TRIAL STATISTICAL ANALYSIS PLAN c16241309-01

BI Trial No.:	1348.6
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
Investigational Product(s):	Telmisartan / amlodipine / hydrochlorothiazide combination tablets
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Date of statistical analysis plan:	31 JAN 2019 SIGNED
Version:	"Final"

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ACE	Angiotensin Converting Enzyme
ADR	Adverse Drug Reaction
ADS	Analysis Data Set
AE	Adverse Event
ARB	Angiotensin Receptor Blocker
BMI	Body Mass Index
BP	Blood Pressure
CCB	Calcium Channel Blocker
CI	Confidence Interval
CRF	Case Report Form
DBP	Diastolic Blood Pressure
eGFR	Estimated glomerular filtration rate
FDC	Fixed-dose combination
MedDRA	Medical Dictionary For Regulatory Activities
MMRM	Mixed model repeated measures
NIS	Non-interventional Study
PMS	Post-Marketing Surveillance
PT	Preferred Term
PV	Protocol Violation
Q1	Lower Quartile
Q3	Upper Quartile
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
ToC	Table of Contents
TSAP	Trial Statistical Analysis Plan

3. INTRODUCTION

The purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Non-interventional Study (NIS) Protocol, including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in NIS Protocol Section 9.7 “DATA ANALYSIS”. Therefore, TSAP readers may consult the NIS Protocol for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size.

SAS Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

There has been no change in the planned analysis from the statistical methods described in the NIS Protocol.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

There is no primary endpoint for effectiveness, the primary objective of the PMS study is the evaluation of safety (see the NIS Protocol Section 9.3.2).

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the protocol.

5.2.2 Secondary endpoint(s)

The secondary endpoints will be used as defined in the NIS Protocol Section 9.3.2.

5.4 OTHER VARIABLE(S)

Demographic and baseline characteristics

- Age [years]
  Actual age based on first administration of Micatrio

- Reason of use: Hypertension, Other
- Duration of hypertension [years]
  [First administration of Micatrio – first diagnosis of hypertension + 1 (if negative value, then 1)] / 365.25

- Height [cm]
- Weight [kg]
- BMI [kg/m^2]

- eGFR [mL/min/1.73 m]
  See NIS Protocol ANNEX 2 for calculation formulas.

Treatment exposure

- Durations of Micatrio treatment [days] = (date of last intake) – (date of first intake) + 1 – (period of treatment interruption [days])
- Duration of Micatrio treatment class [days]: ≤30, 31 to 60, 61 to 90, 91 to 180, 181 to 365, ≥366, unknown
- Total number of tablet of Micatrio
- Number of tablets at first dose of Micatrio [tablet]: 1, Other
- Frequency per day at first dose of Micatrio [time]: 1, Other

Treatment compliance

- Compliance (between first administration and Week 8 or the last intake at the prematurely discontinuation): Good, Not good, Unknown
- Compliance (between Week 8 and Week 52 or the last intake at the prematurely discontinuation): Good, Not good, Unknown

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on treatments, please refer to NIS Protocol Section 9.1. The technical specification for treatment set-up is described in the analysis data set (ADS) plan. For safety analyses, data up to1 day after last treatment intake will be considered as on treatment for AE. For effectiveness analysis, data up to 1 day after last treatment intake will be considered as on treatment for clinic SBP, clinic DBP, home SBP and home DBP.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Table 6.2: 1 Important protocol violations

Category / Code		Description	Requirements	Method	Excluded from
A		**Entrance criteria not met**			
	A1	No hypertension	Reason of use is not hypertension.	Automated	Effectiveness
	A2	Patient received Micatrio treatment before registration	previous medication Drug code=" 214912201"	Automated	Safety Effectiveness
	A3	Participation in a clinical trial	See detail of reason for discontinuation Concomitant medication code blank	Manual	Safety Effectiveness
B		**Trial medication**			
	B1	No treatment with Micatrio		Automated	Safety Effectiveness
C		**Missing data**			
	C1	No patient visit after the entry	Administration status is "No visit since the first visit"	Automated	Safety Effectiveness
	C2	No effectiveness information	• No BP data at baseline, and BP data exist at post-treatment. • BP data exist at baseline, and no BP data at post-treatment. • No BP data at baseline, and no BP data at post-treatment.	Automated	Effectiveness
D		**Trial specific**			
	D1	Multiple registration	Same patient registered more than once All data for the later patient will be not used.	Manual	Safety Effectiveness
	D2	Registration rule not followed	See NIS Protocol section 9.2.2.2 and 9.2.2.3	Manual	Safety Effectiveness
	D3	Site contract is not valid		Manual	Safety Effectiveness

6.3 SUBJECT SETS ANALYSED

The safety set will be the basis of all demographic, baseline and safety analyses. Effectiveness analysis will be on basis of the effectiveness set.

- Safety set:

This patient set includes all patients who don't have important PVs regarding with safety and regulatory issues as marked "Safety" in Table 6.2: 1.

- Effectiveness set:

This patient set includes all patients in safety set with approved indication and have effectiveness information. (Patients marked Effectiveness in Table 6.2: 1 should exclude from effectiveness analysis.)

Table 6.3: 1 Subject sets analysed

	Subject set	
Class of endpoint	Safety Set	Effectiveness Set
Primary endpoints	X	
Secondary endpoints		
Demographic and baseline characteristics	X	
Medical history/concomitant diseases	X	
Treatment exposure	X	

6.5 POOLING OF CENTRES

This section is not applicable because centre is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Incomplete dates for first diagnosis, creatinine measurement, baseline condition, medical history, previous medications, concomitant medications and laboratory test are imputed as follows:

- If both ‘day’ and ‘month’ are missing, then impute the day and month as follows: Set ‘day’ as 1 and ‘month’ as 7 (i.e., July 1).

- If only ‘day’ is missing, then impute the day as follows:
  Set ‘day’ as 15.

Incomplete dates for birth as follows:

- If both ‘day’ and ‘month’ are missing, then impute the day and month as follows:
  Set ‘day’ as 1 and ‘month’ as 1 (i.e., January).

- If only ‘day’ is missing, then impute the day as follows:
  Set ‘day’ as 1.

Incomplete dates for active ingredient of Micatrio before the treatment as follows:

- If both ‘day’ and ‘month’ are missing, then impute the day and month as follows:
  Set ‘day’ as 31 and ‘month’ as 12 (i.e., December 31).

- If only ‘day’ is missing, then impute the day as follows:
  Set ‘day’ as the last day of the month.

Safety:

Missing or incomplete AE dates are imputed according to

(1)

Effectiveness:

Missing effectiveness data will not be imputed.

Note that in general when tabulating AEs, and/or demographic and baseline characteristics variables reported as unknown will be treated as such; otherwise treated as missing data.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline is defined as the time point after entry and directly before Micatrio was first administered.

Effectiveness analyses will be based on calculated visits which will be labelled by ‘Week X’ in tables, listings and graphs. A calculated visit is a visit that corresponds to a time interval based on relative days. The calculated visits form a set of non-overlapping time intervals covering the entire duration of the trial. Calculated visits will usually have a one-to-one correspondence with planned visits.

In case where two visits fall in the same interval and at equal distance to the planned visit, the first one will be taken for the analysis.

The following labels will be used for visits and planned times.

Table 6.7: 1 Baseline, time windows and calculated visits

Planned day	**Actual day* for calculated visit**	**Label**
	The last observed measurement prior to or on the first administration of Micatrio	Baseline
28	2 to ≤41	Week 4
56	42 to ≤69	Week 8
84	70 to ≤125	Week 12
168	126 to ≤209	Week 24
252	210 to ≤307	Week 36
364	≥308	Week 52

* Actual days = Observed date – Administration start date + 1

7. PLANNED ANALYSIS

The detailed description of the planned analyses documented in the NIS Protocol will be given in this section.

For End-Of-Text tables, the set of summary statistics is: N / Mean / SD / Min / Q1 / Median / Q3 / Max.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to 2 decimal places. The category missing will be displayed only if there are actually missing values.

Percentages will be based on all patients in the respective patient set whether they have non-missing values or not.

In addition, individual values on demographics, effectiveness and safety will be presented in subject data listings.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded with the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Only descriptive statistics are planned for previous/concomitant diseases.

Concomitant medication will not be coded or summarised unless otherwise used for defining patient subgroup to explore safety risks and/or effectiveness of Micatrio treatment (for this, see Section 6.4).

7.3 TREATMENT COMPLIANCE

Reported compliance class will be descriptively summarised.

7.4 PRIMARY ENDPOINT(S)

The analysis of the primary endpoint is described in Section 7.8.1.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 (Other) Secondary endpoint(s)

For the change from baseline in SBP and DBP after 52 weeks, summary statistics will be calculated. 95% confidence intervals (CIs) will also be calculated for the mean.

In addition, BP measurements will also be summarised by least square means using mixed model repeated measures (MMRM). The analysis is done based on the observed case data. In the MMRM, patient will be a random effect and variance-covariance structure for each visit by patient is assumed as compound symmetry. The SAS procedure “PROC MIXED” will be used involving the restricted maximum likelihood estimation and the Kenward and Roger approximation of denominator degrees of freedom. Subsequently, least square means are computed that are averaged across repeated measures and their respective standard error, 95% CI estimate and p-value account for the estimated covariance parameters.

7.7 EXTENT OF EXPOSURE

Only descriptive statistics are planned for this section of the report.

7.8 SAFETY ANALYSIS

All safety analyses will be performed the safety set unless otherwise specified.

7.8.1 Adverse events

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

For analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence

For further details on summarization of AE data, please refer (2).

An overall summary of AEs will be presented.

The frequency of patients with ADRs will be tabulated by Micatrio dose at onset, system organ class (SOC) and preferred term (PT) according to the most recent MedDRA version. Separate tables will be provided for patients with SAEs, AEs

For AEs leading to discontinuation of Micatrio and AEs leading to death, a summary table will also be created.

In reporting AEs from the PMS study, frequency summaries are in general provided based on ADR. An ADR is defined as an AE for which either the investigator or the sponsor (or both) assess the causal relationship to Micatrio as “Yes”.

A serious AE is defined as an AE for which either the investigator or the sponsor (or both) assess the seriousness as “Serious”.

The frequency of patients with ADRs will be tabulated by system organ class (SOC) and preferred term (PT) according to the most recent MedDRA version. Separate tables will be provided for patients with ADRs stratified by various patient subgroups defined in Section 6.4, for patients with serious AEs.

The SOCs will be sorted by default alphabetically, and preferred terms will be sorted by frequency (within SOC).

To compare risks of overall ADR and SAE in different patient subgroups, frequency tabulation stratified by different patient subgroups will be provided with odds ratios and exact 95% confidence intervals whenever specified (see Section 6.4).

In addition, summaries for the time to onset of first episode for the ADRs will be tabulated, by duration (<4weeks, 4 to <8 weeks, 8 to <12 weeks, 12 to <24 weeks, 24 to <36 weeks, 36 to <52 weeks, 52 weeks-) by primary SOC, and PT.

7.8.2 Laboratory data

Only clinically relevant findings reported as AE will be analysed as a part of AE analyses.

7.8.3 Vital signs

For pulse rate, descriptive statistics for the changes from baseline over will be calculated at each time point during the observation period.

7.8.4 ECG

Only clinically relevant findings reported as AE will be analysed as a part of AE analyses.

7.8.5 Others

No other safety parameters are defined for analyses.

8. REFERENCES

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**31-JAN-19**		None	This is the final TSAP without any modification.