Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	c04592560-02
BI Study Number:	1348.6
BI Investigational Product(s):	Telmisartan / amlodipine / hydrochlorothiazide combination tablets
Title:	The special drug use-results survey on long-term use of telmisartan 80 mg/amlodipine 5 mg/hydrochlorothiazide 12.5 mg fixed dose combination tablets in Patients with Hypertension
Protocol version identifier:	2.0
Date of last version of protocol:	16 October 2015
PASS:	Yes
EU PAS register number:	Not applicable
Active substance:	Telmisartan (C09CA07) / amlodipine (C08CA01) / hydrochlorothiazide (C03AA03)
Medicinal product:	Micatrio® Combination Tablets
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	Nippon Boehringer Ingelheim Co., Ltd.
Joint PASS:	No
Research question and objectives:	To evaluate real-world safety, effectiveness and appropriate use of Micatrio® Combination Tablets treatment in patients with hypertension
Country(-ies) of study:	Japan
Author:	Phone: Fax:
Marketing authorisation holder(s):	Nippon Boehringer Ingelheim Co., Ltd.

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Date:	12 December 2016
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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ARB	Angiotensin II receptor blocker
CCB	Calcium channel blocker
CRF	Case Report Form
CTP	Clinical Trial Protocol
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU-QPPV	European Union-Qualified Person for Pharmacovigilance
FDC	Fixed-dose combination
GPSP	Good Post-marketing Study Practice
HCTZ	Hydrochlorothiazide
J-RMP	Japanese Risk Management Plan
MedDRA	Medical Dictionary for Regulatory Activities
NBI	Nippon Boehringer Ingelheim Co., Ltd.
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post Marketing Surveillance
PSUR	Periodic Safety Update Report
SAE	Serious Adverse Event
TSAP	Trial Statistical Analysis Plan

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3. RESPONSIBLE PARTIES

Nippon Boehringer Ingelheim Co., Ltd.

Contact details and the list of all investigators will be kept in a stand-alone document. This document will be managed in the special drug use-results survey tracking system which manages the contracts with site and investigators name.

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4. ABSTRACT

Name of company: Nippon Boehringer Ingelheim Co., Ltd.			
Name of finished medicinal product: Micatrio® Combination Tablets			
Name of active ingredient: Telmisartan (C09CA07) / amlodipine (C08CA01) / hydrochlorothiazide (C03AA03)			
Protocol date: 12 December 2016	**Study number:** 1348.6	**Version/Revision:** 2.0	**Version/Revision date:** 16 October 2015
Title of study:	The special drug use-results survey on long-term use of telmisartan 80 mg/amlodipine 5 mg/hydrochlorothiazide 12.5 mg fixed dose combination tablets in Patients with Hypertension Trial Clinical Monitor :		
Rationale and background:	The Japanese Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical requires accumulating safety and effectiveness data of launched products in Japan for re-examination. The PMS plan is a part of the J-RMP. The J-RMP was submitted to the PMDA as a part of J-CTD and need to be approved by PMDA as approval condition. After 4 or 6 years from approval, the results of the PMS are needed to be submitted to the Japanese regulatory authority, the PMDA, as a part of the re-examination dossier.		
Research question and objectives:	This PMS is designed to investigate the safety, effectiveness and appropriate use of Micatrio® Combination Tablets in patients with hypertension under real-world use according to the Japanese package insert.		
Study design:	Non-interventional study based on newly collected data. The study will consist of a baseline visit and follow-up visits at Week 4, 8, 12, 24, 36 and 52 for patients who have newly initiated Micatrio® Combination Tablets. The patients will be followed up until discontinuation of Micatrio® Combination Tablets treatment or the end of study. All patients administrated Micatrio® Combination Tablets after the launch at the sites contracted with the sponsor will be registered.		

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Name of company: Nippon Boehringer Ingelheim Co., Ltd.			
Name of finished medicinal product: Micatrio® Combination Tablets			
Name of active ingredient: Telmisartan (C09CA07) / amlodipine (C08CA01) / hydrochlorothiazide (C03AA03)			
Protocol date: 12 December 2016	**Study number:** 1348.6	**Version/Revision:** 2.0	**Version/Revision date:** 16 October 2015
Population:	Patients who diagnosed with hypertension based upon the most recent JSH guideline, and who comply with inclusion and exclusion criteria may qualify for participation in this study. (if applicable) <u>Inclusion criteria</u> - Patients who are prescribed with Micatrio® Combination Tablets by the discretion of investigators based on the Japanese package insert - Patients who have never been treated with Micatrio® Combination Tablets before enrolment <u>Exclusion criteria</u> - Patients who are participating/ planned to participate in a clinical trial. *Contraindication as per Japanese Package Insert should be respected.		
Variables:	Exposure to Micatrio® Combination Tablets is estimated as time from the day Micatrio® Combination Tablets is initiated until the day the drug is last administrated on a patient-level (or the final contact with last regular observation) and considering dosage. Outcomes: <u>Safety</u> Any suspected ADRs (primary outcome), Serious AEs, AEs for important identified risks and AEs for important potential risks <u>Effectiveness</u> Effectiveness will be assessed with a focus on the following variable as secondary outcome. - Change from the baseline in clinic diastolic blood pressure (DBP)[mmHg] at Week 52 - Change from the baseline in clinic systolic blood pressure (SBP)[mmHg] at Week 52 Others Demographics, Administration of Micatrio® Combination Tablets, adherence, Previous/Concomitant medications, Blood pressure, controlled hypertension, pulse rate and Laboratory tests		

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Name of company: Nippon Boehringer Ingelheim Co., Ltd.			
Name of finished medicinal product: Micatrio® Combination Tablets			
Name of active ingredient: Telmisartan (C09CA07) / amlodipine (C08CA01) / hydrochlorothiazide (C03AA03)			
Protocol date: 12 December 2016	**Study number:** 1348.6	**Version/Revision:** 2.0	**Version/Revision date:** 16 October 2015
Data sources:	CRFs for individual patients will be gathered by the EDC system. After the medical examination and observation at the specified points (Baseline, Week 4, 8, 12, 24, 36 and 52 or discontinuation) are completed, the investigator needs to immediately enter data of the registered patients (including withdrawals and dropouts) in the EDC. Two case books will be used, data are to be transmitted immediately after being entered into EDC at Week 8 (Book 1) and Week 52 (Book 2) after the start of treatment or at discontinuation. In case that any adverse events occur, the data should be immediately entered into EDC and transmitted.		
Study size:	500		
Data analysis:	Due to the nature of the observational study, no confirmatory statistical testing is foreseen in this study. Analyses are descriptive in nature including means, standard deviation, min, Q1, medians, Q3, max, frequency and percentages.		
Milestones:	Start of data collection: 20 January 2017 End of data collection: 30 April 2019 (in plan) Interim report: After Week 8 data will be collected Final report of study results: 1Q 2020(in plan)		

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Figure 1 Flow chart

Item \ Time	Observation period						
	Baseline (before treatment of Micatrio® Combination Tablets)	4W	8W (or at discontinuation)	12W	24W	36W	52W (or at discontinuation)
Patient registration*[1]	X						
Patient demographics	X						
Administration of Micatrio® Combination Tablets		X (to be reported throughout the observation period)					
Previous/concomitant medications	X (to be reported throughout the observation period)						
Administration/adherence of previous anti-hypertensivemedications*[2]	X						
Adherence of Micatrio® Combination Tablets		X	X	X	X	X	X
Blood pressure, pulse rate	X*[4]	X	X	X	X	X	X
Laboratory tests	X	X	X	X	X	X	X
Adverse events	X (to be reported throughout the observation period)						
EDC transmitted time*[3]	←----------X (Book1)→			←----------X (Book2)→			

Observation / Evaluation time points are approximate. Collected data should be reported as those to the closest available visit.
*1: Patients administered Micatrio® Combination Tablets will be registered within 14 days whenever the day of first administration is possible.
*2: Previous anti-hypertensive medications*3: eCRF (electric case report form): Data are to be transmitted immediately after being entered into the eCRF at 8 weeks and 52 weeks after the start of treatment or at discontinuation. In case of occurrence of any adverse events, the data should be immediately entered into the eCRF and transmitted.
*4: Two points (baseline and before a certain period from treatment of Micatrio® Combination Tablets)

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5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
2.0	12 December 2016	Study size	Change the size	Decreased estimate number of patient due to changed "Precautions with related to dosage and administration "
		Milestones	Change the study period	Approved behind schedule
		Planned number of sites	Change the size	Decreased estimate number of patient due to changed "Precautions with related to dosage and administration "
		Data management	Change name of CRO	CRO changed their name
		ANNEX 1. Summary of safety specification in local RMP	Add events	Direction from PMDA

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6. MILESTONES

Milestone	Planned Date
Start of data collection	20 January 2017
End of data collection	30 April 2019 (in plan)
Registration in the EU PASS register	
Final report of study results	1Q 2020 (in plan)

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7. RATIONALE AND BACKGROUND

Blood pressure in hypertensive patients is rarely controlled to an optimal level by one drug alone, often combination of 2 or more drugs is essential to achieve a sufficient antihypertensive effect. Therefore JSH 2014 recommended to combine 3 agents in patients with inadequate control when treated with 2 antihypertensive agents. In addition, JSH 2014 mentions that as the use of small dose of a diuretic rarely causes adverse effects and synergistically increases the hypotensive effect when used with other antihypertensive drugs, it should be used positively in combination therapy.

Micatrio® Combination Tablets is a fixed-dose combination (FDC) tablet of telmisartan, amlodipine and hydrochlorothiazide (HCTZ). Each component of the triple FDC tablet of telmisartan, amlodipine and HCTZ is already approved and marketed in Japan as shown below.

Telmisartan is an Angiotensin II receptor blocker **(**ARB) synthesised by Boehringer Ingelheim GmbH. The efficacy and safety in a dose range of 20 to 80 mg once daily. Telmisartan was approved in October 2002 and marketed in December 2002. The tablet form was later developed to adjust dosage easily and to improve adherence. The telmisartan tablet was approved in August 2004 and marketed in January 2005 in Japan.

Amlodipine besylate is a long-acting Calcium channel blocker (CCB). The onset of action of amlodipine is slow and persistent. Once daily dosing of amlodipine provides antihypertensive and antianginal effects over 24 hours. In Japan, clinical trials in patients with hypertension or angina pectoris were started in 1986, and demonstrated that it has good antihypertensive effect with 2.5-5.0 mg once daily. Amlodipine was approved in October 1993. A dose increase of up to 10 mg was approved for hypertention in February 2009. The clinically recommended dose is 2.5-5.0 mg in Japan.

Hydrochlorothiazide is a diuretic of the benzothiadiazide class marketed in 1959 in Japan. It has been used in clinical practice for a long time. The action mechanism is thought to lower blood pressure through decreasing cardiac output, reducing plasma and extracellular fluid volume and reducing peripheral vascular resistance over the long term by inhibiting the reabsorption of sodium ions at the distal renal tubule and increasing the excretion of sodium and water. The approval dosage is 25-100 mg/day in Japan.

The FDC of telmisartan and HCTZ was approved as the combination of telmisartan 40 mg and HCTZ 12.5 mg and the combination of telmisartan 80 mg and HCTZ 12.5 mg those names are Micombi® AP and Micombi® BP respectively in April 2009 in Japan. And the FDC of telmisartan and amlodipine was approved as the combination of telmisartan 40 mg and amlodipine 5 mg whose name is Micamlo® AP in July 2010 and as the combination of telmisartan 80 mg and amlodipine 5 mg whose name is Micamlo® BP in December 2012 in Japan.

In clinical trials, safety of Micatrio® Combination Tablets has been evaluated in the 2 Phase III clinical trials, 1348.1 and 1348.2 conducted in Japan for the patients with essential hypertension. In the 1348.1 study, T80/A5+H12.5 mg or T80/A5 mg was administered to patients showing poor antihypertensive response to treatment with T80/A5 mg, and safety

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was evaluated for 309 patients. In the 1348.2 study, T80/A5/H12.5 mg or T80/H12.5 mg was administered to patients showing poor antihypertensive response to treatment with T80/H12.5 mg, and safety was evaluated for 132 patients. In addition, in the 1348.2 study, T80/H12.5 mg combination product + A5 mg was administered for 52 weeks in the extension period after the double-blind period and long-term safety was investigated for 129 patients.
In the T80/H12.5/A5 mg group, common events were blood uric acid increased (9.2%), nasopharyngitis (6.9%) and hyperuricaemia (3.7%). Frequencies of blood uric acid increased and hyperuricaemia were higher than those in the T80/H12.5 mg group or the T80/A5 mg group. In the T80/H12.5/A5 mg group, common adverse events were all mild in severity, and causal relationship with the study drug was denied in all of these events except all the events of blood uric acid increased and hyperuricaemia. All adverse reactions in the T80/H12.5/A5 mg group were already known to occur in Micamlo® Combination Tablets or Micombi® Combination Tablets, and no event was newly found in combination with telmisartan, amlodipine and hydrochlorothiazide.

Japanese regulation related to Post Marketing Surveillance (PMS)

This PMS is planned according to the Japanese Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical. The law requires in principle that data on the safety and effectiveness of all launched products to be accumulated under real-world clinical practice. The PMS is a part of the local Risk Management Plan in Japan (J-RMP) to be submitted to PMDA at New Drug Application. After 4 or 6 years from approval of registration, the data collected in the PMS are required to be submitted to the Pharmaceuticals and Medical Devices Agency (PMDA), the local regulatory agency in Japan according to the process of re-examination.

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8. RESEARCH QUESTION AND OBJECTIVES

This PMS is designed to investigate the safety, effectiveness and appropriate use of Micatrio® Combination Tablets in patients with hypertension under real-world use according to the Japanese package insert.

The number of elderly patients was small in clinical trials (34/217[5.7%] in 1348.1 and 1348.2 studies). Also data in Japanese patients and in patients who were administered Micatrio® Combination Tablets for a long period are limited (see Section 7).

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9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional study based on new data collection to gather real-world information (i.e., data under routine medical practice) on safety and effectiveness of the Micatrio® Combination Tablets treatment.

The study will be initiated after the approval of Micatrio® Combination Tablets in Japan. The study will consist of a baseline visit and follow-up visits at Week 4, 8, 12, 24, 36 and 52 for patients who have newly initiated Micatrio® Combination Tablets. The patients will be followed up until discontinuation of Micatrio® Combination Tablets treatment, death or the end of study.

As this is an observational study, no specific treatment is mandated or withheld from the patients. The choice of maintenance treatment for hypertension must be according to regular medical practice and at the discretion of the physician (i.e., no randomised assignment of patient to treatment is performed).

All patients administrated Micatrio® Combination Tables after the launch at the sites contracted with the sponsor will be registered.

Patients participating in the subsequent follow-up will undergo regular observations. These observations should be reported after approximately Week 4, 8, 12, 24, 36 and 52 since the initiation of Micatrio® Combination Tablets as long as they continue to receive the treatment. Patients will not be followed any longer once they are reported to have discontinued the Micatrio® Combionation Tablets treatment.

The primary outcome of this study is the frequency of patients with any suspected adverse drug reactions (ADRs)

The secondary outcome of this study is change from baseline in blood pressure at Week 52.

9.2 SETTING

9.2.1 Site selection

Nippon Boehringer Ingelheim (NBI) will nominate the candidate sites which satisfy the following criteria and NBI ask the nominated sites to participate in the study.

1. Micatrio® Combination Tablets has been delivered to the site.
2. A medical representative will explain the objectives and design of this study to the investigators at study sites and exchange a written contract with the head of the study site (e.g., hospital director).

Planned number of sites: Approximately 100 sites

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9.2.2 Selection of population

9.2.2.1 Inclusion / exclusion criteria

Inclusion criteria

- Patients who are prescribed with Micatrio® Combination Tablets by the discretion of investigators based on the Japanese package insert
- Patients who have never been treated with Micatrio® Combination Tablets before enrolment

Exclusion criteria

- Patients who are participating/planned to participate in a clinical trial.

*Contraindication as per Japanese Package Insert should be respected.

9.2.2.2 Registration period

From 1 January 2017 to 31 January 2018 (System for registration will be available from 1 February 2017)

9.2.2.3 Patient registration method

The registration method will be a continuous investigation system. Patients who begin treatment with Micatrio® Combination Tablets after the conclusion of the contract will be registered by entering necessary information in the EDC within 14 days whenever possible from the day of treatment initiation (inclusive).

Patient registration will stop when the target number of the study is reached. After the end of the registration period, investigators will use a signed form to confirm that patients will be registration continuously at the site. A log of all patients included into the study will be maintained at the site.

Patients will be registered by entering necessary information in the electronic data capture (EDC) system just after initiation of administration of Micatrio® Combination Tablets. The necessary information for registration are gender, date of birth, start date of administration, reason for use of Miactrio® Combination Tablets and previous anti-hypertensitive medicatons.
After the end of registration, investigators will use a signed form to confirm that all patients were registered at the site.

9.2.3 Discontinuation of the study by the sponsor

A log of all patients included into the study will be maintained at the investigational sites.

NBI reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected registration goals overall or at a particular study site

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2. Emergence of any effectiveness/safety information that could significantly affect continuation of the study
3. Violation of Good Post-marketing Study Practice (GPSP), the NIS protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

The study site will be reimbursed for reasonable expenses incurred in case of study termination (except in case of the third reason).

9.3 VARIABLES

9.3.1 Exposures

Exposure to Micatrio® Combination Tablets is estimated as time from the day Micatrio® Combination Tablets is initiated until the day the drug is last administrated on a patient-level and considering dosage.
Dosage and administration: Usually for adults, this fixed dose combination (telmisartan/amlodipine/hydrochlorothiazide 80 mg/5 mg/12.5 mg) is orally administered once a day.

9.3.2 Outcomes

Safety

Safety will be assessed with a focus on the following variables, frequencies and percentages.

- Any suspected ADRs (primary outcome)
- Serious AEs

How to assess and report AEs including the definitions are described in section 11.

Effectiveness

Effectiveness will be assessed with a focus on the following variable as secondary outcome.

- Change from the baseline in clinic diastolic blood pressure (DBP)[mmHg] at Week 52
- Change from the baseline in clinic systolic blood pressure (SBP)[mmHg] at Week 52

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9.3.3 Other

Baseline characteristics and observation items

The following items, demographics, previous/concomitant medications, blood pressure, pulse rate, laboratory tests will be considered as the minimum baseline characteristics. During the observation period, administration of Micatrio® Combination Tablets is also added. For all interventions/measures dates will be recorded.

Demographics:

- Age

- Diagnosis
- Diagnosis start date
- Weight
- Height

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Administration of Micatrio® Combination Tablets:
- Treatment period (Start date, end data)
- Primary reason of discontinuation
- Adherence

Previous/Concomitant medications:

Blood pressure, pulse rate:

Laboratory tests (if applicable):

9.4 DATA SOURCES

Case Report Forms (CRFs) for individual patients will be gathered by the EDC system.

In the EDC system, two case books will be set up; Book 1 includes baseline, Week 4 and 8. Book 2 includes Week 12, 24 and 52.

Data are to be transmitted immediately after being entered into the EDC system at Week 8 (Book 1) and Week 52 (Book 2) after the start of treatment or at discontinuation.

For any adverse events, the data should be immediately entered into the EDC system and transmitted.

9.5 STUDY SIZE

It is planned to collect 500 patients with hypertension.

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With a sample size of 500 patients, any ADR with frequency of 0.6% or higher can be detected with probability of 95% or greater in at least one patient.

- Long-time use:

In Micombi® combination tablets AP/BP PMS (502.542) and Micamlo® combination tablets AP PMS (1235.38), the ratio of patients that each drug was used more than 52 weeks was 48.7% in 502.542 and 45.7% in 1235.38. Assuming collection of data from 500 patients, at least 200 patients (based on lower bound of 95% confidence interval for point estimate of 45.7% in 1235.38) will be used more than 52 weeks.

- Elderly:

In Micardis® tablets PMS (502.500), Micombi® combination tablets AP/BP PMS (502.542) and Micamlo® combination tablets AP PMS (1235.38), the ratio of elderly (more than 65 yrs / more than 75yrs) patients was 54.2% / 22.1% in 502.500, 66.7% / 36.8% in 502.542 and 57.9% / 48.7% in 1235.38. Assuming collection of data from 500 patients, at least 260 patients more than 65 yrs old (based on lower bound of 95% confidence interval for point estimate of 54.2% in 502.500) and 125 patients more than 75 yrs old (based on lower bound of 95% confidence interval for point estimate of 22.1% in 502.500) will be collected.

- Patients with renal dysfunction:

In Micombi® combination tablets AP/BP PMS (502.542) and Micamlo® combination tablets AP PMS (1235.38), the ratio of patients with renal dysfunction was 8.8% in 502.542 and 9.6% in 1235.38. Assuming collection of data from 500 patients, at least 30 patients with renal dysfunction (based on lower bound of 95% confidence interval for point estimate of 8.8% in 502.542) will be collected.

9.6 DATA MANAGEMENT

Patients' data will be gathered by the EDC system provided by external vendor below.

	Contract research organizations 1
Name	

9.7 DATA ANALYSIS

This is a non-interventional study based on new data collection to gather real-world information (i.e., data under routine medical practice) on safety and effectiveness of the Micatrio® combination tablets treatment in patients with hypertension. Analyses for safety, effectiveness and baseline characteristics are descriptive in nature including means, standard deviation, min, Q1, medians, Q3, max, frequency and percentages.

Per local regulation, any patient who meets at least one of the following criteria is treated as ineligible for all analyses:

- No follow-up visit data are available

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- No required registration procedure is followed
- No valid site contract is available

9.7.1 Analyses of outcome events

All outcome events are based on reported AE data which will be handled according to BI standards (see the section below).

9.7.2 Safety analyses

The safety analysis will include all patients registered in the study and receiving the Micatrio® combination tablets treatment except for who meet the ineligible criteria.

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be based on the concept of treatment emergent AEs. To this end, all AEs occurring between first intake of Micatrio® combination tablets prescribed at baseline visit and within 1 days (inclusive) after the last intake will be considered 'treatment emergent'. An AE is considered to be an ADR if either the physician who has reported the AE or the sponsor assesses its causal relationship as 'related'.

The frequency and percentages of ADRs, SAEs, and other AEs will be tabulated by system organ class and preferred term for overall and for subgroups based on the important baseline characteristics (details will be described in the TSAP).

No imputation is planned for missing AE data except for missing onset dates which will be handled according to BI standard.

Descriptive statistics will be calculated for pulse rate.

9.7.3 Effectiveness analyses

Descriptive statistics will be calculated for continuous secondary

For overtime the descriptive statistics will be provided by visit, including actual values and change from baseline

No imputation is planned for missing value of blood pressure.

9.7.4 Interim analyses

Several interim analyses will be performed for the purpose of creating Japanese Periodic Safety Update Reports (PSUR) to the Japanese authority (every 6 to 12 months depending on the time from the approval).

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9.8 QUALITY CONTROL

All processes are conducted according to GPSP SOPs <102-MLS-90-119> and GPSP working instruction <102-MLW-90-118-51>. Appropriate records and documents are stored based on the GPSP SOPs and these processes are checked by internal self-check.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The general scientific objective of this non-interventional study is to obtain an estimate of the occurrence of the adverse events in the population under study. Due to the nature of a single cohort observational study, however, there are issues that may impose limitations in particular on the validity of the assessment based on the study data such as selection bias, loss to follow up, channeling bias and information and recall bias. Thus, comparisons and causal conclusions cannot be made, except for the investigator reported drug-related AEs.

9.10 OTHER ASPECTS

9.10.1 Informed consent, data protection, study records

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the patient's treating physician.

The rights of the investigator and of the sponsor with regard to publication of the results of the use-results survey are described in the contract. As a general rule, no results should be published prior to finalization of the Study Report.

9.10.1.1 Study approval, patient information and informed consent

The review by Institutional Review Board (IRB) is not mandatory for conducting the PMS in Japanese GPSP. The sponsor will enter into a contract with a representative (i.e., head of hospital) in accordance with GPSP. Written informed consent prior to patient participation in the trial is not a regulatory or legal requirement in accordance with GPSP.

9.10.1.2 Data quality assurance

This PMS is to be conducted in accordance with both the in-house PMS SOP and working instructions which are in compliance with GPSP.

9.10.1.3 Records

CRFs for individual patients will be provided by the sponsor via the EDC system.

9.10.1.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current

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medical records must be available. For eCRFs, all data must be delivered from source documents.

9.10.1.3.2 Direct access to source data and documents

Direct access to source data and documents for PMS is not allowed in Japan.

9.10.1.4 Statement of confidentiality

Individual patient medical information obtained as a result of this PMS is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Data generated as a result of the PMS needs to be submitted on request by the regulatory authorities.

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10. PROTECTION OF HUMAN SUBJECTS

There is no need for a clinical trial type insurance of well-being and rights of participants because this is a non-interventional study and there is no risk of an experimental treatment. There is no regulation or requirement for ensuring the well-being and rights of participants.

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11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

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No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.
Collection and Reporting of AEs
The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.
The following must be collected by the investigator in the (e) CRF via the EDC system from first intake of Micatrio® Combination Tablets at baseline visit and within 1 day (inclusive) after last intake.

- all AEs (serious and non-serious)
- all ADRs and AEs with fatal outcome in patients exposed to Micatrio® Combination Tablets as soon as possible

All AEs including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event:
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest a reasonable causal relationship could be:

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative etiologies that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
    - An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal

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relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate: Enough discomfort to cause interference with usual activity
Severe: Incapacitating or causing inability to work or to perform usual activities

The intensity of adverse events should be classified and recorded according to the above referenced definition in the (e)CRF.

Pregnancy

In rare cases, pregnancy might occur in a study. Once a subject, has been enrolled into the study after having taken Micatrio® Combination Tablets, the investigator must report any drug exposure during pregnancy which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.
In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed.
The investigator will report the Pregnancy Monitoring Forms as soon as possible via the unique entry point described in the Site Materials.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than the Micatrio® Combination Tablets according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements.

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12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The interim and final report will be submitted PMDA in Japanese Periodic Safety Update Report (PSUR) and re-examination documents. And the interim and final report are also planned to be used for related publications.

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13. REFERENCES

13.1 PUBLISHED REFERENCES

Not applicable.

13.2 UNPUBLISHED REFERENCES

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ANNEX 1. SUMMARY OF SAFETY SPECIFICATION IN LOCAL RMP

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ANNEX 2. GRADE FOR RENAL AND HEPATIC DYSFUNCTION

Investigator should judge the grade for renal dysfunction by using lab data category as described below and symptoms/concomitant diagnoses.

Enzymatic method:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times \text{Creatinine (mg/dL)}^{-1.094} \times \text{Age}^{-0.287}$$

For female, ×0.739

Jaffe rate assay:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times \text{Creatinine (mg/dL)}^{-1.154} \times \text{Age}^{-0.203}$$

For female, ×0.742

APPROVAL / SIGNATURE PAGE

Document Number: c04592560 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol

Title: The special drug use-results survey on long-term use of telmisartan 80 mg/amlodipine 5 mg/hydrochlorothiazide 12.5 mg fixed dose combination tablets in Patients with Hypertension

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Trial Clinical Monitor		13 Dec 2016 03:30 CET
Approval- Pharmacovigilance		13 Dec 2016 03:32 CET
Author-Trial Statistician		13 Dec 2016 03:45 CET
Approval-Medical		13 Dec 2016 05:39 CET
Approval- Safety Evaluation Therapeutic Area		13 Dec 2016 08:10 CET
Approval-Team Member Medicine		13 Dec 2016 09:07 CET
Approval-Other		19 Dec 2016 11:27 CET
Approval- Established Core Products		20 Dec 2016 08:44 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed