NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Atorvastatin Effectiveness and Safety in Cardiology patients in Real World Setting: A Registry Study in China
Protocol number	A2581197
Protocol version identifier	Version 3.0
Date of last version of protocol	21 September, 2017
Active substance	Atorvastatin
Medicinal product	Atorvastatin
Research question and 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.
Author	PPD , Medical Manager PPD , TA manager

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
FPI	First Patient In
LPLV	Last Patient Last Visit
CK	Creatine Kinase
LDL-C	Low Density Lipoprotein-Cholesterol
LDL	Low Density Lipoprotein
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ULN	Upper Limit of Normal
CHD	Coronary Heart Disease
ACC	American College of Cardiology
AHA	American Heart Association
HMG-CoA	3-hydroxy-3-methyl glutaryl coenzyme A
IDL	Intermediate-Density Lipoprotein
IDL-C	Intermediate-Density Lipoprotein Cholesterol
VLDL	Very-Low-Density Lipoprotein
VLDL-C	Very-Low-Density Lipoprotein Cholesterol
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein Cholesterol
apo B	Apolipoprotein B
total-C	total Cholesterol
AUC	Area Under Curve
HGPRT	Hypoxanthine-Guanine Phosphoribosyl Transferase
ASCVD	Atherosclerotic Cardiovascular Disease
CVD	Cardiovascular Disease
GCP	Good Clinical Practice
eCRF	electronic Case Report Form
EDC	Electronic Data Collection
SAP	Statistical Analysis Plan
CRAs	Clinical Research Associates
IRB/IEC	Institutional Review Board/Independent Ethics committee
EDP	Exposure During Pregnancy

AEM	Adverse Event Monitoring
AE	Adverse Events
SAE	Serious Adverse Events
FDA	Food and Drug Administration
NI	Non-Interventional
NIS	Non-Interventional Study
SRSD	Single Reference Safety Document
CFDA	China Food and Drug Administration
PI	Package Insert
TBIL	Total Bilirubin
TG	Triglyceride
GPP	Good Pharmacoepidemiology Practices
ISPE	International Society for Pharmacoepidemiology
GEP	Good Epidemiological Practice
IEA	International Epidemiological Association
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
CIOMS	Council for International Organizations of Medical Sciences
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
Cr	Creatinine
BUN	Blood urea nitrogen
UA	Uric acid
ACEI	Angiotensin converting enzyme inhibitors
ARB	Angiotensin receptor blockers

2. RESPONSIBLE PARTIES

Leading Principal Investigator

Name, degree(s)	Title	Affiliation	Address
Dr. PPD	Professor	PPD	PPD Beijing PPD

Coordinative Principal Investigator

Name, degree(s)	Title	Affiliation	Address
Dr. PPD	Professor	PPD	PPD Beijing PPD

3. ABSTRACT

Study Title	Atorvastatin Effectiveness and Safety in Cardiology patients in Real World Setting: A Registry Study in China
Sponsor	Pfizer Pharmaceuticals Ltd.
Principle Investigator of the protocol	Professor PPD , PPD
Site Number/ Nationality	Approximately 65 sites/China
Objectives	**Primary objective:** • To measure 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.
Study Classification	Non-interventional study
Study Design	multiple centers, prospective, observational study
Sample Size	Approximate 10,000 subjects
Inclusion Criteria	• Men and women aged ≥18 years; • Cardiology patients[#] who has been prescribed atorvastatin by physician's clinical judgment under normal clinical care. These patients will include those with established coronary heart disease, or having multiple risk factors and at risk for cardiovascular disease, or primary hypercholesterolemia. • Baseline laboratory reports* prior to starting atorvastatin therapy can be tracked, including lipid measurement, liver function, creatine kinase (CK) value and renal function • Evidence of a personally or his/her legally acceptable representative signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study and accept follow-up visit. [#]The proportion of ward inpatients is not more than 20% of the total number of patients. *The date of the baseline reports should be within 1 month before taking atorvastatin or

	within 24hours (h) after starting atorvastatin therapy.
Exclusion Criteria	• Patients who have regularly taken atorvastatin therapy more than 4 weeks before enrollment • Concomitant any other lipid-lower medication at baseline, or during the study conduction on physician clinical judgment
Medicinal Product	Atorvastatin
Dosage Administration	Confirm refer to prescription
Primary Endpoint	• Achievement rate of Low Density Lipoprotein-Cholesterol (LDL-C) goals at 12 weeks of therapy of Atorvastatin according to Chinese Guideline on Dyslipidemia Prevention and Treatment in Adult (2007 version). It will be presented with the proportion of patients who achieve the LDL-C goal value with the corresponding 95% confidence interval. *(Please find the detailed description in the section 8.1.2)* ■ The time of 12-week will be calculated from the day when patient start taking atorvastatin.
Secondary Endpoints	• Dosage distribution of Atorvastatin in cardiology patients with different risk categories at the end of 12-week follow-up • Safety and tolerability will be evaluated by recording the incidence and severity of adverse events, abnormal physical examination findings, and abnormal laboratory values through 12 weeks of treatment. Especially monitoring the proportion of patients who have any following events: ■ Muscle symptoms such as myalgia, fatigue, weakness, creatine kinase values 10 times the upper limit of normal, and rhabdomyolysis ■ Persistent elevations in Alanine Aminotransferase/ Aspartate Aminotransferase (ALT/AST) ＞3 Upper Limit of Normal (ULN). ■ Major adverse cardiovascular events • Dropouts percentage and reason through 12 weeks of follow-up;
Observation Duration	12 weeks
Statistics	Sample size consideration: • The non-interventional (NI) study is designed to detect the

	achievement rate of LDL-C value in cardiology patients with atorvastatin therapy in real world setting. The length of follow-up is designed to be 12 weeks. • In the recently published DYSIS [1] study, the achievement rate of 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), risk stratification (very high risk, high risk, moderate risk and low risk) and baseline disease type (with established Coronary Heart Disease (CHD), having multiple risk factors, and primary hypercholesterolemia) Statistics • Descriptive statistics including number (N), mean, median, standard deviation, minimum and maximum, will be produced for all continuous variables. Frequency tables of number (N) and percentage of subjects will be produced for all categorical variables • All patients who received atorvastatin are included in the safety analysis, and safety data is summarized descriptively without statistical analysis.

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	9th June, 2015	Administrative amendment	3.abstract 5. milestones	1. At Page 7: modified the sponsor from "Pfizer Investment Co. Ltd" to "Pfizer Pharmaceuticals Ltd." 2. At Page 7: revised the study period as "14 August 2015 to 15 November 2016" 3. At Page 11: updated the planned date of milestones.	Sponsor name need to be aligned with payment code
2	16th July, 2015	Administrative amendment	10.1. Single Reference Safety Document	At Page 29: modified the wording, changed "the detail version date" to "current local label"	There is no need to amendment when local label updates
3	6th August, 2015	Administrative amendment	2.Responsible Parties 8.3 Variables 8.6 Data Management	1. At Page 6: add Dr. PPD as Principal Investigator of PPD 2. At Page 18: delete "occupation" in Demographic information and "allergic history" in Medical history 3. At Page 18: change database platform from "data-labs" to "OCRDC"	Add PI to facilitate the management and execution of the study Reduce the variables which is not related with study objectives Alignment with the database change from Pfizer CRDC
4	20th November,2015	Administrative amendment	2.Responsible Parties	1. At Page 6: change Dr. PPD as Leading Principal Investigator; add Dr. PPD PPD as Co-Principal Investigator	Change leading PI to facilitate the management and execution of the study
5	25th January, 2016	Substantial amendment	8.2.1 Study patients 8.5 Study size 8.1.1 Overall design 8.3 Variables 8.2.7 Study procedures 8.1.2 Study	1. Change outpatients to patients 2. Change sample size from 15000 to 10000 3. Change in site number from 75 to 65 4. Add renal function variables 5. Information on baseline and week 12 regular visit is required to record. Any other visits would be recorded as unplanned. 6. Change in how to calculate 12-	Make the study design closer to clinical practice

			endpoint 5. MILESOTNES	week 7. Several wording modifications 8. Updated the planned date of milestone per the latest progression	
6	21st September, 2017	Substantial amendment	5. MILESOTNES 8.2.2 Inclusion Criteria 8.2.7 Study Procedures	1. Update the planned date of all the milestones per the latest progression 2. Allow to collect the baseline lab reports within 24h after starting atorvastatin therapy 3. Change the time limit of unplanned visits to "any date during Week 4 to Week 16 (D29 to D115(±10 days))"	Change the Milestones according to the actual execution Make the study design closer to clinical practice

5. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	January 2016
Start of data collection	June 2016
End of data collection	October 2018
Data lock	January 2019
Final study report	April 2019

6. RATIONALE AND BACKGROUND

Dyslipidemia is one of major risk factors leading to atherosclerotic origin cardiovascular disease (ASCVD). A large number of cohort studies indicated that serum total cholesterol or low density lipoprotein cholesterol is one of the independent risk factors resulting in atherosclerotic coronary heart disease and cerebrovascular disease [2-4]. At present, LDL-C is regarded as the primary targets of therapy for prevention and treatment for CHD in clinical guidelines. As the effective drug to lower plasma LDL-C effectively, atorvastatin is widely used in clinical practice [5-6].

2013 American College of Cardiology/ American Heart Association (ACC/AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adult identified 4 statin benefit groups which focus efforts to reduce atherosclerotic cardiovascular disease events in secondary and primary prevention, and recommended high-intensity and moderate-intensity statin therapy for use in secondary and primary prevention [7]. Due to fail to find randomized control trials evidence to support continued use of specific LDL-C treatment targets, the guideline recommended that the appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit. The new guidelines have already been the subject of controversy, with some observers arguing that some elements of the recommendations are not evidence-based. In China, many cardiology experts believe that the ACC/AHA guideline is not applicable for Chinese patients, e.g. high intensity statin (e.g. atorvastatin 40mg or greater) dosage and new perceptive on LDL-C goals. Chinese experts think that Chinese population has lower LDL-C baseline compared with that of western population, moderate intensity statin (e.g. atorvastatin 10-20mg) maybe enough to control blood lipid level. Additionally, high intensity statin in Chinese population may also bring safety concerns. Atorvastatin have been demonstrated established benefits and well safety profiles in a wealth of high risk patients for primary and secondary prevention, however the data mainly came from western population. There is to date lack of

effectiveness and safety data in Chinese population, especially large-scale study in real world setting. Therefore, the study is to verify atorvastatin effectiveness and safety in Chinese population, and explore the optimal atorvastatin regimens in high-to-moderate risk for ASCVD.

6.1. Clinical Pharmacology

Atorvastatin is a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme that converts HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into high-density lipoprotein (HDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-cholesterol (HDL-C) are associated with a decreased cardiovascular risk.

In animal models, Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; Atorvastatin also reduces LDL production and the number of LDL particles. Atorvastatin reduces LDL-C in some patients with homozygous familial hypercholesterolemia, a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

Atorvastatin reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin also reduces Very-Low-Density Lipoprotein Cholesterol (VLDL-C) and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma

triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

6.2. Toxicology

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma area under curve （AUC）(0–24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0–24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with Salmonella typhimurium and Escherichia coli, the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the in vivo mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Primary Objective:

- To evaluate the effectiveness of atorvastatin in Chinese cardiology patients in real world setting.

7.2. Secondary Objectives:

- To assess atorvastatin safety in cardiology patients in real world setting
- To analyze patterns of atorvastatin prescription in cardiology patients.

8. RESEARCH METHODS

8.1. Study Design

8.1.1. Overall Design

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.

8.1.2. Study Endpoint

- **Primary endpoint**

  - Achievement rate of LDL-C goals at 12 weeks of therapy of Atorvastatin according to Chinese Guideline on Dyslipidemia Prevention and Treatment in Adult (2007 version). It will be presented with the proportion of patients who achieve the LDL-C goal value. LDL-C target value for the patients with different risk level is defined in the section 8.2.5 per guideline.

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

    - The time of 12-week will be calculated from the day when each patient starts taking atorvastatin. .
    - Achievement rate will be summarized overall, within each risk strata, and by dose within each risk strata. 95% confidence intervals will be provided.

- **Secondary endpoint**

  - Dosage distribution of Atorvastatin in cardiology patients with different risk stratification at the end of 12-week follow-up
  - Safety and tolerability will be evaluated by recording the incidence and severity of adverse events, abnormal physical examination findings, and abnormal laboratory values through 12 weeks of treatment. Especially monitoring the patients who have any the following events:
    - Having muscle symptoms such as myalgia, fatigue, weakness, creatine kinase values 10 times the upper limit of normal, or rhabdomyolysis,
    - Having persistent elevation in alanine aminotransferase, aspartate aminotransferase, or both (defined as two consecutive measurements obtained 4 to 10 days apart that is more than three times the upper limit of the normal range).

- Major adverse cardiovascular events will also be recorded as adverse events, including death, myocardial infarction, stroke, documented unstable angina requiring re-hospitalization, revascularization with either percutaneous coronary intervention or coronary-artery bypass grafting.

Adverse events will be summarized overall and by dose within each risk strata.

- Dropout percentage and reason through 12 weeks of follow-up;

8.2. Setting

8.2.1. 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.

8.2.2. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

- Men and women aged ⩾18 years;
- Cardiology patients[#] who has been prescribed atorvastatin by physician's clinical judgment under normal clinical care. These patients will include those with established coronary heart disease, or having multiple risk factors and at risk for cardiovascular disease, or primary hypercholesterolemia.
- Baseline laboratory reports* prior to starting atorvastatin therapy can be tracked, including lipid measurement, liver function, creatine kinase (CK) value, and renal function.
- Evidence of a personally or his/her legally acceptable representative signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study and accept follow-up visit.

[#]The proportion of ward inpatients is not more than 20% of the total number of patients.

*The date of the report should be within 1 month before taking atorvastatin or within 24h after starting atorvastatin therapy.

8.2.3. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

- Patients who have regularly taken atorvastatin therapy more than 4 weeks before enrollment

- Concomitant any other lipid-lower medication at baseline, or during the study conduction on physician clinical judgment

8.2.4. Disease Diagnostic Basis

Refer to local clinical diagnosis and treatment guidelines listed below:

- Refer to chronic stable angina pectoris diagnosis and treatment guideline issued by Chinese Medical Association in 2007, Non-ST-segment elevation acute coronary syndrome diagnosis and treatment guideline issued by Chinese Medical Association in 2012, ST-segment elevation acute myocardial infarction diagnosis and treatment guideline issued by Chinese Medical Association in 2015, respectively to diagnose coronary heart disease

- Refer to Chinese Hypertension Prevention Guideline 2010 to diagnose hypertension.

- Refer to Chinese Guideline on Dyslipidemia Prevention and Treatment in Adult 2007 to diagnose hyperlipidemia.

8.2.5. Risk Stratification and LDL-C Therapy Target Value

Referring to Chinese Guideline on Dyslipidemia Prevention and Treatment in Adult (2007), the cardiovascular disease (CVD) risk stratification and LDL-C therapy target value will be the following:

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

8.2.6. Study Period

According to the overall timeline of the study, First Patient In (FPI) will start on 23 February, 2016, and Last Patient Last Visit (LPLV) will end on 30 December, 2016. Data collection will be finalized during this period.

For each patient, the study period is from the time when patient signs informed consent form to the time the study is closed. Patients' information will be collected at baseline visit, week 12 (D85, ±10 days), and any unplanned visits (if occurrence). The study will be regarded as close when patient completes all the visits or withdraws from the study.

For adverse events, the reporting period begins at the time of the patient's first dose of atorvastatin or the time of the patient's informed consent if s/he is already exposed to atorvastatin, and lasts through the end of the observation period of the study, which should include 28 calendar days following the last administration of a drug under study

8.2.7. Study Procedures

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:

Visits / **Protocol Activity**	**Visit 1**	**Visit 2**	**Any unplanned Visits**
	Baseline Day(D)1	**Week 12 D85 (±10 days)**	**Any date during Week 4 to Week 16 D29~D115(±10 days)**
Signed Informed Consent Form	▲		
Demographic information	▲		
Medical history	▲		
Laboratory examination	▲*	▲	▲
Inclusion/exclusion criteria	▲		

Visits	Visit 1	Visit 2	Any unplanned Visits
Adverse event records	Record at any time during the study period		
Medication records	▲	▲	▲

Notes: Each activity refers to section **8.3 Variables**

∗ The date of the report should be within 1 month before taking atorvastatin or within 24h after starting atorvastatin therapy

8.2.8. Study Drug

The drug used in this study should be paid by patients themselves and administration method should be referred to the doctor's prescription.

8.3. Variables

This study will collect and analyze the effectiveness and safety data from approximately 10,000 eligible subjects from the time of first subject first visit to the time the study is closed. Since this is primarily an observational study, patient subsequent visits are set according to the return dates in clinical practice, which are supposed to be week 12 and any unplanned visits during week 4 to week 16.

- Demographic information includes patients' birth date, gender, body height and weight;
- Medical history includes information on current medical history, previous medical history, family history of premature cardiovascular disease and history of smoking ;
- Laboratory examination includes liver function [ALT, AST, total bilirubin (TBil)], serum lipid parameter (LDL-C, HDL-C, TG, Total-C), creatine kinase value (CK) and renal function [creatinine (Cr), blood urea nitrogen (BUN), uric acid (UA)];
- Major adverse cardiovascular events including death, myocardial infarction, stroke, documented unstable angina requiring re-hospitalization, revascularization with either percutaneous coronary intervention or coronary-artery bypass grafting
- Other adverse events. (Details in Section 10 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS)
- Medication record: dosage and duration of Atorvastatin, as well as any dose change including reasons will be recorded.
- Concomitant drugs: antiplatelet drugs, angiotensin converting enzyme inhibitors (ACEI)/ angiotensin receptor blockers (ARB), β-block, diuretics and calcium antagonist are concomitantly used or not.

8.4. Data Sources

This 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).

8.5. Study Size

- The NI study is designed to detect the achievement rate of LDL-C value in cardiology patients with atorvastatin therapy in real world setting. The length of follow-up is designed to be 12 weeks.

- In the recently published DYSIS [1] study, the achievement rate of LDL-C value was about 60% among Chinese patients 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), 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)。

8.6. Data Management

OCRDC is the EDC system for the study. Discrepancy management is used to identify and manage potential problems with study data. OCRDC generates discrepancies during data entry and discrepancy management whenever there is a missing or inconsistency between the data entered and the validation specifications. OCRDC identifies a problem and creates a discrepancy entry in the database.

The investigator is responsible to collect study data, including the eCRF data, laboratory data, via the EDC system in a timely manner and to ensure the integrity, accuracy, and completeness of the data.

The investigator should keep accurate records of identity of all subjects (sufficient information to link the patients to the corresponding study data), serious adverse event forms, all related source documentation, details of treatment disposition, as well as relevant correspondence details (e.g. letters, emails, meeting minutes, telephone call reports). The investigator record retention period should comply with the local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain

Pfizer's written permission before disposing of any records, even if retention requirements have been met.

8.7. Data Analysis

- Descriptive statistics including number (N), mean, median, standard deviation, minimum and maximum, will be produced for all continuous variables. Frequency tables of number (N) and percentage of subjects will be produced for all categorical variables
- All patients who received atorvastatin are included in the safety analysis, and safety data is summarized descriptively without statistical analysis.
- Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

8.8. Quality Control

During study conduct, Clinical Research Associates (CRAs) or study manager will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on eCRF is accurate. The investigator and institution will allow CRAs or study manager monitors and appropriate regulatory authorities direct access to source documents to perform this verification.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

8.9. Strengths and Limitations of the Research Methods

- Strengths: Large simple size and enrolled patients come from most area of China.
- Limitations: study patient only representatives China cardiology patients, but not a general population.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

- All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except

where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

- The informed consent form must be in compliance with local regulatory requirements and legal requirements.

- The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the Institutional Review Board/Independent Ethics committee (IRB/IEC) and Pfizer before use.

- The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

9.2. Patient Withdrawal

- Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

- If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good

Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

REQUIREMENTS

The table below summarizes the requirements for recording safety events on the case report form and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose,misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	**Recorded on the case report form**	**Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness**
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study where applicable, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, lack of efficacy, and occupational exposure;	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine

the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below)

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of atorvastatin or the time of the patient's informed consent if s/he is already exposed to atorvastatin, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the applicable types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to atorvastatin, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to atorvastatin, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that atorvastatin caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether atorvastatin caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that atorvastatin did not cause the event, this should be clearly documented on the case report form and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error
- Occupational exposure.

;

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

Serious adverse events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;

- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" is considered synonymous. These cases are considered unexpected and handled as serious expedited cases by Pharmacovigilance (PV) personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)

- Administrative admission (e.g., for yearly exam)

- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)

- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) atorvastatin, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to atorvastatin (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to atorvastatin prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with atorvastatin, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to atorvastatin in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic

product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in

accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

    1. An identifiable reporter;

    2. A suspect product;

    3. The event medication error.

Overdose, Misuse

Reports of overdose and misuse, associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

10.1. Single Reference Safety Document

The current Lipitor local label [package insert, (PI)] approved by China Food and Drug Administration (CFDA), will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The single reference safety document (SRSD) should be used by the investigator for prescribing purposes and guidance

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

COMMUNICATION OF ISSUES

The first publication will be the result analysis based on the primary end points of all the research units.

Investigators must inform the sponsor in advance about the publication plan of articles or reports of any study data analysis. The investigator or his/her representative must obtain review and written approval from sponsor when dealing with anything about publication or result report (magazine, abstract of newspaper or oral report, etc.), no matter in whole or in part.

The sponsor will not suppress or veto publication, but will reserve the right to delay publication for the protection of intellectual property right.

COMMUNICATION OF IISUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

12. REFERENCES

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13. LIST OF TABLES

None

14. LIST OF FIGURES

None

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable