Certain information within this clinical study report has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

Note; This document was translated into English and the language in original document was Japanese.

PROTOCOL

<Title>

A Multicenter, Open-label, Long-term, Extension, Phase 3 Study to Evaluate the Safety and Efficacy of TVP-1012 at 1 mg in Early Parkinson's Disease Patients Not Treated with Levodopa

<Short Title>

A Phase 3, Long-term, Extension Study of TVP-1012 (1 mg) in Early Parkinson's Disease Patients

Sponsor: Takeda Pharmaceutical Company Limited

1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan

Study Number: TVP-1012/OCT-001

Amendment No Amendment 2

IND Number: Not Applicable **EudraCT Number** Not Applicable

Compound: TVP-1012 (INN: Rasagiline)

Date: 24 March 2016

Amendment History

Date	Amendment Number	Region
25 November 2014	First edition	All sites
16 December 2014	Amendment 1	All sites
24 March 2016	Amendment 2	All sites

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

A separate contact information list will be provided to each site.

1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

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2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor:
Takeda Pharmaceutical Company Limited</td><td colspan="2">Compound:
TVP-1012</td></tr>
<tr><td>Title of Protocol:
A Multicenter, Open-label, Long-term, Extension, Phase 3 Study to Evaluate the Safety and Efficacy of TVP-1012 at 1 mg in Early Parkinson's Disease Patients Not Treated with Levodopa
(An extension study from TVP-1012/CCT-001)</td><td>IND No.:
Not applicable</td><td>EudraCT No.:
Not applicable</td></tr>
<tr><td colspan="2">Study Number: TVP-1012/OCT-001</td><td colspan="2">Phase: 3</td></tr>
<tr><td colspan="4">Study Design:
This is a multicenter, open-label, long-term, extension, phase 3 study to evaluate the safety and efficacy of long-term administration of TVP-1012 at 1 mg for another 26 weeks in patients with early Parkinson’s disease who have completed the 26-week treatment period in the preceding TVP-1012/CCT-001 study. Among participants of the TVP-1012/CCT-001 study, those consenting to participate in this study prior to undergoing the tests, observations, and assessments at Week 26 of the treatment period (VISIT 8) in the preceding study, and fulfilling the eligibility criteria will be enrolled in this study. From the day after the VISIT 8 of the preceding study, subjects will receive TVP-1012 1 mg once daily for 26 weeks in an unblinded manner.
The visit numbers in this study will be continued from the preceding study, and the study visit week will be counted from the start of the treatment period in the preceding study.
Patients will make a total of 7 visits in this study, i.e., at Weeks 26, 29, 32, 36, 40, 46, and 52 of the treatment period, to undergo designated tests, observations, and assessments.</td></tr>
<tr><td colspan="4">Primary Objective:
To evaluate the long-term safety of TVP-1012 (1 mg/day) in Japanese patients with early Parkinson’s disease</td></tr>
<tr><td colspan="4">Secondary Objective:
To evaluate the long-term efficacy of TVP-1012 (1 mg/day) in Japanese patients with early Parkinson’s disease</td></tr>
<tr><td colspan="4">Subject Population: Japanese patients with early Parkinson’s disease who have completed the 26-week treatment period in the preceding study</td></tr>
<tr><td colspan="2">Number of Subjects:
Approximately 182 continued from the preceding study</td><td colspan="2">Number of Sites:
Approximately 55 sites
(Same study sites as the preceding study)</td></tr>
</table>

Dose Levels: TVP-1012 (1 mg/day) once daily, either before or after breakfast (the timing of the dose must be the same as in the preceding study)	**Route of Administration:** Oral
Duration of Treatment: 26 weeks in total	**Period of Evaluation:** 26 weeks in total

Main Criteria for Inclusion:

- The subject has completed the preceding study.
- The subject has shown no safety issues during the study treatment in the preceding study, in the judgment of the investigator or sub-investigator.

Main Criteria for Exclusion:

- Subject has donated 400 mL or more of his or her blood volume within 90 days prior to the initiation of the investigational drug in this study.
- The subject is required to receive any of the excluded medications or treatments.
- The subject is required surgery or hospitalization for surgery during the study period.

Main Criteria for Evaluation and Analyses:

Primary endpoint

- Adverse events (AEs)

Secondary endpoints

- Clinical laboratory test values, vital signs, electrocardiogram (ECG), and weight
- MDS-UPDRS Part II + Part III total score

Statistical Considerations:

The analyses for this study will be performed using pooled data from the preceding study and this study, in principle, based on data obtained after administration of TVP-1012.

[Analysis methods for the primary endpoint]

The following analysis will be based on the safety analysis set.

A treatment-emergent adverse event (TEAE) is defined as an adverse event whose date of onset occurs on or after the start of treatment period study drug in the preceding study.

TEAEs whose date of onset occurs on or after the start of TVP-1012 will be coded using the MedDRA dictionary. The frequency distribution will be provided using the system organ class and the preferred term for each treatment group as follows:

- All TEAEs
- Drug-related TEAEs
- Intensity of TEAEs
- Intensity of drug-related TEAEs

- TEAEs leading to study drug discontinuation
- Serious TEAEs
- TEAEs over time

Sample Size Justification:

In the preceding study, the planned number of subjects to be randomized was a total of 240 (120 per group) and the planned number of subjects evaluable for the primary endpoint (change in the MDS-UPDRS Part II + Part III total score from baseline to Week 26 of the treatment period (LOCF)) was a total of 220 (110 per group).

Since this study is a long-term extension study in patients with early Parkinson's disease who have completed the 26-week treatment period in the preceding study, considering the potential dropouts in the preceding study, approximately 182 subjects will be enrolled in this study.

In addition, considering the potential dropouts in this study and in the preceding study, it is estimated that 155 subjects will be treated with 1 mg of TVP-1012 for 26 weeks and 59 subjects for 52 weeks.

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BUN	blood urea nitrogen
Cmax	maximum observed serum concentration
COMT	catechol-*O*-methyltranferase
CRO	contract research organization
CYP	Cytochrome P-450
FDA	Food and Drug Administration
GCP	Good Clinical Practice
γ-GTP	γ-glutamyl transpeptidase
hCG	human chorionic gonadotropin
ICH	International Conference on Harmonisation
INN	international nonproprietary name
INR	international normalized ratio
LDH	lactate dehydrogenase
MAO	Monoamine oxidase
MDS	Movement Disorders Society
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
PDQ-39	The 39-item Parkinson's disease questionnaire
PMDA	Pharmaceuticals and Medical Devices Agency
PT	preferred term
PTE	pretreatment event
QOL	quality of life
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
UPDRS	unified Parkinson's disease rating scale
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Parkinson's disease is the second most common neurodegenerative disorder of the central nervous system after Alzheimer's disease. The prevalence of Parkinson's disease is estimated to be 100-150/100,000 in the Japanese population, mostly affecting elderly people with peak age in the late 50s to 60s [1]. A significant increase in the number of patients is expected as the population ages in the future.

The 4 major symptoms of Parkinson's disease are resting tremor, muscle rigidity (muscle stiffness), bradykinesia, and postural instability. These motor symptoms are suspected to occur due to damage or death of substantia nigra dopaminergic neurons in the midbrain, followed by a reduction in dopamine volume in the striatum.

The Japanese therapeutic guideline recommends initially treating motor symptoms of Parkinson's disease with levodopa or a dopamine agonist, in principle, and rich evidence with these drugs used as first-line therapy are available [2].

In clinical practice overseas, the efficacy of initial treatment with MAO-B inhibitors has been demonstrated in Parkinson's disease and the therapeutic algorithm recommends MAO-B inhibitors as the first-line treatment for mild Parkinson's disease in addition to levodopa and dopamine agonists [3][4]. In Japan, selegiline is one of the MAO-B inhibitors available but not approved for first-line treatment of Parkinson's disease. If clinical development of MAO-B inhibitors is promoted in Japan, treatment options for patients with mild or early Parkinson's disease may expand.

TVP-1012 (INN: rasagiline) is a MAO-B inhibitor without an amphetamine structure. In comparison with selegiline, TVP-1012 is characterized by (1) a 5 to 10-fold MAO-B inhibitory effect, and (2) easy drug management due to not having an amphetamine structure and not being designated as ingredient in narcotics. As of September, 2014, rasagiline has been approved in 53 countries in Europe, the United States, and East Asian countries as a monotherapy for early Parkinson's disease, and also as concomitant therapy with levodopa for Parkinson's disease. Currently, clinical development for TVP-1012 as monotherapy for early Parkinson's disease and as an add-on therapy to levodopa for Parkinson's disease is ongoing in Japan.

[redacted]

[redacted]

[redacted]

Efficacy Summary

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Safety Summary

[redacted]

[redacted]

4.2 Rationale for the Proposed Study

[redacted]

Based on these results, this study was planned to evaluate the efficacy and safety of long-term extension administration with TVP-1012 in Japanese patients with early Parkinson's disease who have completed the preceding study (TVP-1012/CCT-001). The comprehensive evaluation of the efficacy and safety of TVP-1012 in early Parkinson's disease will be performed based on the results of this study, Study TVP-1012/CCT-001, and overseas clinical studies.

The clinical development of TVP-1012 as an add-on to levodopa for Parkinson's disease is ongoing in Japan. Currently, a Phase 2/3 study (TVP-1012/CCT-002) and a Phase 3 study (TVP-1012/OCT-002) are underway.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective(s)

- To evaluate the long-term safety of TVP-1012 (1 mg/day) in Japanese patients with early Parkinson's disease

5.1.2 Secondary Objectives(s)

- To evaluate the long-term efficacy of TVP-1012 (1 mg/day) in Japanese patients with early Parkinson's disease

5.2 Endpoints

5.2.1 Primary Endpoint

- Adverse events (AEs)

5.2.2 Secondary Endpoints

- Clinical laboratory test values, vital signs, electrocardiogram (ECG), and weight
- Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II＋Part III total score

5.2.3 Additional Endpoints

- MDS-UPDRS Part I total score
- MDS-UPDRS Part II total score
- MDS-UPDRS Part III total score
- MDS-UPDRS Part IV total score
- MDS-UPDRS tremor score
- MDS-UPDRS bradykinesia score
- MDS-UPDRS muscle rigidity score
- MDS-UPDRS individual score
- Parkinson's Disease Questionnaire-39 (PDQ-39) Summary Index scores for individual domain

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

Patients will make a total of 7 visits in this study, i.e., at Weeks 26, 29, 32, 36, 40, 46 and 52 of the treatment period, to undergo designated tests, observations, and assessments.

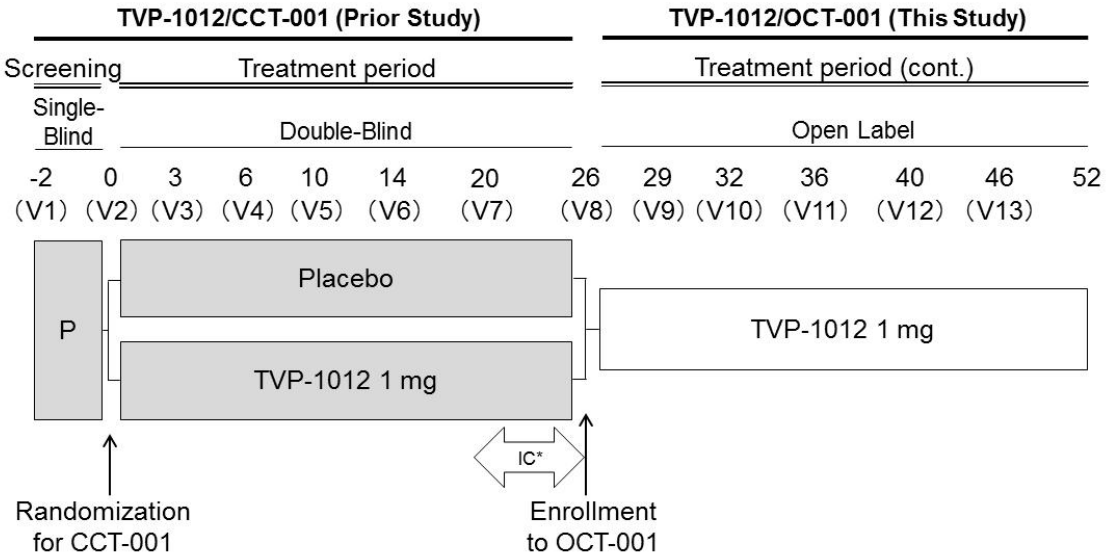
This is a multicenter, open-label, long-term, extension, phase 3 study to evaluate the safety and efficacy of long-term administration of TVP-1012 at 1 mg for another 26 weeks in patients with early Parkinson's disease who have completed the 26-week treatment period in the preceding TVP-1012/CCT-001 study.

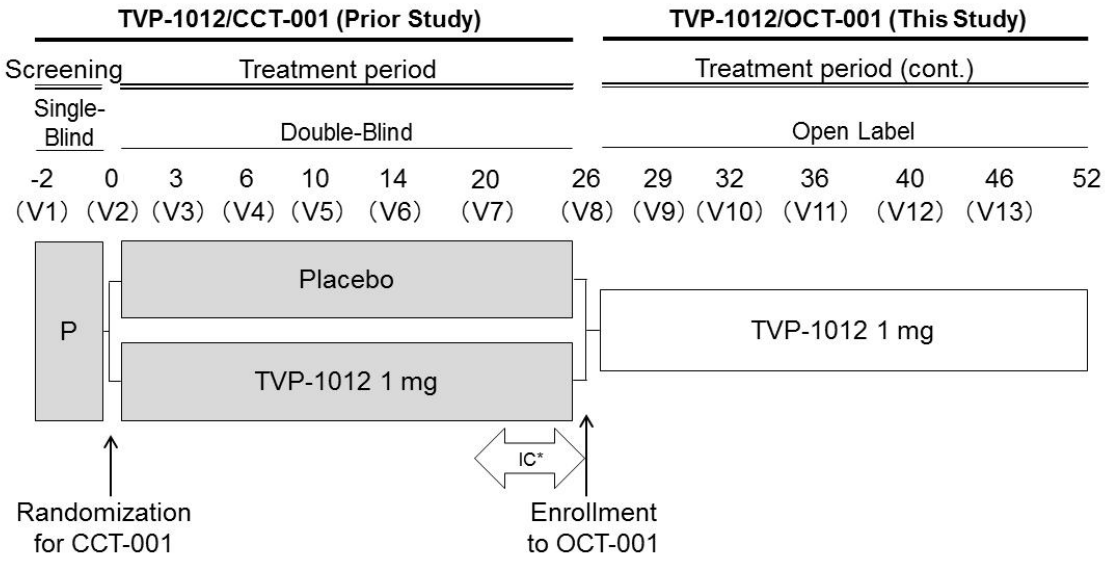
Among participants of the TVP-1012/CCT-001 study, those consenting to participate in this study prior to undergoing the tests, observations, and assessments at Week 26 of the treatment period (VISIT 8) in the preceding study, and fulfilling the eligibility criteria will be enrolled in this study. From the day after the VISIT 8 of the preceding study, subjects will receive TVP-1012 1 mg once daily for 26 weeks in an unblinded manner.

The visit numbers in this study will be continued from the preceding study, and the study visit week will be counted from the start of the treatment period in the preceding study.

This study will be conducted in the same study sites as those of the preceding study (55 sites) and the number of subjects to be enrolled in this study is estimated to be 182 subjects after considering dropouts in the preceding study.

Schematic of Study Design is included as Figure 6.a. A schedule of study procedures is listed in Appendix A.





V: VISIT
* Informed consent for this study must be obtained prior to tests, observations, and assessments at Week 26 of the treatment period in the preceding study. Those who consent to participate in this study and fulfilling the eligibility criteria will be enrolled in this study. Subjects will start dosing from the day after the VISIT 8.

Figure 6.a Schematic of Study Design

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Justification for Study Subject

To evaluate the safety and efficacy of long-term administration of TVP-1012 in Japanese patients with early Parkinson's disease, this study will target subjects who have completed the preceding study and were assessed as not demonstrating safety concerns in the opinion of the investigator or sub-investigator.

6.2.2 Justification for Study Design

This open-label, long-term extension study has a common study design that allows for the evaluation of long-term safety. This study was designed as an extension study following the preceding study, to collect pertinent data on long-term administration in an efficient manner.

See Section 13.3 for Sample Size Justification.

6.2.3 Justification for Dose Regimen

[redacted]

In the preceding study, 1 mg of TVP-1012 or placebo was administered for 26 weeks to evaluate the efficacy and safety of TVP-1012 1 mg.

In this study, the dose of 1 mg of TVP-1012 will be maintained for subjects treated with 1 mg of TVP-1012 in the preceding study, to evaluate administration at 1 mg for 52 weeks. In addition, subjects treated with placebo in the preceding study will be switched to 1 mg of TVP-1012 in this study, to evaluate administration at 1 mg for 26 weeks, for the purpose of evaluating a large number of subjects as much as possible.

[redacted]

[redacted]

6.2.4 Justification for Treatment Period

Parkinson's disease is a progressive disease and long-term administration is anticipated when TVP-1012 is prescribed. Therefore, another 26-week extension of treatment was planned following the 26-week treatment in the preceding study to evaluate the long-term safety of TVP-1012 for 6 months and 12 months.

6.2.5 Justification for Endpoints

In this study, the long-term safety and efficacy of TVP-1012 following the preceding study will be evaluated. As the safety and efficacy will be evaluated in pooled data from this and preceding studies, the same endpoints used for the preceding study were set.

Safety evaluation is the primary objective of this study. Of the safety evaluation variables in the preceding study, the frequency of adverse events (AEs) will be used as the primary endpoint and clinical laboratory test results, vital signs, ECGs, and weight will be used for the assessment of secondary endpoints.

In addition, MDS-UPDRS Part II + Part III total score, which was the primary efficacy endpoint in the preceding study, will be used as a secondary endpoint. The efficacy endpoints in the preceding study other than MDS-UPDRS Part II + Part III total score will be set as additional endpoints.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.

- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB) or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to the administration of the investigational drug.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. In the opinion of the investigator or sub-investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject has completed the preceding study (TVP-1012/CCT-001 study).
4. The subject has shown no safety issues during the study treatment in the preceding study, in the judgment of the investigator or sub-investigator.
5. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent to 1 month after the last dose of the investigational drug.

*Definition of female subjects of chiledbearing potential is defined in Section 9.1.10.
Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.11.

[Justification of Inclusion Criteria]

1, 2 : These criteria were set to include subjects who understand the objective of the study and will cooperate in the study conduct.
3 : This criterion was set as this study is designed to conduct with subjects who have completed the 26-week treatment period in the preceding study.
4 : This criterion was set in consideration of subject safety.
5 : This criterion was set in consideration of safety risk associated with pregnancy.

7.2 Exclusion Criteria

Any subject who meets the following criteria will not qualify for entry into the study:

1. The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
2. Subject has donated 400 mL or more of his or her blood volume within 90 days prior to the initiation of the investigational drug in this study.
3. The subject is required to receive excluded medications or treatments.
4. If female, the subject is intending to become pregnant during, or within 1 month after the last dose of the investigational drug; or intending to donate ova during such time period.
5. The subject requires surgery or hospitalization for surgery during the study period.
6. The subject who, in the opinion of the investigator or sub-investigator, is unsuitable for any other reason.

[Justification of Exclusion Criteria]

1, 5 : These criteria were set as basic matters to conduct clinical studies.
2 : This criterion was set as basic matters to conduct clinical studies in consideration of subject safety.
3 : This criterion was set in consideration of efficacy evaluation and subject safety.
4 : This criterion was set to avoid the safety risk associated with pregnancy to pregnant woman and fetus.
6 : This criterion was set to exclude subjects with unknown factors which might influence the evaluation of efficacy.

7.3 Excluded Medications and Treatments

The list of excluded medications and treatments is shown in Table 7.a. Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator or sub-investigator.

Table 7.a Excluded Medications and Treatments

Medication/Treatment	Duration	Exception
Excluded Medication		
(1) selegiline	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(2) pethidine, tramadol	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(3) reserpine, methyldopa	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(4) Other investigational drug	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(5) levodopa containing drug (6) Dopamine agonist (7) amantadine (8) Anticholinergic agent	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(9) COMT inhibitor (10) droxidopa (11) zonisamide (12) istradefylline	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(13) Psychoneurotic agent (phenothiazine, butyrophenone, benzamide, Atypical antipsychotic drug)	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	Quetiapine may be concomitantly administrered without change in dose regimen throughout the study if the drug has been continuously administered in the preceding study.
(14) Antinauseant with dopamine agonistic property	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	domperidone may be concomitantly administered without change in dose regimen throughout the study if the drug has been continuously administered in the preceding study.
(15) CYP1A2 inhibitor (including ciprofloxacin, enoxacin, fluvoxamine, zafirlukast)	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_

Medication/Treatment	Duration	Exception
(16) dextromethorphan	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(17) Antidepressant	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(18) St. John's Wort (including supplements)	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(19) Narcotic analgesic agent (excluding ≤ 1% of codeine, dihydrocodeine)	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
Excluded Treatment		
(20) Neurosurgical intervention (Pallidotomy, Thalamotomy, deep brain stimulation)	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(21) Transcranial magnetic stimulation	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_

Medications/treatments for AEs during the study period may be administered, provided that these treatments do not deviate from the above range. If a drug listed above is chosen as routine medication after study completion, this medication should be administered following a reasonable interval as needed, based on the precautions for use for each drug.

[Justification of Excluded Medications and Treatments]

(1), (2), (18), (19)
These criteria were set to ensure the safety of subjects, in consideration of adverse drug reactions due to concomitant use.

(3), (13), (14)
These criteria were set since there is a possibility of worsening Parkinsonism, which may affect the efficacy evaluation of TVP-1012; however, some drugs may be used concomitantly, if these drugs do not affect the efficacy evaluation of TVP-1012.

(4)-(12), (20), (21)
These criteria were set because they could influence the evaluation of efficacy.

(15) This criterion was set due to the effect on the pharmacokinetics of TVP-1012, considering the metabolic pathway mainly via CYP1A2.

(16) This criterion was set to ensure the safety of subjects, in consideration of possibly elevating serotonin level due to concomitant use.

(17) This criterion was set to ensure the safety of subjects and to minimize the effect on the efficacy evaluation due to mutually potentiated pharmacological action with concomitant use.

7.4 Diet, Fluid, Activity Control

The investigator, sub-investigator, or study coordinator will give subjects the following instructions:

1. Subjects should be punctual for visit appointments and undergo the physical examinations and prescribed tests. Subjects should also contact the investigator, sub-investigator or study coordinator promptly if they cannot visit the site as planned.
2. Subjects should contact the investigator, sub-investigator, or study coordinator by telephone, etc., to ask for instructions immediately after symptoms worsen between planned visits.
3. Subjects should follow instructions regarding treatment adherence provided by the investigator or sub-investigator. Subjects should visit the site after taking the study drug on planned visit days.* If the subject does not comply with treatment procedures, the subject must report this to the investigator, sub-investigator, or

study coordinator at the next visit. Unused study drug(s) and drug sheet(s) (blister sheet) should be returned at the next visit.

* For the day the serum chemistry is scheduled, the study medication must be taken without having breakfast. In this case, deviation from the original dose timing (not before or after breakfast) will be permitted.

4. Subjects are not allowed to take any medications other than drugs prescribed by the investigator or sub-investigator, including over-the-counter products, without first consulting with the investigator (except for emergency use).
5. If a subject visits another medical institution from signing of the informed consent to 1 month after the last administration of the investigational drug, the investigator should notify the primary care physician that the subject was participating in a clinical study.
6. If a subject visits another medical institution from signing of the informed consent to 1 month after the last administration of the investigational drug, the investigator or sub-investigator should be informed of the circumstances and therapy.
7. On the days on which clinical serum chemistry tests are scheduled, blood must be collected in fasted state (≥ 8 hours), whenever possible.
8. A female subject of childbearing potential who is sexually active with a nonsterilized male partner must agree to use routinely adequate contraception from signing of informed consent to 1 month after the last dose of the investigational drug.
9. Excessive eating, drinking, exercise and drastic change of the meal are not allowed during the study period.
10. Blood donation is not allowed from the start of the investigational drug administration until at least 1 month after the last administration of the investigational drug. Subject must immediately report the blood donation during this period, if any, to the investigator.
11. Subjects should avoid driving vehicles, operating machinery, and working in high areas, etc., in consideration of possible treatment-emergent dizziness, or reduced attention, concentration, or reflex function.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study should be recorded in the case report form ([e]CRF) using the following categories. For screen failure subjects, refer to Section 9.1.15.

1. **Pretreatment Event or AE**
   The subject has experienced a pretreatment event (PTE) or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

- Liver Function Test (LFT) Abnormalities
- Study medication should be discontinued immediately with appropriate clinical follow-up until a subject's laboratory profile has returned to normal or the value immediately after the informed consent (for PTEs), or the value before the initiation of the investigational drug* (for AEs). (See Section 9.1.9) if the following circumstances occur at any time during study medication treatment:

  * The value before the initiation of the study medication is defined as the value prior to the start of the run-in period in the preceding study for AEs occurred before first study medication administration in the treatment period in the preceding study, and as the value at baseline in the preceding study for AEs occurred after first study medication administration in the treatment period in the preceding study.

  - ALT or AST > 8 × ULN, or
  - ALT or AST > 5 × ULN and persists for more than 2 weeks, or
  - ALT or AST > 3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) > 1.5, or
  - ALT or AST > 3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

2. **Significant protocol deviation**
   The discovery after the first dose of study medication that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

3. **Lost to follow-up**
   The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.

4. **Voluntary withdrawal**
   The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the (e)CRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE or lack of efficacy).

5. **Study termination**
   The sponsor, IRB, or regulatory agency terminates the study.

6. **Pregnancy**
   The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.11.

7. **Lack of efficacy**
   The investigator or sub-investigator has determined that the subject is not benefiting from investigational treatment; and, continued participation would pose an unacceptable risk to the subject.

8. **Other**

   Note: The specific reasons should be recorded in the "specify" field of the (e)CRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator or sub-investigator may terminate a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator or sub-investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to all or any of the drugs defined below.

(1) Dosage Form and Manufacturing

Drug substance code number: TVP-1012
Nonproprietary name: rasagiline (INN)
Chemical name: *N*-propargyl-1-(*R*)-aminoindan mesylate

Table 8.a Study Medication

Type of the drug	Dosage form
TVP-1012 1 mg tablet	A white to yellowish white round shape tablet containing rasagiline, engraved with '[redacted] on one surface.

All the study medication were manufactured in [redacted]

(2) Packaging and Labeling

Ten tablets of the TVP-1012 1 mg are encapsulated in an aluminum blister sheet and 19 sheets of the TVP-1012 1 mg tablet are packed in a carton.

The label affixed to the carton containing the investigational drug should include a description that the content is an investigational drug, name of the drug "TVP-1012 1.0 mg tablet", study number "TVP-1012/OCT-001", the name and address of the sponsor, manufacturing number, number of the drugs, and storage.

8.1.2 Storage

The investigational drug must be stored at 1°C to 30°C.

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational drug must be stored under the conditions specified on the label, and remain in the

original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

The administration of the study medication will start on the day after VISIT 8 and the subjects will be orally administered 1 tablet of TVP-1012 1.0 mg once daily before or after breakfast (at the same timing with the preceding study).

The investigator or its designee will supply sufficient amount of the study medication required during the period between study visits. Subjects will be instructed to take study medication in the morning of study visits* and to bring unused study medications and blister sheets to the site at each study visit. Also, compliance of the study medication from the last study visit will be checked by the investigator or sub-investigator (see Section 9.2).

* For the day the serum chemistry is scheduled, the study medication must be taken without having breakfast. In this case, deviation from the timing of dose (not before or after breakfast) will be permitted.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the (e)CRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0, PRETREATMENT EVENTS AND ADVERSE EVENTS.

Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Investigational Drug Assignment and Dispensing Procedures

The same investigational drug is used for all subjects at each study site where the study is conducted. The investigator or sub-investigator will assign the investigational drug allocated to each study site to the subjects according to the study procedure.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

Upon receipt of the procedures for handling, storage, and management of the investigational drug prepared by the sponsor, the investigational drug manager will appropriately manage all the drugs supplied by the sponsor. The investigator will also receive the same procedures from the sponsor. The procedures will define the processes necessary to ensure that receipt, handling, storage, management, and prescription of the sponsor-supplied drugs, as well as collection of the unused drugs from subjects and return to the sponsor or disposal of unused drugs should be performed appropriately and reliably.

The investigational drug manager will return unused drugs to the sponsor immediately after the completion of the clinical study at the study site.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or sub-investigator whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to tests, observations and evaluations at Week 26 (VISIT 8) in the preceding study.

The same identification code provided in the preceding study will be assigned and will be used throughout the study period.

9.1.2 Demographics, Medical History, and Medication History Procedure

The same demographic information, medical history and medication history obtained in the preceding study will be used in this study.

9.1.3 Physical Examination Procedure

A physical examination will consist of the following body systems:

(1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) other.

All subsequent physical examinations should assess clinically significant changes from the values obtained at baseline (VISIT 2).

9.1.4 Skin Examination

A subject should be confirmed as not having melanoma in accordance with separately prepared study procedures. If melanoma is suspected, this subject must visit a dermatologist.

9.1.5 Weight

Weight will be collected in kilograms to 1 decimal place.

9.1.6 Vital Sign Procedure

Vital signs will include body temperature (infra-axillary measurement), sitting systolic/diastolic (mmHg) blood pressure after resting more than 5 minutes, and pulse (bpm).

9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda and all medication including vitamin supplements, over-the-counter medications, oral herbal preparations, and St. John's Wort must be recorded in the (e)CRF. If any antiparkinsonian drug is taken, its dosage and unit per day must be obtained.

9.1.8 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent in the preceding study. Concurrent medical conditions for this study are those investigated in the preceding study.

9.1.9 Procedures for Clinical Laboratory Samples

Table 9.a lists the samples to be collected for each laboratory test. All samples will be collected after fasted for more than 8 hours, whenever possible, in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 6 mL.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells	AST	Protein (qualitative)
Hemoglobin	ALT	Glucose (qualitative)
Hematocrit	γ-GTP	Blood (qualitative)
White blood cells with differential (neutrophil, eosinophil, monocyte, lymphocyte, and basophil)	ALP	Ketone body (qualitative)
	LDH	
	Albumin	
	Total protein	
	Total bilirubin	
Platelets	Total cholesterol	
	Triglycerides	
	Creatinine	
	Blood urea nitrogen (BUN)	
	Urine acid	
	Creatine kinase	
	Sodium	
	Potassium	
	Chlorine	
	Calcium	
	Phosphorus	
Pregnancy Test (for female subjects of childbearing potential only)		
Urine hCG (qualitative)		

The central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. However, the urine hCG (qualitative) will be performed at each study site for women with childbearing potential.

If subjects experience ALT or AST > 3 × ULN, follow-up laboratory tests (at a minimum, serum ALP, ALT, AST, total bilirubin, γ-GTP, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted. (see Section 7.5 and 10.2.3)

If the ALT or AST remains elevated > 3 × ULN on these 2 consecutive occasions, the investigator or sub-investigator must contact the sponsor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies.

The laboratory test results will be evaluated and maintained by the investigator or sub-investigator. And also, the investigator will maintain a copy of the reference ranges for the laboratory used.

9.1.10 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 1 month after last dose of study medication, female subjects of childbearing potential who are sexually active or before menopause with a nonsterilized male partner must use adequate contraception. In addition they must be advised not to donate ova during this period. Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova during the course of the study. During the course of the study, regular urine hCG pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Appendix A).

Subjects also must have a negative urine hCG pregnancy test at each evaluation point.

9.1.11 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued.

If the pregnancy occurs during administration of active study medication, after the end of run-in period of the preceding study and within 1 month of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the Safety Information Emergency Call Center (contact listed specified in the appendix).

Should the pregnancy occur during or after administration of blinded drug, the investigator or sub-investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator or sub-investigator.

If the female subject agrees to the primary care physician (gynecologist) being informed, the investigator or sub-investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.12 ECG Procedure

Standard 12-lead ECGs will be recorded under resting. The investigator or sub-investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The following parameters will be recorded on the (e)CRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval, and QTcB interval. QTcF will be calculated by the sponsor.

9.1.13 MDS-UPDRS

The investigator or sub-investigator will assess the symptoms of Parkinson's disease according to MDS-UPDRS (Part I: non-motor experiences of daily living, Part II: motor experiences of daily living, Part III: motor examination, Part IV: motor complications).

The investigator or sub-investigator (hereinafter referred to as "evaluator") responsible for evaluating MDS-UPDRS scores will undergo training on MDS evaluations prior to study conduct and should be accredited with a training certificate. Only evaluators with a training certificate are allowed to evaluate the MDS-UPDRS for the study.

The evaluator will not evaluate subjects until he/she receives a training certificate for MDS evaluations. If the assigned evaluator is replaced (or added) during the study, a new evaluator should complete the aforementioned training and receive a training certificate for MDS evaluations before starting evaluations in the study. If a new evaluator has already received a training certificate for MDS evaluations, re-training will not be mandatory.

In principle, the same subject will be evaluated by the same evaluator as in the preceding study throughout the study period. The evaluator will record evaluation results for each item in Table 9.b in the CRF.

Table 9.b MDS-UPDRS Score Sheet

Part I			3.1	**Speech**	**(0, 1, 2, 3, 4, UR)**
	Primary source of information	□ Patient □ Caregiver □ Patient and Caregiver	3.2	**Facial expression**	**(0, 1, 2, 3, 4, UR)**
			3.3a	**Rigidity-Neck[b]**	**(0, 1, 2, 3, 4, UR)**
			3.3b	**Rigidity-RUE[b]**	**(0, 1, 2, 3, 4, UR)**
1.1	**Cognitive impairment**	**(0, 1, 2, 3, 4, UR)**	3.3c	**Rigidity-LUE[b]**	**(0, 1, 2, 3, 4, UR)**
1.2	**Hallucinations and psychosis**	**(0, 1, 2, 3, 4, UR)**	3.3d	**Rigidity-RLE[b]**	**(0, 1, 2, 3, 4, UR)**
1.3	**Depressed mood**	**(0, 1, 2, 3, 4, UR)**	3.3e	**Rigidity-LLE[b]**	**(0, 1, 2, 3, 4, UR)**
1.4	**Anxious mood**	**(0, 1, 2, 3, 4, UR)**	3.4a	**Finger tapping-Right hand [c]**	**(0, 1, 2, 3, 4, UR)**
1.5	**Apathy**	**(0, 1, 2, 3, 4, UR)**	3.4b	**Finger tapping-Left hand [c]**	**(0, 1, 2, 3, 4, UR)**
1.6	**Features of DDS**	**(0, 1, 2, 3, 4, UR)**	3.5a	**Hand movements-Right hand [c]**	**(0, 1, 2, 3, 4, UR)**
			3.5b	**Hand movements-Left hand [c]**	**(0, 1, 2, 3, 4, UR)**
Questionnaire			3.6a	**Pronation-supination movements-Right hand [c]**	**(0, 1, 2, 3, 4, UR)**
	Who is filling out this questionnaire:	□ Patient □ Caregiver □ Patient and Caregiver	3.6b	**Pronation-supination movements-Left hand[c]**	**(0, 1, 2, 3, 4, UR)**
			3.7a	**Toe tapping-Right foot[c]**	**(0, 1, 2, 3, 4, UR)**
			3.7b	**Toe tapping-Left foot [c]**	**(0, 1, 2, 3, 4, UR)**
1.7	**Sleep problems**	**(0, 1, 2, 3, 4)**	3.8a	**Leg agility-Right leg [c]**	**(0, 1, 2, 3, 4, UR)**
1.8	**Daytime sleepiness**	**(0, 1, 2, 3, 4)**	3.8b	**Leg agility-Left leg[c]**	**(0, 1, 2, 3, 4, UR)**
1.9	**Pain and other sensations**	**(0, 1, 2, 3, 4)**	3.9	**Arising from chair**	**(0, 1, 2, 3, 4, UR)**
			3.10	**Gait**	**(0, 1, 2, 3, 4, UR)**
1.10	**Urinary problems**	**(0, 1, 2, 3, 4)**	3.11	**Freezing of gait**	**(0, 1, 2, 3, 4, UR)**
1.11	**Constipation problems**	**(0, 1, 2, 3, 4)**	3.12	**Postural stability**	**(0, 1, 2, 3, 4, UR)**
1.12	**Light headedness on standing**	**(0, 1, 2, 3, 4)**	3.13	**Posture**	**(0, 1, 2, 3, 4, UR)**
1.13	**Fatigue**	**(0, 1, 2, 3, 4)**	3.14	**Global spontaneity of movement[c]**	**(0, 1, 2, 3, 4, UR)**
Part II			3.15a	**Postural tremor-Right hand[a]**	**(0, 1, 2, 3, 4, UR)**
2.1	**Speech**	**(0, 1, 2, 3, 4)**	3.15b	**Postural tremor-Left hand[a]**	**(0, 1, 2, 3, 4, UR)**
2.2	**Saliva and drooling**	**(0, 1, 2, 3, 4)**	3.16a	**Kinetic tremor-Right hand[a]**	**(0, 1, 2, 3, 4, UR)**
2.3	**Chewing and swallowing**	**(0, 1, 2, 3, 4)**	3.16b	**Kinetic tremor-Left hand[a]**	**(0, 1, 2, 3, 4, UR)**
2.4	**Eating tasks**	**(0, 1, 2, 3, 4)**	3.17a	**Rest tremor amplitude-RUE[a]**	**(0, 1, 2, 3, 4, UR)**
2.5	**Dressing**	**(0, 1, 2, 3, 4)**	3.17b	**Rest tremor amplitude-LUE[a]**	**(0, 1, 2, 3, 4, UR)**
2.6	**Hygiene**	**(0, 1, 2, 3, 4)**	3.17c	**Rest tremor amplitude-RLE[a]**	**(0, 1, 2, 3, 4, UR)**
2.7	**Handwriting**	**(0, 1, 2, 3, 4)**	3.17d	**Rest tremor amplitude-LLE[a]**	**(0, 1, 2, 3, 4, UR)**
2.8	**Doing hobbies and other activities**	**(0, 1, 2, 3, 4)**	3.17e	**Rest tremor amplitude-Lip/jaw)[a]**	**(0, 1, 2, 3, 4, UR)**
2.9	**Turning in bed**	**(0, 1, 2, 3, 4)**	3.18	**Constancy of rest tremor[a]**	**(0, 1, 2, 3, 4, UR)**
2.10	**Tremor(a)**	**(0, 1, 2, 3, 4)**		Were dyskinesias present during examination?	□No □Yes
2.11	**Getting out of bed, a car, or a deep chair**	**(0, 1, 2, 3, 4)**		If Yes, did these movements interfere with ratings?	□No □Yes
2.12	**Walking and balance**	**(0, 1, 2, 3, 4)**			
2.13	**Freezing**	**(0, 1, 2, 3, 4)**		Hoehn and Yahr Stage	(0, 1, 2, 3, 4, 5)
Part III			**Part IV**		
3a	Is the patient on medication?	□No □Yes	4.1	**Time spent with dyskinesias**	**(0, 1, 2, 3, 4)**

3b	Patient's clinical state	□ON □OFF	4.2	**Functional impact of dyskinesias**	**(0, 1, 2, 3, 4)**
3c	Is the patient on Levodopa?	□No □Yes	4.3	**Time spent in the OFF state**	**(0, 1, 2, 3, 4)**
			4.4	**Functional impact of fluctuations**	**(0, 1, 2, 3, 4)**
3c1	If yes, minutes since last dose:	minutes	4.5	**Complexity of motor fluctuations**	**(0, 1, 2, 3, 4)**
			4.6	**Painful OFF-state dystonia**	**(0, 1, 2, 3, 4)**

0: Normal, 1: Slight, 2: Mild, 3: Moderate, 4: Severe, UR: Unable to Rate
Bolded items represent MDS-UPDRS scores by category. Scores for each bolded item will be added according to Parts and the total score of individual Parts (I to IV) will be calculated. Scores for (a), (b), and (c) will be added separately and (a) tremor score, (b) muscle rigidity score, and (c) akinesia/bradykinesia score will be calculated.

9.1.14 QOL assessment

PDQ-39 is a self-administered questionnaire for QOL. Prior to the assessment, subjects will be provided instructions on how to record PDQ-39 and assess QOL during 1 month prior to the day of the assessment. Answers to all questions will be documented in the CRF.

9.1.15 Documentation of Screen Failure

The investigator should complete the (e)CRF for the subject who signed the informed consent and withdrawn from the study before randomization.

For subjects discontinued the study before the initiation of the investigational drug in this study, the date of signing informed consent, date of birth, sex, eligibility, reason for withdrawal, AE assessment (if any, it must be collected as an AE occurred in the preceding study), concomitant medications, and the date of the last physical examination/evaluations must be recorded in the (e)CRF.

The primary reason for screen failure is recorded in the (e)CRF using the following categories:

- PTE/AEs
- Did not meet inclusion criteria or did meet exclusion criteria <specify reason>.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal <specify reason>.
- Study termination.
- Other <specify reason>.

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.16 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the study. If the subject is found to be not eligible for the study, the investigator or sub-investigator should record the primary reason for failure on the applicable (e)CRF.

9.2 Monitoring Subject Treatment Compliance

Subjects will be instructed to bring unused investigational drugs and blister sheets to the site at each study visit. Also, compliance of the study medication from the last study visit will be checked by the investigator or sub-investigator.

All subjects should be instructed about the dosing requirement during study contacts. If a subject is persistently noncompliant with the sponsor-supplied drugs (50% of the allocated medication for the period since the last visit), it may be appropriate to withdraw the subject from the study. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Study Entrance/Week 26 in Treatment Period

The subject informed consent must be obtained before initiation of tests/observations/evaluations scheduled at Week 26 (VISIT 8).

Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0, and subjects whose eligibility is confirmed will be enrolled in this study. See Section 9.1.15 for procedures for documenting screening failures.

Procedures to be completed at Week 26 (VISIT 8; Day 175 - 189) include:

- Dispense study medication

9.3.2 Treatment Period (Weeks 29, 32, 36, 40, and 46)

9.3.2.1 Week 29 (Treatment Period)

Week 29 (VISIT 9; Day 196-210) include:

- Physical Examination Procedure
- Vital Sign Procedure

- Documentation of Concomitant Medications
- Clinical laboratory tests (including pregnancy test for female subjects of child bearing potential)
- AE assessment
- Compliance of study medication
- Dispense investigational drug

9.3.2.2 Week 32 (Treatment Period)

Procedures to be completed at Week 32 (VISIT 10; Day 217-231) include:

- Physical Examination Procedure
- Vital Sign Procedure
- Documentation of Concomitant Medications
- Clinical laboratory tests (including pregnancy test for female subjects of child bearing potential)
- MDS-UPDRS
- AE assessment
- Compliance of study medication
- Dispense investigational drug

9.3.2.3 Week 36 (Treatment Period)

Procedures to be completed at Week 36 (VISIT 11; Day 245-259) include:

- Physical Examination Procedure
- Vital Sign Procedure
- Documentation of Concomitant Medications
- MDS-UPDRS
- AE assessment
- Compliance of study medication
- Dispense investigational drug

9.3.2.4 Week 40 (Treatment Period)

Week 40 (VISIT 12; Day 273-287) include:

- Physical Examination Procedure
- Weight
- Vital Sign Procedure
- Documentation of Concomitant Medications

- Clinical laboratory tests (including pregnancy test for female subjects of child bearing potential)
- ECG Procedure
- MDS-UPDRS
- QOL
- AE assessment
- Compliance of study medication
- Dispense investigational drug

9.3.2.5 Week 46 (Treatment Period)

Procedures to be completed at Week 46 (VISIT 13; Day 315-329) include:

- Physical Examination Procedure
- Vital Sign Procedure
- Documentation of Concomitant Medications
- Clinical laboratory tests (including pregnancy test for female subjects of child bearing potential)
- MDS-UPDRS
- AE assessment
- Compliance of study medication
- Dispense investigational drug

9.3.3 Week 52 (Treatment Period) or Early Termination

The following procedures will be performed in the last visit scheduled at Week 52 in the treatment period (VISIT 14; Day 357 - 371). For subjects who started the investigational drug adninistration in this study and are withdrawn from the study before the last visit at Week 52, the procedures scheduled at Week 52 should be performed within 7 days from the termination of study medication (the last administration day is defined as day 0), whenever possible.

- Physical Examination Procedure
- Skin examination
- Weight
- Vital Sign Procedure
- Documentation of Concomitant Medications
- Clinical laboratory tests (including pregnancy test for female subjects of child bearing potential)

- ECG Procedure
- MDS-UPDRS
- QOL
- AE assessment
- Compliance of study medication

For all subjects receiving study medication, the investigator must complete the End of Study (e)CRF page.

9.3.4 Post Study Care

The study medication will not be available upon completion of the subject's participation in the study.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in the preceding study but prior to administration of study medication of the run-in period of the preceding study; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses vs signs and symptoms:

Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator or sub-investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions (disease or symptom present before signing of the informed consent in the preceding study):

Pre-existing conditions (present at the time of signing of informed consent in the preceding study) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays etc.) immediately after signing of informed consent in the preceding study should NOT be recorded as PTEs unless related to study procedures. However, if a subject experiences an abnormality (e.g., internal bleeding due to blood collection) related to the procedures for the baseline tests/observations in the preceding study, the abnormality should be recorded as a PTE on the (e)CRF. If the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). The investigator or sub-investigator should ensure that the event term recorded captures the change in the condition (e.g., “worsening of hypertension”).

If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, the investigator or sub-investigator should ensure that the AE term recorded captures the change in the condition from Baseline (e.g. “worsening of…”). If a subject has a degenerative concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, the

investigator or sub-investigator should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Worsening of PTEs or AEs:

If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., worsening of…").

If the subject experiences a worsening or complication of an AE after any change in study medication (including change from a study medication for the CCT-001 study to that for the OCT-001), the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., worsening of…").

Changes in severity of AEs /Serious PTEs:

If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent in the preceding study are not considered PTEs or AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

Elective procedures performed where there is no change in the subject's medical condition (e.g., cosmetic surgery) should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator or sub-investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the (e)CRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the (e)CRF.

10.1.4 SAEs

A SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING*.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

*The term “life threatening” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress (ARDS)	Hepatic necrosis
Torsade de pointes/ventricular fibrillation/ventricular tachycardia	Acute liver failure
Malignant hypertension	Anaphylactic shock
Convulsive seizures (including convulsion and epilepsy)	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anemia	Pulmonary fibrosis (including interstitial pneumonia)
Toxic epidermal necrolysis/mucocutaneous syndrome (Stevens-Johnson syndrome)	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death
	Confirmed or suspected transmission of infectious agent by a medicinal product
	Confirmed or suspected endotoxin shock

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to the investigational drug will be assessed using the following categories:

Term	Definition	Clarification
Unrelated	This category applies to those adverse events which, after careful consideration, are clearly and incontrovertible due to extraneous causes (disease, environment, etc.)	This category applied to those adverse events which, after careful consideration, are clearly and incontrovertible due to extraneous causes (disease, environment, etc.)
Unlikely	In general, this category can be considered applicable to those adverse events which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug.	An adverse experience may be considered unlikely related if or when (must have 2): ・ It does not follow a reasonable temporal sequence from administration of the drug. ・ It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. ・ It does not follow a known pattern of response to the test drug. ・ It does not reappear or worsen when the drug is re-administered.
Possibly	This category applies to those adverse events for which, after carful medical consideration at the time they are evaluated, a connection with the test drug administration appears unlikely but cannot be ruled out with certainty.	An adverse experience may be considered possibly related if or when (at least 2 of the following): ・ It follows a reasonable temporal sequence from administration of the drug. ・ It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. ・ It follows a known pattern of response to the test drug.
Probably	This category applies to those adverse events which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the test drug.	An adverse experience may be considered probably related if or when (at least 3 of the followings): ・ It follows a reasonable temporal sequence from administration of the drug. ・ It could not be reasonable explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. ・ It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia). ・ It follows a known pattern of response to the test drug.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date

The date of onset of a PTE or an AE will be determined according to the following criteria.

PTE or AE	Date of onset
Signs, symptoms, and diseases (diagnoses)	The date on which the subject, the investigator or sub-investigator first noted the signs/symptoms of an AE.
Asymptomatic diseases	The date on which a definitive diagnosis is obtained through tests. The date on which a diagnosis is confirmed should be recorded, even when the test result indicates an old sign(s) of the disease, or an approximate time of onset.
Worsening of concurrent diseases or PTEs Worsening of AEs ovserved in the preceding study	The date on which the subject, the investigator or sub-investigator first noted the first worsening of disease/symptom.
For PTEs: cases in which normal values at the time of screening (i.e., the first test after signing of the informed consent) in the preceding study are abnormal at the subsequent test; For AEs: cases in which abnormal test values are found at the test after the start of administration of the investigational drug	The date on which a clinically abnormal laboratory parameter is observed.

For PTEs: cases in which abnormal test values are found at the first test after signing of the informed consent and they are found to have worsened at the subsequent test; For AEs: cases in which abnormal test values are found at the test after the start of administration of the investigational drug and they worsen at the subsequent test	The date on which a clinically obvious increase/decrease in a laboratory parameter is confirmed based on the time profile of the parameter.

10.1.9 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died. In the event that the stop date of AE/PTE is not comfirmed, AE/PTE will be determined to be continuing.

10.1.10 Frequency

Episodic AEs/PTE (e.g., constipation, diarrhoea, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Medication

Actions associated with the investigational drug will be classified or defined as follows:

Drug withdrawn	A study medication is stopped due to the particular AE (including discontinuation/withdrawal based on the subject's own judgment).
Dose not changed	The particular AE did not require stopping a study medication. Cases in which administration of the investigational drug is discontinued or the dose is reduced or increased because of an AE other than the particular AE. Cases in which administration of the investigational drug is discontinued or its dose is reduced for a reason other than the AE, e.g., inadvertent behavior by the subject.
Unknown	Only to be used if it has not been possible to determine what action has been taken because of loss of follow-up.
Not Applicable	A study medication was stopped for a reason other than the particular AE, or dosing with study medication was already stopped before the onset of the AE.

10.1.12 Outcome

The outcome of a PTE or an AE will be determined according to the following criteria:

Category	Criteria
Recovered/Resolved	・The sign and symptom disappeared or resolved. ・Subject returned to first assessment status (the value before the administration of the investigational drug*) in the preceding study for AEs, or the value at the first test after signing of the informed consent in the preceding study for PTEs.
Recovering/Resolving	・The intensity is lowered by one or more stages. ・The diagnosis or signs/symptoms has almost disappeared. ・The abnormal laboratory value improved, but has not returned to the normal range or to the value before the administration of the investigational drug* in the preceding study (for AEs) or the value at the first test after signing of the informed consent in the preceding study (for PTEs). ・The subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving" (no need to record the date of death).
Not recovered /not resolved	・There is no change in the diagnosis, signs or symptoms. ・The intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started. ・Is an irreversible congenital anomaly. ・The subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved" (no need to record the date of death).
Resolved with sequelae	・The subject recovered from an acute AE/PTE but was left with impairment which interrupts the subject's usual activities.
Fatal	・PTE/AE directly related to death "Direct relationship with the PTE/AE" means that the PTE/AE caused the death or apparently contributed to the death. ・Cases in which the outcome of the PTE/AE observed in the same subject is determined or assumed as not having directly caused the death are not documented as "fatal." ・If the outcome of the PTE/AE is "fatal," the date of death should be documented.
Unknown	・The course of the AE/serious PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

* "The value before the administration of the investigational drug" means the value at the start of the study medications in the run-in period in the preceding study for the PTE/AE occurred before the initiation of administration for the treatment period in the preceding study, and the value at baseline for the AEs occurred after initiation of the investigational drug for the treatment period in the preceding study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the preceding study and continue until the subject is first administered study medication in the run-in period in the preceding study. For subjects who discontinue prior to study medication administration in the run-in period in the preceding study, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication in this study. Routine collection of AEs will continue until tests scheduled at Week 52 in the treatment period (or at early termination).

AEs occurred between at the end of the last laboratory tests in the preceding study (TVP-1012/CCT-001) and before initiation of administration in this study will be collected as AEs occurred in the preceding study and any AEs observed in the preceding study will be monitored continuously throughout this study.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator or sub-investigator will assess whether any subjective AEs have occurred. A neutral question, such as “How have you been feeling since your last visit?” may be asked. Subjects may report AEs occurring at any other time during the study.

Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to the value at the first laboratory test after signing of informed consent of the preceding study or there is a satisfactory explanation for the change (persistent, irreversible PTE). Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline (to the value at the start of the run-in period for AEs occurred before the initiation of the study medications in the treatment period in the preceding study, or the value at baseline for AEs occurred after administration of the study medication in the treatment period in the preceding

study) or until there is a satisfactory explanation for the changes observed (persistent, irreversible PTE). All PTEs and AEs will be documented in the PTE/AE page of the (e)CRF, whether or not the investigator or sub-investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term
- Start and stop date
- Frequency
- Severity
- Investigator's opinion of the causal relationship between the event and administration of study medications (Unrelated, Unlikely, Possibly, Probably)
- Action concerning study medication
- Outcome of event
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure
- Seriousness

AEs and serious PTEs will be followed up until they have resolved or the investigator or sub-investigator judges that the follow-up is no longer necessary.

10.2.2 Collection and Reporting of SAEs

When a SAE occurs through the AE collection period it should be reported according to the following procedure. PTEs that meet the criteria for SAEs described in Section 10.1.4 will be reported in a same manner to that for SAEs.

A SAE should be reported to Safety Information Emergency Call Center (described in the separate contact information list) within 1 business day of first onset or subject's notification of the event. The investigator should submit the completed SAE form within 10 calendar days to Safety Information Emergency Call Center. Also the original document of a Takeda SAE form must be submitted to the sponsor.

The information to be reported within 1 business day should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious

- Subject identification number
- Investigator's or sub-investigator's name
- Name of the study medications
- Causality assessment (relationship with the study medication or study procedure)

Any SAE spontaneously reported to the investigator or sub-investigator following the AE collection period should be reported to the sponsor.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST > 3 × ULN and total bilirubin > 2 × ULN for which an alternative etiology has not been identified, the event should be recorded as a SAE and reported as per Section 10.2.2. The investigator or sub-investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B, other acute liver disease, or a history or concurrent medical condition. Follow-up laboratory tests as described in Section 9.1.9 must also be performed.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator or sub-investigator should complete a follow-up SAE form or provide other written documentation immediately to the sponsor or Safety Information Emergency Call Center. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested by the sponsor or IRB.

All SAEs should be followed up until resolution or permanent outcome of the event.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, IRBs, and the head of the study site, as applicable. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee (CRO), SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current

benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 CRFs (Electronic and Paper)

Completed (e)CRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to (e)CRFs. The sponsor will make arrangements to train the investigator, sub-investigator, and study coordinator in the use of the (e)CRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. (e)CRFs must be completed directly recording data in English.

Corrections to (e)CRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the (e)CRFs for completeness and accuracy and must sign and date the appropriate (e)CRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the (e)CRFs.

The following data will not be recorded directly into the (e)CRFs.

1) Laboratory Test Results Measured at Central Laboratory

After the database lock of clinical study database, any change of, modification of or addition to the data on the (e)CRFs should be made by the investigator sub-investigator with use of change and modification records of CRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the Data Clarification Form for completeness and accuracy, and must sign, or sign and seal, and date the form.

(e)CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the (e)CRFs. The completed (e)CRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator or the head of the site agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms, copies of all paper CRFs, electronic copy of (e)CRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. In addition, the investigator and the head of the site are required to retain essential relevant documents until the day as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the site should discuss how long and how to retain those documents with the sponsor.

1) The day on which marketing approval of the investigational drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2) The day 3 years after the date of early termination or completion of the clinical study.

In addition, the investigator and the head of the institution should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

The analyses for this study will be performed using pooled data from the preceding study and this study, in principle, based on data obtained after administration of TVP-1012.

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock of this study. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to database lock of this study. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

In this study, two kinds of analysis sets are defined: full analysis set (FAS) and safety analysis set. The safety analysis set, the analysis set used for safety analysis, will be defined as “all subjects who were received at least one dose of TVP-1012.” The definition of each analysis set will be described in the Handling Rules for Analysis Data.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, consulting a medical expert as needed. If necessary, the Handling Rules for Analysis Data will be supplemented with new handling rules that were not discussed at the planning stage. The Handling Rules for Analysis Data must be finalized prior to database lock.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized overall and by treatment group of the preceding study using the safety analysis set.

13.1.3 Efficacy Analysis

(1) [Secondary endpoint and its analytical method]

[Secondary endpoint]

- MDS-UPDRS Part II＋Part III total score

[Analysis method]

The following analysis will be performed for FAS.

Descriptive statistics (number of subjects, mean, standard deviation, maximum, minimum, and quartiles) and two-sided 95% confidence intervals of means will be provided for the MDS-UPDRS Part II + Part III total score at each visit and the change from baseline in the MDS-UPDRS Part II + Part III total score at each visit of the treatment period by treatment group in the preceding study.

(2) Additional efficacy endpoints

Refer to Section 5.2.3.

(3) Method of data conversion and handling of missing data

Details will be described in the Handling Rules for Analysis Data and the Statistical Analysis Plan.

(4) Significance level and confidence coefficient

- Confidence coefficient: 95% (two-sided)

13.1.4 Safety Analysis

(1) Primary endpoint and its analytical method

[Primary endpoint]

- Adverse events

[Analytical methods]

The following analyses will be based on the safety analysis set.

A treatment-emergent adverse event (TEAE) is defined as an adverse event whose date of onset occurs on or after the start of treatment period study drug in the preceding study.

TEAEs whose date of onset occurs on or after the start of TVP-1012 will be coded using the MedDRA dictionary. The frequency distribution will be provided using the system organ class and the preferred term for each treatment group of the preceding study as follows:

- All TEAEs
- Drug-related TEAEs
- Intensity of TEAEs

- Intensity of drug-related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- TEAEs over time

(2) Secondary endpoints and their analytical methods

[Secondary endpoints]

- Laboratory test results, vital signs, 12-lead ECGs and weight

[Analytical methods]

The following analyses will be based on the safety analysis set.

For continuous variables, the observed values and the changes from baseline will be summarized by treatment group of the preceding study for each visit using descriptive statistics.
Case plots will also be presented for the observed values by treatment group of the preceding study.

For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided for each treatment group of the preceding study.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

Number of subjects to be enrolled in this study: approximately 182

[Justification of Sample size]

In the preceding study, the planned number of subjects to be randomized was a total of 240 (120 per group) and the planned number of subjects evaluable for the primary endpoint (change in the MDS-UPDRS Part II + Part III total score from baseline to Week 26 of the treatment period (LOCF)) was a total of 220 (110 per group).

Since this study is a long-term extension study in patients with early Parkinson's disease who have completed the 26-week treatment period in the preceding study, considering the potential dropouts in the preceding study, approximately 182 subjects will be enrolled in this study.

In addition, considering the potential dropouts in this study and in the preceding study, it is estimated that 155 subjects will be treated with 1 mg of TVP-1012 for 26 weeks and 59 subjects for 52 weeks.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the (e)CRFs. Source documents are defined as original documents, data, and records. The investigator and the head of the institution guarantee access to source documents by the sponsor or its designee and by the IRB

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, and review of (e)CRFs and associated source documents. It is important that the investigator or sub-investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator or sub-investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained.

The investigator or sub-investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA]). If the study site is contacted for an inspection by a regulatory body, the

sponsor should be notified immediately. The investigator and the head of the institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B.

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the sponsor-supplied drug or before initiation of the run-in period). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., informed consent form) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form and the subject information sheet describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information (to the third party including overseas) for purposes of conducting the study. The informed consent form and the subject information sheet further explains the nature of the study, its objectives, and potential risks and benefits. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form and the subject information sheet. The informed consent form and the subject information sheet must be approved by both the IRB and the sponsor prior to use.

The informed consent form and the subject information sheet must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or sub-investigator to explain the detailed elements of the informed consent form and the subject information sheet to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject determines he or she will participate in the study, then the informed consent form must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator or sub-investigator must also sign and date the informed consent form at the time of consent and prior to subject entering into the study.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator or sub-investigator must document the date the subject signs the

informed consent in the subject's medical record. Copies of the signed informed consent form shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, MHRA, Pharmaceuticals and Medical Devices Agency [PMDA]), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's [e]CRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site

agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator or sub-investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, Takeda will, at a minimum register all clinical trials conducted in patients that it sponsors anywhere in the world on publicly accessible websites, JAPIC-CTI, before trial initiation.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of this clinical trial, regardless of outcome on publicly accessible websites, JAPIC-CTI, as required by applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects.

Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator or sub-investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

[1] Parkinson's disease and related diseases (3) Parkinson's Disease (subsidized by government), Japan Intractable Diseases Information Center: Japan Intractable Diseases Research Foundation/Japan Intractable Diseases Information Center, http://www.nanbyou.or.jp/entry/169 (2014/10/30 accessed)

[2] Preparation Committee for Guidelines on Parkinson's Disease, Japanese Society of Neurology, "Practical Guidelines for Parkinson's Disease 2011" Igaku Shoin, 2011.

[3] Schapira AH. Treatment options in the modern management of Parkinson disease. Arch Neurol. 2007; 64(8): 1083-1088

[4] Schapira AH. Olanow CW. Drug selection and timing of initiation of treatment in early Parkinson's disease. Ann Neurol. 2008; 64(Suppl 2): S47-55

[5] [redacted]

[6] [redacted]

[7] [redacted]

Appendix A Schedule of Study Procedures

Study Week [a]	Treatment period						
	W26	W29	W32	W36	W40	W46	W52/ Early Termination [b]
VISIT Number [c]	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Study Day[d] (Day)	182	203	224	252	280	322	364
Visit Windows [d] (Days)	175 to 189	196 to 210	217 to 231	245 to 259	273 to 287	315 to 329	357 to 371
Informed consent	X [e]						
Inclusion/exclusion criteria	X						
Physical examination	*X* [f]	X	X	X	X	X	X
Skin examination	*X* [f]						X
Weight	*X* [f]				X		X
Vital signs	*X* [f]	X	X	X	X	X	X
Concomitant medications	*X* [f]	X	X	X	X	X	X
Clinical laboratory tests [g]	*X* [f]	X	X		X	X	X
ECG	*X* [f]				X		X
MDS-UPDRS	*X* [f]		X	X	X	X	X
QOL assessment	*X* [f]				X		X
Drug compliance	*X* [f]	X	X	X	X	X	X
Dispense investigational drug	X	X	X	X	X	X	
AE assessment[h]	*X* [f]	X	X	X	X	X	X

(a) The study visit weeks in this study will be counted from the start of the treatment period in the preceding study.
(b) For subjects withdrawn from the study after the initiation of the investigational drug in this study and before Week 52 of the treatment period, the tests, observations, and assessments scheduled for Week 52 of the treatment period should be performed within 7 days following discontinuation of treatment, whenever possible (the day of the last dose regarded as 0 day).
(c) Visit numbers in this study will be continued from the preceding study.
(d) Day 1 is defined as the day of first study medication administration for the treatment period in the preceding study.
(e) Informed consent for this study must be obtained prior to tests, observations, and assessments at Week 26 of the treatment period in the preceding study.
(f) Results of the tests, observations, and assessments at Week 26 of the treatment period in the preceding study will be used also for this study.
(g) To be measured after fasting for at least 8 hours whenever possible. Women of childbearing potential will undergo pregnancy test as well.
(h) AE collection in this study will begin at the initiation of the investigational drug in this study, and continued until Week 52 of the treatment period or early termination. AEs occurring between the final assessment in the preceding study and the initiation of the investigational drug in this study will be captured by the preceding study. AEs that occurred during the preceding study and persisted into this study will be followed up in this study as well.

Appendix B Responsibilities of the Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to the sub-investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the director of the site in advance to get them accepted.
3. Prepare a written informed consent form and other written information, and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications and responsibilities of individual personnel to the sub-investigator and study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing and obtain the written consent.
7. Assume responsibility for all the medical judgment related to the study.
8. Ensure in collaboration with the director of the site that sufficient information on all clinically significant adverse events related to the study are provided to subjects throughout and beyond the period when subjects participate in the study.
9. If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of a SAE, immediately notify the director of the site and the sponsor in writing.
11. Determine the need of emergency key code blinding of a subject in case of emergency.
12. Prepare correct and complete (e)CRFs, and submit them to the sponsor with electronic signature.
13. Check and confirm the contents of (e)CRFs prepared by the sub-investigator or transcribed from the source data by the study collaborator, and submit them to the sponsor with electronic signature.
14. Discuss any proposal from the sponsor including update of the protocol.
15. Notify the director of the site of the end of the study in writing.

Appendix C Detailed Description of Amendments to Text

Amendments made from the Amendment1 of this study protocol are listed below.

Page 60, 13.1.3 Efficacy Analysis

Existing Text

Descriptive statistics (number of subjects, mean, standard deviation, maximum, minimum, and quartiles) and two-sided 95% confidence intervals of means will be provided for the MDS-UPDRS Part II + Part III total score at each visit and the change from *baseline* in the MDS-UPDRS Part II + Part III total score at each visit of the treatment period by treatment group in the preceding study.

Revised Text

Descriptive statistics (number of subjects, mean, standard deviation, maximum, minimum, and quartiles) and two-sided 95% confidence intervals of means will be provided for the MDS-UPDRS Part II + Part III total score at each visit and the change from **baseline** in the MDS-UPDRS Part II + Part III total score at each visit of the treatment period by treatment group in the preceding study.

Rationale for Amendment

Described maintenance

PROTOCOL

<Title>

A Multicenter, Open-label, Long-term, Extension, Phase 3 Study to Evaluate the Safety and Efficacy of TVP-1012 at 1 mg in Early Parkinson's Disease Patients Not Treated with Levodopa

<Short Title>

A Phase 3, Long-term, Extension Study of TVP-1012 (1 mg) in Early Parkinson's Disease Patients

Sponsor: Takeda Pharmaceutical Company Limited
1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan

Study Number: TVP-1012/OCT-001

Amendment No Amendment 1

IND Number: Not Applicable **EudraCT Number** Not Applicable

Compound: TVP-1012 (INN: Rasagiline)

Date: 16 December 2014

Amendment History

Date	Amendment Number	Region
25 November 2014	First edition	All sites
16 December 2014	Amendment 1	All sites

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

A separate contact information list will be provided to each site.

1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

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LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor:
Takeda Pharmaceutical Company Limited</td><td colspan="2">Compound:
TVP-1012</td></tr>
<tr><td>Title of Protocol:
A Multicenter, Open-label, Long-term, Extension, Phase 3 Study to Evaluate the Safety and Efficacy of TVP-1012 at 1 mg in Early Parkinson's Disease Patients Not Treated with Levodopa
(An extension study from TVP-1012/CCT-001)</td><td>IND No.:
Not applicable</td><td>EudraCT No.:
Not applicable</td></tr>
<tr><td colspan="2">Study Number: TVP-1012/OCT-001</td><td colspan="2">Phase: 3</td></tr>
<tr><td colspan="4">Study Design:
This is a multicenter, open-label, long-term, extension, phase 3 study to evaluate the safety and efficacy of long-term administration of TVP-1012 at 1 mg for another 26 weeks in patients with early Parkinson’s disease who have completed the 26-week treatment period in the preceding TVP-1012/CCT-001 study. Among participants of the TVP-1012/CCT-001 study, those consenting to participate in this study prior to undergoing the tests, observations, and assessments at Week 26 of the treatment period (VISIT 8) in the preceding study, and fulfilling the eligibility criteria will be enrolled in this study. From the day after the VISIT 8 of the preceding study, subjects will receive TVP-1012 1 mg once daily for 26 weeks in an unblinded manner.
The visit numbers in this study will be continued from the preceding study, and the study visit week will be counted from the start of the treatment period in the preceding study.
Patients will make a total of 7 visits in this study, i.e., at Weeks 26, 29, 32, 36, 40, 46, and 52 of the treatment period, to undergo designated tests, observations, and assessments.</td></tr>
<tr><td colspan="4">Primary Objective:
To evaluate the long-term safety of TVP-1012 (1 mg/day) in Japanese patients with early Parkinson’s disease</td></tr>
<tr><td colspan="4">Secondary Objective:
To evaluate the long-term efficacy of TVP-1012 (1 mg/day) in Japanese patients with early Parkinson’s disease</td></tr>
<tr><td colspan="4">Subject Population: Japanese patients with early Parkinson’s disease who have completed the 26-week treatment period in the preceding study</td></tr>
<tr><td colspan="2">Number of Subjects:
Approximately 182 continued from the preceding study</td><td colspan="2">Number of Sites:
Approximately 55 sites
(Same study sites as the preceding study)</td></tr>
</table>

Dose Levels: TVP-1012 (1 mg/day) once daily, either before or after breakfast (the timing of the dose must be the same as in the preceding study)	**Route of Administration:** Oral
Duration of Treatment: 26 weeks in total	**Period of Evaluation:** 26 weeks in total

Main Criteria for Inclusion:

- The subject has completed the preceding study.
- The subject has shown no safety issues during the study treatment in the preceding study, in the judgment of the investigator or sub-investigator.

Main Criteria for Exclusion:

- Subject has donated 400 mL or more of his or her blood volume within 90 days prior to the initiation of the investigational drug in this study.
- The subject is required to receive any of the excluded medications or treatments.
- The subject is required surgery or hospitalization for surgery during the study period.

Main Criteria for Evaluation and Analyses:

Primary endpoint

- Adverse events (AEs)

Secondary endpoints

- Clinical laboratory test values, vital signs, electrocardiogram (ECG), and weight
- MDS-UPDRS Part II + Part III total score

Statistical Considerations:

The analyses for this study will be performed using pooled data from the preceding study and this study, in principle, based on data obtained after administration of TVP-1012.

[Analysis methods for the primary endpoint]

The following analysis will be based on the safety analysis set.

A treatment-emergent adverse event (TEAE) is defined as an adverse event whose date of onset occurs on or after the start of treatment period study drug in the preceding study.

TEAEs whose date of onset occurs on or after the start of TVP-1012 will be coded using the MedDRA dictionary. The frequency distribution will be provided using the system organ class and the preferred term for each treatment group as follows:

- All TEAEs
- Drug-related TEAEs
- Intensity of TEAEs
- Intensity of drug-related TEAEs

- TEAEs leading to study drug discontinuation
- Serious TEAEs
- TEAEs over time

Sample Size Justification:

In the preceding study, the planned number of subjects to be randomized was a total of 240 (120 per group) and the planned number of subjects evaluable for the primary endpoint (change in the MDS-UPDRS Part II + Part III total score from baseline to Week 26 of the treatment period (LOCF)) was a total of 220 (110 per group).

Since this study is a long-term extension study in patients with early Parkinson's disease who have completed the 26-week treatment period in the preceding study, considering the potential dropouts in the preceding study, approximately 182 subjects will be enrolled in this study.

In addition, considering the potential dropouts in this study and in the preceding study, it is estimated that 155 subjects will be treated with 1 mg of TVP-1012 for 26 weeks and 59 subjects for 52 weeks.

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BUN	blood urea nitrogen
Cmax	maximum observed serum concentration
COMT	catechol-*O*-methyltranferase
CRO	contract research organization
CYP	Cytochrome P-450
FDA	Food and Drug Administration
GCP	Good Clinical Practice
γ-GTP	γ-glutamyl transpeptidase
hCG	human chorionic gonadotropin
ICH	International Conference on Harmonisation
INN	international nonproprietary name
INR	international normalized ratio
LDH	lactate dehydrogenase
MAO	Monoamine oxidase
MDS	Movement Disorders Society
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
PDQ-39	The 39-item Parkinson's disease questionnaire
PMDA	Pharmaceuticals and Medical Devices Agency
PT	preferred term
PTE	pretreatment event
QOL	quality of life
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
UPDRS	unified Parkinson's disease rating scale
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Parkinson's disease is the second most common neurodegenerative disorder of the central nervous system after Alzheimer's disease. The prevalence of Parkinson's disease is estimated to be 100-150/100,000 in the Japanese population, mostly affecting elderly people with peak age in the late 50s to 60s [1]. A significant increase in the number of patients is expected as the population ages in the future.

The 4 major symptoms of Parkinson's disease are resting tremor, muscle rigidity (muscle stiffness), bradykinesia, and postural instability. These motor symptoms are suspected to occur due to damage or death of substantia nigra dopaminergic neurons in the midbrain, followed by a reduction in dopamine volume in the striatum.

The Japanese therapeutic guideline recommends initially treating motor symptoms of Parkinson's disease with levodopa or a dopamine agonist, in principle, and rich evidence with these drugs used as first-line therapy are available [2].

In clinical practice overseas, the efficacy of initial treatment with MAO-B inhibitors has been demonstrated in Parkinson's disease and the therapeutic algorithm recommends MAO-B inhibitors as the first-line treatment for mild Parkinson's disease in addition to levodopa and dopamine agonists [3][4]. In Japan, selegiline is one of the MAO-B inhibitors available but not approved for first-line treatment of Parkinson's disease. If clinical development of MAO-B inhibitors is promoted in Japan, treatment options for patients with mild or early Parkinson's disease may expand.

TVP-1012 (INN: rasagiline) is a MAO-B inhibitor without an amphetamine structure. In comparison with selegiline, TVP-1012 is characterized by (1) a 5 to 10-fold MAO-B inhibitory effect, and (2) easy drug management due to not having an amphetamine structure and not being designated as ingredient in narcotics. As of September, 2014, rasagiline has been approved in 53 countries in Europe, the United States, and East Asian countries as a monotherapy for early Parkinson's disease, and also as concomitant therapy with levodopa for Parkinson's disease. Currently, clinical development for TVP-1012 as monotherapy for early Parkinson's disease and as an add-on therapy to levodopa for Parkinson's disease is ongoing in Japan.

[redacted]

[redacted]

[redacted]

Efficacy Summary

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Safety Summary

[redacted]

[redacted]

4.2 Rationale for the Proposed Study

[redacted]

Based on these results, this study was planned to evaluate the efficacy and safety of long-term extension administration with TVP-1012 in Japanese patients with early Parkinson's disease who have completed the preceding study (TVP-1012/CCT-001). The comprehensive evaluation of the efficacy and safety of TVP-1012 in early Parkinson's disease will be performed based on the results of this study, Study TVP-1012/CCT-001, and overseas clinical studies.

The clinical development of TVP-1012 as an add-on to levodopa for Parkinson's disease is ongoing in Japan. Currently, a Phase 2/3 study (TVP-1012/CCT-002) and a Phase 3 study (TVP-1012/OCT-002) are underway.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective(s)

- To evaluate the long-term safety of TVP-1012 (1 mg/day) in Japanese patients with early Parkinson's disease

5.1.2 Secondary Objectives(s)

- To evaluate the long-term efficacy of TVP-1012 (1 mg/day) in Japanese patients with early Parkinson's disease

5.2 Endpoints

5.2.1 Primary Endpoint

- Adverse events (AEs)

5.2.2 Secondary Endpoints

- Clinical laboratory test values, vital signs, electrocardiogram (ECG), and weight
- Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II＋Part III total score

5.2.3 Additional Endpoints

- MDS-UPDRS Part I total score
- MDS-UPDRS Part II total score
- MDS-UPDRS Part III total score
- MDS-UPDRS Part IV total score
- MDS-UPDRS tremor score
- MDS-UPDRS bradykinesia score
- MDS-UPDRS muscle rigidity score
- MDS-UPDRS individual score
- Parkinson's Disease Questionnaire-39 (PDQ-39) Summary Index scores for individual domain

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

Patients will make a total of 7 visits in this study, i.e., at Weeks 26, 29, 32, 36, 40, 46 and 52 of the treatment period, to undergo designated tests, observations, and assessments.

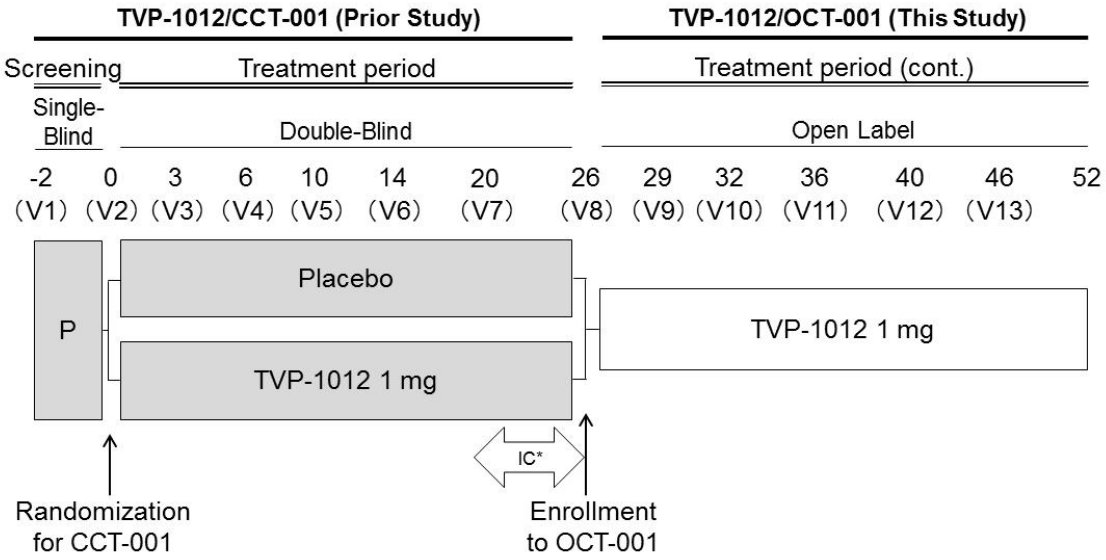
This is a multicenter, open-label, long-term, extension, phase 3 study to evaluate the safety and efficacy of long-term administration of TVP-1012 at 1 mg for another 26 weeks in patients with early Parkinson's disease who have completed the 26-week treatment period in the preceding TVP-1012/CCT-001 study.

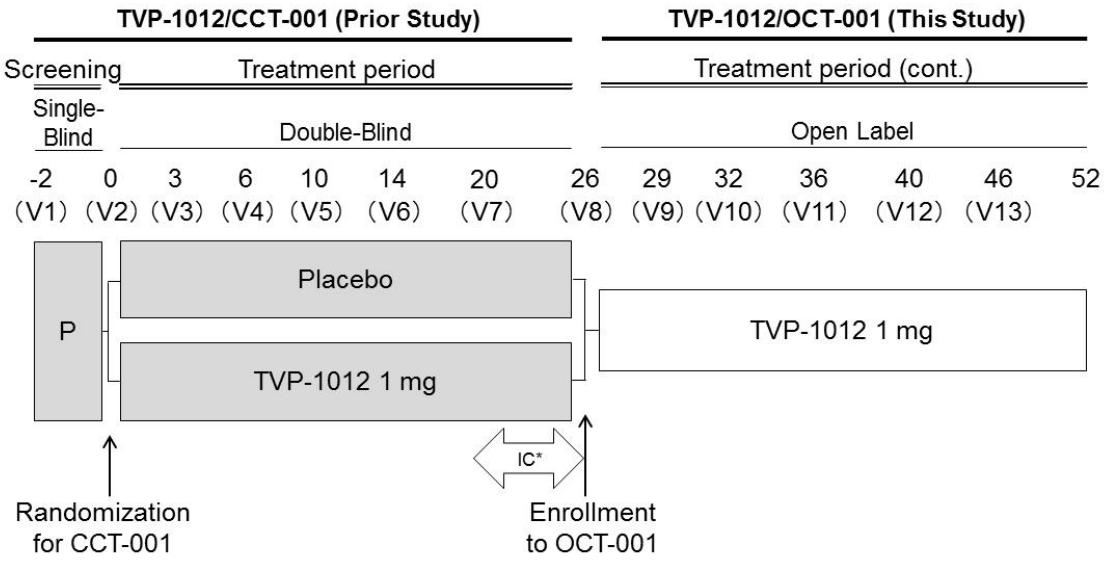
Among participants of the TVP-1012/CCT-001 study, those consenting to participate in this study prior to undergoing the tests, observations, and assessments at Week 26 of the treatment period (VISIT 8) in the preceding study, and fulfilling the eligibility criteria will be enrolled in this study. From the day after the VISIT 8 of the preceding study, subjects will receive TVP-1012 1 mg once daily for 26 weeks in an unblinded manner.

The visit numbers in this study will be continued from the preceding study, and the study visit week will be counted from the start of the treatment period in the preceding study.

This study will be conducted in the same study sites as those of the preceding study (55 sites) and the number of subjects to be enrolled in this study is estimated to be 182 subjects after considering dropouts in the preceding study.

Schematic of Study Design is included as Figure 6.a. A schedule of study procedures is listed in Appendix A.





V: VISIT
* Informed consent for this study must be obtained prior to tests, observations, and assessments at Week 26 of the treatment period in the preceding study. Those who consent to participate in this study and fulfilling the eligibility criteria will be enrolled in this study. Subjects will start dosing from the day after the VISIT 8.

Figure 6.a Schematic of Study Design

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Justification for Study Subject

To evaluate the safety and efficacy of long-term administration of TVP-1012 in Japanese patients with early Parkinson's disease, this study will target subjects who have completed the preceding study and were assessed as not demonstrating safety concerns in the opinion of the investigator or sub-investigator.

6.2.2 Justification for Study Design

This open-label, long-term extension study has a common study design that allows for the evaluation of long-term safety. This study was designed as an extension study following the preceding study, to collect pertinent data on long-term administration in an efficient manner.

See Section 13.3 for Sample Size Justification.

6.2.3 Justification for Dose Regimen

[redacted]

In the preceding study, 1 mg of TVP-1012 or placebo was administered for 26 weeks to evaluate the efficacy and safety of TVP-1012 1 mg.

In this study, the dose of 1 mg of TVP-1012 will be maintained for subjects treated with 1 mg of TVP-1012 in the preceding study, to evaluate administration at 1 mg for 52 weeks. In addition, subjects treated with placebo in the preceding study will be switched to 1 mg of TVP-1012 in this study, to evaluate administration at 1 mg for 26 weeks, for the purpose of evaluating a large number of subjects as much as possible.

[redacted]

[redacted]

6.2.4 Justification for Treatment Period

Parkinson's disease is a progressive disease and long-term administration is anticipated when TVP-1012 is prescribed. Therefore, another 26-week extension of treatment was planned following the 26-week treatment in the preceding study to evaluate the long-term safety of TVP-1012 for 6 months and 12 months.

6.2.5 Justification for Endpoints

In this study, the long-term safety and efficacy of TVP-1012 following the preceding study will be evaluated. As the safety and efficacy will be evaluated in pooled data from this and preceding studies, the same endpoints used for the preceding study were set.

Safety evaluation is the primary objective of this study. Of the safety evaluation variables in the preceding study, the frequency of adverse events (AEs) will be used as the primary endpoint and clinical laboratory test results, vital signs, ECGs, and weight will be used for the assessment of secondary endpoints.

In addition, MDS-UPDRS Part II + Part III total score, which was the primary efficacy endpoint in the preceding study, will be used as a secondary endpoint. The efficacy endpoints in the preceding study other than MDS-UPDRS Part II + Part III total score will be set as additional endpoints.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.

- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB) or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to the administration of the investigational drug.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. In the opinion of the investigator or sub-investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject has completed the preceding study (TVP-1012/CCT-001 study).
4. The subject has shown no safety issues during the study treatment in the preceding study, in the judgment of the investigator or sub-investigator.
5. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent to 1 month after the last dose of the investigational drug.

*Definition of female subjects of chiledbearing potential is defined in Section 9.1.10.
Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.11.

[Justification of Inclusion Criteria]

1, 2 : These criteria were set to include subjects who understand the objective of the study and will cooperate in the study conduct.
3 : This criterion was set as this study is designed to conduct with subjects who have completed the 26-week treatment period in the preceding study.
4 : This criterion was set in consideration of subject safety.
5 : This criterion was set in consideration of safety risk associated with pregnancy.

7.2 Exclusion Criteria

Any subject who meets the following criteria will not qualify for entry into the study:

1. The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
2. Subject has donated 400 mL or more of his or her blood volume within 90 days prior to the initiation of the investigational drug in this study.
3. The subject is required to receive excluded medications or treatments.
4. If female, the subject is intending to become pregnant during, or within 1 month after the last dose of the investigational drug; or intending to donate ova during such time period.
5. The subject requires surgery or hospitalization for surgery during the study period.
6. The subject who, in the opinion of the investigator or sub-investigator, is unsuitable for any other reason.

[Justification of Exclusion Criteria]

1, 5 : These criteria were set as basic matters to conduct clinical studies.
2 : This criterion was set as basic matters to conduct clinical studies in consideration of subject safety.
3 : This criterion was set in consideration of efficacy evaluation and subject safety.
4 : This criterion was set to avoid the safety risk associated with pregnancy to pregnant woman and fetus.
6 : This criterion was set to exclude subjects with unknown factors which might influence the evaluation of efficacy.

7.3 Excluded Medications and Treatments

The list of excluded medications and treatments is shown in Table 7.a. Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator or sub-investigator.

Table 7.a Excluded Medications and Treatments

Medication/Treatment	Duration	Exception
Excluded Medication		
(1) selegiline	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(2) pethidine, tramadol	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(3) reserpine, methyldopa	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(4) Other investigational drug	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(5) levodopa containing drug (6) Dopamine agonist (7) amantadine (8) Anticholinergic agent	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(9) COMT inhibitor (10) droxidopa (11) zonisamide (12) istradefylline	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(13) Psychoneurotic agent (phenothiazine, butyrophenone, benzamide, Atypical antipsychotic drug)	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	Quetiapine may be concomitantly administrered without change in dose regimen throughout the study if the drug has been continuously administered in the preceding study.
(14) Antinauseant with dopamine agonistic property	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	domperidone may be concomitantly administered without change in dose regimen throughout the study if the drug has been continuously administered in the preceding study.
(15) CYP1A2 inhibitor (including ciprofloxacin, enoxacin, fluvoxamine, zafirlukast)	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_

Medication/Treatment	Duration	Exception
(16) dextromethorphan	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(17) Antidepressant	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(18) St. John's Wort (including supplements)	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(19) Narcotic analgesic agent (excluding ≤ 1% of codeine, dihydrocodeine)	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
Excluded Treatment		
(20) Neurosurgical intervention (Pallidotomy, Thalamotomy, deep brain stimulation)	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_
(21) Transcranial magnetic stimulation	From VISIT 8 through VISIT 14, or the day of study site visit for early termination.	_

Medications/treatments for AEs during the study period may be administered, provided that these treatments do not deviate from the above range. If a drug listed above is chosen as routine medication after study completion, this medication should be administered following a reasonable interval as needed, based on the precautions for use for each drug.

[Justification of Excluded Medications and Treatments]

(1), (2), (18), (19)
These criteria were set to ensure the safety of subjects, in consideration of adverse drug reactions due to concomitant use.

(3), (13), (14)
These criteria were set since there is a possibility of worsening Parkinsonism, which may affect the efficacy evaluation of TVP-1012; however, some drugs may be used concomitantly, if these drugs do not affect the efficacy evaluation of TVP-1012.

(4)-(12), (20), (21)
These criteria were set because they could influence the evaluation of efficacy.

(15) This criterion was set due to the effect on the pharmacokinetics of TVP-1012, considering the metabolic pathway mainly via CYP1A2.

(16) This criterion was set to ensure the safety of subjects, in consideration of possibly elevating serotonin level due to concomitant use.

(17) This criterion was set to ensure the safety of subjects and to minimize the effect on the efficacy evaluation due to mutually potentiated pharmacological action with concomitant use.

7.4 Diet, Fluid, Activity Control

The investigator, sub-investigator, or study coordinator will give subjects the following instructions:

1. Subjects should be punctual for visit appointments and undergo the physical examinations and prescribed tests. Subjects should also contact the investigator, sub-investigator or study coordinator promptly if they cannot visit the site as planned.
2. Subjects should contact the investigator, sub-investigator, or study coordinator by telephone, etc., to ask for instructions immediately after symptoms worsen between planned visits.
3. Subjects should follow instructions regarding treatment adherence provided by the investigator or sub-investigator. Subjects should visit the site after taking the study drug on planned visit days.* If the subject does not comply with treatment procedures, the subject must report this to the investigator, sub-investigator, or

study coordinator at the next visit. Unused study drug(s) and drug sheet(s) (blister sheet) should be returned at the next visit.

* For the day the serum chemistry is scheduled, the study medication must be taken without having breakfast. In this case, deviation from the original dose timing (not before or after breakfast) will be permitted.

4. Subjects are not allowed to take any medications other than drugs prescribed by the investigator or sub-investigator, including over-the-counter products, without first consulting with the investigator (except for emergency use).
5. If a subject visits another medical institution from signing of the informed consent to 1 month after the last administration of the investigational drug, the investigator should notify the primary care physician that the subject was participating in a clinical study.
6. If a subject visits another medical institution from signing of the informed consent to 1 month after the last administration of the investigational drug, the investigator or sub-investigator should be informed of the circumstances and therapy.
7. On the days on which clinical serum chemistry tests are scheduled, blood must be collected in fasted state (≥ 8 hours), whenever possible.
8. A female subject of childbearing potential who is sexually active with a nonsterilized male partner must agree to use routinely adequate contraception from signing of informed consent to 1 month after the last dose of the investigational drug.
9. Excessive eating, drinking, exercise and drastic change of the meal are not allowed during the study period.
10. Blood donation is not allowed from the start of the investigational drug administration until at least 1 month after the last administration of the investigational drug. Subject must immediately report the blood donation during this period, if any, to the investigator.
11. Subjects should avoid driving vehicles, operating machinery, and working in high areas, etc., in consideration of possible treatment-emergent dizziness, or reduced attention, concentration, or reflex function.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study should be recorded in the case report form ([e]CRF) using the following categories. For screen failure subjects, refer to Section 9.1.15.

1. **Pretreatment Event or AE**
   The subject has experienced a pretreatment event (PTE) or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

- Liver Function Test (LFT) Abnormalities
- Study medication should be discontinued immediately with appropriate clinical follow-up until a subject's laboratory profile has returned to normal or the value immediately after the informed consent (for PTEs), or the value before the initiation of the investigational drug* (for AEs). (See Section 9.1.9) if the following circumstances occur at any time during study medication treatment:

  * The value before the initiation of the study medication is defined as the value prior to the start of the run-in period in the preceding study for AEs occurred before first study medication administration in the treatment period in the preceding study, and as the value at baseline in the preceding study for AEs occurred after first study medication administration in the treatment period in the preceding study.

  - ALT or AST > 8 × ULN, or
  - ALT or AST > 5 × ULN and persists for more than 2 weeks, or
  - ALT or AST > 3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) > 1.5, or
  - ALT or AST > 3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

2. **Significant protocol deviation**
   The discovery after the first dose of study medication that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

3. **Lost to follow-up**
   The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.

4. **Voluntary withdrawal**
   The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the (e)CRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE or lack of efficacy).

5. **Study termination**
   The sponsor, IRB, or regulatory agency terminates the study.

6. **Pregnancy**
   The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.11.

7. **Lack of efficacy**
   The investigator or sub-investigator has determined that the subject is not benefiting from investigational treatment; and, continued participation would pose an unacceptable risk to the subject.

8. **Other**

   Note: The specific reasons should be recorded in the "specify" field of the (e)CRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator or sub-investigator may terminate a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator or sub-investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to all or any of the drugs defined below.

(1) Dosage Form and Manufacturing

Drug substance code number: TVP-1012
Nonproprietary name: rasagiline (INN)
Chemical name: *N*-propargyl-1-(*R*)-aminoindan mesylate

Table 8.a Study Medication

Type of the drug	Dosage form
TVP-1012 1 mg tablet	A white to yellowish white round shape tablet containing rasagiline, engraved with "[redacted]" on one surface.

All the study medication were manufactured in [redacted]

(2) Packaging and Labeling

Ten tablets of the TVP-1012 1 mg are encapsulated in an aluminum blister sheet and 19 sheets of the TVP-1012 1 mg tablet are packed in a carton.

The label affixed to the carton containing the investigational drug should include a description that the content is an investigational drug, name of the drug "TVP-1012 1.0 mg tablet", study number "TVP-1012/OCT-001", the name and address of the sponsor, manufacturing number, number of the drugs, and storage.

8.1.2 Storage

The investigational drug must be stored at 1°C to 30°C.

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational drug must be stored under the conditions specified on the label, and remain in the

original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

The administration of the study medication will start on the day after VISIT 8 and the subjects will be orally administered 1 tablet of TVP-1012 1.0 mg once daily before or after breakfast (at the same timing with the preceding study).

The investigator or its designee will supply sufficient amount of the study medication required during the period between study visits. Subjects will be instructed to take study medication in the morning of study visits* and to bring unused study medications and blister sheets to the site at each study visit. Also, compliance of the study medication from the last study visit will be checked by the investigator or sub-investigator (see Section 9.2).

* For the day the serum chemistry is scheduled, the study medication must be taken without having breakfast. In this case, deviation from the timing of dose (not before or after breakfast) will be permitted.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the (e)CRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0, PRETREATMENT EVENTS AND ADVERSE EVENTS.

Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Investigational Drug Assignment and Dispensing Procedures

The same investigational drug is used for all subjects at each study site where the study is conducted. The investigator or sub-investigator will assign the investigational drug allocated to each study site to the subjects according to the study procedure.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

Upon receipt of the procedures for handling, storage, and management of the investigational drug prepared by the sponsor, the investigational drug manager will appropriately manage all the drugs supplied by the sponsor. The investigator will also receive the same procedures from the sponsor. The procedures will define the processes necessary to ensure that receipt, handling, storage, management, and prescription of the sponsor-supplied drugs, as well as collection of the unused drugs from subjects and return to the sponsor or disposal of unused drugs should be performed appropriately and reliably.

The investigational drug manager will return unused drugs to the sponsor immediately after the completion of the clinical study at the study site.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or sub-investigator whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to tests, observations and evaluations at Week 26 (VISIT 8) in the preceding study.

The same identification code provided in the preceding study will be assigned and will be used throughout the study period.

9.1.2 Demographics, Medical History, and Medication History Procedure

The same demographic information, medical history and medication history obtained in the preceding study will be used in this study.

9.1.3 Physical Examination Procedure

A physical examination will consist of the following body systems:

(1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) other.

All subsequent physical examinations should assess clinically significant changes from the values obtained at baseline (VISIT 2).

9.1.4 Skin Examination

A subject should be confirmed as not having melanoma in accordance with separately prepared study procedures. If melanoma is suspected, this subject must visit a dermatologist.

9.1.5 Weight

Weight will be collected in kilograms to 1 decimal place.

9.1.6 Vital Sign Procedure

Vital signs will include body temperature (infra-axillary measurement), sitting systolic/diastolic (mmHg) blood pressure after resting more than 5 minutes, and pulse (bpm).

9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda and all medication including vitamin supplements, over-the-counter medications, oral herbal preparations, and St. John's Wort must be recorded in the (e)CRF. If any antiparkinsonian drug is taken, its dosage and unit per day must be obtained.

9.1.8 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent in the preceding study. Concurrent medical conditions for this study are those investigated in the preceding study.

9.1.9 Procedures for Clinical Laboratory Samples

Table 9.a lists the samples to be collected for each laboratory test. All samples will be collected after fasted for more than 8 hours, whenever possible, in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 6 mL.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells	AST	Protein (qualitative)
Hemoglobin	ALT	Glucose (qualitative)
Hematocrit	γ-GTP	Blood (qualitative)
White blood cells with differential (neutrophil, eosinophil, monocyte, lymphocyte, and basophil)	ALP	Ketone body (qualitative)
	LDH	
	Albumin	
	Total protein	
	Total bilirubin	
Platelets	Total cholesterol	
	Triglycerides	
	Creatinine	
	Blood urea nitrogen (BUN)	
	Urine acid	
	Creatine kinase	
	Sodium	
	Potassium	
	Chlorine	
	Calcium	
	Phosphorus	
Pregnancy Test (for female subjects of childbearing potential only)		
Urine hCG (qualitative)		

The central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. However, the urine hCG (qualitative) will be performed at each study site for women with childbearing potential.

If subjects experience ALT or AST > 3 × ULN, follow-up laboratory tests (at a minimum, serum ALP, ALT, AST, total bilirubin, γ-GTP, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted. (see Section 7.5 and 10.2.3)

If the ALT or AST remains elevated > 3 × ULN on these 2 consecutive occasions, the investigator or sub-investigator must contact the sponsor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies.

The laboratory test results will be evaluated and maintained by the investigator or sub-investigator. And also, the investigator will maintain a copy of the reference ranges for the laboratory used.

9.1.10 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 1 month after last dose of study medication, female subjects of childbearing potential who are sexually active or before menopause with a nonsterilized male partner must use adequate contraception. In addition they must be advised not to donate ova during this period. Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova during the course of the study. During the course of the study, regular urine hCG pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Appendix A).

Subjects also must have a negative urine hCG pregnancy test at each evaluation point.

9.1.11 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued.

If the pregnancy occurs during administration of active study medication, after the end of run-in period of the preceding study and within 1 month of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the Safety Information Emergency Call Center (contact listed specified in the appendix).

Should the pregnancy occur during or after administration of blinded drug, the investigator or sub-investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator or sub-investigator.

If the female subject agrees to the primary care physician (gynecologist) being informed, the investigator or sub-investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.12 ECG Procedure

Standard 12-lead ECGs will be recorded under resting. The investigator or sub-investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The following parameters will be recorded on the (e)CRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval, and QTcB interval. QTcF will be calculated by the sponsor.

9.1.13 MDS-UPDRS

The investigator or sub-investigator will assess the symptoms of Parkinson's disease according to MDS-UPDRS (Part I: non-motor experiences of daily living, Part II: motor experiences of daily living, Part III: motor examination, Part IV: motor complications).

The investigator or sub-investigator (hereinafter referred to as "evaluator") responsible for evaluating MDS-UPDRS scores will undergo training on MDS evaluations prior to study conduct and should be accredited with a training certificate. Only evaluators with a training certificate are allowed to evaluate the MDS-UPDRS for the study.

The evaluator will not evaluate subjects until he/she receives a training certificate for MDS evaluations. If the assigned evaluator is replaced (or added) during the study, a new evaluator should complete the aforementioned training and receive a training certificate for MDS evaluations before starting evaluations in the study. If a new evaluator has already received a training certificate for MDS evaluations, re-training will not be mandatory.

In principle, the same subject will be evaluated by the same evaluator as in the preceding study throughout the study period. The evaluator will record evaluation results for each item in Table 9.b in the CRF.

Table 9.b MDS-UPDRS Score Sheet

Part I			3.1	**Speech**	**(0, 1, 2, 3, 4, UR)**
	Primary source of information	□ Patient □ Caregiver □ Patient and Caregiver	3.2	**Facial expression**	**(0, 1, 2, 3, 4, UR)**
			3.3a	**Rigidity-Neck[b]**	**(0, 1, 2, 3, 4, UR)**
			3.3b	**Rigidity-RUE[b]**	**(0, 1, 2, 3, 4, UR)**
1.1	**Cognitive impairment**	**(0, 1, 2, 3, 4, UR)**	3.3c	**Rigidity-LUE[b]**	**(0, 1, 2, 3, 4, UR)**
1.2	**Hallucinations and psychosis**	**(0, 1, 2, 3, 4, UR)**	3.3d	**Rigidity-RLE[b]**	**(0, 1, 2, 3, 4, UR)**
1.3	**Depressed mood**	**(0, 1, 2, 3, 4, UR)**	3.3e	**Rigidity-LLE[b]**	**(0, 1, 2, 3, 4, UR)**
1.4	**Anxious mood**	**(0, 1, 2, 3, 4, UR)**	3.4a	**Finger tapping-Right hand [c]**	**(0, 1, 2, 3, 4, UR)**
1.5	**Apathy**	**(0, 1, 2, 3, 4, UR)**	3.4b	**Finger tapping-Left hand [c]**	**(0, 1, 2, 3, 4, UR)**
1.6	**Features of DDS**	**(0, 1, 2, 3, 4, UR)**	3.5a	**Hand movements-Right hand [c]**	**(0, 1, 2, 3, 4, UR)**
			3.5b	**Hand movements-Left hand [c]**	**(0, 1, 2, 3, 4, UR)**
Questionnaire			3.6a	**Pronation-supination movements-Right hand [c]**	**(0, 1, 2, 3, 4, UR)**
	Who is filling out this questionnaire:	□ Patient □ Caregiver □ Patient and Caregiver	3.6b	**Pronation-supination movements-Left hand[c]**	**(0, 1, 2, 3, 4, UR)**
			3.7a	**Toe tapping-Right foot[c]**	**(0, 1, 2, 3, 4, UR)**
			3.7b	**Toe tapping-Left foot [c]**	**(0, 1, 2, 3, 4, UR)**
1.7	**Sleep problems**	**(0, 1, 2, 3, 4)**	3.8a	**Leg agility-Right leg [c]**	**(0, 1, 2, 3, 4, UR)**
1.8	**Daytime sleepiness**	**(0, 1, 2, 3, 4)**	3.8b	**Leg agility-Left leg[c]**	**(0, 1, 2, 3, 4, UR)**
1.9	**Pain and other sensations**	**(0, 1, 2, 3, 4)**	3.9	**Arising from chair**	**(0, 1, 2, 3, 4, UR)**
			3.10	**Gait**	**(0, 1, 2, 3, 4, UR)**
1.10	**Urinary problems**	**(0, 1, 2, 3, 4)**	3.11	**Freezing of gait**	**(0, 1, 2, 3, 4, UR)**
1.11	**Constipation problems**	**(0, 1, 2, 3, 4)**	3.12	**Postural stability**	**(0, 1, 2, 3, 4, UR)**
1.12	**Light headedness on standing**	**(0, 1, 2, 3, 4)**	3.13	**Posture**	**(0, 1, 2, 3, 4, UR)**
1.13	**Fatigue**	**(0, 1, 2, 3, 4)**	3.14	**Global spontaneity of movement[c]**	**(0, 1, 2, 3, 4, UR)**
Part II					
2.1	**Speech**	**(0, 1, 2, 3, 4)**	3.15a	**Postural tremor-Right hand[a]**	**(0, 1, 2, 3, 4, UR)**
2.2	**Saliva and drooling**	**(0, 1, 2, 3, 4)**	3.15b	**Postural tremor-Left hand[a]**	**(0, 1, 2, 3, 4, UR)**
2.3	**Chewing and swallowing**	**(0, 1, 2, 3, 4)**	3.16a	**Kinetic tremor-Right hand[a]**	**(0, 1, 2, 3, 4, UR)**
2.4	**Eating tasks**	**(0, 1, 2, 3, 4)**	3.16b	**Kinetic tremor-Left hand[a]**	**(0, 1, 2, 3, 4, UR)**
2.5	**Dressing**	**(0, 1, 2, 3, 4)**	3.17a	**Rest tremor amplitude-RUE[a]**	**(0, 1, 2, 3, 4, UR)**
2.6	**Hygiene**	**(0, 1, 2, 3, 4)**	3.17b	**Rest tremor amplitude-LUE[a]**	**(0, 1, 2, 3, 4, UR)**
2.7	**Handwriting**	**(0, 1, 2, 3, 4)**	3.17c	**Rest tremor amplitude-RLE[a]**	**(0, 1, 2, 3, 4, UR)**
2.8	**Doing hobbies and other activities**	**(0, 1, 2, 3, 4)**	3.17d	**Rest tremor amplitude-LLE[a]**	**(0, 1, 2, 3, 4, UR)**
2.9	**Turning in bed**	**(0, 1, 2, 3, 4)**	3.17e	**Rest tremor amplitude-Lip/jaw)[a]**	**(0, 1, 2, 3, 4, UR)**
2.10	**Tremor(a)**	**(0, 1, 2, 3, 4)**			
2.11	**Getting out of bed, a car, or a deep chair**	**(0, 1, 2, 3, 4)**	3.18	**Constancy of rest tremor[a]**	**(0, 1, 2, 3, 4, UR)**
				Were dyskinesias present during examination?	□No □Yes
2.12	**Walking and balance**	**(0, 1, 2, 3, 4)**		If Yes, did these movements interfere with ratings?	□No □Yes
2.13	**Freezing**	**(0, 1, 2, 3, 4)**			
Part III				Hoehn and Yahr Stage	(0, 1, 2, 3, 4, 5)
3a	Is the patient on medication?	□No □Yes	**Part IV**		
			4.1	**Time spent with dyskinesias**	**(0, 1, 2, 3, 4)**

3b	Patient's clinical state	□ON □OFF	4.2	**Functional impact of dyskinesias**	**(0, 1, 2, 3, 4)**
3c	Is the patient on Levodopa?	□No □Yes	4.3	**Time spent in the OFF state**	**(0, 1, 2, 3, 4)**
			4.4	**Functional impact of fluctuations**	**(0, 1, 2, 3, 4)**
3c1	If yes, minutes since last dose:	minutes	4.5	**Complexity of motor fluctuations**	**(0, 1, 2, 3, 4)**
			4.6	**Painful OFF-state dystonia**	**(0, 1, 2, 3, 4)**

0: Normal, 1: Slight, 2: Mild, 3: Moderate, 4: Severe, UR: Unable to Rate
Bolded items represent MDS-UPDRS scores by category. Scores for each bolded item will be added according to Parts and the total score of individual Parts (I to IV) will be calculated. Scores for (a), (b), and (c) will be added separately and (a) tremor score, (b) muscle rigidity score, and (c) akinesia/bradykinesia score will be calculated.

9.1.14 QOL assessment

PDQ-39 is a self-administered questionnaire for QOL. Prior to the assessment, subjects will be provided instructions on how to record PDQ-39 and assess QOL during 1 month prior to the day of the assessment. Answers to all questions will be documented in the CRF.

9.1.15 Documentation of Screen Failure

The investigator should complete the (e)CRF for the subject who signed the informed consent and withdrawn from the study before randomization.

For subjects discontinued the study before the initiation of the investigational drug in this study, the date of signing informed consent, date of birth, sex, eligibility, reason for withdrawal, AE assessment (if any, it must be collected as an AE occurred in the preceding study), concomitant medications, and the date of the last physical examination/evaluations must be recorded in the (e)CRF.

The primary reason for screen failure is recorded in the (e)CRF using the following categories:

- PTE/AEs
- Did not meet inclusion criteria or did meet exclusion criteria <specify reason>.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal <specify reason>.
- Study termination.
- Other <specify reason>.

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.16 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the study. If the subject is found to be not eligible for the study, the investigator or sub-investigator should record the primary reason for failure on the applicable (e)CRF.

9.2 Monitoring Subject Treatment Compliance

Subjects will be instructed to bring unused investigational drugs and blister sheets to the site at each study visit. Also, compliance of the study medication from the last study visit will be checked by the investigator or sub-investigator.

All subjects should be instructed about the dosing requirement during study contacts. If a subject is persistently noncompliant with the sponsor-supplied drugs (50% of the allocated medication for the period since the last visit), it may be appropriate to withdraw the subject from the study. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Study Entrance/Week 26 in Treatment Period

The subject informed consent must be obtained before initiation of tests/observations/evaluations scheduled at Week 26 (VISIT 8).

Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0, and subjects whose eligibility is confirmed will be enrolled in this study. See Section 9.1.15 for procedures for documenting screening failures.

Procedures to be completed at Week 26 (VISIT 8; Day 175 - 189) include:

- Dispense study medication

9.3.2 Treatment Period (Weeks 29, 32, 36, 40, and 46)

9.3.2.1 Week 29 (Treatment Period)

Week 29 (VISIT 9; Day 196-210) include:

- Physical Examination Procedure
- Vital Sign Procedure

- Documentation of Concomitant Medications
- Clinical laboratory tests (including pregnancy test for female subjects of child bearing potential)
- AE assessment
- Compliance of study medication
- Dispense investigational drug

9.3.2.2 Week 32 (Treatment Period)

Procedures to be completed at Week 32 (VISIT 10; Day 217-231) include:

- Physical Examination Procedure
- Vital Sign Procedure
- Documentation of Concomitant Medications
- Clinical laboratory tests (including pregnancy test for female subjects of child bearing potential)
- MDS-UPDRS
- AE assessment
- Compliance of study medication
- Dispense investigational drug

9.3.2.3 Week 36 (Treatment Period)

Procedures to be completed at Week 36 (VISIT 11; Day 245-259) include:

- Physical Examination Procedure
- Vital Sign Procedure
- Documentation of Concomitant Medications
- MDS-UPDRS
- AE assessment
- Compliance of study medication
- Dispense investigational drug

9.3.2.4 Week 40 (Treatment Period)

Week 40 (VISIT 12; Day 273-287) include:

- Physical Examination Procedure
- Weight
- Vital Sign Procedure
- Documentation of Concomitant Medications

- Clinical laboratory tests (including pregnancy test for female subjects of child bearing potential)
- ECG Procedure
- MDS-UPDRS
- QOL
- AE assessment
- Compliance of study medication
- Dispense investigational drug

9.3.2.5 Week 46 (Treatment Period)

Procedures to be completed at Week 46 (VISIT 13; Day 315-329) include:

- Physical Examination Procedure
- Vital Sign Procedure
- Documentation of Concomitant Medications
- Clinical laboratory tests (including pregnancy test for female subjects of child bearing potential)
- MDS-UPDRS
- AE assessment
- Compliance of study medication
- Dispense investigational drug

9.3.3 Week 52 (Treatment Period) or Early Termination

The following procedures will be performed in the last visit scheduled at Week 52 in the treatment period (VISIT 14; Day 357 - 371). For subjects who started the investigational drug adninistration in this study and are withdrawn from the study before the last visit at Week 52, the procedures scheduled at Week 52 should be performed within 7 days from the termination of study medication (the last administration day is defined as day 0), whenever possible.

- Physical Examination Procedure
- Skin examination
- Weight
- Vital Sign Procedure
- Documentation of Concomitant Medications
- Clinical laboratory tests (including pregnancy test for female subjects of child bearing potential)

- ECG Procedure
- MDS-UPDRS
- QOL
- AE assessment
- Compliance of study medication

For all subjects receiving study medication, the investigator must complete the End of Study (e)CRF page.

9.3.4 Post Study Care

The study medication will not be available upon completion of the subject's participation in the study.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in the preceding study but prior to administration of study medication of the run-in period of the preceding study; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses vs signs and symptoms:

Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator or sub-investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions (disease or symptom present before signing of the informed consent in the preceding study):

Pre-existing conditions (present at the time of signing of informed consent in the preceding study) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays etc.) immediately after signing of informed consent in the preceding study should NOT be recorded as PTEs unless related to study procedures. However, if a subject experiences an abnormality (e.g., internal bleeding due to blood collection) related to the procedures for the baseline tests/observations in the preceding study, the abnormality should be recorded as a PTE on the (e)CRF. If the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). The investigator or sub-investigator should ensure that the event term recorded captures the change in the condition (e.g., “worsening of hypertension”).

If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, the investigator or sub-investigator should ensure that the AE term recorded captures the change in the condition from Baseline (e.g. “worsening of…”). If a subject has a degenerative concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, the

investigator or sub-investigator should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Worsening of PTEs or AEs:

If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., worsening of…").

If the subject experiences a worsening or complication of an AE after any change in study medication (including change from a study medication for the CCT-001 study to that for the OCT-001), the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., worsening of…").

Changes in severity of AEs /Serious PTEs:

If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent in the preceding study are not considered PTEs or AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

Elective procedures performed where there is no change in the subject's medical condition (e.g., cosmetic surgery) should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator or sub-investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the (e)CRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the (e)CRF.

10.1.4 SAEs

A SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING*.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

*The term “life threatening” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress (ARDS)	Hepatic necrosis
Torsade de pointes/ventricular fibrillation/ventricular tachycardia	Acute liver failure
Malignant hypertension	Anaphylactic shock
Convulsive seizures (including convulsion and epilepsy)	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anemia	Pulmonary fibrosis (including interstitial pneumonia)
Toxic epidermal necrolysis/mucocutaneous syndrome (Stevens-Johnson syndrome)	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death
	Confirmed or suspected transmission of infectious agent by a medicinal product
	Confirmed or suspected endotoxin shock

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to the investigational drug will be assessed using the following categories:

Term	Definition	Clarification
Unrelated	This category applies to those adverse events which, after careful consideration, are clearly and incontrovertible due to extraneous causes (disease, environment, etc.)	This category applied to those adverse events which, after careful consideration, are clearly and incontrovertible due to extraneous causes (disease, environment, etc.)
Unlikely	In general, this category can be considered applicable to those adverse events which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug.	An adverse experience may be considered unlikely related if or when (must have 2): ・ It does not follow a reasonable temporal sequence from administration of the drug. ・ It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. ・ It does not follow a known pattern of response to the test drug. ・ It does not reappear or worsen when the drug is re-administered.
Possibly	This category applies to those adverse events for which, after carful medical consideration at the time they are evaluated, a connection with the test drug administration appears unlikely but cannot be ruled out with certainty.	An adverse experience may be considered possibly related if or when (at least 2 of the following): ・ It follows a reasonable temporal sequence from administration of the drug. ・ It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. ・ It follows a known pattern of response to the test drug.
Probably	This category applies to those adverse events which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the test drug.	An adverse experience may be considered probably related if or when (at least 3 of the followings): ・ It follows a reasonable temporal sequence from administration of the drug. ・ It could not be reasonable explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. ・ It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia). ・ It follows a known pattern of response to the test drug.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date

The date of onset of a PTE or an AE will be determined according to the following criteria.

PTE or AE	Date of onset
Signs, symptoms, and diseases (diagnoses)	The date on which the subject, the investigator or sub-investigator first noted the signs/symptoms of an AE.
Asymptomatic diseases	The date on which a definitive diagnosis is obtained through tests. The date on which a diagnosis is confirmed should be recorded, even when the test result indicates an old sign(s) of the disease, or an approximate time of onset.
Worsening of concurrent diseases or PTEs Worsening of AEs ovserved in the preceding study	The date on which the subject, the investigator or sub-investigator first noted the first worsening of disease/symptom.
For PTEs: cases in which normal values at the time of screening (i.e., the first test after signing of the informed consent) in the preceding study are abnormal at the subsequent test; For AEs: cases in which abnormal test values are found at the test after the start of administration of the investigational drug	The date on which a clinically abnormal laboratory parameter is observed.

For PTEs: cases in which abnormal test values are found at the first test after signing of the informed consent and they are found to have worsened at the subsequent test; For AEs: cases in which abnormal test values are found at the test after the start of administration of the investigational drug and they worsen at the subsequent test	The date on which a clinically obvious increase/decrease in a laboratory parameter is confirmed based on the time profile of the parameter.

10.1.9 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died. In the event that the stop date of AE/PTE is not comfirmed, AE/PTE will be determined to be continuing.

10.1.10 Frequency

Episodic AEs/PTE (e.g., constipation, diarrhoea, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Medication

Actions associated with the investigational drug will be classified or defined as follows:

Drug withdrawn	A study medication is stopped due to the particular AE (including discontinuation/withdrawal based on the subject's own judgment).
Dose not changed	The particular AE did not require stopping a study medication. Cases in which administration of the investigational drug is discontinued or the dose is reduced or increased because of an AE other than the particular AE. Cases in which administration of the investigational drug is discontinued or its dose is reduced for a reason other than the AE, e.g., inadvertent behavior by the subject.
Unknown	Only to be used if it has not been possible to determine what action has been taken because of loss of follow-up.
Not Applicable	A study medication was stopped for a reason other than the particular AE, or dosing with study medication was already stopped before the onset of the AE.

10.1.12 Outcome

The outcome of a PTE or an AE will be determined according to the following criteria:

Category	Criteria
Recovered/Resolved	・The sign and symptom disappeared or resolved. ・Subject returned to first assessment status (the value before the administration of the investigational drug*) in the preceding study for AEs, or the value at the first test after signing of the informed consent in the preceding study for PTEs.
Recovering/Resolving	・The intensity is lowered by one or more stages. ・The diagnosis or signs/symptoms has almost disappeared. ・The abnormal laboratory value improved, but has not returned to the normal range or to the value before the administration of the investigational drug* in the preceding study (for AEs) or the value at the first test after signing of the informed consent in the preceding study (for PTEs). ・The subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving" (no need to record the date of death).
Not recovered /not resolved	・There is no change in the diagnosis, signs or symptoms. ・The intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started. ・Is an irreversible congenital anomaly. ・The subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved" (no need to record the date of death).
Resolved with sequelae	・The subject recovered from an acute AE/PTE but was left with impairment which interrupts the subject's usual activities.
Fatal	・PTE/AE directly related to death "Direct relationship with the PTE/AE" means that the PTE/AE caused the death or apparently contributed to the death. ・Cases in which the outcome of the PTE/AE observed in the same subject is determined or assumed as not having directly caused the death are not documented as "fatal." ・If the outcome of the PTE/AE is "fatal," the date of death should be documented.
Unknown	・The course of the AE/serious PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

* "The value before the administration of the investigational drug" means the value at the start of the study medications in the run-in period in the preceding study for the PTE/AE occurred before the initiation of administration for the treatment period in the preceding study, and the value at baseline for the AEs occurred after initiation of the investigational drug for the treatment period in the preceding study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the preceding study and continue until the subject is first administered study medication in the run-in period in the preceding study. For subjects who discontinue prior to study medication administration in the run-in period in the preceding study, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication in this study. Routine collection of AEs will continue until tests scheduled at Week 52 in the treatment period (or at early termination).

AEs occurred between at the end of the last laboratory tests in the preceding study (TVP-1012/CCT-001) and before initiation of administration in this study will be collected as AEs occurred in the preceding study and any AEs observed in the preceding study will be monitored continuously throughout this study.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator or sub-investigator will assess whether any subjective AEs have occurred. A neutral question, such as “How have you been feeling since your last visit?” may be asked. Subjects may report AEs occurring at any other time during the study.

Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to the value at the first laboratory test after signing of informed consent of the preceding study or there is a satisfactory explanation for the change (persistent, irreversible PTE). Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline (to the value at the start of the run-in period for AEs occurred before the initiation of the study medications in the treatment period in the preceding study, or the value at baseline for AEs occurred after administration of the study medication in the treatment period in the preceding

study) or until there is a satisfactory explanation for the changes observed (persistent, irreversible PTE). All PTEs and AEs will be documented in the PTE/AE page of the (e)CRF, whether or not the investigator or sub-investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term
- Start and stop date
- Frequency
- Severity
- Investigator's opinion of the causal relationship between the event and administration of study medications (Unrelated, Unlikely, Possibly, Probably)
- Action concerning study medication
- Outcome of event
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure
- Seriousness

AEs and serious PTEs will be followed up until they have resolved or the investigator or sub-investigator judges that the follow-up is no longer necessary.

10.2.2 Collection and Reporting of SAEs

When a SAE occurs through the AE collection period it should be reported according to the following procedure. PTEs that meet the criteria for SAEs described in Section 10.1.4 will be reported in a same manner to that for SAEs.

A SAE should be reported to Safety Information Emergency Call Center (described in the separate contact information list) within 1 business day of first onset or subject's notification of the event. The investigator should submit the completed SAE form within 10 calendar days to Safety Information Emergency Call Center. Also the original document of a Takeda SAE form must be submitted to the sponsor.

The information to be reported within 1 business day should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious

- Subject identification number
- Investigator's or sub-investigator's name
- Name of the study medications
- Causality assessment (relationship with the study medication or study procedure)

Any SAE spontaneously reported to the investigator or sub-investigator following the AE collection period should be reported to the sponsor.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST > 3 × ULN and total bilirubin > 2 × ULN for which an alternative etiology has not been identified, the event should be recorded as a SAE and reported as per Section 10.2.2. The investigator or sub-investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B, other acute liver disease, or a history or concurrent medical condition. Follow-up laboratory tests as described in Section 9.1.9 must also be performed.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator or sub-investigator should complete a follow-up SAE form or provide other written documentation immediately to the sponsor or Safety Information Emergency Call Center. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested by the sponsor or IRB.

All SAEs should be followed up until resolution or permanent outcome of the event.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, IRBs, and the head of the study site, as applicable. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee (CRO), SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current

benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 CRFs (Electronic and Paper)

Completed (e)CRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to (e)CRFs. The sponsor will make arrangements to train the investigator, sub-investigator, and study coordinator in the use of the (e)CRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. (e)CRFs must be completed directly recording data in English.

Corrections to (e)CRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the (e)CRFs for completeness and accuracy and must sign and date the appropriate (e)CRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the (e)CRFs.

The following data will not be recorded directly into the (e)CRFs.

1) Laboratory Test Results Measured at Central Laboratory

After the database lock of clinical study database, any change of, modification of or addition to the data on the (e)CRFs should be made by the investigator sub-investigator with use of change and modification records of CRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the Data Clarification Form for completeness and accuracy, and must sign, or sign and seal, and date the form.

(e)CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the (e)CRFs. The completed (e)CRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator or the head of the site agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms, copies of all paper CRFs, electronic copy of (e)CRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. In addition, the investigator and the head of the site are required to retain essential relevant documents until the day as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the site should discuss how long and how to retain those documents with the sponsor.

1) The day on which marketing approval of the investigational drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2) The day 3 years after the date of early termination or completion of the clinical study.

In addition, the investigator and the head of the institution should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

The analyses for this study will be performed using pooled data from the preceding study and this study, in principle, based on data obtained after administration of TVP-1012.

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock of this study. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to database lock of this study. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

In this study, two kinds of analysis sets are defined: full analysis set (FAS) and safety analysis set. The safety analysis set, the analysis set used for safety analysis, will be defined as “all subjects who were received at least one dose of TVP-1012.” The definition of each analysis set will be described in the Handling Rules for Analysis Data.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, consulting a medical expert as needed. If necessary, the Handling Rules for Analysis Data will be supplemented with new handling rules that were not discussed at the planning stage. The Handling Rules for Analysis Data must be finalized prior to database lock.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized overall and by treatment group of the preceding study using the safety analysis set.

13.1.3 Efficacy Analysis

(1) [Secondary endpoint and its analytical method]

[Secondary endpoint]

- MDS-UPDRS Part II＋Part III total score

[Analysis method]

The following analysis will be performed for FAS.

Descriptive statistics (number of subjects, mean, standard deviation, maximum, minimum, and quartiles) and two-sided 95% confidence intervals of means will be provided for the MDS-UPDRS Part II + Part III total score at each visit and the change from baseline in the MDS-UPDRS Part II + Part III total score at each visit of the treatment period by treatment group in the preceding study.

(2) Additional efficacy endpoints

Refer to Section 5.2.3.

(3) Method of data conversion and handling of missing data

Details will be described in the Handling Rules for Analysis Data and the Statistical Analysis Plan.

(4) Significance level and confidence coefficient

- Confidence coefficient: 95% (two-sided)

13.1.4 Safety Analysis

(1) Primary endpoint and its analytical method

[Primary endpoint]

- Adverse events

[Analytical methods]

The following analyses will be based on the safety analysis set.

A treatment-emergent adverse event (TEAE) is defined as an adverse event whose date of onset occurs on or after the start of treatment period study drug in the preceding study.

TEAEs whose date of onset occurs on or after the start of TVP-1012 will be coded using the MedDRA dictionary. The frequency distribution will be provided using the system organ class and the preferred term for each treatment group of the preceding study as follows:

- All TEAEs
- Drug-related TEAEs
- Intensity of TEAEs

- Intensity of drug-related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- TEAEs over time

(2) Secondary endpoints and their analytical methods

[Secondary endpoints]

- Laboratory test results, vital signs, 12-lead ECGs and weight

[Analytical methods]

The following analyses will be based on the safety analysis set.

For continuous variables, the observed values and the changes from baseline will be summarized by treatment group of the preceding study for each visit using descriptive statistics.
Case plots will also be presented for the observed values by treatment group of the preceding study.

For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided for each treatment group of the preceding study.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

Number of subjects to be enrolled in this study: approximately 182

[Justification of Sample size]

In the preceding study, the planned number of subjects to be randomized was a total of 240 (120 per group) and the planned number of subjects evaluable for the primary endpoint (change in the MDS-UPDRS Part II + Part III total score from baseline to Week 26 of the treatment period (LOCF)) was a total of 220 (110 per group).

Since this study is a long-term extension study in patients with early Parkinson's disease who have completed the 26-week treatment period in the preceding study, considering the potential dropouts in the preceding study, approximately 182 subjects will be enrolled in this study.

In addition, considering the potential dropouts in this study and in the preceding study, it is estimated that 155 subjects will be treated with 1 mg of TVP-1012 for 26 weeks and 59 subjects for 52 weeks.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the (e)CRFs. Source documents are defined as original documents, data, and records. The investigator and the head of the institution guarantee access to source documents by the sponsor or its designee and by the IRB

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, and review of (e)CRFs and associated source documents. It is important that the investigator or sub-investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator or sub-investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained.

The investigator or sub-investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA]). If the study site is contacted for an inspection by a regulatory body, the

sponsor should be notified immediately. The investigator and the head of the institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B.

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the sponsor-supplied drug or before initiation of the run-in period). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., informed consent form) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form and the subject information sheet describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information (to the third party including overseas) for purposes of conducting the study. The informed consent form and the subject information sheet further explains the nature of the study, its objectives, and potential risks and benefits. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form and the subject information sheet. The informed consent form and the subject information sheet must be approved by both the IRB and the sponsor prior to use.

The informed consent form and the subject information sheet must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or sub-investigator to explain the detailed elements of the informed consent form and the subject information sheet to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject determines he or she will participate in the study, then the informed consent form must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator or sub-investigator must also sign and date the informed consent form at the time of consent and prior to subject entering into the study.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator or sub-investigator must document the date the subject signs the

informed consent in the subject's medical record. Copies of the signed informed consent form shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, MHRA, Pharmaceuticals and Medical Devices Agency [PMDA]), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's [e]CRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site

agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator or sub-investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, Takeda will, at a minimum register all clinical trials conducted in patients that it sponsors anywhere in the world on publicly accessible websites, JAPIC-CTI, before trial initiation.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of this clinical trial, regardless of outcome on publicly accessible websites, JAPIC-CTI, as required by applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects.

Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator or sub-investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

[1] Parkinson's disease and related diseases (3) Parkinson's Disease (subsidized by government), Japan Intractable Diseases Information Center: Japan Intractable Diseases Research Foundation/Japan Intractable Diseases Information Center, http://www.nanbyou.or.jp/entry/169 (2014/10/30 accessed)

[2] Preparation Committee for Guidelines on Parkinson's Disease, Japanese Society of Neurology, "Practical Guidelines for Parkinson's Disease 2011" Igaku Shoin, 2011.

[3] Schapira AH. Treatment options in the modern management of Parkinson disease. Arch Neurol. 2007; 64(8): 1083-1088

[4] Schapira AH. Olanow CW. Drug selection and timing of initiation of treatment in early Parkinson's disease. Ann Neurol. 2008; 64(Suppl 2): S47-55

[5] [redacted]

[6] [redacted]

[7] [redacted]

Appendix A Schedule of Study Procedures

Study Week [a]	Treatment period						
	W26	W29	W32	W36	W40	W46	W52/ Early Termination [b]
VISIT Number [c]	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Study Day[d] (Day)	182	203	224	252	280	322	364
Visit Windows [d] (Days)	175 to 189	196 to 210	217 to 231	245 to 259	273 to 287	315 to 329	357 to 371
Informed consent	X [e]						
Inclusion/exclusion criteria	X						
Physical examination	*X* [f]	X	X	X	X	X	X
Skin examination	*X* [f]						X
Weight	*X* [f]				X		X
Vital signs	*X* [f]	X	X	X	X	X	X
Concomitant medications	*X* [f]	X	X	X	X	X	X
Clinical laboratory tests [g]	*X* [f]	X	X		X	X	X
ECG	*X* [f]				X		X
MDS-UPDRS	*X* [f]		X	X	X	X	X
QOL assessment	*X* [f]				X		X
Drug compliance	*X* [f]	X	X	X	X	X	X
Dispense investigational drug	X	X	X	X	X	X	
AE assessment[h]	*X* [f]	X	X	X	X	X	X

(a) The study visit weeks in this study will be counted from the start of the treatment period in the preceding study.
(b) For subjects withdrawn from the study after the initiation of the investigational drug in this study and before Week 52 of the treatment period, the tests, observations, and assessments scheduled for Week 52 of the treatment period should be performed within 7 days following discontinuation of treatment, whenever possible (the day of the last dose regarded as 0 day).
(c) Visit numbers in this study will be continued from the preceding study.
(d) Day 1 is defined as the day of first study medication administration for the treatment period in the preceding study.
(e) Informed consent for this study must be obtained prior to tests, observations, and assessments at Week 26 of the treatment period in the preceding study.
(f) Results of the tests, observations, and assessments at Week 26 of the treatment period in the preceding study will be used also for this study.
(g) To be measured after fasting for at least 8 hours whenever possible. Women of childbearing potential will undergo pregnancy test as well.
(h) AE collection in this study will begin at the initiation of the investigational drug in this study, and continued until Week 52 of the treatment period or early termination. AEs occurring between the final assessment in the preceding study and the initiation of the investigational drug in this study will be captured by the preceding study. AEs that occurred during the preceding study and persisted into this study will be followed up in this study as well.

Appendix B Responsibilities of the Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to the sub-investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the director of the site in advance to get them accepted.
3. Prepare a written informed consent form and other written information, and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications and responsibilities of individual personnel to the sub-investigator and study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing and obtain the written consent.
7. Assume responsibility for all the medical judgment related to the study.
8. Ensure in collaboration with the director of the site that sufficient information on all clinically significant adverse events related to the study are provided to subjects throughout and beyond the period when subjects participate in the study.
9. If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of a SAE, immediately notify the director of the site and the sponsor in writing.
11. Determine the need of emergency key code blinding of a subject in case of emergency.
12. Prepare correct and complete (e)CRFs, and submit them to the sponsor with electronic signature.
13. Check and confirm the contents of (e)CRFs prepared by the sub-investigator or transcribed from the source data by the study collaborator, and submit them to the sponsor with electronic signature.
14. Discuss any proposal from the sponsor including update of the protocol.
15. Notify the director of the site of the end of the study in writing.

Appendix C Detailed Description of Amendments to Text

Amendments made from the first edition of this study protocol are listed below.

Page 14, 4.1 Background, Safety Summary

Existing Text

[redacted]

Revised Text

[redacted]

Rationale for Amendment

To appropriately document the summary of safety results based on the information on the incidence of adverse events in the 2 mg of TVP-1012 monotherapy group

Page 24, 7.3 Excluded Medications and Treatments

Existing Text

(15) CYP1A2 inhibitor

Revised Text

(15) CYP1A2 inhibitor **(including ciprofloxacin, enoxacin, fluvoxamine, zafirlukast)**

Rationale for Amendment

To specify CYP1A2 inhibitors

Page 25, 7.3 Excluded Medications and Treatments

Existing Text

(17) Antidepressant *(excluding trazodone)*

Revised Text

(17) Antidepressant

Rationale for Amendment

Prohibiting concomitant use of all anti-depressants, including trazodone, was determined to be appropriate, considering the safety of subjects and potential effect on efficacy evaluations.

Page 27, 7.4 Diet, Fluid, Activity Control

Existing Text

(No description)

Revised Text

11. Subjects should avoid driving vehicles, operating machinery, and working in high areas, etc., in consideration of possible treatment-emergent dizziness, or reduced attention, concentration, or reflex function.

Rationale for Amendment

Having judged that caution should be made in light of safety of subjects based on descriptions of overseas labeling information of TVP-1012 and Japanese package insert for Parkinson's disease drugs.