Title: AZILECT Tablets Special Drug Use-Results Survey “Survey on Long-term Safety”

NCT Number: NCT03727139

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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 as the language on original version was Japanese.

Statistical Analysis Plan

(Final Analysis)

Name of product	: AZILECT Tablets 0.5 mg, AZILECT Tablets 1 mg
Survey title	: Survey on Long- term Safety
Protocol Number	: Rasagiline-5001
Survey Sponsor	: Takeda Pharmaceutical Company Limited

Takeda Pharmaceutical Company Limited
Director of Biostatistics Department

Seal

Month Day, Year

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List of Terms and Abbreviations

- This drug: AZILECT Tablets is abbreviated as “this drug”.
- Adverse events: Adverse events that occurred after administration of this drug
- ADRs: Adverse drug reactions/infections, defined as adverse events other than those assessed as causally “not related” to this drug by the survey physician. This statistical analysis plan uses "adverse drug reactions/infections" in titles and ADRs in main text and table columns.
- Serious adverse event: An adverse event assessed as "serious" by the survey physician. Also, events listed in the MedDRA Code List (PT code) of the Important Medical Events List are handled as serious events, even if the event is assessed as "non-serious” by the survey physician.
- "Related" to this drug: Adverse events with a causal relationship to this drug other than "not related" are handled as "related", and adverse events with a causal relationship to this drug of "not related" are handled as "not related".
- Summary statistics: This includes the number of patients, mean, standard deviation, maximum, minimum, and quartiles.
- Number of days after administration: The day before initiation of treatment is counted as −1 day, and the day of initiation of treatment is counted as 1 day.
- Treatment duration (days): Therapy end date − Therapy start date + 1
- Disease duration (years): Calculated as (Date of first administration of this drug − Date of disease onset + 1)/365.25. If the month and day of disease onset are unknown, January 1 shall be used. If the day of disease onset is unknown, 1 shall be used as the day. The calculated value shall be rounded to the first decimal place.
- Patients without collected CRFs: Patients who were enrolled but whose CRFs were not collected
- Patients with collected CRFs: Patients who were enrolled and whose CRFs were collected
- Time to adverse event (or ADR) onset: Calculated as “Date of onset of the adverse event (or ADR) − Date of first administration of this drug + 1”.
    - If the month and day of onset of the adverse event (or ADR) are unknown, January 1 shall be used in the calculation. However, if the year of first administration of this drug is the same as the year of onset of the adverse event (or ADR), the month and day of first administration of this drug shall be used in the calculation.
    - If the day of onset of the adverse event (or ADR) is unknown, 1 shall be used as the day. However, if the year and month of first administration of this drug are the same as the year

and month of onset of the adverse event (or ADR), the day of first administration of this drug shall be used in the calculation.

- Unified Parkinson's Disease Rating Scale (UPDRS) Part III total score: Calculated by summing the following scores: "Speech", "Facial expression", "Resting tremor (face, left hand, right hand, left foot, right foot)", "Hand kinetic tremor or postural tremor (left, right)", "Rigidity (neck, left upper extremity, right upper extremity, left lower extremity, right lower extremity)", "Finger tapping (left, right)", "Hand movements (left, right)", "Pronation-supination movements of hands (left, right)", "Leg agility (left, right)", "Arising from chair", "Posture", "Gait", "Postural stability", "Bradykinesia and hypokinesia".
- Unified Parkinson's Disease Rating Scale (UPDRS) Part III tremor score: Calculated by summing the following scores: "Resting tremor (face, left hand, right hand, left foot, right foot)" and "Hand kinetic tremor or postural tremor (left, right)".
- Unified Parkinson's Disease Rating Scale (UPDRS) Part III akinesia/hypokinesia score: Calculated by summing the following scores: "Finger tapping (left, right)", "Hand movements (left, right)", "Pronation-supination movements of hands (left, right)", "Leg agility (left, right)", and "Bradykinesia and hypokinesia".
- Unified Parkinson's Disease Rating Scale (UPDRS) Part III rigidity score: Calculated by summing the following scores: "Rigidity (neck, left upper extremity, right upper extremity, left lower extremity, right lower extremity)".

Analysis Populations

The analysis populations of "safety analysis population" and "efficacy analysis population" will be established in this survey. These analysis populations are defined as follows.

- Safety analysis population

This population is defined as the patients who received this drug, had no major protocol violations, and were evaluable for safety. More specifically, the safety analysis population will exclude patients meeting the following conditions, among those with the CRF data locked:

- No administration of this drug
- Administration of this drug before the contractual period
- Enrollment outside the enrollment period
- Enrollment 15 days or more after the date of prescription of this drug
- Prescription of this drug outside of the contract period
- No information on presence or absence of adverse events
- Withdrawal of consent

- Efficacy analysis population

This population is defined as a subset of the patients in the safety analysis population who had no major protocol violations and were evaluable for efficacy. More specifically, the efficacy analysis population will exclude patients meeting the following conditions,

- No target disease
- Administration of contraindicated medication for this drug (Parkinson's disease medication)

Safety Specification (Important Identified Risks, Important Potential Risks, and Important Missing Information)

- Important identified risks
    - Orthostatic hypotension: Events falling under the adverse event category of “(1) Orthostatic hypotension” in the CRF.
    - Somnolence and sudden onset of sleep: Events falling under the adverse event category of "(2) Somnolence and sudden onset of sleep" in the CRF.
    - Psychiatric symptoms such as hallucination: Events falling under the adverse event category of "(3) Psychiatric symptoms such as hallucination" in the CRF.
    - Dyskinesia: Events falling under the adverse event category of "(4) Dyskinesia" in the CRF.
- Important potential risks: None applicable
- Important missing information: None applicable

Handling of Time Windows

For observation items, data that are evaluable (i.e., not missing and determined to be included in analysis) shall be handled in accordance with the following.

The data that are evaluable and within the allowable time window shall be used. If there are multiple evaluable data within the same allowable time window, the one closest to the standard implementation time point of the examination, observation, or assessment shall be used. If the magnitude of difference from the standard implementation time point is the same, or if the standard implementation time point is not specified, the later data shall be used. The magnitude of the difference from the standard implementation time point shall be determined based on the number of days after administration.

Unified Parkinson's Disease Rating Scale (UPDRS) Part III

Time point of assessment	Standard implementation time point		Allowable time window
			Number of days after administration
At initiation of treatment with this drug (Baseline)	Number of days after administration:	-1	-30 - 1
At 6 months of treatment	Number of days after administration:	182	2 - 273
At 12 months of treatment	Number of days after administration:	365	274 - 456
At 18 months of treatment	Number of days after administration:	547	457 - 638
At 24 months of treatment or discontinuation	Number of days after administration:	730	639 - 821
Final assessment	Number of days after administration:	-	2 - 821

1 Number of survey sites, number of patients enrolled, and disposition of patients

1.1 Disposition of patients (Patient disposition diagram)

Analysis set:	All enrolled patients (Enrolled patients)	
Analysis item(s):	Enrolled patients	
	Number of survey sites	
	Patients without collected CRFs	
	Patients with collected CRFs	
	Patients excluded from the safety analysis population*	
	Reasons for exclusion (patients counted under all applicable categories)	[No administration of this drug, Administration of this drug before the contractual period, Enrollment outside the enrollment period, Enrollment 15 days or more after the date of prescription of this drug, Prescription of this drug outside of the contract period, No information on presence or absence of adverse events, Withdrawal of consent]
	Safety analysis population	
	Patients excluded from the efficacy analysis population*	
	Reasons for exclusion (patients counted under all applicable categories)	[No target disease, Administration of contraindicated medication for this drug (Parkinson's disease medication)]
	Efficacy analysis population	
Analytical methods:	Analyses of the above items will be performed as follows, and a patient disposition diagram will be constructed. For enrolled patients, the number of survey sites shall also be presented. The same medical institution with different departments in the survey shall be counted as one medical institution. Reasons for exclusion are broken into categories; if there are no patients in a certain category, "0" will be indicated. For patients excluded from the safety or efficacy analysis population, the numbers of patients will be counted by reason for exclusion, and a tabulated list will be prepared. *Patients excluded from the safety analysis population refer to patients whose CRF data locked and who were excluded from the safety analysis population. Patients excluded from the efficacy analysis population refer to patients who	

were in the safety analysis population and who were excluded from the efficacy analysis population.

- Frequency tabulation

2 Patient background

2.1 Patient background

Analysis set:	Safety analysis population	
Analysis item(s):	Sex	[Male, Female]
	Age (years)	[Min<= - <65, 65<= - <70, 70<= - <75, 75<= - <80, 80<= - <=Max]
	Duration of Parkinson's disease (years)	[0<= - <5, 5<= - <10, 10<= - <15, 15<= - <=Max, Unknown]
	Inpatient/outpatient status (at initiation of treatment with this drug)	[Outpatient, Inpatient]
	Concurrent diseases	[No, Yes]
	Specific concurrent diseases (patients counted under all applicable categories)	[Diabetes mellitus, Hypertension, Dyslipidemia, Hyperuricaemia]
	Lifestyle-related disease	[Hepatic steatosis, Alcoholic hepatitis, Chronic hepatitis, Hepatic cirrhosis]
	Hepatic disease	[Nephrotic syndrome, Glomerulonephritis, Chronic renal failure]
	Renal disease	[Dementia, Pneumonia aspiration, Constipation]
	Other diseases	
	Dementia	[No, Yes]
	Height (cm)	[Min < =- < =140,141 < =- < =150,151 < =- < =160,161 < =- < =170,171 < =- < =Max, Not measured].
	Body weight (kg)	[Min < =- < 50,50 < =- < 65,65 < =- < =Max, Not measured].
	Smoking history	[Never smoker, Current smoker, Former smoker, Unknown]
	Modified Hoehn & Yahr Severity scale (Stage)	[0, 1, 1.5, 2, 2.5, 3, 4, 5]
	Levodopa use at initiation of treatment with this drug	[No, Yes]
	Wearing-off phenomenon	[No, Yes]

	Note: Only in patients given levodopa at initiation of treatment with this drug	
	Dyskinesia	[No, Yes]
	Note: Only in patients given levodopa at initiation of treatment with this drug	
	UPDRS Part III total score (at initiation of treatment with this drug)	[Min<= - <=10, 11<= - <=20, 21<= - <=30, 31<= - <=40, 41<= - <=50, 51<= - <=60, 61<= - <=Max]
	Tremor score (at initiation of treatment with this drug)	
	Akinesia/hypokinesia score (at initiation of treatment with this drug)	
	Rigidity score (at initiation of treatment with this drug)	
	Treatment stage	[AZILECT alone; AZILECT + other Parkinson's disease medication; Combined with only levodopa, without wearing-off phenomenon; Combined with levodopa and other Parkinson's disease medication, without wearing-off phenomenon; Combined with levodopa, with wearing-off phenomenon]
Analytical methods:	For the above analysis items, discrete data will be summarized using frequency tabulation and continuous data will be summarized using summary statistics.	

3 Treatment details

3.1 Detailed use of this drug

Analysis set:	Safety analysis population	
Analysis item(s):	Daily dose	[1 mg, 0.5 mg, Other]
	Overdose	[No, Yes]
	Any adverse event due to overdose	[No, Yes]
	Reason for use (at initial dose) Note: Only when the daily dose was "0.5 mg"	[Because of the patient's mild hepatic impairment, low body weight, advanced age, or concurrent CYP1A2 inhibitor use; Other]
	Treatment duration (months)	[0<= - <=6, 7<= - <=12, 13<= - <=18, 19<= - <=Max]
	Reason for treatment discontinuation	[Achievement of treatment goal; Adverse event onset; No return to survey site (including referral to another hospital); Pregnancy; Inadequate effectiveness; Withdrawal of consent; Other]
Analytical methods:	For the above analysis items, discrete data will be summarized using frequency tabulation and continuous data will be summarized using summary statistics.	

3.2 Status of treatment compliance with this drug

Analysis set:	Safety analysis population	
Analysis item(s):	Status of treatment compliance with this drug	[90% or more, 70% or more, 50% or more, <50%, No doses were taken, or treatment compliance was unknown]
Analytical methods:	For the above analysis item, data will be summarized using frequency tabulation by time point of assessment (i.e., at 6 months, 12 months, 18 months, and 24 months of treatment or discontinuation).	

3.3 Detailed use of levodopa

Analysis set:	Safety analysis population	
Analysis item(s):	Levodopa use	[No, Yes]
	Daily dose	[<200 mg, 200 to <400 mg, ≥400 mg]

	Treatment duration (months)	[0<= - <=6, 7<= - <=12, 13<= - <=18, 19<= - <=Max]
Analytical methods:	For the above analysis items, discrete data will be summarized using frequency tabulation and continuous data will be summarized using summary statistics.	

3.4 Detailed use of drugs to treat Parkinson's disease other than this drug and levodopa

Analysis set:	Safety analysis population	
Analysis item(s):	Any drugs to treat Parkinson's disease other than AZILECT and levodopa	[No, Yes]
	Name of drug	
Analytical methods:	Frequency tabulation will be performed for the above analysis item.	

3.5 Detailed use of concomitant drugs (Parkinson's disease medication)

Analysis set:	Safety analysis population	
Analysis item(s):	Number of concomitant drugs	[0 (AZILECT alone), 1 (AZILECT + another drug), ≥2 (AZILECT + ≥2 other drugs)]
Analytical methods:	Frequency tabulation will be performed for the above analysis item.	

3.6 Detailed use of concomitant drugs (other than drugs to treat Parkinson's disease)

Analysis set:	Safety analysis population	
Analysis item(s):	Concomitant drugs (Parkinson's disease medication)	[No, Yes]
Analytical methods:	Frequency tabulation will be performed for the above analysis item.	

3.7 Detailed use of concomitant therapies other than pharmacotherapy for Parkinson's disease

Analysis set:	Safety analysis population	
Analysis item(s):	Use of concomitant medications other than medications for Parkinson's disease	[No, Yes]

Analytical methods:	Frequency tabulation will be performed for the above analysis item.

3.8 Distribution of dose by age and body weight

Analysis set:	Safety analysis population	
Analysis item(s):	Daily dose	[1 mg, 0.5 mg]
Stratification factor 1:	Age (years)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
Stratification factor 2:	Body weight	[Min<= - <50, 50<= - <65, 65<= - <=Max]
Analytical methods:	For the above analysis item, patients will be stratified first by Stratification factor 1 and then by Stratification factor 2, with the discrete data summarized using frequency tabulation for each stratum of Stratification factor 2.	

4 Safety data

4.1 Incidence of adverse events and adverse drug reactions/infections

4.1.1 Incidence of adverse events

Analysis set: Safety analysis population

Analysis item(s): Adverse events

Analytical methods: Analyses of the above analysis item will be performed as follows.

1. Number of patients with adverse events
2. Number of adverse events
3. Percentage of patients with adverse events
4. Type of adverse events

All analyses will be accounted for as follows.

[Number of patients with adverse events]

- Number of patients who experienced adverse events.

[Number of adverse events]

- Number of adverse events that occurred. When the same patient experienced multiple episodes of the same adverse event, all episodes will be counted.

[Percentage of patients with adverse events]

- Calculated as “Number of patients with adverse events/Number of patients in the safety analysis population x 100”

[Type of adverse events]

- Adverse events will be coded using MedDRA/J. Events will be classified by SOC and then tabulated by PT. If the SOC is "Investigations", events will be sorted by HLGT (in ascending order of HLGT code, without output) and then tabulated by PT.
- The SOCs will be listed in the internationally agreed order for presentation of the number and percentage of patients with adverse events. When the same patient experienced multiple episodes of the same SOC, they will be counted only once for the SOC.
- The PTs will be listed in ascending order of PT code for presentation of the number and percentage of patients with adverse events. When the same patient experienced multiple episodes of the same PT, they will be counted only once for the PT.

4.1.2 Incidence of adverse drug reactions/infections

Analysis set: Safety analysis population

Analysis item(s): ADRs

Analytical methods: Analyses of the above analysis item will be performed as follows.

1. Number of patients with ADRs
2. Number of ADRs
3. Percentage of patients with ADRs
4. Type of ADRs

All analyses will be accounted for as follows.

[Number of patients with ADRs]

- Number of patients who experienced ADRs.

[Number of ADRs]

- Number of ADRs When the same patient experienced multiple episodes of the same ADR, all episodes will be counted.

[Percentage of patients with ADRs]

- Calculated as “Number of patients with ADRs/Number of patients in the safety analysis population x 100”

[Type of ADRs]

- ADRs will be coded using MedDRA/J. Events will be classified by SOC and then tabulated by PT. If the SOC is "Investigations", events will be sorted by HLGT (in ascending order of HLGT code, without output) and then tabulated by PT.
- The SOCs will be listed in the internationally agreed order for presentation of the number and percentage of patients with ADRs. When the same patient experienced multiple episodes of the same SOC, they will be counted only once for the SOC.
- The PTs will be listed in ascending order of PT code for presentation of the number and percentage of patients with ADRs. When the same patient experienced multiple episodes of the same PT, they will be counted only once for the PT.

4.1.3 Incidence of adverse events and adverse drug reactions/infections relevant to the safety specification

4.1.3.1 Incidence of adverse events relevant to the safety specification (Tabulation by risk item)

Analysis set: Safety analysis population

Analysis item(s): Adverse events relevant to the important identified risks in the safety specification (i.e., Orthostatic hypotension, Somnolence and sudden onset of sleep, Psychiatric symptoms such as hallucinations, Dyskinesia)

Stratification factors: Total

	Seriousness	[Serious, Non-serious]
	Time to onset (days)	[1<= - <=27, 28<= - <=55, 56<= - <=83, 84<= - <=167, 168<= - <=251, 252<= - <=365, 366<= - <=Max]
	Outcome	[Resolved, Resolving, Not resolved, Resolved with sequelae, Death (from the event), Unknown]
	Causal relationship to this drug	[Related, Not related]
	Severity (Somnolence and sudden onset of sleep, Psychiatric symptoms such as hallucination, Dyskinesia)	[Mild, Moderate, Severe]
	Fall or trauma (Orthostatic hypotension, Psychiatric symptoms such as hallucinations, Dyskinesia)	[No, Yes]
	Accident or injury (Somnolence and sudden onset of sleep)	[No, Yes]

Analytical methods: For the above analysis item by risk item, the following analysis will be performed for each stratum of stratification factors. For the risk items to be analyzed, the definitions described in the safety specification (important identified risks, important potential risks, and important missing information) shall be followed.

[Number of patients with adverse events]

- Number of patients who experienced adverse events.

[Number of adverse events]

- Number of adverse events that occurred. When the same patient experienced multiple episodes of the same adverse event, all episodes will be counted.

[Percentage of patients with adverse events]

- Calculated as “Number of patients with adverse events/Number of patients in the safety analysis population x 100”

[Type of adverse events]

- Adverse events will be coded using MedDRA/J. Events will be classified by SOC and then tabulated by PT. If the SOC is "Investigations", events will be sorted by HLGT (in ascending order of HLGT code, without output) and then tabulated by PT.

- The SOCs will be listed in the internationally agreed order for presentation of the number and percentage of patients with adverse events. When the same patient experienced multiple episodes of the same SOC, they will be counted only once for the SOC. For counting by category, if the episodes fall under different categories of a stratification factor, the episodes will be counted once for each of the categories involved. However, in terms of the stratification factors specified at the end of this section, the episodes will be counted only once in the category of highest priority.
- The PTs will be listed in ascending order of PT code for presentation of the number and percentage of patients with adverse events. When the same patient experienced multiple episodes of the same PT, they will be counted only once for the PT. For counting by category, if the episodes fall under different categories of a stratification factor, the episodes will be counted once for each of the categories involved. However, in terms of the following stratification factors, they will be counted only once in the category of highest priority.
  Severity: Severe → Moderate → Mild
  Fall or trauma: Yes → No
  Accident or injury: Yes → No

4.1.3.2 Incidence of adverse drug reactions/infections relevant to the safety specification (Tabulation by risk item)

Analysis set:	Safety analysis population	
Analysis item(s):	ADRs relevant to the important identified risks in the safety specification (i.e., Orthostatic hypotension, Somnolence and sudden onset of sleep, Psychiatric symptoms such as hallucinations, Dyskinesia)	
Stratification factors:	Total	
	Seriousness	[Serious, Non-serious]
	Time to onset (days)	[1<= - <=27, 28<= - <=55, 56<= - <=83, 84<= - <=167, 168<= - <=251, 252<= - <=365, 366<= - <=Max]
	Outcome	[Resolved, Resolving, Not resolved, Resolved with sequelae, Death (from the event), Unknown]

	Severity (Somnolence and sudden onset of sleep, Psychiatric symptoms such as hallucination, Dyskinesia)	[Mild, Moderate, Severe]
	Fall or trauma (Orthostatic hypotension, Psychiatric symptoms such as hallucinations, Dyskinesia)	[No, Yes]
	Accident or injury (Somnolence and sudden onset of sleep)	[No, Yes]

Analytical methods: For the above analysis item by risk item, the following analysis will be performed for each stratum of stratification factors. For the risk items to be analyzed, the definitions described in the safety specification (important identified risks, important potential risks, and important missing information) shall be followed.

[Number of patients with ADRs]

- Number of patients who experienced ADRs.

[Number of ADRs]

- Number of ADRs When the same patient experienced multiple episodes of the same ADR, all episodes will be counted.

[Percentage of patients with ADRs]

- Calculated as “Number of patients with ADRs/Number of patients in the safety analysis population x 100”

[Type of ADRs]

- ADRs will be coded using MedDRA/J. Events will be classified by SOC and then tabulated by PT. If the SOC is "Investigations", events will be sorted by HLGT (in ascending order of HLGT code, without output) and then tabulated by PT.
- The SOCs will be listed in the internationally agreed order for presentation of the number and percentage of patients with ADRs. When the same patient experienced multiple episodes of the same SOC, they will be counted only once for the SOC. For counting by category, if the episodes fall under different categories of a stratification factor, the episodes will be counted once for each of the categories involved. However, in terms of the stratification factors specified at the end of this section, the episodes will be counted only once in the category of highest priority.

- The PTs will be listed in ascending order of PT code for presentation of the number and percentage of patients with ADRs. When the same patient experienced multiple episodes of the same PT, they will be counted only once for the PT. For counting by category, if the episodes fall under different categories of a stratification factor, the episodes will be counted once for each of the categories involved. However, in terms of the following stratification factors, they will be counted only once in the category of highest priority.
  Severity: Severe → Moderate → Mild
  Fall or trauma: Yes → No
  Accident or injury: Yes → No

4.1.3.3 Incidence of adverse drug reactions/infections meeting the safety specification by presence or absence of levodopa use (Tabulation by risk item)

Analysis set:	Safety analysis population	
Analysis item(s):	ADRs relevant to the important identified risks in the safety specification (i.e., Psychiatric symptoms such as hallucinations, Dyskinesia)	
Stratification factor 1:	Levodopa use	[No, Yes]
Stratification factor 2:	Total	
	Seriousness	[Serious, Non-serious]
	Time to onset (days)	[1<= - <=27, 28<= - <=55, 56<= - <=83, 84<= - <=167, 168<= - <=251, 252<= - <=365, 366<= - <=Max]
	Outcome	[Resolved, Resolving, Not resolved, Resolved with sequelae, Death (from the event), Unknown]
	Severity	[Mild, Moderate, Severe]
	Fall or trauma	[No, Yes]
Analytical methods:	The above analysis item by risk item will be analyzed with stratification by Stratification factor 1 and Stratification factor 2, in the same manner as described in Section 4.1.3.2. For the risk items to be analyzed, the definitions described in the safety specification (important identified risks, important potential risks, and important missing information) shall be followed.	

4.1.4 Average event duration per day of adverse drug reactions/infections relevant to the safety specification

4.1.4.1 Average event duration per day of adverse drug reactions/infections relevant to the safety specification (1)

Analysis set:	Safety analysis population
Analysis item(s):	Average event duration per day (hours)
Analytical methods:	For the above analysis item of the ADRs relevant to the important identified risks in the safety specification (Somnolence, Sudden onset of sleep, Psychiatric symptoms such as hallucination, Dyskinesia), summary statistics (of individual patients' average values) will be calculated for each risk item. For the risk items to be analyzed, the definitions described in the safety specification (important identified risks, important potential risks, and important missing information) shall be followed.

4.1.4.2 Average event duration per day of adverse drug reactions/infections relevant to the safety specification (2)

Analysis set:	Safety analysis population
Analysis item(s):	Patient ID number Adverse drug reaction (disease name, disease code) Average event duration per day (hours) Severity Fall or trauma (Psychiatric symptoms such as hallucinations, Dyskinesia) Accident or injury (Somnolence and sudden onset of sleep)
Analytical methods:	For the above analysis item of the ADRs relevant to the important identified risks in the safety specification (Somnolence, Sudden onset of sleep, Psychiatric symptoms such as hallucination, Dyskinesia), a tabulated list will be prepared for each risk item. For the risk items to be analyzed, the definitions described in the safety specification (important identified risks, important potential risks, and important missing information) shall be followed.

4.2 Incidence of adverse events and adverse drug reactions/infections in patients excluded from the safety analysis population

4.2.1 Incidence of adverse events in patients excluded from the safety analysis population

Analysis set:	Patients excluded from the safety analysis population
Analysis item(s):	Adverse events
Analytical methods:	The above item will be analyzed in a similar manner to Section 4.1.1.

4.2.2 Incidence of adverse drug reactions/infections in patients excluded from the safety analysis population

Analysis set:	Patients excluded from the safety analysis population
Analysis item(s):	ADRs
Analytical methods:	The above item will be analyzed in a similar manner to Section 4.1.2.

4.3 Incidence of adverse events and adverse drug reactions/infections by seriousness, time to onset, outcome, and causal relationship to this drug

4.3.1 Incidence of adverse events by seriousness, time to onset, outcome, and causal relationship to this drug

Analysis set:	Safety analysis population	
Analysis item(s):	Adverse events	
Stratification factors:	Total	
	Seriousness	[Serious, Non-serious]
	Time to onset (days)	[1<= - <=27, 28<= - <=55, 56<= - <=83, 84<= - <=167, 168<= - <=251, 252<= - <=365, 366<= - <=Max]
	Outcome	[Resolved, Resolving, Not resolved, Resolved with sequelae, Death (from the event), Unknown]
	Causal relationship to this drug	[Related, Not related]

Analytical methods: For the above analysis item, the following analysis will be performed for each stratum of stratification factors.

1. Number of patients with adverse events
2. Number of adverse events
3. Percentage of patients with adverse events
4. Type of adverse events

All analyses will be accounted for as follows.

[Number of patients with adverse events]

- Number of patients who experienced adverse events.

[Number of adverse events]

- Number of adverse events that occurred. When the same patient experienced multiple episodes of the same adverse event, all episodes will be counted.

[Percentage of patients with adverse events]

- Calculated as “Number of patients with adverse events/Number of patients in the safety analysis population x 100”

[Type of adverse events]

- Adverse events will be coded using MedDRA/J. Events will be classified by SOC and then tabulated by PT. If the SOC is "Investigations", events will be sorted by HLGT (in ascending order of HLGT code, without output) and then tabulated by PT.
- The SOCs will be listed in the internationally agreed order for presentation of the number and percentage of patients with adverse events. When the same patient experienced multiple episodes of the same SOC, they will be counted only once for the SOC. For counting by category, episodes in the same SOC will be counted only once in the category of highest priority specified at the end of this section.
- The PTs will be listed in ascending order of PT code for presentation of the number and percentage of patients with adverse events. When the same patient experienced multiple episodes of the same PT, they will be counted only once for the PT. For counting by category, episodes in the same PT will be counted only once in the category of highest priority as shown below.

  Seriousness: Serious → Non-serious

  Time to onset: 1–27 days → 28–55 days → 56–83 days → 84–167 days → 168–251 days → 252–365 days → 366 days or more

  Outcome: Death (from the event) → Resolved with sequelae → Not resolved → Resolving → Resolved → Unknown

  Relationship to this drug: Related → Not related

4.3.2 Incidence of adverse drug reactions/infections by seriousness, time to onset, and outcome

Analysis set:	Safety analysis population	
Analysis item(s):	ADRs	
Stratification factors:	Total	
	Seriousness	[Serious, Non-serious]
	Time to onset (days)	[1<= - <=27, 28<= - <=55, 56<= - <=83, 84<= - <=167, 168<= - <=251, 252<= - <=365, 366<= - <=Max]

	Outcome	[Resolved, Resolving, Not resolved, Resolved with sequelae, Death (from the event), Unknown]

Analytical methods: For the above analysis item, the following analysis will be performed for each stratum of stratification factors.

1. Number of patients with ADRs
2. Number of ADRs
3. Percentage of patients with ADRs
4. Type of ADRs

All analyses will be accounted for as follows.

[Number of patients with ADRs]

- Number of patients who experienced ADRs.

[Number of ADRs]

- Number of ADRs When the same patient experienced multiple episodes of the same ADR, all episodes will be counted.

[Percentage of patients with ADRs]

- Calculated as “Number of patients with ADRs/Number of patients in the safety analysis population x 100”

[Type of ADRs]

- ADRs will be coded using MedDRA/J. Events will be classified by SOC and then tabulated by PT. If the SOC is "Investigations", events will be sorted by HLGT (in ascending order of HLGT code, without output) and then tabulated by PT.
- The SOCs will be listed in the internationally agreed order for presentation of the number and percentage of patients with ADRs. When the same patient experienced multiple episodes of the same SOC, they will be counted only once for the SOC. For counting by category, episodes in the same SOC will be counted only once in the category of highest priority specified at the end of this section.
- The PTs will be listed in ascending order of PT code for presentation of the number and percentage of patients with ADRs. When the same patient experienced multiple episodes of the same PT, they will be counted only once for the PT. For counting by category, episodes in the same PT will be counted only once in the category of highest priority as shown below.

  Seriousness: Serious → Non-serious

Time to onset: 1–27 days → 28–55 days → 56–83 days → 84–167 days → 168–251 days → 252–365 days → 366 days or more
Outcome: Death (from the event) → Resolved with sequelae → Not resolved → Resolving → Resolved → Unknown

4.4 Factors likely affecting the safety

4.4.1 Incidence of adverse drug reactions/infections by patient background and treatment factor

Analysis set:	Safety analysis population	
Analysis item(s):	ADRs	
Stratification factors:	Sex	[Male, Female]
	Age (years)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Duration of Parkinson's disease (years)	[0<= - <5, 5<= - <10, 10<= - <15, 15<= - <=Max]
	Inpatient/outpatient status (at initiation of treatment with this drug)	[Outpatient, Inpatient]
	Concurrent diseases	[No, Yes]
	Specific concurrent diseases (patients counted under all applicable categories)	[Diabetes mellitus, Hypertension, Dyslipidemia, Hyperuricaemia]
	Lifestyle-related disease	[Hepatic steatosis, Alcoholic hepatitis, Chronic hepatitis, Hepatic cirrhosis]
	Hepatic disease	
	Renal disease	[Nephrotic syndrome, Glomerulonephritis, Chronic renal failure]
	Other diseases	[Dementia, Pneumonia aspiration, Constipation]
	Dementia	[No, Yes]
	Height (cm)	[Min<= - <=140, 141<= - <=150, 151<= - <=160, 161<= - <=170, 171<= - <=Max]
	Body weight (kg)	[Min<= - <50, 50<= - <65, 65<= - <=Max]

Smoking history	[Never smoker, Current smoker, Former smoker, Unknown]
Modified Hoehn & Yahr Severity scale (Stage)	[0, 1, 1.5, 2, 2.5, 3, 4, 5]
Levodopa use at initiation of treatment with this drug	[No, Yes]
Wearing-off phenomenon Note: Only in patients given levodopa at initiation of treatment with this drug	[No, Yes]
Dyskinesia Note: Only in patients given levodopa at initiation of treatment with this drug	[No, Yes]
Concurrent renal disorder	[No, Yes]
Concurrent hepatic disorder	[No, Yes]
Daily dose	[1 mg, 0.5 mg, Other]
Overdose Note: Only when the daily dose was "Other"	[No, Yes]
Any adverse event due to overdose Note: Only when overdose was present	[No, Yes]
Reason for use (at initial dose) Note: Only when the daily dose was "0.5 mg" or "Other"	[Because of the patient's mild hepatic impairment, low body weight, advanced age, or concurrent CYP1A2 inhibitor use; Other]
Treatment stage	[AZILECT alone; AZILECT + other Parkinson's disease medication; Combined with only levodopa, without wearing-off phenomenon; Combined with levodopa and other Parkinson's disease medication, without wearing-off phenomenon;

		Combined with levodopa, with wearing-off phenomenon]
	Number of concomitant drugs	[0 (AZILECT alone), 1 (AZILECT + another drug), ≥2 (AZILECT + ≥2 other drugs)]

Analytical methods: For the above analysis item, the following analysis will be performed for each stratum of stratification factors.

1. Number of patients with ADRs
2. Percentage of patients with ADRs

All analyses will be accounted for as follows.

[Number of patients with ADRs]

- Number of patients who experienced ADRs.

[Percentage of patients with ADRs]

Calculated as "Number of patients with ADRs/Number of patients in the safety analysis population x 100"

4.4.2 Incidence of adverse drug reactions/infections by sex

Analysis set:	Safety analysis population	
Analysis item(s):	ADRs	
Stratification factors:	Sex	[Male, Female]
Analytical methods:	The above item will be analyzed for each stratum of stratification factors in a similar manner to Section 4.1.2.	

4.4.3 Incidence of adverse drug reactions/infections by age category (1)

Analysis set:	Safety analysis population	
Analysis item(s):	ADRs	
Stratification factors:	Age (years)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
Analytical methods:	The above item will be analyzed for each stratum of stratification factors in a similar manner to Section 4.1.2.	

4.4.4 Incidence of adverse drug reactions/infections by age category (2)

Analysis set:	Safety analysis population
Analysis item(s):	ADRs relevant to the important identified risks in the safety specification (i.e., Orthostatic hypotension, Somnolence and sudden onset of sleep, Psychiatric symptoms such as hallucinations, Dyskinesia)

Stratification factor 1:	Number of concomitant medications (Orthostatic hypotension, Psychiatric symptoms such as hallucination)	[0 (AZILECT alone), 1 (AZILECT + another drug), ≥2 (AZILECT + ≥2 other drugs)]
	Daily dose (Orthostatic hypotension, Psychiatric symptoms such as hallucinations, Dyskinesia)	[1 mg, 0.5 mg, Other]
	Body weight (kg) (Orthostatic hypotension, Psychiatric symptoms such as hallucination, Dyskinesia)	[Min<= - <50, 50<= - <65, 65<= - <=Max]
	Presence or absence of dementia (Psychiatric symptoms such as hallucinations)	[No, Yes]
	Presence or absence of dyskinesia (Dyskinesia) Note: Only in patients given levodopa at initiation of treatment with this drug	[No, Yes]
	Presence or absence of Wearing-off phenomenon (Orthostatic hypotension, Psychiatric symptoms such as hallucination) Note: Only in patients given levodopa at initiation of treatment with this drug	[No, Yes]
	Duration of Parkinson's disease (years) (Orthostatic hypotension, Psychiatric symptoms such as hallucination)	[0<= - <5, 5<= - <10, 10<= - <15, 15<= - <=Max]
Stratification factor 2:	Age (years)	[Min<= - <65, 65<= - <75, 75<= - <=Max]

Analytical methods: The above analysis item by risk item will be analyzed as follows, with stratification by Stratification factor 1 and Stratification factor 2. For the risk items to be analyzed, the definitions described in the safety specification (important identified risks, important potential risks, and important missing information) shall be followed.

1. Number of patients with ADRs

2. Percentage of patients with ADRs

4.4.5 Incidence of adverse drug reactions/infections by duration of Parkinson's disease

Analysis set:	Safety analysis population	
Analysis item(s):	ADRs	
Stratification factors:	Duration of Parkinson's disease (years)	[0<= - <5, 5<= - <10, 10<= - <15, 15<= - <=Max]
Analytical methods:	The above item will be analyzed for each stratum of stratification factors in a similar manner to Section 4.1.2.	

4.4.6 Incidence of adverse drug reactions/infections by presence or absence of concurrent diseases

Analysis set:	Safety analysis population	
Analysis item(s):	ADRs	
Stratification factors:	Concurrent diseases	[No, Yes]
Analytical methods:	The above item will be analyzed for each stratum of stratification factors in a similar manner to Section 4.1.2.	

4.4.7 Incidence of adverse drug reactions/infections by body weight

Analysis set:	Safety analysis population	
Analysis item(s):	ADRs	
Stratification factors:	Body weight (kg)	[Min<= - <50, 50<= - <65, 65<= - <=Max]
Analytical methods:	The above item will be analyzed for each stratum of stratification factors in a similar manner to Section 4.1.2.	

4.4.8 Incidence of adverse drug reactions/infections by presence or absence of concurrent renal disorder

Analysis set:	Safety analysis population	
Analysis item(s):	ADRs	
Stratification factors:	Concurrent renal disorder	[No, Yes]
Analytical methods:	The above item will be analyzed for each stratum of stratification factors in a similar manner to Section 4.1.2.	

4.4.9 Incidence of adverse drug reactions/infections by presence or absence of concurrent hepatic disorder

Analysis set:	Safety analysis population

Analysis item(s):	ADRs	
Stratification factors:	Concurrent hepatic disorder	[No, Yes]
Analytical methods:	The above item will be analyzed for each stratum of stratification factors in a similar manner to Section 4.1.2.	

4.4.10 Incidence of adverse drug reactions/infections by treatment stage

Analysis set:	Safety analysis population	
Analysis item(s):	ADRs	
Stratification factors:	Treatment stage	[AZILECT alone; AZILECT + other Parkinson's disease medication; Combined with only levodopa, without wearing-off phenomenon; Combined with levodopa and other Parkinson's disease medication, without wearing-off phenomenon; Combined with levodopa, with wearing-off phenomenon]
Analytical methods:	The above item will be analyzed for each stratum of stratification factors in a similar manner to Section 4.1.2.	

4.4.11 Incidence of adverse drug reactions/infections by daily dose

Analysis set:	Safety analysis population	
Analysis item(s):	ADRs	
Stratification factors:	Daily dose	[1 mg, 0.5 mg, Other]
Analytical methods:	The above item will be analyzed for each stratum of stratification factors in a similar manner to Section 4.1.2.	

4.4.12 Incidence of adverse drug reactions/infections by presence or absence of dementia

Analysis set:	Safety analysis population	
Analysis item(s):	ADRs	
Stratification factors:	Dementia	[No, Yes]
Analytical methods:	The above item will be analyzed for each stratum of stratification factors in a similar manner to Section 4.1.2.	

4.4.13 Incidence of adverse drug reactions/infections by presence or absence of dyskinesia

Analysis set:	Safety analysis population	
Analysis item(s):	ADRs	
Stratification factors:	Dyskinesia	[No, Yes]

	Note: Only in patients given levodopa at initiation of treatment with this drug
Analytical methods:	The above item will be analyzed for each stratum of stratification factors in a similar manner to Section 4.1.2.

5 Efficacy data

5.1 UPDRS Part III total score over time

Analysis set:	Efficacy analysis population
Analysis item(s):	UPDRS Part III total score
Time point of assessment:	Baseline, 6 months, 12 months, 18 months, and 24 months of treatment or discontinuation, final assessment
Analytical methods:	For the above analysis item, summary statistics at each time point of assessment will be presented for the measured value and change (Post-baseline score at respective time point − Baseline score). A line graph will be created for the change.

5.2 UPDRS Part III tremor score over time

Analysis set:	Efficacy analysis population
Analysis item(s):	UPDRS Part III tremor score
Time point of assessment:	Baseline, final assessment
Analytical methods:	For the above analysis item, summary statistics at each time point of assessment will be presented for the measured value and change (Score at final assessment − Baseline score).

5.3 UPDRS Part III akinesia/hypokinesia score over time

Analysis set:	Efficacy analysis population
Analysis item(s):	UPDRS Part III akinesia/hypokinesia score
Time point of assessment:	Baseline, final assessment
Analytical methods:	For the above analysis item, summary statistics at each time point of assessment will be presented for the measured value and change (Score at final assessment − Baseline score).

5.4 UPDRS Part III rigidity score over time

Analysis set:	Efficacy analysis population
Analysis item(s):	UPDRS Part III rigidity score
Time point of assessment:	Baseline, final assessment

Analytical methods:	For the above analysis item, summary statistics at each time point of assessment will be presented for the measured value and change (Score at final assessment − Baseline score).	

5.5 Factors likely affecting the efficacy

5.5.1 Factors likely affecting the efficacy

Analysis set:	Efficacy analysis population	
Analysis item(s):	UPDRS Part III total score	
Time point of assessment:	At 6 months, 12 months, 18 months, and 24 months of treatment with this drug or discontinuation, final assessment	
Stratification factors:	Duration of Parkinson's disease (years)	[0<= - <5, 5<= - <10, 10<= - <15, 15<= - <=Max]
	Body weight (kg)	[Min<= - <50, 50<= - <65, 65<= - <=Max]
	Modified Hoehn & Yahr Severity scale (Stage)	[0, 1, 1.5, 2, 2.5, 3, 4, 5]
	Any drugs to treat Parkinson's disease other than AZILECT and levodopa	[No, Yes]
	Number of concomitant drugs	[0 (AZILECT alone), 1 (AZILECT + another drug), ≥2 (AZILECT + ≥2 other drugs)]
	Treatment stage	[AZILECT alone; AZILECT + other Parkinson's disease medication; Combined with only levodopa, without wearing-off phenomenon; Combined with levodopa and other Parkinson's disease medication, without wearing-off phenomenon; Combined with levodopa, with wearing-off phenomenon]
	Age (years)	[Min<= - <65, 65<= - <70, 70<= - <75, 75<= - <80, 80<= - <=Max]

Analytical methods:	For the above analysis item, for each stratum of stratification factors, summary statistics of the change (Post-baseline score at respective time point − Baseline score) at each time point of assessment will be presented.	

5.5.2 UPDRS Part III total score by age category and number of concomitant drugs

Analysis set:	Efficacy analysis population	
Analysis item(s):	UPDRS Part III total score	
Time point of assessment:	Baseline, 12 months, and 24 months of treatment or discontinuation, final assessment	
Stratification factor 1:	Number of concomitant drugs	[0 (AZILECT alone), 1 (AZILECT + another drug), ≥2 (AZILECT + ≥2 other drugs)]
Stratification factor 2:	Age (years)	[Min<= - <65, 65<= - <70, 70<= - <75, 75<= - <80, 80<= - <=Max]
Analytical methods:	For the above analysis items, with stratification by Stratification factor 1 and Stratification factor 2, summary statistics of the change at each time point of assessment (Post-baseline score at respective time point − Baseline score) will be presented.	

5.5.3 Number of patients continuing treatment with this drug by age category and number of concomitant drugs

Analysis set:	Efficacy analysis population	
Analysis item(s):	Patients who continue to receive this medication	
Time point of assessment:	At 6 months and 12 months of treatment with this drug	
Stratification factor 1:	Number of concomitant drugs	[0 (AZILECT alone), 1 (AZILECT + another drug), ≥2 (AZILECT + ≥2 other drugs)]
Stratification factor 2:	Age (years)	[Min<= - <65, 65<= - <70, 70<= - <75, 75<= - <80, 80<= - <=Max]
Analytical methods:	For the above analysis item, with stratification by Stratification factor 1 and Stratification factor 2, the discrete data at each time point of assessment will be summarized using frequency tabulation.	

5.5.4 Number of patients continuing treatment with this drug by age category

Analysis set:	Efficacy analysis population
Analysis item(s):	Patients who continue to receive this medication

Time point of assessment:	At 6 months and 12 months of treatment with this drug
Stratification factors:	Age (years) [Min<= - <65, 65<= - <75, 75<= - <=Max]
Analytical methods:	For the above analysis item, for each stratum of stratification factors, the discrete data at each time point of assessment will be summarized using frequency tabulation.

5.5.5 Number of patients continuing treatment with this drug by dose

Analysis set:	Efficacy analysis population
Analysis item(s):	Patients who continue to receive this medication
Time point of assessment:	At 6 months and 12 months of treatment with this drug
Stratification factors:	Daily dose [1 mg, 0.5 mg]
Analytical methods:	For the above analysis item, for each stratum of stratification factors, the discrete data at each time point of assessment will be summarized using frequency tabulation.

6 Incidence of adverse drug reactions/infections in the additional pharmacovigilance plan

6.1 Incidence of adverse drug reactions/infections in the additional pharmacovigilance plan (Attached Form 12)

Analysis set:	Safety analysis population
Analysis item(s):	ADRs relevant to the safety specification (important identified risks, important potential risks, and important missing information)
Stratification factors:	Seriousness [Serious, Non-serious]
Analytical methods:	The above analysis item will be analyzed for each stratum of stratification factors, in accordance with Re-examination Notification No. 0325-10 of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, dated March 25, 2020, Attachment Form 12, Notes 1 to 4. 1. Number and percentage of patients with ADRs For the risk names and the listing order of the risk names, the definitions described in the safety specification (important identified risks, important potential risks, and important missing information) shall be followed.

7 Summary of patients in the post-marketing survey/study

7.1 Summary of patients in the post-marketing survey/study (Attached Form 16)

Analysis set:	Safety analysis population
Analysis item(s):	Patient ID number Name of medical institution Sex Date of birth Reason for use (disease code, disease name) Concurrent disease (disease code, disease name) Route of administration Maximum dose Average dose Units Therapy dates (AZILECT therapy period) Concomitant drug (drug code, drug name) Degree of effect Adverse drug reaction (disease code, disease name, outcome) CRF No. Dropout Reason for dropout Adverse drug reaction (safety specification, fall or trauma, accident or trauma)
Analytical methods:	For the above analysis item, a tabulated list will be prepared in accordance with the rules for data entry and file preparation stipulated by Re-examination Notification No. 1119-3 of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, dated November 19, 2020.

History of this document (Version control)

Version	Date	Prepared/revised by	Comments
Initial version	2022.4.15	PPD	Preparation of initial version