Comparison of glimepiride, alogliptin and alogliptin+pioglitazone combination in poorly controlled type 2 diabetic patients

(Protocol: Takeda_ALO-IIT)

Version No: 3.3 date:29/Dec/2016

Principal Investigator's Affiliation: Seoul National University Bundang Hospital

Principal Investigator's Name: Sung Hee Choi

Research Outline

Title of Research	Comparison of glimepiride, alogliptin and alogliptin+pioglitazone combination in poorly controlled type 2 diabetic patients
Principal Investigator	Professor Sung Hee Choi
Institution Supporting Research Expenses	Takeda Pharmaceuticals Korea Co. Ltd.

Research Objective	The primary objective is to compare the change in HbA1c in week 24 in 3 treatment groups: the glimepiride monotherapy treatment group; the alogliptin monotherapy treatment group; the alogliptin - pioglitazone combination therapy treatment group. - The secondary objective is to compare the change in HbA1c in week 12 and fasting plasma glucose (FPG) in week 12 and 24 in the following 3 treatment groups over the course of 3 months (at the Baseline, in Week 12): (the glimepiride monotherapy treatment group, the alogliptin monotherapy treatment group, and the alogliptin - pioglitazone combination therapy treatment group). - Also, the change in parameters of glycemic variability assessed by CGM will be investigated. - Also, for a 6-month period, the average change in the lipid profile will be compared (Baseline, Week 12, Week 24).
Research Plan	• This trial is a three-armed, open label, random assignment trial. • The research subjects are patients who are first starting their treatment or patients who have failed with the metformin treatment and are changing their medication. They will be assigned to one of the following treatment groups: the glimepiride monotherapy treatment group, the alogliptin monotherapy treatment group, and the alogliptin - pioglitazone combination therapy treatment group • This trial is a prospective trial which will conduct surveys 6 times over the course of the 6 months in which each treatment group is administered drugs (Week −2, Baseline, Week 4, Week 12, Week 24, follow-up safety survey). • This trial is a multicenter clinical trial which will be conducted at more than 5 general hospital medical institutions in the vicinity of the capital.
Research Period	Date of IRB Approval –
Research Subjects	Randomly assigned patients with type 2 diabetes who are first starting their treatment or patients who have fail with the metformin treatment and must change their medicine.
Number of Research Subjects	A total of 198 patients (66 blinded patients for each treatment group) will participate in the trial and receive treatment for 6 months.
Trial Drug/Medical Device	**Alogliptin 25mg** **Glimepiride**

	Alogliptin 25mg +pioglitazone 15mg
Usage and Dose	• Alogliptin's nonproprietary name is alogliptin benzoate and is an oval-shaped yellow tablet. A 25 mg dose of this medication is administered once a day and is taken with food or on an empty stomach. • The pioglitazone used in the alogliptin - pioglitazone combination therapy treatment group is pioglitazone hydrochloride and is a grey circular tablet. A 15 mg dose of this medication is administered once a day and is taken with food or on an empty stomach.
Research Methods	• The change in the level of HbAc1 will be compared among the 3 treatment groups – the glimepiride monotherapy treatment group, the alogliptin monotherapy treatment group, and the alogliptin - pioglitazone combination therapy treatment group – until the 24th week after the Baseline is taken. • CGMS will be checked to investigate changes in glycemic variability. • Glimepiride's nonproprietary name is glimepiride; this drug is a snowman shaped tablet. Starting with a 1 mg dosage once a day before the first meal, the investigators will decide to increase the dosage to a maximum of 2 mg in the Week 4. • Dosage adjustment will be conducted for participants proven to have persistent hyperglycemia (in the opinion of the investigator). • Alogliptin's nonproprietary name is alogliptin benzoate and is an oval-shaped yellow tablet. A 25 mg dose of this medication is administered once a day and is taken with food or on an empty stomach. • The pioglitazone used by the alogliptin - pioglitazone combination therapy treatment group is pioglitazone hydrochloride and is a grey circular tablet. A 15 mg dose of this medication is administered once a day and is taken with food or on an empty stomach. • The subjects will have their HbA1c level tested in Week 12 and Week 24 and will have their MAGE checked at the Baseline and in Week 24. • General characteristics (bodyweight and BMI), vital signs, and laboratory tests will be conducted in Week 4, Week 12, and Week 24. • MAGE will be measured using CGMS (continuous glucose monitoring system) for 3 days (72 hours). Education regarding eating, CGMS usage, notices, and correction will be given. • A follow-up safety survey will be conducted 30 days after the last visit.
Primary Selection Criteria	<Selection Conditions> • Subjects selected for this trial will be male and female outpatients 19 – 80 years of age (by date of birth) with type 2 diabetes and with HbA1c levels of 7.5%≤HbA1c≤10%. • Patient's body mass index must be greater than 18 kg/m^2. • Subjects selected for the trial are patients who are starting treatment for the first time or who have failed with more than 8 weeks of treatment with 1,000 mg or the maximum tolerance dose (MTD) of metformin and want to change their medication.
Primary Exclusion Criteria	Exclusion Criteria>

<table>
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- The criteria for exclusion includes the following:
  - If weight loss pills were used in the last 3 months, or hypoglycemic agents or lipid lowering agents used in a clinical trial (not including statins or ezetimibe) were used in the last 3 months.
  - If the subject received systemic corticosteroid treatment or there was a change in the dosage of thyroid hormones in the 6 weeks prior to the study.
  - If insulin was used within the 3 months prior to screening.
  - If the patient's C-peptide level is less than 0.6 ng/mL.
  - If an allergy or a hypersensitivity reaction to the target drug or its ingredients occurs.

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<tr><td>Efficacy Evaluation</td><td>

Primary Evaluation Endpoint:

- The change in HbA1c from baseline at week 24 in treatment groups (the glimepiride monotherapy treatment group; the alogliptin monotherapy treatment group; and the alogliptin - pioglitazone combination therapy group.)

Secondary Evaluation Endpoint:

- The change in HbA1c from baseline at week 12 and FPG levels from baseline at week 12 and 24.
- The change in parameters of glycemic variability assessed by CGM from the Baseline at week 24
- The change in lipid profile from baseline at week 12 and 24

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<tr><td>Safety Evaluation</td><td>Adverse events, vital signs, medical examination by interview, laboratory tests, blood pressure, and weight</td></tr>
<tr><td>Test/Visit Schedule</td><td>

<table>
<tr><th></th><th>Screening and Baseline</th><th>Week 4</th><th>Week 12</th><th>Week 24</th><th>Safety F/U (Week 24 + 30 Days).</th></tr>
<tr><td>Permissible Visit Range</td><td>-</td><td>± 3 Days</td><td>± 7 Days</td><td>± 7 Days</td><td>± 3 Days</td></tr>
<tr><td>General Characteristics[1)]</td><td>O</td><td>O</td><td>O</td><td>O</td><td></td></tr>
<tr><td>HbA1c</td><td>O</td><td></td><td>O</td><td>O</td><td></td></tr>
<tr><td>CGMS(MAGE)</td><td>O</td><td></td><td></td><td>O</td><td></td></tr>
<tr><td>Medical History</td><td>O</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Selection/ Exclusion Criteria</td><td>O</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Vital Signs[2)]</td><td>O</td><td>O</td><td>O</td><td>O</td><td></td></tr>
<tr><td>Laboratory Tets[3)]</td><td>O</td><td>SMBG/FPG</td><td>O</td><td>O</td><td></td></tr>
<tr><td>Adverse Event</td><td>O</td><td>O</td><td>O</td><td>O</td><td>O</td></tr>
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Statistical Analysis Methods	• Descriptive statistics (mean and standard deviation) are used to describe continuous variables of baseline demographic and biochemical parameters, and counts with percentages are presented for categorical variables of baseline demographic and biochemical parameters. • The efficacy and safety analyses were based on the full analysis set population consisting of all the patients who received the investigational drug at least once. • The demographic characteristics of subjects were analyzed using ANOVA for the continuous variables and the chi-squared ($\chi 2$) test for the categorical variables. • Efficacy endpoints at week 12 and week 24 were analyzed using ANCOVA model with Boferroni (baseline value as a covariate) for continuous variables and Pearson chi-square test adjusted by Bonferroni for categorical variables. • Missing data, which is an unavoidable occurrence in prospective studies, will be substituted for using the last observation carried forward (LOCF) method. • A p value <0.05 will be considered to indicate statistical significance and the SPSS (Statistical Package for Social Sciences) Version 25.0 will be used for statistical analysis

1. Research Title

Comparison of glimepiride, alogliptin and alogliptin+pioglitazone combination in poorly controlled type 2 diabetic patients

2. Research Institution Name and Address

Department of Endocrinology, Seoul National University Bundang Hospital
82 Gumi-ro 173 beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do (463-707)

	Name of Clinical Trial Institution	Principal Investigator	Specialty
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3	Kangbuk Samsung Hospital	Eun Jung Rhee	Department of Endocrinology
4	Ajou University Hospital	Hae Jin Kim	Department of Endocrinology
5	Sinchon Severance Hospital	Eun Seok Kang	Department of Endocrinology
6	Ilsan Paik Hospital	Jung Hyun Noh	Department of Endocrinology
7	Soon Chun Hyang University Hospital Cheonan	Sung Wan Chun	Department of Endocrinology
8	Kyung Hee University Hospital	In kyung Jeong	Department of Endocrinology
9	CHA Bundang Medical Center	Soo kyung Kim	Department of Endocrinology

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3. Address and Name of Institution Supporting Research Expenses

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82-02-3484-0824

4. Scheduled Research Period

Date of IRB Approval – Aug. 31, 2020

5. Target Disease of Research

Type 2 Diabetes

6. Research Background and Objective

1) Research Background

According to the National Health Statistics of the United States, the prevalence of diabetes in adults over 30 (age was standardized through an expected patient group in 2005) went from 8.6% in 2001 to 9.8% in 2011, increasing 1.2% over the course of about 10 years.[1)] In Korea, the prevalence of diabetes has been roughly 10% and the prevalence of prediabetes has been roughly 20% for about 30 years. Diabetes is a serious illness in itself, but if it becomes chronic it can cause neuropathy, nephritis, ophthalmologic disease, cardiovascular abnormalities, and other various complications. Moreover, it is known that diabetes can cause death in severely ill patients.[2)]

Furthermore, diabetes has been one of the 5 leading causes of death since 2000. According to the results of statistical data analysis done by the Organization for Economic Co-operation and Development (OECD), it was found that diabetes and diabetic complications accounted for the second highest rate of hospitalization in OECD nations. The expected increase in the number of diabetes patients from 285 million in 2010 to 438 million in 2030 underscores the importance of prevention and treatment.[3)]

Pharmaceutical drugs for treating diabetes are classified as sulfonylureas (SU), biguanides, α-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase (DPP-4) inhibitors, *et cetera*. These drugs have effects on different organs through various methods of action. For example, they act in various roles, such as in controlling insulin sensitivity, insulin resistance, glycometabolism, and hypoglycemia.[4),5)]

However, as the efficacy and safety of these drugs has not been clearly proven, single trials or comparative trials of the drugs, in particular comparative trials comparing sulfonylureas and DPP-4 inhibitors, are currently in progress.[6)–8)]

According to Kim, it was found in recent trials that when a DPP-4 inhibitor (sitagliptin) was administered there was a larger decrease in the concentration of HbA1c than when compared with SU (glimepiride).[6)] Further, according to Nauck, in other trials there was almost no difference in the change in the concentration of HbA1c when sulfonylureas (glipizide) were administered. However, it was found that when these drugs were compared with DPP-4 inhibitors (sitagliptin) a significant increase in bodyweight and hypoglycemia occurred.[7)]

However, sulfonylureas are still the most commonly used drug in Korea, especially in the field of primary care. In particular, it has been suggested that the use of DPP-4 inhibitors, which delay the deactivation of GLP-1 and GIP, would be more effective in Koreans than in Westerners because Koreans (Asians) have fewer pancreatic beta cells than Westerners.[6),9)] In particular, focusing on the improvement of insulin secretion is considered to be therapeutically important in Korea. Compared with that of sulfonylureas, the mechanism of action in DPP-4 inhibitors, which stimulates insulin secretion in Koreans dependent on blood glucose, could be an excellent treatment option. Because of this, it is thought that DPP-4 inhibitors could improve insulin secretion independently of blood glucose levels.

2) Research Hypothesis and Objectives

DPP-4 inhibitors are also referred to as gliptins. Among these drugs, it is known that alogliptin (Alo) is a selective DPP-4 inhibitor with excellent drug tolerance.[10)] When this drug is administered as a single dose, the blood glucose level is decreased, but promising results have been confirmed when it is administered in combination with pioglitazone (Pio), one of the recent thiazolidinedione drugs. There have already been various trials conducted to compare Alo monotherapy and Alo + Pio

combination therapy and it has been confirmed that there are significantly greater results when the drugs are administered in combination in an amount sufficient enough to reduce the level of glycated hemoglobin.[10),11)] However, most of these tests have been conducted only abroad. Until the present date, the typical diabetes treatment in Korea has been sulfonylureas, and there has not been sufficient research comparing sulfonylureas and Alo or comparing sulfonylureas with the combination administration of Alo + Pio.

Accordingly, any changes in blood glucose levels, diabetes index, and related factors that occur in this trial when glimepiride, the most widely used sulfonylurea drug, the DPP-4 inhibitor alogliptin, and a combination therapy of alogliptin and pioglitazone are administered to Korean diabetes patients will be investigated.

Hypothesis:

The effectiveness (efficacy) of treatment with alogliptin, low dose glimepiride, and alogliptin - pioglitazone combination therapy will not be identical.

Primary Goal/Objective

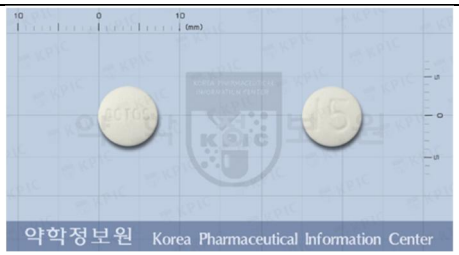
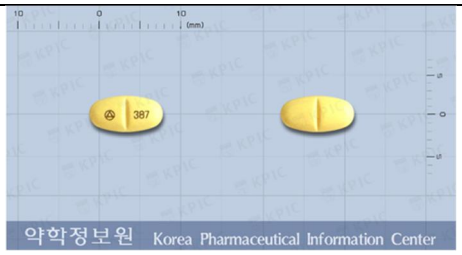
The change in HbA1c from baseline at week 24 in treatment groups (the glimepiride monotherapy treatment group; the alogliptin monotherapy treatment group; and the alogliptin - pioglitazone combination therapy group.)

Secondary Goals/Objectives

- The change in HbA1c from baseline at week 12 and FPG levels from baseline at week 12 and 24.
- The change in parameters of glycemic variability assessed by CGM from the Baseline at week 24
- The change in lipid profile from baseline at week 12 and 24

7. Code Names (and Nonproprietary Name of Main Ingredients) of the Clinical Trial Drugs and Medical Devices, the Quantity of Active Pharmaceutical Ingredients, the Dosage, etc. (Including the Control Drug)

	Pioglitazone (Actos® Tablet)	Alogliptin (Nesina® Tablet)
Nonproprietary Name	Pioglitazone hydrochloride (pioglitazone)	Alogliptin benzoate (alogliptin)
Dosage	15mg	25mg
Quantity of Active Pharmaceutical Ingredients	16.53mg	34mg
Insurance Code	696300140	96300210
Vender	Takeda Pharmaceuticals Korea Co. Ltd.	Takeda Pharmaceuticals Korea Co. Ltd.
Description	White or light gray color convex cylindrical tablet	Pale yellow, oval-shaped, film coated tablet

	Glimepiride (Amaryl® Tablet)	
Nonproprietary Name	Glimepiride	
Dosage	1mg, 2mg	
Quantity of Active Pharmaceutical Ingredients	1mg, 2mg	
Insurance Code	Amaryl® Tablet 1mg – 652100790 / Amaryl® Tablet 2mg – 652100800	
Vender	Handok Pharmaceuticals Co Ltd.	
Description	Amaryl® Tablet 1mg – Pale pink oblong tablet 	Amaryl® Tablet 2mg – Green oblong tablet 

8. Research Subject Selection Criteria, Exclusion Criteria, the Target Number Subjects and the Basis for This Calculation

1) Selection Criteria

This is a two-armed, open label trial. Type 2 diabetes patients who are first starting their treatment or have failed with metformin treatment and must change in their medication will be randomly assigned to one of the following treatment groups: the glimepiride monotherapy treatment group, the alogliptin monotherapy treatment group, or the alogliptin - pioglitazone combination therapy treatment group.

There will be a total of 198 patients (66 blinded patients for each treatment group) participating in the trial and they will receive treatment for 6 months.
The criteria for participating in the trial are as follows:

<Selection Conditions>

- Subjects selected for this trial will be male and female outpatients 19 – 80 years of age (by date of birth) with type 2 diabetes and with HbA1c levels of 7.5%≤HbA1c≤10%.
- Patient's body mass index must be greater than 18 kg/m^2.
- Subjects selected for the trial are patients who are starting treatment for the first time or who have failed with more than 8 weeks of treatment with 1,000 mg or the maximum tolerance dose (MTD) of metformin and want to change their medication.

2) Exclusion Criteria

The criteria for exclusion include the following:

- If weight loss pills were used in the last 3 months, or hypoglycemic agents or lipid lowering agents used in a clinical trial (not including statins or ezetimibe) were used in the last 3 months.

- If the subject received systemic corticosteroid treatment or there was a change in the dosage of thyroid hormones in the 6 weeks prior to the study.
- If insulin was used within the 3 months prior to screening.
- If the patient's C-peptide level is less than 0.6 ng/mL.
- If an allergy or a hypersensitivity reaction to the target drug or its ingredients occurs.

Additional criteria for exclusion are listed below;

- A medical history of type 1 diabetes; acute metabolic complications of diabetes within the past 6 months (e.g., ketoacidosis or a hyperosmolar state (coma or precoma))
- Hematological disorder
- A medical history of angioedema caused by angiotensin converting enzyme inhibitors or angiotensin receptor blockers or a medical history of treatment for diabetic gastroparesis
- If there are clear symptoms of hypothyroidism or hyperthyroidism in the opinion of the investigator.
- Myocardial infarction or PCI (stent nephrostomy or balloon nephrostomy) within the past 6 months
- Serious heart failure or a medical history of heart failure (NYHA Class III or IV heart failure)
- Heart failure, moderate to severe kidney injury (creatinine clearance of <50 mL/min prior to screening)
- Patients with chronic hepatitis, or hepatitis B or C (not including healthy carriers of hepatitis B) or a patient with liver disease (defined as cases in which the alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or serum total bilirubin level is higher than 2.5 times the ULN)
- Hereditary complications, such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption (restricted to drugs including lactase)
- Cardiovascular disease or myocardial infarction; or a percutaneous transluminal coronary angioplasty or coronary artery stent nephrostomy within the past 6 months
- A serious cerebrovascular accident, stroke, or transient ischemic attack within the past 6 months
- Laser treatment for diabetic proliferative retinopathy
- A medical history of alcohol or drug abuse in the past 3 months
- A medical history of cancer in which remission could not be achieved within 5 years
- A medical history of bladder cancer or active bladder cancer
- Uninvestigated macroscopic hematuria
- Has experienced major surgery
- Breast feeding women, pregnant women, or premenopausal for whom pregnancy is possible are not suitable for participation in this trial
- External injury, acute infection, existence of or medical history of other chronic illness

Criteria for exclusion based on laboratory test results are as listed below.

- A fasting blood glucose (FPG) level of >239.6 mg/dL
- Systolic or diastolic blood pressure of >160 mmHg or >100 mmHg respectively
- A serum creatinine level of 1.5 mg/dL for men or 1.4 mg/dL for women
- An albumin/creatinine ratio of 2,000 mg/g
- A fasting triglyceride level of > 5.1 mmol/l (452 mg/dL)

3) Target Number of Subjects and the Basis for This Calculation
Statistical Analysis

After Week 24 of this trial, changes in the level of HbA1c among the 3 treatment groups will be compared, but the level of significance of the compared values of two treatment groups will be divided by 3 to correct for the level of significance of the 3 treatment groups. The number of sample collections

will be calculated using the value which is calculated for the comparison of alogliptin and alogliptin - pioglitazone combination therapy, as is presented below.

$$\frac{(Z_{(\frac{\alpha}{2})} + Z_{(1-\beta)})^2 \times (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

$\alpha = 0.05/3$, $1 - \beta = 0.9$
$\sigma_1 = 1.037$, $\sigma_2 = 1.037$
$\mu_1 = -0.96$, $\mu_2 = -1.71$

According to the above formula, the number of sample collections was calculated for treatment groups of 53 subjects each. However, in consideration of the dropout rate, there is a target of 66 subjects for each treatment group. The dropout rate was estimated on the basis of the dropout rates of existing prospective studies.

4) Research Subject Recruitment Plans

For the recruitment of research subjects for this research, patients who are characteristic of the selection criteria and are currently receiving the outpatient treatment of the principal investigator and the joint investigators who are in accordance with the selection criteria will be recruited. The principal investigator and joint investigators of this research will not exclude any patient who could participate in this research on the basis of ethnicity or socioeconomic status.

9. Research Method

1) Specific Research Methodology

① The research subjects selected for this trial will patients among those who have given their approval to participate in the trial and who are first starting their treatment or who intend to alter their medication because treatment with the existing drugs has failed who satisfy the criteria.

② Patients with a '7.5% ≤ HbA1c ≤ 10%' in the HbA1c test will be chosen.

③ Patients who are intending to change drugs due to the failure of an existing drug treatment must have the use of 1,000 mg or the maximum tolerance dose (MTD) of metformin recorded in his or her medical records.

④ The investigators must confirm the patient's intention to participate in the trial and, starting at the point of the routine laboratory test results, must provide a sufficient explanation of this research to the patients who satisfy the criteria and then must acquire a research subject consent form from these patients. The consent forms must include the trial objectives, the benefits for participants, the risk factors, a confidentiality agreement, the right to withdraw consent, and contact information. The patients must sign the consent forms.

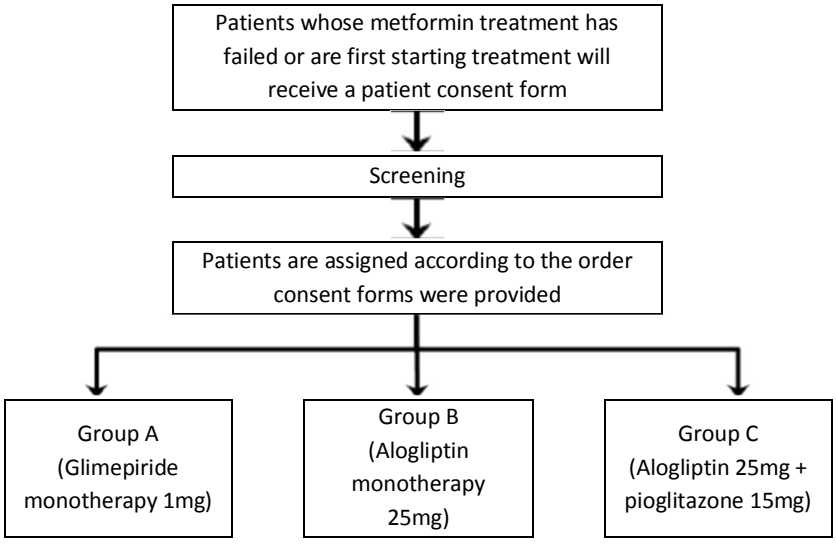
- The change in the level of HbAc1 will be compared among the 3 treatment groups – the glimepiride monotherapy treatment group, the alogliptin monotherapy treatment group, and the alogliptin - pioglitazone combination therapy treatment group – until the 24th week after the Baseline is taken.
- MAGE will be checked to investigate changes in blood glucose.
- Glimepiride's nonproprietary name is glimepiride; this drug is a snowman shaped tablet. Starting with a 1 mg dosage once a day before the first meal, the investigators will decide to increase the dosage to a maximum of 2 mg in the Week 4.
- Dosage adjustment will be conducted for participants proven to have persistent hyperglycemia (in the opinion of the investigator).

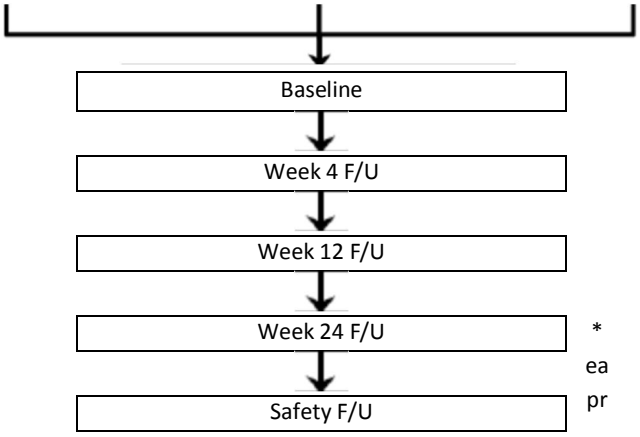
	Week 4	**Week 12**

Alogliptin 25mg	Dosage adjustment is not allowed	Dosage adjustment is not allowed
Glimepiride	1mg → 2mg	Dosage adjustment is not allowed
Alogliptin 25mg +Pioglitazone 15mg	Dosage adjustment is not allowed	Dosage adjustment is not allowed

- Alogliptin's nonproprietary name is alogliptin benzoate and is an oval-shaped yellow tablet. A 25 mg dose of this medication is administered once a day and is taken with food or on an empty stomach.
- The pioglitazone used by the alogliptin - pioglitazone combination therapy treatment group is pioglitazone hydrochloride and is a grey circular tablet. A 15 mg dose of this medication is administered once a day and is taken with food or on an empty stomach.
- The subjects will test the HbA1c level in Week 12 and Week 24 and will check CGMS at the Baseline and in Week 24.
- General characteristics (bodyweight and BMI), vital signs, and laboratory tests will be conducted in Week 4, Week 12, and Week 24.
- MAGE will be measured using CGMS (continuous glucose monitoring system) for 3 days (72 hours). Education regarding eating, CGMS usage, notices, and correction will be given.
- A follow-up safety survey will be conducted 30 days after the last visit.
- Subjects will be enrolled in the trial for 6 months and following this a follow-up survey will be conducted.
- Approximately 12 months will be required for the total trial period based on the last patient (6 months) to have their Baseline enrollment conducted.
- Patients will be asked to come to the clinical research institution after Week 4, Week 12, and Week 24 (for Week 12 and Week 24, a period of ±7 days is permitted) after the Baseline (or the first) visit. In addition, patients will be requested to take a call 30 days after their last visit for the safety follow-up survey.
- Subjects with a drug compliance of less than 80% will be eliminated.
- Subjects with an HbA1c level of more than 9.0% in Week 12 will be eliminated.
  Subjects who sign the trial subject consent form and participate in the trial but do not finish will be eliminated. The elimination of a subject can be determined at any time during the trial. Withdrawal of consent by the subject will also be considered as an elimination and the reason for the withdrawal of consent must be clearly recorded. Furthermore, if an adverse event and/or a serious adverse event occurs during the trial, the corresponding subject will be immediately eliminated from the trial.

Trial Flowchart





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*The checklist for each follow-up survey (F/U) is shown in table 1.

2) Comparison Group Selection and Random Assignment Method

All trial subjects who are eligible to participate will be randomly assigned and will receive a random assignment number. Subjects will be identified by their random assignment numbers in all procedures that are carried out after random assignment.

Samples will be assigned to Group A (glimepiride), Group B (alogliptin), and Group C (alogliptin-pioglitazone) by random assignment using the order in which patients consented to participate in the open-label trial. If the designated patient Baseline process is completed for each treatment group, the subject recruitment will end.

3) Trial Drug Administration · Dosage, Administration · Usage Methods, Combination Therapy, Reason for the Selection of the Control Drug Used

	Dose	Usage
Test Group A	Glimepiride 1mg (*If necessary, increase in dosage to 2 mg possible until Week 4*)	Oral administration of single dose once a day in the morning before eating
Test Group B	Alogliptin 25mg single dose (*fixed dose*)	Oral administration of single dose once a day in the morning before eating
Test Group C	Alogliptin 2mg + pioglitazone 15mg combination dose (*fixed dose*)	Oral administration of single dose once a day in the morning before eating

4) Details of Observation, Details of Pregnancy Test, Observational Test Methods

Table 1) Checklist of each patient visit during the trial period

	Screening and Baseline	Week 4	Week 12	Week 24	Safety F/U (Week 24 + 30 Days).
Permissible Visit Range	-	± 3 Days	± 7 Days	± 7 Days	± 3 Days
General Characteristics[1)]	O	O	O	O	
HbA1c	O		O	O	
MAGE (CGMS)	O			O	
Medical History	O				
Selection/Exclusion Criteria	O				
Vital Signs[2)]	O	O	O	O	
Laboratory Tets[3)]	O	SMBG/FPG	O	O	
Adverse Event	O	O	O	O	O

*Results from within 4 weeks of the screening and baseline tests can be used.

1) Sex, age, height (sex, age, and height will only be checked at the Baseline), bodyweight, BMI
2) Systolic and diastolic blood pressure (measured immediately after subjects have been in a supine position for 5 minutes), pulse, body temperature
3) Laboratory tests
   * Laboratory tests for efficacy: fasting plasma glucose (FPG), C-peptide, fasting insulin, serum lipid profile (triglyceride, cholesterol (total, HDL and LDL)): * fasting C-peptide & insulin = screening/Baseline & Week 24
   * Week 4: blood glucose self-testing (blood glucose stick) & FPG
   * Laboratory tests for safety
   - Blood chemistry: creatinine, total protein, albumin, AST, ALT, total bilirubin, ALP, BUN, Ca, P, Gamma-glutamyl transpeptidase, uric acid
   - Blood test: hemoglobin, hemocrit, RBC, WBC (white blood cell), neutrophil, eosinophil, basophil, lymphocyte, monocyte, platelet
   - Urine Test: SG, color, pH, glucose, albumin, bilirubin, blood, ketone, RBC, WBC, squamous cell
4) Urine Pregnancy Test (applies only to fertile women)

5) Effectiveness Evaluation Criteria and Evaluation Method

Primary Goal/Objective:

The primary objective is to compare the change in HbA1c in Week 24 in 3 treatment groups: the glimepiride monotherapy treatment group; the alogliptin monotherapy treatment group; the alogliptin - pioglitazone combination therapy treatment group.
- Also, for a 6-month period, the average change in the lipid profile will be compared (Baseline, Week 12, Week 24).

Secondary Goals/Objectives:

- The secondary objective is to compare the change in HbA1c and fasting plasma glucose (FPG) in the following 3 treatment groups over the course of 3 months (Baseline, Week 12): (the glimepiride monotherapy treatment group, the alogliptin monotherapy treatment group, and the alogliptin - pioglitazone combination therapy treatment group)
- Also, within the blood glucose regulation process, the parameters of glycemic variability assessed by CGM will be investigated.

Primary Evaluation Endpoint:

The change in HbA1c from baseline at week 24 in treatment groups (the glimepiride monotherapy treatment group; the alogliptin monotherapy treatment group; and the alogliptin - pioglitazone combination therapy group.)

Secondary Evaluation Endpoint:

The change in HbA1c from baseline at week 12 and FPG levels from baseline at week 12 and 24.
The change in parameters of glycemic variability assessed by CGM from the Baseline at week 24
The change in lipid profile from baseline at week 12 and 24

6) Benefit and Risk to Research Subjects

Adverse Event

1. Definition

An adverse event (AE) is defined as the occurrence of an undesirable medical incident occurring in a clinical trial subject who has been administered drugs. It is not necessary for the treatment to have a causal relationship with the adverse event.
Therefore, an AE is any undesirable and unintended sign (e.g., abnormal laboratory test level findings), symptom, or chronic illness which correspond chronologically with the use of the corresponding pharmaceuticals regardless of whether it is determined to be related to the pharmaceuticals.

2. SAEs

All SAEs related to this treatment will be collected for this research protocol. An SAE is defined as a case in which the following undesirable medical incidents occur from an unspecified dose.

1. If death is caused.
2. If the situation is life threatening.

"Life threatening" will be used to describe instances in which the subject encountered the risk of death at the time of the incident. It will be used for cases which were more severe than had been anticipated and could have caused death.

3. If hospitalization or an extension to an existing hospitalization period is required.
4. If persistent or significant handicap/disability is caused.
5. If a congenital anomaly/birth defect is caused.
6. If it corresponds to a significant medical incident which satisfies the following:

    Intervention may be necessary to prevent the above clauses 1 – 5.

Even though the corresponding event was not immediately life threatening, was non-fatal, or did not cause hospitalization, it could have put the research subject at risk.

The case described or an equivalent case is included in Takeda's list of medically significant AEs.

3. Severity of AEs

The categories of intensity (severity) are as classified below:

Mild:	The case is temporary and the subject can easily endure it.
Moderate:	The case causes discomfort to the subject and causes a hindrance to daily life.
Severe:	The case causes a considerable hindrance to the subject's daily life.

4. Collection and Reporting of Adverse Events of Special Interest

The trial investigator must report pancreatitis, hypersensitivity reactions including Stevens–Johnson Syndrome, hepatic effects, bladder cancer, and other related adverse events of special interest.

Bladder Cancer: Bladder Cancer is an adverse event of special interest of pioglitazone. The patient must quickly notify the investigator if macroscopic hematuria or other symptoms related to urination (dysuria or overactive bladder) occur while the corresponding drugs are being administered. If a bladder cancer diagnosis is confirmed, it must be reported to Takeda.
Bladder Cancer Withdrawal Criteria: - If there is a patient with a medical history of bladder cancer or unexplained hematuria, risk factors for bladder cancer (age, smoking history, exposure to some surgeries/chemotherapy (e.g., cyclophosphamide or radiation therapy of the pelvic region)) must be evaluated before the start of treatment. Whether or not macroscopic hematuria is present must be evaluated before treatment.

- The patient must quickly notify the investigator if macroscopic hematuria or other symptoms related to urination (dysuria or overactive bladder) occur while the corresponding drugs are being administered. The administration of the corresponding drug must be suspended while additional examinations are done to make a diagnosis. - The investigator must fill out the sections related to AE/SAEs in the CRF. - If a definite diagnosis of bladder cancer is made, the administration of the corresponding drug must be permanently suspended.

- If the administration of the corresponding drug is suspended in the subject because of suspension criteria related to bladder cancer, it must be recorded as an AE along with the reason for the suspension.
- An early termination review must be conducted along with monitoring for subjects who were suspended.

5. Collection and Reporting of SAEs

In the event that an SAE occurs during the AE collection period after the consent form has been signed, it must be reported in accordance with the following procedures:

The trial investigator must immediately fill out and sign a Takeda SAE Report Form in English on the first day of the incident or within 1 business day of the date the investigator was notified of the incident. As much information as possible should be fully included on the form and the form must include a minimum of the following information:

A brief explanation of the case and the reason for categorizing the case as a serious event.
Subject identification number
Name of the trial investigator
Name of the trial drug
Evaluation of the causal relationship

The SAE report form must be sent to the addressee listed below within 1 business day:
<Safety Report Emergency Contact Information>
Liaison: Kate Yoo, Drug Safety Officer
Deputy Liaison: Iann Chun, Deputy Drug Safety Officer
Email: DSO-KR@takeda.com
Fax: 82 2 501 7489
Phone Number: 82 2 3458 0227 / 82 10 3054 2482
After the AE collection period, any SAEs voluntarily reported to the investigator must be reported to Taekda.

6. Follow-up Survey of SAEs

If information which was unavailable at the time of the initial report is later obtained, the investigator must fill out the Follow-up Survey SAE Report Form or supply other written documents and promptly send via fax within 1 business day of receiving the information. If requested, a copy of any related data collected from the hospital records (e.g., ECGs, laboratory tests, discharge summary reports, autopsy results) must be sent to the corresponding address.
Follow-up surveys must be carried out until cases related to an SAE are resolved or until there is a permanent result. The deadline and procedure for the follow-up survey are the same as the deadline and procedure for the first report.

7. Safety Reports for Trial Investigators, IRBs or ECs, and Regulatory Authorities

Takeda or an appointee must report all relevant SAEs to the regulatory authorities, trial investigators, and the IRBs or ECs if applicable under the national regulations of the country in which the trial is being conducted. Further, if other safety issues are confirmed which are sufficient enough to significantly change the result of the risk-benefit evaluation of the trial drug or to require consideration of a change to the administration of the trial drug or the whole execution of the trial, Takeda or an appointee will fill out an expedited report about these issues.

Takeda or an appointee will report any unexpected SAEs which are potentially related to the trial drug in the expedited report. In accordance with all relevant laws and regulations, a copy will be send to all relevant regulatory authorities, the trial investigators, and the IRBs or ECs. If it is affiliated with a clinical trial institution, a copy of the expedited report will be sent to the institution's IRB or EC.

8. SAEs Follow-up Survey

If information which was unavailable at the time of the initial report is later obtained, the investigator will fill out the follow-up survey SAE report form or supply other written documents and will promptly send via fax within 1 business day of receiving the information. If requested, a copy of any related data collected in the hospital records (e.g., ECGs, laboratory tests, discharge summary reports, autopsy results) must be sent to the corresponding address.

Until cases related to a SAE are resolved or until there is a permanent result, follow-up surveys must be carried out. The deadline and process for the follow-up survey are the same as the deadline and process for the first report.

Subject Risk and Benefit

A follow-up, report, and follow-up survey will be conducted for any symptoms listed in precautions.

- Precautions for Alogliptin

1) Pancreatitis: There are post market reports of acute pancreatitis in patients who have taken NESINA. After starting NESINA treatment, the patient must be monitored carefully for signs and symptoms of pancreatitis. If there is suspicion of pancreatitis, the NESINA treatment must be immediately suspended and appropriate management must be started. It is not known whether the risk of contracting pancreatitis increases while taking NESINA for patients with a medical history of pancreatitis.

2) Hypersensitivity Reactions: There are post market reports of serious hypersensitivity reactions in patients who received treatment with NESINA. These reactions included severe adverse drug events of the skin such as anaphylaxis, angioedema, and Stevens–Johnson Syndrome. If there is suspicion of a serious hypersensitivity reaction, the NESINA treatment will be suspended, other potential causes of the incident will be evaluated, and an alternative diabetes treatment will be started. Extreme care should be taken in the administration of a different DPP-4 inhibitor in patients with a medical history of angioedema because it is not known whether angioedema can occur during NESINA treatment.

3) Hepatic Effects: Although some of the existing clinical research reports do not include sufficient information to determine the cause, there are post market reports of fatal and non-fatal hepatic failure in patients who took NESINA [reference Adverse Drug Events (6.2)]. In a randomized, controlled trial, an increase in the of the serum alanine aminotransferase (ALT) of 3 times the upper limit of normal (ULN) was observed in 1.3% of patients receiving alogliptin treatment and 1.5% of the patients in all control drug treatment groups. Type 2 diabetes patients can suffer from fatty liver disease, which can cause abnormal findings in hepatic function tests. These patients can also have other forms of liver disease and most of these cases of liver disease can be cured or managed. Therefore, it is recommended that the results of the hepatic function test be collected and that the patient be evaluated before starting

NESINA treatment. In patients with abnormal hepatic function test findings, extreme care must be taken when starting NESINA treatment. A hepatic function test should be run promptly if there is a patient with symptoms which could indicate liver damage (including fatigue, loss of appetite, abdominal discomfort, dark urine, or jaundice). In this clinical context, if it is confirmed that the patient has a clinically significant increase in the levels of hepatic enzyme or that the hepatic function tests continue to show abnormal findings or have worsened, NESINA treatment must be suspended and an investigation into the possible causes must be conducted. If there are no other explanations for the abnormal hepatic liver function test findings, the patient may not restart treatment with NESINA.

4) Use of Medication Known to Cause Hypoglycemia: Insulin and insulin secretagogues (e.g., sulfonylureas) are known to cause hypoglycemia. Therefore, a smaller dose of insulin or insulin secretogogues must be used to reduce the risk of hypoglycemia when these drugs are taken in combination with NESINA.

5) Macrovascular Outcomes: There are no clinical trials which show conclusive evidence of how to reduce macrovascular risks when NESINA or other diabetes treatments are administered.

- Precautions for Pioglitazone

Actos must be used with caution in the following patients:

1) Combination therapy with other oral hypoglycemic agents
2) Premenopausal women
3) Edema

7) Suspension • Elimination Criteria

Subjects with a drug compliance of less than 80% will be eliminated.
Subjects with an HbA1c level of more than 9.0% in Week 12 will be eliminated.
Subjects who sign the trial subject consent form and participate in the trial but do not finish will be eliminated. The elimination of a subject can be determined at any time during the trial. Withdrawal of consent by the subject will also be considered as an elimination and the reason for the withdrawal of consent must be clearly recorded. Furthermore, if an adverse event and/or a serious adverse event occurs during the trial, the corresponding subject will be immediately eliminated from the trial.

8) Safety Evaluation Criteria (Including Side Effects), Evaluation Methods, and Reporting Methods

Data Safety Monitoring Plan (DSMP)
According to existing research results, this trial is expected to be low risk because of the possibility and

severity of risk and discomfort which could occur in this in trial. The principal investigator is planned to continuously monitor for this risk and discomfort. Safety monitoring for this research will be conducted during every visit through an oral interview, a physical exam, laboratory tests, *et cetera*. If any of these results correspond to an SAE, it will be reported to the IRB.

- If there are any deviations from the protocol, the investigator will report major deviations to the IRB within 15 days of the point at which he or she becomes aware of the deviation and if there are minor deviations, the investigator will gather incidents of minor deviations and report them to the IRB at least once a year.
- Adverse events and all other information relating to safety will be reported in a safety information summary report. If there are incidents related to safety, a summary of the accumulated non-individual data should be compiled and reported at least once every 6 months in the form of a summary.

- Cases related to danger to the research subjects or other persons in which the case is judged to be an unexpected problem or in which it is life threatening should be reported to the IRB within 7 days and within 15 days for all other cases.
- The principal investigator or the subinvestigator will collect data and safety information, examine major efficacy evaluation endpoints, and conduct continuous monitoring every 6 months after the start of research.

9) Data Analysis and Statistical Analysis Methods

- Descriptive statistics (mean and standard deviation) are used to describe continuous variables of baseline demographic and biochemical parameters, and counts with percentages are presented for categorical variables of baseline demographic and biochemical parameters.
- The efficacy and safety analyses were based on the full analysis set population consisting of all the patients who received the investigational drug at least once.
- The demographic characteristics of subjects were analyzed using ANOVA for the continuous variables and the chi-squared ($\chi 2$) test for the categorical variables.
- Efficacy endpoints at week 12 and week 24 were analyzed using ANCOVA model with Boferroni (baseline value as a covariate) for continuous variables and Pearson chi-square test adjusted by Bonferroni for categorical variables.
- Missing data, which is an unavoidable occurrence in prospective studies, will be substituted for using the last observation carried forward (LOCF) method.
- A p value <0.05 will be considered to indicate statistical significance and the SPSS (Statistical Package for Social Sciences) Version 25.0 will be used for statistical analysis

10. Measures for the Protection of Research Subject Safety

1) Fundamental Measures to Ensure Research Ethicality

The Declaration of Helsinki (Revised 2013) and the ICH-GCP will be followed.
IRB approval is scheduled to be received before the start of this research. At the start of research after IRB approval, the research objectives and process will be sufficiently explained to the research subjects. An examination consent form will be received from persons who understand these and voluntarily choose to participate.

Prior to the start of the trial, the trial investigator must acquire the written approval of the institutional review board of the relevant trial institutions and/or regulatory commissions regarding the conduct of the trial and must send a copy to Takeda (gma.externalresearch@takeda.com). If alteration of the trial is necessary, the investigator must acquire the written approval of the institutional review board of the relevant trial institutions and/or regulatory commissions regarding the conduct of the trial and must send a copy to Takeda (gma.externalresearch@takeda.com).
As the research relates to human subjects, the investigators must register this trial at clinical trials.gov and any other relevant institutions if necessary.

2) Research Subject Consent Process

<Research Subject Consent Process>
The supervising investigator and joint investigators must receive written consent from each research subject or his or her representative prior to participation in the trial. Consent must be recorded in writing. The research subject or his or her representative must sign and date the consent form and the person who led the discussion about consent must also sign and date the consent form. A copy of the signed and dated consent form must be sent to the research subject before they participate in clinical research. Before acquiring consent, an explanation of the research methods, the trial drugs, and the expected discomfort, risk, and benefit to research subject must be explained in such a way that these

can be sufficiently understood. After an explanation is given to the research subjects, the subjects must be allotted sufficient time to consider participating in the trial. After such time (expected to take more than 30 minutes), the consent process will proceed. Research subjects will voluntarily participate in the research according to their own volition. Even if they do not participate in the research, they can receive future treatment and will therefore not incur any disadvantage. The explanation of the research must be provided in language such that the research subject or his or her representative will be able to understand. All written information supplied to the research subjects such as the initial consent form, later revised consent forms, etc., must receive the approval of the IRB prior to use. If new information is obtained which could relate to the willingness of the research subjects who will continue to participate in this clinical trial, the research subjects must be promptly notified and this notification must be given in writing.

3) Research Subject Compensation Plan

The research subjects will be paid a transportation fee of 30,000 won.

4) Research Subject Personal Information Protection Measures

Strict personal information and non-disclosure procedures will be used to prevent the disclosure of any information pertaining to the research subject's medical records to any persons other than the investigators. The Institutional Review Board does not infringe on the personal information of patients and the personal information of the patients will not be infringed upon in the process of monitoring or investigating the research. A patient's medical records can be directly inspected for a data credibility verification, which may be compulsory at the requirement of a relevant law or regulatory authority.
To ensure that other persons or other institutions will not be able to obtain any information relating to the research subjects, information which could directly identify a subject such as his or her name or other information will not be included on samples or medical records. To protect personal information, only the research subject number will be used on samples, and the research subject's name or other information which could directly identify the research subject will not leave the research institution. Moreover, the key which connects personal information to the research subject codes will be stored in a separate file under the supervision of the supervising investigator to protect personal information. Furthermore, for any results obtained from this research, a designated key supervisor who did not participate in this research will store the key file, and before any report is provided to an investigator, all identifiable information must be removed by encoding to protect personal information.
Medical records relating to this research will be stored safely for a maximum of 10 years for future research, records, and follow-ups. After this time, the research subject's clinical specimens will be disposed of biologically and records relating to the research will be also disposed of.

5) Plan for Supplemental Protective Measures If Vulnerable Research Subjects Are Included

Not applicable

11. Plan for the Storage and Disposal of Human Biological Materials

Human biological materials obtained through the research will be stored until the end of the research period and disposed of in accordance with the relevant laws.