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Prescribing decisions should be made based on the approved package insert in the country of prescription.*

Sponsor: Sanofi	Study Identifiers: NCT02842359, U1111-1182-8092
Drug substance(s): Irbesartan/Atorvastatin	Study code: ATOIRL07827
Title of the study: Effect of Irbesartan/Atorvastatin fixed dose combination on metabolic, antiinflammatory and antioxidative parameters in type 2 diabetes mellitus patients with hypercholesterolemia and hypertension	
Study center(s): Ten institutions of which eight enrolled patients in Korea only.	
Study period: Date first patient enrolled: 23/Aug/2016 Date last patient completed: 19/Apr/2018	
Phase of development: 4	
Objectives: Primary objective To investigate the change from baseline in FMD (flow mediated dilatation) after 4 weeks of treatment with irbesartan/atorvastatin fixed dose combination compared with irbesartan or atorvastatin alone in type 2 diabetic patients with hypercholesterolemia and hypertension in the three groups. Secondary objectives To evaluate the effect of irbesartan/atorvastatin fixed dose combination on blood pressure (BP) and parameters of hypercholesterolemia, and the extent of changes in immunosenescent T cell fraction and T cell-induced inflammatory factors in type 2 diabetic patients with hypercholesterolemia and hypertension who have well-controlled glucose levels.	
Methodology: This was a randomized (1:1:1 allocation ratio), multicenter, open-label study in Korea, where the investigational products were given to type 2 diabetic patients with hypercholesterolemia and hypertension who were naive to treatments for hypercholesterolemia and hypertension. (Discontinuation of antihypercholesterolemic/antihypertensive agents for \geq 2 months was also considered being naive to treatment.) The duration of this study was up to 7 weeks. Subjects who were considered clinically eligible by screening and signed an informed consent at Visit 1, were randomized to either irbesartan/atorvastatin combination group or irbesartan alone or atorvastatin alone group at Visit 2, followed by 4 weeks of treatment period. The study ended after the 4 weeks of treatment with the investigational product and a subsequent visit to the study site for effectiveness and safety assessments.	
Rationale for no. of patients: The key endpoint was the percent change in the primary and secondary effectiveness variables before and after treatment with the investigational product in diabetic patients with hypertension and hypercholesterolemia who had well-controlled glucose levels. According to a clinical study published in 2005 in the Circulation, atorvastatin and irbesartan treatment, alone and in combination, resulted in an FMD of 7.6, 7.8, and 9.8 in respective groups, with a standard deviation of 2.7. Therefore, the estimated number of subjects required in this study to show between-group differences with a two-sided significance level of 5% and a power of 80%, was 84 in total, 28 per group, assuming a 10% dropout rate.	

<p>Number of subjects:</p> <p>Planned: 84</p> <p>Randomized: 11</p> <p>Treated: 10</p> <p>Evaluated:</p> <p>Efficacy: 9</p> <p>Safety: 10</p>	
<p>Diagnosis and criteria for inclusion:</p> <p>Eligible subjects fulfilled all of the following criteria.</p> <ol style="list-style-type: none"> Subjects aged ≥ 19 and < 75 years Subjects with type 2 diabetes mellitus who were diagnosed with hypercholesterolemia* and non-severe hypertension† (SBP ≥ 130 mmHg, < 160 mmHg or DBP ≥ 80 mmHg, < 100 mmHg should be met regardless of the use of antihypertensive agents at screening) and naive to treatments for hypercholesterolemia and hypertension other than CCBs, β-blockers, diuretics, and nitrates within 2 months prior to study entry Subjects who consent to the use of their data <p>*Defined as LDL-C ≥ 100 mg/dL.</p> <p><u>Diagnostic criteria for diabetes mellitus:</u></p> <ul style="list-style-type: none"> HbA1c $\geq 6.5\%$, An ≥ 8-h fasting plasma glucose (FPG) level ≥ 126 mg/dL, Plasma glucose level ≥ 200 mg/dL at 2 hours after a 75-g oral glucose tolerance test, or Typical symptoms of diabetes mellitus (polyuria, polydipsia, and unexplained weight loss) and a random plasma glucose level ≥ 200 mg/dL <p>†May include subjects who are taking calcium channel blockers (CCBs), β-adrenergic blockers, diuretics or nitrates at screening, which should be interrupted, however, at least 48 hours before the baseline and last FMD measurements. (The above-mentioned classes of antihypertensive agents can be used during the study using the same dosage regimen as before study entry, except for 48 hours before the baseline and last FMD measurements). BP is based on a mean of 3 BP measurements.</p> <p>††For subjects with confirmed diagnosis of diabetes mellitus who are naive to hypoglycemic therapy, test results within 6 months prior to screening should meet any one of the aforementioned diagnostic criteria for diabetes mellitus with the presence of corresponding medical records. (Among the aforementioned diagnostic criteria for diabetes mellitus, any HbA1c finding within 6 months must be recorded in the CRF.). Those who meet the diagnostic criteria for diabetes mellitus but with an HbA1c $< 6\%$ at screening, are not eligible.</p> <p>†††Subjects on hypoglycemic therapy may be included without additional diagnosis at Visit 1 and Visit 2.</p> <p>Subjects fulfilling any one of the following criteria were excluded from study entry.</p> <ol style="list-style-type: none"> Subjects with contraindications specified in the label of Rovelito Pregnant/lactating women Difference in SBP of ≥ 20 mmHg or in DBP of ≥ 10 mmHg for a selected arm at Visit 1 screening Use of angiotensin II receptor blockers or angiotensin converting enzyme inhibitors within 2 months Use of antihypercholesterolemic agents, such as HMG-CoA reductase inhibitors, within 2 months Subjects on insulin therapy Subjects with type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus (HbA1c $\geq 9\%$) Any change in the type and dose of oral hypoglycemic agent in the last 6 months Subjects with plans to change concomitant medication during the study, or whose condition makes such a change predictable (antihypertensive, antihypercholesterolemic, and antidiabetic agents only) Subjects with the need or possibility to take any of the prohibited concomitant medications during the study Resistance or hypersensitivity to any constituent of angiotensin II receptor blockers, HMG-CoA reductase inhibitors, or the study drug, or history of multi-drug allergy Hereditary angioedema or history of angioedema during treatment with ACE inhibitors or angiotensin II receptor blockers Fibromyalgia, myopathy, rhabdomyolysis, abrupt onset of myalgia, etc., or previous experience of a side effect during treatment with statins Creatine phosphokinase (CPK) $> 5x$ the upper limit of normal (ULN) at screening 	

15. Subjects diagnosed with secondary hypertension by the investigator or suspected of having secondary hypertension (coarctation of the aorta, primary aldosteronism, renal artery stenosis, renal hypertension, pheochromocytoma, Cushing's syndrome, etc.)
16. Uncontrolled hypothyroidism despite treatment
17. Arrhythmia requiring separate treatments
18. History of the following conditions:
 - Severe cerebrovascular disease (cerebral infarction, cerebral haemorrhage, etc.), hypertensive encephalopathy, and transient cerebral ischemic attack (TIA) within 6 months prior to screening
 - Severe heart disease (heart failure of NYHA class III-IV), clinically significant valvular heart disease, and myocardial infarction and unstable angina in the last 6 months
 - Angioplasty or coronary artery bypass graft (CABG) surgery within 1 year prior to screening
19. Clinically significant renal or hepatic disease, or significant hematologic findings at screening (serum creatinine ≥ 2 mg/dL, AST or ALT ≥ 3 x ULN)
20. Pancreatitis or active gallbladder disease suspected by the investigator
21. Any one of the following surgical or medical disease that may significantly alter the absorption, distribution, metabolism and excretion of drug (including but not limited to the following): major gastrointestinal surgical history, such as gastrectomy, gastro-enterostomy or bowel resection, gastrointestinal bypass surgery, gastrointestinal stapling, and gastrointestinal bending; current active inflammatory bowel syndrome or its history in the last 12 months; current presence of active gastritis, ulcer, or gastrointestinal/rectal hemorrhage; or urinary obstruction considered clinically significant by the investigator
22. Volume depletion clinically determined by the investigator based on vital signs, skin turgor, mucosal wetness, laboratory findings, etc.
23. Any chronic inflammatory condition requiring chronic antiinflammatory treatment
24. History of autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus
25. History of clinical alcohol or drug abuse
26. History of malignant tumors including leukemia and lymphoma in the last 5 years
27. Use of other investigational products within 30 days prior to study entry (based on the informed consent)
28. Presence of a congenital or secondary cause in the bilateral brachial artery that is determined by the investigator to preclude FMD measurement
29. Subjects who are considered by the investigator to be inappropriate for the study for any other reason

Study treatments

Investigational medicinal product(s):

1. Rovelito 150/10 mg
 - Appearance and dosage form: White, oval, film-coated tablet
 - Active ingredient and strength: Irbesartan 150 mg, atorvastatin calcium anhydrous 10.36 mg (atorvastatin 10 mg)
 - Storage condition: Store in a tight container at room temperature (1-30 °C).
2. Aprovel Tab. 150 mg
 - Appearance and dosage form: White to off-white, biconvex, and oval-shaped film-coated tablet with a heart debossed on one side and the number 2872 engraved on the other side
 - Active ingredient and strength: Irbesartan 150 mg
 - Storage condition: Store in a tight container at ≤ 30 °C in a dry place.
3. Newvast Tab. 10mg
 - Appearance and dosage form: White, oval, film-coated tablet
 - Active ingredient and strength: Atorvastatin strontium 11.595 mg (atorvastatin 10 mg)
 - Storage condition: Store in a tight container at room temperature (1-30 °C).

From the day after randomization, the investigational product was to be taken 1 tablet at a time, once daily, at the same time each morning for 4 weeks, regardless of meals.

The investigational product assigned to each group was repackaged for the study and supplied during the treatment period.

Group	Investigational Product
Group A	Rovelito 150/10 mg
Group B	Aprovel Tab. 150 mg
Group C	Newvast Tab. 10 mg

Duration of treatment: 4 weeks

Duration of observation: up to 7 weeks

Criteria for evaluation:

Efficacy:**Primary effectiveness endpoint**

- Percent change from baseline in FMD at Week 4

Secondary effectiveness endpoints

- Percent change from baseline in nitrotyrosine at Week 4
- Percent change from baseline in ICAM-1 at Week 4
- Percent change from baseline in IL-6 at Week 4
- Percent change from baseline in CRP at Week 4
- Mean change from baseline in sit SBP and DBP at Week 4 in Group A (combination group) and Group B (irbesartan group)
- Percent change from baseline in LDL-C, and change and percent change from baseline in TC, HDL-C, TG, Apo A1, and Apo B, at Week 4 in Group A (combination group) and Group C (atorvastatin group)
- Proportion of subjects with a reduction from baseline of ≥ 20 mmHg in sit SBP or ≥ 10 mmHg in sit DBP at Week 4 in Group A (combination group) and Group B (irbesartan group)
- Percent change from baseline in immunosenescent T cell fraction (MCP-1, MIP1a, MIP1b, CX3CL1, and Granzyme B) at Week 4 in the three groups
- Percent change from baseline in T cell-induced inflammatory factors (CXCL9, CXCL10, and CXCL 11) at Week 4 in the three groups

Safety:

Adverse events (AEs), vital signs, clinical laboratory tests, pregnancy test, electrocardiogram (ECG), X-ray, and physical examination

Statistical methods:

Since there were only 9 enrolled subjects who completed the study, no separate analysis was performed.

Summary:

Due to poor subject enrollment (planned number of subjects: 84, actual completed subjects: 9), this study was prematurely terminated by the sponsor without effectiveness and safety analyses.

Population characteristics:

Following an informed consent, 17 subjects were screened at overall 8 study sites and 6 of them failed the screening test, leaving overall 11 subjects for randomization (Rovelito 150/10 mg, n=3; Aprovel Tab. 150 mg, n=3, and Newvast Tab. 10 mg, n=5). Out of the 11 randomized subjects, 10 subjects received the investigational product except 1 subject who did not (Rovelito 150/10 mg, n=3; Aprovel Tab. 150 mg, n=3, and Newvast Tab. 10 mg, n=4).

Nine subjects (Rovelito 150/10 mg, n=3; Aprovel Tab. 150 mg, n=2, and Newvast Tab. 10 mg, n=4) out of the 11 randomized subjects completed the study, except overall 2 withdrawn subjects – one in the Aprovel Tab. 150mg group and the other in the Newvast Tab. 10 mg group. The first one was withdrawn due to an adverse event, and the second one due to violation of the exclusion criteria (ALT level $\geq 3x$ ULN).

Out of overall 11 subjects, 7 were males and 4 were females.

Subjects were enrolled if their HbA1c and LDL-C findings at screening fulfilled HbA1c $\geq 6.5\%$ and LDL-C ≥ 100 mg/dL, and those with HbA1c $<6.5\%$ were also eligible, regardless of HbA1c level, if they were diabetic patients with ≥ 8 -h FPG level of ≥ 126 mg/dL or on hypoglycemic therapy.

Efficacy results:

Since there were only 9 enrolled subjects who completed the study, no separate analysis was performed.

Safety results:

There were overall 4 AEs (upper respiratory tract infection, headaches, blood pressure increased, rash), including 3 adverse drug reactions (ADRs) (headaches, blood pressure increased, and rash) that were considered to be in a causal relationship with the investigational product. Serious AEs (SAEs) and AEs of special interest (AESIs) were not reported during the study period.

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