Sponsor: Sanofi **Drug substance:** Rosuvastatin/ezetimibe	**Study Identifiers:** U1111-1227-3920; NCT04669041 **Study code:** LPS16135

Title of the study: A randomized double-blinded, double dummy, active-controlled, parallel design, Phase 3 clinical trial to evaluate the efficacy and the safety of single pill combination (SPC) ezetimibe/rosuvastatin in Chinese adult patients with primary hypercholesterolemia, not adequately controlled on statin therapy

Study centers: This study was conducted at 40 centers that screened at least one participant in China.

Study period:

Date first participant enrolled: 08/Dec/2020

Date last participant completed: 15/Jun/2022

Study Status: Completed

Phase of development: Phase 3

Objectives:

Primary:

To demonstrate the superiority of the single pill combination (SPC) rosuvastatin 10 mg/ezetimibe 10 mg (R10/E10) compared to rosuvastatin 10 mg (R10), in the reduction of low density lipoprotein cholesterol (LDL-C) after 8 weeks.

Secondary:

- To evaluate the proportion of patients who attain their LDL-C goal.
- To evaluate the effect of SPC (R10/E10) compared to rosuvastatin 10 mg (R10) in reduction of LDL-C at Week 4.
- To evaluate the effect of SPC (R10/E10) compared to R10 on other lipid parameters at Week 4 and Week 8.
- To evaluate the safety of SPC (R10/E10) and R10.

Methodology:

This was a randomized, double-blind, double-dummy, active-controlled, parallel-design Phase 3 study in participants with primary hypercholesterolemia who were not adequately controlled with a 10 mg stable daily dose of rosuvastatin or equipotent statin, without any other lipid modifying therapy (LMT).

Number of participants:

Approximately 658 participants were planned to be enrolled in the open-label stabilization run-in phase in order to achieve 296 randomly assigned to study intervention.
The actual number of participants analyzed per analysis population is as follows:

- Run-in population: 512 participants
- Run-in safety population: 506 participants
- Randomized population: 305 participants
- Modified Intent-to-Treat (mITT) population: 292 participants
- Double-blind safety population: 304 participants

Diagnosis and criteria for inclusion:

This study enrolled participants with primary hypercholesterolemia. All adult participants with primary hypercholesterolemia who were not adequately controlled (defined by screening LDL-C >2.6 mmol/L [100 mg/dL] and ≤4.9 mmol/L [190 mg/dL]) with a 10 mg stable daily dose of rosuvastatin, or equipotent statin for 4 weeks prior to the screening visit, without any other LMT were eligible to be included in the run-in period. Participants who were not adequately controlled based on sample taken at qualifying pre-randomization visit, despite stabilized dose of rosuvastatin 10 mg (defined by measured LDL-C ≥2.6 mmol/L [100 mg/dL] and ≤4.9 mmol/L [190 mg/dL]) were eligible to be included in the double-blind period.

Study products

Investigational medicinal product(s):

Formulation:

- The open-label stabilization run-in period: commercially packaged product rosuvastatin 10 mg (Crestor® 10 mg tablets marketed in China).
- The randomized double-blind double dummy period: single pill combination and matching placebo were provided as tablet(s). Rosuvastatin (tablet) and matching placebo were encapsulated in capsule(s).

Route of administration: all IMPs were administered orally.

Duration of study intervention:

The study duration included a screening period of up to 2 weeks, followed by an open-label stabilization run-in period of 4-week duration (±3 days), an 8-week (±3 days) randomized double blind double dummy period and a 2-week (±3 days) post-treatment safety follow-up period.

Thus, the study duration per participant was about 16 weeks (±3 days).

Criteria for evaluation:

Primary endpoint:

The percent change in measured low density lipoprotein cholesterol (LDL-C) from baseline (the last available measured LDL-C value obtained up to randomization) to Week 8.

Secondary endpoint:

- The proportion of patients who attain lipid goal (measured LDL-C <2.6 mmol/L [100 mg/dL]) at Week 8.
- Percent change in measured LDL-C serum level from baseline to Week 4.
- Percent change in total cholesterol (TC) from baseline to Week 8.
- Percent change in TC from baseline to Week 4.
- Percent change in triglyceride (TG) serum levels from baseline to Week 8.
- Percent change in TG serum levels from baseline to Week 4.
- Percent change in high density lipoprotein cholesterol (HDL-C) from baseline to Week 8.
- Percent change in HDL-C from baseline to Week 4.
- All adverse events (AEs).
- In addition, other safety parameters including laboratory data (hematology, biochemistry, creatine kinase [CK], liver function tests, kidney function, fasting blood glucose, glycated hemoglobin A1c [HbA1c]) and vital signs were assessed throughout the study.

Statistical methods:

- **Analysis population**

  - Efficacy population: mITT population contained all randomized participants who had an evaluable primary efficacy endpoint. The primary efficacy endpoint was considered evaluable when both following conditions were met:

    - The baseline measured LDL-C value was available.

    - At least one post baseline measured LDL-C value was available.

  - Safety population for the open-label stabilization run-in period: treated population contained all open-label stabilization run-in period participants who received at least one dose or part dose of open-label IMP.

  - Safety population for the randomization period: treated population contained all randomized participants who received at least one dose or part dose of double-blind IMP analyzed according to the treatment actually received.

- **Observation period**

  The observation period was as follows:

  - The pre-treatment period was defined from the signed informed consent up to the first dose of open-label IMP administration.

  - The run-in on-treatment period (ie, run-in treatment-emergent [TE] period) for run-in period was defined as the period from the first dose of open-label IMP up to the day before the intake of the first dose of double-blind IMP (up to the last dose of open-label IMP + 5 days for participants not receiving double-blind IMP).

  - The double-blind on-treatment period (ie, double-blind TE period) for double-blind period was defined as the period from the intake of the first to the last dose of double-blind IMP + 5 half-lives (ie, 5 days).

  - The post-treatment period: the post-treatment period started from the day after the end of the double-blind on-treatment period (last dose of double-blind IMP + 5 days) up to the end of study. The post-treatment period was only applicable for double-blind period, not applicable for run-in period.

- **Primary analysis**

  The percent change in measured LDL-C from baseline to Week 8 was analyzed in the mITT population using mixed-effect model with repeated measures (MMRM). The model included the fixed categorical effects of treatment group (SPC versus R10), time point (Week 4, Week 8), treatment-by-time point interaction, as well as the continuous fixed covariates of baseline measured LDL-C value and baseline value-by-time point interaction.

  The percent change was defined as:

  - 100 × (measured LDL-C value at postbaseline - measured LDL-C value at baseline) / measured LDL-C value at baseline

- **Analysis of secondary endpoints**

  Only if the superiority of single pill combination R10/E10 over R10 has been demonstrated for the primary endpoint, the secondary endpoints were tested within the frame of a hierarchical testing procedure (see objectives and endpoints table for the order).

  For the comparison of R10/E10 versus R10, the analyses were performed as described below:

  - The percent of participants at lipid goal (measured LDL-C <2.6 mmol/L [100 mg/dL]) was compared between treatment arms using a logistic regression adjusted on the baseline measured LDL-C value.

  - Continuous secondary endpoints anticipated to have a normal distribution (ie, lipids other than TG) were analyzed in the mITT population using the same MMRM model as for the primary endpoint with the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction. Continuous secondary endpoints anticipated to have a non-normal distribution (ie, TG) were analyzed in the mITT population using robust regression.

  For efficacy analysis, the baseline value was defined generally as the last available value up to randomization.

- Analysis of safety

  Safety analyses (AEs, laboratory data, and vital signs) were descriptive, based on the run-in safety population and the double-blind safety population.

  The safety analysis focused on treatment-emergent adverse events (TEAEs) during run-in period and TEAEs during double-blind period.

  The AEs were analyzed in the following 4 categories:

  - Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.

  - TEAEs during run-in period: AEs that developed, worsened or became serious during the run-in treatment-emergent period.

  - TEAEs during double-blind period: AEs that developed, worsened or became serious during the double-blind treatment-emergent period.

  - Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period.

  For safety analysis, the baseline in the open-label stabilization run-in period was the last available value obtained up to the first dose of open-label IMP (R10). The baseline in the randomization period was the last available value obtained up to the first dose of double-blind IMP (SPC or R10).

Summary Results:

Demographic and other baseline characteristics:

All participants were Asian. Demographic data, as well as disease characteristics at baseline were similar in both groups. The median age was 57 years (range: 25 to 80 years) and a majority of participants (56.4%) were females. Half (52.1%) of participants were either overweight or obese. Median duration of primary hypercholesterolemia was 2.08 years (range: 0.0 to 23.1 years). A majority of last statin treatment prior to screening was Rosuvastatin 10 mg (50.2%) or Atorvastatin 20 mg (45.2%). Hypertension was reported in 120 (39.3%) participants. Myocardial infarction was reported in 22 (7.2%) participants. Heart failure was reported in 3 (1.0 %) of participants. Stroke and diabetes mellitus were reported in 46 (15.1%) participants and 37 (12.1%) participants, respectively.

Exposure:

The mean duration of IMP exposure during double-blind period was similar in both the intervention groups (R10/E10 group: 56.1 days and R10 group: 55.2 days).

Efficacy:

Primary endpoint:

The LS mean of percent change in LDL-C from baseline to Week 8 was −21.98% (95% CI: −26.35% to −17.60%) for the R10/E10 group, and −8.12% (95% CI: −12.63% to −3.61%) for the R10 group. Superiority of SPC R10/E10 over R10 at Week 8 of primary analysis had been demonstrated with LS mean difference of −13.85% (95% CI: −20.15% to −7.56%; p<0.0001).

Key secondary endpoints:

According to hierarchical testing procedure in the prioritized order for the multiplicity consideration, statistical significance was demonstrated for the first 5 (out of 8) key secondary endpoints. Statistical significance was not reached for percent change in TG from baseline to Week 4. Consequently, subsequent two key secondary endpoints were not tested: percent change in HDL-C from baseline to Week 8 and to Week 4. P-values presented in this report for these endpoints are for descriptive purposes.

- The proportion of participants with LDL-C <2.6 mmol/L (100 mg/dL) at Week 8 was significantly greater in the R10/E10 group (80 participants [54.1%]) than in the R10 group (42 participants [29.2%]), with odds ratio 2.80 (95% CI: 1.70% to 4.61%; p<0.0001).
- Superiority of SPC R10/E10 group over R10 group has also been demonstrated with LS mean difference of percent change in LDL-C from baseline to Week 4: −14.40% (95% CI: −20.04% to −8.75%, p<0.0001).
- The percent change in TC from baseline to Week 4 and Week 8 were both significantly greater in the R10/E10 group than in the R10 group. The LS mean difference was −10.22% (95% CI: −13.98% to −6.46%; p<0.0001) at Week 4 and −9.77% (95% CI: −13.70% to −5.85%; p<0.0001) at Week 8 for R10/E10 group versus R10 group.
- The adjusted mean percent change in TG from baseline to Week 8 was significantly greater in the R10/E10 group than in the R10 group, with an adjusted mean difference for R10/E10 versus R10 group of −7.02% (95% CI: −14.01% to −0.04%, p=0.0488), although there were similar reductions in TG from baseline to Week 4 between the R10/E10 group and the R10 group, the statistical significance was not reached with an adjusted mean difference for R10/E10 versus R10 group of −5.21% (95% CI: −12.17% to 1.74%, p=0.1420).
- The statistical significance of the following two key secondary endpoints were not tested: percent change in HDL-C from baseline to Week 8 and percent change in HDL-C from baseline to Week 4. At Week 8, there were increases in HDL-C from baseline in the R10/E10 group (LS mean percent change: 3.58%) and the R10 group (LS mean percent change: 0.95%), with LS mean difference for R10/E10 versus R10 group of 2.63% (95% CI: −0.63% to 5.89%, p=0.1131). Similar tendency was observed at Week 4, with an LS mean difference for R10/E10 versus R10 group of 2.17% (95% CI: −1.14% to 5.47%, p=0.1978).

Safety results:

Treatment emergent adverse events (TEAEs) were reported during double-blind period with similar incidence across both intervention groups: TEAEs were reported in 44 (28.9%) and in 35 (23.0%) participants in R10/E10 and R10 groups, respectively, few participants experienced SAE (3 [2.0%] in each group), of which one due to sudden cardiac death, with outcome fatal, not related to IMP was reported in the R10/E10 group. There was no notable imbalance across intervention groups in participants with any adverse events of special interest (AESI) (none in the R10/E10 group and 2 participants in the R10 group experienced an AESI of blood creatine phosphokinase increased) or in participants with any TEAE related to double-blind IMP (10 [6.6%] in the R10/E10 group and 15 [9.9%] in the R10 group).

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