Clinical Study Protocol

NCT Number: NCT05107960

Title: Special Drug Use Surveillance; AZILVA Tablets and AZILVA Granules 1% in Pediatric Use

Study Number: TAK-536-4001

Document Version and Date: Version 4 / 14-MAY-2024

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

A summary of changes to previous protocol versions is appended to the end of the document.

Note; This document was translated into English as the language on original version was Japanese.

Special Drug Use Surveillance Protocol

Azilva Tablets, Azilva Granules 1%
<Pediatric Use>
Special Drug Use Surveillance

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol Number	**TAK-536-4001**
Version	**Ver. 4**
Prepared on	**May 14, 2024**

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1.0 IMPLEMENTATION BACKGROUND

In pediatric hypertensive patients, appropriate blood pressure management in the early stages is important because hypertension that persists from childhood may lead to organ damage, such as cardiovascular disease and renal disorders, which may have a serious impact on patient quality of life and prognosis, during childhood as well as in the future.

When Azilva (azilsartan) was being developed, many antihypertensives were available for adults, but only a limited number of antihypertensives had been approved for pediatric hypertension in Japan, only two of which were angiotensin II receptor antagonists (ARBs) at that point in time. Also, none of the pediatric formulations for which there is strong demand in the clinical setting were being developed, and it could not be said that a suitable therapeutic setting for pediatric hypertension had yet been achieved. Furthermore, all of the drugs had been publicly filed based on information in the literature or drug use surveillance, for example, without documentation of any clinical study data on pediatric hypertensive patients in Japan.

In light of the therapeutic setting for pediatric hypertension, it would make sense to collect clinical trial data in Japanese pediatric hypertensive patients during treatment with azilsartan, which has been shown to be safe and effective for adult hypertensive patients, so as to develop a pediatric formulation as a new treatment option for pediatric hypertension.

A special drug use surveillance (referred to as the present surveillance) to investigate the efficacy and safety of azilsartan in pediatric patients was planned for the following reasons: in the Japanese Phase 3 long-term treatment study on azilsartan in pediatric hypertensive patients 6 to less than 16 years of age (TAK-536/OCT-101) (referred to below as the study), the number of patients was relatively small (27 patients); no children were enrolled in the special drug use surveillance of Azilva tablets in adults ("long-term use" and "hypertension with diabetes mellitus"); and there is limited experience with the use of azilsartan in pediatric patients 6 to less than 16 years of age.

The present surveillance will be conducted in compliance with the GPSP Ministerial Ordinance and other relevant regulatory requirements.

2.0 OBJECTIVE

The objective is to study the safety and efficacy of routine clinical use of azilsartan in pediatric hypertensive patients 6 to less than 16 years of age.

3.0 SAFETY SPECIFICATION AND EFFICACY CONSIDERATIONS

Important identified risk: hypotension-related events

No efficacy considerations were identified.

4.0 PLANNED SAMPLE SIZE AND RATIONALE

4.1 PLANNED SAMPLE SIZE

Five pediatric hypertensive patients (number of patients in safety analysis set)

4.2 RATIONALE

In view of the feasibility of enrollment and pediatric prescription of azilsartan, the planned sample size in the present surveillance was established as five patients in the safety analysis set.

5.0 SUBJECTS

Pediatric hypertensive patients 6 to less than 16 years of age will be included as subjects. However, subjects must meet the following inclusion criteria and cannot conflict with any of the exclusion criteria. In addition, please refer to the current package insert .

5.1 INCLUSION CRITERIA

Patients must meet all of the following criteria:

① 6 to less than 16 years of age

② Have hypertension

5.2 EXCLUSION CRITERIA

Patients who meet the following criteria are not eligible.

Azilsartan is contraindicated

6.0 DOSAGE AND ADMINISTRATION

Usually, the initial once-daily oral dose in children 6 years of age or older is 2.5 mg azilsartan for children weighing less than 50 kg and is 5 mg azilsartan for children weighing 50 kg or more. The dose may be adjusted, depending on age, body weight, and symptoms, but the maximum daily dose will be 20 mg for children weighing less than 50 kg and will be 40 mg for children weighing 50 kg or more. In addition, please refer to the current package insert .

7.0 PLANNED NUMBER OF SITES BY DEPARTMENT

Pediatrics, etc.: Approximately 5 sites

8.0 METHOD

8.1 OBSERVATION PERIOD AND RATIONALE

Up to 12 months

<Rationale for Observation Period>

As the duration of treatment was 52 weeks in the clinical study, an observation period of up to 12 months was established for comparison with the clinical study data. It is believed that an observation period of up to 12 months will allow comparison with the "long-term use" data from the special drug use surveillance in which the safety of azilsartan was assessed in adult hypertensive patients.

For patients who discontinue treatment during the observation period, the reason for discontinuation will be documented, and the details leading to discontinuation will be checked.

8.2 Clinical Site Contracts

Takeda Pharmaceutical Company Limited will conclude a written agreement with study sites to conduct the present surveillance.

8.3 Patient Enrollment Method

The surveillance will be conducted via "centralized enrollment" using a web-based electronic data capture (EDC) system.

For patients prescribed azilsartan after the start of the contract period, investigators will enter patient enrollment-related information into the EDC no later than 14 days after the initial azilsartan prescription date (where "day 0" indicates the prescription date, and "day 1 after" indicates the day after the prescription date). Retrospective enrollment will be allowed for patients who started treatment prior to the conclusion of the contract if treatment had been initiated on or after December 16, 2021, when the granule dosage form was first marketed.

8.4 Preparation and Submission of CRFs

Information will be collected using the EDC.

Investigators will promptly enter data into the EDC system after necessary observations for all enrolled patients. Cases where treatment compliance could not be confirmed should be entered (subsequent entries do not need to be completed).

Patients who discontinue azilsartan treatment during the observation period due to the occurrence of an adverse event will continue to be observed after discontinuation, if possible, until the adverse event resolves, and the data will be entered into the EDC.

Investigators will electronically sign the EDC to ensure the accuracy and reliability of the data recorded in the EDC.

9.0 PLANNED DURATION OF SURVEILLANCE

Surveillance period: After start of granule dosage form marketing to August 31, 2024

Patient enrollment period: After start of granule dosage form marketing to May 31, 2024

10.0 SURVEILLANCE PARAMETERS

Investigators will enter the following parameters into the EDC: The schedule for the present surveillance is shown in Appendix 1.

10.1 PATIENT ENROLLMENT

1) Surveillance parameters

Azilsartan prescription date, patient identification number, patient initials, sex, date of birth or age (at the time that Azilsartan is prescribed), inclusion criteria, exclusion criteria

2) Time point

At patient enrollment

10.2 PATIENT CHARACTERISTICS

1) Surveillance parameters

Time of hypertension diagnosis, inpatient/outpatient status (at start of azilsartan treatment), comorbidities (details, if any), medical history (details, if any), height, and predisposition to hypersensitivity (details, if any).

2) Time point

At start of azilsartan treatment

10.3 TREATMENT

1) Surveillance parameters

Azilsartan treatment status (dosage form, daily dose, start date, end date, and reason for discontinuation), concomitant medication (antihypertensives other than azilsartan)* treatment status (name of drug(s) if used, route of administration, daily dose, and treatment duration), and concomitant medication (other than antihypertensive) treatment status (name of drug(s) if used, route of administration, and purpose of treatment).

*Including antihypertensives discontinued within 3 months prior to starting of azilsartan treatment

2) Time points

From start of azilsartan treatment up to 12 months later (or at discontinuation)

10.4 TEST/OBSERVATION PARAMETERS

Data will be entered into the EDC whenever tests/observations are conducted at the various surveillance time points during routine clinical use.

10.4.1 Vital Signs/Body Weight

1) Test/observation parameters

Pulse rate, office blood pressure (systolic/diastolic), body weight

2) Time points

Measurement time points at baseline, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, and 12 months (or at treatment discontinuation)

10.4.2 Laboratory Tests

1) Test parameters

Serum creatinine, BUN, serum potassium

2) Time points

Test time points at baseline, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, and 12 months (or at treatment discontinuation)

10.4.3 Other Observation Parameters

1) Observation parameters

Pregnancy status during the observation period (women only)

2) Time points

From start of azilsartan treatment up to 12 months later (or at discontinuation)

10.5 ADVERSE EVENTS

1) Surveillance parameters

Adverse events (see Table 1), adverse event terms, date of onset, seriousness and rationale for seriousness (see Table 2), reason for discontinuation of azilsartan, date outcome assessed, outcome, causal relationship to azilsartan* (see Table 3), and changes over time in clinically significant laboratory values related to adverse events**

Follow-up should be performed, if possible, whenever the outcome is determined to be unresolved or unknown.

Hypotension-related event, renal impairment-related events, and hyperkalaemia-related events should also be followed, if possible.

*The rationale for determining no causal relationship to azilsartan should be documented.

**Laboratory test values at the start of azilsartan treatment (before the start of azilsartan treatment), when adverse events occur, and when the outcome of adverse events is determined will be documented, if possible.

2) Time points

From start of azilsartan treatment up to 12 months later (or at discontinuation)

Table 1 Definition of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product (including domestic investigational products for expanded indications, for example), whether or not it is related to the medicinal product.

Note) An abnormal worsening of the target disease, that is, a worsening of the expected disease state beyond its natural history, etc., will be classified as an adverse event.

Table 2 Seriousness Criteria

①Results in death (death)

②Is life-threatening (risk of death)

The term "life-threatening" refers to an event in which the patient 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 had been more severe.

③Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolongation of hospitalization)

④Results in persistent or significant disability or incapacity (disability)

⑤May cause a congenital anomaly/birth defect (congenital anomaly)

⑥Although not immediately life-threatening or resulting in death or hospitalization, jeopardizes the patient or requires intervention to prevent any of the above outcomes from ① through ⑤

Note) Any adverse event reported as being not serious but assessed as serious by Takeda Pharmaceutical Company Limited will be handled as a serious adverse event.

Table 3 Criteria for Determining Causal Relationship Between Adverse Events and Azilsartan

Determination	Criteria
Related	Adverse events for which a causal relationship cannot be ruled out because there is a temporal relationship (including during the course after discontinuation of treatment) or because there is at least a reasonable possibility of having been caused by the medicinal product even though other factors such as underlying disease, comorbidity, concomitant medication, or concomitant procedure may also be implicated.
Not Related	Adverse events that are not temporally related with the medicinal product or may reasonably be attributed to other factors such as underlying disease, comorbidity, concomitant medication, or concomitant procedure.

11.0 ANALYTIC PARAMETERS AND METHODS

11.1 PATIENT DISPOSITION-RELATED MATTERS

The number of enrolled patients, the number of patients for whom CRFs were collected, the number of patients in the safety and efficacy analysis sets, the number of patients excluded from analysis, and the reasons for exclusion will be tabulated.

11.2 PATIENT CHARACTERISTICS

Patient characteristics such as sex, age, disease duration, and comorbidities will be tabulated.

11.3 TREATMENT

Azilsartan and concomitant medication (antihypertensive and non-antihypertensive) treatment status will be tabulated.

11.4 SAFETY INFORMATION

The following will be tabulated in the safety analysis set. AEs will be coded using MedDRA/J, and will be summarized by preferred term (PT) and system organ class (SOC).

11.4.1 Incidence of Adverse Events

The frequency of adverse events occurring during the observation period will be tabulated by type, time of onset, seriousness, and causal relationship to azilsartan, for example.

11.4.2 Factors Potentially Affecting Safety

Adverse reactions occurring during the observation period, patient characteristics (such as sex, age, and comorbidity), and azilsartan treatment status, for example, will be listed.

11.5 EFFICACY INFORMATION

The following will be tabulated in the efficacy analysis set.

11.5.1 Changes in Blood Pressure Over Time

Blood pressure values and changes at each time point (laboratory values at each time point after the start of azilsartan treatment - laboratory values at the start of azilsartan treatment) will be tabulated. Listings will be provided when there are 2 or fewer patients in the efficacy analysis set.

11.5.2 Factors Potentially Affecting Efficacy

Blood pressure values, patient characteristics (such as age, sex, and comorbidity), and treatment (such as azilsartan treatment status, and concomitant medication (antihypertensive) treatment status) will be listed.

12.0 REGISTRATION OF SURVEILLANCE INFORMATION

Information about the present surveillance will be registered on the following public websites

before the start of the surveillance.

- Japan Registry of Clinical Trials (jRCT)
- ClinicalTrials.gov (National Institutes of Health registry of clinical trials)

13.0 ORGANIZATIONAL STRUCTURE

13.1 CHART OF ORGANIZATIONAL STRUCTURE FOR POST-MARKETING SURVEILLANCE

See attachment

14.0 CONTRACT RESEARCH ORGANIZATIONS

(1) [redacted]

Responsibilities: Data management, archiving of records, and post-marketing surveillance support

(2) [redacted]

Responsibilities: EDC installation and management

(3) [redacted]

Responsibilities: Statistical analysis

(4) [redacted]

Responsibilities: Monitoring tasks

15.0 SCHEDULE AND RATIONALE FOR MILESTONES FOR CONDUCT OF SURVEILLANCE AND ASSESSMENT OF RESULTS OR REPORTS TO THE PHARMACEUTICALS AND MEDICAL DEVICES AGENCY

Periodic Safety Reports: for comprehensive review of safety information.

Final tabulation: for final tabulation when data is locked after the completion of the observation period for all patients

16.0 ADDITIONAL ACTION THAT MAY BE TAKEN BASED ON SURVEILLANCE RESULTS, AND CRITERIA FOR INITIATING SUCH ACTION

The Risk Management Plan will be reviewed at each milestone time point based on the following:

Whenever any new findings regarding the Safety Specification come to light, we will review whether there is any need to modify the RMP, including revisions of the package insert.

We will review whether there is any need to supplement or modify pharmacovigilance activities or the establishment of the RMP, including new Safety Specifications.

17.0 OTHER REQUIREMENTS

17.1 PROTOCOL AMENDMENT

In the course of the surveillance, we will assess, for example, the progress of the surveillance, the emergence of adverse reactions and serious adverse reactions that are unexpected based on the Precautions, whether there are any increases in the incidence of specific adverse reactions, and the appropriateness of surveillance parameters, and the protocol will be reviewed and amended as needed. If partial changes in the dosage and administration or indications are approved during the surveillance, the need for revising the protocol will be reviewed as necessary, and the protocol will be revised as necessary.

17.2 ACTIONS TO BE TAKEN WHEN PROBLEMS OR QUESTIONS ARE IDENTIFIED

Whenever any safety or efficacy problems are identified, the response will be assessed upon a detailed examination of the data.

Appendix 1 Observation Schedule [Note)]

Note) An observation period of up to 12 months has been described, and the observation period for all patients who start azilsartan treatment on or after June 1, 2023 should be comparable.

Surveillance time points / Surveillance parameters		Observation period														
		At patient enrollment	At start of treatment	After 1 month	After 2 months	After 3 months	After 4 months	After 5 months	After 6 months	After 7 months	After 8 months	After 9 months	After 10 months	After 11 months	After 12 months	At treatment discontinuation
Number of base days (days)[(a)]		-	1	30	60	90	120	150	180	210	240	270	300	330	360	-
Patient enrollment	Azilsartan prescription date	○														
	Patient identification number	○														
	Patient initials	○														
	Sex	○														
	Date of Birth or Age (when azilsartan prescribed)	○														
	Inclusion/exclusion criteria assessed	○														
Patient characteristics	Time of hypertension diagnosis		○													
	Inpatient/outpatient status (at start of azilsartan treatment)		○													
	Comorbidity		○													
	Medical history		○													
	Body height		○													
	Predisposition to hypersensitivity		○													
Treatment details	Azilsartan treatment status		← ○ →													○
	Concomitant medication (antihypertensive) treatment status[(b)]		← ○ →													○
	Concomitant medication (other than antihypertensive) treatment status		← ○ →													○
Test/observation parameters	Office blood pressure (systolic/diastolic)		○	○	○	○	○	○	○	○	○	○	○	○	○	○
	Pulse		○	○	○	○	○	○	○	○	○	○	○	○	○	○
	Body weight		○	○	○	○	○	○	○	○	○	○	○	○	○	
	Serum creatinine[(c)]		○	○	○	○	○	○	○	○	○	○	○	○	○	
	BUN[(c)]		○	○	○	○	○	○	○	○	○	○	○	○	○	
	Serum potassium[(c)]		○	○	○	○	○	○	○	○	○	○	○	○	○	
	Pregnancy status (women only)		← ○ →													○
	Adverse Events		← ○ →													○

○: During routine clinical practice

← ○ →: Throughout this period during routine clinical practice

(a): Day 1 indicates date treatment first started (at start of treatment).

(b): Document antihypertensives other than azilsartan that are administered for 3 months prior to the start of azilsartan treatment (including antihypertensives discontinued within 3 months prior to the start of azilsartan treatment).

(c): At the surveillance time points noted in 10.4.2 2), if possible.

Document History

Version	Date	Comments
original version	September 14, 2021	New document
Version 2	May 10, 2022	13.0 ORGANIZATIONAL STRUCTURE
Version 3	May 9, 2023	1.0 IMPLEMENTATION BACKGROUND 4.1 PLANNED SAMPLE SIZE 4.2 RATIONALE 7.0 PLANNED NUMBER OF SITES BY DEPARTMENT 8.1 OBSERVATION PERIOD AND RATIONALE 8.3 PATIENT ENROLLMENT METHOD 8.4 PREPARATION AND SUBMISSION OF CRFS 9.0 PLANNED DURATION OF SURVEILLANCE 10.3 TREATMENT 10.4 TEST/OBSERVATION PARAMETERS 10.5 ADVERSE EVENTS 11.4 SAFETY INFORMATION 11.5 EFFICACY INFORMATION
Version 4	May 14, 2024	8.1 OBSERVATION PERIOD AND RATIONALE