These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi **Drug substance(s):** Gemigliptin (LC15-0444)	**Study Identifiers:** U1111-1165-9138, NCT02343926 **Study code:** GEMIGL07185

Title of the study: A multicentre, national, randomized, parallel-group, phase 3 study to compare the efficacy and safety of gemigliptin and vildagliptin as add-on therapy to metformin in people with type 2 diabetes inadequately controlled with metformin

Study center(s): 32 sites in Russian Federation

Study period:

Date first subject enrolled: 30/Dec/2014

Date last subject completed: 29/Apr/2016

Phase of development: Phase 3

Objectives:

Primary:

- To compare the clinical efficacy of gemigliptin and vildagliptin as add-on therapy to metformin in terms of change in HbA1c reduction from baseline to week 24.

Secondary:

- To compare the safety and tolerability of gemigliptin and vildagliptin:
  - Number of patients who experienced at least one episode of hypoglycemia
  - Number of patients who experienced an adverse event (AE) /serious adverse event (SAE)
- Assessment of patients' compliance to treatment on the basis of counting the number of returned tablets.

Pharmacokinetic sampling:

- PK study population on gemigliptin treated patients (n=55)

Methodology: A multicenter, comparative, two-arm, randomized (1:1), open-label study. Both male and female subjects with type 2 diabetes mellitus inadequately controlled with metformin (7% < HbA1c < 9,5%) were allocated in 2 treatment groups for 24-week treatment period to receive gemigliptin 50 mg or vildagliptin 100 mg as add-on therapy to metformin. Subjects were evaluated through 4 mandatory visits during the study: Visit 1 (Week -2, screening), Visit 2 (Week 0, randomization), Visit 3 (Week 12, efficacy and safety evaluation), and Visit 4 (Week 24, efficacy and safety evaluation).

Number of subjects**:** Planned: 440

Randomized: 443

Treated: 443

Evaluated:

Efficacy: 376

Safety: 443

Pharmacokinetics: 55

Diagnosis and criteria for inclusion: Male and female subjects 18-75 years old with Type 2 Diabetes Mellitus inadequately controlled with maximal effective and tolerated dose of metformin for at least 12 weeks or receiving stable dose of metformin ≥1500mg daily for a minimum of ≥4 weeks, 7% < HbA1c < 9,5%. Signed informed consent obtained prior to any study procedures.

Study treatments

Investigational medicinal product(s):

Gemigliptin

Formulation: Tablets 50 mg

Route(s) of administration: Oral

Dose regimen: 1 tablet (50 mg) once a day

Investigational medicinal product(s):

Vildagliptin

Formulation: Tablets 50 mg

Route(s) of administration: Oral

Dose regimen: The daily dose is 2 tablets (100 mg), one dose of 50 mg in the morning and one dose of 50 mg in the evening.

Duration of treatment: 24 weeks

Duration of observation: 26 weeks

Criteria for evaluation:

Primary criterion:

- Change in HbA1c vs. vildagliptin between baseline and week 24

Secondary criteria:

- Change in fasting plasma glucose (FPG) level, from baseline visit to week 24
- Change in body weight from baseline visit to week 24
- Percentage of patients with HbA1c < 7% and <6.5 % at week 24
- Number of patients with at least one episode of hypoglycemia during the study
- Number of episodes of hypoglycemia (symptomatic, asymptomatic, severe)
- Number of AEs, SAEs
- Change in 7-points self-monitoring of plasma glucose profile from visit 2 to week 24
- Percentage of withdrawal from protocol and percentage of patients with rescue therapy
- Number of tablets returned by patients

Safety was evaluated as a number of Adverse Events, Serious Adverse Events, hypoglycemia, vital signs and laboratory results (frequencies and percentages) throughout the entire study.

Pharmacokinetics: PK profiles of 44 patients on gemigliptin.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Blood samples for pharmacokinetics (PK) collected in a subset of 55 patients allocated to the gemigliptin arm (44 patients completed PK session and 11 patients dropped out) at randomization visit (week 0), week 12, and week 24 before dosing and 2 hours after dosing.

Blood samples were collected at C_{max} (~ 2hours) after the first administration with an additional collection at distance of the first one on the same day, then concomitant to study visits planned at week 12 and week 24 for efficacy evaluation, a PK blood sample were collected just prior the oral administration of the current visit day, and then an additional one at distance of the oral administration on the same day (i.e. corresponding to in total to 6 blood collections per patient participating in the PK sub-study). Blood samples were assessed by a validated liquid chromatography tandem-mass spectrometry (LC-MS/MS).

Statistical methods:

The statistical analysis included a description of the study population, an evaluation of the baseline comparability, an efficacy analysis, and a safety evaluation.

This is non-inferiority clinical trial. The comparison between the two groups of the HbA1c percentage reduction after 24 weeks of treatment has been done through Student's t-test, non-parametric Mann–Whitney U test, and covariance analysis, correcting the values with the glycosylated hemoglobin entry variable.

The difference between the secondary variables in the two groups of treatment analyzed through a repeated measurement analysis, crossed tables using Pearson's chi-squared test.

Values of descriptive statistics are presented for demographic data, baseline characteristics and safety variables for all patients and every treatment group.

Gemigliptin plasma concentrations summarized using arithmetic and geometric means, standard derivation (SD), coefficient of variation (CV %), median, minimum, and maximum at each visit.

Summary:

Local randomized non-inferiority study was conducted to compare the clinical efficacy and safety of gemigliptin and vildagliptin as add-on therapy to metformin therapy in people with type 2 diabetes inadequately controlled on metformin alone. 443 patients were included into the study, 22 subjects withdrawn during treatment period and 421 completed the study.

Population characteristics:

Five hundred ninety (590) subjects with type 2 diabetes inadequately controlled on metformin were screened for the study and 443 eligible subjects were randomized, among them 287 were female (65%). Screen failure rate was 24,9% (147 subjects screen failure). Baseline characteristics of analysis population were: average age – 57,4 ± 8,9 years (18-75 years), BMI – 32,1±4,2 kg/m2 (21,50-39,9 kg/m^2), mean HbA1c value was 8,02±0,64 % (7,1-9,4 %), FPG – 8,80±2,46 mmol/L (3,90-22,60 mmol/L), SBP – 130,00±8,41 mm Hg (100,00 – 160,00 mm Hg), DBP – 79,80±6,01 mm Hg (60,00 – 100,00 mm Hg), HR – 72,50±6,64 beats/min (49,00-92,00 beats/min). Average diabetes mellitus duration was 5,6±4,7 years (0,1-37,2 years), mean daily dose of metformin was 1922,0±354,0 mg (500,0-3000,0 mg).

According to the Protocol, 220 (49,6%) of 443 subjects were randomly allocated to treatment group with gemigliptin 50 mg and 223 (50,4%) - to treatment group with vildagliptin 100 mg. Both treatment groups were comparable with respect to sex, age, weight, baseline HbA1c, and FPG level, but BMI was slightly higher in gemigliptin group (32,72±4,35 vs. 31,88±3,93 kg/m^2, p<0,05).

Four hundred twenty-one (421) (95,0%) subjects completed the study as of protocol. Among them, 376 subjects were included in clinical efficacy analysis - Per protocol population (PP) in accordance with the Protocol. Twenty-two (22) patients had withdrawn the study during treatment period. Forty-five (45) patients were excluded from the PP population due to protocol deviations (8 patients were randomized with presence of exclusion criteria, 33 had HbA1c out of Protocol defined range on Visit 2, and 4 had significant deviations of treatment compliance). Subject samples are summarized in Figure 1 and Table 1.

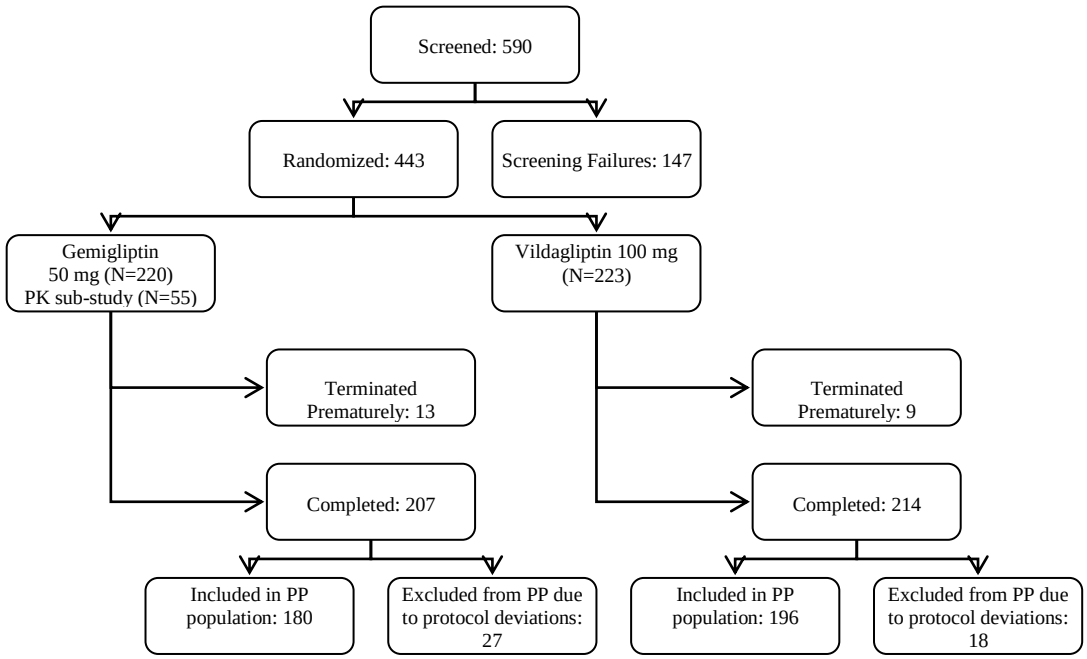

Figure 1. Flow chart of subject disposition.

Study populations are summarized in Table 1. Intent to treat population (ITT) included all the patients receiving at least one dose of the study medication. ITT population was identical to Randomized population and had been used for safety and tolerability analysis. Modified ITT population (mITT) included all patients for whom HbA1c value was available at baseline and at study end, whatever the date of the study end is. Per protocol population (PP) served as a basic population for clinical efficacy analysis. Protocol predefined non-inferiority margin was 0.4.

Table 1. Analysis population.

Population	Gemigliptin 50 mg	Vildagliptin 100 mg	All subjects
Complete population	220 (100,0%)	223 (100,0%)	443 (100,0%)
Randomized population	220 (100,0%)	223 (100,0%)	443 (100,0%)
Intent to treat population (ITT)	220 (100,0%)	223 (100,0%)	443 (100,0%)
Modified ITT (mITT)	211 (95,9%)	217 (97,3%)	428 (96,6%)
Per protocol population (PP)	180 (81,8%)	196 (87,9%)	376 (84,9%)

Note: Percentages are based on the number of subjects in Complete population.

The below table provides cumulative statistical values of the test population (see Table 2). Baseline lipid profile is summarized in Table 3.

Table 2. Demographic and baseline characteristic of the study population (PP).

Test		Gemigliptin 50 mg	Vildagliptin 100 mg	All patients
Sex	Male	58 (32%)	80 (41%)	138 (37%)
	Female	122 (68%)	116 (59%)	238 (63%)
Age (years)	Mean	56,9	57,8	57,4
	SD	9,28	8,54	8,90
	Median	58,0	59,5	59,0
	Min	18	31	18
	Max	74	75	75
	SE	0,69	0,61	0,46
Weight (kg)	Mean	89,7	89,2	89,4
	SD	14,63	13,18	13,88
	Median	88,6	88,0	88,3
	Min	53,7	56,0	53,7
	Max	126,2	132,1	132,1
	SE	1,09	0,94	0,72
Height (cm)	Mean	166,0	167,8	166,9
	SD	8,78	9,05	8,95
	Median	165,0	167,5	165,0
	Min	146	150	146
	Max	190	192	192
	SE	0,65	0,65	0,46
BMI (kg/m2)	Mean	32,5	31,7	32,1
	SD	4,50	3,94	4,23
	Median	32,5	31,3	31,6
	Min	22,0	21,5	21,5
	Max	39,9	39,9	39,9
	SE	0,34	0,28	0,22
HbA1c (%)	Mean	8,07	7,98	8,02
	SD	0,68	0,59	0,64
	Median	8,0	7,9	8,0
	Min	7,1	7,1	7,1
	Max	9,4	9,4	9,4
	SE	0,05	0,04	0,03
FPG (mmol/L)	Mean	9,0	8,6	8,8
	SD	2,61	2,31	2,46
	Median	8,2	8,0	8,1
	Min	5,4	3,9	3,9
	Max	22,6	20,9	22,6
	SE	0,19	0,17	1,13
SBP (mm Hg)	Mean	130,0	130,1	130,0
	SD	8,41	8,43	8,41
	Median	130,0	130,0	130,0
	Min	105	100	100
	Max	155	160	160
	SE	0,63	0,60	0,43

Test		Gemigliptin 50 mg	Vildagliptin 100 mg	All patients
DBP (mm Hg)	Mean	80,1	79,4	79,8
	SD	6,22	5,81	6,01
	Median	80,0	80,0	80
	Min	65	60	60
	Max	100	92	100
	SE	0,46	0,41	0,31
HR (beats/min)	Mean	72,3	72,6	72,5
	SD	6,62	6,67	6,64
	Median	72,0	72,0	72
	Min	49	52	49
	Max	92	90	92
	SE	0,49	0,48	0,34
Diabetes mellitus duration (years)*	Mean	5,38	5,84	5,62
	SD	5,03	4,38	4,7
	Median	3,9	5,2	4,8
	Min	0,1	0,2	0,1
	Max	37,2	29,7	37,2
	SE	0,376	0,313	0,243
Daily dose of metformin**	Mean	1930,0	1915,0	1922,0
	SD	353,0	356,0	354,0
	Median	2000,0	2000,0	2000,0
	Min	500,0	850,0	500,0
	Max	3000,0	3000,0	3000,0
	SE	27,3	26,2	18,9

* n=179 (gemigliptin group), n=196 (vildagliptin group), n=375 (all patients)

** n=167 (gemigliptin group), n=184 (vildagliptin group), n=351 (all patients)

Table 3. Baseline lipide profile (PP population).

Test		Gemigliptin 50 mg	Vildagliptin 100 mg	All patients
HDL (mmol/L)	n	179	195	374
	Mean	1,26	1,27	1,27
	SD	0,3	0,34	0,32
	Min	0,56	0,52	0,52
	Max	2,56	2,12	2,56
	SE	0,02	0,02	0,02
LDL (mmol/L)	n	177	195	372
	Mean	3,25	3,2	3,23
	SD	1,03	1,02	1,03
	Min	0,05	1	0,05
	Max	6,37	8,1	8,1
	SE	0,08	0,07	0,05

Test		Gemigliptin 50 mg	Vildagliptin 100 mg	All patients
Triglycerides (mmol/L)	n	179	196	375
	Mean	2,05	2,02	2,03
	SD	1,08	1,14	1,11
	Min	0,24	0,18	0,18
	Max	7,23	9,46	9,46
	SE	0,08	0,08	0,06
Total cholesterol (mmol/L)	n	179	196	375
	Mean	5,33	5,33	5,33
	SD	1,12	1,09	1,1
	Min	1,48	2,91	1,48
	Max	8,64	9,44	9,44
	SE	0,08	0,08	0,06

In the study population medical history, most frequent concomitant disorders were vascular (95,0%), metabolism and nutrition disorders (85,3%), cardiac (33,2%), and nervous system disorders (31,6%). Tables below present distribution of subjects depending on most frequent concomitant diseases reported (≥5%): diabetes related complications (Table 4), metabolic syndrome compounds (Table 5) and other concomitant diseases (Table 6).

Table 4. Medical Histories - Diabetes related complications. Most Frequent Preferred Terms (≥5%).

System Organ Class name /MedDRA Preferred Term		Gemigliptin 50 mg n = 220	Vildagliptin 100 mg n = 223	All patients n = 443
Nervous system disorders	Diabetic neuropathy	41 (18,6%)	44 (19,7%)	85 (19,2%)
Eye disorders	Diabetic retinopathy	12 (5,5%)	14 (6,3%)	26 (5,9%)

Note: Percentages are based on the number of subjects in the Randomized population.

Table 5. Medical Histories - Metabolic syndrome compounds. Most Frequent Preferred Terms (≥5%).

System Organ Class name /MedDRA Preferred Term		Gemigliptin 50 mg n = 220	Vildagliptin 100 mg n = 223	All patients n = 443
Vascular disorders	Essential hypertension	179 (81,4%)	178 (79,8%)	357 (80,6)
Metabolism and nutrition disorders	Obesity	100 (45,5%)	103 (46,2%)	203 (45,8%)
	Dyslipidaemia	75 (34,1%)	83 (37,2%)	158 (35,7%)
Hepatobiliary disorders	Hepatic steatosis	23 (10,5%)	21 (9,4%)	44 9,9%)

Note: Percentages are based on the number of subjects in the Randomized population.

Table 6. Medical Histories - Other concomitant diseases. Most Frequent Preferred Terms (≥5%).

System Organ Class name /MedDRA Preferred Term		Gemigliptin 50 mg n = 220	Vildagliptin 100 mg n = 223	All patients n = 443
	Vascular encephalopathy	9 (4,1%)	13 (5,8%)	22 (5,0%)
Musculoskeletal and connective tissue disorders	Osteochondrosis	25 (11,4%)	27 (12,1%)	52 (11,7%)
	Osteoarthritis	14 (6,4%)	20 (9,0%)	34 (7,7%)
	Cardiac failure chronic	15 (6,8%)	21 (9,4%)	36 (8,1%)
Cardiac disorders	Angina pectoris	11 (5,0%)	18 (8,1%)	29 (6,5%)
	Coronary artery disease	24 (10,9%)	16 (7,2%)	40 (9,0%)
Eye disorders	Cataract	17 (7,7%)	19 (8,5%)	36 (8,1%)
Renal and urinary disorders	Pyelonephritis chronic	18 (8,2%)	15 (6,7%)	33 (7,4%)
Endocrine disorders	Goitre	17 (7,7%)	14 (6,3%)	31 (7,0%)
Renal and urinary disorders	Nephrolithiasis	15 (6,8%)	12 (5,4%)	27 (6,1%)

Note: Percentages are based on the number of subjects in the Randomized population.

Efficacy:

The primary objective

Analysis of covariance (ANCOVA) performed for the primary endpoint, using covariates of baseline HbA1c, patient's age and BMI. Search of covariates affected HbA1c dynamics was performed. Based on regression analysis only baseline HbA1c had statistically significant interaction with HbA1c changes, the referred parameter was included in ANCOVA model as covariate.

Adjusted least square mean for HbA1c change from baseline for each treatment group was calculated, and the two-sided 95% confidence interval for the difference of these values between the test group and the reference group was presented. Results were based on the number of subjects in the Per Protocol (PP) population (Table 7) and were confirmed by Modified ITT (mITT) population data analysis (Table 8).

Both treatment groups demonstrated similar significant HbA1c reduction after 24 weeks with mean HbA1c changes -0,77±1,17% for gemigliptin and -0,79±1,11% for vildagliptin groups (Figure 2). The least squares (LS) means of difference in HbA1c from baseline to week 24 were -0,58% (95% CI -0,75 to -0,42) in gemigliptin group and -0,80% (95% CI -0,95 to -0,65) in vildagliptin group (Figure 3). Mean difference between HbA1c changes was 0,22% (95% confidence interval (CI) 0,15-0,29). The upper end of 95% CI for the difference between HbA1c changes was 0,29 that less than protocol predefined equivalence limit difference - 0,4 (Figure 4). It confirms non-inferiority of gemigliptin treatment effect comparing to vildagliptin ($p<0,001$).

Non-inferiority of gemigliptin therapy regimen was demonstrated as early as week 12 persisted through week 24 (Table 7). LS mean of HbA1c change from baselines at week 12 were -0,62% (95% CI -0,77 to -0,48) in gemigliptin group and -0,82% (95% CI -0,96 to -0,68) in vildagliptin group; mean difference between changes was 0,19% (95% CI 0,13-0,25).

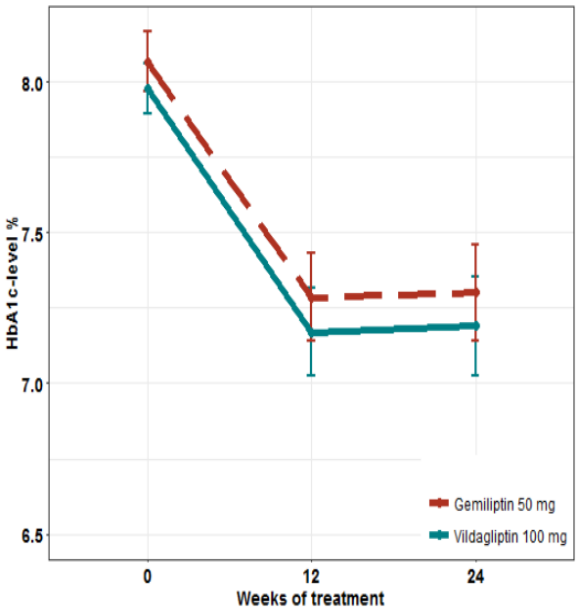

Figure 2. HbA1c changes after 24 weeks of gemigliptin 50 mg and vildagliptin 100 mg treatment; p<0,001 compared with baseline values (n=180 for gemigliptin, n=196 for vildagliptin).

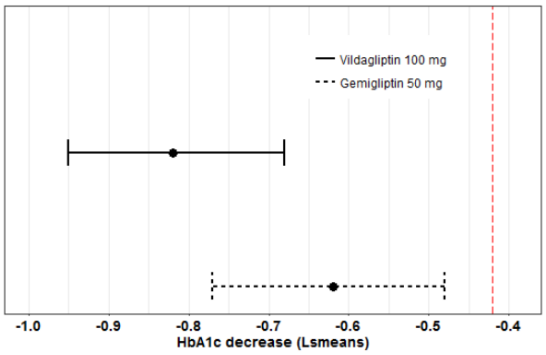

Figure 3. LS-means of HbA1c changes from baseline up to Week 24; p<0,001 compared with baseline values.

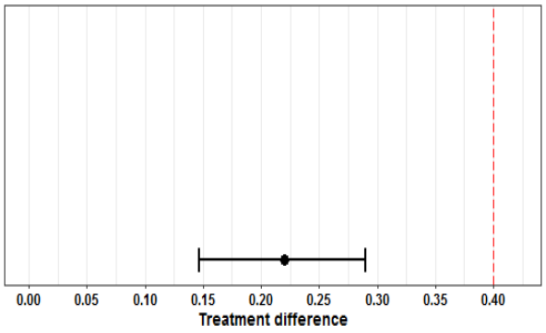

Figure 4. Difference of HbA1c changes after 24 weeks of gemigliptin 50 mg versus vildagliptin 100 mg treatment.

Table 7. HbA1c (%) values at baseline, Week 12 and Week 24 (PP population).

Visit/ Treatment group		Gemigliptin 50 mg n = 180	Vildagliptin 100 mg n = 196	All patients n = 376
Visit 2 (Baseline)	Mean	8,07±0,68	7,98±0,59	8,02±0,64
Visit 3 (Week 12)	Mean	7,29±0,99	7,17±1,04	7,22±1,02
	Difference*	-0,78±1,05	-0,81±0,98	-0,79±1.01
	LS-means of difference***	-0,62 [-0,77 – -0,48]	-0,82 [-0,95 – -0,68]	NA
Visit 4 (Week 24)	Mean	7,30±1,08	7,19±1,17	7,24±1,12
	Difference*	-0,77±1,17**	-0,79±1,11**	-0,78±1,14
	LS-means of difference***	-0,58 [-0,75 – -0,42]	-0,80 [-0,95 – -0,65]	NA

* Difference from baseline; **p<0,001; *** Data presented as LS-mean [CI]

Based on mITT population data analysis significant HbA1c reduction after 24 weeks was -0,73±1,18% in gemigliptin group and -0,80±1,13% in vildagliptin group. The least squares (LS) means of difference in HbA1c from baseline to week 24 were -0,75% (95% CI -0,90 to -0,61) in gemigliptin group and -0,70% (95% CI -0,85 to -0,55) in vildagliptin group (Table 8). Mean difference between HbA1c changes was 0,05% (95% confidence interval (CI) -0,07 - -0,04). The upper end of 95% CI for the difference between HbA1c changes was -0,04 that less than protocol predefined equivalence limit difference - 0,4, that confirmed non-inferiority of gemigliptin treatment effect comparing to vildagliptin.

Table 8. HbA1c (%) values at baseline, Week 12 and Week 24 (mITT population).

Visit/ Treatment group		Gemigliptin 50 mg n = 211	Vildagliptin 100 mg n = 217	All patients n =428
Visit 2 (Baseline)	Mean	7,97±0,76	7,94±0,68	7,95±0,72
Visit 3 (Week 12)	Mean	7,23±0,98	7,14±1,03	7,18±1,01
	Difference*	-0,73±1,03	-0,81±0,99	-0,77±1.01
	LS-means of difference***	-0,75 [-0,88 – -0,62]	-0,70 [-0,83 – -0,57]	NA
Visit 4 (Week 24)	Mean	7,23±1,14	7,14±1,14	7,18±1,14
	Difference*	-0,73±1,18**	-0,80±1,13**	-0,77±1,16
	LS-means of difference***	-0,75 [-0,90 – -0,61]	-0,70 [-0,85 – -0,55]	NA

* Difference from baseline; **p<0,001; *** Data presented as LS-mean [CI]

The proportion of subjects achieved HbA1c levels less than 7% at Week 24 was slightly higher in vildagliptin group than in gemigliptin group, but the difference between treatment groups was not statistically significant (See Table 9). As for proportion of subjects, achieved 6,5% reduction, there was a significant difference found at Week 24 between groups (p <0,05) (Table 10). 41% and 45% patients achieved HbA1c level less than 7% in gemigliptin and vildagliptin groups respectively. Proportion of patients achieving HbA1c level less than 6,5% was 18% in gemigliptin and 27% in vildagliptin groups.

Table 9. Proportion of subjects achieved HbA1c levels < 7% at Week 12 and Week 24 (PP population).

Visit/ Treatment group	Patients achieved HbA1c levels < 7%		All patients
	Gemigliptin 50 mg	Vildagliptin 100 mg	n = 376
	n = 180	n = 196	
Visit 3 (Week 12)	66 (37%)	84 (43%)	150 (40%)
Visit 4 (Week 24)	74 (41%)	88 (45%)	162 (43%)

Table 10. Proportion of subjects achieved HbA1c levels <6,5% at Week 12 and Week 24 (PP population).

Visit/ Treatment group	Patients achieved HbA1c levels < 6.5%		All patients
	Gemigliptin 50 mg	Vildagliptin 100 mg	n = 376
	n = 180	n = 196	
Visit 3 (Week 12)	33 (18%)	44 (22%)	77 (20%)
Visit 4 (Week 24)	32 (18%)	53 (27%)*	85 (23%)

* Statistically significant difference in frequencies between groups

Significant (p<0,001) FPG reduction from baseline up to week 24 was demonstrated in both treatment groups: difference from baseline was -0,82±2,58 mmol/L (95% CI from -1.196 to -0.438) in gemigliptin group and -0,67±2,35 (95% CI from -1.0 to -0.3) in vildagliptin group. However, the difference between treatment groups was not statistically significant (Table 11).

Table 11. FPG (mmol/l) at baseline, Week 12 and Week 24 (PP population).

Visit/ Treatment group		Gemigliptin 50 mg n = 180	Vildagliptin 100 mg n = 193	All patients n = 373	Intergroup difference (t-test, Wilcox)
Visit 2 (Baseline)	Mean	9,00±2,61	8,62±2,31	8,80±2,46	p>0,05
Visit 3 (Week 12)	Mean	8,10±1,98	7,94±2,31	8,02±2,15	p>0,05
	Difference*	-0,90±2,11	-0,68±2,48	-0,79±2,31	p>0,05
Visit 4 (Week 24)	Mean	8,18±2,46	7,96±2,52	8,07±2,49	p>0,05
	Difference**	-0,82±2,58	-0,67±2,35	-0,74±2,46	p>0,05

* Gemigliptin V3-V2: 95% CI [-1.213 – -0.592] p<0.001; Vildagliptin V3-V2: 95% CI [-1.0 – -0.3] p<0.001
** Gemigliptin V4-V2: 95% CI [-1.196 – -0.438] p<0.001; Vildagliptin V4-V2: 95% CI [-1.0 – -0.3] p<0.001

7-points self-monitoring plasma glucose profile was assessed at week 0 and partially at week 12 and week 24 (Table 12). Patients were instructed to perform 7-points self-monitoring test one day (or one other day) on week 1 and before visit 4 on the week proceeding week 24, preferable the day before visit. Some patients performed 7-points glucose self-monitoring test on week 12, instead of week 24. The distribution of patients depending on time point of 7-points self-monitoring test is presented in Table 12.

Results of 7-points self-monitoring plasma glucose are presented in Tables 13, 14 and 15.

Table 12. The distribution of patients provided 7-point plasma glucose profile.

7-point plasma glucose profile provided	Gemigliptin 50 mg		Vildagliptin 100 mg		All patients	
	Number*	%	Number*	%	Number*	%
Week 0	167	92,8%	183	93,4%	350	93,1%
Week 12	50	27,8%	65	33,2%	115	30,6%
Week 24	117	65,0%	118	60,2%	235	62,5%

*- numbers and percentages of patients with available 7-point plasma glucose profile results presented

Table 13. 7-points self-monitoring of plasma glucose (mmol/L) results (Week 0) (PP population).

Group	Time-point	Number	Mean	SD	Median	Min	Max
Gemigliptin 50 mg	Before breakfast	167	8,04	1,77	7,8	4,8	14,5
	2 h after breakfast	167	9,22	2,71	8,6	4,0	19,3
	Before lunch	167	7,36	1,74	7,0	4,2	15,3
	2 h after lunch	167	8,96	2,37	9,0	4,2	23,4
	Before dinner	167	8,10	2,29	7,8	4,5	17,7
	2 h after dinner	167	9,10	2,36	8,6	5,2	17,2
	At bedtime	167	8,30	2,19	7,9	5,0	17,1
Vildagliptin 100 mg	Before breakfast	183	7,86	1,55	7,7	4,8	13,2
	2 h after breakfast	183	8,83	2,26	8,4	5,2	16,4
	Before lunch	183	7,28	1,76	7,2	4,2	15,0
	2 h after lunch	182	8,72	2,05	8,5	4,9	17,4
	Before dinner	183	7,65	1,73	7,3	4,5	15,6
	2 h after dinner	183	8,56	2,15	8,1	4,9	16,3
	At bedtime	183	7,98	1,96	7,7	4,5	16,1

Table 14. 7-points self-monitoring of plasma glucose (mmol/L) results (Week 12).

Group	Time-point	Number	Mean	SD	Median	Min	Max
Gemigliptin 50 mg	Before breakfast	50	7,24	1,50	7,0	5,2	12,7
	2 h after breakfast	50	8,57	2,23	8,2	5,3	14,9
	Before lunch	50	6,98	1,53	6,9	4,5	13,8
	2 h after lunch	50	9,08	2,60	8,3	5,0	19,3
	Before dinner	50	7,20	1,68	6,8	4,6	12,3
	2 h after dinner	50	8,47	1,99	8,0	4,5	14,1
	At bedtime	50	7,55	1,45	7,3	5,1	12,7
Vildagliptin 100 mg	Before breakfast	65	7,08	1,25	7,0	4,1	11,4
	2 h after breakfast	65	8,49	2,12	8,4	5,3	19,4
	Before lunch	65	7,10	1,77	6,8	4,2	13,4
	2 h after lunch	65	8,69	2,31	8,1	4,7	18,5
	Before dinner	64	7,63	2,30	7,2	4,7	16,5
	2 h after dinner	64	8,58	1,92	8,3	5,3	13,9
	At bedtime	65	7,81	1,59	7,5	4,8	12,0

Table 15. 7-points self-monitoring of plasma glucose (mmol/L) results (Week 24).

Group	Time-point	Number	Mean	SD	Median	Min	Max
Gemigliptin 50 mg	Before breakfast	117	7,38	1,52	7,2	4,5	11,6
	2 h after breakfast	117	8,53	2,14	8,2	4	15,7
	Before lunch	117	7,07	1,69	6,8	4,2	13,8
	2 h after lunch	117	8,46	2,09	8,1	5,1	17,5
	Before dinner	117	7,34	1,46	7,2	4,7	12,6
	2 h after dinner	117	8,52	1,96	8,3	4,4	14,0
	At bedtime	116	7,57	1,69	7,3	4,1	13,0
Vildagliptin 100 mg	Before breakfast	118	7,32	1,77	7,0	4,8	17,0
	2 h after breakfast	118	7,97	1,93	7,6	5,3	17,2
	Before lunch	118	6,97	1,71	6,6	4,6	16,7
	2 h after lunch	118	7,93	1,99	7,6	4,7	17,7
	Before dinner	118	7,27	1,77	7,0	4,0	15,4
	2 h after dinner	118	8,07	2,06	7,7	5,0	16,9
	At bedtime	118	7,32	1,82	7,0	4,2	15,2

Based on 7-points self-monitoring of plasma glucose results from week 0 to week 12 significant reduction of glucose measured before breakfast was demonstrated in both treatment groups, but significant reduction of glucose levels measured 2 hours after breakfast, before dinner and at bedtime reported only in gemigliptin group (Table 16, Figure 5).

Statistically significant reduction of glucose from week 0 to week 24 was demonstrated in both treatment groups at following time-points: before breakfast, 2 hours after breakfast and at bedtime measurement. Significant glucose level reduction before and 2 hours after dinner was reported in gemigliptin group only, but 2 hours after lunch reduction in vildagliptin group only. A difference between groups in glucose changes was assessed as not significant (p>0,05) (See Table 17, Figure 6).

Table 16. 7-points self-monitoring of glucose (mmol/L) changes from week 0 to week 12.

Time-point of glucose measurement	Gemigliptin 50 mg		Vildagliptin 100 mg		t-statistic	p-value
	Mean change	SD	Mean change	SD		
Before breakfast	-0,70*	1,49	-0,67*	1,41	-0,11	0.91
2 h after breakfast	-0,80*	2,66	-0,29 (n.s.)	1,89	-1,16	0.25
Before lunch	-0,36 (n.s.)	2,07	-0,25 (n.s.)	1,49	-0,32	0.75
2 h after lunch	-0,11 (n.s.)	3,08	-0,31 (n.s.)	2,47	0,38	0.70
Before dinner	-0,92*	2,31	-0,20 (n.s.)	2,35	-1,62	0.11
2 h after dinner	-0,61 (n.s.)	2,58	-0,28 (n.s.)	1,91	-0,75	0.46
At bedtime	-0,60*	2,12	-0,24 (n.s.)	1,98	-0,94	0.35

*p<0,05 (Student's t-test) for the comparison between the mean values at week 0 and in 12 weeks, n.s. – non-significant difference between mean values at week 0 and week 12

Table 17. 7-points self-monitoring of glucose (mmol/l) changes from week 0 to week 24.

Time-point of glucose measurement	Gemigliptin 50 mg (n=117)		Vildagliptin 100 mg (n= 118)		t-statistic	p-value
	Mean change	SD	Mean change	SD		
Before breakfast	-0,69*	2,09	-0,59*	1,79	-0,39	0.69
2 h after breakfast	-0,62*	2,81	-0,90*	1,96	0,87	0.39
Before lunch	-0,29 (n.s.)	2,05	-0,28 (n.s.)	1,95	-0,07	0.95
2 h after lunch	-0,40 (n.s.)	2,63	-0,64*	1,93	0,81	0.42
Before dinner	-0,75*	2,14	-0,26 (n.s.)	2,08	-1,78	0.08
2 h after dinner	-0,59*	2,50	-0,29 (n.s.)	2,22	-0,94	0.35
At bedtime	-0,79*	2,35	-0,62*	2,13	-0,56	0.57

*p<0,05 (Student's t-test) for the comparison between the mean values at week 0 and in 24 weeks, n.s. – non-significant difference between the mean values at week 0 and week 24

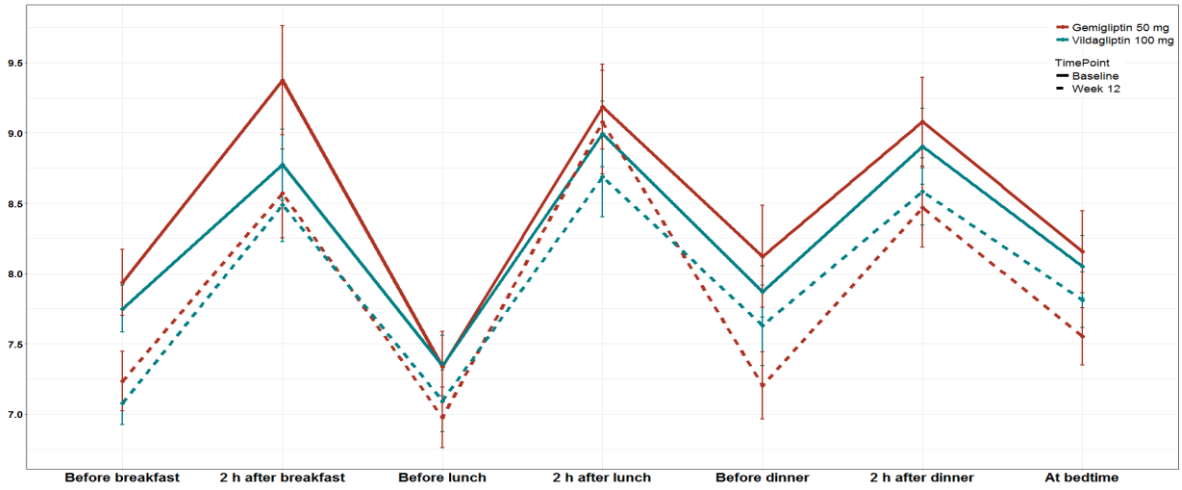

Figure 5. 7-points self-monitoring of glucose (mmol/l) changes from week 0 to week 12 (n=50 for gemigliptin, n=65 for vildagliptin).

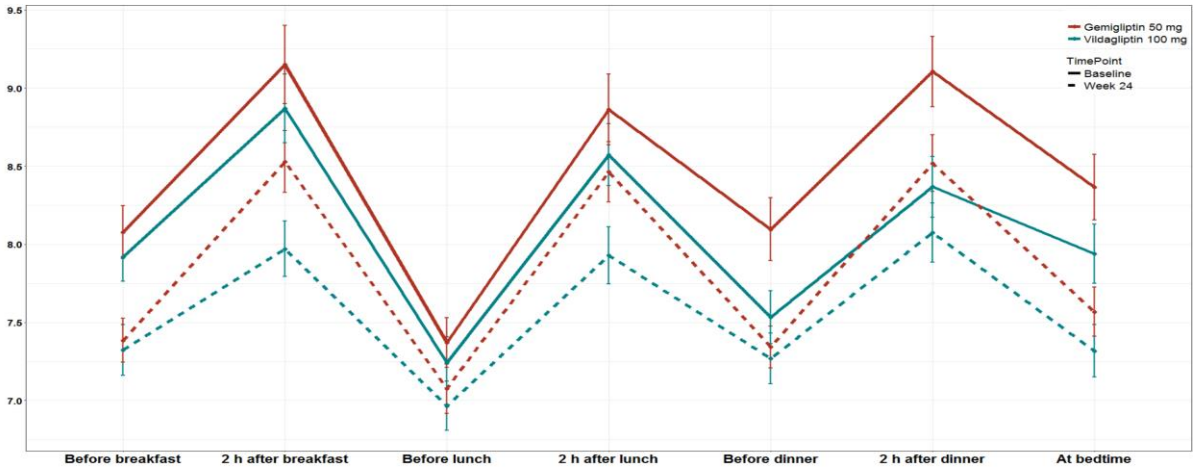

Figure 6. 7-points self-monitoring of glucose (mmol/l) changes from week 0 to week 24 (n=117 for gemigliptin, n=118 for vildagliptin).

Body weight significantly decreased in each treatment group after 24 weeks of therapy (Table 18 and Table 19). Mean difference in body weight from baseline up to week 24 was -0,84±2,47 kg in gemigliptin group and -0,68±2,69 kg in vildagliptin group. There were no statistically significant differences between groups in body weight reduction (p>0,05) (Table 20).

Table 18. Dynamics of body weight after 24 weeks of gemigliptin treatment (PP population).

Visit 2 (Baseline) (n=180)		Visit 4 (Week 24) (n=180)		t-statistic	p-value
Body weight mean (kg)	SD	Body weight mean (kg)	SD		
89,65	14,63	88,81	14,3	-4,56	< 0,001

Table 19. Dynamics of body weight after 24 weeks of vildagliptin treatment (PP population).

Visit 2 (Baseline) (n=196)		Visit 4 (Week 24) (n=196)		t-statistic	p-value
Body weight mean (kg)	SD	Body weight mean (kg)	SD		
89,19	13,18	88,50	13,11	-3.56	< 0,001

Table 20. Comparison of body weight (kg) difference from Baseline to Week 24 between groups (PP population).

Gemigliptin 50 mg (n=180)		Vildagliptin 100 mg (n= 196)		t-statistic	p-value
Mean difference	SD	Mean difference	SD		
-0,84	2,47	-0,68	2,69	-0,58	0,56

Total cholesterol slightly increased after 24 weeks of treatment in both groups: mean difference was 0,05 mmol/L (p<0,05) in gemigliptin group and 0,1 mmol/L (p>0,05) in vildagliptin group. Other lipid profile parameters have not been significantly changing. There were no statistically significant differences in comparison of both groups also (Table 21).

Table 21. Lipid profile changes after 24 weeks of treatment (PP population).

Test	Gemigliptin 50 mg			Vildagliptin 100 mg			t-statistic	p-value
	n	Mean difference	SD	n	Mean difference	SD		
Total cholesterol (mmol/l)	179	0,05*	0,33	195	0,1	0,76	-0,805	0,42
LDL (mmol/l)	177	-0,01	1,04	194	0,25	2,71	-1,233	0,22
HDL (mmol/l)	179	-0,08	0,88	196	-0,02	1,02	-0,581	0,56
Triglycerides (mmol/l)	179	0,04	1,16	196	0,12	1,02	-0,677	0,50

*p<0,05 (Student's t-test)

Treatment compliance was calculated based on the number of returned tablets. Percentage of compliance for a patient was defined as the difference between the number of tablets dispensed to and returned by the patient divided by the total number of tablets that the patient had been planned to take during the treatment.

Both treatment groups in 100% had treatment compliance more than 80%. For 2 subjects included in PP sample treatment, compliance had not been calculated due to postponed dates of visit 4.

Safety results:

Safety analysis was based on gemigliptin Investigator's Brochure and included 443 patients who received at least one dose of gemigliptin or vildagliptin (ITT population).

Hypoglycaemia

Hypoglycaemia was defined as:

Symptomatic: event with clinical symptoms that are considered to result from hypoglycaemia. Documented symptomatic hypoglycaemia is such an event confirmed by a measured plasma glucose (PG) level≤70 mg/dL [3.9 mmol/L].

Asymptomatic: measured plasma glucose (PG) level≤70mg/dL [3.9 mmol/L] not associated with typical symptoms of hypoglycaemia.

Severe symptomatic: event with clinical symptoms that are considered to result from hypoglycaemia, requiring the assistance of another person for active administration of carbohydrate, glucagon or other countermeasure and meeting one of the following criteria:

- event confirmed by a measured plasma glucose (PG) level ≤36mg/dl [2 mmol/L],
- or, where plasma glucose cannot be measured, quick resolution of hypoglycaemia symptoms upon oral administration of carbohydrate.

Eleven cases of symptomatic hypoglycemia were reported in 7 (1,58%) patients:

- 5 cases in 3 (1,4%) patients in gemigliptin group
- 6 cases in 4 (1,8%) patients in vildagliptin group.

Four (0,9%) patients reported only 1 episode of hypoglycemia, 2 (0,5%) patients – 2 episodes and 1 (0,2%) – 3 episodes.

There were no statistically significant difference in hypoglycemia reporting between the groups (p>0,05). In all above cases the patients continued the study drug administration without any treatment changes.

No cases of severe or asymptomatic hypoglycemia were reported during the study. No cases of rescue therapy administration were reported in the study.

Sixty-four (64) adverse events (AE) including 4 serious adverse events (SAE) were reported in 49 patients (11,1%). All reported AEs were considered as treatment-emergent adverse events (TEAE). 34 (53,1%) AEs were reported in gemigliptin treatment group and 30 (46,9%) AEs in vildagliptin group. AEs' distribution is summarised in Table 22. The difference between groups was non-significant in frequency of reported AEs and SAEs (p>0,05).

There were 4 SAEs reported in 4 (0,9%) patients:

A 58-year-old man was hospitalized with a hemorrhagic stroke after 89 days of gemigliptin treatment and died in 9 days. It was the only AE with the fatal outcome. Two (2) non-fatal SAEs required hospitalization were reported during the study: myocardial infarction (severe by intensity) in 59 years old male subject was reported after 118 days of gemigliptin treatment and open-angle glaucoma of both eyes (moderate by intensity) in 52 years old female subject was reported after 127 days of gemigliptin treatment. These both SAEs required treatment and resolved without sequelae at the moment of last follow-up. Study medication was continued without any change in both cases. All 3 SAEs above occurred in gemigliptin group and in the opinion of Investigator had no reasonable possibility for a causal relationship with study drug.

One (1) AESI (adverse event of special interest) was reported as SAE - exacerbation of chronic pancreatitis in a female subject (57 years old) treated with vildagliptin for 62 days. The SAE was moderate by intensity and required treatment. Study medication was discontinued due to event and the subject was withdrawn from the study. The SAE fully resolved within 2 weeks after registration. Investigator considered this SAE as related with study medication

Table 22. Summary of Adverse Events^.

	Gemigliptin n=220	Vildagliptin n=223	All patients n=443	Chi-square	Df	p
Adverse Events (by SOC):						
Blood and lymphatic system disorders	2 (0,9%) 2	1 (0,4%) 1	3 (0,7%) 3	NA*	NA	p>0.05
Cardiac disorders	1 (0,5%) 1	0 (0,0%) 0	1 (0,2%) 1	NA*	NA	p>0.05
Endocrine disorders	5 (2,3%) 5	7 (3,1%) 7	12 (2,7%) 12	0.07	1	p>0.05
Eye disorders	2 (0,9%) 2	0 (0,0%) 0	2 (0,5%) 2	NA*	NA	p>0.05
Gastrointestinal disorders	1 (0,5%) 1	4 (1,8%) 4	5 (1,1%) 5	NA*	NA	p>0.05
Immune system disorders	0 (0,0%) 0	1 (0,4%) 1	1 (0,2%) 1	NA*	NA	p>0.05
Infections and infestations	8 (3,6%) 8	8 (3,6%) 8	16 (3,6%) 16	NA*	NA	p>0.05
Metabolism and nutrition disorders	7 (3,2%) 7	3 (1,3%) 3	10 (2,3%) 10	0.96	1	p>0.05
Musculoskeletal and connective tissue disorders	4 (1,8%) 4	0 (0,0%) 0	4 (0,9%) 4	NA*	NA	p>0.05
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0,0%) 0	1 (0,4%) 1	1 (0,2%) 1	NA*	NA	p>0.05
Nervous system disorders	3 (1,4%) 3	1 (0,4%) 1	4 (0,9%) 4	NA*	NA	p>0.05
Respiratory, thoracic and mediastinal disorders	1 (0,5%) 1	0 (0,0%) 0	1 (0,2%) 1	NA*	NA	p>0.05
Vascular disorders	0 (0,0%) 0	4 (1,8%) 4	4 (0,9%) 4	NA*	NA	p>0.05
Total	27 (12,3%) 34	22 (9,9%) 30	49 (11,1%) 64	0.511	1	p>0.05
Serious adverse events	3 (1,3%) 3	1 (0,4%) 1	4 (0,9%) 4	NA*	NA	p>0,05

*NA – too few observations to provide a reliable data analysis,

^Note: Data provided as n (%) E, where n – number of subjects, (%) –percentages of events, E – number of events. The data are based on the number of subjects in the ITT population.

Twenty-two (22) patients withdrew from the study during treatment period: 13 (5,9%) in gemigliptin group against 9 (4,0%) in vildagliptin group, but the difference between groups was non-significant (Table 23).

Table 23. Patients withdrawn the study (n(%)).

Gemigliptin 50 mg (n=220)	Vildagliptin 100 mg (n= 223)	Chi-square	Df	p
13 (5,9%)	9 (4,0%)	0,47431	1	0,491

Two (0,45%) patients withdrew from the study due to adverse events: one patient due to exacerbation of chronic pancreatitis (SAE/AESI) and another patient due to hemorrhagic stroke led to death (SAE). From other premature withdrawals, 12 (2,70%) patients refused to continue study participation due to personal reasons, 7 (1,58%) patients were excluded due to inclusion/exclusion criteria deviation, and 1 (0,23%) patient was excluded due to low treatment compliance.

Pharmacokinetic results: Russian GEMIGL07185 data was compared with predicted interval from final Pop PK model parameters as depicted in Figure 1. Comparison using Confidence Interval-Visual Predictive Check (CI-VPC) revealed that the final PK model covered concentration-time data from Russian GEMIGL07185 study, which is consistent with the results of covariate analysis for race/ethnicity in PMLC15-0444-02 report. The primary objective of this analysis was to identify any potential PK differences of gemigliptin and LC15-0636 between Russian and other ethnic populations such as Korean. In conclusion, current analysis using CI-VPC indicates that Russian patient populations are not different from other ethnic groups including Korean and Caucasian.

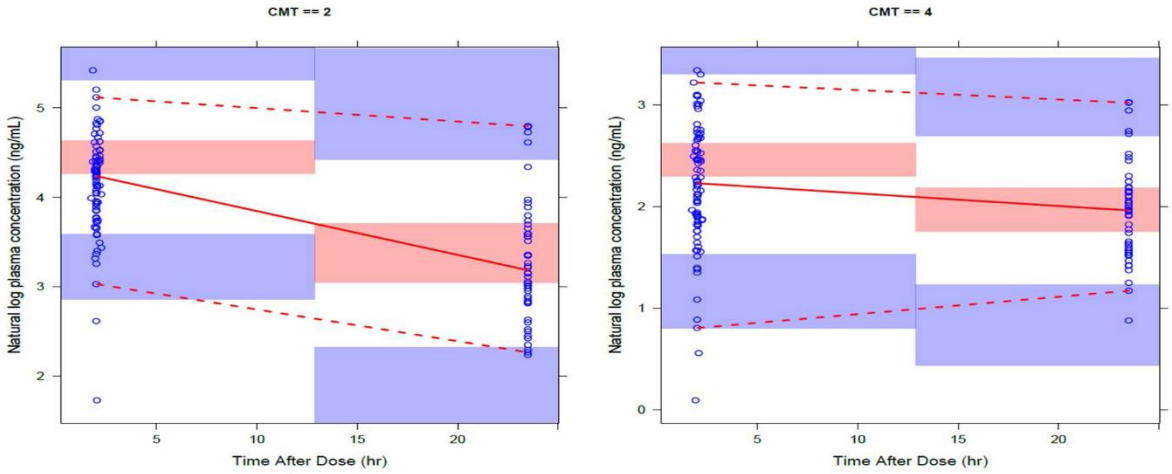

Figure 7. Confidence Interval-Visual Predictive Check for comparison between sparse concentration- time data from Russian GEMIGL07185 study and the final Pop PK model after once daily dosing of 50 mg gemigliptin. Gemigliptin (CMT=2) and LC15-0636 (CMT=4) concentrations were either predicted using the final Pop PK model or observed from Russian GEMIGL07185 study.

Note: Blue area = 90% CI of 5th and 95th percentile of 1,000 model simulations; Red area = 90% CI of median of 1,000 model simulations; red line = 5th, 50th and 95th percentile of observed data.

Issue date: 12-Jul-2017