risperidone and polymer content was found in the depot tissue samples excised 32 days after injection.

Conducting laboratory and location: (b) (4)

GLP compliance: No

Methods

Dose and frequency of dosing: 50 mg/animal, single SC dose

TV-46000 Batch N 30-030-01-F1M1701-ARE-190314 (Dose volume 0.145 mL/animal)

Route of administration:	SC
Formulation/Vehicle:	Solution / ready to use dosage form (prefilled vial)
Species/Strain:	Minipig
Number/Sex/Group:	3 (test) 4(control)/M/group
Age:	7 months (15 kg)
Unique design:	Three groups received a single SC injection of TV-46000 at a dose of 50 mg/animal each. Massage of the injection site was applied to group 1 at 1 h, 2 h, 3 h, and 6 h after injection, and to group 2 at 24 h, 48 h, and 72 h after injection. No massage was applied to animals of group 3. (Massage was performed using the lateral side of a 10-cc syringe, rolling over the marked injection site for 1 min with at least 30 back-and-forth rolls). Plasma for PK was collected from pre-dose up to 720 h post

	dose from all animals, and up to 1752 h post dose from 2 non-massaged recovery animals (group 3). SC tissue samples were excised 32 days after injection from 3 minipigs for evaluation of the remaining risperidone and polymer content in the depot.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Clinical signs: Risperidone-related decreased activity and tremors on days 1 and 2, in all animals and all groups. Massage applied to the injection site of groups 1 and 2 had no effect on clinical signs. Body weights were unaffected by treatment. No changes of toxicological concern were observed in hematology, coagulation and clinical chemistry parameters.

Injection site: No substantial differences in local tolerability between animals subjected to massage and not subjected to massage at the injection site.

TK: Release of risperidone and its PK profile was not affected by massage. Exposure to risperidone and 9-OH-risperidone, as expressed by C_{max} and AUC_{0-t} , was similar for all groups. No spike in post-massage plasma concentrations was observed vs. pre-massage plasma samples. All animals were exposed to risperidone and its metabolite 9-OHrisperidone to a similar extent.

No residual risperidone and polymer content was found in the depot tissue samples excised 32 days after injection.

Table 3. Pharmacokinetics Parameter Values (Mean [CV%]) for Total Active Moiety Following a Single Subcutaneous Administration of TV-46000 at 50 mg/minipig

Analyte	Groups	$t_{1/2}$ (h)	t_{max}^a (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)	$AUC_{0-\infty}$ (h*ng/mL)
Total active moiety ^b	Group 1 Massage at 1, 2, 3 and 6 h postdose	96.7 (30.4)	3 (1.5-6.5)	23.61 (20.6)	2880.3 (19.3)	3033.1 (14.9)
	Group 2 Massage at 24, 48, and 72 h postdose	112 (27.7)	3 (1-168)	15.39 (42.4)	2528.7 (26.4)	2663.2 (26.8)
	Group 3 No massage	144.0 (30.5)	3.3 (2-6.5)	18.9 (50.1)	3152.3 (38.8)	3407.9 (36.1)

a Median (minimum-maximum).

b Total active moiety is the sum of risperidone and 9-OH-risperidone.

AUC_{0-t} =area under the plasma drug concentration-time curve from time 0 to the time of the last measurable drug concentration.

$AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity.

C_{max} =maximum observed plasma drug concentration; CV=coefficient of variation; OH=hydroxy; $t_{1/2}$ =elimination half-life; t_{max} =time to maximum observed concentration

(Source: Pharmacokinetics Written Summary, Table 18, p.26)

Study title /number: Effect of Rubbing Site of Injection on Pharmacokinetic After Single Dose Subcutaneous Administration of Risperidone Formulation TV-46000 to Beagle Dogs/ DP-2018-931

Key Study Findings:

- Transient increase in TAM plasma exposure (by 33% for AUC_{0-t} and 23% for C max) occurred upon rubbing the injection site immediately post injection, however rubbing from 0.5 h to 4 h post injection did not cause increase in risperidone, active metabolite or TAM exposure.
- No evidence of dose dumping or effects on extended-release characteristics of TV-46000, and the depot still formed effectively when subjected to this challenge.

Conducting laboratory and location:

(b) (4)

GLP compliance: No

Methods

Dose and frequency of dosing: 12.5 mg/animal, single SC dose

TV-46000 Batch N S-RIS-136 (Dose volume 35 µL/animal)

Route of administration:	SC
Formulation/Vehicle:	Solution / ready to use dosage form (prefilled vial)
Species/Strain:	Dog/Beagle
Number/Sex/Group:	6/M/group
Age:	10-18 months (7.6-13 kg)
Unique design:	Five groups received a single SC injection of TV-46000 at a dose of 12.5 mg/animal each. Rubbing was applied to all groups except for group 1 (control). Groups 2, 3, 4, and 5 were rubbed at 0, 0.5, 1 or 4 h post-injection, respectively, by applying moderate pressure in a back- and-forth motion of administrator's fingers, for 30 sec. This study was intended to replicate a pilot clinical study in healthy volunteers (RISPE1ZG15EU), and therefore, clinical formulation of TV-46000 was used, at similar dose level as in the clinical study, and the same rubbing technique and duration as in the clinical study. Injection sites were observed twice during the 1st week post-injection, then once weekly throughout the study. Plasma levels of risperidone, 9-OH-risperidone and total active moiety were determined in samples collected from all animals at designated sampling times.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

No clinical signs were noted during the study and body weights were unaffected by treatment.

Injection site: there were no signs of irritation, edema, erythema, or pain at the injection sites, except for one case of transient swelling in the group rubbed at 0.5 h post injection (Group 3). There were no differences in local tolerability between animals subjected and not subjected to rubbing at the injection site. Rubbing of injection site, at all tested times post injection, was well tolerated.

TK: No dose dumping or unexpected rapid elevation in TAM plasma levels were observed in any group. A 33% increase in TAM plasma exposure (AUC_{0-t}) and a 22% increase in C_{max} was observed with rubbing of the injection site immediately post injection (group 2) vs. control without rubbing (Group 1). Rubbing from 0.5 h to 4 h post injection did not cause increase in risperidone, active metabolite, or TAM exposure.

The increase in exposure with rubbing immediately post injection was consistent with the results obtained in a pilot clinical study, in which rubbing immediately post-injection resulted in similar increase in C_{max} and AUC (Study RISPE1ZG15EU).

The results suggest that the extended-release characteristic of TV-46000 over time did not change, and the depot still formed effectively when subjected to this challenge.

5.5.2. Genetic Toxicology

Genotoxicity studies were not performed with TV-46000 because relevant data for risperidone are available in the label for the listed drug, Risperdal. The assessment of excipients in the TV-46000 clinical formulation included an Ames test to evaluate the potential mutagenicity of the copolymers.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Evaluation of the Mutagenic Activity of mPEG-PDLLA and PDLLAPEG-PDLLA Copolymers in DMSO in the Salmonella Typhimurium Reverse Mutation Assay and the Escherichia Coli Reverse Mutation Assay /Study DS-2015-050

Summary of results and Study Findings:

The mutagenic potential of the vehicle used in TV-46000 (7:5 mixture of two copolymers: methoxy-poly(ethylene glycol)-co-poly(D,L-lactide) [mPEG-PDLLA] and poly(D,L-lactide)-co-poly(ethylene glycol)-co-poly(D,L-lactide) [PDLLA-PEG-PDLLA] suspended in dimethyl sulfoxide [DMSO]) was tested in a GLP Ames test in TA1535, TA1537, TA98, TA100 Salmonella typhimurium strains, and in WP2uvrA Escherichia coli strains with and without S9 liver activation system at concentrations up to 5000 µg/plate. In this study, the top dose contained 5000 µg/plate of the copolymers (3000 µg/plate of the mPEG-PDLLA and 2000 µg/plate of the PDLLA-PEG-PDLLA). The results showed no increase in the number of revertant colonies in any of the tester strains compared to the negative control and thus the mixture is considered non-mutagenic under the conditions of this assay.

GLP compliance: Yes: Appropriate positive controls were used and the negative and positive control values were within acceptable ranges. Study appropriately conducted per OECD guidelines # 471.

Test system: TA1535, TA1537, TA98, TA100 Salmonella typhimurium strains, and in WP2uvrA Escherichia coli strains with and without S9 liver activation system

Study is valid: Yes

5.5.3. Carcinogenicity

No carcinogenicity studies were conducted with TV-46000

5.5.4. Reproductive and Developmental Toxicology

No reproductive and developmental toxicity studies were conducted with TV-46000

5.5.5. Other Toxicology Studies

Toxicity of excipients and potential degradation products

Toxicity assessment of the excipients in TV-46000 clinical formulation (specifically, the potential degradation products of the copolymers) included two single-dose intravenous toxicity studies in rats, evaluating the acute toxicity of copolymers' intermediate degradation products

(b) (4) (representative degradation by-products of (b) (4) the di-block copolymer of TV-46000 before the final degradation into (b) (4) (b) (4)

Study title /number: (b) (4) **Single Dose Toxicity and excretion Pilot Study in Rats/**
DS-2015-056

Key Study Findings: The intermediate degradation product (b) (4) a representative degradation by-product of methoxy-poly(ethylene glycol)-co-poly(D,L-lactide) [(b) (4) the di-block copolymer in TV-46000] did not cause any adverse findings in rats after a single IV administration at doses up to (b) (4) mg/kg.

Conducting laboratory and location: (b) (4)
GLP compliance: No

Methods

Dose and frequency of dosing: (b) (4) (b) (4) mg/kg, single dose

(Dose volume: (b) (4) mL/kg)

(b) (4) (b) (4) mg/kg, single dose

(Dose volume: (b) (4) mL/kg)

Route of administration:	IV
Formulation/Vehicle:	Solution/ Phosphate Buffered Saline pH 7.4
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	3/M/group
Age:	9 weeks (mean weight 335 g)
Unique design:	The acute toxicity of monodispersed (b) (4) a representative degradation by-product of (b) (4) (the di-block copolymer in TV-46000), was tested in comparison

	to that of (b) (4) following a single IV administration. Four groups of rats received a single IV (slow bolus) dose of (b) (4) at (b) (4) mg/kg, or (b) (4) at (b) (4) and (b) (4) mg/kg. Assessments included mortality, morbidity, body weight, hematology, clinical chemistry, and gross pathology. In addition, the amount of (b) (4) was quantified in urine after iv injection of (b) (4) and (b) (4).
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Both (b) (4) at (b) (4) mg/kg and (b) (4) at doses up to (b) (4) mg/kg were well tolerated.

No treatment-related effects on clinical signs, body weight, hematology, clinical chemistry parameters, or macroscopic pathology were observed. Similar amounts of (b) (4) were excreted in urine of animals injected with (b) (4) mg/kg (b) (4) and in animals injected with a comparable amount of (b) (4) (b) (4) mg/kg). (b) (4) was mainly excreted within 24 h post-administration, with similar total cumulative excretion of (b) (4) up to 96 hours post-injection. There was no difference in urinary parameters (T_{max} , C_{max} and AUC_{0-t}) of (b) (4) after administration of (b) (4) or (b) (4). Total amount of (b) (4) excreted cumulatively up to 4 days in the urine increased dose-proportionally.

Study title /number: (b) (4) **Single Dose Toxicity and Excretion Pilot Study by Intravenous Route in Male Sprague-Dawley Rats/ DS-2015-046**

Key Study Findings: The copolymers' intermediate degradation product (b) (4) a representative degradation by-product of TV-46000 di-block copolymer poly(D,L-lactide)-co-poly(ethylene glycol)-co-poly(D,L-lactide) did not cause any adverse findings in rats after a single IV administration at doses up to (b) (4) mg/kg.

Conducting laboratory and location: (b) (4)
GLP compliance: No

Methods

Dose and frequency of dosing: (b) (4) (b) (4) mg/kg, single dose
(Dose volume: (b) (4) mL/kg)
(b) (4) (b) (4) mg/kg, single dose
(Dose volume: (b) (4) mL/kg)

Route of administration:	IV
Formulation/Vehicle:	Solution/ Phosphate Buffered Saline pH 7.4
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	3/M/group

Age:	10 weeks (mean weight 363 g)
Unique design:	The acute toxicity of (b) (4) a representative degradation by-product of (b) (4) (the di-block copolymer of TV-46000), was tested in comparison to that of (b) (4) following a single iv administration. Four groups of rats received a single iv (slow bolus) dose of (b) (4) at (b) (4) mg/kg, or (b) (4) at (b) (4) and (b) (4) mg/kg. The high dose was selected using the worst-case scenario assuming that all the drug products is degraded at once into (b) (4). Assessments included mortality, morbidity, body weight, hematology, clinical chemistry, and gross pathology. In addition, the amount of (b) (4) was quantified in urine after iv injection of (b) (4) and (b) (4).
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Both (b) (4) and (b) (4) did not induce any clinical signs and were well tolerated at all dose levels. Observed changes were limited to a slight (- 3%) decrease in body weight at HD of (b) (4). There were no drug-related macroscopic changes.

Following single intravenous administration of (b) (4) at (b) (4) mg/kg, the total cumulative excretion of (b) (4) in urine over a 96-h period was systematically higher than the total cumulative excretion of (b) (4) after IV administration of (b) (4) at (b) (4) and (b) (4) mg/kg. The total amount of (b) (4) excreted cumulatively in the urine over 96-hours, increased less than dose-proportionally between (b) (4) and (b) (4) mg/kg and dose proportionally between (b) (4) and (b) (4) mg/kg. The maximum excretion rate of (b) (4) was reached at 12 h post-dosing for all groups and test items.

5.5.6. Qualification of the inactive ingredients

- The **diblock and triblock copolymers** in the TV-46000 formulation, (b) (4) (b) (4) (b) (4) are well-characterized polymers used in many approved medical applications. The combination of these two polymers as block copolymers also exists in approved marketed drug products. The copolymers are degraded into (b) (4) (b) (4) of no toxicological concern. Intermediate degradants of the copolymers that are expected to be sufficiently water soluble to reach the systemic circulation are the (b) (4). Based on published literature, these (b) (4) are presumed to be degraded to (b) (4), which are nontoxic and are ultimately excreted via the urine.

Support for the safety of these copolymers was provided by the single- and repeat-dose general toxicology SC studies conducted with TV-46000 in rats, dogs and minipigs. These studies included a control group with the copolymers alone (as vehicle control) in addition to a saline control. In these studies, the total dose and volume of copolymers tested were equal or higher than those intended for SC administration to humans (as shown in the table under Section 5.5). The results of these studies indicate that SC injection of the vehicle control (the copolymers in DMSO) is well tolerated with no systemic toxicity. The local effects at the vehicle injection site consisted of expected non-adverse signs (nodule and induration at the depot of the vehicle and a transient erythema) that are a typical foreign body reaction, characterized microscopically by circumscribed granulomatous reaction surrounded by a fibrotic capsule and considered non-adverse. The acute toxicity of (b) (4) soluble intermediate degradation products of the copolymers, was assessed after IV administration to rats; no adverse effects were noted in the treated animals (see Section 5.5.5.1. Toxicity of potential degradation products). Thus, TV-46000 nonclinical studies indicate that the administration of these copolymers alone does not induce systemic toxicity and adverse local signs.

A computational in silico analysis for structural alerts for mutagenicity conducted by the Sponsor resulted in a negative prediction for mutagenicity for all potential degradation products of the copolymers in TV-46000. An Ames test with a 7:5 ratio mixture of (b) (4) and (b) (4) in DMSO was negative indicating a lack of mutagenicity (see Section 5.5.2 Genetic Toxicology).

Overall, the extensive use in chronic medical applications of (b) (4) individually as well as copolymers, together with the data generated by the Applicant qualify the copolymers at the levels in the highest intended clinical dose of 250 mg TV-46000.

- **DMSO**, the only solvent in the TV-46000 formulation, is present at a level of (b) (4) mg in the maximal intended clinical dose of 250 mg TV-46000. The systemic and local safety of DMSO levels in TV-46000 was demonstrated in the 3-month repeat-dose SC study in dogs. In this study, the vehicle control group received up to 690 mg of DMSO to ~10 kg dogs (~70 mg/kg) by SC administration once a month for 3 months which did not result in adverse systemic or local reactions. This DMSO amount is 6-fold greater (on a mg/m² body surface basis) than the maximal amount of DMSO ((b) (4) mg) at a maximal clinical dose of 250 mg TV-46000. Therefore, DMSO is qualified at the highest intended dose of the TV-46000 formulation.

6 Clinical Pharmacology

6.1. Executive Summary

Teva Neuroscience Inc. has developed a new formulation of risperidone, as an extended-release injectable suspension for subcutaneous (sc) administration (TV-46000) that is proposed for treatment of patients with schizophrenia. Upon sc administration of TV-46000, a depot is formed under the skin which slowly degrades over time and risperidone is released into the systemic circulation. The slow release of risperidone from the depot enables TV-46000 to be administered q1m or q2m. TV-46000 is presented as a ready to use suspension in a PFS and delivered by sc injection at dosages of 50, 75, 100, or 125 mg (q1m) or 100, 150, 200, or 250 mg (q2m). These doses are comparable to oral risperidone doses of two, three, four, or five mg/day, respectively. The development of TV-46000 follows the 505(b)(2) application process with the LD of oral risperidone (Risperdal tablets; NDA020272). The current submission provided information on the clinical pharmacology, safety, efficacy, and in vitro/vivo performance of TV-46000, while relying in part on literature and the Agency's previous findings of efficacy and safety for the LD.

The clinical pharmacology program for TV-46000 consisted of three clinical studies: a phase 1 study in adult healthy subjects (Study RISPE1ZG15EU) and two phase 1 studies in adult patients with schizophrenia or schizoaffective disorder (Study 10055 and Study 10148).

Additionally, there are two phase 3 studies in adult and adolescent patients with schizophrenia (Study TV-46000-CNS-30072 and Study TV-46000-CNS-30078). Based on the result of the OSI inspection, there were some discrepancies identified in the conduct and collection of data for the phase 3 studies. The main issues raised by the OSI inspection were: 1. dosing error; 2. lack of documentation of IP administration; 3. duplicate enrollment; and 4. unblinding. The impact of these discrepancies on the analyses and recommendations that rely on dosing data from the phase 3 studies in the clinical pharmacology section of the review are not known. If the extent of discrepancies in conduct of studies and collection of data are more far reaching than currently known, then it may impact the recommendations for dosing and switching between dosing regimens as well as other PK related recommendations. For the OSI inspection results, refer to the OSI consult review.

Data from these studies were used to characterize the single- and multiple-dose pharmacokinetics of TV-46000, establish the optimum doses and dosing regimens, assess dose proportionality of TV-46000, determine the effects of rubbing and site of injection on the pharmacokinetics of TV-46000, determine the relative bioavailability (BA) of TV-46000 compared to that of oral risperidone, and bridge the intended for commercial use (PFS) presentation with the vial presentation used throughout the majority of the TV-46000 clinical development.

Moreover, PopPK modeling and simulations were performed with the aim to characterize the pharmacokinetics of risperidone, 9-OH-risperidone, and TAM in patients with schizophrenia. Exposure-response analysis was performed to describe the relationships between TV-46000

exposure and measures of efficacy and safety. The results of these analyses were used to aid selection of doses, dosing regimens, appropriate injection sites, switching instruction from oral risperidone to TV-46000, and dosing flexibility.

The review is primarily focused to address:

1. Is the proposed dosing recommendation of TV-46000 appropriate for the treatment of schizophrenia?
2. Is the site of injection (upper arm vs abdomen) of TV-46000 acceptable?
3. Is the exposure difference between PFS and vial presentation of TV-46000 clinically meaningful?
4. Are q1m and q2m dosing interchangeable?
5. Is the proposed dosing strategy acceptable when a patient misses a dose of TV-46000 and what is the impact of early or late administration of the next dose?
6. Were there any incidents of unexplained drug concentrations (i.e., dose dumping) with TV-46000 injections?

Although most of the clinical pharmacology information is from phase 1 studies which can be relied upon for regulatory decision making, given that the dosing information in the phase 3 studies cannot be relied upon based on the issues identified by OSI inspections, the Office of Clinical Pharmacology has determined that there is insufficient information provided in the NDA package to support a recommendation of approval for TV-46000. For the final determination of reliability of the phase 3 data, refer to the clinical review.

6.2. Summary of Clinical Pharmacology Assessment

Based on the results from the three individual phase 1 clinical studies (Study RISPE1ZG15EU, Study 10055, and Study 10148), PopPK analyses of all five clinical studies, and an exposure-response analysis of the efficacy and safety data from the phase 3 studies (Study TV-46000-CNS-30072 and Study TV-46000-CNS-30078), the clinical pharmacology of TV-46000 has been evaluated with the following conclusions:

- TV-46000 has a rapid initial absorption, predictable systemic exposure, and acceptable inter-subject variability.
- TAM median t_{max} ranged between 8 to 14 days (192 to 336 hours).
- The release of risperidone is rapid within 6 to 24 hours depending on dose after the first TV-46000 sc administration. Therefore, oral supplementation treatment or loading doses are not required.
- TAM exposure increases in a dose proportional manner over the therapeutic dose range from 50 to 125mg for the TV-46000 q1m regimen and from 100 to 250 mg for the TV-46000 q2m regimen.
- The apparent volume of distribution and apparent clearance were estimated to be 66.3 L and 14.3 L/h, respectively based on the PopPK model, which is consistent with those reported for oral risperidone.

- TV-46000 TAM mean $t_{1/2}$ ranged from 15 to 21 days, compared to 23.4 to 27.1 hours for oral risperidone.
- Steady-state is fully attained within 6 months for both the q1m and q2m dose regimens
- Exposure differences between vial and PFS presentations were not clinically meaningful.
- Studies 10148 and 10055 supported the main pharmacokinetic bridge between TV-46000 and the LD. TV-46000 exposure provided comparable exposure to daily oral risperidone exposure of 2 to 5 mg daily doses.
- Deviations from the dosing interval can be handled flexibly since the impact of early or late administration of the next dose ($\pm$ one week for q1m and q2m) on TAM exposure was minimal.
- The two injection sites (abdomen and back of the upper arm) were found to be interchangeable. The differences in exposure after single administration were not clinically meaningful and the exposures were overlapping at steady state.
- All pharmacokinetic and pharmacodynamic drug-drug interactions that apply to the use of oral risperidone are also applicable for TV-46000 since they are unrelated to the route of administration
- Intrinsic factors such as age, weight sex and race do not affect the pharmacokinetics of TV-46000.
- Due to the consistency of hepatic and renal clearance of risperidone and 9-OH-risperidone irrespective of the route of administration, it is assumed that the effect of hepatic impairment or renal clearance on the pharmacokinetics of TV-46000 will be similar to that of oral risperidone

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of action: The mechanism of action of risperidone is unclear. The drug's therapeutic activity in schizophrenia could be mediated through a combination of dopamine Type 2 (D2) and serotonin Type 2 (5-HT2) receptor antagonism.

Pharmacologic activity of 9-hydroxyrisperidone (9-OH-risperidone; also referred to as paliperidone [active metabolite of risperidone]), a major metabolite in humans, is known to be comparable to that of the parent drug, risperidone. To minimize pharmacokinetic variability, often the efficacy and safety of risperidone is evaluated based on the sum of the risperidone and 9-OH-risperidone concentrations (TAM).

Pharmacokinetics: The pharmacokinetic characteristics of TV-46000 were evaluated in both healthy subjects at subtherapeutic doses, and in patients with schizophrenia or schizoaffective disorder at the therapeutic dose range. Similar characteristics were obtained between the two populations, including delayed t_{max} , sustained release and prolonged $t_{1/2}$. In the final PopPK model, disease status (healthy versus schizophrenia) was also not found to be a covariate affecting TV-46000 absorption or clearance.

Absorption: TV-46000 shows dual absorption comprised of a fast absorption process that was associated with an initial uptake of risperidone into the systemic circulation, followed by a secondary absorption phase lasting several days to weeks. The median t_{max} for TAM ranged

from 8 to 14 days (192 to 336 hours) following a single-dose administration and from 8 to 13 days (180 to 312 hours) following multiple-dose administration.

The TV-46000 characteristics showed that after the first TV-46000 sc administration, the release of risperidone was rapid with no requirement for loading dose or supplementation. Steady-state plasma concentrations were fully attained by 6 months for both the q1m and q2m dose regimens. Median accumulation ratios for AUC_{ss} were 2.0 and 1.5 for the q1m and q2m dosing regimens, respectively; the median accumulation ratios for $C_{max,ss}$ were 1.9 and 1.4, and for $C_{trough,ss}$ were 2.4 and 1.5 for the q1m and q2m dosing regimens, respectively.

Administration of the same TV-46000 doses into the abdomen or the upper arm resulted in comparable pharmacokinetic profiles, therefore these injection sites can be used interchangeably. Rubbing of the injection site resulted in slight increase in exposure of the product (23% increase in C_{max} and a 35% increase in the $AUC_{0-\infty}$ of TAM), while depot still seemed to be formed effectively as TV-46000 extended-release characteristics and a multiphasic elimination slope were maintained following this manipulation of injection site, and no burst or uncontrolled release from the depot was evident.

Distribution: No designated studies were assigned to explore TV-46000 distribution. However, it is assumed that the distribution of TV-46000 will be comparable to that of oral risperidone.

As described in oral risperidone label, upon oral administration, risperidone is rapidly distributed, with a volume of distribution between 1 and 2 L/kg. In plasma, risperidone is bound to albumin and α 1-acid glycoprotein. The plasma protein binding of risperidone is approximately 90% and for 9-OH-risperidone, 77%. Neither risperidone nor 9-OH-risperidone displaces each other from the plasma binding sites. High therapeutic concentration of sulfamethazine (100 μ g/mL), warfarin (10 μ g/mL) and carbamazepine (10 μ g/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-OH-risperidone at 50 ng/mL, the clinical significance of which is unknown.

The protein binding characteristics of risperidone and 9-OH-risperidone are not expected to be altered by the route of administration. The final PopPK model estimates for apparent volume of distribution (V) of risperidone and 9-OH-risperidone were 66.3 L and 95.7 L, respectively and similar to the observed apparent volume of distribution after extravascular dose (V/F) for oral risperidone (between 1 and 2 L/kg).

Metabolism: No specific studies were conducted to explore TV-46000 metabolism. However, it is assumed that the metabolism of TV-46000 will be comparable to oral risperidone.

As described in the LD label, risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-OH-risperidone by the enzyme, CYP2D6 (b) (4). A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-OH-risperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug results from the combined concentrations of risperidone and 9-OH-risperidone (TAM). CYP2D6, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP2D6 is subject to genetic polymorphism (about 6 to 8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by

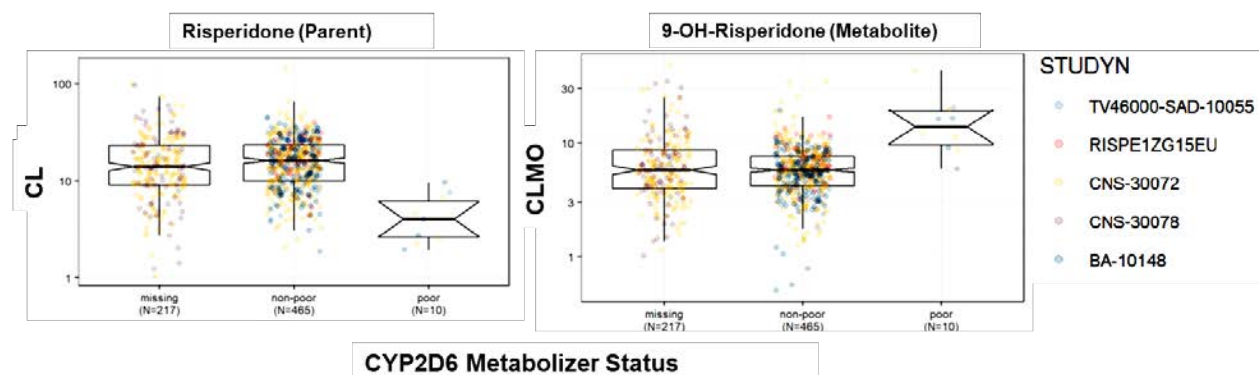
a variety of substrates and some non-substrates, notably quinidine. Extensive CYP2D6 metabolizers convert risperidone rapidly into 9-OH-risperidone, whereas poor CYP2D6 metabolizers convert it much more slowly. Modulation or genetic polymorphism of CYP2D6 may have little if any impact on efficacy because the exposure of risperidone and 9-OH-risperidone increases or decreases in opposite directions in response to CYP2D6 induction or inhibition, and there is no dose adjustment for oral risperidone based on CYP2D6 status.

The final PopPK model estimates for CL of risperidone and 9-OH-risperidone were 14.3 L/h and 5.78 L/h, respectively. The final PopPK model determined that poor CYP2D6 metabolizer status is associated with relatively lower risperidone clearance, and the apparent clearance for metabolite (CL_m) for 9-OH-risperidone is typically higher in subjects with poor CYP2D6 metabolizer status (Figure 1). These findings are in line with the mechanism of CYP2D6 mediated 9-hydroxylation of risperidone. In subjects with poor CYP2D6 metabolizer status, risperidone clearance is lower, and the fraction metabolized to 9-OH-risperidone is lower, resulting in higher apparent CL_m. However, similarly as for oral risperidone, since the overall pharmacologic activity of risperidone is governed by TAM, the effect of the above demographic factors on the CL of risperidone and CL_m for 9-OH-risperidone is not considered to be clinically meaningful, and therefore CYP2D6 metabolizer status requires no TV-46000 dose adjustment.

Excretion: Following TV-46000 sc administration, the mean apparent t_½ of TAM ranged between 15 and 21.3 days (355.0 to 511.7 hours) following single-dose administration and between 19 and 22 days (464.1 and 531.6 hours) following multiple-dose administration. After approximately 30 days, TAM concentrations declined exponentially. Evaluation of the pharmacokinetics of TV-46000 revealed a complex and multiphasic absorption profile, representing a rapid absorption phase, and a prolonged disposition/elimination process, typical of the "flip-flop" kinetics. The prolonged t_½ results from prolonged risperidone absorption taking place into the elimination phase. Based on the PopPK model, the apparent clearance of risperidone following TV-46000 administration is 14.3 L/h at steady-state, which is consistent with estimates reported for oral risperidone.

As per the LD label, risperidone and its metabolites are (b) (4) eliminated via the urine, and to a much lesser extent via the feces. As illustrated by a mass balance study of a single one mg oral dose of ¹⁴C-risperidone administered as an oral solution to three healthy male volunteers, total recovery of radioactivity at one week was 84%, including 70% in the urine and 14% in the feces.

Figure 1: Risperidone (Parent) and 9-OH-Risperidone (Metabolite) - Apparent Clearance Stratified by Poor and Non-Poor CYP2D6 Metabolizer Status



9-OH-risperidone = 9-hydroxyrisperidone also referred to as paliperidone (active metabolite of risperidone); CL = apparent clearance; CLMO = apparent clearance metabolite; N = number of subjects; STUDYN = study number.
 Source: Derived from Applicant's Final PopPK report, Figure 26 and Figure 27

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

TV-46000 is to be administered as an abdominal or upper arm subcutaneous injection only. Each injection is to be administered by a healthcare professional using the prefilled syringe and enclosed safety needle. For patients who have never taken risperidone, tolerability with oral risperidone prior to starting TV-46000 should be established.

TV-46000 can be initiated as either:

- Once Monthly: 50 mg, 75 mg, 100 mg, 125 mg; or
- Once Every two Months: 100 mg, 150 mg, 200 mg, 250 mg

TV-46000 can be initiated at the clinically appropriate dose based on Table 4 and then dose can be adjusted according to clinical need at the next administered dose.

Table 4: TV-46000 Dosage Selection Guide

Dosing Regimen	TV-46000 Doses (mg)			
TV-46000 Once Monthly*	50	75	100	125
TV-46000 Once Every 2 Months**	100	150	200	250
Daily Oral Risperidone	2 mg	3 mg	4 mg	5 mg

*Administer 1 dose per month

**Administer 1 dose every 2 months

Source: The Applicant's proposed label.

Patients who are on stable oral risperidone doses lower than 2 mg/day or higher than 5 mg/day may not be candidates for TV-46000 as comparable doses have not been studied. Patients can switch between doses of TV-46000 once monthly and once every 2 months by administering the first dose of the new dosing regimen on the next scheduled date of administration in the original dosing regimen. The dose administration schedule can be adjusted accordingly to reflect the change. No loading dose or supplementation with oral risperidone is required. A patient who misses a dose should receive the next dose as soon as possible and the administration schedule should be adjusted accordingly.

Therapeutic Individualization

No dedicated studies in patients with hepatic or renal impairment and drug interaction studies were conducted with TV-46000. This application relies on intrinsic (hepatic/renal impairment) and extrinsic (drug interactions) factor studies from the LD.

Hepatic or renal impairment: TV-46000 have not been studied in patients with hepatic impairment or renal impairment; however, such effect has been investigated with oral risperidone. As per the LD label, for patients with severe renal impairment ($Cl_{cr} < 30$ mL/min) or hepatic impairment (10-15 points on Child Pugh System), the initial starting dose is 0.5 mg twice daily. The dose may be increased in increments of 0.5 mg or less, administered twice daily. For doses above 1.5 mg twice daily, increase in intervals of one week or greater. Since for TV-46000 oral comparable doses lower than 2 mg/day have not been studied; before considering initiation of TV-46000 with these patients, tolerability must be established with oral risperidone. It is advisable that patients be carefully titrated up to at least 2 mg daily of oral risperidone and only if 2 mg is well tolerated, switching to TV-46000 can be considered at the lowest dose of 50 mg once monthly or 100 mg once every two months.

Strong CYP2D6 inhibitors: When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of TV-46000 prior to the planned start of fluoxetine or paroxetine therapy to adjust for the expected increase in plasma concentrations of risperidone.

When fluoxetine or paroxetine is initiated in patients receiving the recommended dose of 50 mg once monthly or 100 mg once every two months of TV-46000, it is recommended to continue treatment with these doses unless clinical judgment necessitates interruption of TV-46000 or reducing the frequency of TV-46000 administration. The efficacy of TV-46000 administered at a reduced frequency or at dosing less than 50 mg once monthly and 100 mg once every two months has not been investigated in clinical trials. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. Clinical Pharmacology Questions

Is the proposed dosing recommendation of TV-46000 appropriate for the treatment of schizophrenia?

Yes, the proposed dosing recommendation of TV-46000 is appropriate for the treatment of schizophrenia.

Data from study 10055 compared the exposure of risperidone after the 3rd injection of TV-46000 (Day 57) at doses of 75 and 150 mg, to those observed after oral risperidone administration over the dose range of 3 to 5 mg at steady-state. The TAM exposure (C_{max} , C_{trough} , C_{avg}) over a 28-day period was comparable between the sc injection of TV-46000 and oral risperidone (Table 5).

Table 5: Summary of Pharmacokinetic Parameters for Multiple Doses of TV-46000 75 mg and 150 mg Versus Oral Risperidone 3 mg and 5 mg

Geometric mean parameter (unit)	Steady-state oral risperidone dose (mg)		Multiple dose (approx. steady-state) TV-46000 dose (mg)	
	3 mg min dose	5 mg max dose	75 mg min dose	150 mg max dose
C_{max} (ng/mL)	39.8	62.2	33.9	69.6
C_{trough} (ng/mL) ^a	9.86	18.8	15.1	37.6
C_{avg} (ng/mL) ^b	20.7	31.9	18.7	40.1
% Fluctuation ^c	132	128	168	137

^a C_{24h} for oral risperidone and C_{84d} for multiple dose TV-46000. ^b C_{avg24h} for oral risperidone, $C_{avg0-56d}$ and $C_{avg0-84d}$ for multiple dose TV-46000.

^c Calculated as $(C_{max} - C_{min})/C_{avg} \times 100$.

C_{24h} = observed concentration values at 24 hours postdose; C_{84d} = observed plasma concentration on day 84; C_{avg} = average plasma drug concentration; C_{avg24h} = average observed plasma drug concentration from time 0 to 24 hours postdose; $C_{avg0-56d}$ = average observed plasma drug concentration from time 0 to the end of the 56-day dosing interval; $C_{avg0-84d}$ = average observed plasma drug concentration from time 0 to the end of the 84-day dosing interval.

Source: Applicant's study report for Study TV-46000-SAD-10055 CSR, Table 20.

TV-46000 TAM exposure at steady-state ($C_{avg,ss}$, $C_{trough,ss}$ and $C_{max,ss}$) were simulated at all doses and dosing regimens using the final PopPK model. Oral risperidone (1 to 16 mg/day) exposure was obtained from the observed data from TV-46000 phase 1 studies as well as data from literature. The daily $C_{avg,ss}$ of TV-46000 was comparable to that of corresponding doses of oral risperidone (Table 6). Moreover, the $C_{trough,ss}$ and $C_{max,ss}$ of TV-46000 was within the range of exposures for the recommended daily dose range of oral risperidone for the treatment of schizophrenia (2 to 8 mg/day).

In addition, the efficacy of TV-46000 in vials was tested in the pivotal efficacy and safety study (Study TV-46000-CNS-30072). The safety of TV-46000 in PFS is evaluated in the ongoing safety

study (Study TV-46000-CNS-30078). The exposure of PFS presentation was ~16 to 17% higher than that of vial presentation based on Study 10148.

Table 6: Median Total Active Moiety Pharmacokinetic Parameters for TV-46000 (Model Predicted) and for Oral Risperidone (Observed, Simulated, and Literature Reported Values)

Data source	Dose	N	AUC at ss (ng.h/mL)	C _{max,ss} (ng/mL)	C _{trough,ss} (ng/mL)	C _{avg,ss} (ng/mL)
Study 10055/ Study 10148 Oral Risperidone – Observed data	2 mg/day	24	324.5	26.4	8.8	13.6
	3 mg/day	24	485	39.4	12.0	20.2
	4 mg/day	10/ 55	648.0/ 610.3	60.9/ 47.9	14.5/ 12.4	27.0/ 25.4
	5 mg/day	25	818.0	72.0	20.2	34.1
	6 mg/day	12	645.0	60.0	14.7	26.9
Korell et al 2017 Oral Risperidone – model simulated data	1 mg/day	500	187.0	12.3	4.5	7.8
	2 mg/day	500	374.0	24.7	9.0	15.6
	3 mg/day	500	561.0	37.0	13.5	23.4
	4 mg/day	500	749.0	49.3	17.9	31.2
	5 mg/day	500	936.0	61.6	22.4	39.0
	6 mg/day	500	1120.0	74.0	26.9	46.8
	8 mg/day	500	1500.0	98.6	35.9	62.4
	16 mg/day	500	2990.0	197.0	71.8	125.0
Eerdeken et al 2004 Oral Risperidone – Observed data ^a	2 mg/day	21	428.3	32.8	11.1	17.8
	4 mg/day	31	859.1	67.2	18.1	35.8
	6 mg/day	26	1289.7	101.0	29.1	53.7
TV-46000 q1m – Model predicted, median daily AUC at ss	50 mg	500	475.2	25.1	12.1	19.8
	75 mg	500	712.5	36.4	19.5	29.7
	100 mg	500	947.2	47.5	26.8	39.5
	125 mg	500	1183.6	58.7	34.2	49.3
TV-46000 q2m – Model predicted, median daily AUC at ss	100 mg	500	479.1	32.6	7.7	20.0
	150 mg	500	717.0	47.2	12.8	29.9
	200 mg	500	952.2	61.4	17.6	39.7
	250 mg	500	1189.9	76.0	22.8	49.6

AUC = area under the plasma concentration-time curve; C_{avg,ss} = average plasma drug concentration at steady-state; C_{max,ss} = maximum plasma drug concentration at steady-state; CSR = clinical study report; C_{trough,ss} = trough plasma drug concentration at steady-state; N = total number of subjects/patients; q1m = once monthly; q2m = once every 2 months; ss = steady-state.

Source: Applicant's study report for Study TV-46000-SAD-10055, Ad-hoc Table 6; Applicant's study report for Study TV-46000-BA-10148, Ad-hoc Table 29; Final PopPK report, Table 27, Table 28, Table 29, Table 30, and Table 31; Applicant's summary of clinical pharmacology Table 27.

^aAUC_{ss} and C_{avg,ss} presented as least square mean values.

It is worth noting that median TAM $C_{trough,ss}$ values following TV-46000 q2m administration presented similar or slightly lower values compared to oral risperidone (7.7 ng/mL for q2m vs 8.8 ng/mL for oral dosing). The $C_{trough,ss}$ values were also found to be lower for q2m dose as compared to the q1m dose (7.7 ng/mL for q2m vs 12.1 ng/mL for q1m dosing).

Is the site of injection (upper arm vs abdomen) of TV-46000 acceptable?

Yes. The interchangeability of two sc injection sites (abdomen and back of the upper arm) for TV-46000 was evaluated in the phase 1 Study RISPE1ZG15EU and in the phase 1 Study 10055. In Study RISPE1ZG15EU, the interchangeability of injection sites was investigated with subtherapeutic doses of TV-46000 (25 mg). There was no significant difference in TAM exposure between the injection sites, with $\leq 10\%$ change in C_{max} and AUC_{0-t} (Table 7).

Site of injection interchangeability was evaluated at therapeutic doses in Study 10055. The geometric mean ratio of C_{max} , C_{28d} , $C_{avg0-28d}$, and AUC_{0-28d} were all about 30% higher when administered sc to the upper arm compared to the abdomen though overall exposure in terms of $AUC_{0-\infty}$ and AUC_{0-t} were comparable (17% higher, and 7% lower respectively).

Table 7: Comparison of Total Active Moiety Pharmacokinetic Parameters by Subcutaneous Injection Site

Study/Dose	PK parameter (unit) ^a	Abdomen (Cohort 5)	Upper-Arm (Cohort 8)	Ratio of Geometric Means
RISPE1ZG15EU/ TV-46000 25 mg	C_{max} (ng/mL)	7.3 (32.0) ^b	7.7 (48.8) ^b	1.05
	$AUC_{0-\infty}$ (ng.h/mL)	4710 (21.1) ^b	5410 (31.2) ^c	1.15
	AUC_{0-t} (ng.h/mL)	4200 (24.8) ^b	4630 (30.6) ^b	1.10
TV46000-SAD- 10055/ TV-46000 225 mg	C_{max} (ng/mL)	53.9 (55.6) ^d	69.3 (50.2) ^e	1.29
	C_{28d} (ng/mL)	28.2 (38.8) ^f	35.6 (70.4) ^f	1.26
	$C_{avg0-28d}$ (ng/mL)	36.0 (49.8) ^d	45.6 (35.8) ^f	1.27
	$AUC_{0-\infty}$ (ng.h/mL)	47524.9 (25.4) ^g	55499 (32.8) ^b	1.17
	AUC_{0-t} (ng.h/mL)	45195.1 (28.8) ^d	42082.5 (44.3) ^e	0.93
	AUC_{0-28d} (ng.h/mL)	24212.4 (49.8) ^d	30646.9 (35.8) ^f	1.27

^a All parameters presented as geometric mean (coefficient of variation %); ^b n = 10; ^c n = 9; ^d n = 12; ^e n = 13 ^f n = 11 ^g n = 7

AUC_{0-28d} = area under the plasma concentration-time curve from time 0 to the end of the 28-day dosing interval; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration time curve from time 0 to the last measurable concentration; C_{28d} = observed plasma concentration on day 28; $C_{avg0-28d}$ = average observed plasma drug concentration from time 0 to the end of the 28-day dosing interval.

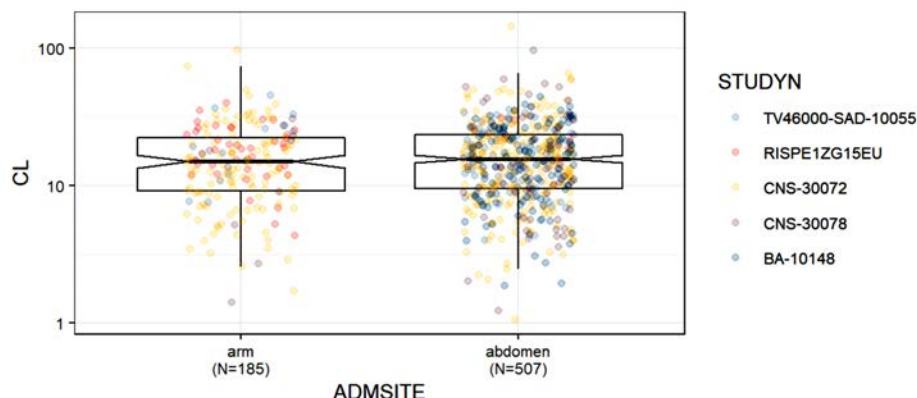
Source: Applicant's study report for Study RISPE1ZG15EU, Table 16; Applicant's study report for Study TV-46000-SAD-10055 CSR, Table 15 and Table 18.

Comparability of the two injection sites was also evaluated using the final PopPK model which included pooled pharmacokinetic data from the phase 1 and phase 3 clinical studies. Although site of administration was a significant covariate in the parent model, no impact of the site of injection on the overall steady-state TV-46000 exposure is observed (Figure 2). Following the

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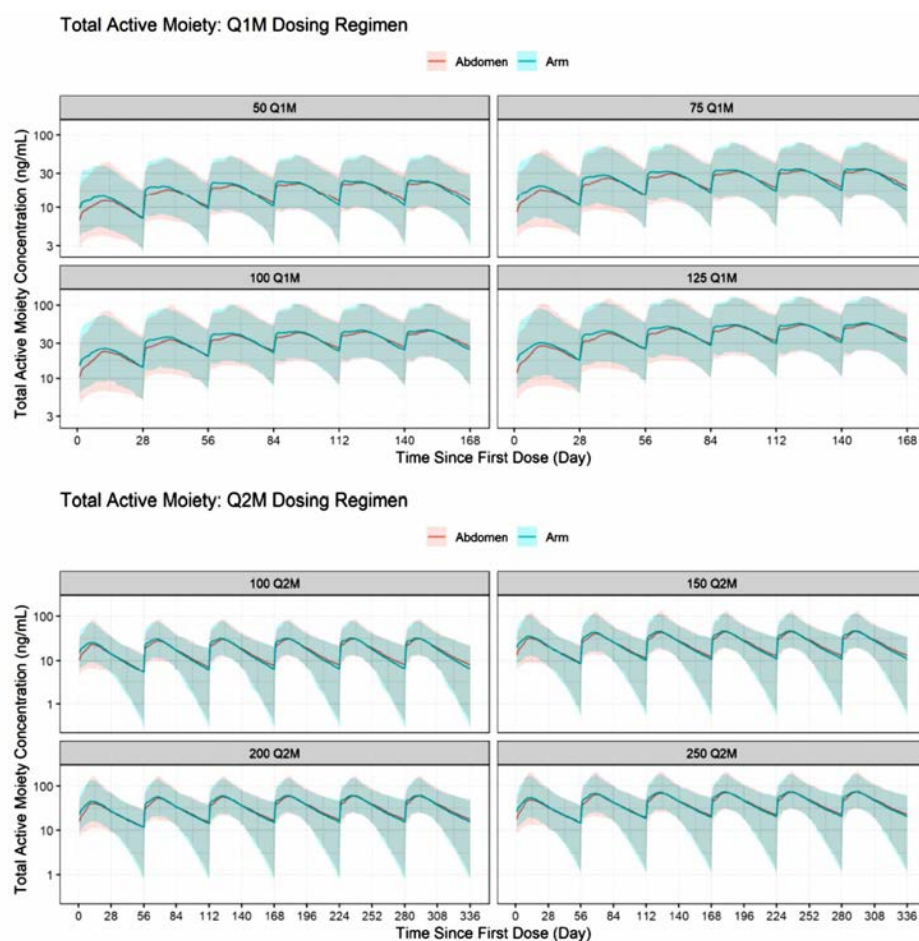
first dose administration, some minor differences were apparent. However, these minor differences were eliminated upon reaching steady state (Figure 3).

Figure 2: Risperidone Final Model - Stratified by Administration Site



Source: Applicant's study report for Final PopPK report, Figure 101. ADMSITE=administration site; CL = apparent clearance; N=number of subjects; STUDYN=study number.

Figure 3: Comparison of Injection Site on Total Active Moiety Exposure



Source: Applicant's study report for Final PopPK report, Figure 35. Q1M = once monthly; Q2M = once every 2 months.

Because the safety and efficacy are comparable between the injection sites (refer to Section 8), the minimal changes in single dose exposures (approx. 30% for C_{max} , C_{28d} , $C_{avg0-28d}$, and AUC_{0-28d}) with injection in upper arm compared to injection in abdomen were considered clinically irrelevant. Therefore, the review team considers that TV-46000 can be administered to either injection site.

Is the exposure difference between PFS and Vial presentations of TV-46000 clinically meaningful?

No, the exposure difference between PFS and vial presentation of TV-46000 is not expected to be clinically meaningful.

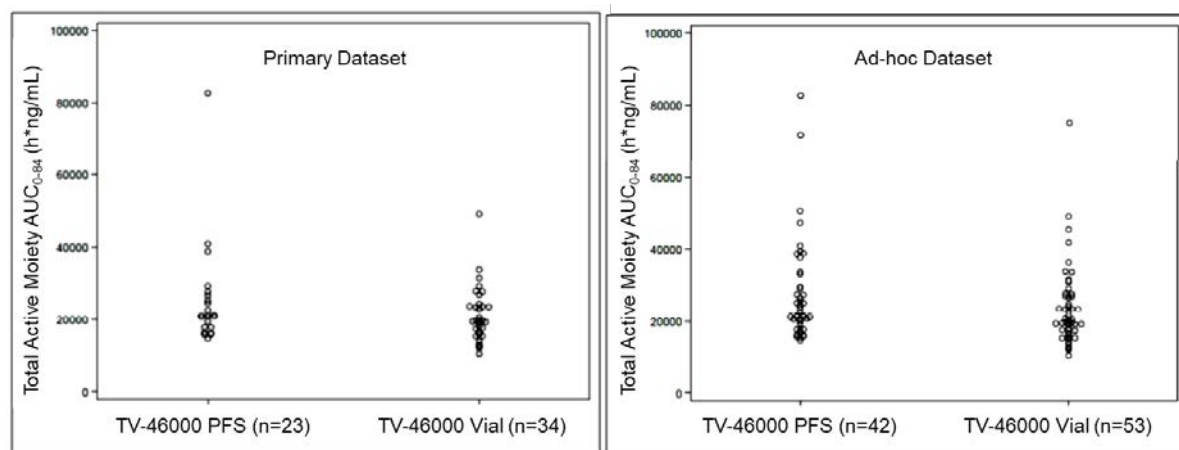
The PFS presentation is intended to be the commercial presentation of TV-46000. The TV-46000 vial presentation has been used in phase 1 studies (Study RISPE1ZG15EU, Study 10055, and Study 10148) and in the pivotal phase 3 study (Study TV-46000-CNS-30072). The TV-46000 PFS presentation has been used in a phase 1 study (Study 10148) and in the ongoing phase 3, long-term safety study (Study TV-46000-CNS-30078). The primary objective of Study 10148 was to assess the relative BA of a single dose of 100 mg TV-46000 in vials compared to that in PFS. The relative BA was evaluated by comparing the exposure of the 2 treatment groups over 84 days (area under the plasma concentration-time curve from time 0 to the end of the 84-day dosing interval [AUC_{0-84d}]).

For both presentations, the qualitative and quantitative formulation is unchanged, while the primary packaging differs. TV-46000 is filled into either (b) (4) (vial presentation) or into a single-use 1-mL, luer-locked, glass, clear PFS (PFS presentation). Both TV-46000 presentations are administered manually using the same needle (21-gauge, 5/8" needle closed with a sterile protective cap). Both TV-46000 presentations presented qualitatively comparable pharmacokinetic profiles.

All patients received oral risperidone 4 mg qd for seven days (administered either on an inpatient or outpatient basis; Period 1), followed by a seven-day inpatient washout period. Patients were then randomly assigned into 1 of the 2 treatment groups in which a single-dose of TV-46000 100 mg in vials (reference treatment) or in PFS (test treatment). Many patients presented higher than expected predose TAM plasma concentrations (non-zero predose concentrations >5% of the corresponding C_{max} of TV-46000) which were to be excluded from the analysis dataset based on a pre-specification in the statistical analysis plan. This resulted in excluding 39/95 patients from the primary analysis dataset. Although pharmacokinetic evaluations were conducted on the primary analysis dataset ($n = 57$), given the large proportion of patients lost due to this condition, an ad-hoc analysis dataset including all evaluable patients ($n = 95$) was created and used in all data analyses. Data analysis from this study therefore includes a primary analysis dataset and an ad-hoc analysis dataset.

Overall, the distribution of exposures was found to be similar using scatter plots for AUC_{0-84d} using the primary and the ad-hoc analysis dataset (Figure 4)

Figure 4: Scatter Plot of TV-46000 PFS and TV-46000 Vial Total Active Moiety AUC_{0-84d} (Primary Dataset and Ad-hoc Dataset)



Source: Applicant's study report for Study TV-46000-BA-10148, Figures 6 and 7. AUC_{0-84d} = area under the plasma concentration-time curve from time 0 to the end of the 84-day dosing interval; PFS = prefilled syringe.

The relative BA analysis of TV-46000 in PFS or in vial was performed using an analysis of variance (ANOVA) model on natural log transformed AUC_{0-84d} with treatment (PFS, vial) and categorized screening body weight (three categories: <75 kg, 75-99 kg, and >99 kg) as fixed effects.

Results from this analysis demonstrated ~16 to 17% higher exposure for TAM over 84 days (AUC_{0-84d}) upon administration of TV-46000 in PFS in comparison to that in vial (primary and ad-hoc datasets, respectively), with a 90% CI for the test/reference geometric mean ratios of AUC_{0-84d} of 0.991 to 1.356 and 1.024 to 1.340 for primary and ad-hoc datasets, respectively. The Applicant stated that the patients randomized to the PFS treatment group appears to have higher TAM exposures of oral risperidone compared to those randomized to the vial treatment group. To compensate for this phenomenon, an additional covariate for oral exposure (AUC_{0-tau, ss}), was included in the analysis of covariance (ANCOVA) for the primary endpoint for both datasets. While treatment group and weight were not found to be significant in this analysis, oral AUC_{0-tau, ss} was a statistically significant covariate for both datasets, indicating that the difference observed between TV-46000 vial and PFS presentations may be attributed to the study population heterogeneity and not necessarily by the treatment.

Upon oral risperidone exposure (AUC_{0-tau, ss}) normalization, differences between the treatment groups were minimized and closer comparability of the relative BA for TV-46000 PFS and TV-46000 vial presentations was demonstrated in both primary and ad-hoc datasets, with a 90% CI for the test/reference geometric least squares mean ratios of AUC_{0-84d} of 0.956 to 1.288 and 0.965 to 1.217 for primary and ad-hoc datasets, respectively (Table 8).

Table 8: Relative Bioavailability of TV-46000 PFS as Compared to TV-46000 Vial

Analyses	Parameter (unit)	Geometric LS Means				Comparison	
		TV-46000 100 mg (PFS) (Test)		TV-46000 100 mg (Vial) (Reference)		Geo LS Mean Ratio	90% CI of Ratio
		n	Geo LS Mean	n	Geo LS Mean	(Test/Ref)	(Test/Ref)
Primary analysis: Relative bioavailability of TV-46000 PFS as compared to TV-46000 vial							
Primary dataset	AUC _{0-84d} (ng.h/mL)	23	22483.507	34	19394.995	1.159	0.991, 1.356
Ad-hoc dataset ^a		42	24845.100	53	21212.670	1.171	1.024, 1.340
Ad-hoc analysis: Relative bioavailability of TV-46000 PFS as compared to TV-46000 vial with oral risperidone AUC _{0-tau,ss} as a covariate							
Primary dataset	AUC _{0-84d} (ng.h/mL)	22	22286.049	33	20092.333	1.109	0.956, 1.288
Ad-hoc dataset ^a		41	24294.820	52	22411.151	1.084	0.965, 1.217

Source: Applicant's study report for Study TV-46000-BA-10148 Table 20, Table 21 and Table 22.

^a Includes patients with non-zero predose concentrations >5% of C_{max}.

AUC_{0-84d} = area under the plasma concentration-time curve from time 0 to the end of the 84-day dosing interval; AUC_{0-tau} = area under the plasma concentration-time curve for 1 dosing interval (tau) of a multiple-dose regimen; AUC_{0-tau,ss} = area under the plasma concentration-time curve for 1 dosing interval (tau) of a multiple-dose regimen at steady-state; CI = confidence interval; C_{max} = maximum observed plasma drug concentration; Geo = geometric; LS = least squares; Geo LS Mean = Least Squares Geometric Mean calculated by taking exp (Least Squares Mean); Geo LS Mean Ratio = Least Squares Geometric Mean Ratio calculated by taking exp (Least Squares Mean Difference); n = number of patients participating in the analysis who belonged to the PK analysis set, were PK evaluable, satisfied Crit Flag, and belonged to the principal stratum for the variable of interest as defined in statistical analysis plan; PK = pharmacokinetic; PFS = prefilled syringe.

Regardless of the oral risperidone exposure (AUC_{0-tau,ss}) normalization differences, the relative BA for TV-46000 PFS and TV-46000 vial presentations were not considered to be clinically meaningful by the review team. The TV-46000 exposures were within the overall exposure range observed following daily administration of oral risperidone. Further, the safety profile of TV-46000 in PFS, as demonstrated in Study TV-46000-CNS-30078, is consistent with the safety profile of TV-46000 in vials (collected in Study TV-46000-CNS-30072), and with the known safety profiles for other formulations of risperidone. Therefore, any differences observed in the exposure from PFS or vial are not considered clinically meaningful.

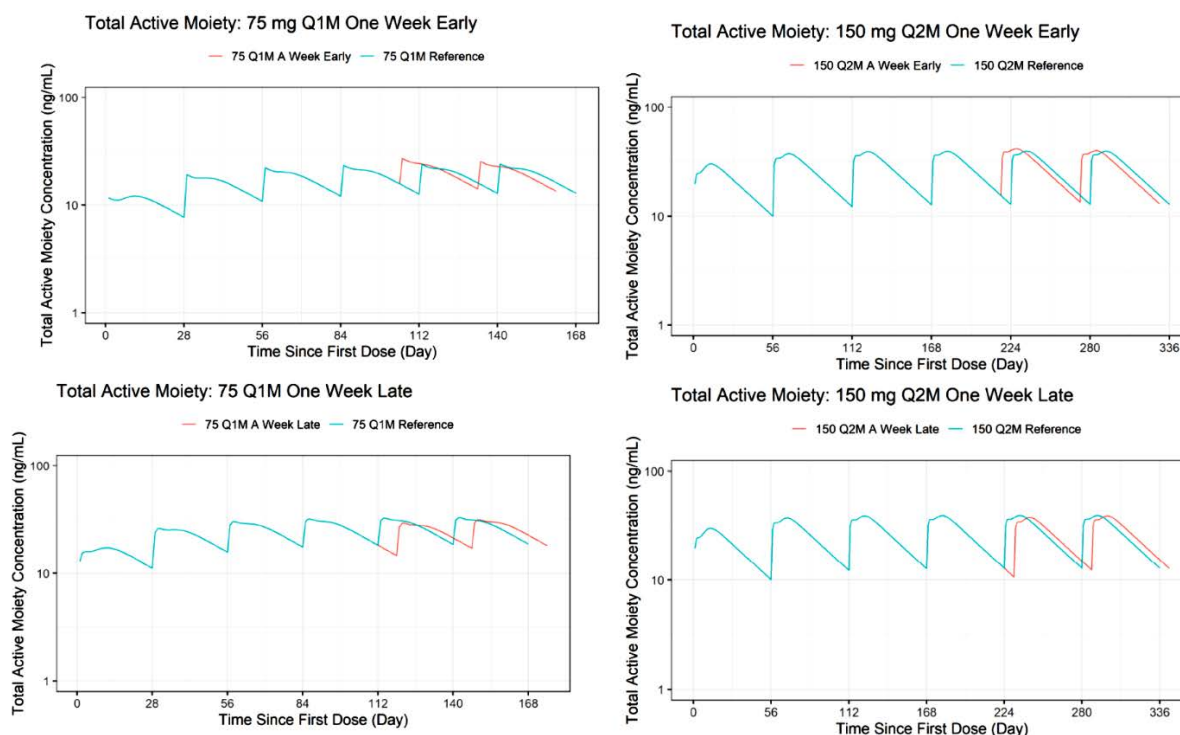
Is the proposed dosing strategy acceptable when a patient misses a dose of TV-46000 and what is the impact of early or late administration of the next dose?

Deviations from the defined dosing interval can be handled flexibly in a clinical setting since the impact of early or late administration of the next dose (± 1 week for q1m and q2m) on TAM exposure is expected to be minimal (Figure 5). As TV-46000 TAM concentrations for all the proposed doses and dose regimens rise rapidly within 24 hours in case of a missed dose or delayed dose, TV-46000 should be administered with no adjustments such as loading dose or initiation period. In case of an early dose the overall exposure is not increased very significantly to be a safety concern. In case of a missed dose, the exposure upon dosing with next dose of

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TV-46000 leads to achieving desired TAM concentrations early enough that no oral supplementation is needed in the interim.

Figure 5: Impact of Early or Late TV-46000 Administration of the Next Dose on Total Active Moiety Concentrations



q1m = once monthly; q2m = once every 2 months.

Source: Applicant's Final PopPK report, Figure 35 and 36.

Are dosing recommendations for switching from oral to sc risperidone and from q1m to q2m dosing acceptable?

Using the final PopPK model of TV-46000, individual exposure estimates were calculated for TV-46000 TAM at steady-state to support the switching from oral to sc risperidone and from q1m to q2m dosing. Despite the delayed t_{max} compared to oral risperidone, the release of risperidone was rapidly within 24 hours, with no lag time. Therefore, dose initiation with TV-46000 can be done without the need of a loading dose or oral supplementation. In the event of switching from oral risperidone treatment to TV-46000, treatment could be initiated immediately with no intervening dosing requirement.

Model-predicted pharmacokinetic parameters at steady-state were summarized for the different doses and dose regimens in Table 9. The median exposures of TAM, such as the daily AUC and $C_{avg,ss}$ are similar when comparing any dose from the q1m regimen with corresponding dose from the q2m regimen (i.e., 100 mg q1m versus 200 mg q2m). It is notable that the C_{trough} values for q2m were lower than those for q1m (7.7 ng/mL for q2m vs 12.1 ng/mL for q1m) or oral dose of 2 mg/day (7.7 ng/mL for q2m vs 8.8 ng/mL for oral) dosing, but covered by the starting dose of 1 mg/day (7.7 ng/mL for q2m vs 4.5 ng/mL for oral) (Table 6). Moreover, both q1m and q2m dosing regimen were shown to be efficacious in the pivotal phase 3 trial. There

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was a numerical increase in impending relapse for q2m dosing when compared to q1m dosing (Table 10), but both met the primary end point compared to placebo. For further discussion on efficacy of the two dosing regimens refer to the reviews from the clinical and biostats review teams.

Based on simulations conducted by the clinical pharmacology review team upon switching from q1m to q2m dosing (after three doses of q1m) the PK profiles are not significantly altered after switching (Figure 6). Additionally, when switching from q1m dosing to q2m dosing, the trough concentrations predicted are higher for q2m dosing than what would be expected for patients that start their regimen with q2m dosing due to earlier attainment of steady state. This further indicates that switching from q1m to q2m dosing won't have significant impact on exposure and hence the efficacy of the product.

Therefore, it can be concluded that the q1m and q2m doses could be switched based on clinical judgment as per currently available information.

Table 9: Median Total Active Moiety Pharmacokinetic Parameters for TV-46000 Dosing Regimens (Model Simulated)

Regimen	Dose	N	AUC at ss (ng.h/mL)	Daily AUC ^a (ng.h/mL)	C _{max,ss} (ng/mL)	C _{trough,ss} (ng/mL)	C _{avg,ss} (ng/mL)
TV-46000 q1m	50 mg	500	13306	475.2	25.1	12.1	19.8
	75 mg	500	19951	712.5	36.4	19.5	29.7
	100 mg	500	26521	947.2	47.5	26.8	39.5
	125 mg	500	33141	1183.6	58.7	34.1	49.3
TV-46000 q2m	100 mg	500	26829	479.1	32.6	7.7	20.0
	150 mg	500	40152	717.0	47.2	12.8	29.9
	200 mg	500	53321	952.2	61.4	17.6	39.7
	250 mg	500	66634	1189.9	76.0	22.8	49.6

^a Divided by the dosing interval; AUC = area under the plasma concentration-time curve; Ca

C_{max,ss} = maximum plasma drug concentration at steady-state; C_{trough,ss} = plasma drug concentration at the end of dosing interval at steady-state; q1m = once monthly; q2m = once every 2 months; N = total number of subjects/patients; ss = steady-state.

Source: Applicant's Final PopPK report, Table 26, Table 27, Table 28, Table 29, Table 30.

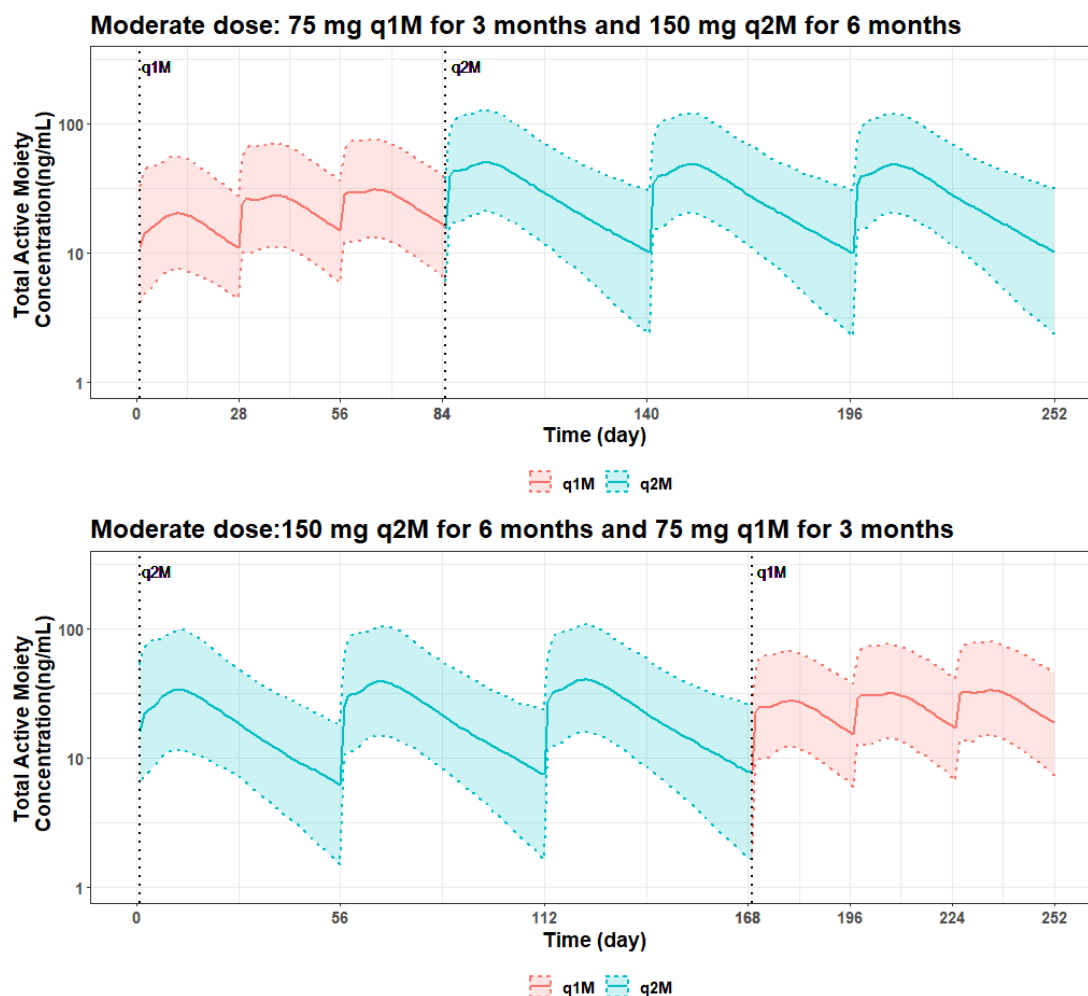
Table 10: Number of Patients and Incidence of Efficacy Endpoints by Study and Treatment Group for Patients Included in the Efficacy Exposure-Response Analysis

Selected efficacy endpoint	Pooled data from Study 30072 and Study 30078 ^a					
	Placebo (N=179)		q1m (N=215)		q2m (N=210)	
	N	Incidence% (95% CI)	N	Incidence% (95% CI)	N	Incidence% (95% CI)
Impending relapse	53	29.6 (22.2, 37.9)	13	6.05 (2.96, 10.7)	24	11.4 (6.99, 17.3)

Individual exposure parameters from 2 patients (b) (6) in Study 300 TV-46000-CNS-30072 were unavailable and these patients were excluded from the dataset.

Source: Applicant's Exposure-Response report, Table 15.

Figure 6: Impact of interchange of q1m and q2m dosing regimen on the Total Active Moiety Exposure



Source: Reviewer's Analysis

Were there any incidents of unexplained drug concentrations (i.e., dose dumping) with TV-46000 injections?

No. There were no incidents of unexplained plasma concentrations in the clinical trials conducted with TV-46000. No evidence of dose dumping was observed in pharmacokinetic data collected for TV-46000. Detailed assessment of the individual subject and patient pharmacokinetic data collected from all phase 1 clinical studies with extensive pharmacokinetic sampling (N = 267) following administration of TV-46000 (Study RISPE1ZG15EU, Study 10148 and Study 10055) was undertaken. Dose dumping, or unexplainable rise, or uncontrolled release was evaluated by reviewing the plasma exposure of risperidone (parent). Visual inspection of all individual pharmacokinetic profiles demonstrated that none of the subjects or patients in these studies showed any rapid or unpredictable rise in risperidone exposure after

TV-46000 sc administration. The lack of any abrupt spikes in risperidone exposure suggests that there was no dose dumping or leakage after the TV-46000 sc injection.

Additionally, observed TAM concentrations following TV-46000 administration across all doses and all studies did not exceed concentrations of 300 ng/mL, which is comparable to the C_{max} observed following oral administrations of 16 mg/day. Therefore TV-46000 administration resulted in an exposure that was within the approved range of oral risperidone with an acceptable safety profile. The safety profile of TV-46000 from all clinical studies conducted to date provides supportive evidence of an overall lack of any new or unexpected safety findings with TV-46000 administered as a sc injection compared to oral risperidone. Safety evaluation did not find any anomalies in adverse events or vital signs that would be consistent with dose dumping or of risperidone overdose.

In the clinical studies, patients were not instructed to take any unusual precautions to protect the site of injection from the effect of extrinsic factors (e.g., heat, pressure, or exercise). Several nonclinical studies were undertaken to show the robustness of the formulation to applied challenges of heat and pressure. Dose dumping was not observed in any of the animal studies, despite the extreme conditions utilized, including heating or rubbing of the TV-46000 injection site, immediately after injection or later point. Controlled release characteristics of TV-46000 were maintained. *In vitro* studies revealed a very small trend of an increase of soluble fraction with an increase of temperature from room temperature to 37°C and 42°C. However, all the results indicate that a maximum of only four percent of risperidone would be available for immediate absorption post injection of TV-46000, regardless of the change in temperature, or difference in particle size distribution of the suspended drug substance.

A 34% and 35% increase in the exposure of TAM was observed following administration of TV-46000 with rubbing of the injection site (Test) compared to exposure following administration without rubbing (Reference), as measured by AUC_{0-t} and AUC_{0-∞}, respectively, and the difference in C_{max} was 23% in Study RISPE1ZG15EU (Table 11). Overall, though some increase in exposure was observed in the rubbing cohort, the extended-release characteristic of the formulation over time did not change (Figure 7) and the depot still formed very effectively when subjected to this extreme challenge, as reflected by the mean t_{1/2} values for non-rubbing and rubbing cohorts (199 hours versus 194 hours, respectively). Hence, even injection site manipulation did not result in burst release.

The impact of increased exposure upon rubbing immediately after injection may not be clinically relevant. Firstly, the study was done with a subtherapeutic dose with much lower injection volume. The PopPK model suggested that the effect of injection volume on absorption of the drug was more pronounced with the subtherapeutic doses of 12.5 mg and 25 mg (administration volume 0.035 mL and 0.07 mL, respectively), compared to therapeutic doses of ≥50 mg (administration volume ≥0.139 mL). Hence the impact of rubbing on the exposure may not be as pronounced therapeutic doses with larger injection volumes. Additionally non-clinical studies were performed to identify the impact of time of rubbing the injection site on the exposure. In this study, the same dose level and rubbing procedure as the clinical rubbing study were applied (6 dogs per group) at different time points 0 to 4 hours postdose. Rubbing of the dog injection site immediately post 12.5 mg TV-46000 sc injection resulted in a similar increase

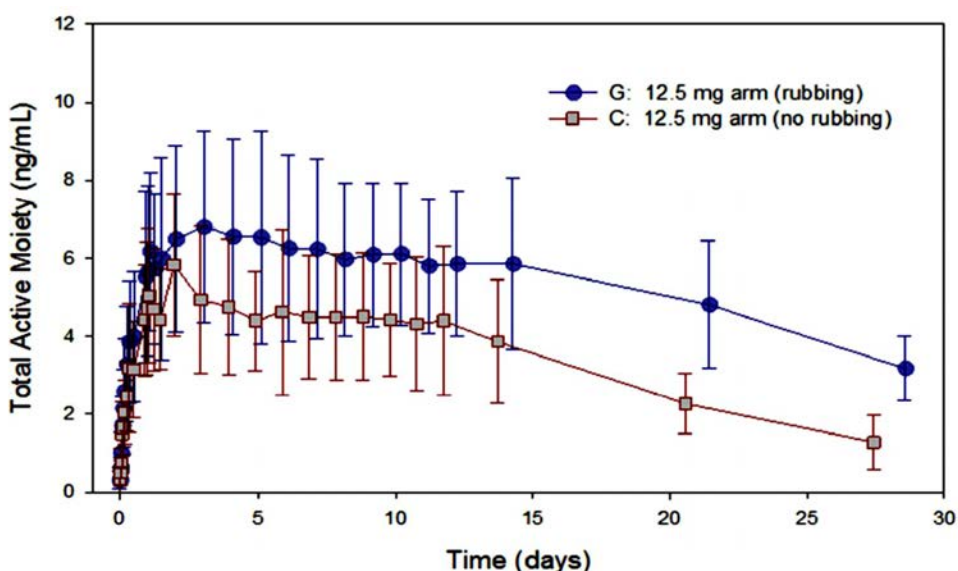
of exposure parameters, as was observed in the clinical study, while rubbing at 0.5, 1 and 4 hours post injection had no effect on exposure parameters. (b) (4)

Table 11: Comparison of Injection Site Manipulation on Total Active Moiety Exposure Following a Single Subcutaneous Dose of TV-46000 (Study RISPE1ZG15EU)

Contrast	Test	Reference	PK parameter	Test geom mean (CV%)	Reference geom mean (CV%)	Ratio (%) ^a
Rubbing	Cohort G 12.5 mg TV-46000 Grade 1, arm, Rubbing (N = 10)	Cohort C 12.5 mg, TV-46000 Grade 1, arm no rubbing (N = 9)	C _{max} (ng/mL)	7.38 (33.3)	6.00 (30.4)	123.0
			AUC _{0-t} (ng.h/mL)	3440 (27.1)	2570 (25.6)	133.9
			AUC _{0-∞} (ng.h/mL) ^b	3590 (25.8)	2660 (25.6)	135.0

^a Calculated as (geometric mean [test] / geometric mean [reference]) x 100. ^b Risperidone overall exposure (based on AUC_{0-∞}) was similar between the rubbing and no rubbing cohorts (867 ng.h/mL and 846 ng.h/mL, respectively; Study RISPE1ZG15EU CSR, Table 10). AUC_{0-∞} = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last measurable concentration; CI = confidence interval; C_{max} = maximum observed plasma drug concentration; CSR = clinical study report; CV = coefficient of variation; geom = geometric; GMR = geometric mean ratio; N = total number of subjects; PK = pharmacokinetic Note: Adjusted GMRs, associated 90% CIs and p-values for C_{max} and AUC_{0-t}, are provided in the Study RISPE1ZG15EU CSR, Table 17. Source: Applicant's complete study report for Study RISPE1ZG15EU, Table 16 and 17.

Figure 7 : Mean (± SD) Plasma Total Active Moiety Concentrations (ng/mL) for Cohort C (TV-46000 12.5 mg; no rubbing) and Cohort G (TV-46000 12.5 mg; rubbing) Presented on a Linear Scale



Source: Applicant's complete study report for Study RISPE1ZG15EU, Table 14.2.1.2.3.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 12. Listing of Clinical Trials for TV-46000

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Pts Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
TV-46000-CNS-30072 (RISE) (phase 3)	NCT03503318	Multicenter, randomized, double-blind, placebo-controlled study (Randomized withdrawal)	TV-46000 • q1m at doses of 50 mg, 75 mg, 100 mg, and 125 mg - OR • q2m at doses of 100 mg, 150 mg, 200 mg, and 250 mg sc (comparable to 2 to 5 mg/day of oral risperidone), per the oral dose on which the patient was stabilized in Stage 1 - OR • placebo q1m sc	Primary efficacy endpoint: time to impending relapse Secondary endpoints: • efficacy in a total population (adults and adolescents) and in adolescent patients with schizophrenia • safety and tolerability in the	12 weeks of the oral conversion/stabilization stage (Stage 1) ^a , and the double-blind maintenance stage (Stage 2). Stage 2 was variable in duration, with pts continuing until they experienced a relapse event;	Enrolled ^b : 858 Not randomized: 314 pts Randomized: 544 pts	Pts with schizophrenia	69 centers ^c United States and Bulgaria

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
Uzedy (risperidone extended release injection)

			Pts were randomized to the 3 treatment arms in a 1:1:1 ratio.	total population PK of oral risperidone and TV-46000 after administration of multiple doses in adults, adolescents, and the total population	met 1 or more of the study discontinuation or withdrawal criteria, or remained relapse- free at the time of study termination			
Studies to Support Safety								
TV-46000-CNS-30078 (SHINE) (phase 3)	NCT03893825	Multicenter, double-blind, parallel-group, uncontrolled ^d study	TV-46000 - q1m at doses of 50 mg, 75 mg, 100 mg, and 125 mg, or - q2m at doses of 100 mg, 150 mg, 200 mg, and 250 mg sc (comparable to 2 to 5 mg/day of oral risperidone), per the oral dose on which the patient was stabilized in Stage 1. New pts, as well as rollover pts that	Primary endpoint: the frequency of all adverse events, including serious adverse events.	For new pts: 12 weeks of the oral conversion/stabilization stage (Stage 1) ^a and a double-blind maintenance stage (Stage 2) of up to 56 weeks. For roll-over pts: Double-blind maintenance stage (Stage 2) of up to 56	Enrolled ^b : 150 ^e Not randomized: 42 pts Randomized: 108 new pts 227 rollover pts Total randomized including roll-overs: 335 pts	Pts with schizophrenia	60 centers ^f United States and Bulgaria

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			were administered placebo in Study TV-46000-CNS-30072, were randomized to receive doses of TV-46000 q1m or TV-46000 q2m sc injections in a 1:1 ratio. Pts on active treatment in Study TV-46000-CNS-30072 continued with the same treatment in Study TV-46000-CNS-30078.		weeks.			
Other Studies Pertinent to the Review Of Efficacy Or Safety (e.g., Clinical Pharmacological Studies)								
RISPE1ZG 1 5EU (QCL1174 36) (phase 1)	N/A	Part 1: open-label, non-randomized ascending dose design Part 2: open-label, non-randomized, 2- treatment	All doses were administered sc to the posterior aspect of the upper arm on day 1 unless otherwise specified. Cohort A: a 35 µL SD of vehicle Cohort B: a 70 µL SD of vehicle Cohort C^g: a SD of	Part 1: • Safety and tolerability of the Vehicle was assessed by physical examination, safety laboratory tests, vital signs, ECG, AEs and injection site	Single dose of vehicle or TV-46000 Cohorts A and B: 29 days. Cohorts C to G: 69 days.	Enrolled and treated (overall): 59 subjects Vehicle cohorts: 6 subjects TV-46000 cohorts: 53 enrolled;	Healthy subjects	Single-Center United Kingdom

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
 Uzedy (risperidone extended release injection)

		design	12.5 mg of risperidone 360 mg/mL prolonged-release suspension for sc injection, administered as a 35 µL injection. Cohort D^g: a SD of 25 mg of risperidone 360 mg/mL prolonged-release suspension for sc injection, administered as a 70 µL injection Cohort E^g: a SD of 25 mg of risperidone 360 mg/mL prolonged-release suspension for sc injection, administered as a 70 µL injection Cohort F^g: a SD of 25 mg of risperidone 360 mg/mL prolonged-release suspension for sc injection, administered as a	examination • Safety and tolerability of the risperidone 360 mg/mL prolonged-release suspension for sc injection was assessed by: physical examination, safety laboratory tests, vital signs, ECG, AEs and injection site examination • PK parameters for risperidone, 9-OH risperidone and • total active moiety Part 2: • Safety and tolerability was assessed by physical examination,		50 treated		
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 Uzedy (risperidone extended release injection)

			70- µL injection to the abdomen. Cohort G: a SD of 12.5 mg of risperidone 360 mg/mL prolonged-release suspension for sc injection, administered as a 35 µL injection (with rubbing of the injection site)	safety laboratory tests, vital signs, ECG, AEs and injection site examination				
TV-46000-SAD-10055 (phase 1)	N/A	Open-label, sequential, single and multiple ascending dose study	All doses were administered sc in the abdomen on day 1, unless otherwise specified ^h . Cohort 1: 50 mg SD Cohort 2: 75 mg SD Cohort 3: 100 mg SD Cohort 4: 150 mg SD Cohort 5: 225 mg SD Cohort 6: 75 mg MD on days 1, 29, and 57 (3 injections) Cohort 7: 150 mg	Safety, tolerability, and pharmacokinetics of single ascending doses and multiple doses of TV-46000 for sc use	Single dose (Cohorts 1-5 and 8) or multiple doses (Cohorts 6 and 7) of TV- 46000 and follow- up period: For Cohorts 1 and 2 - up to 84 days; For Cohorts 3,4,5 and 8 - up to day 112; For Cohorts 6 and 7 - up to day 140.	Enrolled and Treated (overall): 99 pts	Pts with schizophrenia or schizo-affective disorder	3 centers United States

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 Uzedy (risperidone extended release injection)

			MD on days 1, 29, and 57 (3 injections) Cohort 8: 225 mg SD on day 1 (upper arm)					
TV- 46000- BA-10148 (phase 1)	N/A	Open-label, parallel- design, single dose study	Group 1: 100 mg TV-46000, SD on day 1, from vial, sc. Group 2: 100 mg TV-46000, SD on day 1, from PFS, sc.	Primary endpoint: Relative bioavailability of a single dose of 100 mg TV-46000 administered sc from vials compared to PFS. Secondary endpoints: safety and tolerability of oral risperidone and TV-46000 sc administration from vials or PFS.	Single dose of TV-46000j from PFS or vials and a follow-up period of up to day 84.	Enrolled in Period 1: 197 pts Treated (Vial and PFS): 120 pts	Pts with schizophrenia or schizo- affective disorder	3 centers United States

SD= single dose; MD= multiple doses; Pts= patients; N/A= not applicable; RISE= The Risperidone Subcutaneous Extended-release Study; SHINE= Safety in Humans of TV-46000 sc Injection Evaluation;
 PFS= prefilled syringes

^a Oral risperidone was mandated for use in Stage 1 of this study; however, for the purposes of this study, it was not considered an investigational medicinal product.

^b The term "enrolled" refers to the number of patients who entered Stage 1 of the study. The numbers shown are of the enrolled patients set.

^c This is the total number of study centers, which screened at least 1 patient; 61 in the United States, 8 in Bulgaria.

^d There was no placebo arm in this study. TV-46000 Placebo was administered in this study to patients in the TV-46000 q2m treatment group in order to maintain the blind.

^e As of the cutoff date of the TV-46000-CNS-30078 interim CSR (01 September 2020), 147 patients were enrolled.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586

Uzedry (risperidone extended release injection)

^f This is the total number of study centers which screened at least 1 patient; 16 centers enrolled new patients in the United States, 37 roll-over centers in the United States and 7 roll-over centers in Bulgaria.

^g Subjects received oral risperidone 2 mg once daily (qd) for 7 days followed by a washout period of a minimum of 7 days prior to receiving the TV-46000 injection.

^h Prior to treatment with TV-46000, patients were administered oral risperidone for 7 days, followed by a 7-day washout period.

^j Prior to treatment with TV-46000, patients received 4 mg/day oral risperidone for 7 days (days -14 through -8), followed by a 7-day inpatient washout period. Abbreviations: AE=adverse events; AIMS= Abnormal Involuntary Movement Scale; AUC(0-inf)=area under the plasma concentration-time curve from time 0 to infinity; AUC%extrap= percentage of AUC(0-inf) extrapolated beyond last measured time point; AUC(0-last)= area under the plasma concentration vs time curve from 0 time to last measurable concentration; BARS= Barnes Akathisia Rating Scale; C_{avg}= the average concentration over the dosing interval; CDSS= Calgary Depression Scale for Schizophrenia; CGI-SS= Clinical Global Impression-Severity of Suicidality; C_{max}= maximum observed concentration; C-SSRS= Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EPS= extrapyramidal symptoms; Frel=relative bioavailability; lambda-z= the slope of the apparent elimination phase; MRT=mean residence time; N/A=Not applicable; NCT No.=National Clinical Trial number; PD=pharmacodynamics; PFS=prefilled syringe; PK=pharmacokinetics; q1m=once-monthly; q2m=once every 2 months; SAS= Simpson-Angus Scale; sc=subcutaneous(ly); T_{1/2}= the apparent elimination half-life; Tlag= the elapsed time from dosing at which the analyte is first quantifiable in a concentration vs time profile.

7.2. Review Strategy

The efficacy review of this application focused on the single efficacy study, Study TV-46000-CNS-30072.

The safety review examined deaths, non-fatal serious adverse events (SAEs), and discontinuations due to adverse events from all five studies in the development program. The only randomized, placebo-controlled study was Study TV-46000-CNS-30072. Therefore, analyses of changes in laboratory parameters, vital signs, and electrocardiogram (ECG) measures were examined within Study TV-46000-CNS-30072 to evaluate safety findings after patients began treatment with this product. Study TV-46000-CNS-30078 safety data were also reviewed for potential safety findings that emerged with longer term treatment.

Studies TV-46000-CNS-30072 and TV-46000-CNS-30078 allowed enrollment of adolescent patients, but only three adolescent patients were screened with one randomized and treated in Study TV-46000-CNS-30072, and only seven adolescent patients screened with three randomized and treated in Study TV-46000-CNS-30078. There is an expectation that the safety profile of TV-46000 could differ between adolescents and adults based on the known safety profile of risperidone and other antipsychotics with respect to dystonic reactions and metabolic changes. The safety data collected in these studies are not sufficient to evaluate safety in the adolescent patient population. Thus, efficacy and safety analyses in the review are limited to the adult population only.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study TV-46000-CNS-30072

Overview and Objectives

Study Title: “A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Risperidone Extended-Release Injectable Suspension (TV-46000) for Subcutaneous Use as Maintenance Treatment in Adult and Adolescent Patients with Schizophrenia (The RISE Study – The Risperidone Subcutaneous Extended-release Study)”

Primary Objectives:

- To evaluate the efficacy of TV-46000 during maintenance treatment in adult patients with schizophrenia

Secondary Objectives:

- To evaluate the efficacy of TV-46000 during maintenance treatment in a total population (adults and adolescents) and in adolescent patients with schizophrenia
- To evaluate the safety and tolerability of TV-46000 in the total population
- To evaluate the pharmacokinetics of oral risperidone and TV-46000 after administration of multiple doses in adults, adolescents, and the total population

Trial Design

This study was a randomized, double-blind, multinational, multicenter, parallel-group, placebo-controlled, relapse prevention study to evaluate the efficacy, safety, and tolerability of TV-46000 in adult or adolescent patients with schizophrenia at dose of 50 to 125 mg sc q1m or at dose of 100 to 250 mg sc q2m. These doses were comparable to 2 to 5 mg/day of oral risperidone.

Key inclusion criteria:

- Diagnosis of schizophrenia according to the DSM-5 for >1 year (diagnosis must have been reconfirmed by the Structured Clinical Interview for DSM-5, SCID-5) and had ≥one episode of relapse in the last 24 months.

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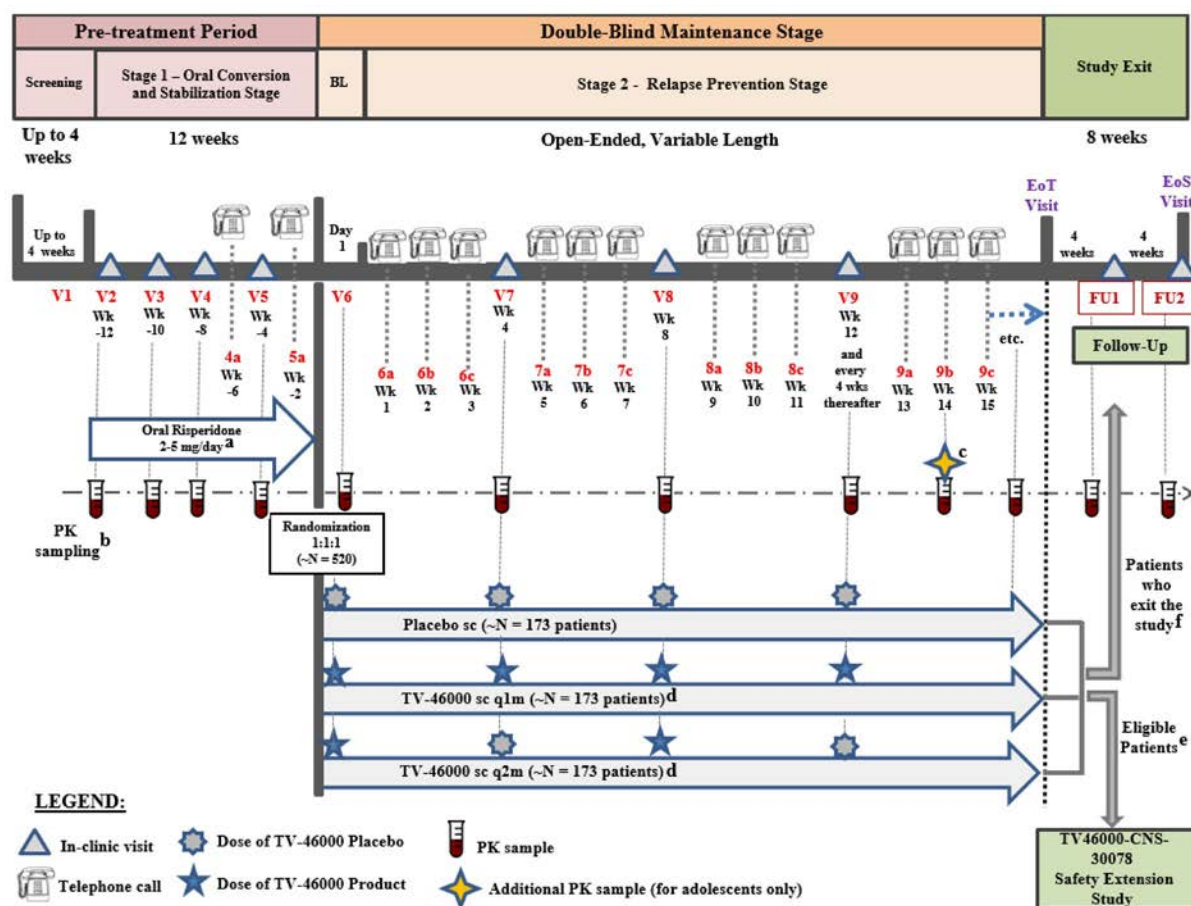
- Patient responsive to an antipsychotic treatment (other than clozapine) in the past year based on investigator judgment (and discussions with family members, caregivers, or healthcare professionals as applicable).
- PANSS total score lower than 100
- Male or female of any ethnic origin, 13 through 65 years of age
- Body mass index (BMI) between 18.0 and 38.0 kg/m², inclusive
- Patient in adequate health

Key exclusion criteria:

- Clinically significant comorbidity with DSM-5 diagnosis other than schizophrenia
- Patient on clozapine or electroconvulsive therapy in the last 12 months
- History of epilepsy or seizures, neuroleptic malignant syndrome, clinically significant tardive dyskinesia, or other medical condition that would expose the patient to undue risk
- Positive serology for HIV-1, HIV-2, hepatitis B surface antigen, and/or hepatitis C
- Substance use disorder (excluding nicotine and caffeine)
- Significant risk of violent behavior
- Significant risk of committing suicide
- Clinically significant deviation from normal in the physical examination, laboratory findings, ECG, or urinalysis results
- Prolonged QT interval (defined as a Fridericia's formula, QTcF, interval of >450 msec for males and >470 msec for females) at screening or baseline
- Clinically significant uncontrolled medical condition
- Patient pregnant or lactating
- Use of medications prohibited in the protocol

After a screening/assessment phase, the study consisted of two stages (Figure 8).

Figure 8. Study Schema



Source: Applicant's Clinical Study Report for Study TV-46000-CNS-30072, Figure 1, p. 32

Stage 1. Oral conversion and stabilization stage (12 weeks in duration)

During this stage, patients not already on risperidone, were to be converted to oral risperidone to ensure that they tolerated risperidone and that the doses were adequate to treat their positive symptoms. Patients who were already on risperidone but could still benefit from the study based on the investigator's judgment were also to undergo the oral conversion and stabilization stage. The optimal dose of oral risperidone was to be based on clinical judgment and could range from 2 to 5 mg per day. Adolescent patients were to receive a maximal dose of 4 mg/day. Patients who required doses of oral risperidone outside these ranges were not to be randomized to the next stage.

Patients were to be treated for 12 weeks, with a face to face visit at Weeks -12, -10, -8, and -4 for dose adjustments, or more frequently, if required in the judgment of the investigator. Telephone contacts were to take place at Weeks -6 and -2 or more frequently, if required in the

judgment of the investigator.

Stability was defined as meeting all the following criteria for at least four consecutive weeks prior to the baseline visit:

- Outpatient status
- PANSS total score ≤ 80
- Minimal presence of specific psychotic symptoms on the PANSS, as measured by a score of ≤ 4 on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content
- Clinical Global Impression-Severity (CGI-S) score ≤ 4 (moderately ill)
- Clinical Global Impression-Severity of Suicidality (CGI-SS) score ≤ 2 (mildly suicidal) on Part 1 and ≤ 5 (minimally worsened) on Part 2

Stage 2. Double-blind maintenance stage (variable in duration)

Randomization and blinding

In Stage 2 of the study, patients were to be randomized to receive TV-46000 q1m sc injections, TV-46000 q2m sc injections, or placebo q1m sc injections in a 1:1:1 ratio. Randomization was to be stratified by gender (male or female) and the dose of oral risperidone on which the patient was stabilized during Stage 1. The dose of TV-46000 (q1m or q2m) was to be comparable to the oral risperidone dose on which the patients were stabilized in Stage 1 (Table 13).

Table 13. Conversion Table Between Oral Risperidone and TV-46000 Doses

Frequency of TV-46000 Administration	Oral Risperidone Doses and Corresponding TV-46000 Doses			
	2 mg/day	3 mg/day	4 mg/day	5 mg/day (Adults Only)
TV-46000 q1m	50 mg	75 mg	100 mg	125 mg
TV-46000 q2m	100 mg	150 mg	200 mg	250 mg

Source: Applicant's Clinical Study Report for Study TV-46000-CNS-30072, Table 3, pg. 52.

q1m=once monthly; q2m=once every two months

Patients randomized to TV-46000 q1m or placebo sc were to receive an sc injection of TV-46000 or placebo, respectively, at baseline and every four weeks thereafter. Patients randomized to TV-46000 q2m were to receive a TV-46000 sc injection at baseline and every eight weeks thereafter and a placebo sc injection four weeks after baseline and every eight weeks thereafter to ensure blinding of the doses and durations of the TV-46000 injections and the placebo injections. Treatments were to be administered by an unblinded independent nurse

not associated with rating the patient. Patients and investigators were to remain blinded to the identity of the treatment administered to each patient.

Location of dose administration

In general, TV-46000 was administered to patients in the abdomen, but some investigational centers were selected for injection of TV-46000 into the back of the upper arm, instead of the abdomen, to all or some of the randomized patients at these sites. The injection site that was chosen for an individual patient remained consistent throughout the study. If the chosen site was the arm, the injection was administered in an alternating manner between the right arm and the left. If the chosen site was the abdomen, the injection was administered in an alternating manner to the right and to the left of the umbilicus.

Study duration

Stage 2 was variable in duration, with patients continuing until they experienced a relapse event; met one or more of the study discontinuation or withdrawal criteria; or remained relapse-free during the double-blind phase until the study was terminated because at least 90 relapse events were recorded in the study.

Study Assessment

The efficacy and safety of TV-46000 were evaluated for the Stage 2 according to the schedule of assessments (Table 12).

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
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Table 14. Schedule of Assessments for Study TV-46000-CNS-30072

Study Period	Double-Blind Maintenance Stage ^a															Follow-Up		N/A
	BL	Stage 2: Relapse Prevention														Exit ^b		Unscheduled Visit ^c
	BL		The 24-week series from Visit 7 to Visit 12c repeats (Visits 13-18c, 19-24c, etc) until patient completion, relapse or early termination.												End of Treatment (EoT)/Early Termination (ET) Visit			
Visit number	V6	V6a, 6b, 6c	V7	V7a, 7b, 7c	V8	V8a, 8b, 8c	V9	V9a, 9b, 9c,	V10	V10a, 10b, 10c	V11	V11a, 11b, 11c	V12	V12a, 12b, 12c		FU1	FU2	As deemed necessary by the investigator
Time point	Day1	Wk 1-3	Wk 4	Wk 5-7	Wk 8	Wk 9-11	Wk 12	Wk 13-15	Wk 16	Wk 17-19	Wk 20	Wk 21-23	Wk 24	Wk 25-27		4 Wks after last dosing visit	8 Wks after last dosing visit (EoS)	
Procedures and assessments																		
Allowed time window	±3 days															±3 days		N/A
In-clinic visit	X		X		X		X		X		X		X		X	X	X	X
Telephone call ^{d, e}		X		X		X		X		X		X		X				
Inclusion and exclusion criteria	X ^f																	
Clinical laboratory tests ^{g,h}	X				X				X				X		X	X	X	
Urine drug screen	X														X			
Concomitant medication inquiry	X		X		X		X		X		X		X		X	X	X	X
Fully physical examination, including weight	X														X	X	X	
Vital signs measurement ⁱ	X		X		X		X		X		X		X		X	X	X	X
12-lead ECG ^j	X				X				X				X		X ^k	X	X	
Serum β-HCG test for women of childbearing potential	X															X	X	
Urine β-HCG test for women of childbearing potential ^l	X		X		X		X		X		X		X		X			
Inquiry about pregnancy status (for women of childbearing potential)		X		X		X		X		X		X		X				
PANSS	X		X		X		X		X		X		X		X	X	X	X
CGI-S	X		X		X		X		X		X		X		X	X	X	
CGI-SS	X		X		X		X		X		X		X		X	X	X	
CGI-I ^m			X		X		X		X		X		X		X	X	X	
AIMS	X		X		X		X		X		X		X		X	X	X	
BARS	X		X		X		X		X		X		X		X	X	X	
SAS	X		X		X		X		X		X		X		X	X	X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PSP (in adult patients only)	X				X		X ⁿ						X		X		X	

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
Uzedy (risperidone extended release injection)

SQLS (in adult patients only)	X				X		X ⁿ						X		X		X	
EQ-5D-5L (in adult patients only)	X				X		X ⁿ						X		X		X	
CDSS	X		X		X		X		X		X		X		X		X	
Healthcare resource utilization	X						X ⁿ						X		X		X	
DAI-10 (in adult patients only)	X														X		X	
Blood sample for pharmacogenetic analysis	X ^o																	
Blood sample for biomarker analysis ^p	X														X	X	X	
Blood samples for plasma drug concentration ^q	X		X		X		X		X		X		X		X	X	X	X ^r
Blood samples for plasma drug concentration (Adolescents only)							X ^s											
Assessment of stability	X ^t																	
Randomization	X																	
Placebo sc administration ^u	X		X		X		X		X		X		X		X ^v			
TV-46000 q1m sc administration ^u	X		X		X		X		X		X		X		X ^v			
TV-46000 q2m sc administration ^{u, w}	X				X				X				X		X ^v			
Questions to assess ease of study drug administration ^x	X		X		X													
Adverse event inquiry (including SAE reporting, injection site-related events including pain) ^y	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inquiry regarding alcohol consumption/illicit drug use	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Brief set of clinical questions to detect psychotic symptoms ^z		X		X		X		X		X		X		X				

Source: Applicant's Clinical Study Report for Study TV-46000-CNS-30072, Table 2, page 37-41.

Study Endpoints

Primary endpoints

The primary efficacy endpoint was time to impending relapse. Patients meeting any one or more of the below impending relapse criteria were considered relapsed.

Relapse was defined as one or more of the following items:

- Clinical Global Impression-Improvement (CGI-I) of ≥ 5 (greater than or equal to minimally worse, i.e., minimally worse, much worse or very much worse) AND
- an increase of any of the following individual PANSS items: conceptual disorganization,

Uzedy (risperidone extended release injection)

hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 with an absolute increase of ≥ 2 on that specific item since randomization, OR

O an increase in any of the following four individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 and an absolute increase of ≥ 4 on the combined score of these four PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) since randomization

- Hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), excluding hospitalization for psychosocial reasons
- CGI-SS of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2
- Violent behavior resulting in clinically significant self-injury, injury to another person, or property damage

Secondary endpoints

- Time to impending relapse in the total population (adults and adolescents)
- Impending relapse rate at Week 24
- Percentage of patients who maintain stability at endpoint
- Percentage of patients achieving remission at endpoint
- Observed rate of impending relapse at endpoint
- Drug Attitudes Inventory 10-item version
- Schizophrenia Quality of Life Scale
- Time to impending relapse in adolescent patients with schizophrenia

Clinical and statistical reviewer's comment:

(b) (4)

(b) (4)

(b) (4)

Statistical Analysis Plan

The Applicant defined three populations of interest for analysis:

- The intent to treat (ITT) analysis set included adult patients randomized to the double-blind maintenance stage (Stage 2), regardless of if they have received treatment or not. In the ITT analysis set, treatment was assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.
- The extended intent-to-treat (eITT) analysis set included all patients (adults and adolescents) randomized to the double-blind maintenance stage (Stage 2), regardless of if they received treatment or not. In the eITT analysis set, treatment was assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. Given that there was only one adolescent patient (in the TV-46000 q2m group) recruited in the study, separate summary tables for adolescents and summary tables of the eITT analysis set were not presented and the presentation for eITT was replaced with presentation for the ITT analysis set.
- The per-protocol (PP) analysis set included all patients in the ITT analysis set who had no important protocol deviations that were deemed to be related to the primary analysis and to be excluded from the PP analysis; a case-by-case evaluation of which important protocol deviations deemed to be related to the primary endpoint was conducted before unblinding. In this analysis set, treatment was assigned based on the treatment patients actually received. If patients erroneously received a wrong drug assignment in some visits, a decision about which treatment group they were assigned was determined on a case-by-case manner before unblinding.

The primary efficacy analysis, time to impending relapse for TV-46000 q1m and TV-46000 q2m versus placebo, was compared using the stratified log-rank test. Kaplan-Meier curves were

provided to present impending relapse rate data over time. Hazard ratios and their 2-sided 95% confidence intervals for TV-46000 q1m and q2m versus placebo were estimated using a stratified Cox proportional hazard (PH) model, with treatment as a covariate, and stratification factors of gender and the dose of oral risperidone on which the patient was stabilized were incorporated into the baseline hazard component of the model. The stratified Cox PH model was used as supportive evidence and for quantification of treatment effect. The hazard ratio (HR) proportionality of the three treatment groups was tested using the Wald test for linear hypothesis testing and could be plotted over time to explore the treatment effect.

In addition, the Applicant conducted the following sensitivity analyses to assess the robustness of the primary efficacy analysis results:

- The primary analysis was repeated using the PP analysis set
- Interval censoring rule was performed as a sensitivity analysis for the primary endpoint
- Sensitivity of the primary efficacy analysis due to potential informative censoring using a “Tipping Point” approach

The Applicant-proposed sample size was estimated using the following assumptions:

- A placebo effect (namely, median time to impending relapse of 7 months in the placebo group) similar to that observed in a similarly-designed study (Kane et al 2012)
- A HR of 2.50 (placebo vs each TV-46000 arm)
- A randomization ratio of 1:1:1 (q1m:q2m:placebo), with two primary hypotheses to be tested (q1m vs placebo and q2m vs placebo) at a 2-sided alpha of 0.050

To control for the family-wise type-I error (multiplicity) of the primary endpoint family, a fixed sequential (hierarchical) testing procedure was used. The total number of events was calculated to attain a statistical power of at least 90% in both comparisons of q1m and q2m versus placebo.

Assuming the above, a total of at least 90 relapse events will need to be observed during Stage 2 of the study in the ITT analysis set (adult patients) in the three treatment groups (combined) in order to attain at least 90% power to meet success criteria in both comparisons.

Statistical Reviewer’s Comment: *The Sponsor proposed a number of secondary endpoints in the first draft of the protocol. In addition, in Amendment 2 to the protocol, they proposed to use fixed sequential testing procedure to control the overall Type I error rate. However, the advice letter sent to the Sponsor on May 21, 2020, for Amendment 2, pointed out:*

Uzedy (risperidone extended release injection)

Prespecified secondary endpoints: You are proposing eight prespecified (“key”) secondary endpoints. We previously advised (on your submission dated November 18, 2019, in Sequence No. 56) that the secondary endpoints should not provide redundant information; however, the secondary endpoints of “Impending relapse rate at Week 24,” and “Observed rate of impending relapse at endpoint” provide redundant information (b) (4). If the trial is positive and is used to support an efficacy indication, we expect labeling will include a Kaplan-Meier plot displaying the cumulative percent of patients experiencing impending relapse over time.

We also do not agree with the secondary endpoints “Percentage of patients who maintain stability at endpoint” and “Percentage of patients achieving remission at endpoint.” “Stability” and “remission” do not have standard definitions (b) (4).

Your reference to “endpoint” in defining some of the prespecified secondary endpoints is unclear (i.e., a fixed time point versus the time of treatment discontinuation). Regardless, neither definition is acceptable. From a statistical perspective, as previously conveyed to you, the statistical analyses for variables measuring change from baseline to endpoint suffer from competing risk—particularly for such a long period of time. Because of this fundamental concern, we have not accepted variables measuring change from baseline to endpoint as secondary endpoints in studies designed to assess time-to-event. We note, for these secondary endpoints, you only plan to compare the pooled treatment arms with placebo. The results from such comparisons would be considered exploratory.

We also consider the secondary endpoints of Drug Attitudes Inventory (DAI-10) and Schizophrenia Quality of Life Scale (SQLS) to be exploratory (b) (4).

Therefore, this review will focus on the primary efficacy endpoint and consider all the Sponsor-proposed key secondary endpoints exploratory in nature. It is to be noted that the testing procedure for secondary endpoints considered only the order of these secondary endpoints with both doses pooled. (b) (4) However, the pooling issue was not conveyed to the Sponsor and only noted internally, given the fundamental concerns conveyed as described above.

Protocol Amendments

There were three amendments to the protocol for Study TV-46000-CNS-30072, all made prior to unblinding of the study data:

- Amendment 01 (dated December 6, 2018) was finalized after 184 patients were enrolled into the study. The primary reason for this amendment was to allow adolescent patients (aged 13 to 17 years) to enroll in this clinical study and receive treatment with TV-46000. The following major procedural changes (not all-inclusive) were made to the protocol:
 - Changes to provide for enrolling adolescent patients (including eligibility criteria, maximum dose to be administered, up to three additional PK samples to be collected from adolescents, etc.)
 - Urine pregnancy test was added to the baseline visit

Uzedy (risperidone extended release injection)

- o Clarification of which scales were only to be performed in adult patients
 - o Definition of treatment completers added
 - o Clarification that collection of the unscheduled PK samples is only relevant for Stage 2
 - o Clarification regarding blinding per updated Sponsor template to enhance patient safety and ensure that the patient's needs are first addressed
 - o Correction of blood volumes per updated laboratory manual
 - o Clarification regarding a positive urine drug screen result due to the high prevalence of recreational and medical use of various substances in this patient population
- Amendment 02 (dated October 16, 2019) was finalized after 649 patients were enrolled into the study. The primary reason for this amendment was to revise the number of relapse events at which the formal, prespecified interim analysis was to be conducted. In this amendment, the following major procedural changes (not all-inclusive) were made to the protocol:
 - o In addition to the originally planned single interim analysis that was to be conducted when 125 relapse events were observed, an earlier interim analysis (when 90 relapse events were reached) was introduced
 - o Prolongation of study duration (although in case of a successful interim analysis, the study would be terminated earlier)
 - o Change of inclusion criterion k to omit the BMI percentile limitation
 - o Updates to the planned number of enrolled patients per updated projections
 - o Clarification of procedures to be performed during unscheduled visits
 - o Updates to vendor information and personnel details following changes of responsibilities
 - o Clarification regarding highly effective birth control methods (i.e., only highly effective birth control methods should have been used in this study)

Amendment 02 also reorganized the statistical analyses with the introduction of the fixed sequential (hierarchy) method to control the overall type-I error for the primary analyses and a reconsideration and hierarchy of the key secondary endpoints (see above for details of the key secondary endpoints).

- Amendment 03 (dated April 19, 2020) was finalized after 863 patients were enrolled into the study. The primary reason for this amendment was to rescind the previous interim analyses strategy, and to perform the final statistical analysis of the study data when at least 90 relapse events were observed, without any interim analysis, due to the low relapse event rate. The following major procedural changes (not all-inclusive) were made to the protocol:
 - o Changes related to the planned earlier final analysis
 - o Change of medical expert responsibilities
 - o Blood volumes updated to reflect longer treatment duration in Stage 2 of the study
 - o COVID-19 pandemic-related operational updates and contingency measures were added to the study as a new appendix

Clinical and Statistical Reviewer Comment: The protocol amendments were made prior to unblinding and do not impact data integrity.

8.1.2. Study Results of TV-46000-CNS-30072

Compliance with Good Clinical Practices

The Applicant states that the study was conducted in full accordance with the International Conference on Harmonization Good Clinical Practice (GCP) Consolidated Guideline (E6 [R2]) and any applicable national and local laws and regulations (e.g., Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314; EU Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). The Applicant states that information regarding any investigational study centers participating in this study that could not comply with these standards were documented. The Applicant states that audits were conducted at nine sites, and all protocols and amendments were reviewed by each clinical site's Institutional Review Board. An attestation was included in Section 5 of the Clinical Study Report (CSR).

Financial Disclosure

The study was conducted at 69 study sites by 76 principal investigators, with 61 study sites in the United States and 8 study sites in Bulgaria. Only 59 sites randomized patients. None of the principal investigators or subinvestigators disclosed reportable financial interests. Financial disclosure forms were not provided for two investigators in two different study sites.

Reviewer's comment: An Information Request was sent to the Applicant to clarify why two investigators did not provide financial disclosure forms. The Applicant reported that during the site startup activities, there was an investigator change at one site and the new investigator

took over before the original investigator signed the financial disclosure form. In the second case, the financial disclosure form was incorrectly signed by the principal investigator and by the time this error was identified, the investigator had departed the site and was no longer part of the study team. An evaluation of data obtained from that specific site revealed no outliers or unusual results.

Patient Disposition

The number of subjects in various analysis sets are summarized in Table 15 and subject disposition for the ITT analysis set (primary efficacy analysis set) is summarized in Table 16. Briefly, a total of 1267 patients with schizophrenia were screened for participation, 542 of which received at least one dose of study drug or placebo and were evaluated for safety in the study.

Table 15. Summary of Analysis Sets (All Subjects)

	Placebo Group	Treatment Group		Total
		TV-46000 q1m	TV-46000 q2m	
Screened				1267
Screened, not enrolled				404
Enrolled				863
Enrolled, not randomized				319
Enrolled patients set				858
eITT analysis set	181 (100)	183 (100)	180 (100)	544 (100)
ITT analysis set	181 (100)	183 (100)	179 (>99)	543 (>99)
Randomized, not treated	2 (1)	0	0	2 (<1)
Per-protocol analysis set	179 (99)	182 (>99)	179 (>99)	540 (99)
Safety analysis set	179 (99)	183 (100)	180 (100)	542 (>99)
PK analysis set	179 (99)	183 (100)	180 (>99)	542 (>99)

Source: Table 8 of Study TV-46000-CNS-30072 CSR.

Table 16. Disposition of Subjects (ITT Analysis Set)

	Placebo Group (N=181)	Treatment Group		Total (N=543)
		TV-46000 q1m (N=183)	TV-46000 q2m (N=179)	
Completed treatment	113 (62)	112 (61)	113 (63)	338 (62)
Discontinued treatment	68 (38)	71 (39)	66 (37)	205 (38)
Death	1 (<1)	0	4 (2)	5 (1)
Adverse event	10 (6)	21 (11)	14 (8)	45 (8)
Withdrawal by subject	23 (13)	24 (13)	23 (13)	70 (13)
Noncompliance with study drug	4 (2)	2 (1)	2 (1)	8 (1)
Protocol deviation	10 (6)	3 (2)	4 (2)	17 (3)
Lost to follow-up	9 (5)	13 (7)	9 (5)	31 (6)
Lack of efficacy	0	0	1 (<1)	1 (1)
Other	11 (6)	8 (4)	9 (5)	28 (5)
Completed study	142 (78)	144 (79)	139 (78)	425 (78)
Discontinued study	39 (22)	39 (21)	40 (22)	118 (22)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586

Uzedy (risperidone extended release injection)

Death	1 (<1)	0	4 (2)	5 (1)
Adverse event	3 (2)	4 (2)	2 (1)	9 (2)
Withdrawal by subject	12 (7)	17 (9)	16 (9)	45 (8)
Protocol deviation	5 (3)	0	3 (2)	8 (1)
Lost to follow-up	17 (9)	15 (8)	12 (7)	44 (8)
Other	1 (<1)	3 (2)	3 (2)	7 (1)

Source: Statistical Reviewer's summary using Subject-Level Analysis Dataset (ADSL.xpt).

Clinical Reviewer's comment: There is not a clinically significant imbalance in discontinuation rates and reasons across treatment groups.

Protocol Violations/Deviations/Duplications

Protocol Deviations

In Stage 1, a total of 69 (13%) patients who were later randomized into Stage 2 had one or more important protocol deviations: 27 (15%) patients who were later randomized to the placebo treatment group, 22 (12%) patients who were later randomized to the TV-46000 q1m treatment group, and 20 (11%) patients who were later randomized to the TV-46000 q2m treatment group. The protocol deviations were: 25 (5%) patients had a protocol deviation associated with the study procedures or tests, 18 (3%) had protocol deviations associated with the study visit schedule, and 16 (3%) had Informed Consent Form (ICF) issues.

In Stage 2, a total of 317 (58%) patients had one or more important protocol deviations: 109 (60%) patients in the placebo treatment group, 107 (58%) patients in the TV-46000 q1m treatment group, and 101 (56%) patients in the TV-46000 q2m treatment group. The types of protocol deviations were: 165 (30%) had a protocol deviation associated with the study procedures or tests, 107 (20%) had protocol deviations associated with the study drug, and 102 (19%) had protocol deviations associated with laboratory tests.

All protocol deviations leading to discontinuation of treatment and leading to discontinuation of study are described in the detailed listing. There were 18 protocol deviations leading to discontinuation of treatment: 1 patient in the TV-46000 q1m treatment group, 4 patients in the TV-46000 q2m treatment group, and 13 patients in the placebo treatment group. The protocol deviations leading to discontinuation of treatment were noncompliance with study visit schedule, use of prohibited concomitant medications, and noncompliance with study drug.

There were five protocol deviations leading to discontinuation from the study, all during the 8-week follow-up period: three patients in the TV-46000 q2m treatment group and two patients in the placebo treatment group. In the TV-46000 q2m treatment group, one participant (b) (4) was discontinued from the study due to the principal investigator's decision based on the subject not wanting to complete the follow up period and "lack of efficacy". Two additional subjects in the TV-46000 q2m treatment group were discontinued due to delays in communication between the Sponsor and the site and missed doses/study visits. In the placebo group, one participant (b) (6) was randomized while awaiting laboratory results and then terminated from the study when the laboratory results were exclusionary. In the same group,

Uzedy (risperidone extended release injection)

another participant (b) (6) missed the study treatment injection due to a family emergency.

For all other protocol deviations, the Applicant reported that the deviations were reviewed in each case and discussed among the study team, and a determination was made that the potential confound on efficacy and safety would be minimal and the patient was allowed to continue in the study.

Reviewer's comment: I reviewed all protocol deviations in the detailed listing. Overall, protocol deviations do not appear significant enough to affect results. Higher rates of protocol deviations leading to treatment discontinuation, such as poor compliance with visit schedule or treatment and concomitant use of other antipsychotics, were reported in the placebo group. This result is expected and can be explained by the untreated underlying condition. Of note, the OSI consult review identified IP dosing errors and lack of documentation of IP administration that were not reported in the detailed listing.

Protocol Duplications

The Applicant identified 10 duplicate patients and one triplicate patient in Study TV-46000-CNS-30072. The duplication occurred with patients who participated in Study TV-46000-CNS-30072, and at certain time points were enrolled as new patients in Study TV-46000-CNS-30078 or as a new patient in the same study TV-46000-CNS-30072 but at a different clinical site. Overall, out of the 11 patients, 9 received overlapping active treatment (TV-46000) or oral risperidone when simultaneously enrolled in both studies or in the same study but in more than one clinical center, and four patients that received placebo in Study TV-46000-CNS-30072, received TV-46000 in Study TV-46000-CNS-30078 in parallel. Because the treatment effects of the primary endpoint were robust, the Applicant did not make any changes to the efficacy analysis to account for these protocol deviations.

The impact of the four placebo patients enrolled and randomized in Study TV-46000-CNS-30072, who in parallel received risperidone in Study TV-46000-CNS-30078, minimally reduced the observed treatment effect when compared to the potential treatment effect had they not received the active study drug. The Applicant concluded and the statistical reviewer confirmed that the impact of the nine patients who received overlapping active treatment when simultaneously enrolled in both studies on the study results is considered minimal, as the risk of relapse in both q1m group and q2m group was already very low.

Reviewer's comment: These deviations alone are not expected to have a significant effect on efficacy results, given the robust treatment effects observed. However, see section 4 regarding OSI inspection findings, which identified other IP dosing errors and lack of IP administration documentation.

Table of Demographic Characteristics

Demographic characteristics were generally balanced among the three treatment groups except that the TV-46000 q2m group had slightly less subjects between age 45 and 65 years old. Overall, there were more male (61%) subjects than female subjects, there were slightly more Black or African Americans (59%) subjects, and most study subjects (79%) were not Hispanics or Latinos. The mean age in the study was approximately 49 years old.

Table 17. Demographic characteristics of the ITT analysis set

Demographic Parameters	Placebo Group (N=181) n (%)	Treatment Group (N=362)		Total (N=543) n (%)
		TV-46000 q1m (N=183) n (%)	TV-46000 q2m (N=179) n (%)	
Sex				
Male	110 (61)	112 (61)	110 (61)	332 (61)
Female	71 (39)	71 (39)	69 (39)	211 (39)
Age				
Mean years (SD)	49.2 (11.43)	50.6 (10.30)	48.3 (10.86)	49.3 (10.89)
Median (years)	52.0	54.0	51.0	52.0
Min, max (years)	19, 65	19, 65	20, 65	19, 65
Age Group				
18-30	20 (11)	11 (6)	16 (9)	47 (9)
>30 – 45 years	32 (18)	41 (22)	45 (25)	118 (22)
>45 – 65 years	129 (71)	131 (72)	118 (66)	378 (69)
Race				
White	68 (38)	72 (39)	66 (37)	206 (38)
Black or African American	104 (57)	108 (59)	110 (61)	322 (59)
Asian	4 (2)	1 (<1)	2 (1)	7 (1)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or Other Pacific Islander	1 (<1)	1 (<1)	0	2 (<1)
Not reported	2 (1)	1 (<1)	0	3 (<1)
Other	2 (1)	0	1 (<1)	3 (<1)
Ethnicity				
Not Hispanic or Latino	139 (77)	144 (79)	144 (80)	427 (79)
Hispanic or Latino	42 (33)	39 (21)	35 (20)	116 (21)
Region (optional)¹				
United States	163 (90)	159 (87)	158 (88)	480 (88)
Bulgaria	18 (10)	24 (13)	21 (12)	63 (12)

SD: standard deviation

¹ The study was conducted at 69 centers in the United States and Bulgaria (61 in the US and 8 in Bulgaria)

Source: Summary 15.2.3 of Study TV-46000-CNS-30072 CSR and Statistical Reviewer's summary for region using Subject-Level Analysis Dataset (ADSL.xpt).

Baseline disease characteristics were generally balanced among the three treatment groups. All patients enrolled in the study were required to have a diagnosis of schizophrenia for more than 1 year with at least one episode of relapse in the last 24 months. The overall mean duration of

Uzedy (risperidone extended release injection)

disease across the treatment groups was 20.8 years prior to enrollment; 20.6, 22.9, and 19.0 years in the placebo, TV-46000 q1m, and TV-46000 q2m groups, respectively. Median time since the most recent relapse was 9.3, 8.1, and 7.8 months, respectively. Mean baseline (i.e., last observed data before the first study drug injection) overall PANSS scores were 61, 61.5, and 61.4, respectively. Mean baseline CGI-S scores were 3.3, 3.3, and 3.2, respectively. A total of 177 (33%) patients had pre-study risperidone exposure, including 57 (31%), 61 (33%), and 59 (33%) patients in the placebo, TV-46000 q1m, and TV-46000 q2m treatment groups, respectively.

Table 18. Baseline Disease Characteristics (e.g., disease characteristics, important concomitant drugs, ITT analysis set)

Baseline Characteristics	Placebo Group (N=181) n (%)	Treatment Group (N=362)		Total (N=543) n (%)
		TV-46000 q1m (N=183) n (%)	TV-46000 q2m (N=179) n (%)	
Oral risperidone at randomization				
2 mg	61 (34)	47 (26)	59 (33)	16 (31) 167 (31)
3 mg	30 (17)	46 (25)	32 (18)	108 (20)
4 mg	68 (38)	68 (37)	67 (37)	203 (37)
5 mg	22 (12)	22 (12)	21 (12)	65 (12)
Disease length				
Mean years (SD)	20.6 (12.21)	22.9 (11.86)	19.0 (12.30)	20.8 (12.21)
Median (years)	19.4	21.0	17.8	19.6
Min, max (years)	2, 48	1, 48	1, 51	1, 51
Disease length categorization				
< 3	5 (3)	3 (2)	4 (2)	12 (2)
3 -5	12 (7)	7 (4)	18 (10)	37 (7)
>5 – 10	30 (17)	19 (10)	36 (20)	85 (16)
>10 – 20	45 (25)	60 (33)	47 (26)	152 (28)
>20	89 (49)	94 (51)	74 (41)	257 (47)
Time since the most recent relapse (months)				
Mean (SD)	10.5 (6.80)	9.7 (6.67)	10.2 (7.48)	10.2 (6.98)
Median	9.3	8.1	7.8	8.2
Min, Max	0, 27	0, 25	0, 35	0, 35
Injection site				
Arm	49 (27)	57 (31)	66 (37)	172 (32)
Abdomen	130 (72)	126 (69)	113 (63)	369 (68)
Not treated	2 (1)	0	0	2 (<1)
CYP2D6 metabolizer status				
Poor	6 (3)	3 (2)	2 (1)	11 (2)
Non-poor	111 (61)	108 (59)	106 (59)	325 (60)
Missing	62 (34)	72 (39)	71 (40)	205 (38)
Not treated	2 (1)	0	0	2 (<1)

Overall PANSS score				
Mean (SD)	61 (10.38)	61.5 (9.60)	61.4 (10.29)	61 (10.08)
Median	62.0	61.0	61.0	61
Min, max	34, 79	38, 80	38, 79	34, 80
CGI-S				
Mean (SD)	3.3 (0.67)	3.3 (0.59)	3.2 (0.66)	3.3 (0.64)
Median	3.0	3.0	3.0	3
Min, max	1, 4	2, 4	2, 4	1, 4

SD: standard deviation

Source: Table 10 of Study TV-46000-CNS-30072 CSR and Statistical Reviewer's Summary based on ITT analysis set using Subject-Level Analysis Dataset (ADSL.xpt).

The treatment groups were also comparable in their use of other prior medications. The majority (>95%) of patients in each treatment group received medications prior to study entry. Medications most frequently used by patients before the study included psycholeptics (495 [91%] patients), psychoanaleptics (159 [29%] patients), and agents acting on the renin-angiotensin system (94 [17%] patients).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The treatment groups were comparable in their use concomitant medications as summarized in the table below.

Table 19. Therapeutic Classification of Concomitant Medications – Stage 2 (ITT Analysis Set)

Therapeutic Class	Placebo Group (N=181) n (%)	Treatment Group (N=362)	
		TV-46000 q1m (N=183) n (%)	TV-46000 q2m (N=179) n (%)
Patients receiving concomitant medications	138 (76)	132 (72)	141 (79)
Agents acting on the renin angiotensin system	30 (17)	36 (20)	34 (19)
Analgesics	29 (16)	16 (9)	27 (15)
Anesthetics	2 (1)	0	1 (1)
Anti-Parkinson drugs	15 (8)	28 (15)	29 (16)
Antianemic preparations	6 (3)	8 (4)	7 (4)
Antibacterials for systemic use	11 (6)	17 (9)	13 (7)
Antibiotics and chemotherapeutics for dermatological use	1 (<1)	1 (<1)	1 (1)
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	1 (<1)	1 (<1)	1 (1)
Antiemetics and antinauseants	3 (2)	2 (1)	2 (1)
Antiepileptics	1 (<1)	2 (1)	0
Antifungals for dermatological use	3 (2)	2 (1)	1 (1)
Antigout preparations	3 (2)	0	0
Antihistamines for systemic use	2 (1)	5 (3)	12 (7)
Antihypertensives	1 (<1)	5 (3)	3 (2)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586

Uzedy (risperidone extended release injection)

Anti-inflammatory and antirheumatic products	34 (19)	18 (10)	23 (13)
Antimycobacterials	0	1 (<1)	0
Antimycotics for systemic use	0	1 (<1)	1 (1)
Antiprotozoals	0	1 (<1)	0
Antipruritics, incl. antihistamines, anesthetics, etc.	1 (<1)	2 (1)	0
Antithrombotic agents	10 (6)	9 (5)	17 (9)
Antivirals for systemic use	1 (<1)	0	1 (1)
Beta blocking agents	10 (6)	12 (7)	12 (7)
Blood substitutes and perfusion solutions	3 (2)	1 (<1)	3 (2)
Calcium channel blockers	14 (8)	23 (13)	14 (8)
Cardiac therapy	1 (<1)	0	2 (1)
Corticosteroids for systemic use	2 (1)	2 (1)	3 (2)
Corticosteroids, dermatological Preparations	3 (2)	5 (3)	1 (1)
Cough and cold preparations	1 (<1)	8 (4)	3 (2)
Diuretics	19 (10)	12 (7)	13 (7)
Drugs for acid related disorders	24 (13)	14 (8)	16 (9)
Drugs for constipation	5 (3)	2 (1)	6 (3)
Drugs for functional gastrointestinal disorders	2 (1)	0	1 (1)
Drugs for obstructive airway diseases	27 (15)	14 (8)	16 (9)
Drugs for treatment of bone diseases	2 (1)	0	1 (1)
Drugs used in diabetes	23 (13)	25 (14)	29 (16)
Ectoparasiticides, incl. scabicides, insecticides and repellents	1 (<1)	1 (<1)	1 (1)
Emollients and protectives	0	3 (2)	0
General nutrients	0	2 (1)	1 (1)
Gynecological anti-infectives and antiseptics	1 (<1)	0	0
Immunosuppressants	0	1 (<1)	1 (1)
Lipid modifying agents	33 (18)	26 (14)	23 (13)
Mineral supplements	3 (2)	1 (<1)	6 (3)
Muscle relaxants	3 (2)	2 (1)	5 (3)
Nasal preparations	4 (2)	3 (2)	6 (3)
Ophthalmologicals	2 (1)	1 (<1)	6 (3)
Other dermatological preparations	0	1 (<1)	1 (1)
Other gynecologicals	1 (<1)	0	3 (2)
Other nervous system drugs	8 (4)	3 (2)	13 (7)
Pancreatic hormones	0	0	1 (1)
Peripheral vasodilators	1 (<1)	0	0
Psychoanaleptics	46 (25)	37 (20)	50 (28)
Psycholeptics	66 (36)	50 (27)	49 (27)
Sex hormones and modulators of the genital system	5 (3)	4 (2)	3 (2)
Stomatological preparations	2 (1)	0	0
Throat preparations	1 (<1)	1 (<1)	1 (1)

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Thyroid therapy	1 (<1)	7 (4)	4 (2)
Topical products for joint and muscular pain	2 (1)	1 (<1)	1 (1)
Unspecified herbal and traditional medicine	0	0	1 (1)
Urologicals	6 (3)	4 (2)	5 (3)
Vaccines	2 (1)	1 (<1)	1 (1)
Vasoprotectives	1 (<1)	0	0
Vitamins	15 (8)	16 (9)	14 (8)

N: number of patients in the ITT analysis set (i.e., number of adults randomized); n: number of adults took the concomitant medicine.

Source: Table 13 of Study TV-46000-CNS-30072 CSR and Statistical Reviewer's summary based on Concomitant Medications Analysis Dataset (ADCM.xpt).

Efficacy Results – Primary Endpoint

The final analysis was to be conducted when 90 relapse events were observed in the adult patients (ITT analysis set). The study was stopped when 90 relapse events were observed; however, one of the relapse events was experienced by the only randomized adolescent patient, who was randomized to the TV-46000 q2m arm. Given that the results were found to be statistically significant for both TV-46000 q1m and q2m groups in adults, the absence of the 90th relapse event in adults did not affect the study results and the overall conclusion.

The primary efficacy variable, the time to impending relapse, showed statistically significant differences from placebo in favor of study drug for both TV-46000 q1m and TV-46000 q2m (Table 20), as supported by the Kaplan-Meier curves (Figure). The proportion of patients with impending relapse was lower in the TV-46000 group (13 [7%] patients in the TV-46000 q1m group and 23 [13%] patients in the TV-46000 q2m group) compared to the placebo group (53 [29%] patients).

Overall, of the patients that met the relapse criterion, the majority met the relapse criterion of CGI-I ≥ 5 (i.e., minimally worse, much worse, or very much worse) and an increase of any of the following individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, to a score of >4 with an absolute increase of ≥ 2 on that specific item since randomization, or an absolute increase of ≥ 4 on the combined score of these 4 PANSS items). The relapse criteria met by the treatment groups are as follows:

- For the criteria of having CGI-I ≥ 5 and
 - having an increase of any of the above individual PANSS items to a score of >4 with an absolute increase of ≥ 2 on that specific item since randomization, in the placebo group (n=53 total relapse cases), there were 42 (23%) patients; in the TV-46000 q1m group (N=13 total relapse cases), there were 9 (5%) patients; in the TV-46000 q2m group (N=23 total relapse cases), there were 15 (5%) patients.
 - having an increase of any of the above individual PANSS items to a score of >4 , and an absolute increase of ≥ 4 on the combined PANSS score of these 4 PANSS items, there

Uzedy (risperidone extended release injection)

were 43 (24%) patients in the placebo group; in the TV-46000 q1m group, there were 10 (5%) patients; in the TV-46000 q2m group, there were 19 (11%) patients.

- For the criteria of hospitalizations due to worsening of psychotic symptoms, there were 7 (4%) patients in the placebo group; in the TV-46000 q1m group, there were 2 (1%) patients; in the TV-46000 q2m group, there were 2 (1%) patients.
- For the criteria of having CGI-SS of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2, there were 2 (1%) patients in the placebo group; in the TV-46000 q1m group, there were 2 (1%) patients; in the TV-46000 q2m group, there was 1 (<1%) patient.
- For the criteria of having violent behavior, there was 1 (<1%) patient in the placebo group; none of the patients in the two TV-46000 groups had violent behavior.

Table 20. Primary Efficacy Results: Time to Impending Relapse (Study TV-46000-CNS-30072, ITT analysis set)

Variable, n (%)	Placebo (N=181) n (%)	TV-46000 q1m (N=183) n (%)	TV-46000 q2m (N=179) n (%)
Patients with impending relapse ^a	53 (29)	13 (7)	23 (13)
Patients who met the relapse criterion			
Increase of CGI-I of ≥ 5	45 (25)	10 (5)	20 (11)
Increase of CGI-I ≥ 5 and increase in any of the 4 PANSS items to a score of >4 with an absolute increase of ≥ 2 on that specific item since randomization ^b	42 (23)	9 (5)	15 (8)
Increase of CGI-I ≥ 5 and increase in any of the 4 PANSS items to a score of >4 with an absolute increase of ≥ 4 on the combined PANSS score of the 4 items	43 (24)	10 (5)	19 (11)
Hospitalization due to worsening of psychotic symptoms	7 (4)	2 (1)	2 (1)
Suicidality	2 (1)	2 (1)	1 (<1)
Violent behavior	1 (<1)	–	–
Patients who discontinued treatment early without relapse	68 (38)	71 (39)	66 (37)
Log-rank test p-value		<0.0001 ^e	<0.0001 ^e
Hazard ratio (95% CI) ^d		0.200 (0.109, 0.367)	0.375 (0.227, 0.618)
Proportional hazards test p-value ^f	0.7251		

Source: Table 17 of Study TV-46000-CNS-30072 CSR.

CI: confidence interval; N: number of patients in the ITT analysis set (i.e., number of adults randomized); n: number of adults with an event.

^a A patient may have been counted in more than 1 relapse criterion.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586

Uzedy (risperidone extended release injection)

^b The 4 PANSS items are as follows: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content.

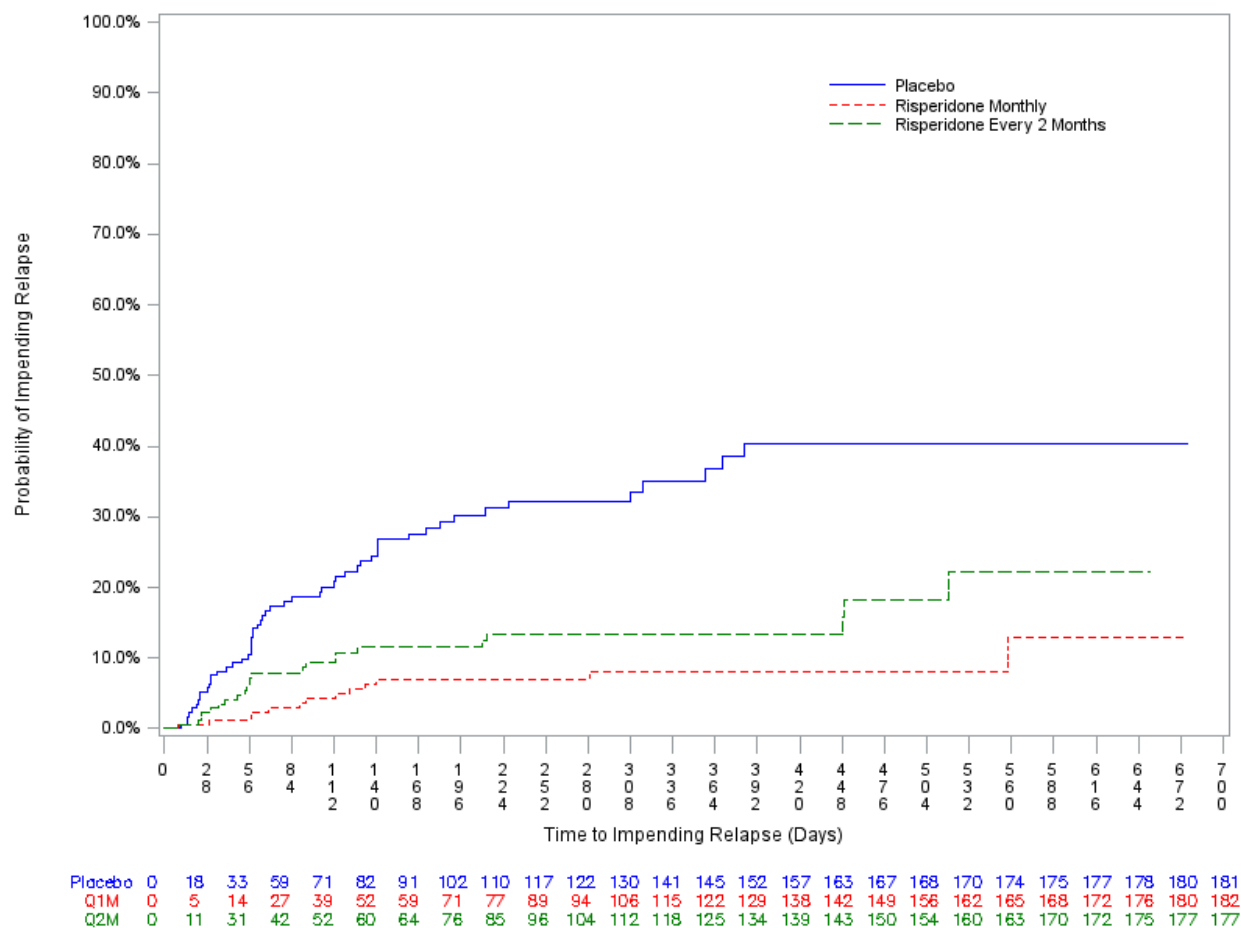
^c CGI-SS of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2.

^d The hazard ratio (95% CI) coming from the stratified Cox proportional hazard model, with treatment (placebo, TV-46000 q1m and TV-46000 q2m, or placebo and TV-46000 overall [including q1m and q2m]) as exploratory variable and sex-dose as a stratification factor, and the stratified log-rank test p-value (sex-dose as a stratification factor) refer to TV-46000/placebo comparison.

^e The p-values refer to the analyses of primary endpoints.

^f The proportional hazards test p-value tests the overall proportional hazard assumption for the primary model.

Figure 9. Kaplan-Meier Estimation of Percent of Impending Relapse by Treatment Group (ITT Analysis Set)



Source: Statistical reviewer's analysis using Data for the Time to Event Analyses (ADTTE.xpt) dataset.

The Applicant-reported hazard ratio was based on the Cox PH model. An assumption of PH regression is that the hazard ratio is constant over time, which indicates that the relative likelihood of disease resolution (or progression in this study) in treated versus control subjects remains relatively constant at any given point in time. The Applicant reported p-value of 0.7251 for testing the overall PH assumption, which indicates that the PH assumption seems to be reasonable.

One of the underlying assumptions of the log-rank test and Cox PH model used in this study is that censoring is non-informative, which means that the censoring is not related to alteration in

the risk for relapse. However, some of the reasons for early dropouts may potentially be related to alteration of risk for relapse. The Applicant used a “tipping point” approach to assess the sensitivity of the observed results to this assumption.

Overall, 205 patients withdrew from treatment early without relapse during Stage 2. The Applicant reviewed these patients in a case-by-case manner before unblinding and assessed whether they had suspected informative/non-informative censoring at withdrawal based on clinical judgment. Tipping point analysis was based on imputed time for relapse values for those patients who were classified as having suspected informative censoring. When the risk for relapse after early termination (ET) for suspected reasons in patients on TV-46000 was 25 times higher than that for similar patients in the same group, the result of the tipping point sensitivity analysis supports the robustness of the primary analysis results to the assumption of non-informative censoring.

The statistical reviewer conducted additional supplementary analyses to further assess the sensitivity of the observed results to the assumption of non-informative censoring:

- where there was suspected informative censoring were considered events
- where subjects who discontinued treatment due to lack-of-efficacy, adverse events, or deaths were considered events
- and where all treatment discontinuations were considered events

All these analyses (Table 21) support the robustness of the primary analysis results.

Table 21. Statistical Reviewer’s Supplementary Analyses

Variable, n (%)	Placebo (N=181) n (%)	TV-46000 q1m (N=183) n (%)	TV-46000 q2m (N=179) n (%)
Subjects who discontinued treatment due to death, AE, or lack-of-efficacy as events			
Patients with impending relapse ^a	64 (35)	34 (19)	42 (23)
Log-rank test p-value		<0.0001	0.0058
Hazard ratio (95% CI) ^b		0.55 (0.43, 0.703)	0.673 (0.53, 0.856)
Suspected informative censoring as events			
Patients with impending relapse ^a	92 (51)	39 (21)	44 (25)
Log-rank test p-value		<0.0001	<0.0001
Hazard ratio (95% CI) ^b		0.322 (0.248, 0.419)	0.395 (0.306, 0.510)

All treatment discontinuation as events			
Patients with impending relapse ^a	121 (67)	84 (46)	89 (50)
Log-rank test p-value		<0.0001	0.0011
Hazard ratio (95% CI) ^b		0.548 (0.414, 0.725)	0.634 (0.481, 0.836)

CI: confidence interval; N: number of patients in the ITT analysis set (i.e., number of adults randomized); n: number of adults with an event.

^a A patient may have been counted in more than 1 relapse criterion.

^b The hazard ratio (95% CI) coming from the stratified Cox proportional hazard model, with treatment (placebo, TV-46000 q1m and TV-46000 q2m, or placebo and TV-46000 overall [including q1m and q2m]) as exploratory variable and sex-dose as a stratification factor, and the stratified log-rank test p-value (sex-dose as a stratification factor) refer to TV-46000/placebo comparison.

Source: Stat Reviewer's Analyses using Data for the Time to Event Analyses (ADTTE.xpt) dataset.

Data Quality and Integrity

The submission contains all required components of the electronic common technical document (eCTD). The overall quality and integrity of the datasets appear to be acceptable. Requests for additional information from the Applicant throughout the review process were addressed in a timely fashion.

Efficacy Results – Secondary and other relevant endpoints

As noted in Section 8.1, all the Applicant-proposed key secondary endpoints are considered exploratory in nature; therefore, the results of these secondary endpoints are presented below as part of secondary or exploratory COA (PRO) endpoints.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

For the Applicant-defined secondary endpoints, the results of both TV-46000 q1m and q2m treatment groups were numerically better than placebo for these endpoints (see Table 22).

Table 22. Secondary/Exploratory Endpoints (ITT Analysis Set)

Secondary Endpoints		Placebo (N=181)	TV-46000 q1m (N=183)	TV-46000 q2m (N=179)
Impending relapse rate at week 24	Observed (95% CI)	0.28 (0.205, 0.347)	0.07 (0.03, 0.109)	0.11 (0.065, 0.165)
	Observed Difference (95% CI)	--	0.21 (-0.288, -0.125)	-0.16 (-0.248, -0.074)
Percentage of Patients Who Maintain Stability at Endpoint	Overall, n (%)	110 (61)	159 (87)	143 (80)
	Observed Difference (95% CI)	--	-26 (-35, -17)	-19 (-28, -10)
Percentage of Patients Achieving Remission at Endpoint	Overall, n (%)	130 (72)	133 (73)	133 (74)
	Observed Difference (95% CI)	--	-1 (-10, 8)	-2 (-12, 7)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
Uzedy (risperidone extended release injection)

Observed Rate of Impending Relapse at Endpoint	Overall, n (%)	53 (29)	13 (7)	23 (13)
Drug Attitudes Inventory 10-Item Version (EoT)	Observed Mean (SD)	-0.9 (3.42)	0.3 (2.84)	0.3 (2.84)
Schizophrenia Quality of Life Scale (EoT)	Observed Mean (SD)	-2.3 (13.26)	-7.2 (13.79)	-7.3 (12.3)

CI: confidence interval; N: number of patients in the ITT analysis set (i.e., number of adults randomized); n: number of adults with an event.
EoT: end of treatment.

Source: Tables 15.11.1, 15.11.2, 15.11.3, 15.11.4, 15.11.5 of Study TV-46000-CNS-30072 CSR.

Statistical Reviewer's Comments: The results of these secondary/exploratory endpoints supported the treatment effect of TV-46000 versus placebo. However, it should be noted that the secondary endpoints of "Impending relapse rate at Week 24," and "Observed rate of impending relapse at endpoint" provide redundant information with the primary efficacy results. We also do not agree with the endpoints of "Percentage of patients who maintain stability at endpoint" and "Percentage of patients achieving remission at endpoint" since "stability" and "remission" do not have standard definitions. For endpoints based on change from baseline (such as the endpoints in the last two rows of the table), statistical analyses are problematic because of competing risks (or informative censoring).

Additional Analyses Conducted on the Individual Trial

Subpopulations

Subgroup analysis of the time to impending relapse based on gender, race, age, region, and baseline PANSS score were performed. All the subgroup analyses results were consistent with those seen for the overall population for each demographic subgroup.

Table 23. Subgroup analysis

Subgroup	Patients with impending relapse (n) / Number of Patients in the subgroup (N) (%)	Placebo (N=181)	TV-46000 q1m (N=183)	TV-46000 q2m (N=179)
Sex				
Male	n/N (%)	35/110 (32)	8/112 (7)	16/110 (15)
	HR (95% CI)		0.181 (0.084, 0.390)	0.395 (0.218, 0.716)
Female	n/N (%)	18/71 (25)	5/71 (7)	7/69 (10)
	HR (95% CI)		0.217 (0.080, 0.586)	0.359 (0.150, 0.861)
Time from Diagnosis				
<10 years	n/N (%)	18/47 (38)	3/29 (10)	7/59 (12)
	HR (95% CI)		0.190 (0.055, 0.652)	0.246 (0.101, 0.596)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586

Uzedy (risperidone extended release injection)

≥10 years and <20 years	n/N (%)	10/45 (22)	2/60 (3)	4/47 (9)
	HR (95% CI)		0.132 (0.029, 0.606)	0.318 (0.098, 1.033)
≥20 years	n/N (%)	25/89 (28)	8/94 (9)	12/74 (16)
	HR (95% CI)		0.258 (0.116, 0.574)	0.512 (0.254, 1.032)
Race				
White	n/N (%)	22/68 (32)	6/72 (8)	9/66 (14)
	HR (95% CI)		0.178 (0.072, 0.441)	0.339 (0.154, 0.745)
Black or African Am	n/N (%)	29/104 (28)	7/108 (6)	14/110 (13)
	HR (95% CI)		0.214 (0.094, 0.490)	0.404 (0.209, 0.781)
Other	n/N (%)	1/2 (50)	n/a	n/a
	HR (95% CI)			
Not Reported	n/N (%)	1/2 (50)	n/a	n/a
	HR (95% CI)			
Region¹				
USA	n/N (%)	41/163 (25)	9/159 (6)	21/158 (13)
	HR (95% CI)		0.198 (0.096, 0.408)	0.469 (0.274, 0.803)
Bulgaria	n/N (%)	12/18 (67)	4/24 (17)	2/21 (10)
	HR (95% CI)		0.127 (0.040, 0.404)	0.086 (0.019, 0.394)
PANSS Score				
≤54	n/N (%)	10/49 (20)	1/42 (2)	6/56 (11)
	HR (95% CI)		0.123 (0.016, 0.963)	0.553 (0.198, 1.540)
<54 PANSS ≤61	n/N (%)	14/39 (36)	3/53 (6)	3/34 (9)
	HR (95% CI)		0.113 (0.032, 0.396)	0.210 (0.06, 0.738)
<61 PANSS ≤70	n/N (%)	13/53 (25)	5/50 (10)	9/41 (22)
	HR (95% CI)		0.308 (0.109, 0.868)	0.659 (0.277, 1.567)
>70	n/N (%)	16/38 (42)	4/38 (11)	5/48 (10)
	HR (95% CI)		0.198 (0.066, 0.596)	0.212 (0.077, 0.585)

CI: confidence interval; HR: hazard ratio.

¹ The study was conducted at 69 centers in the United States and Bulgaria (61 in the US and 8 in Bulgaria).

Source: Tables 15.10.1, 15.10.2, 15.10.3, 15.10.4, 15.10.5 of Study TV-46000-CNS-30072 CSR.

Summary of Efficacy Results

Study TV-46000-CNS-30072 was conducted to support the efficacy and safety of TV-46000. This study met its prespecified primary endpoint for both the TV-46000 q1m and q2m dosing regimens and demonstrated statistically significant ($p < 0.0001$) prolongation in the time to impending relapse versus placebo based on the stratified log rank test, stratified by gender and the dose of oral risperidone on which the patient was stabilized. The proportion of patients with impending relapse was lower in the TV-46000 group (13 [7%] patients in the TV-46000

q1m group and 23 [13%] patients in the TV-46000 q2m group) compared to the placebo group (53 [29%] patients). Results of supplementary analyses were robust and consistent with the main analysis. Results of secondary and exploratory endpoints were supportive of the treatment benefit of TV-46000 versus placebo. Subgroup analyses by gender, age, race, and baseline PANSS scores did not suggest any clear evidence of different response.

8.1.3. Assessment of Efficacy Across Trials

Not applicable.

8.1.4. Integrated Assessment of Effectiveness

Study TV-46000-CNS-30072 met its prespecified primary endpoint for both the TV-46000 q1m and q2m dosing regimens and demonstrated statistically significant ($p < 0.0001$) prolongation in the time to impending relapse versus placebo. OSI inspection did not identify discrepancies in the primary efficacy endpoint data from this study. However, the data on dosing from the study cannot be relied upon and the doses of IP that provided benefit to patients in Study TV-46000-CNS-30072 could not be verified. Given the differences in the PK profile between the listed drug and TV-46000 and the potential for trough levels to lead to relapse in patients, it is important to understand what IP doses patients actually received. Several instances of patients receiving IP doses higher than the assigned dose have already been identified. Should there be systemic inflation of actual doses received upon a full audit of dosing data, the dosage and administration section of labeling could be impacted. Therefore, it cannot be determined whether the dose range proposed for marketing is supported by the results of Study TV-46000-CNS-30072.

8.2. Review of Safety

8.2.1. Safety Review Approach

This safety review will examine subjects with schizophrenia in the TV-46000 clinical trial program. The safety evaluation of the NDA for TV-46000 sc injection is based principally on data from the placebo-controlled phase 3 study (Study TV-46000-CNS-30072), as well as on data on the long-term safety uncontrolled phase 3 study (Study TV-46000-CNS-30078) and data from phase 1 studies (Study RISPE1ZG15EU, Study TV-46000-SAD-10055, and Study TV-46000-BA-10148).

The safety analysis set includes all patients treated with oral risperidone (2 to 5 mg/day) who received at least one dose of TV-46000 or placebo IP. For Study TV-46000-CNS-30072, pooled data for all TV-46000 dose levels are presented as well as by dose level.

Risperdal oral tablet was approved in the United States in 2003 and its safety profile is well-characterized. The Applicant has provided pharmacokinetic data to support reliance in part on the systemic safety of Risperdal tablets. Because TV-46000 is a sc dosage form, this safety

review focuses primarily on adverse events of local reaction and severity and timing of systemic ARs. The following findings were used to assess safety in phase 1 and phase 3 studies:

- Adverse events
- Extrapyrimal symptoms, as measured by the Extrapyrimal Symptom Rating Scale (ESRS)
- Local injection site tolerance and pain, evaluated by the Injection Site Numeric Pain Rating Scale (NPRS)
- Laboratory parameters: hematology, chemistry, thyroid panel, serum pregnancy test, follicle-stimulating hormone, prolactin, urinalysis, urine pregnancy test, and urine drug screen
- Vital signs: blood pressure (BP), pulse, respiratory rate, tympanic temperature
- Physical examination
- ECG
- Concomitant medication usage
- Calgary Depression Scale for Schizophrenia (CDSS)
- Clinical Global Impression-Severity (CGI-S)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

In addition, in phase 3 studies the following findings were used to assess safety:

- Abnormal Involuntary Movement Scale (AIMS)
- Simpson-Angus Scale (SAS) of drug-induced parkinsonian symptoms
- Barnes Akathisia Rating Scale (BARS)
- Clinical Global Impression-Severity of Suicidality (CGI-SS)
- Rescue medication
- Discontinuation rate due to adverse events

- o Time to all-cause discontinuation
- o All-cause discontinuation rates

8.2.2. Review of the Safety Database

Overall Exposure

Per the Applicant, with the exception of the one ongoing Study TV-46000-CNS-30078, all four other studies (RISPE1ZG15EU, Study TV-46000-BA-10148, Study TV-46000-SAD-10055, and Study TV-46000-CNS-30072) were completed at the time of the 120-Day Safety Update cutoff date of May 1, 2021. Regarding Study TV-46000-CNS-30078, as of the cutoff date of May 1, 2021, a small number of adult patients were in End of Treatment (EoT) and follow-up visits. The composition of the safety population is described in Table 24.

Table 24. Safety Population for TV-46000 Development

Clinical Trial Groups	TV-46000 (n= 521)
Primary safety study TV-46000-CNS-30072	362
Long-term safety-study TV-46000-CNS-30078	159 (106 new patients, 53 placebo rollovers from TV-46000-CNS-30072)
phase 1 PK SAD-10055 study	99
phase 1 BA BA-10148 study	120
phase 1 RISPE1ZG15EU	53
Controlled trials conducted for other indications	0

Source: Applicant's Tabular Listing of Clinical Studies and Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) of 120-day-safety report.

Adequacy of the safety database:

In the placebo-controlled Study TV-46000-CNS-30072, the total number of subjects exposed for >26 weeks was 237 subjects and for >52 weeks was 129 subjects, with 64 patients exposed to q1m and 65 patients to q2m (Table 25). In the long-term safety Study TV-46000-CNS-30078, the total number of subjects exposed for >26 weeks was 297 subjects and for >52 weeks was 237 subjects, with 119 patients exposed to q1m and 128 patients to q2m (Table 26).

Table 25. Exposure to TV-46000 (Study TV-46000-CNS-30072)

Exposure (Weeks)	Placebo N=179 n (%)	TV-46000 q1m N=183 n (%)	TV-46000 q2m N=179 n (%)
<=13 weeks	64 (35)	36 (20)	37 (21)
>13 to <=26 weeks	28 (16)	25 (14)	27 (15)
>26 to <=39 weeks	26 (15)	29 (16)	25 (14)
>39 to <=52 weeks	25 (14)	29 (16)	25 (14)
>52 weeks	36 (20)	64 (35)	65 (35)

Source: Applicant's Clinical Study Report of Study TV-46000-CNS-30072, Table 22, page 134.

Table 26. Exposure to TV-46000 (Study TV-46000-CNS-30078)

Exposure (Weeks)	TV-46000 q1m N=171 n (%)	TV-46000 q2m N=160 n (%)	All N=331 n (%)
<=13 weeks	16 (9)	9 (5)	25 (8)
>13 to <=26 weeks	2 (1)	7 (4)	9 (3)
>26 to <=39 weeks	10 (6)	6 (4)	16 (5)
>39 to <=52 weeks	24 (14)	20 (13)	44 (13)
>52 to <=56 weeks	10 (6)	14 (9)	24 (7)
>56 weeks	109 (64)	104 (65)	213 (64)

Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) of 120-day-safety report.

Clinical Reviewer's comment: The size of the safety database appears adequate to draw meaningful conclusions from the study results. In addition, risperidone is a currently marketed drug, with a known safety profile. However, the open-label titration period with oral risperidone prior to randomization in study TV-46000-CNS-30072 limits the interpretability of the controlled safety data.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

One patient had triplicate overlapping active treatment and seven patients had duplicate overlapping active treatment. For these patients, adverse events, exposure to oral risperidone and TV-46000, clinical scales, laboratory results, ECG and associated protocol deviations were reviewed and they did not have a clinically significant effect on the overall safety findings.

Four patients in the placebo group in Study TV-46000-CNS-30072 were treated with active treatment in Study TV-46000-CNS-30078 in parallel. The impact of the four placebo patients enrolled and randomized in Study TV-46000-CNS-30072, who in parallel received risperidone in Study TV-46000-CNS-30078, may have reduced the differences between placebo and active treatment in reported AEs.

Reviewer's comment: Theoretically, the use of an active treatment by a participant while in the placebo arm, may have reduced the differences observed in frequency of AEs between placebo and active drug. Notwithstanding this possibility, overall, the number of cases does not appear significant enough to affect safety results. However, the OSI inspection indicated that in addition to these duplications there were also IP dosing errors and lack of documentation of IP administration identified. Therefore, the exposure data by dose cannot be relied upon and the exposure-response assessment of safety cannot be relied upon.

Categorization of Adverse Events

The studies used Medical Dictionary for Regulatory Activities (MedDRA) versions 23. AEs were recorded at each study visit for all studies, and the Applicant appeared to use standard methods for severity coding. Verbatim and preferred terms (PTs) were inspected and most of the Applicant's mapping were acceptable. Clinical judgment was used to review available data and narratives for AE adjudication apart from those the Applicant included. As a result, the clinical review includes some AE analysis adjustment varying from the Applicant's analyses for tables in Section 8.2.4. (Applicant AE data tables were used for the other sections; refer to the source under each table, as needed).

The following terms were grouped together:

Schizophrenia: Psychotic disorder, hallucination auditory, psychotic symptoms, acute psychosis, paranoia, hallucination

Somnolence: Sedation

Hyperprolactinemia: Galactorrhea, gynecomastia

Liver function test increased: Alanine aminotransferase increase, aspartate aminotransferase increased, hepatic enzyme increase, transaminases increased, blood bilirubin increase

Depression: Depressed mood, depressed symptom, major depression, tearfulness

Hyperlipidemia: Hypercholesterolemia, hypertriglyceridemia, blood triglycerides increased, High density lipoprotein decreased

Abdominal pain: Abdominal discomfort, abdominal pain upper

Blood glucose increased: Diabetes mellitus, Diabetes mellitus inadequate control, hyperglycemia

BP decreased: Hypotension

BP increased: Hypertension

Extrapyramidal disorder: Dyskinesia, joint stiffness, musculoskeletal stiffness, oromandibular dystonia, resting tremor, tremor, akathisia, muscle rigidity, muscle twitching, dystonia, muscle spasms, muscle tightness, hypertonia, nuchal rigidity, torticollis

Injection site reactions: Injection site nodule, injection site rash, injection site pruritus, injection site swelling, injection site pain, injection site mass, injection site bruising, injection site induration, injection site dermatitis, injection site oedema, injection site discoloration, injection site erythema, injection site irritation, injection site dryness, injection site inflammation,

injection site injury, injection site paresthesia, injection site hematoma, injection site abscess, injection site warmth, injection site hypoesthesia

Routine Clinical Tests

The schedule for collection of routine clinical tests is presented in Session 8.1.1, Table 14. The scheduling of clinical tests was adequate to support the clinical safety review with two exceptions. Local tolerability assessments were administered only to patients who reported injection site ARs. This approach may have resulted in underreporting of local toxicity and these assessments should have been done in every participant. Also, orthostatic blood pressure (BP) measurements were not performed and therefore risk of orthostatic hypotension could not be assessed.

8.2.4. Safety Results

Deaths

As of the cut-off date of the 120-Day Safety Update (May 1, 2021), a total of nine deaths occurred in the development program. The deaths were as follows: one patient in Study TV-46000-SAD-10055, five patients in Study TV-46000-CNS-30072, and three patients in Study TV-46000-CNS-30078. The narrative summary for each death case was reviewed.

Deaths in Study TV-46000-CNS-30072.

Patient (b) (6) Three weeks after administration of the 16th dose of the study drug (TV-46000 250mg q2m, abdomen) the patient died due to combined buprenorphine and risperidone intoxication.

Clinical Reviewer's comments: Not enough information to determine reasons for buprenorphine use. Onset occurred three weeks after q2m injection, making study drug involvement due to diminished efficacy less likely.

Patient (b) (6) A few days after a surgical-diagnostic lung procedure, the patient died from unspecified procedural complications. Additional information was not provided.

Clinical Reviewer's comment: unknown death cause. Not enough information to determine reasons for a surgical-diagnostic lung procedure. Not enough information to determine causality.

Patient (b) (6) Patient died of respiratory failure eight days after receiving the 9th dose of the study drug (150 mg q2m TV-46000, abdomen).

Clinical Reviewer's comments: The patient had several risk factors for respiratory failure, including asthma, smoking habit, chronic obstructive pulmonary disease (COPD).

Patient (b) (6) Patient died from acute respiratory failure, sepsis, encephalopathy, and accidental overdose of multiple substances (opioid and cocaine). An autopsy was not performed. Of note, inquiries regarding alcohol consumption and illicit drug use were negative at all study visits.

Clinical Reviewer's comments: Patient died of overdose. A causality related to study drug is unlikely.

Patient (b) (6) Patient died of a fatal myocardial infarction (MI) during the double-blind relapse prevention stage of the study, twelve days after the administration of the first and only dose of the study drug (placebo, abdomen).

Deaths in Study TV-46000-CNS-30078.

Patient (b) (6) Patient had a fatal MI during the double-blind maintenance stage of the study, three weeks after administration of the 3rd dose of the study drug (75 mg TV-46000 q1m, abdomen).

Clinical Reviewer's comment: The patient's several risk factors for MI, including tetralogy of Fallot, diabetes mellitus, and hypertension, associated with a surge in myocardial oxygen demand (running) likely resulted in MI.

Patient (b) (6) Patient died of an acute MI during the double-blind maintenance stage of the study, the day of administration of the 5th dose of the study drug (200 mg TV-46000 q2m, abdomen).

Clinical Reviewer's comment: The patient had several risk factors for MI, including age and hypertension, and a causality related to study drug is unlikely.

Patient (b) (6) Patient experienced a cerebrovascular accident during the double-blind maintenance stage of the study, about two weeks after administration of the 8th dose of the study drug (50 mg TV-46000 q1m, abdomen). He died two months later.

Clinical Reviewer's comment: The patient's age was a risk factor. Unknown if an autopsy to evaluate brain aneurysm or arteriovenous malformations was performed. Causality related to study drug is unlikely.

Death in Study TV-46000-SAD-10055.

Patient (b) (6) Patient died by suicide.

Clinical Reviewer's comments: Underlying disease is a confounding factor. Not enough information to determine causality.

Nonfatal Serious Adverse Events

Schizophrenia relapses, which indicate a lack of efficacy, were not included in the count of SAEs because with an expected higher schizophrenia relapse rate in the placebo group they could obscure a difference between treatment arms. Percentages of SAEs were similar across the three arms in Study TV-46000-CNS-30072 (3% in placebo group, 4% in q1m group and 2% in q2m group, Table 27). Each SAE was reported in no more than one patient, except for suicidal ideation, which was reported in two patients in the TV-46000 q1m group.

Table 27. Serious adverse events (Study TV-46000-CNS-30072)

Preferred Term	Placebo N=179 n (%)	TV-46000 q1m N=183 n (%)	TV-46000 q2m N=179 n (%)
Patients with any SAEs	6 (3)	8 (4)	3 (2)
Myocardial infarction	1 (<1)	0	0
Intestinal perforation	0	1 (<1)	0
Pancreatitis acute	1 (<1)	0	0
Cholelithiasis	1 (<1)	0	0
Bronchitis	0	0	1 (<1)
COVID-19	0	1 (<1)	0
Osteomyelitis	0	0	1 (<1)
Pneumonia	1 (<1)	0	0
Upper respiratory tract infection	0	1 (<1)	0
Type 2 diabetes mellitus	0	1 (<1)	0
Spinal pain	0	0	1 (<1)
Syncope	1 (<1)	0	0
Mental status changes	0	1 (<1)	0
Suicidal ideation	1 (<1)	2 (1)	0
Pulmonary embolism	0	1 (<1)	0

Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) of Study TV-46000-CNS-30072 (deaths and schizophrenia relapses were excluded).

This table was generated excluding deaths, which are summarized separately, and schizophrenia relapses, which are disease-related.

SAEs in the long-term safety Study TV-46000-CNS-30078 were evenly distributed between q1m and q2m dose regimens. No SAE was present in more than one patient (Table 28).

Table 28.Serious adverse events (Study TV-46000-CNS-30078)

Preferred Term	TV-46000 q1m N = 169 n (%)	TV-46000 q2m N = 159 n (%)
Patients with any SAEs	5 (3)	5 (3)
Anemia	0	1 (<1)
Atrial fibrillation	1 (<1)	0
Angina pectoris	0	1 (<1)
Hyperglycemia	1 (<1)	0
Panic attack	0	1 (<1)
Major depression	1 (<1)	0
Substance-induced psychotic disorder	1 (<1)	0
Self-injurious ideation	0	1 (<1)
Chronic obstructive pulmonary diseases	0	1 (<1)
Deep vein thrombosis	1 (<1)	0

Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) of Study TV-46000-CNS-30078 (deaths and schizophrenia relapses were excluded).

Clinical Reviewer's comment: All the SAEs were reported for one subject only, except for suicidal ideation (two subjects in Study TV-46000-CNS-30072 and one self-injurious ideation in Study TV-46000-CNS-30078), which is likely related to schizophrenia, not the medication. SAEs are mainly psychiatric in nature and likely related to the condition being treated. SAEs that could be related to TV-46000 are those that could be sequelae of metabolic changes. The SAEs did not raise any new safety concerns.

Dropouts and/or Discontinuations Due to Adverse Effects

In Study TV-46000-CNS-30072, the percentage of patients with AEs leading to treatment discontinuation was higher in the q1m group (12%) and q2m group (8%) compared to the placebo group (4%). These AEs included AEs at the injection site, metabolic disorders (such as diabetes mellitus), and nervous system disorders including parkinsonism and sedation (Table 29).

Table 29. Discontinuations due to adverse events (Study TV-46000-CNS-30072)

System Organ Class (Preferred Term)	Placebo N=179 n (%)	TV-46000 q1m N=183 n (%)	TV-46000 q2m N=179 n (%)
Discontinuation due to any AE	7 (4)	22 (12)	15 (8)
Gastrointestinal disorders	1 (<1)	1 (<1)	
Injection site discoloration, mass, nodule, pruritus, swelling	0	3 (2)	4 (2)
Immune system disorders (Hypersensitivity)	0	0	1 (<1)
Infections and infestations	0	1 (<1)	
Investigations (Weight increased/decreased, LFTs increase)	1 (<1)	2 (1)	2 (1)
Metabolism and nutrition disorders (Hypertriglyceridemia, Diabetes)	0	1 (<1)	1 (<1)
Nervous system disorders (akathisia, EPS, TD, somnolence, tremor)	2 (1)	9 (5)	3 (2)
Psychiatric disorders (alcoholism, anxiety, mental status changes)	1 (<1)	4 (2)	1 (<1)
Renal and urinary disorders (urinary incontinence)	0	0	1 (<1)
Reproductive system and breast disorders (Galactorrhea)	0	1 (<1)	1 (<1)
Skin and subcutaneous tissue disorders	2 (<1)	0	1 (<1)

Source: Clinical Reviewer's Summary based on individual patient narratives of withdrawals due to AEs, and Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) of Study TV-46000-CNS-30072 (deaths and schizophrenia relapses were excluded). Patients who had multiple AEs in a system organ class leading to discontinuation were counted only once.

This table was generated excluding deaths, which are summarized separately, and schizophrenia relapses, which are disease-related.

In new patients enrolled in Study TV-46000-CNS-30078, there was only one AE leading to treatment discontinuation (acute MI leading to death; subject (b) (6)). Cases of treatment discontinuation in patients who rolled over from Study TV-46000-CNS-30072 to Study TV-46000-CNS-30078 were cardiac disorders (two patients, one experienced atrial fibrillation and the other one angina pectoris), injection site mass/nodule (two patients), headache (one patient), and fatigue (one patient).

Clinical Reviewer's comment: Overall, the safety findings from Study TV-46000-CNS-30072 and Study TV-46000-CNS-30078 are consistent with the safety profile of Risperdal, the LD, except for injection site AEs, which are expected for a long-acting injection formulation. The relationship to the dose administered for major safety findings cannot be assessed, given that the dosing data could not be verified.

Significant Adverse Events

In Study TV-46000-CNS-30072, Stage 2, most adverse events in the placebo, TV-46000 q1m, and TV-46000 q2m treatment groups were reported as mild to moderate in severity. Each group had similar incidence of severe AEs, i.e., 7% in the placebo group, 3% in patients in the TV-46000 q1m group, and 6% in patients in the TV-46000 q2m group. Akathisia and headache were the only severe AEs besides schizophrenia relapse that occurred in more than one patient (akathisia in two patients in the TV-46000 q1m group; headache in two patients in the TV-46000 q2m group).

Treatment Emergent Adverse Events and Adverse Reactions

Table 30 presents the most frequent treatment-emergent adverse events (TEAEs) (adverse events starting only during the active treatment period with the IP) occurring in Study TV-46000-CNS-30072 in greater than 2% of patients on drug and greater than placebo. The most commonly reported PT under the General Disorders and Administration Site Conditions (System Organ Class) was injection site reactions; these events were more common in the q1m and q2m groups than placebo. As expected, AEs in the nervous system (e.g., akathisia, extrapyramidal disorder, dizziness, and somnolence) had higher incidence in the q1m and q2m groups compared to placebo, as well as AEs in reproductive system and breast disorder (erection dysfunction) and are consistent with the oral risperidone safety profile.

Table 30. Most common TEAEs (>2%, TV-46000>Placebo) (Study TV-46000-CNS-30072)

System Organ Class Preferred Term	Placebo N=179 n (%)	TV-46000 q1m N=183 n (%)	TV-46000 q2m N=179 n (%)
Patients with any AEs	91 (51)	111 (61)	121 (67)
General disorders and administration site conditions	26 (15)	41 (22)	39 (22)
Injection site nodule	6 (3)	12 (7)	13 (7)
Injection site pruritus	4 (2)	10 (5)	7 (4)
Injection site erythema	2 (1)	6 (3)	8 (4)
Injection site mass	1 (<1)	3 (2)	6 (3)
Injection site swelling	0	2 (1)	3 (2)
Infections and infestations	19 (11)	32 (17)	22 (12)
Urinary tract infection	4 (2)	7 (4)	8 (4)
Nasopharyngitis	5 (3)	9 (5)	4 (2)
Upper respiratory tract infection	5 (3)	7 (4)	2 (1)
Investigations	15 (8)	21 (11)	23 (13)
Weight increased	6 (3)	10 (5)	13 (7)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
Uzedy (risperidone extended release injection)

Metabolism and nutrition disorders	15 (8)	10 (5)	14 (8)
Diabetes mellitus (incl subtypes) and Hyperglycemia	1 (<1)	5 (3)	6 (3)
Increased appetite	2 (1)	4 (2)	2 (1)
Nervous system disorders	22 (12)	44 (24)	47 (26)
Akathisia, EPS, Tremor	7 (4)	21 (11)	22 (12)
Sedation, Somnolence, Dizziness, Drooling	6 (3)	18 (10)	19 (11)
Reproductive system and breast disorders	1 (<1)	4 (2)	9 (5)
Erection and ejaculation conditions and disorders	0	1 (<1)	3 (2)
Gastrointestinal disorders	18 (10)	18 (10)	21 (12)
Nausea	2 (1)	4 (2)	4 (2)
Dry mouth	1 (<1)	2 (1)	3 (2)
Salivary hypersecretion	1 (<1)	2 (1)	3 (2)
Vomiting	2 (1)	3 (2)	0
Dyspepsia	0	3 (2)	1 (<1)
Injury, poisoning and procedural complications	8 (4)	4 (2)	9 (5)
Ligament sprain	1 (<1)	1 (<1)	3 (2)
Psychiatric disorders	33 (18)	25 (14)	20 (11)
Restlessness	0	0	3 (2)
Respiratory, thoracic and mediastinal disorders	4 (2)	10 (5)	6 (3)
Cough	1 (<1)	3 (2)	1 (<1)
Skin and subcutaneous tissue disorders	9 (5)	7 (4)	4 (2)
Rash	2 (1)	1 (<1)	4 (2)

Source: Table 25, pg 138-140 of Applicant's Clinical Study Report of Study TV-46000-CNS-30072 and Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) of Study TV-46000-CNS-30072 (deaths and schizophrenia relapses were excluded).

Laboratory Findings

The laboratory values were examined for clinical significance. Overall, laboratory results in all the studies did not show any significant or concerning clinical or toxicity-related issues, except for prolactin changes. Prolactin shift values from low-to-normal range at baseline to greater than the upper limit of normal (ULN) post-baseline occurred more frequently in the TV-46000 I groups compared to the placebo group (Table 31).

Table 31. Shift in prolactin level (Study TV-46000-CNS-30072)

	Placebo N=167 n (%)	TV-46000 q1m N=175 n (%)	TV-46000 q2m N=168 n (%)
Normal to High	11 (7)	30 (17)	24 (14)
High to High	22 (13)	57 (33)	47 (28)
High to Low	1 (<1)	0	0
High to Normal	40 (24)	22 (13)	29 (17)
Low to Normal	0	0	1 (<1)
Normal to Low	1 (<1)	1 (<1)	0
Normal to Normal	92 (55)	65 (37)	67 (40)

Source: Clinical Reviewer's Summary based on Laboratory Analysis Dataset (ADLB.xpt) of Study TV-46000-CNS-30072

Increase in prolactin can lead to galactorrhea and gynecomastia. All adverse events of galactorrhea (one patient in the TV-46000 q1m group and two patients in the TV-46000 q2m group) and gynecomastia (one patient in the TV-46000 q1m group and one patient in the TV-46000 q2m group) were considered related to study drug. Galactorrhea and gynecomastia led to study withdrawal in one patient in the TV-46000 q2m group. All events of galactorrhea and gynecomastia were mild in severity and considered nonserious.

Shifts in serum creatinine values from the normal range at baseline to values outside the normal range for at least one time point were noticed during Stage 2 in Study TV-46000-CNS-30072 in higher number of participants in TV-46000 q1m group and TV-46000 q2m group compared to placebo (10 patients in TV-46000 q1m group, 6 patients in TV-46000 q2m, and 2 patients in placebo group). However, only one patient, who was not randomized, had serum creatinine values that exceeded the clinically significant serum values predefined for the study (creatinine ≥ 177 $\mu\text{mol/L}$).

Shifts in serum chemistry values and clinically meaningful differences for the other parameters were equally distributed across the three treatment groups.

Given that in clinical trials and/or postmarketing experience, events of leukopenia, neutropenia, and agranulocytosis have been reported temporally related to antipsychotic agents, including oral risperidone (LD), abnormal hematology values were carefully evaluated in TV-46000 treatment groups compared to placebo group. In Study TV-46000-CNS-30072, Stage 2, there were no clinically meaningful trends in mean changes from baseline for any hematology variable and no significant trends in neutrophil levels or cases of agranulocytosis were observed. Shifts in hematology values from the normal range at baseline to values outside the normal range for at least one time point during Stage 2 occurred with comparable frequency in the placebo and TV-46000 treatment groups, and none of these shifts were clinically meaningful. An adverse event of anemia occurred in one patient in the TV-46000 q1m group and two patients in the TV-46000 q2m group. One patient in the placebo group

experienced iron deficiency anemia, one patient in the TV-46000 q1m treatment group experienced thrombocytosis, and one patient in the TV-46000 q2m group experienced platelet count increased. None of these adverse events were serious, related to study drug, or led to withdrawal from the study.

Vital Signs

Vital sign measurements performed during Stage 2 of Study TV-46000-CNS-30072 included systolic and diastolic blood pressure (BP), respiratory rate, tympanic temperature, and pulse. Assessments were done at baseline, then monthly. There were no clinically meaningful trends in mean changes from baseline for any vital signs.

The systolic and diastolic BP values remained stable throughout the treatment period, and no aggregate trends in vital signs were observed. A total of 11 patients in the placebo group, 18 patients in the TV-46000 q1m group, and 19 patients in the TV-46000 q2m group had changes in:

- Pulse (decreased in 11 patients in the TV-46000 q1m group, and 7 patients in the TV-46000 q2m group; increased in 1 patient in the placebo group, 1 patient in the TV-46000 q1m group, and 2 patients in the TV-46000 q2m group)
- Systolic BP (decreased in six patients in the placebo group, one patient in the TV-46000 q1m group, and six patients in the TV-46000 q2m group; increased in one patient in the placebo group)
- Diastolic BP (increased in six patients in the placebo group, four patients in the TV-46000 q1m group, and five patients in the TV-46000 q2m group; decreased in one patient in the TV-46000 q1m group)

An adverse event of hypertension was reported across the three treatment groups with comparable frequency (three patients in the placebo group, four patients in the TV-46000 q1m group, and two patients in the TV-46000 q2m group). There was one report of BP decrease and palpitations in each treatment group.

Electrocardiograms

In Study TV-46000-CNS-30072, twelve-lead ECGs were recorded at screening, baseline, and monthly visits. At screening and baseline, measurements were done in triplicate. The mean of the three measurements was used to determine study eligibility. Single measurements were performed at all other in-clinic visits. The ECG was conducted before study drug administration.

ECG values across the treatment groups in Study TV-46000-CNS-30072 were comparable for mean PR interval, QRS duration, QT interval, QTc interval (QT interval corrected using Bazett's formula - QTcB - or QTcF), and respiratory rate interval measurements during the study. Small mean changes from baseline to the last assessment (Stage 2) endpoint in the ECG parameters

were seen among patients across the treatment groups. The changes were consistent across time and were not considered to be clinically meaningful.

Shifts from normal to abnormal ECG findings were observed in 11 (7%) patients in the placebo group, 6 (3%) patients in the TV-46000 q1m group, and 5 (3%) patients in the TV-46000 q2m group.

ECG mean heart rate <60 beats per minute (bpm) was observed in 47 (28%) patients in the placebo group, 61 (35%) patients in the TV-46000 q1m group, and 60 (35%) patients in the TV-46000 q2m group. ECG mean heart rate >100 bpm was observed in 10 (6%) patients in the placebo group, 7 (4%) patients in the TV-46000 q1m group, and 10 (6%) patients in the TV-46000 q2m group.

Clinical Reviewer's comment: Given that the frequencies of ECG abnormalities were equally distributed across the three treatment group, attribution of these changes to TV-46000 is unlikely. Overall, ECG results do not show clinically significant trends consistent with a new safety signal for TV-46000.

QT

No patient had a QTc interval (QTcB or QTcF) greater than 500 msec at the last assessment (Stage 2) time point. QTcF interval >450 msec was reported in 8 (5%) patients in the placebo group, 6 (3%) patients in the TV-46000 q1m group, and 12 (7%) patients in the TV-46000 q2m group. QTcF interval change of >30 msec was reported in 14 (8%) patients in the placebo group, 20 (11%) patients in the TV-46000 q1m group, and 18 (11%) patients in the TV-46000 q2m group.

Clinical Reviewer's comment: The degree of QTcF prolongation was mild and not clinically significant.

Immunogenicity

Drug hypersensitivity was reported in higher frequency in the placebo group (n=23, 13%), compared to the TV-46000 q1m group (n=8, 4%), and TV-46000 q2m group (n=12, 7%), suggesting the hypersensitivity was not causally related to the active moiety of the study drug.

Patient (b) (6) a 56-year-old male in TV-46000 q2m group, experienced hypersensitivity during the double-blind relapse prevention stage of the study, four weeks after the administration of the first dose of the study drug (TV-46000 q2m) (per emergency room report: allergic reaction with no known allergen). The patient was treated with oral diphenhydramine and oral paracetamol and the event was assessed as resolved that same day. The investigator assessed the event of hypersensitivity as mild in severity and related to the study drug. Study treatment was withdrawn. At ET visit the next day, no significant abnormalities were detected on physical examination. Hematology lab testing was not performed.

Clinical Reviewer's comment: Not enough information to determine hypersensitivity causality.

8.2.5. Analysis of Submission-Specific Safety Issues

Injection Site Reactions

Local pain and other injection site reactions are a potential safety concern with the administration of risperidone sc long-acting injection. Injection site assessments were performed at each visit during Stage 2 of the study TV-46000-CNS-30072, in which the sc injections were administered. If an adverse event related to an injection site reaction was reported, an assessment of pain, redness, swelling, and induration of the sc injection site was made. The injection type (placebo or TV-46000 dose) was identical to the treatment arm for the placebo and TV-46000 q1m patients, while the TV-46000 q2m patients appeared under two categories because patients in this arm alternated between receiving TV-46000 and placebo injections each month to maintain the blind. If a TV-46000 q2m patient had an adverse event after placebo injection and before a TV-46000 injection, the adverse event was attributed to placebo and if a TV-46000 q2m patient had an adverse event after a TV-46000 injection and before a placebo injection, the adverse event was attributed to TV-46000. In Study TV-46000-CNS-30072, 34% of patients received TV-46000 in the upper arm, the rest in the abdomen.

Injection site AEs (including injection site pain, nodule, induration, and pruritus) were reported in higher frequency in patients in the TV-46000 q1m group and patients in the TV-46000 q2m group than in patients in the placebo group (Table 32). None of the injection site AEs were serious. One patient in the TV-46000 q1m group had a severe adverse event of injection site pruritus, which resolved after six days. Three patients in the TV-46000 q1m group and four patients in the q2m group discontinued due to injection site AEs compared to no patients in the placebo group. Table 32 summarizes all injection site adverse events using a reviewer-generated customized grouping of preferred terms.

Table 32. Injection Site Adverse Events (Study TV-46000-CNS-30072)

Custom Query	Preferred Term	Placebo N=179 n (%)	TV-46000 q1m N=183 n (%)	TV-46000 q2m N=179 n (%)
Injection Site Reactions	All	22 (12)	39 (21)	38 (21)
	Nodule	6 (3)	12 (7)	13 (7)
	Pruritus	4 (2)	10 (5)	7 (4)
	Erythema	2 (1)	6 (3)	8 (4)
	Mass	1 (<1)	3 (2)	6 (3)
	Swelling	0	2 (1)	3 (2)

Source: Table 25, pg 138, and Summary 15.16.1.3 of Applicant's Clinical Study Report of Study TV-46000-CNS-30072 and Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) of Study TV-46000-CNS-30072.

Patients who received injections of TV-46000 in the arm reported a lower incidence of injection site AEs compared to patients who received injections of TV-46000 in the abdomen (13% versus 26%, respectively). No difference was observed in the placebo group regarding injection site location (arm versus abdomen) (12% irrespectively of site location). The majority of these injection site adverse events were reported during the 1st or 2nd injections, with a generally decreasing trend in subsequent injections. For each injection, most of the injection site adverse events were reported within one week of the last injection.

In Study TV-46000-CNS-30078, two patients discontinued treatment due to injection site AEs (one subject received injection in the arm, the other subject received injection in the abdomen).

Clinical Reviewer's comment: Injection in the arm seems to be associated with lower incidence of injection site AEs, although the discrepancy in sizes between the group that received the injection in the arm and the group that received the injection in the abdomen does not allow a definitive conclusion.

A difference in injection site AEs between patients in study drug groups (q1m and q2m) and placebo indicates that the reaction is likely caused by the response to the active ingredient, and it is not simply caused by the procedure or vehicle.

Given that the dosing data could not be verified per OSI inspection results, adverse reactions by dose could not be evaluated and the assessment on injection site adverse reactions is incomplete.

Other adverse events of special interest

Weight increased, somnolence, extrapyramidal symptoms

Weight increased, somnolence, extrapyramidal symptoms, and tremor are frequently observed with risperidone use and were reported with a higher incidence in the TV-46000 groups compared to placebo (Table 33). No clinically meaningful trends in mean changes from baseline for AIMS, SAS, CDSS, BARS scales were reported.

Table 33. Adverse Events Of Special Interest (Only >2% Reported) (Study TV-46000-CNS-30072)

	Preferred Term	Placebo N=179 n (%)	TV-46000 q1m N=183 n (%)	TV-46000 q2m N=179 n (%)
EPS	Akathisia, Muscle Rigidity, Tremor	11 (6)	17 (9)	18 (10)
Investigations	Weight Increase	6 (3)	10 (5)	13 (7)

Somnolence	Somnolence/Sedation	2 (1)	9 (5)	8 (4)
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Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) of Study TV-46000-CNS-30072.

Metabolic syndrome and hyperglycemia

Metabolic syndrome and hyperglycemia are frequently observed with risperidone use. Triglyceride level increase and hyperglycemia were reported with higher incidence following TV-46000 treatment compared to placebo (Table 34, Table 36).

Table 34. Proportion of Patients with Fasting Triglycerides <150 mg/dL and Shifts to ≥200 mg/dL by Treatment Group (Study TV-46000-CNS-30072)

Triglycerides Shift	Placebo N=138 n (%)	TV-46000 q1m N=145 n (%)	TV-46000 q2m N=141 n (%)
Shift Low\Normal\Borderline to High	11 (8)	21 (14)	23 (16)

Source: Applicant's Response dated February 02, 2022, to FDA's Information Request.

Table 35. Proportion of Adult Patients with Fasting Glucose <100 mg/dL and Shifts to ≥126 mg/dL by Treatment Group (Study TV-46000-CNS-30072)

Glucose Shift	Placebo N=138 n (%)	TV-46000 q1m N=145 n (%)	TV-46000 q2m N=141 n (%)
<100 mg/dL at baseline to ≥126 mg/dL during Period 2	10 (7)	16 (11)	16 (11)

Source: Applicant's Response dated February 02, 2022, to FDA's Information Request.

Clinical Reviewer's comment: The safety profile of the long-acting formulation of risperidone for these submission specific safety issues was similar to that seen with the oral formulation, with the exception of injection site adverse reactions, which are expected for a long-acting injection formulation. Given that the dosing data could not be verified per OSI inspection results, adverse reactions by dose could not be evaluated and the assessment is incomplete.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

The limited number of exposures in this development program precludes meaningful subgroup analyses.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9. Additional Safety Explorations

Dose-dependent adverse reactions

Both EPS and injection site ARs were dose-dependent based on the dose-dependent analysis, using primary safety data from Study TV-46000-30072 and long-term safety data from Study TV-46000-CNS-30078 (Table 36).

Table 36. Dose-dependent analysis of adverse reactions (Study TV-46000-CNS-30072 and Study TV-46000-CNS-20078)

Study TV-46000-CNS-30072									
Adverse Reactions	50 mg TV-46000 q1m N = 47 (%)	75 mg TV-46000 q1m N = 46 (%)	100 mg TV-46000 q1m N = 68 (%)	125 mg TV-46000 q1m N = 22 (%)	100 mg TV-46000 q2m N = 58 (%)	150 mg TV-46000 q2m N = 31 (%)	200 mg TV-46000 q2m N = 67 (%)	250 mg TV-46000 q2m N = 19 (%)	Placebo N = 178 (%)
EPS	1 (2)	5 (10)	8 (12)	3 (14)	4 (7)	3 (10)	7 (10)	3 (16)	11 (6)
Injection site reactions	6 (13)	6 (13)	21 (31)	6 (27)	10 (17)	6 (19)	15 (23)	4 (21)	22 (12)
Study TV-46000-CNS-30078									
Adverse Reactions	50 mg TV-46000 q1m N = 43 (%)	75 mg TV-46000 q1m N = 41 (%)	100 mg TV-46000 q1m N = 70 (%)	125 mg TV-46000 q1m N = 15 (%)	100 mg TV-46000 q2m N = 55 (%)	150 mg TV-46000 q2m N = 22 (%)	200 mg TV-46000 q2m N = 66 (%)	250 mg TV-46000 q2m N = 16 (%)	
EPS	0	2 (5)	3 (4)	1 (6)	1 (2)	3 (14)	2 (3)	1 (6)	
Injection site reactions	2 (5)	3 (7)	9 (13)	5 (33)	6 (11)	1 (5)	6 (9)	3 (19)	

Source: Clinical Reviewer's Summary based on Subject-Level Analysis Dataset (ADSL.xpt) and Adverse-Event Analysis Dataset (ADAE.xpt) of Study TV-46000-CNS-30072 and Study TV-46000-CNS-30078.

Clinical reviewer's comment: Given that the dosing data could not be verified per OSI inspection results, these results cannot be relied upon.

Human Carcinogenicity or Tumor Development

No new information about human carcinogenicity or tumor development was submitted in this application.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No analyses or assessments regarding overdose, drug abuse potential, withdrawal, or rebound were conducted in these studies. Our understanding of these areas are mainly informed by Risperdal, the LD.

Ten subjects were dually enrolled and one subject was triply enrolled, as described in detail in section 8.1.2 Protocol Violations/Deviations/Duplications. None of these subjects seem to have received doses higher than the equivalent of 16 mg oral risperidone per day (the upper limit of the dosage range for Risperdal tablets), although for the subject who was triply enrolled there is a theoretical risk of drug accumulation that may have led to exposures higher than the 16 mg oral risperidone equivalent. A careful evaluation of investigations and AEs for this participant revealed moderate tremor of hands as AEs, which may be consistent with an overdose of risperidone. No other AEs were reported or observed.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

TV-46000 is not currently marketed in any other country.

Expectations on Safety in the Postmarket Setting

The full dose range for oral risperidone is not covered by the strengths proposed for marketing based on the PK data and prescribers could use more than one injection to achieve higher daily dose equivalents, which has not been studied. Labeling should include language instructing prescribers not to administer more than one dose of TV-46000 per dosing interval.

In addition, there are insufficient safety data to complete a pediatric assessment for the 13 to 17 year-old age group and off-label use may occur. Labeling should reflect that the safety of TV-46000 has not been established in this age group.

8.2.11. Integrated Assessment of Safety

TV-46000 was associated with increased incidence of weight gain, dyslipidemia, hyperglycemia, increased prolactin, sedation/somnolence, and extrapyramidal symptoms compared to placebo. These are all expected adverse reactions based on the known safety profile of other

risperidone products. Orthostatic vital signs were not measured and the risk of orthostatic hypotension could not be evaluated.

The local tolerability assessments were limited because clinical examination of the injection site at study visits was limited to subjects who reported an injection site adverse event and the safety findings for local tolerability may have been underreported. Subjects experienced injection site reactions with higher incidence in the active treatment arms, but based on the available data these reactions are not appreciably worse than other long-acting injectable formulations.

Because the dosing data cannot be relied upon, the dose-response relationship for the safety findings cannot be evaluated.

8.3. Statistical Issues

There were no statistical issues that impact the overall clinical or statistical review conclusions.

8.4. Conclusions and Recommendations

Study TV-46000-CNS-30072 met its prespecified primary endpoint for both the TV-46000 q1m and q2m dosing regimens and demonstrated statistically significant ($p < 0.0001$) prolongation in the time to impending relapse versus placebo. OSI inspection did not identify discrepancies in the primary efficacy endpoint data from this study. However, the data on dosing from the study cannot be relied upon and the doses of IP that provided benefit to patients in Study TV-46000-CNS-30072 could not be verified.

The assessment of safety findings from the long-acting formulation of risperidone was similar to that seen with the oral formulation, with the exception of injection site adverse reactions, which are expected for a long-acting injection formulation. However, OSI inspection results indicate that the dosing data obtained in the pivotal efficacy study, TV-46000-CNS-30072, and the long-term safety study, TV-46000-CNS-30078, failed to meet the quality standard necessary to assure data integrity to conduct a clinical review with conclusive results.

The review team recommends a Complete Response action due to the inability to establish the effective dose range for TV-46000 and the inability to characterize the exposure-response relationship of TV-46000 for efficacy and safety.

9 Advisory Committee Meeting and Other External Consultations

There are multiple risperidone-containing products approved for marketing for the treatment of schizophrenia, including long-acting injectable products, and there were no novel scientific issues that warranted discussion at an at an Advisory Committee meeting.

10 Pediatrics

The onset of schizophrenia prior to 13 years of age is quite uncommon, with a prevalence estimated at 1 per 10,000 population, and symptom presentation differs making diagnosis more difficult to establish. For this age group, a waiver for a pediatric assessment is justified because collecting data in a sufficient number of patients with schizophrenia is not feasible due to the low prevalence.

For patients aged 13 to 17 years, efficacy can be extrapolated from adults and the PK profile is expected to be comparable to adults. However, safety cannot be extrapolated from adult data with this product or from the safety findings in this age group for the listed drug, Risperdal oral tablets, because the safety profile of TV-46000 may be expected to differ between the adolescent and adult patient populations and the adolescent safety profile may differ between TV-46000 and oral risperidone. Specifically, the risk for severe and serious dystonic reactions and metabolic adverse reactions with second generation antipsychotics, including risperidone is higher in younger patients than older patients (Taurines et al, 2022). In addition, severe dystonic reactions with risperidone do not appear to have a dose-response relationship in adults based on the available literature (Christodoulou and Kalaitzi, 2005; Çirakli S, 2021). The oral risperidone adolescent safety assessment is not adequate to make an assessment of safety for this product in the adolescent age range because this product differs in its PK profile and safety data to characterize the risks of this product in adolescents is needed to make a benefit-risk assessment and to inform labeling. This is particularly important with a long-acting injectable (LAI) product given that, in contrast to oral risperidone, the risperidone from this product will be present in the patient for one to two months after administration and cannot be reversed in the event of a severe or serious adverse reaction. In addition, there is precedent for not labeling LAI risperidone products for adolescents based on oral risperidone pediatric safety data and adult product-specific safety data (waivers were granted for two LAI risperidone products approved for marketing).

For patients with schizophrenia aged 13 to 17 years, the Applicant attempted to enroll adolescents into the phase 3 TV-46000 program. Despite the effort to recruit adolescents to the two phase 3 studies, only four adolescent patients received TV-46000. (b) (4)

The scant data collected in adolescents revealed no novel findings in the adolescent patients compared to adults but are inadequate to support a pediatric assessment due to the small number of patients enrolled. Moreover, the use of long-acting agents in adolescents 13 to 17 years of age is not usually recommended by treatment guidelines (McClellan et al, 2013) because, by the time adolescent patients have been stabilized on a specific agent (considered a precursor to being switched from oral to depot preparations), these patients typically approach adulthood. Further studies in adolescents should not be required because the Applicant has made a good faith effort to enroll adolescents and these efforts indicate that enrollment of an adequate number of adolescents to support a safety

assessment is not feasible. A final determination about granting a full waiver will be deferred because a complete response action on the application is recommended.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Because a complete response action is recommended due to potential data integrity issues, the Agency and the Applicant did not reach final agreement on product labeling.

12 Risk Evaluation and Mitigation Strategies (REMS)

No issues were identified in the review that warrant a risk evaluation and mitigation strategy.

13 Postmarketing Requirements and Commitment

Because a complete response action will be recommended, postmarketing requirements (PMRs) and commitments (PMCs) were not finalized during this review cycle. Refer to section 4 for the PMRs/PMCs recommended by OPQ.

14 Division Director (Clinical) Comments

The above review reflects my edits and feedback. I agree with the findings as described by the review team and concur with the decision to issue a Complete Response based on the deficiencies identified by OSI.

15 Appendices

15.1. References

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15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): TV-46000-CNS-30072

The submitted information including a list of clinical investigators are noted.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>591</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3)		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. Bioanalytical Method Validation

Risperidone and its active metabolite, 9-OH-risperidone, were quantified in (b) (4)

followed by reversed phase-high performance liquid chromatography with tandem mass spectrometric detection (RP-LC-MS/MS) using validated bioanalytical methods. Initially, method IRD-MA-117 was validated for a lower range of 0.02-20.0 ng/mL for both risperidone and 9-OH-risperidone (validation report SA-2015-005). This method was utilized for analysis of plasma samples of the pilot study RISPE1ZG15EU. Later, method IRD-MA-115 was validated for the higher range of 0.1-100.0 ng/mL for risperidone and 0.3-300 ng/mL for 9-OH-risperidone (validation report SA-2015-002). This method was further partially validated due to the introduction of the Tomtec Quadra 4SPE pipetting system for sample clean-up procedure (SA-2017-033). Additional partial validation was conducted due to introducing an additional chromatographic column type (Kinetex XB) for the analysis and additional stability test (SA-2019-009). An overview of the validated bioanalytical assays used in the TV-46000 clinical studies is provided in Table 37.

Table 37. Overview of Validated Bioanalytical Assays Used in TV-46000 Clinical Studies

Assay type	Assay methodology	Sample	Calibration curve	Bioanalytical method no.	Validation study / report no.	Clinical studies		
						Phase	Study no.	Bioanalytical study no.
PK	Validated RP-LC-MS/MS method	Human plasma	0.02-20.0 ng/mL (20–20000 pg/mL) for both risperidone and 9-OH-risperidone	IRD-MA-117	SA-2015-005	1	RISPE1ZG15EU	SA-2015-030
	Validated RP-LC-MS/MS method	Human plasma	0.1-100 ng/mL for risperidone and 0.3-300 ng/mL for 9-OH-risperidone	IRD-MA-115	SA-2015-002 SA-2017-033 (partial validation) SA-2019-009 (partial validation)	1	TV46000-SAD-10055	SA-2016-019
						1	TV46000-BA-10148	SA-2018-032
						3	TV46000-CNS-30072	SA-2018-021
						3	TV46000-CNS-30078	SA-2019-029

9-OH-risperidone = 9-hydroxyrisperidone (active metabolite of risperidone); PK = pharmacokinetics; RP-LC-MS/MS = reversed phase-high performance liquid chromatography with tandem mass spectrometric detection.

Source: Applicant's Summary of Biopharm, Table 7;

The TAM of risperidone was calculated as the sum of risperidone and 9-OH-risperidone plasma concentrations, corrected by molecular weight, according to the following formula:

$$[\text{Active Moiety}](\text{ng/mL}) = [\text{risperidone}](\text{ng/mL}) + [9\text{-OH-risperidone}](\text{ng/mL}) \times (410/426)$$

The range, precision, accuracy, and stability of the IRD-MA-117 and IRD-MA-115 bioanalytical methods are summarized in Table 38 below:

Table 38. Summary of Method Validation for Analysis of Risperidone and 9-OH-Risperidone by RP-LC-MS/MS in Human K2EDTA Plasma

Validation study / report no. (Bioanalytical method no.)	Analyte	Standard curve range	Precision (%CV) ^a		Accuracy over assay range (%) ^b		Stability
			Intra	Inter	Intra	Inter	
SA-2015-005 (IRD-MA-117)	Risperidone	0.02-20.0 ng/mL	1.5 to 3.6	3.1 to 6.0	-0.8 to 12.3	0.8 to 8.2	Room temperature: 24 hours Freeze/thaw: 3 cycles Long-term stability: 232 days at -70°C
	9-OH-Risperidone	(20-20000 pg/mL)	1.4 to 3.8	4.3 to 5.8	-5.3 to 9.6	-0.1 to 4.1	
SA-2015-002 (IRD-MA-115) ^c	Risperidone	0.1-100 ng/mL	0.8 to 5.9	2.0 to 4.5	-9.8 to 7.7	-7.6 to -5.1	Room temperature: 24 hours Freeze/thaw: 5 cycles (from -20 and -70°C) Long-term stability: 450 days at -20°C and -70°C
	9-OH-Risperidone	0.3-300 ng/mL	0.8 to 5.9	2.3 to 3.6	-8.7 to 5.3	-7.1 to -2.0	
SA-2017-033 (partial validation) (IRD-MA-115)	Risperidone	0.1-100 ng/mL	1.7 to 4.8	2.7 to 8.1	-5.2 to 11.1	0.4 to 6.5	
	9-OH-Risperidone	0.3-300 ng/mL	1.1 to 5.2	2.5 to 4.7	-0.4 to 7.0	0.2 to 4.7	
SA-2019-009 (partial validation) (IRD-MA-115)	Risperidone	0.1-100 ng/mL	2.0 to 9.3	NC	-14.2 to 10.7	NC	
	9-OH-Risperidone	0.3-300 ng/mL	1.7 to 5.0	NC	-10.0 to 3.2	NC	

^a Precision: (SD/Mean Measured Concentration) x 100. ^b Accuracy: %Bias = [(Mean Measured Concentration – Nominal Concentration) x 100]/Nominal Concentration. ^c Validation report was updated with Amendment 01 Dated January 2017.

9-OH-risperidone = 9-hydroxyrisperidone (active metabolite of risperidone); CV = coefficient of variation; K2EDTA = dipotassium ethylenediaminetetraacetic acid; NC = not calculated; RP-LC-MS/MS = reversed phase-high performance liquid chromatography with tandem mass spectrometric detection; SD = standard deviation.

Source: Applicant's Summary of Biopharm, Table 8;

Note: Validation studies, as well as all TV-46000 clinical plasma bioanalytical sample analysis were conducted by Teva Pharmaceutical Works Private Ltd. Co. in accordance with the applicable principles of GLP in a GLP certified facility, Test Facility Standard Operation Procedures and approved Bioanalytical Study Plans. Since the efficacy and safety were mainly derived from the pivotal study (Study TV-46000-CNS-30072) and the long-term safety study (Study TV-46000-CNS-30078), an inspection of the facilities for the phase 1 study were not deemed necessary.

Clinical Pharmacology Reviewer's comments: The bioanalytical methods are acceptable and satisfy the criteria for 'method validation' and 'Application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development'.

15.3.2. Summary of clinical pharmacology studies

Study RISPE1ZG15EU

Study RISPE1ZG15EU was a 2-part study conducted in healthy subjects to evaluate the safety, tolerability, and pharmacokinetics of TV-46000 (Part 1) and to evaluate the influence of manipulation of the injection site, as well as the site of administration on the pharmacokinetics of TV-46000 (Part 2). Vehicle solution and 2 subtherapeutic doses of TV-46000, 12.5 and 25 mg (comparable to 0.5 and 1 mg/day oral risperidone, respectively), were tested. The effects of manipulation of the injection site were evaluated by rubbing immediately after the sc injection of a TV-46000 12.5 mg dose in the arm compared with no rubbing (Cohort G and Cohort C, respectively). Additionally, the study included 2 cohorts (Cohort E and Cohort D) to assess the influence of (b) (4) respectively) on the pharmacokinetics of TV-46000.

The summary of Key PK parameters from the study are summarized in Table 39.

Table 39: Geometric Mean (%CV) Total Active Moiety Plasma Pharmacokinetic Parameters from Cohorts C to G, Following a Single 12.5 mg or 25 mg Subcutaneous Dose of TV-46000

PK parameter (unit) ^a	Cohort C 12.5 mg/ 35 µL Grade 1 upper arm N=9	Cohort D 25 mg/ 70 µL Grade 4 upper arm N=10	Cohort E 25 mg/ 70 µL Grade 1 upper arm N=11	Cohort F 25 mg/ 70 µL Grade 4 abdomen N=10	Cohort G 12.5 mg/ 35 µL Grade 1 upper arm, rubbing N=10
t _{max} (h) ^a	30.0 (24.1-289.0)	204.0 (48.0-503.9)	48.0 (26.0-336.0)	48.0 (26.0-120.0)	132.0 (26.0-336.1)
C _{max} (ng/mL)	6.0 (30.4)	7.7 (48.8)	8.8 (41.1)	7.3 (32.0)	7.4 (33.3)
AUC _{0-t} (ng.h/mL)	2570 (25.6)	4630 (30.6)	5040 (42.5)	4200 (24.8)	3440 (27.1)
AUC _{0-∞} (ng.h/mL)	2660 (25.6)	5410 (31.2) ^b	5420 (41.2)	4710 (21.1)	3590 (25.8)
t _{1/2} (h)	199.4 (84.3)	298.8 (93.3) ^b	240.5 (75.2)	375.2 (36.2)	193.7 (86.4)

^a All parameters presented as geometric mean (geometric %CV), except for t_{max} which are presented as median (range). ^b n = 9
AUC_{0-t} = area under the plasma concentration time curve from time 0 to the last measurable concentration; AUC_{0-∞} = area under the plasma concentration- time curve from time 0 to infinity; C_{max} = maximum observed plasma drug concentration; %CV = percentage coefficient of variation; N = total number of subjects; n = number of subjects with evaluable data; PK = pharmacokinetics; t_{1/2} = apparent elimination half-life; t_{max} = time to maximum observed drug concentration.

Source: Applicant's complete study report for study RISPE1ZG15EU, Table 16.

Given that this study was performed in healthy volunteers with a subtherapeutic dose, this review focused mainly on the effects of injection site manipulation on the depot formation, burst release and PK of TV-46000. A 34% and 35% increase in the exposure of TAM was observed following administration of TV-46000 with rubbing of the injection site (Test)

compared to exposure following administration without rubbing (Reference), as measured by AUC_{0-t} and $AUC_{0-\infty}$, respectively, and the difference in TAM peak exposure was 23% as measured by C_{max} (Table 11). Although some increase in exposure was evident in the rubbing cohort, the extended-release characteristic of the formulation over time did not change and the depot still formed and there was no burst release. (b) (4)

Study TV-46000-SAD-10055

Study 10055 was a phase 1 open-label, single and multiple dose study in sequential groups of patients with a diagnosis of schizophrenia or schizoaffective disorder to evaluate the safety, tolerability, and pharmacokinetics of TV-46000. Study participants were clinically stable patients who were not currently on antipsychotic treatment other than oral risperidone.

The study consisted of a screening period; an inpatient oral risperidone period of 7 days, followed by a 7-day inpatient washout period; (Period 1); an inpatient and outpatient TV-46000 treatment period (Period 2) of up to approximately 4 weeks (Cohorts 1 and 2) or up to 12 weeks (Cohorts 3 through 8); and a follow-up period of approximately 8 weeks (Cohorts 1, 2, 6, and 7) or 4 weeks (Cohorts 3, 4, 5, and 8) that included pharmacokinetic blood sampling, safety assessments, and an end-of-study (EoS) visit.

A starting dose of TV-46000 50 mg was selected based on results from Study RISPE1ZG15EU, with supportive nonclinical data that demonstrated the comparability of TV-46000 50 mg administered q1m to RISPERDAL Consta® 25 mg administered biweekly (comparable to 2 mg oral daily dose). This study had a flexible design, based on ongoing cumulative safety, tolerability, and pharmacokinetic assessments, including stopping criteria between each cohort. The doses were to be increased in a gradual manner up to a 300 mg dose, accompanied by online pharmacokinetic assessment and including stopping criteria between each cohort. The initially planned maximal TV-46000 dose was 300 mg. However, based on emerging pharmacokinetic and safety data, the sponsor decided not to continue dose escalation beyond 225mg, and to administer a single 225 mg dose in the upper arm rather than the abdomen, to enable assessment of the interchangeability of injection sites in Cohort 8. The treatment allocation for patients enrolled into this study is provided in Table 40.

Table 40: Study 10055 Treatment Allocation Scheme

Cohort	Oral risperidone dose ^a	Number of patients ^b	TV-46000 dose and dosing regimen
1	2 mg daily	12	50 mg single dose on day 1
2	2 mg daily	12	75 mg single dose on day 1
3	3 mg daily	12	100 mg single dose on day 1
4	4 mg daily	12	150 mg single dose on day 1
5	6 mg daily	12	225 mg single dose on day 1
6	3 mg daily	12	75 mg multiple doses on days 1, 29, and 57 (total of 3 injections)
7	5 mg daily	12	150 mg multiple doses on days 1, 29, and 57 (total of 3 injections)
8	5 mg daily	15	225 mg single dose (in the triceps skin fold of the upper arm) on day 1

^a Prior to treatment with TV-46000, patients received oral risperidone on days -14 through -8, followed by a 7-day washout period. The planned oral risperidone dose for Cohort 1 was 2 mg daily; for Cohort 2 the planned daily oral risperidone dose could range between 2 to 3 mg and for Cohorts 3 through 8 could range between 2 to 6 mg daily, with the intention to achieve a maximum observed concentration approximately similar to that of the TV-46000 dose for the same cohort, based on cumulative pharmacokinetics and safety from previous cohorts.

^b Number of patients in the safety analysis set.

Source: Applicant's complete study report TV-46000-SAD-10055, Table 1 and Table 11.

A total of 99 patients aged between 20 and 56 years, inclusive, were enrolled and 86 (86.9%) patients completed the study. A total of 95 (96%) patients had sufficient data to calculate at least 1 pharmacokinetic parameter for risperidone and/or 9-OH-risperidone and were included in pharmacokinetic analysis population. Patients who completed the TV-46000 treatment period of up to 4 weeks for Cohorts 1 and 2 or up to 12 weeks for Cohorts 3 through 8 were defined as completers. Most patients in this study were men (81% men and 19% women) and most patients were Black or African American (96%) or White (4%).

The TAM pharmacokinetic parameters following the last oral administration of risperidone on day 7 are displayed in Table 41. Median time to maximum observed drug concentration (t_{max}) at steady state for TAM ranged from 1.5 to 2 hours across all dose levels, and TAM levels decreased in a multiphasic manner after reaching peak concentrations.

The systemic exposure (i.e., C_{max}, area under the plasma concentration-time curve [AUC]) of TAM increased with dose in an approximate dose-proportional manner from 2 mg to 5 mg, the exposure levels for the 6 mg/day dose were less than proportional compared with the lower doses of oral risperidone.

Table 41: Geometric Mean (%CV) Total Active Moiety Plasma Pharmacokinetic Parameters for Oral Risperidone (Study 10055)

PK parameter (unit) ^a	Oral risperidone dose in period 1				
	2 mg N=24	3 mg N=24	4 mg N=12	5 mg N=27	6 mg N=12
	Day 7	Day 7	Day 7	Day 7	Day 7
t _{max} (h)	1.8 (1-12)	1.8 (0.5-8)	1.8 (0.5-3) ^b	2.0 (0-6) ^c	1.5 (1-6)
C _{max} (ng/mL)	25.0 (40.2)	39.8 (27.3)	53.8 (42.4) ^b	62.2 (36.3) ^c	44.0 (40.0)
C _{24h} (ng/mL)	8.2 (46.0)	11.9 (37.2)	14.1 (43.6) ^b	18.8 (56.1) ^c	9.9 (66.1)
C _{24h} /Dose ((ng/mL)/mg)	4.1 (46.0)	4.0 (37.3)	3.5 (43.5) ^b	3.8 (55.9) ^c	1.6 (66.1)
C _{avg} (ng/mL) ^d	13.4 (39.7)	20.7 (30.2)	24.7 (36.5) ^b	31.9 (41.6) ^c	21.3 (47.5)
% Fluctuation (%)	121.1 (29.6)	131.6 (25.5)	157.6 (28.9) ^b	128.0 (40.9) ^c	147.4 (35.1)
AUC _{0-24h} (ng.h/mL)	321.4 (39.6)	495.6 (30.2)	593.1 (36.6) ^b	765.3 (41.6) ^c	511.6 (47.5)
AUC _{0-28d} (ng.h/mL) ^e	8998.7 (39.6)	13876.0 (30.2)	16607.5 (36.6) ^b	21428.8 (41.6) ^c	14325.6 (47.5)
t _{1/2} (h)	25.3 (6.0)	23.6 (4.3)	24.2 (6.1) ^b	27.1 (12.2) ^c	23.4 (2.9)

^a All parameters presented as geometric mean (CV %), except for t_{max} which is presented as median (range) and t_{1/2} which is presented as mean (standard deviation).

^b n = 10

^c n = 525

^d was estimated as (AUC_{0-24h})/24 hours

^e AUC_{0-28d} was estimated for oral risperidone as 28 x daily AUC_{0-24h}.

AUC_{0-24h} = area under the plasma concentration-time curve from time 0 to 24 hours after study drug administration; AUC_{0-28d} = area under the plasma concentration-time curve from time 0 to the end of the 28-day dosing interval; C_{24h} = observed concentration values at 24 hours postdose; C_{24h}/Dose = dose-normalized concentration at 24 hours post last dose; C_{avg} = average plasma concentration; C_{max} = maximum observed plasma drug concentration; CSR = clinical study report; CV = coefficient of variation; N = total number of patients; n = number of patients with evaluable data; PK = pharmacokinetic; t_{1/2} = apparent elimination half-life; t_{max} = time to maximum observed drug concentration. Source: Applicant's Complete Study Report TV-46000-SAD-10055, Table 13.

The TAM pharmacokinetic profiles following a single sc injection administration of ascending doses of TV-46000 are displayed in Figure 4. After TV-46000 sc administration, median t_{max} ranged from approximately 8 to 14 days (192 to 336 hours). After reaching peak concentrations, TAM levels decreased in an apparently multiphasic manner until the last sample collection time points of 84 days (Cohorts 1 and 2) or 112 days (Cohorts 3 through 5 and Cohort 8).

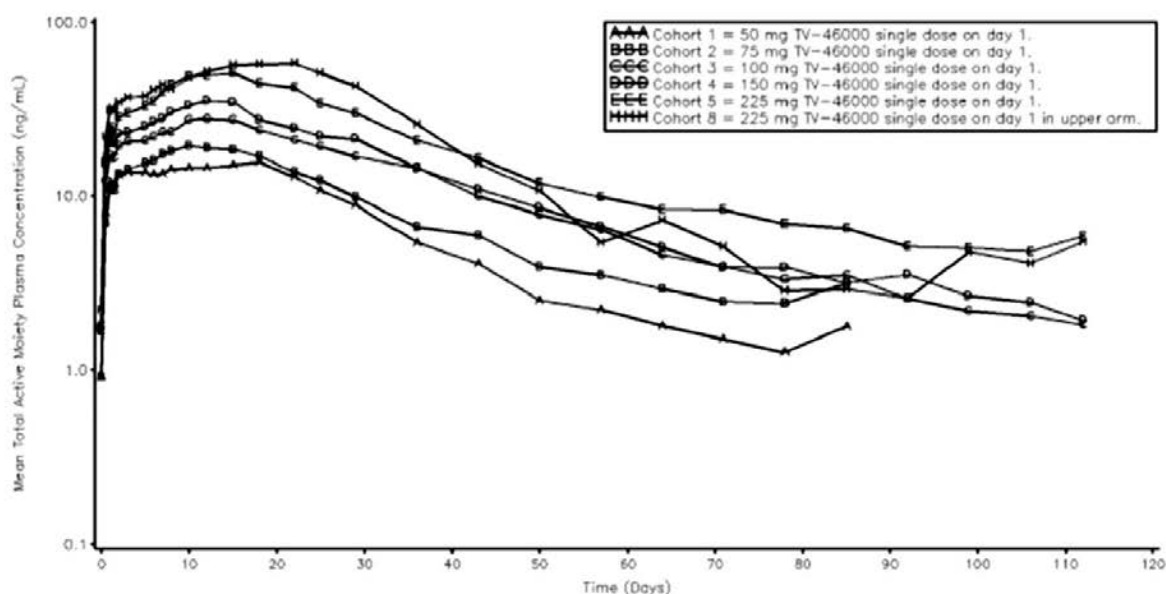
The plasma pharmacokinetic parameters of TV-46000 after a single sc administration are summarized in Table 11. TV-46000 demonstrated an extended-release of risperidone across all dose levels. In general, the TV-46000 pharmacokinetic profiles were qualitatively similar, with each dose demonstrating a rapid initial absorption phase, a slower secondary absorption phase, and a steady exponential decline in TAM concentrations from about day 20.

While TV-46000 presented delayed t_{max} (≥ 192 hours; ≥8 days) compared to oral risperidone, initial increase in concentrations of the TAM was rapid leading to quick attainment of therapeutic levels comparable to oral product. These levels were maintained for 28 to 56 days, depending on the dose (Figure 10).

The mean t_{1/2} for TAM following sc administration, ranged from 355 to 512 hours (15 to 21 days), compared with 23.4 to 27.1 hours after oral administration (Table 42 and Table 41, respectively). The prolonged t_{1/2} is since absorption of risperidone is still taking place during the terminal phase i.e., "flip-flop kinetics". No rapid or unpredictable rise in risperidone exposure

after TV-46000 sc administration was observed. The lack of any abrupt spikes in risperidone exposure suggests that there was no dose dumping after the TV-46000 sc injection. Within the therapeutic dose range, TV-46000 exhibited favorable characteristics of an extended-release formulation such as rapid initial absorption and prolonged systemic exposure, and TAM exposures (based on C_{max} and AUC) increased proportionally with increasing dose over the range tested in the study.

Figure 10: Mean ($\pm$ SD) Plasma Total Active Moiety Concentrations (ng/mL) Following TV-46000 Single Subcutaneous Dose Administration



Source: Applicant's Complete Study Report TV-46000-SAD-10055, Figure 3.

Table 42: Geometric Mean (%CV) Total Active Moiety Plasma Pharmacokinetic Parameters by Dose Following a Single Subcutaneous TV-46000 Dose

PK parameter (unit) ^a	TV-46000 cohort and dose in period 2					
	Cohort 1 50 mg N=12	Cohort 2 75 mg N=12	Cohort 3 100 mg N=12	Cohort 4 150 mg N=12	Cohort 5 225 mg N=12	Cohort 8 (upper arm) 225 mg N=15
t _{max} (h)	252 (72-576)	192 (48-507)	240 (12-840)	336 (95.9-672) ^b	264 (144-481)	336 (24-576) ^c
C _{max} (ng/mL)	17.6 (49.0)	21.5 (36.2)	30.7 (43.0)	39.6 (39.8) ^b	53.9 (55.6)	69.3 (50.2) ^c
C _{max} /Dose ((ng/mL)/mg)	0.4 (49.0)	0.3 (36.2)	0.3 (43.0)	0.3 (39.8) ^b	0.2 (55.7)	0.3 (50.3) ^c
C _{min} (ng/mL)	0.6 (154.1)	0.8 (98.5)	1.0 (113.0)	1.7 (153.3) ^b	1.0 (87.1)	1.4 (173.5) ^c
C _{28d} (ng/mL)	7.9 (51.0) ^d	8.9 (48.7)	16.0 (30.5)	20.1 (39.8) ^e	28.2 (38.8) ^d	35.6 (70.4) ^d
C _{avg} (ng/mL) ^f	6.4 (76.5)	6.4 (34.0)	10.1 (49.4)	12.6 (56.5) ^b	13.5 (51.9)	17.7 (64.3) ^c
C _{avg0-28d} (ng/mL) ^g	12.0 (42.3)	14 (40.5)	20.6 (37.9)	24.8 (30.4) ^c	36.0 (49.8)	45.6 (35.8) ^d
AUC ₀₋₄ (ng.h/mL)	11990.3 (36.9)	14442.9 (42.1)	26085.3 (21.4)	27722.7 (29.6) ^b	45195.1 (28.8)	42082.5 (44.3) ^c
AUC _{0-∞} (ng.h/mL)	15797.5 (26.3) ^h	15356.2 (28.0) ^c	27352.4 (23.0) ^b	30475.9 (28.5) ^h	47524.9 (25.4) ^h	55499.0 (32.8) ^b
AUC _{0-28d} (ng.h/mL)	8032.8 (42.4)	9395.6 (40.6)	13850.0 (37.9)	16632.0 (30.5) ^c	24212.4 (49.8)	30646.9 (35.8) ^d
AUC _{0-28d} /Dose (ng.h/mL/mg)	160.6 (42.5)	125.3 (40.6)	138.5 (38.0)	110.9 (30.5) ^c	107.6 (49.8)	136.2 (35.9) ^d
t _{1/2} (h)	387.9 (212.5) ^b	511.7 (274.1) ^c	475.0 (346.7) ^b	426.0 (186.2) ^h	355.0 (127.6) ^h	473.8 (284.0) ^b

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^aAll parameters presented as geometric mean (CV (standard deviation).

^b n = 10

^c n = 13

^d n = 11

^e n = 9

^f was estimated as (AUC_{0-24h})/24 hours

^g was estimated as (AUC_{0-28d})/(28 days × 24 hours)

^h n = 7

AUC_{0-24h} = area under the plasma concentration-time curve from time 0 to 24 hours after study drug administration; AUC_{0-28d} = area under the plasma concentration-time curve from time 0 to the end of the 28-day dosing interval; AUC_{0-28d}/Dose = dose normalized area under the plasma concentration-time curve from time 0 to the end of the 28-day dosing interval; AUC_{0-∞} = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration; C_{28d} = observed plasma concentration on day 28; C_{avg} = average plasma concentration; C_{avg0-28d} = average observed plasma drug concentration from time 0 to the end of the 28-day dosing interval; C_{max} = maximum observed plasma drug concentration; C_{max}/Dose = dose normalized maximum observed plasma drug concentration; C_{min} = plasma drug concentration at the end of the dosing interval; CV = coefficient of variation; N = total number of patients; n = number of patients with evaluable data; PK = pharmacokinetic; t_{1/2} = apparent elimination half-life; t_{max} = time to maximum observed drug concentration.

Source: Applicant's Complete Study Report TV-46000-SAD-10055, Table 15.

The exposure of risperidone was comparable over the 28-day period between the oral and sc administration from 2 to 5 mg oral and 50-150 mg TV-46000 respectively. The similarity in the dose normalized values for C_{max} and AUC also suggest that the exposure of TV-46000 was dose proportional across the dose range studied.

Multidose PK: The multiple-dose pharmacokinetics of TAM was evaluated following administration of either 75 or 150 mg of TV-46000 for 3 consecutive monthly injections. The plasma pharmacokinetic parameters of TV-46000 after each administration (days 1, 29 and 57) are summarized in Table 43. TV-46000 exhibited pharmacokinetic characteristics associated with extended-release behavior. After 3 monthly sc administrations, median time to maximum concentration ranged from 7.5 to 9 days (180 to 216 hours) and values were similar to those observed after a single sc administration of 75 mg and 150 mg TV-46000 (Table 43). After reaching peak concentration, TAM levels declined slowly until the last sample collection. The

Uzedy (risperidone extended release injection)

increase in TAM exposure appeared to be proportional to the increase in dose in the multiple dose cohorts. The mean $t_{1/2}$ for TAM following the 3rd sc injection of TV-46000 on day 57 was 19 days (464 hours) and 22 days (532 hours) for doses of 75 and 150 mg, respectively (Table 43). The $t_{1/2}$ of TV-46000 multiple-doses was similar to single-doses of 75 and 150 mg, respectively.

Another objective of this study was to determine the time to reach steady-state upon repeated monthly dosing of TV-46000. Following the 3rd TV-46000 dose of 75 or 150 mg every 28 days, C_{max} and AUC_{0-28d} increased relative to the first dose by approximately 60 to 80%. After 3 consecutive monthly doses, systemic exposure (geometric mean of C_{max} , and AUC_{0-28d}) appeared to be approaching a plateau for the 75 mg dose group but not for the 150 mg dose group (Table 44). Although, TAM exposure after the 3rd TV-46000 75 mg dose may be approaching steady-state, results from this study could not confirm that steady-state of TV-46000 had been reached. Therefore, steady-state exposure was explored with the final PopPK modeling and simulations.

Noncompartmental analysis indicated that after the 3rd injection of TV-46000 (Day 57) at doses of 75 and 150 mg, systemic exposure (C_{max} , trough plasma drug concentration [C_{trough}], average plasma concentration [C_{avg}]) over a 28-day period was comparable to the systemic exposure observed after oral risperidone administration over the dose range of 3 to 5 mg at steady-state (Table 45). These data were used to support dose justification and the pharmacokinetic bridge established between oral risperidone and TV-46000 in Study 10148 and the final PopPK model.

Table 43: Geometric Mean (%CV) Total Active Moiety Plasma Pharmacokinetic Parameters by Dose Following Multiple TV-46000 75 mg and 150 mg Subcutaneous Doses

PK parameter (unit) ^a	TV-46000 cohort and dose	
	Cohort 6 75 mg N=12	Cohort 7 150 mg N=12
Pharmacokinetic parameters following first dose		
t _{max} (h)	372 (24-504)	216 (48-431)
C _{max} (ng/mL)	21.3 (27.9)	39.2 (45.4)
C _{max} /Dose ([ng/mL]/mg)	0.3 (27.9)	0.3 (45.4)
C _{trough}	9.5 (29.1)	16.4 (70.4)
C _{avg} (ng/mL) ^b	6.9 (36.8)	15.2 (43.6)
AUC _{0-t} (ng.h/mL)	9539.6 (27.0)	16821.0 (44.4)
AUC _{0-28d} (ng.h/mL)	9539.6 (27.0)	18190.4 (41.9) ^c
AUC _{0-28d} /Dose (ng.h/mL/mg)	127.2 (27.0)	121.3 (41.9) ^c
Pharmacokinetic parameters following third dose		
t _{max} (h)	180 (30.1-336) ^c	216 (23.6-503) ^c
C _{max} (ng/mL)	33.9 (23.9) ^c	69.6 (44.2) ^c
C _{max} /Dose ([ng/mL]/mg)	0.5 (23.9) ^c	0.5 (44.2) ^c
C _{trough} (ng/mL)	15.1 (43.5)	37.6 (36.3)
C _{avg} (ng/mL) ^b	18.7 (30.0) ^c	40.1 (39.7) ^c
C _{avg0-28d} (ng/mL) ^d	22.5 (18.8) ^c	49.0 (39.6) ^c
AUC _{0-t} (ng.h/mL)	23855.2 (25.2) ^c	60117.9 (40.1) ^c
AUC _{0-28d} (ng.h/mL)	15146.2 (18.8) ^c	32918.4 (39.7) ^c
AUC _{0-28d} /Dose (ng.h/mL/mg)	201.9 (18.9) ^c	219.7 (39.6) ^c
t _{1/2} (h)	464.1 (177.6) ^c	531.6 (260.5) ^e
% Fluctuation ^f	167.9 (42.9) ^c	136.8 (50.9) ^c
Accumulation ratio AUC ^g	1.6 (24.8) ^c	1.8 (26.0) ^c
Accumulation ratio C _{max} ^h	1.6 (26.9) ^c	1.7 (27.9) ^c

^a All parameters presented as geometric mean (%CV), except for t_{max} which is presented as median (range) and t_{1/2} which is presented as mean (standard deviation); ^b was estimated as (AUC_{0-24h})/24 hours; ^c n = 10; ^d was estimated as (AUC_{0-28d})/(28 days × 24 hours); ^e n = 7;

^f Calculated as (C_{max} - C_{min})/C_{avg}*100; ^g Accumulation ratio AUC was calculated as the ratio of AUC_{0-28d} following the third dose/ AUC_{0-28d} following the first dose. ^h Accumulation ratio C_{max} was calculated as the ratio of C_{max} following the third dose/ C_{max} following the first dose.

Source: Applicant's Complete Study Report for study TV-46000-SAD-10055, Table 19, and Summary 15.8.3.3 (C_{trough} values).

Table 44: Comparison of Systemic Exposure by TV-46000 Dosing Interval

Geometric mean Parameter (unit)	TV-46000 cohort and dose					
	Cohort 6 75 mg N=12			Cohort 7 150 mg N=12		
	First dose (Day 1)	Second dose (Day 29)	Third dose (Day 57)	First dose (Day 1)	Second dose (Day 29)	Third dose (Day 57)
C _{max} (ng/mL)	21.3	31.7	33.9 ^a	39.2	54.8 ^a	69.6 ^a
C _{avg0-28d} (ng/mL)	14.2	20.8 ^a	22.5 ^a	27.1 ^a	38.7 ^a	49.0 ^a
AUC _{0-28d} (ng.h/mL)	9540	13954 ^a	15146 ^a	18190 ^a	26031 ^a	32918 ^a
C _{trough} (ng/mL)	9.5	12.0 ^a	15.1 ^a	16.4 ^a	29.0 ^a	37.6 ^a

a n = 10

Source: Applicant's Complete Study Report for study TV-46000-SAD-10055, Table 21 and Summary 15.8.3.3 (Ctrough values).

Table 45: Summary of Pharmacokinetic Parameters for Multiple Doses of TV-46000 75 mg and 150 mg Versus Oral Risperidone 3 mg and 5 mg

Geometric mean parameter (unit)	Steady-state oral risperidone dose (mg)		Multiple dose (approx. steady-state) TV-46000 dose (mg)	
	3 mg min dose	5 mg max dose	75 mg min dose	150 mg max dose
C _{max} (ng/mL)	39.8	62.2	33.9	69.6
C _{trough} (ng/mL) ^a	9.86	18.8	15.1	37.6
C _{avg} (ng/mL) ^b	20.7	31.9	18.7	40.1
% Fluctuation ^c	132	128	168	137

a C24h for oral risperidone and C84d for multiple dose TV-46000.

b Cavg24h for oral risperidone, Cavg0-56d and Cavg0-84d for multiple dose TV-46000.

c Calculated as (C_{max} - C_{min})/C_{avg}*100.

Source: Applicant's Complete Study Report for study TV-46000-SAD-10055, Table 20

Study TV-46000-BA-10148

Study 10148 was an open-label, single sequence study in parallel groups of patients with a diagnosis of schizophrenia or schizoaffective disorder to assess the relative BA of TV-46000 administered sc from vials compared to the PFS presentation. Study participants had a current confirmed diagnosis of schizophrenia or schizoaffective disorder, were clinically stable patients who were not receiving antipsychotic treatment other than oral risperidone, and were aged 18 to 60 years. All patients received oral risperidone 4 mg (Risperdal) qd for 7 days (administered either on an inpatient or outpatient basis; Period 1), followed by a 7-day inpatient washout period. Patients were then randomly assigned into 1 of the 2 treatment groups in which a single-dose of TV-46000 100 mg sc was administered from vials (reference treatment) or PFS (test treatment) presentations and pharmacokinetics followed over a period of up to 13 weeks (Period 2). The primary objective of this study was to assess the relative BA of a single dose of 100 mg TV-46000 administered sc from vials compared to PFS in patients with schizophrenia or schizoaffective disorder.

As pre-specified in the statistical analysis plan, patients with TAM plasma concentrations after oral risperidone administration (period 1) and a 7-day washout exceeding 5% of C_{max} of TV-46000 plasma concentrations following sc administration were to be excluded from primary analysis. This resulted in excluding 39/95 patients from the primary analysis dataset. Therefore, in addition to the pharmacokinetic evaluations conducted on the primary dataset ($n = 57$) and given the large proportion of patients lost due to this requirement, an ad-hoc dataset including all evaluable patients ($n = 95$) was created and used in all data analyses. The Applicant's justification for this approach entailed that the remaining residue of any analyte (risperidone or 9-OH-risperidone) will be eliminated within hours after TV-46000 dosing and is expected to have a limited impact on the assessment of pharmacokinetic parameters over 84 days after TV-46000 administration (AUC_{0-84d}) from the vial or PFS presentations.

Following sc administration of TV-46000 from PFS and vials, there was an immediate increase in TAM concentrations with each treatment group. The prolonged $t_{1/2}$ and the delayed C_{max} observed, are typical for extended-release formulations and are known as "flip-flop kinetics". The predose TAM plasma concentrations did not appear to have an impact on this rapid increase, as geometric mean values ranged between 0.69 through 1.32 ng/mL, for both the primary and ad-hoc datasets. The primary pharmacokinetic parameter that was used for comparison between the 2 presentations was AUC_{0-84d} . After administration of TV-46000 using the PFS or vial presentation, the geometric mean estimates for systemic exposure as measured by AUC_{0-84d} were 22865.8 ng.h/mL and 19965.9 ng.h/mL, with corresponding %CV estimates of 41% and 34%, respectively (Table 46). In the ad-hoc dataset the geometric mean estimates for systemic exposure as measured by AUC_{0-84d} for the PFS presentation were 25377.9 ng.h/mL and for the vial presentation 21571.7 ng.h/mL, with corresponding %CV estimates of 43.0% and 39.6%, respectively (Table 47).

Table 46: Geometric Mean (%CV) Total Active Moiety Plasma Pharmacokinetic Parameters by Treatment Group (TV-46000 PFS, TV-46000 Vial) for Pharmacokinetic Evaluable Patients (Primary Analysis Dataset)

Parameter (unit)	Statistic	TV-46000 Vial (N=59)	TV-46000 PFS (N=60)	TV-46000 Vial + PFS (N=119)
t_{max} (h)	n	35	24	59
	Median	313.1	285.9	287.3
	Min, max	72, 1849	30, 1178	30, 1849
AUC_{0-28d} (ng.h/mL)	n	35	24	59
	Geometric mean	11891.8	13938.7	12685.5
	Geometric %CV	43.4	39.3	42.3
AUC_{0-56d} (ng.h/mL)	n	35	23	58
	Geometric mean	18114.4	20018.3	18846.7
	Geometric %CV	45.8	36.8	42.4
AUC_{0-84d} (ng.h/mL)	n	34	23	57
	Geometric mean	19965.9	22865.8	21088.9
	Geometric %CV	33.5	40.6	36.8
$AUC_{0-\infty}$ (ng.h/mL)	n	22	19	41
	Geometric mean	20613.1	23712.4	21995.5
	Geometric %CV	23.8	27.0	26.0
C_{max} (ng/mL)	n	35	24	59
	Geometric mean	32.3	36.3	33.9
	Geometric %CV	67.4	43.5	58.1
$C_{avg0-28d}$ (ng/mL)	n	35	24	59
	Geometric mean	17.7	20.7	18.9
	Geometric %CV	43.4	39.3	42.3
$C_{avg0-56d}$ (ng/mL)	n	35	23	58
	Geometric mean	13.5	14.9	14.0
	Geometric %CV	45.8	36.8	42.4
$C_{avg0-84d}$ (ng/mL)	n	34	23	57
	Geometric mean	9.9	11.3	10.5
	Geometric %CV	33.5	40.6	36.8
C_{24h} (ng/mL)	n	34	24	58
	Geometric mean	12.1	13.4	12.6
	Geometric %CV	32.5	36.9	34.4
C_{28d} (ng/mL)	n	34	24	58
	Geometric mean	12.4	13.4	12.8
	Geometric %CV	62.4	52.4	58.0
C_{56d} (ng/mL)	n	34	22	56
	Geometric mean	4.8	3.3	4.1
	Geometric %CV	120.5	136.3	128.2
$t_{1/2}$ (h)	n	27	21	48
	Geometric mean	466.8	387.5	430.3
	Geometric %CV	62.0	65.8	63.9
	Min, max	114, 1051	188, 1361	114, 1361

Source: Applicant's Complete Study Report for study TV-46000-BA-10148, Table 18.

Table 47: Geometric Mean (%CV) Total Active Moiety Plasma Pharmacokinetic Parameters by Treatment Group (TV-46000 PFS, TV-46000 Vial) for Pharmacokinetic Evaluable Patients (Ad-hoc Analysis Dataset)

Parameter (unit)	Statistic	TV-46000 Vial (N=59)	TV-46000 PFS (N=60)	TV-46000 Vial+ PFS (N=119)
t_{max} (h)	n	54	47	101
	Median	287.7	286.9	287.3
	Min, max	48, 1849	30, 2013	30, 2013
AUC_{0-28d} (ng.h/mL)	n	53	46	99
	Geometric mean	12318.9	14052.6	13096.1
	Geometric %CV	46.3	40.3	43.9
AUC_{0-56d} (ng.h/mL)	n	54	43	97
	Geometric mean	19005.4	21435.2	20046.5
	Geometric %CV	47.1	38.3	43.6
AUC_{0-84d} (ng.h/mL)	n	53	42	95
	Geometric mean	21571.7	25377.9	23178.5
	Geometric %CV	39.6	43.0	41.8
$AUC_{0-\infty}$ (ng.h/mL)	n	34	29	63
	Geometric mean	23162.8	26796.9	24770.0
	Geometric %CV	38.4	33.8	36.9
C_{max} (ng/mL)	n	54	47	101
	Geometric mean	30.7	34.8	32.5
	Geometric %CV	63.4	45.7	55.7
$C_{avg0-28d}$ (ng/mL)	n	53	46	99
	Geometric mean	18.3	20.9	19.5
	Geometric %CV	46.3	40.3	43.9
$C_{avg0-56d}$ (ng/mL)	n	54	43	97
	Geometric mean	14.1	15.9	14.9
	Geometric %CV	47.1	38.3	43.6
$C_{avg0-84d}$ (ng/mL)	n	53	42	95
	Geometric mean	10.7	12.6	11.5
	Geometric %CV	39.6	43.0	41.8
C_{24h} (ng/mL)	n	53	47	100
	Geometric mean	13.2	15.2	14.1
	Geometric %CV	38.2	44.0	41.5
C_{28d} (ng/mL)	n	53	47	100
	Geometric mean	13.5	14.0	13.7
	Geometric %CV	60.8	48.1	54.8
C_{56d} (ng/mL)	n	52	42	94
	Geometric mean	5.3	5.3	5.3
	Geometric %CV	103.5	130.3	114.4
$t_{1/2}$ (h)	n	46	39	85
	Geometric mean	531.5	508.0	520.6
	Geometric %CV	65.2	71.4	67.6
	Min, max	114, 1541	188, 1850	114, 1850

Source: Applicant's Complete Study Report for study TV-46000-BA-10148, Table 19.

The relative BA analysis of TV-46000 administered using the PFS or vial presentation was performed using an analysis of variance (ANOVA) model on natural log transformed AUC_{0-84d} with treatment (PFS, vial) and categorized screening body weight (3 categories: <75 kg, 75-99 kg, and >99 kg) as fixed effects. Equal variance among the treatment groups was assumed. The least squares mean for each treatment, the least squares mean difference between the treatments, and 90% confidence interval (CI) of the least squares mean difference was derived from the model. These were back transformed to derive the least squares geometric mean, least squares geometric mean ratio and corresponding 90% CI of the geometric mean ratio. Results from this analysis demonstrated ~16 to 17% higher exposure for TAM over 84 days (AUC_{0-84d}) upon administration of TV-46000 from PFS in comparison to administration from vials (primary and ad-hoc datasets, respectively), with a 90% CI for the test/reference geometric mean ratios of AUC_{0-84d} of 0.991 to 1.356 and 1.024 to 1.340 for primary and ad-hoc datasets, respectively.

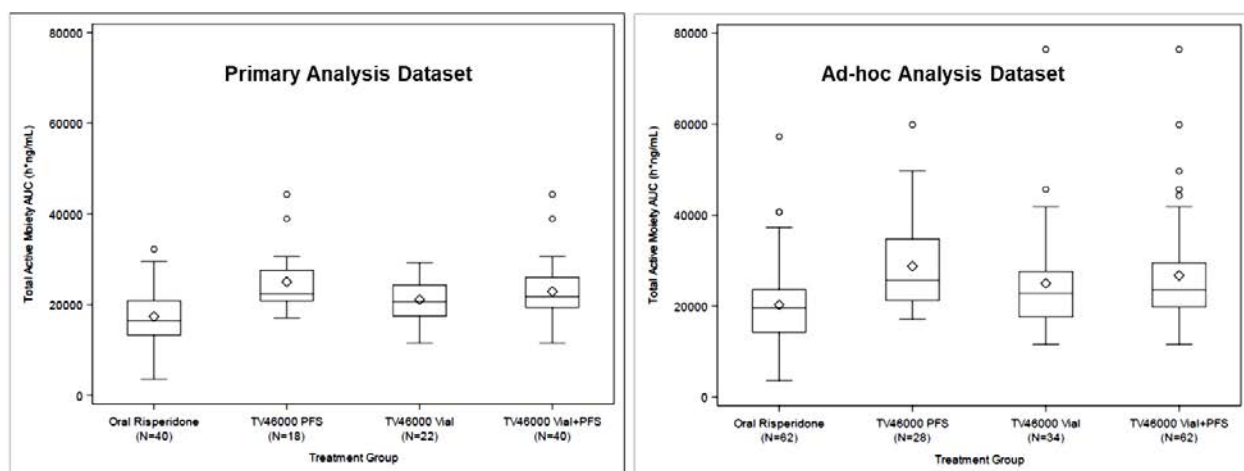
During data evaluation, the Applicant identified that the study population displayed an intrinsic heterogeneity in TAM exposure, as demonstrated by apparent predisposition of patients subsequently randomized into the PFS treatment group towards higher TAM exposures upon oral risperidone administration compared to those of patients subsequently randomized to the vial treatment group. To compensate for this phenomenon, an additional covariate for oral exposure ($AUC_{0-\tau, ss}$), was included in the analysis of covariance (ANCOVA) for the primary endpoint for both datasets. Upon oral risperidone exposure ($AUC_{0-\tau, ss}$) normalization, differences between the treatment groups were minimized and closer comparability of the relative BA for TV-46000 PFS and TV-46000 vial presentations was demonstrated in both primary and ad-hoc datasets, with a 90% CI for the test/reference geometric least squares mean ratios of AUC_{0-84d} of 0.956 to 1.288 and 0.965 to 1.217 for primary and ad-hoc datasets, respectively (Table 8). Overall, the exposure differences between the PFS and Vial were not found to be clinically meaningful by the clinical pharmacology review team (section 6.3.1)

To compare TV-46000 versus oral risperidone within this study, TAM $AUC_{0-\infty}$ was used as variable for TV-46000 PFS and TV-46000 vial and TAM AUC_{0-28d} calculated for oral risperidone, both of which reflect the steady-state AUC over the 1-month dosing interval. A higher mean exposure was achieved following TV-46000 administration using the PFS or vial presentations and with combining both presentations in comparison to 4 mg oral risperidone. However, TV-46000 exposures were within the overall exposure range observed following daily administration of 4 mg oral risperidone over 28 days, as measured by $AUC_{0-\infty}$ for TV-46000 vial in both the primary and ad-hoc datasets. Additionally, TAM exposure of individual patients following 100 mg TV-46000 administered from the PFS and vial combined, or PFS and vial presentations, was within the range of exposure of individual patients following oral risperidone administration of 4 mg/day over 28 days (for Primary Dataset and for the ad-hoc dataset)(Figure 11). Similarly, the exposure range for oral risperidone (plasma drug concentration at the end of the dosing interval (C_{min} to C_{max}) was comparable to the exposure range for both TV-46000 presentations. The C_{max} values for TV-46000 were generally lower than those for oral risperidone. However, based on the anticipated accumulation ratio for TV-46000 at steady-state, both the drug concentration at the end of dosing interval (C_{trough}) at steady-state ($C_{min,ss}$) and maximum plasma drug concentration at steady-state ($C_{max,ss}$) are expected to

Uzedy (risperidone extended release injection)

increase by approximately 2-fold and are anticipated to be comparable to that of oral risperidone, resulting in a comparable exposure range of TV-46000 to the corresponding oral risperidone dose.

Figure 11: Box Plot of TV-46000 Vial, TV-46000 PFS, TV-46000 Vial + PFS for $AUC_{0-\infty}$ and of Oral Risperidone for AUC_{0-28d} , calculated (Total Active Moiety) for Primary and Ad-hoc datasets



Source: Applicant's Complete Study Report for study TV-46000-BA-10148, Figures 10 and 11.

Table 48: Selected Pharmacokinetic Parameters of TV-46000 by Treatment Group Compared to Oral Risperidone Tablets for the Primary and Ad-hoc Datasets

Parameter	Primary dataset					Ad-hoc dataset			
	Statistic	Oral risperidone (N=155) ^a	TV-46000 PFS (N=60)	TV-46000 Vial (N=59)	TV-46000 Vial+ PFS (N=119)	Oral risperidone (N=155) ^a	TV-46000 PFS (60)	TV-46000 Vial (N=59)	TV-46000 Vial+ PFS (N=119)
t _{max} (h)	n	55	24	35	59	93	47	54	101
	Median	1.5	285.9	313.1	287.3	1.5	286.9	287.7	287.3
	Min, max	0, 6	30, 1178	72, 1849	30, 1849	0, 12	30, 2013	48, 1849	30, 2013
AUC ₀₋₂₈ (ng*h/mL) ^b	n	55	24	35	59	93	46	53	99
	Geometric mean	16530.443	13938.744	11891.838	12685.468	19303.856	14052.593	12318.903	13096.118
	Geometric %CV	39.177	39.291	43.397	42.253	41.729	40.346	46.273	43.943
AUC ₀₋₅₆ (ng*h/mL)	n		23	35	58		43	54	97
	Geometric mean		20018.337	18114.355	18846.697		21435.155	19005.35	20046.501
	Geometric %CV		36.795	45.789	42.351		38.256	47.065	43.572
AUC ₀₋₈₄ (ng*h/mL)	n		23	34	57		42	53	95
	Geometric mean		22865.785	19965.934	21088.946		25377.941	21571.717	23178.473
	Geometric %CV		40.593	33.511	36.822		43.012	39.602	41.825
AUC _{0-∞} (ng*h/mL)	n		19	22	41		29	34	63
	Geometric mean		23712.428	20613.06	21995.49		26796.912	23162.804	24770.016
	Geometric %CV		26.992	23.804	26.035		33.83	38.438	36.898
AUC ₀₋₁₂₀ (ng*h/mL)	n	55				93			
	Geometric mean	590.373				689.423			
	Geometric %CV	39.177				41.729			
C _{max} (ng/mL)	n	55	24	35	59	93	47	54	101
	Geometric mean	47.941	36.261	32.306	33.86	54.377	34.804	30.702	32.547
	Geometric %CV	38.948	43.473	67.362	58.146	40.084	45.723	63.423	55.728
C _{min} (ng/mL)	n	55				93			
	Geometric mean	11.91				14.593			
	Geometric %CV	53.245				59.741			
C _{min1-28} (ng/mL)	n		24	35	59		46	53	99
	Geometric mean		10.248	9.348	9.704		11.417	10.225	10.762
	Geometric %CV		36.786	33.224	34.714		40.683	37.438	39.206

Source: Applicant's Complete Study Report for study TV-46000-BA-10148, Table 25 and 26.

15.3.3. Pharmacometric Review

Based on the result of the OSI inspection, there were some discrepancies identified in the conduct and collection of data for the phase 3 studies. The main issues raised by the OSI inspection were: 1. dosing error; 2. lack of documentation of IP administration; 3. duplicate enrollment; and 4. unblinding. The impact of these discrepancies on the analyses and recommendations that rely on dosing data from the phase 3 studies in the Pharmacometrics section of the review are not known. If the extent of discrepancies in conduct of studies and collection of data are more far reaching than currently known, then it may impact the conclusions and recommendations made in this review document. For the OSI inspection results, refer to the OSI consult review.

Applicant's Analysis

Population PK Analysis

The final PopPK model was developed from a dataset of 25638 evaluable plasma concentrations (12829 risperidone concentration and 12809 9-OH risperidone concentration) from 694 subjects enrolled in five clinical studies to quantitatively describe the clinical PK of risperidone and its major metabolites 9-OH risperidone and identify sources of interindividual variability. A nonlinear mixed effects modeling approach with the first-order conditional estimation with interaction (FOCEI) method in NONMEM, version 7.4.3. (b) (4) was used for the PopPK analysis.

Table 49: Summary of studies included in the population PK analysis

Study	Title	Dose	PK sampling times	No. of Subjects
RISPE1ZG15EU	phase 1, single-dose study, targeting subtherapeutic plasma concentrations in healthy volunteers.	Single dose 12.5-25 mg	Dense sampling schedule	55
TV-46000-SAD-10055	phase 1, single dose and 3 consecutive monthly doses in schizophrenia patients stable on oral risperidone.	Single dose 50-225 mg q1m 75-150 mg	Dense sampling schedule	96

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586

Uzedy (risperidone extended release injection)

TV-46000-BA-10148	phase 1, Single-sequence study in parallel groups of schizophrenia patients to assess the relative bioavailability of TV-46000 from pre-filled syringe.	Single dose 100 mg vial or pre-filled syringe	Dense sampling schedule	Approximately 110
TV-46000-CNS-30072	phase 3, TV-46000 sc q1m and q2m and placebo sc in a 1:1:1 ratio. Oral conversion and stabilization stage (12 weeks), double-blind maintenance stage (up to approximately 13 months), and follow-up (8 weeks).	q1m 50-125 mg q2m 100-250 mg	Stage 1 (Oral, at weeks 12, 10, 8, and 4), Stage 2 (TV-46000, at baseline, every 4 weeks for up to approximately 13 months, and follow-up).	Approximately 596, including placebo
TV-46000-CNS-30078	Safety extension study of Study TV-46000-CNS-30072. TV-46000 sc q1m and q2m in a 1:1 ratio.	q1m 50-125 mg; q2m 100-250 mg	Stage 1 (Oral, at weeks 12 and 4), Stage 2 (TV-46000, at baseline, every 4 weeks, and follow-up).	Approximately 300 in Stage 2

Source: Adapted from Applicant's PopPK/PD report, Page 18-19, Table 2

Table 50: Summary of Demographics in the Population PK Development Dataset

	TV46000- SAD-10055 (N=97)	RISPE1ZG15EU (N=50)	CNS- 30072 (N=363)	CNS- 30078 (N=103)	BA-10148 (N=120)	Overall (N=733)
Sex						
Female	19 (19.6%)	9 (18.0%)	141 (38.8%)	21 (20.4%)	27 (22.5%)	217 (29.6%)
Male	78 (80.4%)	41 (82.0%)	222 (61.2%)	82 (79.6%)	93 (77.5%)	516 (70.4%)
Age (y)						
Mean (SD)	44.4 (8.84)	35.5 (10.1)	49.3 (10.8)	49.4 (10.6)	47.4 (9.77)	47.4 (10.9)
Median (CV%)	47.0 (19.9)	33.5 (28.6)	52.0 (21.8)	50.0 (21.5)	51.0 (20.6)	50.0 (23.0)
[Min, Max]	[20.0, 56.0]	[19.0, 54.0]	[16.0, 65.0]	[16.0, 64.0]	[21.0, 60.0]	[16.0, 65.0]
Race						
White	4 (4.1%)	38 (76.0%)	138 (38.0%)	41 (39.8%)	13 (10.8%)	234 (31.9%)
Black or African American	93 (95.9%)	3 (6.0%)	218 (60.1%)	59 (57.3%)	101 (84.2%)	474 (64.7%)
Asian	0 (0%)	5 (10.0%)	3 (0.8%)	1 (1.0%)	1 (0.8%)	10 (1.4%)
Missing	0 (0%)	4 (8.0%)	4 (1.1%)	2 (1.9%)	5 (4.2%)	15 (2.0%)
Weight (kg)						
Mean (SD)	87.3 (14.9)	77.1 (11.3)	86.0 (16.5)	89.8 (17.7)	87.0 (16.1)	86.3 (16.3)
Median (CV%)	87.2 (17.1)	77.7 (14.6)	85.8 (19.2)	87.0 (19.7)	86.0 (18.5)	85.4 (18.9)
[Min, Max]	[57.8, 113]	[53.6, 96.4]	[42.0, 132]	[55.9, 131]	[51.1, 122]	[42.0, 132]
Height (cm)						
Mean (SD)	175 (7.98)	175 (8.56)	172 (9.79)	173 (9.06)	175 (8.63)	173 (9.27)
Median (CV%)	175 (4.6)	176 (4.9)	171 (5.7)	173 (5.2)	175 (4.9)	173 (5.4)
[Min, Max]	[152, 189]	[157, 191]	[149, 201]	[155, 198]	[152, 198]	[149, 201]

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
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	TV46000-SAD-10055 (N=97)	RISPE1ZG15EU (N=50)	CNS-30072 (N=363)	CNS-30078 (N=103)	BA-10148 (N=120)	Overall (N=733)
BMI (kg/m²)						
Mean (SD)	28.6 (4.38)	25.1 (2.52)	29.0 (4.92)	29.9 (4.91)	28.3 (4.75)	28.7 (4.81)
Median (CV%)	30.0 (15.3)	24.9 (10.0)	28.7 (17.0)	29.3 (16.4)	28.5 (16.8)	28.7 (16.8)
[Min, Max]	[19.6, 34.8]	[19.5, 30.1]	[18.0, 38.0]	[19.3, 38.0]	[18.5, 35.4]	[18.0, 38.0]
Disease status						
Healthy subject	0 (0%)	50 (100%)	0 (0%)	0 (0%)	0 (0%)	50 (6.8%)
Chronic schizophrenia	97 (100%)	0 (0%)	363 (100%)	103 (100%)	120 (100%)	683 (93.2%)

Source: 20210428.Expl.v12-qc.html.

Abbreviations: CV = coefficient of variation; Max = maximum; Min = minimum; N = number of subjects; SD = standard deviation.

Source: Applicant's PopPK/PD report, Page35, Table 8

Table 51: Summary of Laboratory Parameters in the Population PK Development Dataset

	TV46000-SAD-10055 (N=97)	RISPE1ZG15EU (N=50)	CNS-30072 (N=363)	CNS-30078 (N=103)	BA-10148 (N=120)	Overall (N=733)
CYP2D6						
Poor	1 (1.0%)	0 (0%)	5 (1.4%)	0 (0%)	4 (3.3%)	10 (1.4%)
Intermediate	15 (15.5%)	4 (8.0%)	26 (7.2%)	0 (0%)	14 (11.7%)	59 (8.0%)
Extensive	74 (76.3%)	46 (92.0%)	164 (45.2%)	0 (0%)	99 (82.5%)	383 (52.3%)
Ultra rapid	3 (3.1%)	0 (0%)	7 (1.9%)	0 (0%)	3 (2.5%)	13 (1.8%)
Missing	4 (4.1%)	0 (0%)	161 (44.4%)	103 (100%)	0 (0%)	268 (36.6%)
CRCL (mL/min)						
Mean (SD)	115 (24.4)	NA (NA)	120 (35.6)	128 (41.1)	119 (29.6)	121 (34.3)
Median (CV%)	114 (21.1)	NA (NA)	113 (29.6)	122 (32.2)	119 (24.8)	116 (28.4)
[Min, Max]	[69.4, 175]	[NA, NA]	[48.3, 279]	[50.7, 296]	[55.6, 206]	[48.3, 296]
Missing	1 (1.0%)	50 (100%)	1 (0.3%)	0 (0%)	0 (0%)	52 (7.1%)

Source: 20210428.Expl.v12-qc.html.

Abbreviations: CRCL = creatinine clearance/estimated glomerular filtration rate (mL/min) based on the Cockcroft Gault formula; CV = coefficient of variation; Max = maximum; Min = minimum; N = number of subjects; SD = standard deviation; NA = not applicable.

Source: Applicant's PopPK/PD report, Page36, Table 9

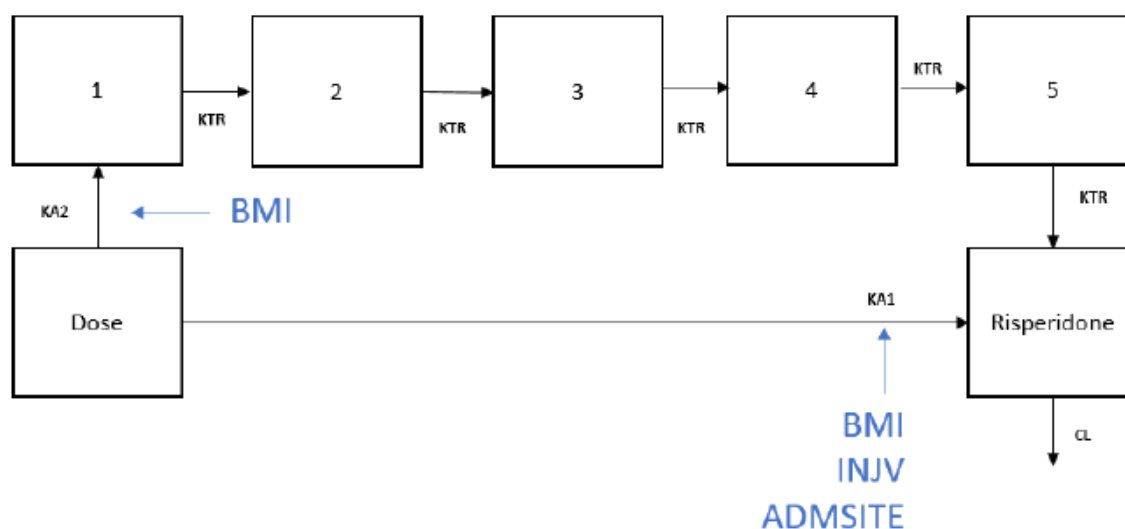
A sequential parent-metabolite model building approach was used, where the PK of the parent molecule (risperidone) was first described using a 1-compartmental model with double first-

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order absorption route and first-order elimination. Absorption from the sc depot was described by a direct absorption route, with a fast component (KA1; absorption rate constant route 1) and an indirect absorption process, with a slow absorption route (KA2; absorption rate constant route 2) including 5 transit compartments, as illustrated in Figure 12. The model including a BMI effect on KA1 and KA2 as well as the effects of administration site and injection volume on KA1, but without effects of age and sex on CL, was accepted as the final model.

The PK of risperidone's active metabolite, 9-OH-risperidone, was described using individual risperidone pharmacokinetic parameters as input into the final metabolite PopPK model. The 9-OH-risperidone model was also described by a 1-compartmental model with a first order conversion from risperidone and a first order elimination, as depicted in Figure 13. The following covariates were included in the SCM: age, body weight, body mass index, creatinine clearance, sex and race.

Figure 12: Final PopPK Model Schematic for Risperidone



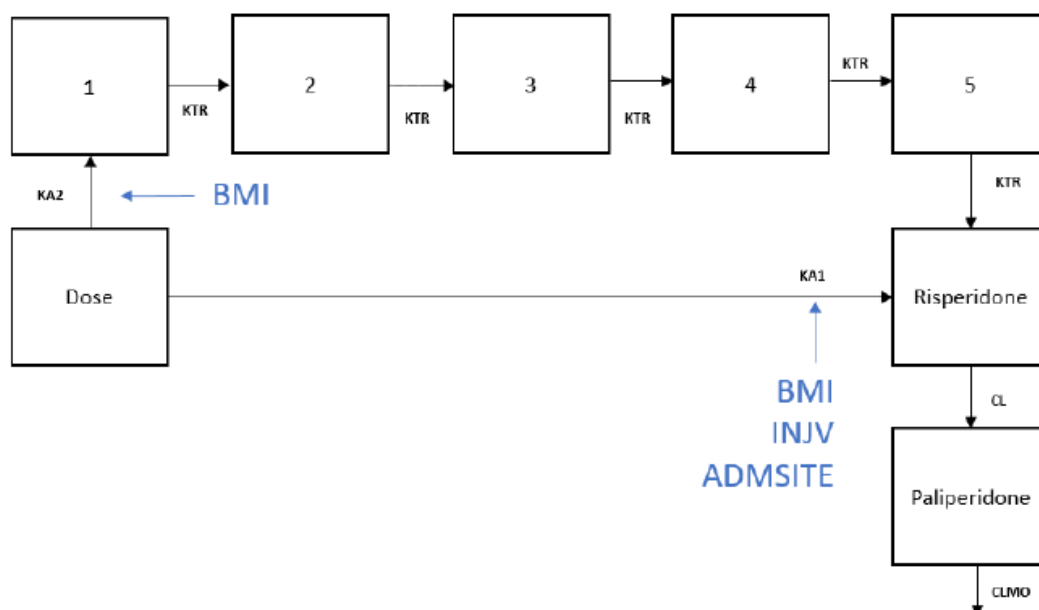
Source: Diagram.parent.model.PNG.

Abbreviations: ADMSITE = administration site; BMI = body mass index; CL = apparent clearance;

INJV = injection volume; KA1 = absorption rate constant 1; KA2 = absorption rate constant 2; KTR = transit rate constant.

Source: Applicant's PopPK/PD report, Page 53, Figure 10

Figure 13: Final PopPK Model Schematic for Metabolite (9-OH Risperidone)



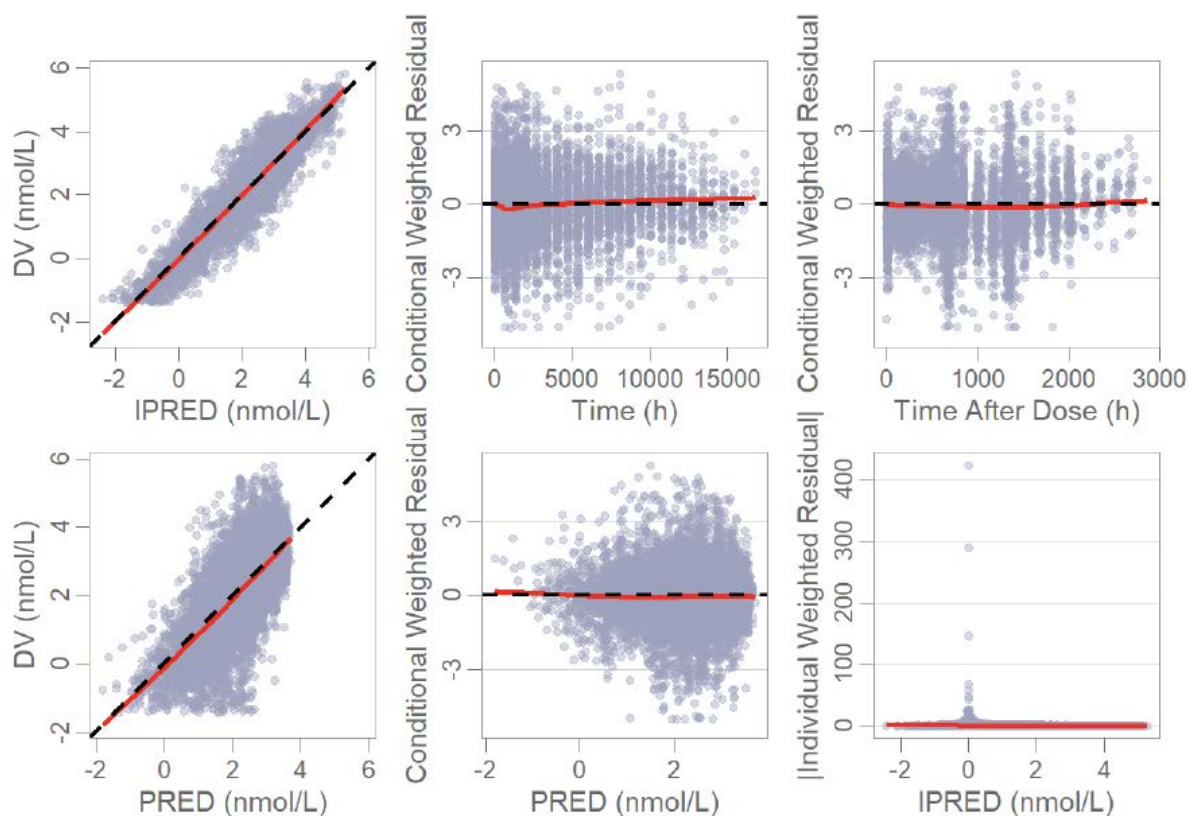
Source: Diagram.metabolite.model.PNG.

Abbreviations: ADMSITE = administration site; BMI = body mass index; CL = apparent clearance;
 CLMO = apparent clearance of metabolite; INJV = injection volume; KA1 = absorption rate constant route 1;
 KA2 = absorption rate constant route 2; KTR = absorption rate constant transit compartments.

Source: Applicant's PopPK/PD report, Page 64, Figure 16

The final PK model for risperidone and 9-OH-risperidone was assessed with diagnostics plots including goodness-of-fit (Figure 14 and Figure 15) and pcVPC (Figure 16 and Figure 17). The parameter estimates of the final popPK model for parent and metabolite are shown in Table 52 and Table 53, respectively.

Figure 14: Goodness-of-fit plots for Final PopPK Model for Risperidone



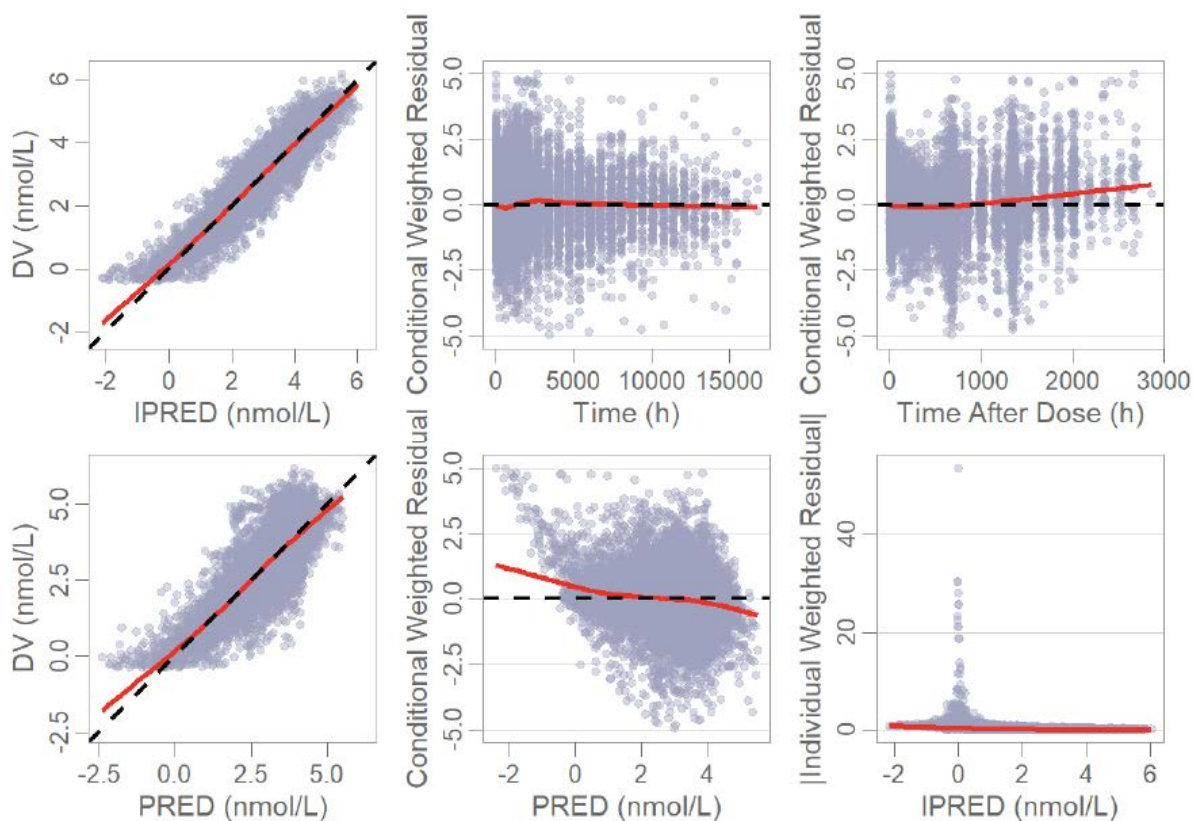
Source: run020.report.v16-qc.2021-04-29.html.

Abbreviations: DV = dependent variable (usually observation); GOF = goodness-of-fit; IPRED = individual prediction(s); LOESS = locally estimated scatterplot smoothing; PRED = population prediction(s).

Notes: Blue dots are individual data points, and solid lines are smoothed LOESS lines. The dashed lines are lines of identity.

Source: Applicant's PopPK/PD report, Page 52, Figure 9

Figure 15: Goodness-of-fit plots for Final PopPK Model for 9OH-Risperidone



Source: run055.report.2021-04-29.html.

Abbreviations: CWRES = conditional weighted residuals; DV = dependent variable (usually observation);

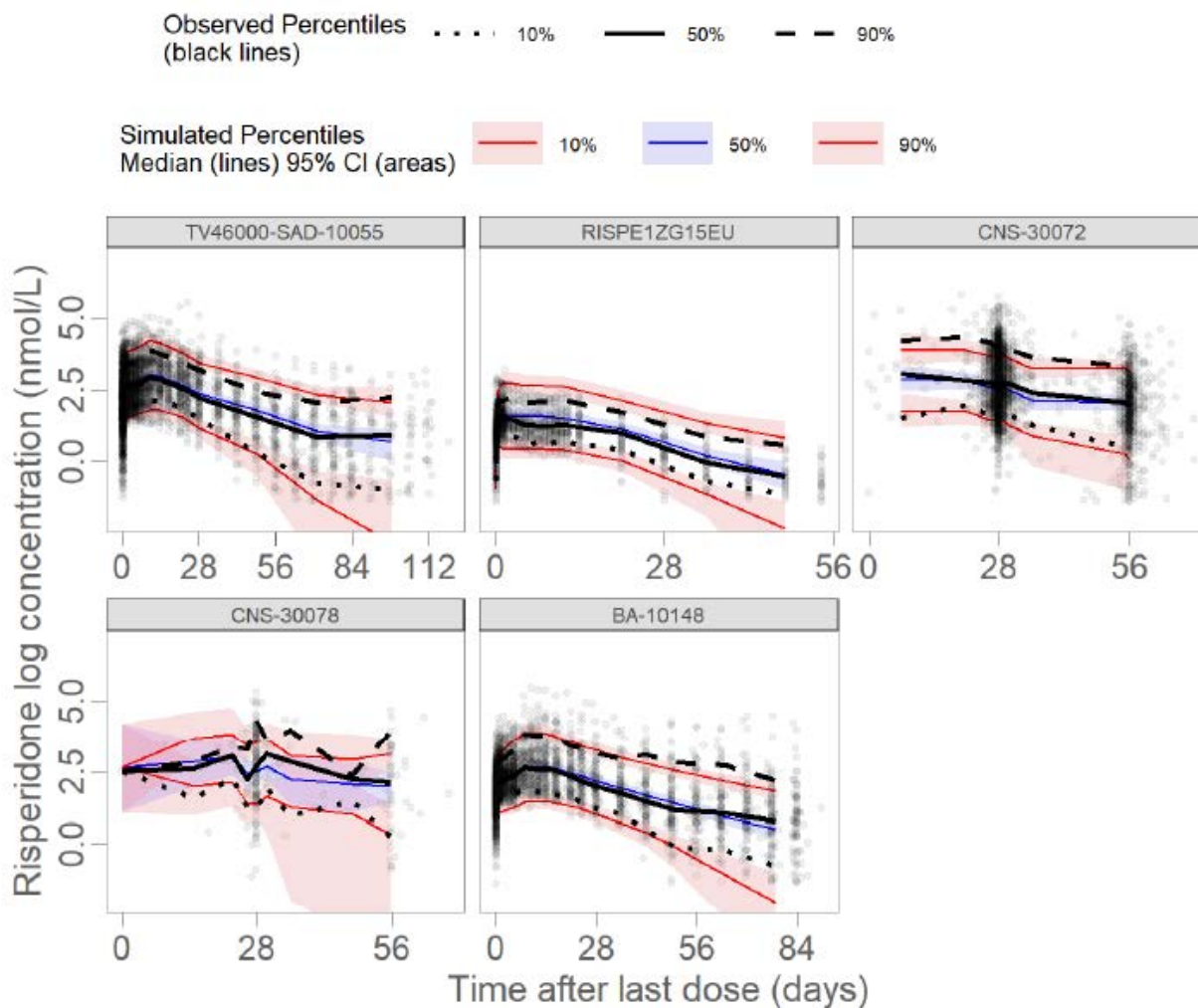
GOF = goodness-of-fit; IPRED = individual prediction(s); LOESS = locally estimated scatterplot smoothing;

PRED = population prediction(s).

Notes: Blue dots are individual data points, and solid red lines are smoothed LOESS lines. The dashed black lines are lines of identity.

Source: Applicant's PopPK/PD report, Page 63, Figure 15

Figure 16: Prediction-corrected Visual Predictive Check per Study for the Final Parent Model



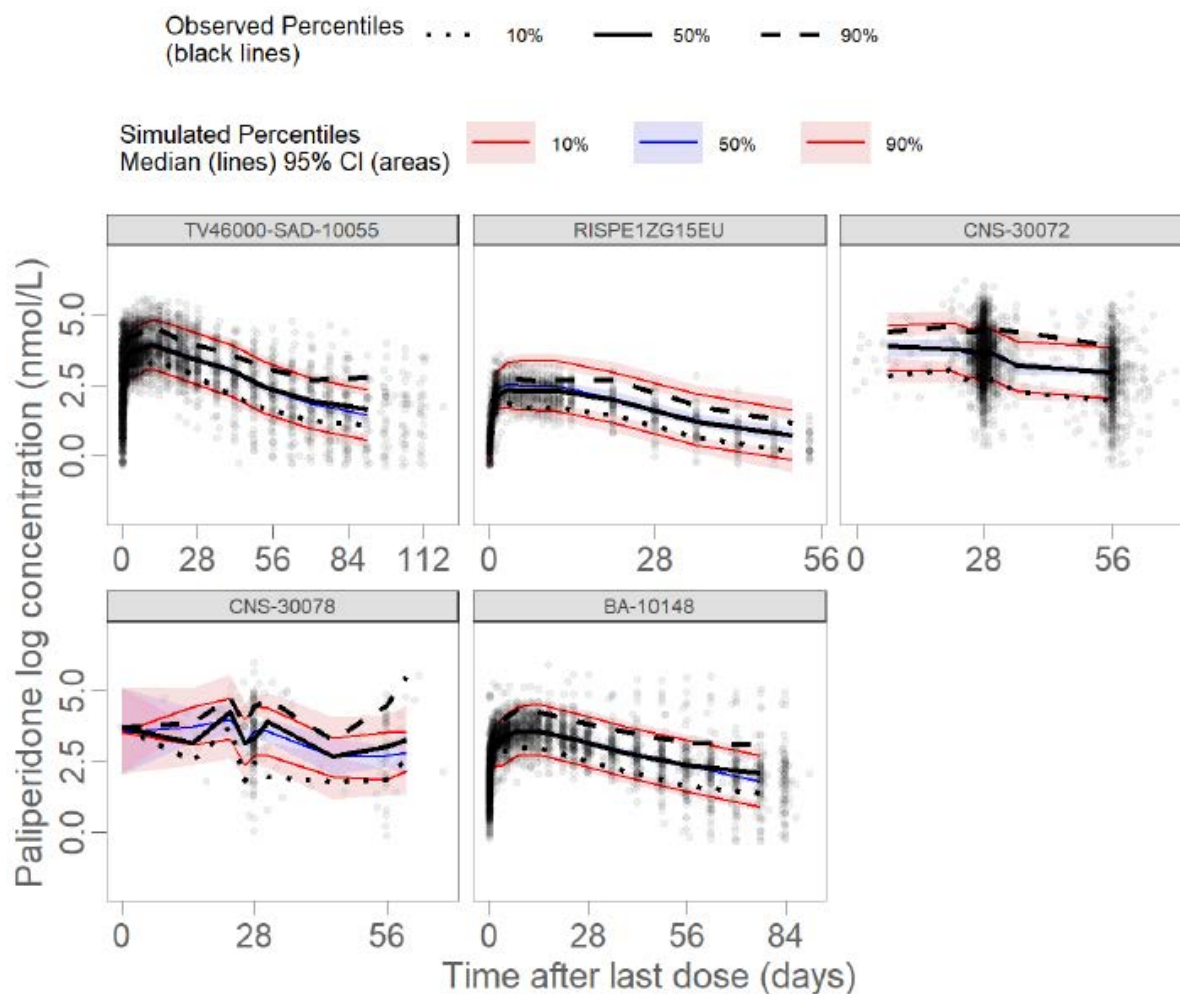
Source: run020.VPC.parent.v2.html.

Abbreviations: CI = confidence interval; p10 = 10th percentile; p90 = 90th percentile; VPC = visual predictive check(s).

Notes: Gray dots are the observed data points; black solid line is the observed median; black dotted and dashed lines are observed p10 and p90, respectively. The blue line is the simulated median, and the red lines are the simulated p10 and p90. The blue area is the 95% CI of the simulated median, and the pink areas are the 95% CIs of the simulated p10 and p90.

Source: Applicant's PopPK/PD report, Page 68, Figure 19

Figure 17: Prediction-corrected Visual Predictive Check per Study for the Final Metabolite Model



Source: run055.VPC.metabolite.v2.html.

Abbreviations: CI = confidence interval; p10 = 10th percentile; p90 = 90th percentile; VPC = visual predictive check(s).

Notes: Gray dots are the observed data points; black solid line is the observed median; black dotted and dashed lines are observed p10 and p90, respectively. The blue line is the simulated median, and the red lines are the simulated p10 and p90. The blue area is the 95% CI of the simulated median, and the pink areas are the 95% CIs of the simulated p10 and p90.

Source: Applicant's PopPK/PD report, Page 71, Figure 22

Table 52: Final Model Parameter Estimates for TV-46000 Parent PK

Parameter	Estimates	%RSE	95%CI	Bootstrap median [95%CI]	
CL [L/h]	14.3	2.9	13.4-15.1	14.3	[13.4-15.1]
V [L]	66.3	4.4	60.6-71.9	66.2	[61.1-72]
KA2 [1/h]	0.000408	9.9	0.000329-0.000486	0.000409	[0.00034-0.000486]
KTR [1/h]	0.0252	4.8	0.0228-0.0275	0.0252	[0.0227-0.0275]
KA1 [1/h]	0.000632	3.6	0.000588-0.000676	0.000631	[0.000591-0.000675]
KA1ADMSITE1	0.331	34.2	0.109-0.553	0.336	[0.147-0.546]
KA1BMT1	-1.1	16.6	-1.46-0.745	-1.09	[-1.48-0.716]
KA1INJV1	-0.384	11.3	-0.469-0.298	-0.384	[-0.474-0.297]
KA2BMT1	1.7	21.3	0.992-2.41	1.69	[0.798-2.55]
Random effects	Estimates (%CV)	%RSE [%Shrinkage]	95%CI	Bootstrap median [95%CI]	
IIV on KA2 [%]	254.2	5.2 [25.8]	198.8-320.1	252.8	[205.1-321.9]
Correlation IIV KA2 and KA1 [%]	42.8	14.7		43.7	[28.8-55.7]
IIV on KA1 [%]	51.0	6.0 [32.7]	44.0-57.5	51.0	[43.7-57.8]
IIV on CL [%]	82.3	3.3 [6.6]	75.3-89.3	82.2	[75.9-88.9]
Residual error	Estimates	%RSE [%Shrinkage]		Bootstrap median [95%CI]	
EP [%]	40.5	2.3 [5.8]		40.4	[38.5-42.2]

Source: Applicant's PopPK/PD report, Page 53-54, Table 19

Table 53: Final Model Parameter Estimates for TV-46000 Metabolite PK

Parameter	Estimates	%RSE	95%CI	Bootstrap median [95%CI]	
CLMO [L/h]	5.78	2.322	5.52-6.04	5.79	[5.54-6.06]
VMO [L]	95.7	3.822	88.5-103	95.6	[89-103]
Random effects	Estimates (%CV)	%RSE [%Shrinkage]	95%CI	Bootstrap median [95%CI]	
IIV on CLMO [%]	65.1	4.0 [5.5]	58.9-71.1	65.1	[59.4-71.4]
Residual error	Estimates	%RSE [%Shrinkage]		Bootstrap median [95%CI]	
EP [%]	38.3	2.0 [2.7]		38.2	[36.7-40.0]

Source: Applicant's PopPK/PD report, Page 64, Table 23

For a typical male patient aged 50 years old with BMI of 28.7 kg/m², for the risperidone, the estimated apparent clearance (CL) was 14.3 L/hr, volume of distribution (V) was 66.3 L, absorption rate constant route 1 (KA1) was 0.00063/hr, and absorption rate constant route 2 (KA2) was 0.00041/hr. Interindividual variability on KA2, KA1 and CL were 254.2%, 42.8% and 82.3%, respectively. The estimated apparent clearance of metabolite (CLMO) was 5.78 L/hr, and volume of distribution of metabolite (VMO) was 95.7 L, the interindividual variability on CLMO was 65.1%.

For covariate analysis in the parent model, the impact of age, body weight, BMI, creatinine clearance (CRCL), and injection volume, sex, race, administration site, and product presentation (vial or pre-filled syringe [PFS]) on the PK of risperidone were investigated. Graphical evaluation of covariates revealed a small bias for lower BMI range on ETA KA2 and ETA CL. Furthermore, the graphical analysis indicated a small bias for ETA KA1 and ETA KA2 versus administration site. Another trend for ETA KA1 versus injection volume was detected. A small trend for ETA CL versus sex was observed. There were no trends observed for ETAs versus race, product presentation, and CRCL.

The stepwise covariate model (SCM) using final base model as starting point was implemented to evaluate the significance of covariates in the model. Injection volume, BMI, and administration site had a statistically significant effect on the absorption rate but did not have a clinically meaningful impact on the TAM exposure (Refer to Section 6.2.2 of Clinical Pharmacology Review). Body weight and product presentation (pre-filled syringe versus vial) were not identified as covariates of TV-46000 PK. Post-hoc evaluations to assess the impact of CYP2D6 metabolizer status on risperidone clearance showed that poor metabolizer status was associated with relatively lower risperidone clearance (Figure 1 in Section 6.2.1 of Clinical Pharmacology Review).

Using the sequential parent-metabolite population PK model of TV-46000, individual exposure estimates (C_{avg,ss}, AUC_{ss}, and C_{max,ss}) were calculated at steady state to support the final TV-46000 doses and proposed dosing regimens including 2 simulation scenarios:

- q1m regimen at doses of 50, 75, 100, or 125 mg
- q2m regimen at doses of 100, 150, 200, or 250 mg

The q1m dosing interval is equal to 28 days, whereas q2m is equal to 56 days.

For the calculation of the model predicted TAM, risperidone (RISP) and paliperidone (PALI) were predicted by the sequential parent-metabolite model and unit conversion was applied.

$$RISP \left[\frac{ng}{mL} \right] = RISP \left[\frac{nmol}{L} \right] * \frac{MW_{RISP}}{1000}$$

$$PALI \left[\frac{ng}{mL} \right] = PALI \left[\frac{nmol}{L} \right] * \frac{MW_{PALI}}{1000}$$

Model-predicted pharmacokinetic parameters and steady-state TAM exposure at selected time points were summarized for the different doses and dose regimens, please refer to section 6.3.1. Clinical Pharmacology Question 1 for more details.

The Applicant also assessed the impact of early or late administration of the next dose (± 1 week for q1m and q2m) on TAM exposure by simulation, and it is expected to be minimal (please refer to section 6.3.1. Clinical Pharmacology Question 4 for more details).

Pharmacometrics Reviewer's Comments

Overall, the Applicant's population PK models for parent and metabolite is adequate to describe the risperidone and 9-OH risperidone PK profiles though large between-subject variability observed in absorption rate constant from slower indirect absorption route process (KA2) as well as appear clearance for risperidone. Generally, the Applicant final PK models are acceptable to conduct simulation support PK bridging between TV-46000 and oral risperidone, dosing regimen, and provide dosing instruction for missing dose scenarios. Model-predicted pharmacokinetic parameters and steady-state TAM exposure such as daily AUC and average plasma concentration during the dosing interval at steady-state were similar when comparing any dose from the q1m regimen with the equivalent dose from the q2m regimen.

Reviewer's Analysis

Methods

Data Sets

Data sets used are summarized in Table 54.

Table 54: Analysis Data Sets

Datasets

Study	Name	Link to EDR
TV-46000-SAD-10055; RISPE1ZG15EU; CNS-30072; CNS-30078; BA-10148	ppk3.xpt ppk5.xpt	\\CDSESUB1\evsprod\nda213586\0010\m5\datasets\cp-18-11\poppk\analysis\datasets\ppk3.xpt \\CDSESUB1\evsprod\nda213586\0010\m5\datasets\cp-18-11\poppk\analysis\datasets\ppk5.xpt

Software

Population PK model fitting was performed in NONMEM 7.4.3 and Pirana 2.9.9. Primary analysis and plotting were performed in R 4.0.2.

Results

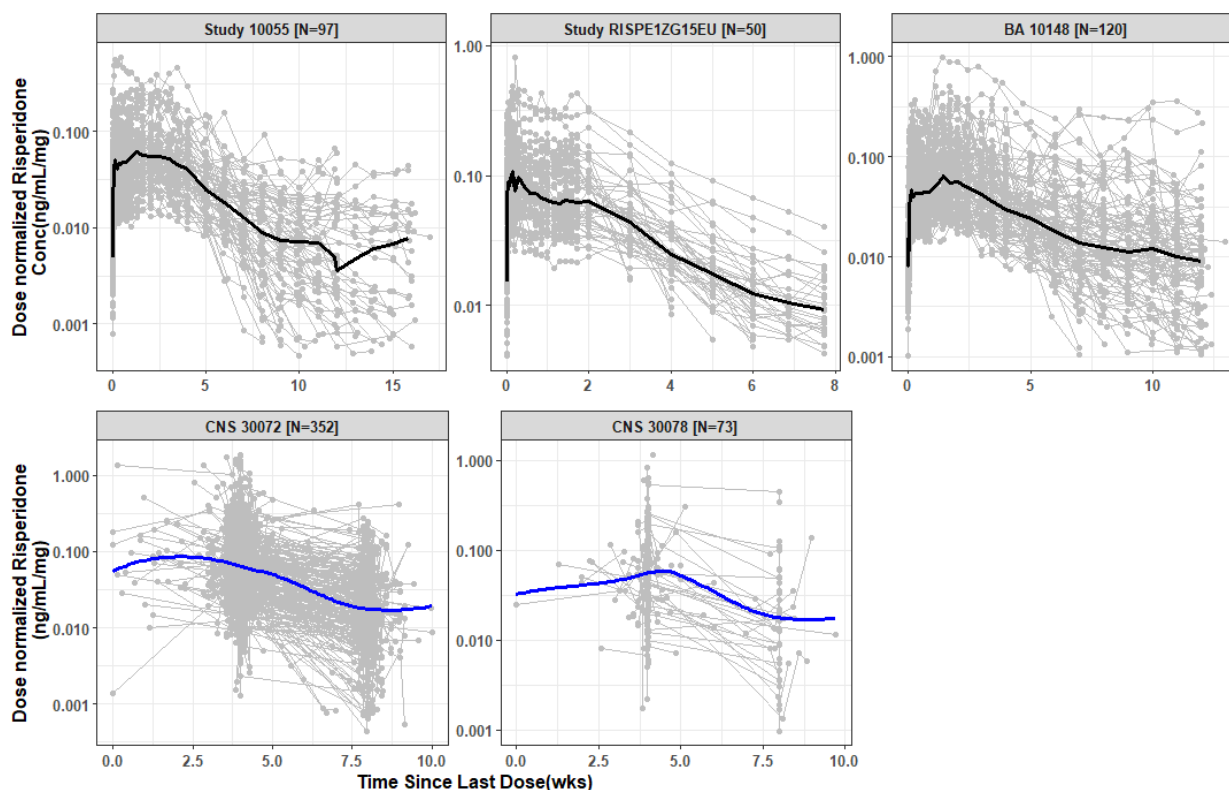
The reviewer was able to reproduce the Applicant's PopPK results with NONMEM, with no significant discordance identified. The Applicant's PopPK analysis is adequate for characterizing the PK profiles for risperidone, 9-OH risperidone and TAM.

Overview of Observed Data

Figure 18 and Figure 19 present individual measurable dose-normalized risperidone and 9-OH risperidone plasma drug concentration, respectively, versus time after last dose (semi-log), stratified by study. Doses are normalized by the average daily dose to ensure comparability between q1m and q2m regimens. For single dose and q1m regimens, concentrations are normalized by dose/28 days. For q2m regimens, concentrations are normalized by dose/56 days.

These plots indicate a mostly slow absorption after TV-46000 administration with maximum concentrations being reached after approximately 1 to 2 weeks, with early peaks for selected subjects in Study RISPE1ZG15EU. No evidence of dose dumping was observed in PK data collected for TV-46000.

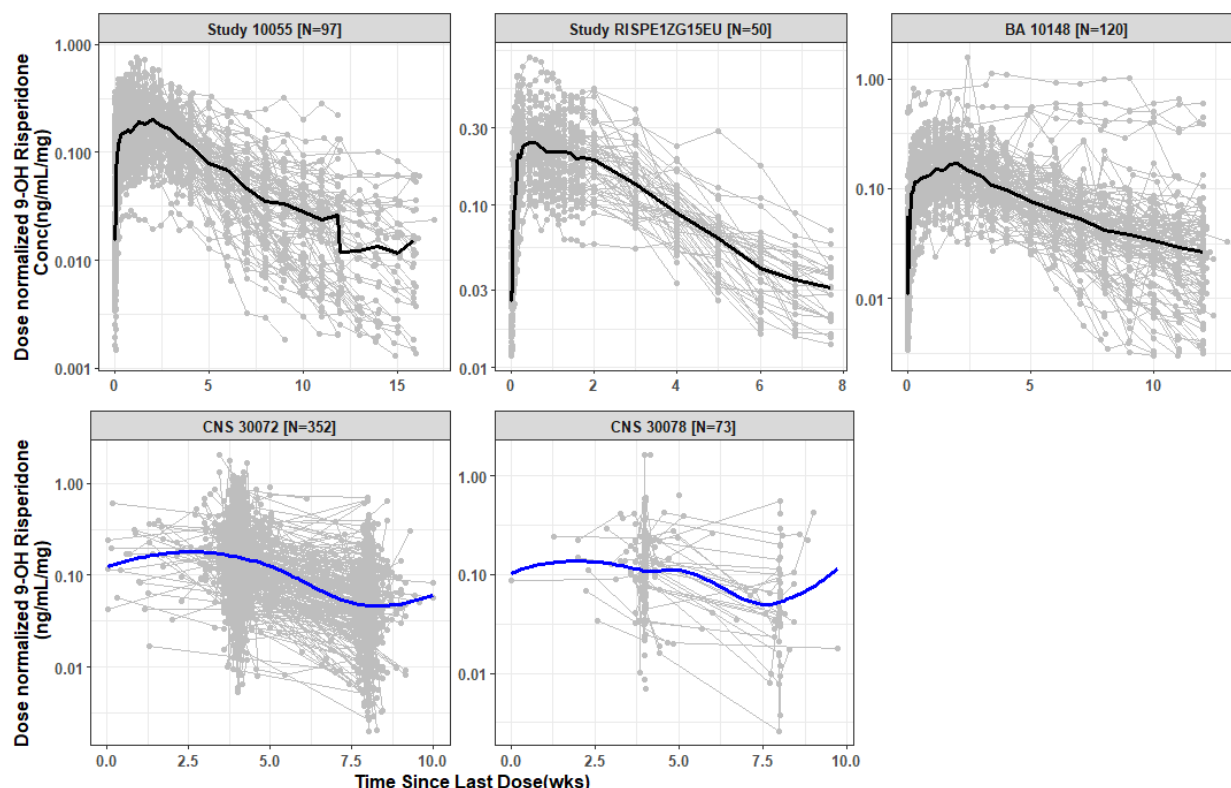
Figure 18: Dose-Normalized Risperidone Concentration Versus Time After Dose by Study



Note: Observed values are indicated by solid grey circles, the black solid lines represent the observed medians, and the blue solid lines represent loess smooth lines

Source: Reviewer's Analysis

Figure 19 : Dose-Normalized 9-OH Risperidone Concentration Versus Time After Dose by Study



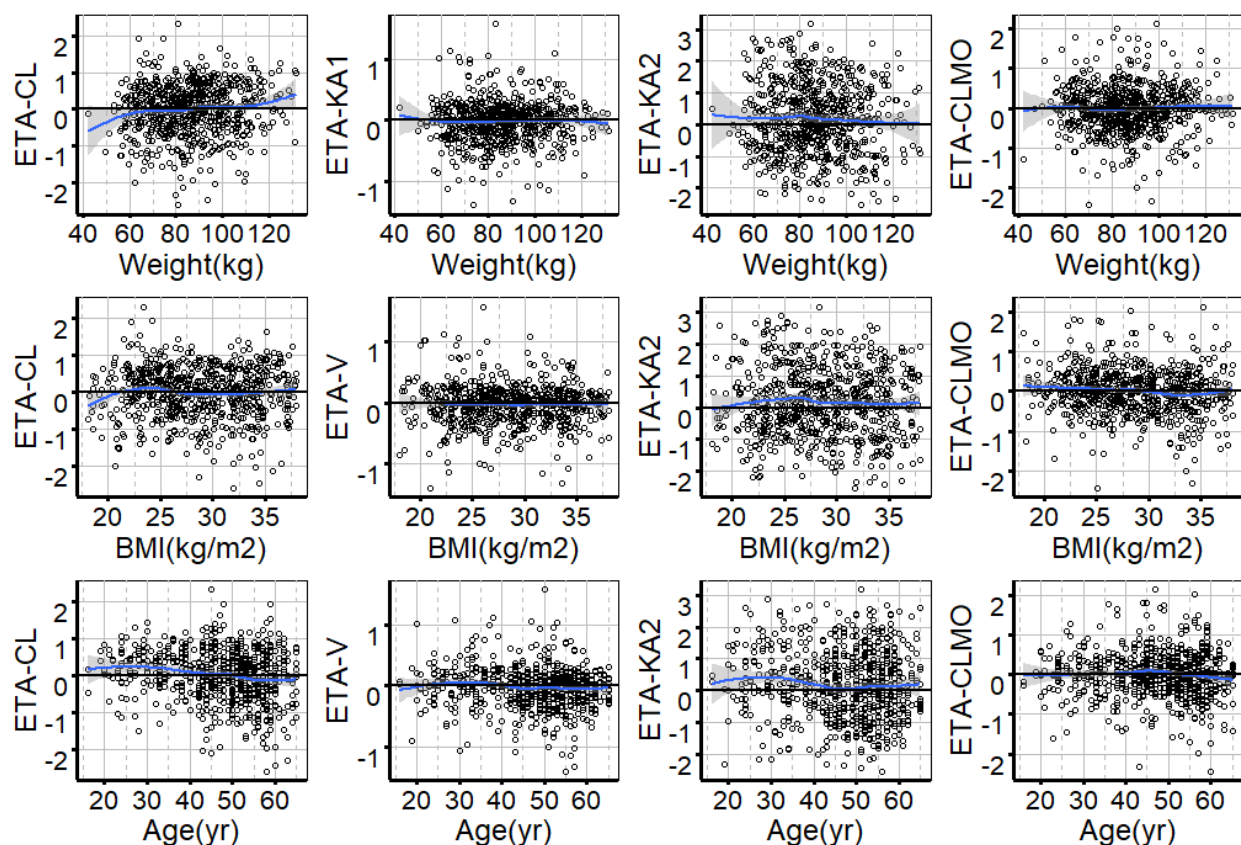
Note: Observed values are indicated by solid grey circles, the black solid lines represent the observed medians, and the blue solid lines represent loess smooth lines

Source: Reviewer's Analysis

Evaluation of PopPK Analysis

The impact of age, sex, race, bodyweight and CYP2D6 metabolizer status on the PK of risperidone and 9-OH risperidone were investigated. No clear trends in change in ETA with these covariates were observed with BMI allometric scaling in the final PopPK models (Figure 20 and Figure 21). Therefore, after inclusion of BMI in the final parent PopPK model, age, sex and bodyweight were not found to influence PK of risperidone and 9-OH risperidone. According to the PopPK results, poor CYP2D6 metabolizer status is associated with relatively lower risperidone clearance, and the apparent clearance for metabolite (CLMO) for 9-OH-risperidone is typically higher in subjects with poor CYP2D6 metabolizer status (Figure 21).

Figure 20: Individual Random Effects versus Weight, BMI and Age for Final PopPK Models

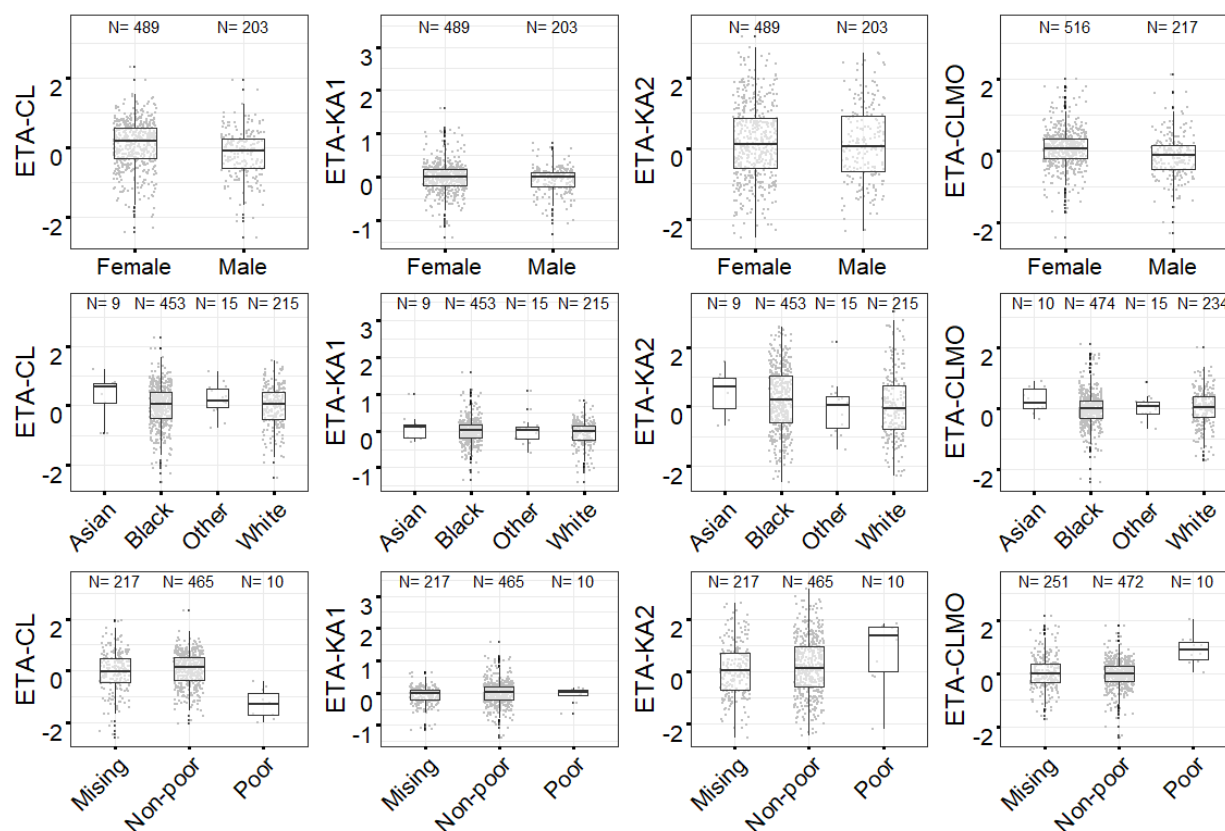


CL = apparent clearance; KA1 = absorption rate constant route 1; KA2 = absorption rate constant route 2; CLMO=apparent clearance metabolite

Source: Reviewer's Analysis

Figure 21 : Individual Random Effects versus Sex, Race, CYP2D6 Metabolizer Status and for Final PopPK Models

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213586
Uzedy (risperidone extended release injection)



CL = apparent clearance; KA1 = absorption rate constant route 1; KA2 = absorption rate constant route 2; CLMO=apparent clearance metabolite

Source: Reviewer's Analysis

To evaluate the dose regimen switching recommendation in the label, the reviewer conducted simulation by sampling with replacement from the 672 subjects from Applicant's phase 3 clinical studies including Study TV-46000-CNS-30072 and Study TV-46000-CNS-30078 (N=1000). (Figure 6).

Listing of Analyses Codes and Output Files

File Name	Description	Location
Risperidone LAI pk analysis.R	PK and PopPK analysis file	M:\Review\NDA 213586-Risperidone\Reviewer\PK analysis\Rscript

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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