



Protocol A2581197

Atorvastatin Effectiveness and Safety in Cardiology
patients in Real World Setting: A Registry Study in China

Statistical Analysis Plan (SAP)

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TABLE OF CONTENTS

1	AMENDMENTS FROM PREVIOUS VERSION(S)	4
2	INTRODUCTION	4
2.1	STUDY DESIGN	4
2.2	STUDY OBJECTIVES	5
	• <i>Primary objective</i>	5
	• <i>Secondary objectives</i>	5
2.3	SAMPLE SIZE AND POWER CALCULATIONS	6
3	INTERIM ANALYSES	6
4	HYPOTHESES AND DECISION RULES	6
4.1	STATISTICAL HYPOTHESES	6
4.2	STATISTICAL DECISION RULES	6
5	ANALYSIS SETS/ POPULATIONS	6
5.1	FULL ANALYSIS SET (FAS)	6
5.2	SAFETY ANALYSIS SET (SAS)	6
5.3	ENROLLED POPULATION (EP)	7
5.4	SUBGROUPS	7
	• <i>Age at Baseline</i>	7
	• <i>Dose Groups</i>	7
	• <i>Baseline Variables</i>	7
6	ENDPOINTS AND COVARIATES	7
6.1	PRIMARY (EFFICACY) ENDPOINT	7
6.2	SECONDARY ENDPOINTS	8
	• <i>Duration on Study</i>	9
	• <i>Adverse Events</i>	9
	• <i>Adverse Events Special Interest (AESI)</i>	9
	• <i>Abnormal Laboratory Data</i>	9
6.3	OTHER ENDPOINTS	10
6.4	COVARIATES	10
7	HANDLING OF MISSING VALUES	10
8	STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES	10
8.1	STATISTICAL METHODS	10
	• <i>Analyses for Continuous Data</i>	10
	• <i>Analyses for Categorical Data</i>	10
	• <i>Analyses for Binary endpoints</i>	10
8.2	STATISTICAL ANALYSES	11
	• <i>Analysis of Primary (Efficacy) Endpoint</i>	11
	• <i>Secondary Endpoints and Safety Analyses</i>	11

Lipid Parameters	11
Study Drug Exposure	11
Adverse Events	12
Dropouts.....	12
Laboratory Data	12
Prior and Concomitant Medications	12
8.3 OTHER ANALYSES	12
Subject Disposition	12
Demographics and Baseline Characteristics	13
Subgroup Analysis	13
9 LIST OF TABLES AND TABLE SHELLS	13
10 REFERENCES.....	13
11 APPENDICES	13
11.1 APPENDIX 1: DATA DERIVATION DETAILS	14
A1.1 <i>Definition of visit windows.....</i>	<i>14</i>
A1.2 <i>Demographic and Baseline Variables</i>	<i>14</i>
A1.3 <i>Definition of Derived Variables.....</i>	<i>14</i>
Age.....	14
Body Mass Index (BMI)	14
CVD risk level (strata)	14
Reference Normal Laboratory Ranges.....	15
A2.1 <i>SAS code for exact method.....</i>	<i>15</i>

1 AMENDMENTS FROM PREVIOUS VERSION(S)

- Status of study when amendment (version 2) made: Study Ongoing
- Descriptions of and rationale for the changes:

Details of the Changes Rationale for the Changes

Details of the Changes	Rationale for the Changes
Week 12 is defined as Study Day 85 ± 28 days from the Day 1 study drug taken.	The LDL results at 8 weeks (2 months) from the study drug start are expected to be similar to the results at 12 weeks. Therefore in order to not unnecessarily exclude patients from the analysis, the Week 12 window has been expanded from 85 ± 10 days to 85 ± 28 days

2 INTRODUCTION

This document describes the planned data summaries and statistical analyses for Protocol A2581197, entitled “Atorvastatin Effectiveness and Safety in Cardiology patients in Real World Setting: A Registry Study in China”. It is meant to supplement the study protocol which should be referred to for details regarding the objectives and design of the study. Any deviation to this analysis plan will be described in the Clinical Study Report.

Note: in this document any text taken directly from the protocol is *italicized*.

2.1 STUDY DESIGN

Overview

This is a multi-center, prospective, observational study, which will be completed by Beijing Anzhen Hospital, Capital Medical University and approximately 64 other clinical sites.

At baseline visit, patient inclusion/exclusion and demographic information, medical history, medication records, concomitant drugs and laboratory examination results prior to atorvastatin therapy such as liver function, blood lipid parameter, creatine kinase value and renal function will be collected by investigators in the study. At week 12 visit and any unplanned visits, the laboratory examination results and medication records will be collected. Adverse events will be recorded at any time during the study period. Schedule of Activities is as follows:

Table 1: Schedule of Activities

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Visits	Visit 1	Visit 2	Any un planned visits
Protocol Activity	Baseline Day 1	Week 12 Day 85 (± 28 days)	Any Date During Week 4 to Study Close
Signed Informed Consent Form	▲		
Demographic information	▲		
Medical history	▲		
Laboratory examination	▲*	▲	▲
Inclusion/exclusion criteria	▲		
Adverse event records	Record at any time during the study period		
Medication records	▲	▲	▲

* The date of the report should be within 1 month before taking atorvastatin.

Study population

Judged by investigators, patients in cardiology department who are eligible for inclusion and exclusion criteria can be included into this study. Estimated total sample size is 10,000 and will be conducted in approximately 65 hospitals in China.

Data source

This Non-Interventional (NI) study data will be recorded in the medical records by investigators, and then input to electronic Data Collection (EDC) system as the form of electronic Case Report Form (eCRF).

Treatment/dose group

The study drug (atorvastatin) is from the doctor's prescription and will be recorded on Day 1, Week 12, and within Week 4 to end of the study. The analysis by dose groups will be taken the dose level recorded at Week 12 (Visit 2) on the prescription level or the last dose in the unplanned visit if the Week 12 is not available.

The dose groups will be in four daily dose levels, 10 mg, 20 mg, 40 mg and > 40 mg.

2.2 STUDY OBJECTIVES

- **Primary objective**
 - *To evaluate the effectiveness of atorvastatin in Chinese cardiology patients in real world setting.*
- **Secondary objectives**
 - *To assess atorvastatin safety in cardiology patients in real world setting*
 - *To analyze patterns of atorvastatin prescription in cardiology patients*

2.3 SAMPLE SIZE AND POWER CALCULATIONS

In the recently published DYSIS^[1] study, the achievement rate of Low-Density Lipoprotein Cholesterol (LDL-C) value was about 60% among Chinese outpatients taking 3 months lipid-lowering therapy. In this NI study, we assumed the achievement rate of LDL-C of 60%, allowable error rate of 1.1 %, type I error of 0.05, we calculated a required sample size of 7600 patients. Considering 24% loss to follow-up in real-world setting, the sample size will be 10,000.

This sample size will also allow for stratification by sex, age (<65 years vs \geq 65 years), risk stratification (very high risk, high risk, moderate risk and low risk) and baseline disease type (with established CHD, having multiple risk factors, and primary hypercholesterolemia).

3 INTERIM ANALYSES

No interim analysis is planned.

4 HYPOTHESES AND DECISION RULES

4.1 STATISTICAL HYPOTHESES

There are no formal hypotheses specified for the study.

4.2 STATISTICAL DECISION RULES

Not applicable.

5 ANALYSIS SETS/ POPULATIONS

5.1 FULL ANALYSIS SET (FAS)

The FAS analysis population will include all enrolled in the study that received at least one dose of atorvastatin and completed 12- week follow-up. The FAS population will be the primary analysis set for the primary endpoint.

5.2 SAFETY ANALYSIS SET (SAS)

The Safety Analysis population will include all patients who receive at least one dose of study drug atorvastatin. The SAS will be the primary analysis population for all safety reporting.

5.3 ENROLLED POPULATION (EP)

The enrolled population will consist of all patients who signed informed consent.

5.4 SUBGROUPS

Primary and secondary endpoints described in Section 6 will be summarized descriptively in all analysis populations except EP in these subgroups.

- **Age at Baseline**
 - 18 – 64 years old
 - ≥ 65 years old
- **Dose Groups**

The dose groups will be in four Atorvastatin daily dose levels:

- 10 mg
- 20 mg
- 40 mg
- > 40 mg

- **Baseline Variables**

Subgroup analyses may be performed within the following categories.

- CVD risk level: low, moderate, high, very high, per definition in [Table 2](#).
- Disease type: established CHD (Coronary Heart Disease), multiple risk factors, and hypercholesterolemia

6 ENDPOINTS AND COVARIATES

6.1 PRIMARY (EFFICACY) ENDPOINT

- *The primary efficacy endpoint is the proportion of patients who achieve the LDL-C goal value. Achievement rate of LDL-C goals at 12 weeks of therapy of atorvastatin are evaluated according to Chinese Guideline on Dyslipidemia Prevention and Treatment in Adult (2007 version).*

$$\text{Achievement Rate} = \frac{\text{No. subjects who achieve LDL-C target value}}{\text{No. subjects who complete 12-week follow up}}$$

The Chinese Guideline on Dyslipidemia Prevention and Treatment in Adult (2007), the Cardiovascular Disease (CVD) risk stratification and LDL-C therapy target value are defined in Table 2.

Table 2: CVD Risk Stratification and LDL-C Therapy Target Value

Risk stratification	Beginning of drug therapy	Therapy target value
Low-risk: 10 years CV risk <5%	LDL-C \geq 4.92 mmol/L (190mg/dl)	LDL-C < 4.14 mmol/L (160mg/dl)
Medium/ Moderate risk: 10 years CVD risk 5% - 10%	LDL-C \geq 4.14 mmol/L (160mg/dl)	LDL-C < 3.37 mmol/L (130mg/dl)
High risk: CHD or CHD risk equivalents, or 10 years CV risk 10% - 15%	LDL-C \geq 2.59 mmol/L (100mg/dl)	LDL-C < 2.59 mmol/L (100mg/dl)
Very high risk: acute coronary syndromes, or ischemic cardiovascular disease combined with diabetes	LDL-C \geq 2.07 mmol/L (80mg/dl)	LDL-C < 2.07 mmol/L (80mg/dl)

Target achievement rate will be summarized overall, within each risk strata, and by dose within each risk strata. 95% confidence intervals will be provided.

6.2 SECONDARY ENDPOINTS

- Lipid parameters (LDL-C, *High-Density Lipoprotein Cholesterol* (HDL-C), Total Cholesterol (TC), and Triglycerides (TG)) at week 12, change from baseline in lipid parameters, and %change from baseline in lipid parameters at week 12, overall, and by CVD risk group.
- *Dosage distribution of atorvastatin in patients by CV risk stratification at the end of 12-week follow-up defined as follows:*

- The atorvastatin total dose in each patient will be calculated from Day 1 to Week 12/or last dose day.
- The patient daily dose will be the total dose divided by the total days of receiving atorvastatin.
- The Week 12 dose will be the dose taken at Week 12.

- **Duration on Study**

Duration on treatment group for each subject will be calculated as last treatment day – first dose date +1

- **Adverse Events**

Any new findings or worsening of findings at post-baseline visits will be reported as adverse events.

An adverse event is considered treatment emergent relative to a given treatment if:

- the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment, or
- the event was seen prior to the start of treatment but increased in severity during treatment.

- **Adverse Events Special Interest (AESI)**

The Adverse Events Special Interest (AESI) will be categorized as below:

- Muscle symptoms: myalgia, fatigue, weakness, creatine kinase values 10 times the upper limit of normal, or rhabdomyolysis, and muscle damage based on significant elevated creatine kinase (CK)
- Major cardiovascular events: myocardial infarction, stroke, unstable angina requiring re-hospitalization, revascularization with either percutaneous coronary intervention or coronary-artery bypass grafting
- Death

- **Abnormal Laboratory Data**

The following elevated abnormal laboratory data will be summarized.

- Significant elevated CK: CK values 10 times the upper limit of normal,
-

- Persistent elevation in alanine aminotransferase, aspartate aminotransferase, or both: two consecutive measurements obtained 4 to 10 days apart that is more than three times the upper limit of the normal range
- **Dropout**
Dropout percentages and reason through 12 weeks of follow-up

6.3 OTHER ENDPOINTS

N/A

6.4 COVARIATES

Not applicable as there is no formal hypothesis testing for treatment comparisons.

7 HANDLING OF MISSING VALUES

For all endpoints, individual missing data will not be imputed.

8 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1 STATISTICAL METHODS

SAS[®] Version 9.4 or later will be used to produce all listings and summary tables.

Summary tables presented by visit will include results from scheduled visits such as Day 1 and Week 12. Unscheduled visits will be listed but not summarized except in the event that an unscheduled result qualifies as a baseline result or other derived endpoint.

- **Analyses for Continuous Data**

Summary statistics for continuous variables/endpoints will be presented with number of observations (n), mean, SD, median, minimum (min), and maximum (max).

- **Analyses for Categorical Data**

Summary statistics for categorical variables/endpoints will be presented with number of observations (n) and percentages.

- **Analyses for Binary endpoints**

Exact methods (Clopper-Pearson Interval) will be used to calculate confidence interval (CI) for the primary (efficacy) endpoint: achievement rate of LDL-C at Week 12.

$$\left[\frac{r}{r + (n - r + 1)F_{1-\alpha/2; 2(n-r+1), 2r}}, \frac{(r + 1)F_{1-\alpha/2; 2(r+1), 2(n-r)}}{(n - r) + (r + 1)F_{1-\alpha/2; 2(r+1), 2(n-r)}} \right]$$

Where r is the proportion of patients who met therapy target level and n is the total number of patients who completed 12-weeks.

8.2 STATISTICAL ANALYSES

• Analysis of Primary (Efficacy) Endpoint

The primary (efficacy) analysis will be conducted in the FAS analysis population. The proportion of Achievement rate for LDL-C at Week 12 defined as the primary endpoint will be analyzed by calculating a point estimate with confidence interval (CI).

Achievement rate for LDL-C will be summarized overall, within each CVD risk strata, and by dose group within each CVD risk strata. 95% confidence intervals will be estimated.

In addition, percentage of patients who achieve LDL-C therapy target will also be tabulated by sex, age group, dose group and baseline disease type.

• Secondary Endpoints and Safety Analyses

Analysis of lipid values and change and percent change in lipid values at week 12 will be performed on the FAS populations. Analysis of the remaining secondary endpoints and safety data will be done on SAS (See [Section 5.2](#)). Data summaries will be presented in tabular and/or and summarized descriptively, where appropriate.

Lipid Parameters

Descriptive summary will be tabulated overall and by dose group within each CVD risk level for percent (%) change from baseline for TC, HDL-C and LDL-C and TG at Week 12.

Study Drug Exposure

Exposure to atorvastatin will be summarized descriptively overall, and by CVD risk level. Duration (days) of study drug taken, daily dose, dose at week 12, and total dose will be summarized. Listings of dosing records with the reason of change dose will also be provided.

Adverse Events

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. The severity of adverse events will be graded according to the principal investigatory judgment and collected in CRF.

Adverse events (such as treatment emergent adverse events; treatment-related adverse events; and serious adverse events, adverse event from early termination to final visit, will be summarized by system organ class (SOC) and preferred term (PT) according to MedDRA terminology.

Adverse events will be summarized overall and by dose group within each CVD risk strata by SOC and preferred term.

Adverse events of special interest ([section 6.2](#)) will be tabulated by preferred term (PT) overall and by dose group within each CVD risk level.

Adverse events leading to discontinuation of trial treatment will be presented overall and by dose group within each CDV risk level.

Dropouts

Percentage of patients who drop out of the study and reasons for discontinuation will be summarized overall and by dose group within each CVD risk level.

Laboratory Data

The percentage of patients with abnormal laboratory values will be summarized overall and by dose group within each CVD risk level for CK, Aspartate Aminotransferase (AST), and Alanine Aminotransferase (ALT).

Descriptive summary will be provided for change from baseline for clinical laboratory by overall and dose group within each CVD risk level.

The baseline is the last non-missing value prior to treatment start.

Prior and Concomitant Medications

Prior and concomitant medications will be coded by WHO medical dictionary; patients who received these medications will be listed and summarized overall, and by dose group within each CVD risk level.

8.3 OTHER ANALYSES

Subject Disposition



The number of patients screened and the number and percentage of patients enrolled and in each population will be summarized and listed for the enrolled population.

The number and percentage of patients who complete the study as well as the number and percentage of patients who discontinued the study drug and study will be summarized and listed. The primary reason for early discontinuation will be summarized and listed for all enrolled patients (EP).

Demographics and Baseline Characteristics

Demographic data (including age, gender, height, body weight and BMI) will be summarized by dose group. Baseline characteristics obtained from laboratory reports, including lipid measurement, liver function, creatine kinase (CK) value. Renal function and CVD risk level will be summarized by study dose group, and overall.

Baseline disease will be summarized in each dose group for established CHD, having multiple risk factors, and primary hypercholesterolemia.

Medical history at screening will be collected in the case report form and will be listed in a data listing.

Subgroup Analysis

Additional subgroup by risk factors and other exploratory analyses may be conducted as appropriate.

9 LIST OF TABLES AND TABLE SHELLS

The table shells will be provided by analysis team.

10 REFERENCES

[1] Zhao Shuiping, Wang Yongjun, Mu Yiming, etc. Prevalence of dyslipidaemia in patients treated with lipid-lowering agents in China: Results of the DYSlipidemia International Study (DYSIS). *Atherosclerosis*. 2014, 235:463-469

11 APPENDICES

11.1 APPENDIX 1: DATA DERIVATION DETAILS

A1.1 Definition of visit windows

- Baseline (Day 1) is defined after informed consent date signed within one month prior to receive a study drug.
- Study Day = date of assessment – date of first dose of study drug + 1
- Week 12 is defined as Study Day 85 ± 28 days from the Day 1 study drug taken.
- Duration of Study Drug = Date of last dose – date of first dose +1
- End of Study: The Day completion of the study or discontinuation from the study.

A1.2 Demographic and Baseline Variables

- Demographic information : age, gender, height , body weight and BMI
- Medical histories:current or previous medical history, family history of premature atherosclerotic cardiovascular disease (ASCVD) and history of smoking
- Baseline Variables: strata
 - CVD risk level: low, moderate, high, very high, per definition in section 5.4.
 - Liver function tests: ALT, AST, total bilirubin (TBil)
 - Renal function tests: Creatinine (Cr), Blood Urea Nitrogen (BUN), Uric Acid (UA)
 - Serum lipid parameters :LDL-C, HDL-C, TG, Total-C
 - Creatine kinase value (CK)
 - Disease type: established CHD (Coronary Heart Disease), multiple risk factors, and hypercholesterolemia

A1.3 Definition of Derived Variables

Age

- Age = integer of [(informed consent date – date of birth)/ 365.25]
- Age groups: 18 – 64 years old, ≥ 65 years old

Body Mass Index (BMI)

- $BMI = \text{Weight (kg)} / [\text{Height (m)}]^2$

CVD risk level (strata)

The CVD risk level is based on Chinese Guideline on Dyslipidemia Prevention and Treatment in Adult (2007), the cardiovascular disease (CVD) risk stratification. The 10 years CVD risk factors are calculated based on age, sex, total cholesterol, HDL-C, hypertension, smoking history, medical history, and family history.

The CVD risk level for dyslipidemia will be derived.

Reference Normal Laboratory Ranges

The normal laboratory ranges will be defined by local lab facilities.

A2.1 SAS code for exact method

```
proc freq data=Lipitor order=freq;  
  tables LDL-C Goal / binomial (exact) alpha=.05;  
  title 'Exact methods of 95% confidence interval (CI) for rate of LDL-C' ;  
run;
```

