BALANCE Study
: Safety and Efficacy of Gemigliptin and Rosuvastatin as Fixed Dose Combination Therapy

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BACKGROUND

- Diabetes is highly likely to be accompanied with dyslipidemia and the risk of cardiovascular disease occurrence is significantly increased.
- Controlling blood glucose and LDL-C in patients with type 2 diabetes mellitus (T2DM) have direct effects on the occurrence of cardiovascular disease; a complex treatment approach is necessary.
- This study was to demonstrate the efficacy and safety of the fixed-dose combination (FDC) therapy of gemigliptin, a potent and selective DPP-4 inhibitor, and rosuvastatin, a potent HMG-CoA reductase inhibitor, compared to each mono-therapy in T2DM patients with dyslipidemia.

METHODS

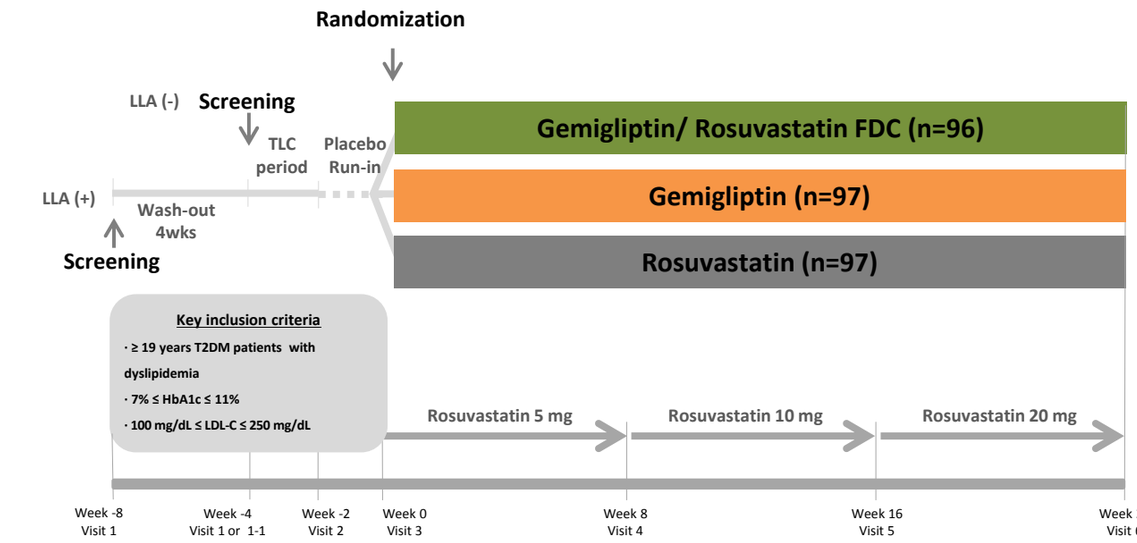
Study Population

- Patients aged ≥19 years accompanying T2DM with dyslipidemia who met the following criteria:
  - Patients who have taken a stable dose of the monotherapy with Metformin (≥ 1000 mg/day) more than 6 weeks before Visit 1 (screening)
  - 7% ≤ HbA1c ≤ 11%
  - 100mg/dL ≤ Low Density Lipoprotein cholesterol (LDL-C) ≤ 250mg/dL

Study Design

- A multicenter, randomized, placebo-controlled, double-blind design
- After therapeutic lifestyle change (TLC) followed by run in for 2 weeks, patients were randomized to the study group (Gemigliptin/Rosuvastatin FDC) and the control group (Gemigliptin or Rosuvastatin) in the ratio of 1:1:1
- All patients were administrated investigational products for 24 weeks

Figure 1. Study Design



Endpoints

- **Primary efficacy endpoints**
  - Changes at Week 24 from baseline
    1) HbA1c (Gemigliptin/Rosuvastatin FDC vs. Rosuvastatin)
    2) LDL-C (Gemigliptin/Rosuvastatin FDC vs. Gemigliptin)

- **Secondary efficacy endpoints**
  - Changes at Week 24 from baseline
    1) HbA1c (Gemigliptin/Rosuvastatin FDC vs. Gemigliptin)
    2) LDL-C (Gemigliptin/Rosuvastatin FDC vs. Rosuvastatin)

- **Tertiary efficacy endpoints** : fasting plasma glucose (FPG), fasting lipid parameters (Total cholesterol (TC)), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), Triglyceride (TG)), fasting serum Apo A-I, fasting serum Apo B, responder rate (HbA1C<7%, HbA1c<6.5%, LDL-C<100mg/dL)

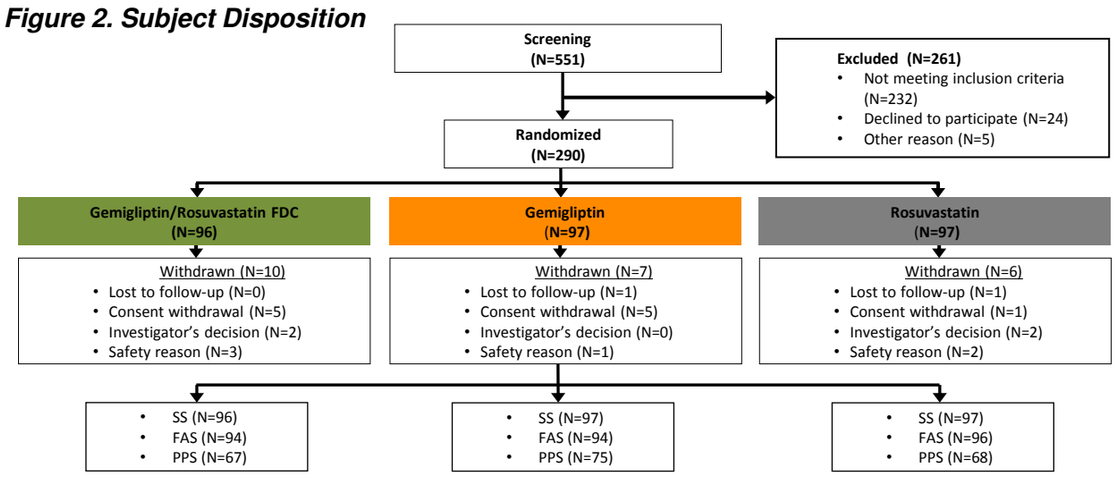
- **Safety endpoints** : Adverse events(including hypoglycemia), vital signs, laboratory tests

Statistical Analysis

- Efficacy analyses were conducted using the full analysis set (FAS).
- Efficacy endpoints were assessed using an analysis of covariance (ANCOVA) model, least squares (LS) means and two-sided 95% confidence intervals (CIs) were calculated for FDC group versus each mono-therapy group.
- LS estimates derived from the ANCOVA and ANCOVA model included baseline as covariate.
- Safety analyses were performed on the safety set, which were treated with the study medication at least once after randomization.

RESULTS

Figure 2. Subject Disposition



Demographics and Baseline Characteristics

Table 1. Baseline Characteristics

		Gemigliptin /Rosuvastatin FDC (N=94)	Gemigliptin (N=94)	Rosuvastatin (N=96)	P-value
Demographics					
Sex(n(%))	**Male**	55 (57.29)	41 (42.27)	49 (50.52)	0.1124[a]
Age, year		55.54 (±10.95)	56.05 (±10.12)	56.22 (± 9.20)	0.8913[b]
Height, cm		163.61 (±8.28)	162.29 (±9.01)	162.48 (± 8.26)	0.5183[b]
Weight, kg		68.63 (±11.58)	67.57 (± 10.65)	66.75 (± 11.09)	0.4835[c]
BMI, kg/m²		25.58 (±3.55)	25.56 (± 2.66)	25.22 (± 3.29)	0.4267[c]
Waist circumference, cm		89.33 (± 9.71)	89.41 (± 8)	88.31 (± 8.07)	0.7683[c]
Disease Characteristics					
Duration of T2DM (Years)		6.19 (± 5.54)	6.84 (± 5.95)	6.77 (± 5.59)	0.6449[c]
HbA1c (%) at Baseline		7.79 (± 0.79)	7.79 (± 0.78)	7.78 (± 0.78)	0.9900[c]
FPG at Baseline		143.28 (± 32.93)	147.74 (± 38.26)	148.82 (± 30.52)	0.2408[c]
LDL-C (mg/dL) at Baseline		133.39 (± 25.84)	141.99 (± 29.58)	133.63 (± 27.2)	0.0267[c]

Efficacy

- In the full analysis set (FAS), by comparing HbA1c changes between Gemigliptin/Rosuvastatin FDC group and Rosuvastatin group as well as LDL-C percentage changes between Gemigliptin/Rosuvastatin FDC group and Gemigliptin group, superiority of Gemigliptin/Rosuvastatin FDC group was proved.

➢ **Primary Endpoint**

- **HbA1c : Change of HbA1c (%) at week 24** (Gemigliptin/Rosuvastatin FDC vs Rosuvastatin)

Figure 3. Change in HbA1c at Week 24 (FAS)

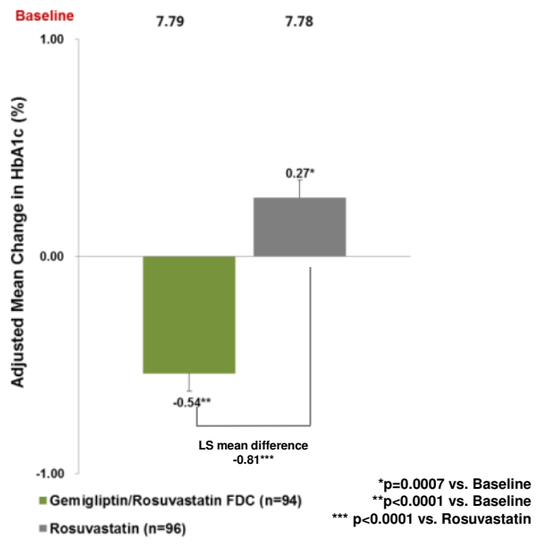
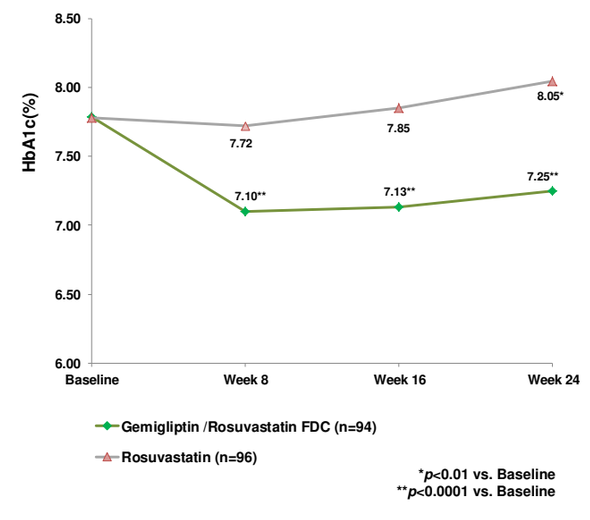


Figure 4. Change in HbA1c at Each Visit (FAS)



- **LDL-C : Percent(%) Change of LDL-C at Week 2** (Gemigliptin/Rosuvastatin FDC vs Gemigliptin)

Figure 5. % Change in LDL-C at Week 24 (FAS)

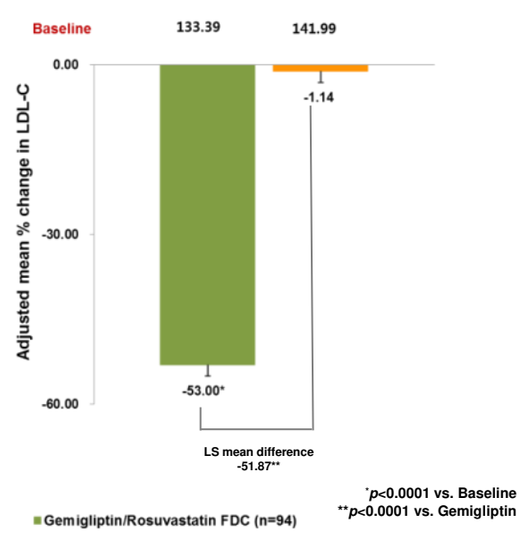
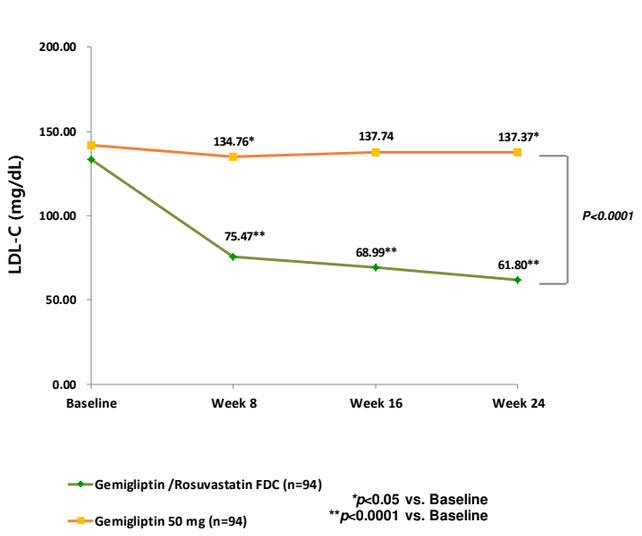


Figure 6. Change in LDL-C at Each Visit (FAS)



Safety

- In this study, a total of 201 treatment-emergent adverse events was reported in 112 subjects (38.6%).
- Adverse events were reported in 45.8%, 30.9% and 39.2% in Gemigliptin/Rosuvastatin FDC, Gemigliptin and Rosuvastatin groups, respectively. There was not statistical difference between the groups (Table 2).
- Most of adverse events were mild to moderate by intensity.
- No hypoglycemia was reported in this study.

Table 2. Summary of Adverse Events

Adverse Events Summary	Gemigliptin/Rosuvastatin FDC (N=96)		Gemigliptin (N=97)		Rosuvastatin (N=97)		*P-value*
	No. of Subject (%)	No. of AE (%)	No. of Subject (%)	No. of AE (%)	No. of Subject (%)	No. of AE (%)	
Adverse Events	44 (45.8)	84 (100.0)	30 (30.9)	54 (100)	38 (39.2)	63 (100)	0.1033
Adverse Drug Reactions	6 (6.3)	9 (10.7)	1 (1.0)	1 (1.9)	2 (2.1)	2 (3.2)	0.1068
Serious Adverse Events	6 (6.3)	6 (7.1)	2 (2.1)	2 (3.7)	7 (7.2)	7 (11.1)	0.2268
Withdrawal due to AEs	3 (3.1)	6 (7.1)	1 (1.0)	1 (1.9)	2 (2.1)	4 (6.4)	0.5396

CONCLUSION

- Gemigliptin/Rosuvastatin FDC has demonstrated its superiority of HbA1c lowering effect compared to Rosuvastatin and LDL-C lowering effect compared to Gemigliptin.
- Gemigliptin/Rosuvastatin FDC is effective in reducing both blood glucose and LDL-C levels in T2DM patients with dyslipidemia.
- Gemigliptin/Rosuvastatin FDC could be a new therapeutic choice in T2DM patients with dyslipidemia.

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LG Chem

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