



Title: Nesina Tablets Special Drug Use Surveillance: Mild Type 2 Diabetes Mellitus

NCT Number: NCT01964963

Statistical analysis plan Approve Date: 04-Feb-2019

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

Note; This document was translated into English as the language on original version was Japanese.

Statistical Analysis Plan

Nesina Tablets Special Drug Use Surveillance: Mild Type 2 Diabetes Mellitus

(Final Analysis)

Takeda Pharmaceutical Company Limited.

PPD

A rectangular area of the document is redacted with a solid blue color.

PPD

A large rectangular area of the document is redacted with a solid blue color.

Version 3.0, Created on February 4, 2019

Table of Contents

1.0	Definition of Terms and Handling of Laboratory/Measured Data.....	1
1.1	Definitions	1
1.2	Important Identified Risks, Potential Risks, and Missing Information.....	10
1.3	Display digit.....	11
1.4	Level of Significance and Confidence Coefficient.....	12
1.5	Handling of Laboratory/Measured Data	12
1.6	Display Data Digit.....	12
2.0	Disposition of Patients (Patient Diagram).....	14
3.0	Patient Demographics	15
4.0	Details of Treatment.....	18
4.1	Initial Dose of Nesina and Mean Daily Dose of Nesina, by Severity of Renal Impairment.....	19
5.0	Safety Tabulation and Analysis	21
5.1	Occurrence of adverse events and adverse drug reactions / infections.....	21
5.1.1	Occurrence of adverse events.....	21
5.1.2	Occurrence of adverse drug reactions / infections.....	21
5.1.3	Important Identified Risks, Important Potential Risks, and Important Missing Information....	22
5.2	Occurrence of Adverse Events and Adverse Drug Reactions / Infections in the Not Safety Analysis Set	23
5.2.1	Occurrence of Adverse Events	23
5.2.2	Occurrence of adverse drug reactions / infections.....	24
5.3	Occurrence of Adverse Drug Reactions / Infections by Severity, Onset Period, and Outcome	25
5.3.1	Occurrence of Adverse Drug Reactions / Infections by Severity, Onset Period, and Outcome	25
5.4	Patient Demographics and Frequency of Adverse Drug Reactions / Infections by Treatment	26
5.4.1	Patients demographics and Frequency of Adverse Drug Reactions / Infections by Treatment	26
5.5	Occurrence of Adverse Drug Reactions / Infections by Age.....	27
5.6	Occurrence of Adverse Drug Reactions / Infections by Sex.....	28
5.7	Occurrence of Adverse Drug Reactions / Infections by Liver Disorder	28
5.8	Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Renal Disorder.	28
5.9	Occurrence of Adverse Drug Reactions / Infections by Severity of Renal Impairment	29
5.10	Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Heart Disease...	29
5.11	Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Heart Failure....	29
5.12	Occurrence of Adverse Drug Reactions / Infections by Severity of Heart Failure.....	30
5.13	Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Stroke-related Disease	30
5.14	Occurrence of Adverse Drug Reactions / Infections by Mean Daily Dose of Nesina	30
5.15	Occurrence of Adverse Drug Reactions / Infections by Mean Daily Dose of Nesina in Patients with Special Demographics (Patients with Moderate or Higher Renal Impairment).....	31
5.16	Occurrence of Adverse Drug Reactions / Infections by Administration of Concomitant Medication	

(Diabetic Drug).....	31
5.17 Occurrence of Adverse Drug Reactions / Infections by Concomitant Medication (Diabetic Drug)	
31	
5.18 Occurrence of Adverse Drug Reactions / Infections by Presence of Concomitant Protease Inhibitors	32
5.19 Occurrence of Adverse Drug Reactions / Infections by Presence of Concomitant Renal Excretory Drug	32
5.20 Change in Laboratory/Measured Data.....	32
5.20.1 Vital Signs	32
5.20.2 Laboratory Values	33
6.0 Efficacy Tabulation and Analysis	34
6.1 Changes in HbA1c.....	34
6.2 Glycemic control achievement rate (HbA1c).....	34
6.3 Changes in Fasting blood glucose level and Fasting insulin level	34
6.4 Changes in HbA1c, etc. by Factor Probably Affecting Efficacy	35
6.5 Changes in HbA1c, etc. in Patients with Special Demographics	35

1.0 Definition of Terms and Handling of Laboratory/Measured Data

1.1 Definitions

Term	Definition
Nesina	Nesina tablet(s) is abbreviated as Nesina in this statistical analysis plan.
SOC	System Organ Class of MedDRA/J MedDRA/J version 20.1 is used for this document.
HLGT	High level group term of MedDRA/J
PT	Preferred term of MedDRA/J
LLT	Lowest level term of MedDRA/J
Registered patients	Patients whose registration was approved
Survey sheet (electronic) collected patients	Patients whose survey sheets were sent via CCI [REDACTED]
Survey sheet (electronic) uncollected patients	Of the registered patients, patients whose survey sheets (electronic) were uncollected.
Safety Analysis Set	Of the survey sheet (electronic) collected patients, patients who were evaluated for safety analysis. For tabulation, the description of “total” means the Safety Analysis Set.
Not Safety Analysis Set	Of the survey sheet (electronic) collected patients, patients who were excluded from safety analysis
Efficacy Analysis Set	Of the Safety Analysis Set, patients who were evaluated for efficacy analysis
Not Efficacy Analysis Set	Of the Safety Analysis Set, patients who were excluded from the efficacy analysis
First date of Nesina treatment	Of the start dates of the Nesina treatment period in patients, the earliest date is defined as the first date of Nesina treatment.
Last date of Nesina treatment	Of the last dates of the Nesina treatment period in patients, the latest date is defined as the last date of Nesina treatment. If Nesina treatment is continued and the year, month, and date of the continued treatment period are specified, the year, month, and date of the continued treatment period are defined as the last date of Nesina treatment. If the data for the year, month, and date of the continued treatment period are missing, the following date is defined as the last date of Nesina treatment. (1) First date of Nesina treatment + 3 years (same month and date), if Nesina treatment is continued based on the survey sheet (electronic) after 36 months of treatment* (2) For other than the above, the first date of Nesina treatment + 1 year (same month and date), if Nesina treatment is continued based on the survey sheet (electronic) after 12 months of treatment**

Term	Definition
	<p>For the continued treatment of Nesina, the following is considered as the “treatment to be continued:”</p> <ul style="list-style-type: none"> ● [End of Nesina tablet treatment] <ul style="list-style-type: none"> * If “No” for “Did you discontinue Nesina tablets by 12 to 36 months after the start of treatment?” ** If “No” for “Did you discontinue Nesina tablets by 12 months after the start of treatment?”
Adverse drug reactions, etc.	<p>Abbreviation of “adverse drug reactions / infections”</p> <p>Of the adverse events, events for which causal relationship to Nesina was assessed as “Not related” by the Investigator.</p> <p>In this statistical analysis plan, “adverse drug reactions / infections” is used in the headings, while “adverse drug reactions, etc.” is used in the sentences and tables.</p>
Serious adverse events	<p>Adverse events assessed as “serious” by the Investigator.</p> <p>Events described in the MedDRA coding list in the Takeda Medically Significant AE List will be handled as serious even if the Investigator assesses as “Not serious.”</p>
Serious adverse drug reactions	<p>Abbreviation of “serious adverse drug reactions / infections”</p> <p>Of the “serious adverse events,” the events for which causal relationship to Nesina was assessed as “Not related” by the Investigator</p>
Number of patients with events	Number of patients with adverse events or adverse drug reactions, etc.
Number of events	Number of adverse events or adverse drug reactions, etc.
Percent of patients with events	<p>[For safety analysis calculation in the Safety Analysis Set]</p> <p>The formula is: $\text{Number of patients with events} / \text{Number of Safety Analysis Set} \times 100$.</p> <p>[For safety analysis calculation in the Not Safety Analysis Set]</p> <p>The formula is: $\text{Number of patients with events} / \text{Number of Not Safety Analysis Set} \times 100$.</p>
Percent of events	<p>[For safety analysis calculation in the Safety Analysis Set]</p> <p>The formula is: $\text{Number of events} / \text{Number of the Safety Analysis Set} \times 100$.</p> <p>[For safety calculation in the Not Safety Analysis Set]</p> <p>The formula is: $\text{Number of events} / \text{Number of Not Safety Analysis Set} \times 100$.</p>
Onset period	<p>The formula is: Onset date of adverse events (or adverse drug reactions, etc.) – start date of Nesina treatment + 1.</p>

Term	Definition
	For unknown onset date of adverse events (or adverse drug reactions, etc.), the onset period will be calculated as 1 day. However, if the start month and date of Nesina treatment are same as the onset month and date of adverse events (or adverse drug reactions, etc.), the onset period will be calculated as the start date of Nesina treatment.
Mild type 2 diabetes mellitus	Patients who have type 2 diabetes mellitus with HbA1c (NGSP value) of \leq 7.4% at the start date of Nesina treatment
Patients with diabetic complication	Patients with any of the following complications: diabetic nephropathy, diabetic retinopathy, or diabetic neuropathy.
Patients with diabetic nephropathy	Patients with complication of PT Code 10012660 (diabetic end stage renal disease) or 10061835 (diabetic nephropathy).
Patients with diabetic retinopathy	Patients with complication of PT Code 10012688 (diabetic retinal oedema) or 10012689 (diabetic retinopathy).
Patients with diabetic neuropathy	Patients with complication of PT Code 10012645 (diabetic autonomic neuropathy), 10012676 (diabetic mononeuropathy), or 10012680 (diabetic neuropathy).
Patients with concurrent hypertension	Patients with concurrent disease of the Standardised MedDRA Query (hereinafter SMQ) Code 20000147 (hypertension (SMQ) narrow).
Patients with concurrent dyslipidemia	Patients with concurrent disease of the SMQ Code 20000026 (dyslipidaemia (SMQ) narrow).
Patients with concurrent hyperuricemia	Patients with concurrent disease of the PT code meeting the Takeda MedDRA Query 20.1 (hereinafter, TMQ 20.1) (blood uric acid increased).
Patients with concurrent liver disorder	Patients with concurrent disease of the SMQ Code 20000005 (hepatic disorders (narrow)).
Patients with concurrent hepatic steatosis	Patients with concurrent disease of the PT Code 10019708 (hepatic steatosis).
Patients with concurrent alcoholic hepatitis	Patients with concurrent disease of the PT Code 10019728 (hepatitis alcoholic).
Patients with concurrent chronic hepatitis	Patients with concurrent disease of the PT Code 10008909 (chronic hepatitis).
Patients with concurrent hepatic cirrhosis	Patients with concurrent disease of the PT Code 10019641 (hepatic cirrhosis).
Patients with concurrent renal disorder	Patients with concurrent disease of the TMQ 20.1 (renal disease).
Patients with concurrent nephrotic syndrome	Patients with concurrent disease of the PT Code 10029164 (nephrotic syndrome).
Patients with concurrent glomerulonephritis	Patients with concurrent disease of the PT Code 10018364 (glomerulonephritis) or the PT Code 10018367 (glomerulonephritis chronic).

Term	Definition
Patients with concurrent chronic renal failure	Patients with concurrent disease of the PT Code 10064848 (chronic kidney disease) or the PT Code 10038435 (renal failure).
Patients with concurrent heart disease	Patients with concurrent disease of the SOC Code 10007541 (cardiac disorders).
Patients with concurrent cardiac failure	Patients with concurrent disease of the SMQ Code 20000004 (cardiac failure (SMQ) narrow).
Patients with concurrent myocardial infarction	Patients with concurrent disease of the SMQ Code 20000047 (myocardial infarction (SMQ) narrow).
Patients with concurrent angina pectoris	Patients with concurrent disease of the SOC Code 10007541 (cardiac disorders) and the PT Code 10036759 (prinzmetal angina), PT Code 10002383 (angina pectoris), PT Code 10058144 (postinfarction angina), PT Code 10002388 (angina unstable), or LLT Code 10065566 (microvascular angina).
Patients with concurrent stroke-related disease	Patients with concurrent disease of cerebral infarction, cerebral haemorrhage, subarachnoid haemorrhage, or transient ischaemic attack, described below.
Patients with concurrent disease cerebral infarction	Patients with concurrent disease of the SOC Code 10029205 (nervous system disorders) and the PT Code 10006147 (brain stem infarction), PT Code 10008118 (cerebral infarction), PT Code 10008119 (cerebral infarction foetal), PT Code 10008034 (cerebellar infarction), PT Code 10019005 (haemorrhagic cerebral infarction), PT Code 10051078 (lacunar infarction), PT Code 10056237 (migrainous infarction), PT Code 10058571 (spinal cord infarction), PT Code 10060839 (embolic cerebral infarction), PT Code 10060840 (ischaemic cerebral infarction), PT Code 10064961 (thalamic infarction), PT Code 10067347 (thrombotic cerebral infarction), or PT Code 10069020 (basal ganglia infarction).
Patients with concurrent cerebral hemorrhage	Patients with concurrent disease of the SOC Code 10029205 (nervous system disorders) and the PT Code 10006145 (brain stem haemorrhage), PT Code 10008111 (cerebral haemorrhage), PT Code 10008112 (cerebral haemorrhage neonatal), PT Code 10008030 (cerebellar haemorrhage), PT Code 10018985 (haemorrhage intracranial), PT Code 10022840 (intraventricular haemorrhage), PT Code 10022841 (intraventricular haemorrhage neonatal), PT Code 10042365 (subdural haemorrhage neonatal), PT Code 10049236 (spinal epidural haemorrhage), PT Code 10048992 (spinal cord haemorrhage), PT Code 10050157 (cerebral haemorrhage foetal), PT Code 10052593 (meningorrhagia), PT Code 10058939 (thalamus haemorrhage), PT Code 10058940 (putamen haemorrhage), PT Code 10067057 (basal ganglia haemorrhage), PT Code 10067277 (cerebral microhaemorrhage), PT Code 10071205 (brain stem microhaemorrhage), PT Code 10071206 (cerebellar microhaemorrhage), PT Code 10072043 (central nervous system

Term	Definition
	haemorrhage), or PT Code 10073563 (Spinal subdural haemorrhage).
Patients with concurrent subarachnoid hemorrhage	Patients with concurrent disease of the PT Code 10042316 (subarachnoid haemorrhage), PT Code 10042317 (subarachnoid haemorrhage neonatal), PT Code 10073564 (spinal subarachnoid haemorrhage), LLT Code 10072201 (Asymptomatic subarachnoid haemorrhage).
Patients with concurrent transient ischemic attack	Patients with concurrent disease of the SOC Code 10029205 (nervous system disorders) and the PT Code 10044390 (transient ischaemic attack).
Patients with concurrent allergic disease	Patients with concurrent disease of bronchial asthma, pollinosis, allergic rhinitis, or allergic dermatitis, described below.
Patients with concurrent bronchial asthma	Patients with concurrent disease of the SOC Code 10038738 (respiratory, thoracic and mediastinal disorders) and the PT Code 10003553 (asthma), PT Code 10075084 (aspirin-exacerbated respiratory disease), PT Code 10003557 (asthma exercise induced), PT Code 10003559 (asthma late onset), PT Code 10041961 (status asthmaticus), PT Code 10001890 (alveolitis allergic), PT Code 10049585 (infantile asthma), PT Code 10070836 (occupational asthma), or PT Code 10064823 (asthmatic crisis).
Patients with concurrent pollinosis	Patients with concurrent disease of the PT Code 10048908 (seasonal allergy).
Patients with concurrent allergic rhinitis	Patients with concurrent disease of the PT Code 10039085 (rhinitis allergic).
Patients with concurrent allergic dermatitis	Patients with concurrent disease of the PT Code 10012434 (dermatitis allergic).
Patients with concurrent malignant tumor	Patients with concurrent disease of the SOC Code 10029104 (neoplasms benign, malignant and unspecified (incl cysts and polyps)).
Patients with concurrent malignant tumor (narrow sense)	Patients with concurrent disease of the SMQ Code 20000194 (malignant tumour (SMQ) narrow).
Patients with other concurrent disease	Patients with concurrent disease other than the above (diabetic complication, hypertension, dyslipidaemia, hyperuricaemia, liver disease, renal disease, heart disease, stroke-related disease, allergic disease, malignant tumor, or malignant tumor (narrow sense)).
Severity of renal impairment	Severity of renal impairment in the patient demographic section

Term	Definition
Age	If the start month and date of Nesina treatment is earlier than the birth month and date, calculate using the following formula: Start year of Nesina treatment – birth year – 1. If the birth month and date is earlier than or equal to the start month and date of Nesina treatment, calculate using the following formula: Start year of Nesina treatment – birth year. For unknown birth date, the birth date will be calculated as the 1st day of the birth month.
BMI	Calculate using the following formula: Weight (kg) / (0.0001 × Height (cm) × Height (cm)). Indicate to one decimal place rounded from two decimals.
Disease duration of type 2 diabetes mellitus (year)	Calculate using the following formula: (start date of Nesina treatment – diagnosis period of type 2 diabetes mellitus + 1) / 365.25. For unknown diagnosis month, calculate as January. Indicate to one decimal place rounded from two decimals.
Prior medication	Medications that patients were taking within 3 months before initiation of Nesina therapy.
Concomitant medication	Medications that patients were taking after the start date of Nesina treatment.
Start date of other diabetic drug and concomitant medication (other than diabetic drug)	Calculate as the start date of survey sheet (electronic).
End date of other diabetic drug and concomitant medication (other than diabetic drug)	Calculate as the end date of survey sheet (electronic).
Diabetic drugs	Drugs of the National Health Insurance (NHI) Drug List Code starting with 3969, 3961, 3962, 2492, 2499410, 2499411, 2499415, or 2499416.
α-glucosidase inhibitors	Drugs of the NHI Drug List Code starting with 3969003, 3969004, 3969009, or 3969102.
Thiazolidines	Drugs of the NHI Drug List Code starting with 3969005, 3969007, 3969100, 3969101, or 3969103.
Sulfonylureas	Drugs of the NHI Drug List Code starting with 3961 or 3969101.
Biguanides	Drugs of the NHI Drug List Code starting with 3962, 3969100, 3969104, or 3969105.
Rapid-acting insulin secretagogues	Drugs of the NHI Drug List Code starting with 3969006, 3969008, 3969013, or 3969102.
Insulin preparations	Drugs of the NHI Drug List Code starting with 2492.
DPP-4 inhibitors	Drugs of the NHI Drug List Code starting with 3969010, 3969011, 3969012, 3969014, 3969015, 3969016, 3969017, 3969024, 3969025, 3969103, 3969104, or 3969105.

Term	Definition
GLP-1 receptor agonists	Drugs of the NHI Drug List Code starting with 2499410, 2499411, 2499415, or 2499416.
SGLT2 inhibitors	Drugs of the NHI Drug List Code starting with 3969018, 3969019, 3969020, 3969021, 3969022, or 3969023.
Combination of diabetic drugs	Drugs of the NHI Drug List Code starting with 3969100, 3969101, 3969102, 3969103, 3969104, or 3969105.
Other diabetic drugs	Other diabetic drugs not classified into the above diabetic drug categories (α -glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, insulin preparations, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, or combination of diabetic drugs).
Hypertension drugs	<p>ARB Drugs of the NHI Drug List Code starting with the following 7 numbers: 2149039, 2149040, 2149041, 2149042, 2149044, 2149046, 2149048, 2149100, 2149110, 2149111, 2149112, 2149113, 2149114, 2149115, 2149116, 2149117, 2149118, 2149119, 2149120, 2149121, 2149122</p> <p>Ca antagonists Drugs of the NHI Drug List Code starting with the following numbers: 2149019, 2149022, 2149027, 2149030, 2149034, 2149035, 2149037, 2149038, 2149043, 2149400, 2171006, 2171014, 2171019, 2171020, 2171021, 2171022, 2171405, 2190001, 2149114, 2149115, 2149116, 2149117, 2149118, 2149120, 2149121, 2149122, 2190101, 2190102, 2190103, 2190104</p> <p>ACE inhibitors Drugs of the NHI Drug List Code starting with the following 4 numbers: 2144</p> <p>Diuretics Drugs of the NHI Drug List Code starting with numbers 213 or the following 7 numbers: 2149003, 2149007, 2149012, 2149110, 2149111, 2149112, 2149113, 2149119, 2149122</p> <p>α blockers Drugs of the NHI Drug List Code starting with the following numbers: 1234400, 214200210, 2149002, 2149015, 2149023, 2149026, 1152, 1149107, 1149114, 1149115, 2531001, 2149020</p> <p>$\alpha\beta/\beta$ blockers Drugs of the NHI Drug List Code starting with the following numbers: 2149032, 2149018, 2123014, 2149009, 2123013, 2123003, 2149008, 2149016, 2442001, 2123011, 2149036, 2123016, 2149700, 2149031, 2149010, 2123001, 2123F01, 2149029, 2123008, 2149014, 2149021,</p>

Term	Definition
	2149028, 2123015, 2123005, 2149025, 2123009, 2123403, 2149033, 2149011 Complication of hypertension drugs Drugs of the NHI Drug List Code starting with the following numbers: 2149110, 2149111, 2149112, 2149113, 2149114, 2149115, 2149116, 2149117, 2149118, 2149119, 2149120, 2149121, 2149122 Other Drugs of the NHI Drug List Code starting with the following numbers: 2149047, 2142004, 2149001, 2149017, 2145
Dyslipidaemia drugs	Statins Drugs of the NHI Drug List Code starting with the following numbers: 2189010, 2189011, 2189012, 2189013, 2189015, 2189016, 2189017, 2190101, 2190102, 2190103, 2190104 Fibrates Drugs of the NHI Drug List Code starting with the following numbers: 2183001, 2183002, 2183003, 2183004, 2183005, 2183006 EPA/DHA Drugs of the NHI Drug List Code starting with the following numbers: 2189019, 3399004 Other Drugs of the NHI Drug List Code starting with the following numbers: Dugs, other than the above, of the NHI Drug List Code starting with 218, 2900002, or 3133001.
Concomitant medication (other)	Drugs other than the above (diabetic drugs, hypertension drugs, or dyslipidaemia drugs).
Protease Inhibitor	Use the results of the drug name in the survey sheet (electronic) coded with the NHI Drug List (Appendix 1. List of Protease Inhibitors).
Renal excretory drugs	Use the results of the drug name in the survey sheet (electronic) coded with the NHI Drug List (Appendix 2. List of Renal Excretory Drugs).
Nesina treatment period (days)	Actual treatment period from the start date to the end date of Nesina treatment. However, the washout period is excluded from the treatment period. Calculate using the following formula: End of Nesina treatment – start date of Nesina treatment + 1 (grand total). (Consider the washout period.)
Mean daily dose of Nesina	Calculate using the following formula: Total of “daily dose of Nesina × Nesina treatment period at the relevant dose” / Nesina treatment period. For the calculation of Nesina treatment period, refer to the above. If the daily dose of Nesina is a number outside specification in the survey sheet (electronic) and is actual number, use the relevant number.

Term	Definition
HbA1c (NGSP value)	<p>The NGSP value only will be used in this analysis.</p> <p>For the HbA1c (JDS value), calculate using the following formula: $\text{NGSP value (\%)} = 1.02 \times \text{JDS value (\%)} + 0.25\%$ </p> <p>The HbA1c (international standard value) will be handled as the NGSP value.</p>
Change in HbA1c	<p>For HbA1c converted to the NGSP value, calculate using the following formula: Laboratory value – Laboratory value at the start of Nesina treatment.</p>
Glycemic control achievement rate	<p>Divide the following two categories for the Glycemic control achievement rate:</p> <p>HbA1c (NGSP converted value) [Unit %] NGSP (%): < 6.0, ≥6.0 / < 7.0, ≥ 7.0</p>
non-HDL cholesterol	<p>Calculate using the following formula: “Total cholesterol” – “HDL cholesterol.”</p>
Summary statistics	<p>Number of patients, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum.</p>

1.2 Important Identified Risks, Potential Risks, and Missing Information

Term	Definition
Important identified risk	
Hypoglycemia	Adverse events of the following PT Codes (term) are defined as hypoglycemia. 10020994(Hypoglycaemia neonatal) 10040576(Shock hypoglycaemic) 10021000(Hypoglycaemic coma) 10020993(Hypoglycaemia) 10065981(Hypoglycaemic unconsciousness) 10021002(Hypoglycaemic encephalopathy) 10048803(Hypoglycaemic seizure) 10020997(Hypoglycaemia unawareness) 10077216(Hyperinsulinaemic hypoglycaemia) 10059035(Postprandial hypoglycaemia)
Acute pancreatitis	Adverse events of the SMQ Code 20000022 (acute pancreatitis (SMQ) narrow scope are defined as acute pancreatitis.
Hepatic impairment / jaundice	Adverse events of the SMQ Code 20000005 (hepatic disorders (SMQ) broad) are defined as hepatic impairment / jaundice.
Skin disorder including oculomucocutaneous syndrome (Stevens-Johnson syndrome) / erythema multiforme	Adverse events of the SMQ Code 20000020 (severe skin adverse reactions (SMQ) narrow) are defined as skin disorder including oculomucocutaneous syndrome (Stevens-Johnson syndrome) / erythema multiforme.
Rhabdomyolysis	Adverse events of the SMQ Code 20000002 (rhabdomyolysis/myopathy (SMQ) narrow) are defined as rhabdomyolysis.
Intestinal obstruction	Adverse events of the SMQ Code 20000105 (gastrointestinal obstruction (SMQ) narrow) or the HLGT Code 10018008 (gastrointestinal stenosis and obstruction) or HLT Code 10052736 (non-mechanical ileus) are defined as intestinal obstruction.
Interstitial pneumonia	Adverse events of the SMQ Code 20000042 (interstitial lung disease (SMQ) narrow) are defined as interstitial pneumonia.
Angioedema	Adverse events of the SMQ Code 20000024 (angioedema (SMQ) narrow) are defined as angioedema.
Important potential risk	
Infection	Adverse events of SOC Code 10021881(infections and infestations) are defined as infection.
Malignant tumor	Adverse events of the SOC Code 10029104 (neoplasms benign, malignant and unspecified (incl cysts and polyps)) are defined as malignant tumor.
Malignant tumor (narrow)	Adverse events of the SMQ Code 20000194 (malignant tumors (SMQ)

Term	Definition
sense)	narrow) are defined as malignant tumor (narrow sense).
Pemphigoid	Adverse events of the PT Code 10067776 (ocular pemphigoid) or 10034277 (pemphigoid) are defined as pemphigoid.

Term	Definition
Important missing information	
Cardiovascular system risk	<p>Adverse events of the SMQ Code 20000047 (myocardial infarction (SMQ) broad) or SMQ Code 20000061 (central nervous system haemorrhages and cerebrovascular conditions (SMQ) broad) are defined as cardiovascular system risk.</p> <p>“Central nervous system haemorrhage and cerebrovascular conditions (SMQ) broad” includes the following SMQ classes.</p> <ul style="list-style-type: none"> ➤ 20000166(Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ) broad) ➤ 20000064(Cerebrovascular disorder haemorrhagic (SMQ) broad) ➤ 20000063(Cerebrovascular disease ischaemic (SMQ) broad)

1.3 Display digit

Term	Definition
Percentage (%)	<p>Percent of patients with adverse events or adverse drug reactions, etc. or percent of adverse events or adverse drug reactions, etc. :</p> <p>Indicate to two decimal places rounded from three decimals.</p> <p>Other than the above:</p> <p>Indicate to one decimal place rounded from two decimals.</p>
Summary statistics	<p>Mean, median, first quartile, and third quartile:</p> <p>Indicate one lower digit rounded from two lower digits than the digit of the to-be evaluated data.</p> <p>Standard deviation:</p> <p>Indicate two lower digits rounded from three lower digits of the to-be evaluated data.</p> <p>Minimum and maximum</p> <p>Indicate the same digit number as that of the to-be evaluated data (refer to Section 1.6).</p>
p-value	Indicate to three decimal places rounded down from four decimals.

Term	Definition
	If the data is rounded down from four decimal places and less than 0.001, display as $p < 0.001$.

1.4 Level of Significance and Confidence Coefficient

Two-sided 5%, two-sided 95%.

1.5 Handling of Laboratory/Measured Data

- VISIT as described in the survey sheet will be used for data other than 12 months and 36 months after Nesina treatment.
- 12 months after Nesina treatment: data at 12 months after Nesina treatment will be used for the 12 months survey sheet (electronic) for patients who continued treatment.
For patients who discontinued treatment, data at 12 months after Nesina treatment will not be used for the 12 months survey sheet (electronic).
- 36 months after Nesina treatment: data at 36 months after Nesina treatment will be used for the 36 months survey sheet (electronic) for patients who continued treatment.
For patients who discontinued treatment, data at 36 months after Nesina treatment will not be used for the 36 months survey sheet (electronic).
- At the last evaluation: The last VISIT data within the evaluation period will be used.

1.6 Display Data Digit

Display digits are described as below.

Term	Display digit	Unit
HbA1c	0.1	%
Fasting blood glucose level	1	mg/dL
Fasting insulin level	0.1	μU/mL
Fasting triglyceride	1	mg/dL
Total cholesterol	1	mg/dL
HDL-cholesterol	1	mg/dL
LDL-cholesterol	1	mg/dL
Non-HDL cholesterol	1	mg/dL
Systolic blood pressure	1	mmHg
Diastolic blood pressure	1	mmHg
Weight	0.1	kg
BMI	0.1	kg/m ²
Age	1	Year
Disease duration of type 2 diabetes mellitus	0.1	Year
Height	1	cm
Week of pregnancy	1	Week
Nesina treatment period	1	Day
Mean daily dose of Nesina	0.01	mg

2.0 Disposition of Patients (Patient Diagram)

(1) Patients to be tabulated and analyzed

Registered patients

(2) Details of tabulation and analysis

The following will be tabulated: the number of registered patients, number of medical site at which patients is registered, number of patients whose survey sheets (electronic) are collected, number of patients whose survey sheets (electronic) are not collected, number of patients in the Safety Analysis Set, number of patients in the Not Safety Analysis Set, number of patients in the Efficacy Analysis Set, and number of patients in the Not Efficacy Analysis Set.

For the number of medical sites at which patients are registered, do not duplicate the same medical site with different departments.

For patients whose survey sheets (electronic) are not collected, tabulate the number of patients for each reason for not collected survey sheets.

For the Not Safety Analysis Set and Not Efficacy Analysis Set, the number of patients will be tabulated for each reason for exclusion to create the list.

The following is the handling of the decision whether patients who meet the following criteria should be evaluated:

Criterion	Safety evaluation	Efficacy evaluation
Pre-agreement administration [found after administration]	×	×
Registration 15 days after the start of Nesina treatment [found after registration]	×	×
Nesina taking not confirmed [after the end of patient registration period]	×	×
No data for post-administration of Nesina	×	×
Data reliability was not confirmed	×	×
Other than patients with mild type 2 diabetes mellitus	○	×

○ Included, × Excluded or not evaluated

(3) Number of tables and figures

Figure 2.0-1 and Table 2.0-1

3.0 Patient Demographics

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Each parameter will be classified by the categories described below to tabulate the number of patients and frequency.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Category
Sex	Male, Female
Age	Summary statistics
	< 65 years, ≥ 65 years
	< 75 years, ≥ 75 years
	< 20 years, 20 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, 70 to 79 years, ≥ 80 years
Disease duration of type 2 diabetes mellitus (year)	Summary statistics
	< 2 years, 2 to < 5 years, 5 to < 10 years, ≥ 10 years, Unknown
Height	Summary statistics
Category of clinical practice	Outpatient, Inpatient
Pregnancy (only females)	No, Yes
Severity of renal impairment	Normal, Mild, Moderate, Severe
	Normal + Mild, Moderate + Severe
Concurrent disease	No, Yes
Diabetic complication	No, Yes
Details of diabetic complication (overlapped)	Diabetic nephropathy, diabetic retinopathy, diabetic neuropathy For the proportion, the number of patients with diabetic complication will be denominator.
Concurrent hypertension	No, Yes
Concurrent dyslipidemia	No, Yes
Concurrent hyperuricemia	No, Yes
Concurrent liver disorder	No, Yes
Details of concurrent	Hepatic steatosis, alcoholic hepatitis, chronic hepatitis, hepatic

Parameter	Category
liver disorder (overlapped)	cirrhosis, or other For the proportion, the number of with concurrent liver disorder will be denominator.
Concurrent renal disorder	No, Yes
Details of concurrent renal disorder (overlapped)	Nephrotic syndrome, glomerulonephritis, chronic glomerulonephritis, other For the proportion, the number of with concurrent renal disorder will be denominator.
Concurrent heart disease	No, Yes
Details of concurrent heart disease (overlapped)	Cardiac failure, myocardial infarction, angina pectoris, other For the proportion, the number of with concurrent heart disease will be denominator.
Concurrent cardiac failure	No, Yes
Severity classification of cardiac failure (NYHA classification)	Classes NYHA I, NYHA II, NYHA III, and NYHA IV, Unknown For the proportion, the number of with concurrent cardiac failure will be denominator.
Concurrent stroke-related disease	No, Yes
Details of concurrent stroke-related disease (overlapped)	Cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, transient ischaemic attack For the proportion, the number of with concurrent stroke-related disease will be denominator.
Concurrent allergic disease	No, Yes
Concurrent malignant tumour	No, Yes
Concurrent malignant tumour (narrow sense)	No, Yes
Other concurrent disease	No, Yes
Past medical history	No, Yes, Unknown
Hypersensitivity predisposition	No, Yes, Unknown
Alcohol history (drinking alcoholic)	Yes, No, Unknown

Parameter	Category
drinks almost on a daily basis)	
Smoking history	Never, Smoking, Smoked, Unknown
HbA1c(NGSP value) (at the start of Nesina treatment)	Summary statistics < 6.0%, 6.0% to < 7.0%, 7.0% to < 8.0%, ≥ 8.0%, Unknown ≥7.4%, > 7.4%, Unknown
Weight	Summary statistics
BMI	Summary statistics < 18.5 kg/m ² , 18.5 to < 25 kg/m ² , 25 to < 30 kg/m ² , ≥ 30 kg/m ² , Unknown < 25 kg/m ² , ≥25 kg/m ² , Unknown
Dietary intervention (at the start of Nesina treatment)	Yes, No
Exercise intervention (at the start of Nesina treatment)	Yes, No

(3) Number of tables and figures

Table 3.0-1

4.0 Details of Treatment

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Each parameter will be classified by the categories described below to tabulate the number of patients and frequency.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Category
Initial dose of Nesina	25 mg, 12.5 mg, 6.25 mg, or other
Mean daily dose of Nesina	> 25 mg, 25 to >12.5 mg, 12.5 to > 6.25 mg, or ≤6.25 mg
Nesina treatment period	Summary statistics
Administration of prior medication (diabetic drug)	No, Yes
Prior medications (diabetic drugs)	<p>α-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, insulin preparations, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, combination of diabetic drugs, or other diabetic drugs</p> <p>For the proportion, the number of patients with “Yes” for administration of prior medication (diabetic drug) will be denominator.</p>
Administration of prior medication (other than diabetic drug)	No, Yes
Administration of concomitant medication (diabetic drug)	No, Yes
Concomitant medications (diabetic drugs) (overlapped)	<p>α-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, shortrapid-acting insulin secretagogues, insulin preparations, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, combination of diabetic drugs, or other diabetic drugs</p> <p>For the proportion, the number of patients with “Yes” for administration of concomitant medication (diabetic drug) will be denominator.</p>
Administration of concomitant medication	No, Yes

Parameter	Category
(hypertension drug)	
Concomitant medications (hypertension drugs) (overlapped)	ARB, Ca antagonists, ACE inhibitors, diuretics, α blockers, $\alpha\beta/\beta$ blockers, Complication of hypertension drugs, or other For the proportion, the number of patients with “Yes” for administration of concomitant medication (hypertension drug) will be denominator.
Administration of concomitant medication (dyslipidaemia drug)	No, Yes
Concomitant medications (dyslipidaemia drugs) (overlapped)	Statins, fibrates, EPA/DHA, or other For the proportion, the number of patients with “Yes” for administration of concomitant medication (dyslipidaemia drug) will be denominator.
Administration of concomitant medication (protease drug)	No, Yes
Administration of concomitant medication (combined with renal excretory drug)	No, Yes
Administration of concomitant medication (other)	No, Yes

(3) Number of tables and figures

Table 4.0-1

4.1 Initial Dose of Nesina and Mean Daily Dose of Nesina, by Severity of Renal Impairment

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Cross tabulation will be used for the initial dose of Nesina and the mean daily dose of Nesina, by severity of renal impairment.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Category
Severity of renal impairment	Normal, Mild, Moderate, Severe

Parameter	Category
	Normal + Mild, Moderate + Severe
Initial dose of Nesina	25 mg, 12.5 mg, 6.25 mg, or other
Mean daily dose of Nesina	> 25 mg, 25 to >12.5 mg, 12.5 to > 6.25 mg, or \leq 6.25 mg

(3) Number of tables and figures

Tables 4.1-1 and 4.1-2

5.0 Safety Tabulation and Analysis

5.1 Occurrence of adverse events and adverse drug reactions / infections

5.1.1 Occurrence of adverse events

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

The following will be tabulated for adverse events.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Details of analysis
Number of patients with adverse events	Number of patients who experienced adverse events.
Number of adverse events	Number of adverse events. Count as an event if the same adverse event (LLT) occur multiple times in a patient. Count as different events for different LLTs even if they have the same PT.
Percent of patients with adverse events	Described in Section 1.1.
Type of adverse events	Will be broadly divided into the SOCs and tabulated by PT in the SOCs. In case of the laboratory test-related events, type of adverse events will be broadly divided into the SOCs and HLGTs for tabulation by PT. For the SOCs, the number of patients with adverse events and percent of patients with events will be described in the order of SOCs agreed internationally. For the PTs, the number of adverse events and percent of events will be described in the ascending order of PT codes. Count as an event if the same adverse event (LLT) occur multiple times in a patient. Count as different events for different LLTs even if they have the same PT.

(3) Number of tables and figures

Table 5.1.1-1

5.1.2 Occurrence of adverse drug reactions / infections

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

The following will be tabulated for adverse drug reactions, etc. and serious adverse drug reactions, etc.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Details of tabulation and analysis
Number of patients with adverse drug reactions, etc.	Number of patients who experienced adverse drug reactions, etc.
Number of adverse drug reactions, etc.	Number of adverse drug reactions, etc. Count as an event if the same adverse drug reactions, etc. (LLT) occur multiple times in a patient. Count as different events for different LLTs even though they have the same PT.
Percent of patients with adverse drug reactions, etc.	Described in Section 1.1.
Type of adverse drug reactions, etc.	Will be broadly divided into the SOCs and tabulated by PT in the SOCs. In case of the laboratory test-related events, type of adverse events will be broadly divided into the SOCs and HLGTS for tabulation by PT. For the SOCs, the number of patients with adverse drug reactions, etc. and percent of patients with adverse drug reactions, etc. will be described in the order of SOCs agreed internationally. For the PTs, the number of adverse drug reactions, etc. and percent of adverse drug reactions, etc. will be described in the ascending order of PT codes. Count as an event if the same adverse drug reactions, etc. (LLT) occur multiple times in a patient. Count as different events for different LLTs even though they have the same PT.

- (3) Number of tables and figures
Tables 5.1.2-1 and 5.1.2-2

5.1.3 Important Identified Risks, Important Potential Risks, and Important Missing Information

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

The following will be tabulated for important identified risks, important potential risks, and important missing information (described in Section 1.2).

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Details of tabulation and analysis
Number of patients with adverse events (or adverse drug reactions, etc.)	Number of patients who experienced adverse events (or adverse drug reactions, etc.) with important identified risks, important potential risks, and important missing information.

Parameter	Details of tabulation and analysis
Number of adverse events (or adverse drug reactions, etc.)	Number of adverse events (or adverse drug reactions, etc.) with important identified risks, important potential risks, and important missing information. Count as an event if the same adverse event (or adverse drug reaction, etc.) (LLT) occur multiple times in a patient. Count as different events for different LLTs even if they have the same PT.
Percent of patients with adverse events (or adverse drug reactions, etc.)	Described in Section 1.1.
Type of adverse events (or adverse drug reactions, etc.)	Will be broadly divided into the important identified risks, important potential risks, and important missing information and tabulated by PT in them. For the PTs, the number of adverse events (or adverse drug reactions, etc.) and percent of adverse events (or adverse drug reactions, etc.) will be described in the ascending order of PT codes. Count as an event if the same adverse event (or adverse drug reaction, etc.) (LLT) occur multiple times in a patient. Count as different events for different LLTs even though they have the same PT.

- (3) Number of tables and figures
Tables 5.1.3-1 and 5.1.3-2

5.2 Occurrence of Adverse Events and Adverse Drug Reactions / Infections in the Not Safety Analysis

Set

5.2.1 Occurrence of Adverse Events

- (1) Patients to be tabulated and analyzed

Not Safety Analysis Set

- (2) Details of tabulation and analysis

The following will be tabulated.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Details of tabulation and analysis
Number of patients with adverse events	Number of patients who experienced adverse events.
Number of adverse events	Number of adverse events. Count as an event if the same adverse event (LLT) occur multiple times in a patient.

Parameter	Details of tabulation and analysis
	Count as different events for different LLTs even if they have the same PT.
Percent of patients with adverse events	Described in Section 1.1.
Type of adverse events	<p>Will be broadly divided into the SOCs and tabulated by PT in the SOCs. In case of the laboratory test-related events, type of adverse events will be broadly divided into the SOCs and HLGTS for tabulation by PT.</p> <p>For the SOCs, the number of patients with adverse events and percent of patients with events will be described in the order of SOCs agreed internationally.</p> <p>For the PTs, the number of adverse events and percent of events will be described in the ascending order of PT codes. Count as an event if the same adverse event (LLT) occur multiple times in a patient. Count as different events for different LLTs even though they have the same PT.</p>

(3) Number of tables and figures

Table 5.2-1

5.2.2 Occurrence of adverse drug reactions / infections

(1) Patients to be tabulated and analyzed

Not Safety Analysis Set

(2) Details of tabulation and analysis

The following will be tabulated.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Details of tabulation and analysis
Number of patients with adverse drug reactions, etc.	Number of patients who experienced adverse drug reactions, etc.
Number of adverse drug reactions, etc.	<p>Number of adverse drug reactions, etc. Count as an event if the same adverse drug reactions, etc. (LLT) occur multiple times in a patient.</p> <p>Count as different events for different LLTs even if they have the same PT.</p>
Percent of patients with adverse drug reactions, etc.	Described in Section 1.1.
Type of adverse drug reactions, etc.	Will be broadly divided into the SOCs and tabulated by PT in the SOCs. In case of the laboratory test-related events, type of adverse

	<p>events will be broadly divided into the SOCs and HLGs for tabulation by PT.</p> <p>For the SOCs, the number of patients with adverse drug reactions, etc. and percent of patients with adverse drug reactions, etc. will be described in the order of SOCs agreed internationally.</p> <p>For the PTs, the number of adverse drug reactions, etc. and percent of adverse drug reactions, etc. will be described in the ascending order of PT codes. Count as an event if the same adverse drug reactions, etc. (LLT) occur multiple times in a patient. Count as different events for different LLTs even though they have the same PT.</p>
--	--

(3) Number of tables and figures

Table 5.2-2

5.3 Occurrence of Adverse Drug Reactions / Infections by Severity, Onset Period, and Outcome

5.3.1 Occurrence of Adverse Drug Reactions / Infections by Severity, Onset Period, and Outcome

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Each parameter will be categorized by the categories described below to tabulate the type of adverse drug reactions, etc.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Category
Severity	Serious, Not serious
Onset period	1 to 14 days, 15 to 28 days, 29 to 84 days, 85 to 168 days, 169 to 336 days, 337 to 504 days, 505 to 672 days, 673 to 840 days, 841 to 1008 days, ≥ 1009 days, or Unknown
Outcome	Resolved, Resolving, Not resolved, Resolved with sequelae, Death, or Unknown

The method for tabulation of type adverse drug reactions, etc. is described below:

Parameter	Details of tabulation and analysis
Type of adverse drug reactions, etc.	<p>Will be broadly divided into the SOCs and tabulated by PT in the SOCs. In case of the laboratory test-related events, type of adverse events will be broadly divided into the SOCs and HLGs for tabulation by PT.</p> <p>For the SOCs, the number of patients with adverse drug reactions, etc. will be described in the order of SOCs agreed internationally.</p> <p>For the PTs, the number of adverse drug reactions, etc. will be</p>

Parameter	Details of tabulation and analysis
	<p>described in the ascending order of PT codes. Count as an event if the same adverse drug reactions, etc. (LLT) occur multiple times in a patient. Count as different events for different LLTs even if they have the same PT. However, evaluate an event for the same LLT in accordance with the following order of priority:</p> <p>Onset period: earlier event</p> <p>Severity: Serious → Not serious</p> <p>Outcome: Death → Resolved with Sequelae → Not resolved → Resolving → Resolved → Unknown</p>

(3) Number of tables and figures

Tables 5.3-1 to 5.3-3

5.4 Patient Demographics and Frequency of Adverse Drug Reactions / Infections by Treatment

5.4.1 Patients demographics and Frequency of Adverse Drug Reactions / Infections by Treatment

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Each parameter will be categorized by the categories described below to tabulate the percent of patients with adverse drug reactions, etc.

The Fischer exact test will be used for parameters without rank data. The Mann-Whitney U test will be used for parameters with rank data. (The tests will be used for parameters with asterisk [*].)

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Category
Sex*	Male, Female
Age*	< 65 years, ≥65 years
	< 75 years, ≥75 years
Severity of renal impairment*	Normal + Mild, Moderate + Severe
Concurrent liver disorder*	No, Yes
Concurrent renal disorder*	No, Yes
Concurrent heart disease*	No, Yes
Details of concurrent heart disease	Cardiac failure, myocardial infarction, or angina pectoris

Parameter	Category
(overlapped)	
Concurrent cardiac failure*	No, Yes
Severity classification of cardiac failure (NYHA classification)*	Classes NYHA I, NYHA II, NYHA III, and NYHA IV
Concurrent stroke-related disease*	No, Yes
Mean daily dose of Nesina	> 25 mg, 25 to >12.5 mg, 12.5 to > 6.25 mg, or ≤6.25 mg
Administration of concomitant medication (diabetic drug)	No, Yes
Concomitant medications (diabetic drugs) (overlapped)	α-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, or insulin preparations
Administration of concomitant medication (protease drug)*	No, Yes
Administration of concomitant medication (combined with renal excretory drug)*	No, Yes

(3) Number of tables and figures

Table 5.4.1-1

5.5 Occurrence of Adverse Drug Reactions / Infections by Age

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Age will be classified into < 65 years, ≥65 years and < 75 years, and ≥75 years for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Tables 5.5-1 to 5.5-2

5.6 Occurrence of Adverse Drug Reactions / Infections by Sex

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Sex will be classified into male or female for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.6-1

5.7 Occurrence of Adverse Drug Reactions / Infections by Liver Disorder

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Concurrent liver disorder will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.7-1

5.8 Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Renal Disorder

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Concurrent renal disorder will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.8-1

5.9 Occurrence of Adverse Drug Reactions / Infections by Severity of Renal Impairment

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

Severity of renal impairment will be classified into normal + mild or moderate + severe for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.9-1

5.10 Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Heart Disease

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

Concurrent heart disease will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.10-1

5.11 Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Heart Failure

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

Concurrent heart failure will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.11-1

5.12 Occurrence of Adverse Drug Reactions / Infections by Severity of Heart Failure

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

Severity of heart failure will be classified into Class NYHA I, NYHA II, NYHA III, or NYHA IV for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.12-1

5.13 Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Stroke-related Disease

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

Concurrent stroke-related disease will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.13-1

5.14 Occurrence of Adverse Drug Reactions / Infections by Mean Daily Dose of Nesina

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

The mean daily dose of Nesina will be classified into > 25 mg, 25 to > 12.5 mg, 12.5 to > 6.25 mg, or ≤6.25 mg for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.14-1

5.15 Occurrence of Adverse Drug Reactions / Infections by Mean Daily Dose of Nesina in Patients with Special Demographics (Patients with Moderate or Higher Renal Impairment)

(1) Patients to be tabulated and analyzed

Patients with moderate or higher renal impairment in the Safety Analysis Set

(2) Details of tabulation and analysis

The mean daily dose of Nesina will be classified into > 25 mg, 25 to > 12.5 mg, 12.5 to > 6.25 mg, or ≤6.25 mg for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.15-1

5.16 Occurrence of Adverse Drug Reactions / Infections by Administration of Concomitant Medication (Diabetic Drug)

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Administration of concomitant medication (diabetic drug) will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.16-1

5.17 Occurrence of Adverse Drug Reactions / Infections by Concomitant Medication (Diabetic Drug)

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Concomitant medications (diabetic drugs) will be classified into the following drugs: α -glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, or insulin preparations, for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.17-1

5.18 Occurrence of Adverse Drug Reactions / Infections by Presence of Concomitant Protease Inhibitors

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

Concomitant protease inhibitor will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.18-1

5.19 Occurrence of Adverse Drug Reactions / Infections by Presence of Concomitant Renal Excretory

Drug

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

Concomitant renal excretory drug be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.19-1

5.20 Change in Laboratory/Measured Data

5.20.1 Vital Signs

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

For blood pressure (systolic/diastolic) and weight, summary statistics will be calculated at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation). For changes from the start of Nesina treatment, summary statistics and the mean 95% confidence intervals will be calculated.

Measured values (mean and standard deviation) of blood pressure (systolic/diastolic) and weight will be plotted. For the changes, the mean changes will be created using a bar graph.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.20.1-1 and Figures 5.20.1-1 to 5.20.1-6

5.20.2 Laboratory Values

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

For laboratory values of fasting triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, and non-HDL cholesterol, summary statistics will be calculated at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation). For changes from the start of Nesina treatment, summary statistics and the mean 95% confidence intervals will be calculated.

The individual laboratory values described above (mean and standard deviation) will be plotted.

For the changes, the mean changes will be created using a bar graph.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.20.2-1 and Figures 5.20.2-1 to 5.20.2-10

6.0 Efficacy Tabulation and Analysis

6.1 Changes in HbA1c

(1) Patients to be tabulated and analyzed

Efficacy Analysis Set

(2) Details of tabulation and analysis

For HbA1c (NGSP values), summary statistics will be calculated at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation). For changes, summary statistics and the mean 95% confidence intervals will be calculated and the paired t-test will be performed.

Measured values of HbA1c (NGSP values) will be plotted and for the changes a bar graph will be created excluding the unknown category at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation).

(3) Number of tables and figures

Table 6.1-1 and Figure 6.1-1

6.2 Glycemic control achievement rate (HbA1c)

(1) Patients to be tabulated and analyzed

Efficacy Analysis Set

(2) Details of tabulation and analysis

The Glycemic control achievement rate for HbA1c (NGSP value) will be tabulated ($< 7.0\%$, $\geq 7.0\%$ / $< 6.0\%$, $\geq 6.0\%$) and a bar graph will be created ($< 7.0\%$, $\geq 7.0\%$ / $< 6.0\%$, $\geq 6.0\%$) at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation) (the unknown category will be excluded for the bar graph).

(3) Number of tables and figures

Table 6.2-1 and Figure 6.2-1

6.3 Changes in Fasting blood glucose level and Fasting insulin level

(1) Patients to be tabulated and analyzed

Efficacy Analysis Set

(2) Details of tabulation and analysis

For fasting blood glucose level and fasting insulin level, summary statistics will be calculated at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation). For changes, summary statistics and the mean 95% confidence intervals will be calculated and the paired t-test will be performed.

Measured values of fasting blood glucose level and fasting insulin level will be plotted and for

the changes a bar graph will be created excluding the unknown category at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation).

(3) Number of tables and figures

Tables 6.3-1 and 6.3-2 and Figures 6.3-1 and 6.3-2

6.4 Changes in HbA1c, etc. by Factor Probably Affecting Efficacy

(1) Patients to be tabulated and analyzed

Efficacy Analysis Set

(2) Details of tabulation and analysis

For changes in HbA1c (NGSP values), summary statistics and the mean 95% confidence intervals will be calculated and the paired t-test will be performed at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 24 months, and 36 months after Nesina treatment and last evaluation).

The Glycemic control achievement rate for HbA1c ($< 7.0\%$, $\geq 7.0\%$ / $< 6.0\%$, $\geq 6.0\%$) at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 24 months, and 36 months after Nesina treatment and last evaluation) will be tabulated at the following parameters:

i Sex (Male, Female)

ii Age (< 65 years, ≥ 65 years)

iii Age (< 75 years, ≥ 75 years)

iv Concurrent renal disorder (No, Yes)

v HbA1c (NGSP value) at the start of Nesina treatment ($< 6.0\%$, 6.0% to $< 7.0\%$, 7.0% to $< 8.0\%$, $\geq 8.0\%$)

vi Mean daily dose of Nesina (> 25 mg, 25 to > 12.5 mg, 12.5 to > 6.25 mg, or 6.25 mg)

vii Concomitant diabetic drugs (α -glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, or insulin preparations)

(3) Number of tables and figures

Tables 6.4-1 to 6.4-14

6.5 Changes in HbA1c, etc. in Patients with Special Demographics

(1) Patients to be tabulated and analyzed

Efficacy Analysis Set.

However, patients will be evaluated for Parameter (ii) in (2) Details of tabulation and analysis.

Patients with moderate or higher renal impairment in the Efficacy Analysis Set.

(2) Details of tabulation and analysis

For changes in HbA1c (NGSP values), summary statistics and the mean 95% confidence intervals will be calculated and the paired t-test will be performed at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 24 months, and 36 months after

Nesina treatment and last evaluation).

The Glycemic control achievement rate for HbA1c ($< 7.0\%$, $\geq 7.0\%$ / $< 6.0\%$, $\geq 6.0\%$) at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 24 months, and 36 months after Nesina treatment and last evaluation) will be tabulated at the following parameters:

- i. Severity of renal impairment (Normal + Mild, Moderate + Severe)
- ii. Mean daily dose of Nesina (> 25 mg, 25 to > 12.5 mg, 12.5 to > 6.25 mg, or 6.25 mg)

(3) Number of tables and figures

Tables 6.5-1 to 6.5-4

Statistical Analysis Plan

Nesina Tablets Special Drug Use Surveillance: Mild Type 2 Diabetes Mellitus

(Final Analysis)

Takeda Pharmaceutical Company Limited.

PPD

A rectangular area of the document is redacted with a solid blue color.

PPD

A large rectangular area of the document is redacted with a solid blue color.

Version 2.0, Created on January 30, 2018

Table of Contents

1.0	Definition of Terms and Handling of Laboratory/Measured Data.....	1
1.1	Definitions	1
1.2	Important Identified Risks, Potential Risks, and Missing Information.....	10
1.3	Display digit.....	11
1.4	Level of Significance and Confidence Coefficient.....	12
1.5	Handling of Laboratory/Measured Data	12
1.6	Display Data Digit.....	12
2.0	Disposition of Patients (Patient Diagram).....	14
3.0	Patient Demographics	15
4.0	Details of Treatment.....	18
4.1	Initial Dose of Nesina and Mean Daily Dose of Nesina, by Severity of Renal Impairment.....	19
5.0	Safety Tabulation and Analysis	21
5.1	Occurrence of adverse events and adverse drug reactions / infections.....	21
5.1.1	Occurrence of adverse events.....	21
5.1.2	Occurrence of adverse drug reactions / infections.....	21
5.1.3	Important Identified Risks, Important Potential Risks, and Important Missing Information....	22
5.2	Occurrence of Adverse Events and Adverse Drug Reactions / Infections in the Not Safety Analysis Set	23
5.2.1	Occurrence of Adverse Events	23
5.2.2	Occurrence of adverse drug reactions / infections.....	24
5.3	Occurrence of Adverse Drug Reactions / Infections by Severity, Onset Period, and Outcome	25
5.3.1	Occurrence of Adverse Drug Reactions / Infections by Severity, Onset Period, and Outcome	25
5.4	Patient Demographics and Frequency of Adverse Drug Reactions / Infections by Treatment	26
5.4.1	Patients demographics and Frequency of Adverse Drug Reactions / Infections by Treatment	26
5.5	Occurrence of Adverse Drug Reactions / Infections by Age.....	27
5.6	Occurrence of Adverse Drug Reactions / Infections by Sex.....	28
5.7	Occurrence of Adverse Drug Reactions / Infections by Liver Disorder	28
5.8	Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Renal Disorder.	28
5.9	Occurrence of Adverse Drug Reactions / Infections by Severity of Renal Impairment	29
5.10	Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Heart Disease...	29
5.11	Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Heart Failure....	29
5.12	Occurrence of Adverse Drug Reactions / Infections by Severity of Heart Failure.....	30
5.13	Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Stroke-related Disease	30
5.14	Occurrence of Adverse Drug Reactions / Infections by Mean Daily Dose of Nesina	30
5.15	Occurrence of Adverse Drug Reactions / Infections by Mean Daily Dose of Nesina in Patients with Special Demographics (Patients with Moderate or Higher Renal Impairment).....	31
5.16	Occurrence of Adverse Drug Reactions / Infections by Administration of Concomitant Medication	

(Diabetic Drug).....	31
5.17 Occurrence of Adverse Drug Reactions / Infections by Concomitant Medication (Diabetic Drug)	
31	
5.18 Occurrence of Adverse Drug Reactions / Infections by Presence of Concomitant Protease Inhibitors	32
5.19 Occurrence of Adverse Drug Reactions / Infections by Presence of Concomitant Renal Excretory Drug	32
5.20 Change in Laboratory/Measured Data.....	32
5.20.1 Vital Signs	32
5.20.2 Laboratory Values	33
6.0 Efficacy Tabulation and Analysis	34
6.1 Changes in HbA1c.....	34
6.2 Glycemic control achievement rate (HbA1c).....	34
6.3 Changes in Fasting blood glucose level and Fasting insulin level	34
6.4 Changes in HbA1c, etc. by Factor Probably Affecting Efficacy	35
6.5 Changes in HbA1c, etc. in Patients with Special Demographics	35

1.0 Definition of Terms and Handling of Laboratory/Measured Data

1.1 Definitions

Term	Definition
Nesina	Nesina tablet(s) is abbreviated as Nesina in this statistical analysis plan.
SOC	System Organ Class of MedDRA/J MedDRA/J version 20.1 is used for this document.
HLGT	High level group term of MedDRA/J
PT	Preferred term of MedDRA/J
LLT	Lowest level term of MedDRA/J
Registered patients	Patients whose registration was approved
Survey sheet (electronic) collected patients	Patients whose survey sheets were sent via CCI [REDACTED]
Survey sheet (electronic) uncollected patients	Of the registered patients, patients whose survey sheets (electronic) were uncollected.
Safety Analysis Set	Of the survey sheet (electronic) collected patients, patients who were evaluated for safety analysis. For tabulation, the description of “total” means the Safety Analysis Set.
Not Safety Analysis Set	Of the survey sheet (electronic) collected patients, patients who were excluded from safety analysis
Efficacy Analysis Set	Of the Safety Analysis Set, patients who were evaluated for efficacy analysis
Not Efficacy Analysis Set	Of the Safety Analysis Set, patients who were excluded from the efficacy analysis
First date of Nesina treatment	Of the start dates of the Nesina treatment period in patients, the earliest date is defined as the first date of Nesina treatment.
Last date of Nesina treatment	Of the last dates of the Nesina treatment period in patients, the latest date is defined as the last date of Nesina treatment. If Nesina treatment is continued and the year, month, and date of the continued treatment period are specified, the year, month, and date of the continued treatment period are defined as the last date of Nesina treatment. If the data for the year, month, and date of the continued treatment period are missing, the following date is defined as the last date of Nesina treatment. (1) First date of Nesina treatment + 3 years (same month and date), if Nesina treatment is continued based on the survey sheet (electronic) after 36 months of treatment* (2) For other than the above, the first date of Nesina treatment + 1 year (same month and date), if Nesina treatment is continued based on the survey sheet (electronic) after 12 months of treatment**

Term	Definition
	<p>For the continued treatment of Nesina, the following is considered as the “treatment to be continued:”</p> <ul style="list-style-type: none"> ● [End of Nesina tablet treatment] <ul style="list-style-type: none"> * If “No” for “Did you discontinue Nesina tablets by 12 to 36 months after the start of treatment?” ** If “No” for “Did you discontinue Nesina tablets by 12 months after the start of treatment?”
Adverse drug reactions, etc.	<p>Abbreviation of “adverse drug reactions / infections”</p> <p>Of the adverse events, events for which causal relationship to Nesina was assessed as “Not related” by the Investigator.</p> <p>In this statistical analysis plan, “adverse drug reactions / infections” is used in the headings, while “adverse drug reactions, etc.” is used in the sentences and tables.</p>
Serious adverse events	<p>Adverse events assessed as “serious” by the Investigator.</p> <p>Events described in the MedDRA coding list in the Takeda Medically Significant AE List will be handled as serious even if the Investigator assesses as “Not serious.”</p>
Serious adverse drug reactions	<p>Abbreviation of “serious adverse drug reactions / infections”</p> <p>Of the “serious adverse events,” the events for which causal relationship to Nesina was assessed as “Not related” by the Investigator</p>
Number of patients with events	Number of patients with adverse events or adverse drug reactions, etc.
Number of events	Number of adverse events or adverse drug reactions, etc.
Percent of patients with events	<p>[For safety analysis calculation in the Safety Analysis Set]</p> <p>The formula is: $\text{Number of patients with events} / \text{Number of Safety Analysis Set} \times 100$.</p> <p>[For safety analysis calculation in the Not Safety Analysis Set]</p> <p>The formula is: $\text{Number of patients with events} / \text{Number of Not Safety Analysis Set} \times 100$.</p>
Percent of events	<p>[For safety analysis calculation in the Safety Analysis Set]</p> <p>The formula is: $\text{Number of events} / \text{Number of the Safety Analysis Set} \times 100$.</p> <p>[For safety calculation in the Not Safety Analysis Set]</p> <p>The formula is: $\text{Number of events} / \text{Number of Not Safety Analysis Set} \times 100$.</p>
Onset period	<p>The formula is: Onset date of adverse events (or adverse drug reactions, etc.) – start date of Nesina treatment + 1.</p>

Term	Definition
	For unknown onset date of adverse events (or adverse drug reactions, etc.), the onset period will be calculated as 1 day. However, if the start month and date of Nesina treatment are same as the onset month and date of adverse events (or adverse drug reactions, etc.), the onset period will be calculated as the start date of Nesina treatment.
Mild type 2 diabetes mellitus	Patients who have type 2 diabetes mellitus with HbA1c (NGSP value) of \leq 7.4% at the start date of Nesina treatment
Patients with diabetic complication	Patients with any of the following complications: diabetic nephropathy, diabetic retinopathy, or diabetic neuropathy.
Patients with diabetic nephropathy	Patients with complication of PT Code 10012660 (diabetic end stage renal disease) or 10061835 (diabetic nephropathy).
Patients with diabetic retinopathy	Patients with complication of PT Code 10012688 (diabetic retinal oedema) or 10012689 (diabetic retinopathy).
Patients with diabetic neuropathy	Patients with complication of PT Code 10012645 (diabetic autonomic neuropathy), 10012676 (diabetic mononeuropathy), or 10012680 (diabetic neuropathy).
Patients with concurrent hypertension	Patients with concurrent disease of the Standardised MedDRA Query (hereinafter SMQ) Code 20000147 (hypertension (SMQ) narrow).
Patients with concurrent dyslipidemia	Patients with concurrent disease of the SMQ Code 20000026 (dyslipidaemia (SMQ) narrow).
Patients with concurrent hyperuricemia	Patients with concurrent disease of the PT code meeting the Takeda MedDRA Query 20.1 (hereinafter, TMQ 20.1) (blood uric acid increased).
Patients with concurrent liver disorder	Patients with concurrent disease of the SMQ Code 20000005 (hepatic disorders (narrow)).
Patients with concurrent hepatic steatosis	Patients with concurrent disease of the PT Code 10019708 (hepatic steatosis).
Patients with concurrent alcoholic hepatitis	Patients with concurrent disease of the PT Code 10019728 (hepatitis alcoholic).
Patients with concurrent chronic hepatitis	Patients with concurrent disease of the PT Code 10008909 (chronic hepatitis).
Patients with concurrent hepatic cirrhosis	Patients with concurrent disease of the PT Code 10019641 (hepatic cirrhosis).
Patients with concurrent renal disorder	Patients with concurrent disease of the TMQ 20.1 (renal disease).
Patients with concurrent nephrotic syndrome	Patients with concurrent disease of the PT Code 10029164 (nephrotic syndrome).
Patients with concurrent glomerulonephritis	Patients with concurrent disease of the PT Code 10018364 (glomerulonephritis) or the PT Code 10018367 (glomerulonephritis chronic).

Term	Definition
Patients with concurrent chronic renal failure	Patients with concurrent disease of the PT Code 10064848 (chronic kidney disease) or the PT Code 10038435 (renal failure).
Patients with concurrent heart disease	Patients with concurrent disease of the SOC Code 10007541 (cardiac disorders).
Patients with concurrent cardiac failure	Patients with concurrent disease of the SMQ Code 20000004 (cardiac failure (SMQ) narrow).
Patients with concurrent myocardial infarction	Patients with concurrent disease of the SMQ Code 20000047 (myocardial infarction (SMQ) narrow).
Patients with concurrent angina pectoris	Patients with concurrent disease of the SOC Code 10007541 (cardiac disorders) and the PT Code 10036759 (prinzmetal angina), PT Code 10002383 (angina pectoris), PT Code 10058144 (postinfarction angina), PT Code 10002388 (angina unstable), or LLT Code 10065566 (microvascular angina).
Patients with concurrent stroke-related disease	Patients with concurrent disease of cerebral infarction, cerebral haemorrhage, subarachnoid haemorrhage, or transient ischaemic attack, described below.
Patients with concurrent disease cerebral infarction	Patients with concurrent disease of the PT Code 10006147 (brain stem infarction), PT Code 10008118 (cerebral infarction), PT Code 10008119 (cerebral infarction foetal), PT Code 10008034 (cerebellar infarction), PT Code 10019005 (haemorrhagic cerebral infarction), PT Code 10051078 (lacunar infarction), PT Code 10056237 (migrainous infarction), PT Code 10058571 (spinal cord infarction), PT Code 10060839 (embolic cerebral infarction), PT Code 10060840 (ischaemic cerebral infarction), PT Code 10064961 (thalamic infarction), PT Code 10067347 (thrombotic cerebral infarction), or PT Code 10069020 (basal ganglia infarction).
Patients with concurrent cerebral hemorrhage	Patients with concurrent disease of the SOC Code 10029205 (nervous system disorders) and the PT Code 10006145 (brain stem haemorrhage), PT Code 10008111 (cerebral haemorrhage), PT Code 10008112 (cerebral haemorrhage neonatal), PT Code 10008030 (cerebellar haemorrhage), PT Code 10018985 (haemorrhage intracranial), PT Code 10022840 (intraventricular haemorrhage), PT Code 10022841 (intraventricular haemorrhage neonatal), PT Code 10042365 (subdural haemorrhage neonatal), PT Code 10049236 (spinal epidural haemorrhage), PT Code 10048992 (spinal cord haemorrhage), PT Code 10050157 (cerebral haemorrhage foetal), PT Code 10052593 (meningorrhagia), PT Code 10058939 (thalamus haemorrhage), PT Code 10058940 (putamen haemorrhage), PT Code 10067057 (basal ganglia haemorrhage), PT Code 10067277 (cerebral microhaemorrhage), PT Code 10071205 (brain stem microhaemorrhage), PT Code 10071206 (cerebellar microhaemorrhage), PT Code 10072043 (central nervous system haemorrhage), or PT Code 10073563 (Spinal subdural haemorrhage).

Term	Definition
Patients with concurrent subarachnoid hemorrhage	Patients with concurrent disease of the SOC Code 10029205 (nervous system disorders) and the PT Code 10042316 (subarachnoid haemorrhage), PT Code 10042317 (subarachnoid haemorrhage neonatal), PT Code 10073564 (spinal subarachnoid haemorrhage), LLT Code 10072201 (Asymptomatic subarachnoid haemorrhage).
Patients with concurrent transient ischemic attack	Patients with concurrent disease of the SOC Code 10029205 (nervous system disorders) and the PT Code 10044390 (transient ischaemic attack).
Patients with concurrent allergic disease	Patients with concurrent disease of bronchial asthma, pollinosis, allergic rhinitis, or allergic dermatitis, described below.
Patients with concurrent bronchial asthma	Patients with concurrent disease of the SOC Code 10038738 (respiratory, thoracic and mediastinal disorders) and the PT Code 10003553 (asthma), PT Code 10075084 (aspirin-exacerbated respiratory disease), PT Code 10003557 (asthma exercise induced), PT Code 10003559 (asthma late onset), PT Code 10041961 (status asthmaticus), PT Code 10001890 (alveolitis allergic), PT Code 10049585 (infantile asthma), PT Code 10070836 (occupational asthma), or PT Code 10064823 (asthmatic crisis).
Patients with concurrent pollinosis	Patients with concurrent disease of the PT Code 10048908 (seasonal allergy).
Patients with concurrent allergic rhinitis	Patients with concurrent disease of the PT Code 10039085 (rhinitis allergic).
Patients with concurrent allergic dermatitis	Patients with concurrent disease of the PT Code 10012434 (dermatitis allergic).
Patients with concurrent malignant tumor	Patients with concurrent disease of the SOC Code 10029104 (neoplasms benign, malignant and unspecified (incl cysts and polyps)).
Patients with concurrent malignant tumor (narrow sense)	Patients with concurrent disease of the SMQ Code 20000194 (malignant tumour (SMQ) narrow).
Patients with other concurrent disease	Patients with concurrent disease other than the above (diabetic complication, hypertension, dyslipidaemia, hyperuricaemia, liver disease, renal disease, heart disease, stroke-related disease, allergic disease, malignant tumor, or malignant tumor (narrow sense)).
Severity of renal impairment	Severity of renal impairment in the patient demographic section

Term	Definition
Age	If the start month and date of Nesina treatment is earlier than the birth month and date, calculate using the following formula: Start year of Nesina treatment – birth year – 1. If the birth month and date is earlier than or equal to the start month and date of Nesina treatment, calculate using the following formula: Start year of Nesina treatment – birth year. For unknown birth date, the birth date will be calculated as the 1st day of the birth month.
BMI	Calculate using the following formula: Weight (kg) / (0.0001 × Height (cm) × Height (cm)). Indicate to one decimal place rounded from two decimals.
Disease duration of type 2 diabetes mellitus (year)	Calculate using the following formula: (start date of Nesina treatment – diagnosis period of type 2 diabetes mellitus + 1) / 365.25. For unknown diagnosis month, calculate as January. Indicate to one decimal place rounded from two decimals.
Prior medication	Medications that patients were taking within 3 months before initiation of Nesina therapy.
Concomitant medication	Medications that patients were taking after the start date of Nesina treatment.
Start date of other diabetic drug and concomitant medication (other than diabetic drug)	Calculate as the start date of survey sheet (electronic).
End date of other diabetic drug and concomitant medication (other than diabetic drug)	Calculate as the end date of survey sheet (electronic).
Diabetic drugs	Drugs of the National Health Insurance (NHI) Drug List Code starting with 3969, 3961, 3962, 2492, 2499410, 2499411, 2499415, or 2499416.
α-glucosidase inhibitors	Drugs of the NHI Drug List Code starting with 3969003, 3969004, 3969009, or 3969102.
Thiazolidines	Drugs of the NHI Drug List Code starting with 3969005, 3969007, 3969100, 3969101, or 3969103.
Sulfonylureas	Drugs of the NHI Drug List Code starting with 3961 or 3969101.
Biguanides	Drugs of the NHI Drug List Code starting with 3962, 3969100, 3969104, or 3969105.
Rapid-acting insulin secretagogues	Drugs of the NHI Drug List Code starting with 3969006, 3969008, 3969013, or 3969102.
Insulin preparations	Drugs of the NHI Drug List Code starting with 2492.
DPP-4 inhibitors	Drugs of the NHI Drug List Code starting with 3969010, 3969011, 3969012, 3969014, 3969015, 3969016, 3969017, 3969024, 3969025, 3969103, 3969104, or 3969105.

Term	Definition
GLP-1 receptor agonists	Drugs of the NHI Drug List Code starting with 2499410, 2499411, 2499415, or 2499416.
SGLT2 inhibitors	Drugs of the NHI Drug List Code starting with 3969018, 3969019, 3969020, 3969021, 3969022, or 3969023.
Combination of diabetic drugs	Drugs of the NHI Drug List Code starting with 3969100, 3969101, 3969102, 3969103, 3969104, or 3969105.
Other diabetic drugs	Other diabetic drugs not classified into the above diabetic drug categories (α -glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, insulin preparations, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, or combination of diabetic drugs).
Hypertension drugs	<p>ARB Drugs of the NHI Drug List Code starting with the following 7 numbers: 2149039, 2149040, 2149041, 2149042, 2149044, 2149046, 2149048, 2149100, 2149110, 2149111, 2149112, 2149113, 2149114, 2149115, 2149116, 2149117, 2149118, 2149119, 2149120, 2149121, 2149122</p> <p>Ca antagonists Drugs of the NHI Drug List Code starting with the following numbers: 2149019, 2149022, 2149027, 2149030, 2149034, 2149035, 2149037, 2149038, 2149043, 2149400, 2171006, 2171014, 2171019, 2171020, 2171021, 2171022, 2171405, 2190001, 2149114, 2149115, 2149116, 2149117, 2149118, 2149120, 2149121, 2149122, 2190101, 2190102, 2190103, 2190104</p> <p>ACE inhibitors Drugs of the NHI Drug List Code starting with the following 4 numbers: 2144</p> <p>Diuretics Drugs of the NHI Drug List Code starting with numbers 213 or the following 7 numbers: 2149003, 2149007, 2149012, 2149110, 2149111, 2149112, 2149113, 2149119, 2149122</p> <p>α blockers Drugs of the NHI Drug List Code starting with the following numbers: 1234400, 214200210, 2149002, 2149015, 2149023, 2149026, 1152, 1149107, 1149114, 1149115, 2531001, 2149020</p> <p>$\alpha\beta/\beta$ blockers Drugs of the NHI Drug List Code starting with the following numbers: 2149032, 2149018, 2123014, 2149009, 2123013, 2123003, 2149008, 2149016, 2442001, 2123011, 2149036, 2123016, 2149700, 2149031, 2149010, 2123001, 2123F01, 2149029, 2123008, 2149014, 2149021,</p>

Term	Definition
	2149028, 2123015, 2123005, 2149025, 2123009, 2123403, 2149033, 2149011 Complication of hypertension drugs Drugs of the NHI Drug List Code starting with the following numbers: 2149110, 2149111, 2149112, 2149113, 2149114, 2149115, 2149116, 2149117, 2149118, 2149119, 2149120, 2149121, 2149122 Other Drugs of the NHI Drug List Code starting with the following numbers: 2149047, 2142004, 2149001, 2149017, 2145
Dyslipidaemia drugs	Statins Drugs of the NHI Drug List Code starting with the following numbers: 2189010, 2189011, 2189012, 2189013, 2189015, 2189016, 2189017, 2190101, 2190102, 2190103, 2190104 Fibrates Drugs of the NHI Drug List Code starting with the following numbers: 2183001, 2183002, 2183003, 2183004, 2183005, 2183006 EPA/DHA Drugs of the NHI Drug List Code starting with the following numbers: 2189019, 3399004 Other Drugs of the NHI Drug List Code starting with the following numbers: Dugs, other than the above, of the NHI Drug List Code starting with 218, 2900002, or 3133001.
Concomitant medication (other)	Drugs other than the above (diabetic drugs, hypertension drugs, or dyslipidaemia drugs).
Protease Inhibitor	Use the results of the drug name in the survey sheet (electronic) coded with the NHI Drug List (Appendix 1. List of Protease Inhibitors).
Renal excretory drugs	Use the results of the drug name in the survey sheet (electronic) coded with the NHI Drug List (Appendix 2. List of Renal Excretory Drugs).
Nesina treatment period (days)	Actual treatment period from the start date to the end date of Nesina treatment. However, the washout period is excluded from the treatment period. Calculate using the following formula: End of Nesina treatment – start date of Nesina treatment + 1 (grand total). (Consider the washout period.)
Mean daily dose of Nesina	Calculate using the following formula: Total of “daily dose of Nesina × Nesina treatment period at the relevant dose” / Nesina treatment period. For the calculation of Nesina treatment period, refer to the above. If the daily dose of Nesina is a number outside specification in the survey sheet (electronic) and is actual number, use the relevant number.

Term	Definition
HbA1c (NGSP value)	<p>The NGSP value only will be used in this analysis.</p> <p>For the HbA1c (JDS value), calculate using the following formula: $\text{NGSP value (\%)} = 1.02 \times \text{JDS value (\%)} + 0.25\%$ </p> <p>The HbA1c (international standard value) will be handled as the NGSP value.</p>
Change in HbA1c	<p>For HbA1c converted to the NGSP value, calculate using the following formula: Laboratory value at each testing time point – Laboratory value at the start of Nesina treatment.</p>
Glycemic control achievement rate	<p>Divide the following two categories for the Glycemic control achievement rate:</p> <p>HbA1c (NGSP converted value) [Unit %] NGSP (%): < 6.0, ≥6.0 / < 7.0, ≥ 7.0</p>
non-HDL cholesterol	<p>Calculate using the following formula: “Total cholesterol” – “HDL cholesterol.”</p>
Summary statistics	<p>Number of patients, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum.</p>

1.2 Important Identified Risks, Potential Risks, and Missing Information

Term	Definition
Important identified risk	
Hypoglycemia	Adverse events of the following PT Codes (term) are defined as hypoglycemia. 10020994(Hypoglycaemia neonatal) 10040576(Shock hypoglycaemic) 10021000(Hypoglycaemic coma) 10020993(Hypoglycaemia) 10065981(Hypoglycaemic unconsciousness) 10021002(Hypoglycaemic encephalopathy) 10048803(Hypoglycaemic seizure) 10020997(Hypoglycaemia unawareness) 10077216(Hyperinsulinaemic hypoglycaemia) 10059035(Postprandial hypoglycaemia)
Acute pancreatitis	Adverse events of the SMQ Code 20000022 (acute pancreatitis (SMQ) narrow scope are defined as acute pancreatitis.
Hepatic impairment / jaundice	Adverse events of the SMQ Code 20000005 (hepatic disorders (SMQ) broad) are defined as hepatic impairment / jaundice.
Skin disorder including oculomucocutaneous syndrome (Stevens-Johnson syndrome) / erythema multiforme	Adverse events of the SMQ Code 20000020 (severe skin adverse reactions (SMQ) narrow) are defined as skin disorder including oculomucocutaneous syndrome (Stevens-Johnson syndrome) / erythema multiforme.
Rhabdomyolysis	Adverse events of the SMQ Code 20000002 (rhabdomyolysis/myopathy (SMQ) narrow) are defined as rhabdomyolysis.
Intestinal obstruction	Adverse events of the SMQ Code 20000105 (gastrointestinal obstruction (SMQ) narrow) or the HLGT Code 10018008 (gastrointestinal stenosis and obstruction) or HLT Code 10052736 (non-mechanical ileus) are defined as intestinal obstruction.
Interstitial pneumonia	Adverse events of the SMQ Code 20000042 (interstitial lung disease (SMQ) narrow) are defined as interstitial pneumonia.
Angioedema	Adverse events of the SMQ Code 20000024 (angioedema (SMQ) narrow) are defined as angioedema.
Important potential risk	
Infection	Adverse events of SOC Code 10021881(infections and infestations) are defined as infection.
Malignant tumor	Adverse events of the SOC Code 10029104 (neoplasms benign, malignant and unspecified (incl cysts and polyps)) are defined as malignant tumor.
Malignant tumor (narrow)	Adverse events of the SMQ Code 20000194 (malignant tumors (SMQ)

Term	Definition
sense)	narrow) are defined as malignant tumor (narrow sense).
Pemphigoid	Adverse events of the PT Code 10067776 (ocular pemphigoid) or 10034277 (pemphigoid) are defined as pemphigoid.

Term	Definition
Important missing information	
Cardiovascular system risk	<p>Adverse events of the SMQ Code 20000047 (myocardial infarction (SMQ) broad) or SMQ Code 20000061 (central nervous system haemorrhages and cerebrovascular conditions (SMQ) broad) are defined as cardiovascular system risk.</p> <p>“Central nervous system haemorrhage and cerebrovascular conditions (SMQ) broad” includes the following SMQ classes.</p> <ul style="list-style-type: none"> ➤ 20000166(Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ) broad) ➤ 20000064(Cerebrovascular disorder haemorrhagic (SMQ) broad) ➤ 20000063(Cerebrovascular disease ischaemic (SMQ) broad)

1.3 Display digit

Term	Definition
Percentage (%)	<p>Percent of patients with adverse events or adverse drug reactions, etc. or percent of adverse events or adverse drug reactions, etc. :</p> <p>Indicate to two decimal places rounded from three decimals.</p> <p>Other than the above:</p> <p>Indicate to one decimal place rounded from two decimals.</p>
Summary statistics	<p>Mean, median, first quartile, and third quartile:</p> <p>Indicate one lower digit rounded from two lower digits than the digit of the to-be evaluated data.</p> <p>Standard deviation:</p> <p>Indicate two lower digits rounded from three lower digits of the to-be evaluated data.</p> <p>Minimum and maximum</p> <p>Indicate the same digit number as that of the to-be evaluated data (refer to Section 1.6).</p>
p-value	Indicate to three decimal places rounded down from four decimals.

Term	Definition
	If the data is rounded down from four decimal places and less than 0.001, display as $p < 0.001$.

1.4 Level of Significance and Confidence Coefficient

Two-sided 5%, two-sided 95%.

1.5 Handling of Laboratory/Measured Data

- VISIT as described in the survey sheet will be used for data other than 12 months and 36 months after Nesina treatment.
- 12 months after Nesina treatment: data at 12 months after Nesina treatment will be used for the 12 months survey sheet (electronic) for patients who continued treatment.
For patients who discontinued treatment, data at 12 months after Nesina treatment will not be used for the 12 months survey sheet (electronic).
- 36 months after Nesina treatment: data at 36 months after Nesina treatment will be used for the 36 months survey sheet (electronic) for patients who continued treatment.
For patients who discontinued treatment, data at 36 months after Nesina treatment will not be used for the 36 months survey sheet (electronic).
- At the last evaluation: The last VISIT data within the evaluation period will be used.

1.6 Display Data Digit

Display digits are described as below.

Term	Display digit	Unit
HbA1c	0.1	%
Fasting blood glucose level	1	mg/dL
Fasting insulin level	0.1	μU/mL
Fasting triglyceride	1	mg/dL
Total cholesterol	1	mg/dL
HDL-cholesterol	1	mg/dL
LDL-cholesterol	1	mg/dL
Non-HDL cholesterol	1	mg/dL
Systolic blood pressure	1	mmHg
Diastolic blood pressure	1	mmHg
Weight	0.1	kg
BMI	0.1	kg/m ²
Age	1	Year
Disease duration of type 2 diabetes mellitus	0.1	Year
Height	1	cm
Week of pregnancy	1	Week
Nesina treatment period	1	Day
Mean daily dose of Nesina	0.01	mg

2.0 Disposition of Patients (Patient Diagram)

(1) Patients to be tabulated and analyzed

Registered patients

(2) Details of tabulation and analysis

The following will be tabulated: the number of registered patients, number of medical site at which patients is registered, number of patients whose survey sheets (electronic) are collected, number of patients whose survey sheets (electronic) are not collected, number of patients in the Safety Analysis Set, number of patients in the Not Safety Analysis Set, number of patients in the Efficacy Analysis Set, and number of patients in the Not Efficacy Analysis Set.

For the number of medical sites at which patients are registered, do not duplicate the same medical site with different departments.

For patients whose survey sheets (electronic) are not collected, tabulate the number of patients for each reason for not collected survey sheets.

For the Not Safety Analysis Set and Not Efficacy Analysis Set, the number of patients will be tabulated for each reason for exclusion to create the list.

The following is the handling of the decision whether patients who meet the following criteria should be evaluated:

Criterion	Safety evaluation	Efficacy evaluation
Pre-agreement administration [found after administration]	×	×
Registration 15 days after the start of Nesina treatment [found after registration]	×	×
Nesina taking not confirmed [after the end of patient registration period]	×	×
No data for post-administration of Nesina	×	×
Other than patients with mild type 2 diabetes mellitus	○	×

○ Included, × Excluded or not evaluated

(3) Number of tables and figures

Figure 2.0-1 and Table 2.0-1

3.0 Patient Demographics

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Each parameter will be classified by the categories described below to tabulate the number of patients and frequency.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Category
Sex	Male, Female
Age	Summary statistics
	< 65 years, ≥ 65 years
	< 75 years, ≥ 75 years
	< 20 years, 20 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, 70 to 79 years, ≥ 80 years
Disease duration of type 2 diabetes mellitus (year)	Summary statistics
	< 2 years, 2 to < 5 years, 5 to < 10 years, ≥ 10 years, Unknown
Height	Summary statistics
Category of clinical practice	Outpatient, Inpatient
Pregnancy (only females)	No, Yes
Severity of renal impairment	Normal, Mild, Moderate, Severe
	Normal + Mild, Moderate + Severe
Concurrent disease	No, Yes
Diabetic complication	No, Yes
Details of diabetic complication (overlapped)	Diabetic nephropathy, diabetic retinopathy, diabetic neuropathy For the proportion, the number of patients with diabetic complication will be denominator.
Concurrent hypertension	No, Yes
Concurrent dyslipidemia	No, Yes
Concurrent hyperuricemia	No, Yes
Concurrent liver disorder	No, Yes
Details of concurrent	Hepatic steatosis, alcoholic hepatitis, chronic hepatitis, hepatic

Parameter	Category
liver disorder (overlapped)	cirrhosis, or other For the proportion, the number of with concurrent liver disorder will be denominator.
Concurrent renal disorder	No, Yes
Details of concurrent renal disorder (overlapped)	Nephrotic syndrome, glomerulonephritis, chronic glomerulonephritis, other For the proportion, the number of with concurrent renal disorder will be denominator.
Concurrent heart disease	No, Yes
Details of concurrent heart disease (overlapped)	Cardiac failure, myocardial infarction, angina pectoris, other For the proportion, the number of with concurrent heart disease will be denominator.
Concurrent cardiac failure	No, Yes
Severity classification of cardiac failure (NYHA classification)	Classes NYHA I, NYHA II, NYHA III, and NYHA IV, Unknown For the proportion, the number of with concurrent cardiac failure will be denominator.
Concurrent stroke-related disease	No, Yes
Details of concurrent stroke-related disease (overlapped)	Cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, transient ischaemic attack For the proportion, the number of with concurrent stroke-related disease will be denominator.
Concurrent allergic disease	No, Yes
Concurrent malignant tumour	No, Yes
Concurrent malignant tumour (narrow sense)	No, Yes
Other concurrent disease	No, Yes
Past medical history	No, Yes, Unknown
Hypersensitivity predisposition	No, Yes, Unknown
Alcohol history (drinking alcoholic)	Yes, No, Unknown

Parameter	Category
drinks almost on a daily basis)	
Smoking history	Never, Smoking, Smoked, Unknown
HbA1c(NGSP value) (at the start of Nesina treatment)	Summary statistics < 6.0%, 6.0% to < 7.0%, 7.0% to < 8.0%, ≥ 8.0%, Unknown ≥7.4%, > 7.4%, Unknown
Weight	Summary statistics
BMI	Summary statistics < 18.5 kg/m ² , 18.5 to < 25 kg/m ² , 25 to < 30 kg/m ² , ≥ 30 kg/m ² , Unknown < 25 kg/m ² , ≥25 kg/m ² , Unknown
Dietary intervention (at the start of Nesina treatment)	Yes, No
Exercise intervention (at the start of Nesina treatment)	Yes, No

(3) Number of tables and figures

Table 3.0-1

4.0 Details of Treatment

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Each parameter will be classified by the categories described below to tabulate the number of patients and frequency.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Category
Initial dose of Nesina	25 mg, 12.5 mg, 6.25 mg, or other
Mean daily dose of Nesina	> 25 mg, 25 to >12.5 mg, 12.5 to > 6.25 mg, or ≤6.25 mg
Nesina treatment period	Summary statistics
Administration of prior medication (diabetic drug)	No, Yes
Prior medications (diabetic drugs)	<p>α-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, insulin preparations, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, combination of diabetic drugs, or other diabetic drugs</p> <p>For the proportion, the number of patients with “Yes” for administration of prior medication (diabetic drug) will be denominator.</p>
Administration of prior medication (other than diabetic drug)	No, Yes
Administration of concomitant medication (diabetic drug)	No, Yes
Concomitant medications (diabetic drugs) (overlapped)	<p>α-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, insulin preparations, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, combination of diabetic drugs, or other diabetic drugs</p> <p>For the proportion, the number of patients with “Yes” for administration of concomitant medication (diabetic drug) will be denominator.</p>
Administration of concomitant medication	No, Yes

Parameter	Category
(hypertension drug)	
Concomitant medications (hypertension drugs) (overlapped)	ARB, Ca antagonists, ACE inhibitors, diuretics, α blockers, $\alpha\beta/\beta$ blockers, Complication of hypertension drugs, or other For the proportion, the number of patients with “Yes” for administration of concomitant medication (hypertension drug) will be denominator.
Administration of concomitant medication (dyslipidaemia drug)	No, Yes
Concomitant medications (dyslipidaemia drugs) (overlapped)	Statins, fibrates, EPA/DHA, or other For the proportion, the number of patients with “Yes” for administration of concomitant medication (dyslipidaemia drug) will be denominator.
Administration of concomitant medication (protease drug)	No, Yes
Administration of concomitant medication (combined with renal excretory drug)	No, Yes
Administration of concomitant medication (other)	No, Yes

(3) Number of tables and figures

Table 4.0-1

4.1 Initial Dose of Nesina and Mean Daily Dose of Nesina, by Severity of Renal Impairment

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Cross tabulation will be used for the initial dose of Nesina and the mean daily dose of Nesina, by severity of renal impairment.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Category
Severity of renal impairment	Normal, Mild, Moderate, Severe

Parameter	Category
	Normal + Mild, Moderate + Severe
Initial dose of Nesina	25 mg, 12.5 mg, 6.25 mg, or other
Mean daily dose of Nesina	> 25 mg, 25 to >12.5 mg, 12.5 to > 6.25 mg, or \leq 6.25 mg

(3) Number of tables and figures

Tables 4.1-1 and 4.1-2

5.0 Safety Tabulation and Analysis

5.1 Occurrence of adverse events and adverse drug reactions / infections

5.1.1 Occurrence of adverse events

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

The following will be tabulated for adverse events.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Details of analysis
Number of patients with adverse events	Number of patients who experienced adverse events.
Number of adverse events	Number of adverse events. Count as an event if the same adverse event (LLT) occur multiple times in a patient. Count as different events for different LLTs even if they have the same PT.
Percent of patients with adverse events	Described in Section 1.1.
Type of adverse events	Will be broadly divided into the SOCs and tabulated by PT in the SOCs. In case of the laboratory test-related events, type of adverse events will be broadly divided into the SOCs and HLGTs for tabulation by PT. For the SOCs, the number of patients with adverse events and percent of patients with events will be described in the order of SOCs agreed internationally. For the PTs, the number of adverse events and percent of events will be described in the ascending order of PT codes. Count as an event if the same adverse event (LLT) occur multiple times in a patient. Count as different events for different LLTs even if they have the same PT.

(3) Number of tables and figures

Table 5.1.1-1

5.1.2 Occurrence of adverse drug reactions / infections

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

The following will be tabulated for adverse drug reactions, etc. and serious adverse drug reactions, etc.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Details of tabulation and analysis
Number of patients with adverse drug reactions, etc.	Number of patients who experienced adverse drug reactions, etc.
Number of adverse drug reactions, etc.	Number of adverse drug reactions, etc. Count as an event if the same adverse drug reactions, etc. (LLT) occur multiple times in a patient. Count as different events for different LLTs even though they have the same PT.
Percent of patients with adverse drug reactions, etc.	Described in Section 1.1.
Type of adverse drug reactions, etc.	Will be broadly divided into the SOCs and tabulated by PT in the SOCs. In case of the laboratory test-related events, type of adverse events will be broadly divided into the SOCs and HLGTS for tabulation by PT. For the SOCs, the number of patients with adverse drug reactions, etc. and percent of patients with adverse drug reactions, etc. will be described in the order of SOCs agreed internationally. For the PTs, the number of adverse drug reactions, etc. and percent of adverse drug reactions, etc. will be described in the ascending order of PT codes. Count as an event if the same adverse drug reactions, etc. (LLT) occur multiple times in a patient. Count as different events for different LLTs even though they have the same PT.

- (3) Number of tables and figures
Tables 5.1.2-1 and 5.1.2-2

5.1.3 Important Identified Risks, Important Potential Risks, and Important Missing Information

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

The following will be tabulated for important identified risks, important potential risks, and important missing information (described in Section 1.2).

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Details of tabulation and analysis
Number of patients with adverse events (or adverse drug reactions, etc.)	Number of patients who experienced adverse events (or adverse drug reactions, etc.) with important identified risks, important potential risks, and important missing information.

Parameter	Details of tabulation and analysis
Number of adverse events (or adverse drug reactions, etc.)	Number of adverse events (or adverse drug reactions, etc.) with important identified risks, important potential risks, and important missing information. Count as an event if the same adverse event (or adverse drug reaction, etc.) (LLT) occur multiple times in a patient. Count as different events for different LLTs even if they have the same PT.
Percent of patients with adverse events (or adverse drug reactions, etc.)	Described in Section 1.1.
Type of adverse events (or adverse drug reactions, etc.)	Will be broadly divided into the important identified risks, important potential risks, and important missing information and tabulated by PT in them. For the PTs, the number of adverse events (or adverse drug reactions, etc.) and percent of adverse events (or adverse drug reactions, etc.) will be described in the ascending order of PT codes. Count as an event if the same adverse event (or adverse drug reaction, etc.) (LLT) occur multiple times in a patient. Count as different events for different LLTs even though they have the same PT.

- (3) Number of tables and figures
Tables 5.1.3-1 and 5.1.3-2

5.2 Occurrence of Adverse Events and Adverse Drug Reactions / Infections in the Not Safety Analysis

Set

5.2.1 Occurrence of Adverse Events

- (1) Patients to be tabulated and analyzed

Not Safety Analysis Set

- (2) Details of tabulation and analysis

The following will be tabulated.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Details of tabulation and analysis
Number of patients with adverse events	Number of patients who experienced adverse events.
Number of adverse events	Number of adverse events. Count as an event if the same adverse event (LLT) occur multiple times in a patient.

Parameter	Details of tabulation and analysis
	Count as different events for different LLTs even if they have the same PT.
Percent of patients with adverse events	Described in Section 1.1.
Type of adverse events	<p>Will be broadly divided into the SOCs and tabulated by PT in the SOCs. In case of the laboratory test-related events, type of adverse events will be broadly divided into the SOCs and HLGTS for tabulation by PT.</p> <p>For the SOCs, the number of patients with adverse events and percent of patients with events will be described in the order of SOCs agreed internationally.</p> <p>For the PTs, the number of adverse events and percent of events will be described in the ascending order of PT codes. Count as an event if the same adverse event (LLT) occur multiple times in a patient. Count as different events for different LLTs even though they have the same PT.</p>

(3) Number of tables and figures

Table 5.2-1

5.2.2 Occurrence of adverse drug reactions / infections

(1) Patients to be tabulated and analyzed

Not Safety Analysis Set

(2) Details of tabulation and analysis

The following will be tabulated.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Details of tabulation and analysis
Number of patients with adverse drug reactions, etc.	Number of patients who experienced adverse drug reactions, etc.
Number of adverse drug reactions, etc.	<p>Number of adverse drug reactions, etc. Count as an event if the same adverse drug reactions, etc. (LLT) occur multiple times in a patient.</p> <p>Count as different events for different LLTs even if they have the same PT.</p>
Percent of patients with adverse drug reactions, etc.	Described in Section 1.1.
Type of adverse drug reactions, etc.	Will be broadly divided into the SOCs and tabulated by PT in the SOCs. In case of the laboratory test-related events, type of adverse

	<p>events will be broadly divided into the SOCs and HLGs for tabulation by PT.</p> <p>For the SOCs, the number of patients with adverse drug reactions, etc. and percent of patients with adverse drug reactions, etc. will be described in the order of SOCs agreed internationally.</p> <p>For the PTs, the number of adverse drug reactions, etc. and percent of adverse drug reactions, etc. will be described in the ascending order of PT codes. Count as an event if the same adverse drug reactions, etc. (LLT) occur multiple times in a patient. Count as different events for different LLTs even though they have the same PT.</p>
--	--

(3) Number of tables and figures

Table 5.2-2

5.3 Occurrence of Adverse Drug Reactions / Infections by Severity, Onset Period, and Outcome

5.3.1 Occurrence of Adverse Drug Reactions / Infections by Severity, Onset Period, and Outcome

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Each parameter will be categorized by the categories described below to tabulate the type of adverse drug reactions, etc.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Category
Severity	Serious, Not serious
Onset period	1 to 14 days, 15 to 28 days, 29 to 84 days, 85 to 168 days, 169 to 336 days, 337 to 504 days, 505 to 672 days, 673 to 840 days, 841 to 1008 days, ≥ 1009 days, or Unknown
Outcome	Resolved, Resolving, Not resolved, Resolved with sequelae, Death, or Unknown

The method for tabulation of type adverse drug reactions, etc. is described below:

Parameter	Details of tabulation and analysis
Type of adverse drug reactions, etc.	<p>Will be broadly divided into the SOCs and tabulated by PT in the SOCs. In case of the laboratory test-related events, type of adverse events will be broadly divided into the SOCs and HLGs for tabulation by PT.</p> <p>For the SOCs, the number of patients with adverse drug reactions, etc. will be described in the order of SOCs agreed internationally.</p> <p>For the PTs, the number of adverse drug reactions, etc. will be</p>

Parameter	Details of tabulation and analysis
	<p>described in the ascending order of PT codes. Count as an event if the same adverse drug reactions, etc. (LLT) occur multiple times in a patient. Count as different events for different LLTs even if they have the same PT. However, evaluate an event for the same LLT in accordance with the following order of priority:</p> <p>Onset period: earlier event</p> <p>Severity: Serious → Not serious</p> <p>Outcome: Death → Resolved with Sequelae → Not resolved → Resolving → Resolved → Unknown</p>

(3) Number of tables and figures

Tables 5.3-1 to 5.3-3

5.4 Patient Demographics and Frequency of Adverse Drug Reactions / Infections by Treatment

5.4.1 Patients demographics and Frequency of Adverse Drug Reactions / Infections by Treatment

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Each parameter will be categorized by the categories described below to tabulate the percent of patients with adverse drug reactions, etc.

The Fischer exact test will be used for parameters without rank data. The Mann-Whitney U test will be used for parameters with rank data. (The tests will be used for parameters with asterisk [*].)

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Category
Sex*	Male, Female
Age*	< 65 years, ≥65 years
	< 75 years, ≥75 years
Severity of renal impairment*	Normal + Mild, Moderate + Severe
Concurrent liver disorder*	No, Yes
Concurrent renal disorder*	No, Yes
Concurrent heart disease*	No, Yes
Details of concurrent heart disease	Cardiac failure, myocardial infarction, or angina pectoris

Parameter	Category
(overlapped)	
Concurrent cardiac failure*	No, Yes
Severity classification of cardiac failure (NYHA classification)*	Classes NYHA I, NYHA II, NYHA III, and NYHA IV
Concurrent stroke-related disease*	No, Yes
Mean daily dose of Nesina	> 25 mg, 25 to >12.5 mg, 12.5 to > 6.25 mg, or ≤6.25 mg
Administration of concomitant medication (diabetic drug)	No, Yes
Concomitant medications (diabetic drugs) (overlapped)	α-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, or insulin preparations
Administration of concomitant medication (protease drug)*	No, Yes
Administration of concomitant medication (combined with renal excretory drug)*	No, Yes

(3) Number of tables and figures

Table 5.4.1-1

5.5 Occurrence of Adverse Drug Reactions / Infections by Age

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Age will be classified into < 65 years, ≥65 years and < 75 years, and ≥75 years for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Tables 5.5-1 to 5.5-2

5.6 Occurrence of Adverse Drug Reactions / Infections by Sex

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Sex will be classified into male or female for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.6-1

5.7 Occurrence of Adverse Drug Reactions / Infections by Liver Disorder

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Concurrent liver disorder will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.7-1

5.8 Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Renal Disorder

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Concurrent renal disorder will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.8-1

5.9 Occurrence of Adverse Drug Reactions / Infections by Severity of Renal Impairment

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

Severity of renal impairment will be classified into normal + mild or moderate + severe for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.9-1

5.10 Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Heart Disease

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

Concurrent heart disease will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.10-1

5.11 Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Heart Failure

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

Concurrent heart failure will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.11-1

5.12 Occurrence of Adverse Drug Reactions / Infections by Severity of Heart Failure

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

Severity of heart failure will be classified into Class NYHA I, NYHA II, NYHA III, or NYHA IV for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.12-1

5.13 Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Stroke-related Disease

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

Concurrent stroke-related disease will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.13-1

5.14 Occurrence of Adverse Drug Reactions / Infections by Mean Daily Dose of Nesina

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

The mean daily dose of Nesina will be classified into > 25 mg, 25 to > 12.5 mg, 12.5 to > 6.25 mg, or ≤6.25 mg for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.14-1

5.15 Occurrence of Adverse Drug Reactions / Infections by Mean Daily Dose of Nesina in Patients with Special Demographics (Patients with Moderate or Higher Renal Impairment)

(1) Patients to be tabulated and analyzed

Patients with moderate or higher renal impairment in the Safety Analysis Set

(2) Details of tabulation and analysis

The mean daily dose of Nesina will be classified into > 25 mg, 25 to > 12.5 mg, 12.5 to > 6.25 mg, or ≤6.25 mg for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.15-1

5.16 Occurrence of Adverse Drug Reactions / Infections by Administration of Concomitant Medication (Diabetic Drug)

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Administration of concomitant medication (diabetic drug) will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.16-1

5.17 Occurrence of Adverse Drug Reactions / Infections by Concomitant Medication (Diabetic Drug)

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Concomitant medications (diabetic drugs) will be classified into the following drugs: α -glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, or insulin preparations, for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.17-1

5.18 Occurrence of Adverse Drug Reactions / Infections by Presence of Concomitant Protease Inhibitors

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

Concomitant protease inhibitor will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.18-1

5.19 Occurrence of Adverse Drug Reactions / Infections by Presence of Concomitant Renal Excretory

Drug

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

Concomitant renal excretory drug be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

- (3) Number of tables and figures

Table 5.19-1

5.20 Change in Laboratory/Measured Data

5.20.1 Vital Signs

- (1) Patients to be tabulated and analyzed

Safety Analysis Set

- (2) Details of tabulation and analysis

For blood pressure (systolic/diastolic) and weight, summary statistics will be calculated at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation). For changes from the start of Nesina treatment, summary statistics and the mean 95% confidence intervals will be calculated.

Measured values (mean and standard deviation) of blood pressure (systolic/diastolic) and weight will be plotted. For the changes, the mean changes will be created using a bar graph.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.20.1-1 and Figures 5.20.1-1 to 5.20.1-6

5.20.2 Laboratory Values

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

For laboratory values of fasting triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, and non-HDL cholesterol, summary statistics will be calculated at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation). For changes from the start of Nesina treatment, summary statistics and the mean 95% confidence intervals will be calculated.

The individual laboratory values described above (mean and standard deviation) will be plotted.

For the changes, the mean changes will be created using a bar graph.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.20.2-1 and Figures 5.20.2-1 to 5.20.2-10

6.0 Efficacy Tabulation and Analysis

6.1 Changes in HbA1c

(1) Patients to be tabulated and analyzed

Efficacy Analysis Set

(2) Details of tabulation and analysis

For HbA1c (NGSP values), summary statistics will be calculated at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation). For changes, summary statistics and the mean 95% confidence intervals will be calculated and the paired t-test will be performed.

Measured values of HbA1c (NGSP values) will be plotted and for the changes a bar graph will be created excluding the unknown category at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation).

(3) Number of tables and figures

Table 6.1-1 and Figure 6.1-1

6.2 Glycemic control achievement rate (HbA1c)

(1) Patients to be tabulated and analyzed

Efficacy Analysis Set

(2) Details of tabulation and analysis

The Glycemic control achievement rate for HbA1c (NGSP value) will be tabulated ($< 7.0\%$, $\geq 7.0\%$ / $< 6.0\%$, $\geq 6.0\%$) and a bar graph will be created ($< 7.0\%$, $\geq 7.0\%$ / $< 6.0\%$, $\geq 6.0\%$) at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation) (the unknown category will be excluded for the bar graph).

(3) Number of tables and figures

Table 6.2-1 and Figure 6.2-1

6.3 Changes in Fasting blood glucose level and Fasting insulin level

(1) Patients to be tabulated and analyzed

Efficacy Analysis Set

(2) Details of tabulation and analysis

For fasting blood glucose level and fasting insulin level, summary statistics will be calculated at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation). For changes, summary statistics and the mean 95% confidence intervals will be calculated and the paired t-test will be performed.

Measured values of fasting blood glucose level and fasting insulin level will be plotted and for

the changes a bar graph will be created excluding the unknown category at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation).

(3) Number of tables and figures

Tables 6.3-1 and 6.3-2 and Figures 6.3-1 and 6.3-2

6.4 Changes in HbA1c, etc. by Factor Probably Affecting Efficacy

(1) Patients to be tabulated and analyzed

Efficacy Analysis Set

(2) Details of tabulation and analysis

For changes in HbA1c (NGSP values), summary statistics and the mean 95% confidence intervals will be calculated and the paired t-test will be performed at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 24 months, and 36 months after Nesina treatment and last evaluation).

The Glycemic control achievement rate for HbA1c ($< 7.0\%$, $\geq 7.0\%$ / $< 6.0\%$, $\geq 6.0\%$) at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 24 months, and 36 months after Nesina treatment and last evaluation) will be tabulated at the following parameters:

i Sex (Male, Female)

ii Age (< 65 years, ≥ 65 years)

iii Age (< 75 years, ≥ 75 years)

iv Concurrent renal disorder (No, Yes)

v HbA1c (NGSP value) at the start of Nesina treatment ($< 6.0\%$, 6.0% to $< 7.0\%$, 7.0% to $< 8.0\%$, $\geq 8.0\%$)

vi Mean daily dose of Nesina (> 25 mg, 25 to > 12.5 mg, 12.5 to > 6.25 mg, or 6.25 mg)

vii Concomitant diabetic drugs (α -glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, or insulin preparations)

(3) Number of tables and figures

Tables 6.4-1 to 6.4-14

6.5 Changes in HbA1c, etc. in Patients with Special Demographics

(1) Patients to be tabulated and analyzed

Efficacy Analysis Set.

However, patients will be evaluated for Parameter (ii) in (2) Details of tabulation and analysis.

Patients with moderate or higher renal impairment in the Efficacy Analysis Set.

(2) Details of tabulation and analysis

For changes in HbA1c (NGSP values), summary statistics and the mean 95% confidence intervals will be calculated and the paired t-test will be performed at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 24 months, and 36 months after

Nesina treatment and last evaluation).

The Glycemic control achievement rate for HbA1c ($< 7.0\%$, $\geq 7.0\%$ / $< 6.0\%$, $\geq 6.0\%$) at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 24 months, and 36 months after Nesina treatment and last evaluation) will be tabulated at the following parameters:

- i. Severity of renal impairment (Normal + Mild, Moderate + Severe)
- ii. Mean daily dose of Nesina (> 25 mg, 25 to > 12.5 mg, 12.5 to > 6.25 mg, or 6.25 mg)

(3) Number of tables and figures

Tables 6.5-1 to 6.5-4

Statistical Analysis Plan

Nesina Tablets Special Drug Use Surveillance: Mild Type 2 Diabetes Mellitus

(Final Analysis)

Takeda Pharmaceutical Company Limited.

PPD

A rectangular area of the document is redacted with a solid blue color.

PPD

A large rectangular area of the document is redacted with a solid blue color.

Version 1.0, Created on December 18, 2017

Table of Contents

1.0	Definition of Terms and Handling of Laboratory/Measured Data.....	1
1.1	Definitions	1
1.2	Important Identified Risks, Potential Risks, and Missing Information.....	10
1.3	Display digit.....	11
1.4	Level of Significance and Confidence Coefficient.....	12
1.5	Handling of Laboratory/Measured Data	12
1.6	Display Data Digit.....	12
2.0	Disposition of Patients (Patient Diagram).....	14
3.0	Patient Demographics	15
4.0	Details of Treatment.....	18
4.1	Initial Dose of Nesina and Mean Daily Dose of Nesina, by Severity of Renal Impairment.....	19
5.0	Safety Tabulation and Analysis	21
5.1	Occurrence of adverse events and adverse drug reactions / infections.....	21
5.1.1	Occurrence of adverse events.....	21
5.1.2	Occurrence of adverse drug reactions / infections.....	21
5.1.3	Important Identified Risks, Important Potential Risks, and Important Missing Information....	22
5.2	Occurrence of Adverse Events and Adverse Drug Reactions / Infections in the Not Safety Analysis Set.....	23
5.2.1	Occurrence of Adverse Events	23
5.2.2	Occurrence of adverse drug reactions / infections.....	24
5.3	Occurrence of Adverse Drug Reactions / Infections by Severity, Onset Period, and Outcome	25
5.3.1	Occurrence of Adverse Drug Reactions / Infections by Severity, Onset Period, and Outcome	25
5.4	Patient Demographics and Frequency of Adverse Drug Reactions / Infections by Treatment	26
5.4.1	Patients demographics and Frequency of Adverse Drug Reactions / Infections by Treatment	26
5.5	Occurrence of Adverse Drug Reactions / Infections by Age.....	27
5.6	Occurrence of Adverse Drug Reactions / Infections by Sex.....	28
5.7	Occurrence of Adverse Drug Reactions / Infections by Liver Disorder	28
5.8	Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Renal Disorder.	28
5.9	Occurrence of Adverse Drug Reactions / Infections by Severity of Renal Impairment	29
5.10	Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Heart Disease...	29
5.11	Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Heart Failure....	29
5.12	Occurrence of Adverse Drug Reactions / Infections by Severity of Heart Failure.....	30
5.13	Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Stroke-related Disease	30
5.14	Occurrence of Adverse Drug Reactions / Infections by Mean Daily Dose of Nesina	30
5.15	Occurrence of Adverse Drug Reactions / Infections by Mean Daily Dose of Nesina in Patients with Special Demographics (Patients with Moderate or Higher Renal Impairment).....	31
5.16	Occurrence of Adverse Drug Reactions / Infections by Administration of Concomitant	

Medication (Diabetic Drug).....	31
5.17 Occurrence of Adverse Drug Reactions / Infections by Concomitant Medication (Diabetic Drug) 31	
5.18 Occurrence of Adverse Drug Reactions / Infections by Presence of Concomitant Protease Inhibitors	32
5.19 Occurrence of Adverse Drug Reactions / Infections by Presence of Concomitant Renal Excretory Drug	32
5.20 Change in Laboratory/Measured Data.....	32
5.20.1 Vital Signs	32
5.20.2 Laboratory Values	33
6.0 Efficacy Tabulation and Analysis	34
6.1 Changes in HbA1c.....	34
6.2 Glycemic control achievement rate (HbA1c).....	34
6.3 Changes in Fasting blood glucose level and Fasting insulin level	34
6.4 Changes in HbA1c, etc. by Factor Probably Affecting Efficacy	35
6.5 Changes in HbA1c, etc. in Patients with Special Demographics	35

1.0 Definition of Terms and Handling of Laboratory/Measured Data

1.1 Definitions

Term	Definition
Nesina	Nesina tablet(s) is abbreviated as Nesina in this statistical analysis plan.
SOC	System Organ Class of MedDRA/J MedDRA/J version 20.1 is used for this document.
HLGT	High level group term of MedDRA/J
PT	Preferred term of MedDRA/J
LLT	Lowest level term of MedDRA/J
Registered patients	Patients whose registration was approved
Survey sheet (electronic) collected patients	Patients whose survey sheets were sent via CCI XXXXXXXXXX
Survey sheet (electronic) uncollected patients	Of the registered patients, patients whose survey sheets (electronic) were uncollected.
Safety Analysis Set	Of the survey sheet (electronic) collected patients, patients who were evaluated for safety analysis. For tabulation, the description of “total” means the Safety Analysis Set.
Not Safety Analysis Set	Of the survey sheet (electronic) collected patients, patients who were excluded from safety analysis
Efficacy Analysis Set	Of the Safety Analysis Set, patients who were evaluated for efficacy analysis
Not Efficacy Analysis Set	Of the Safety Analysis Set, patients who were excluded from the efficacy analysis
First date of Nesina treatment	Of the start dates of the Nesina treatment period in patients, the earliest date is defined as the first date of Nesina treatment.
Last date of Nesina treatment	Of the last dates of the Nesina treatment period in patients, the latest date is defined as the last date of Nesina treatment. If Nesina treatment is continued and the year, month, and date of the continued treatment period are specified, the year, month, and date of the continued treatment period are defined as the last date of Nesina treatment. If the data for the year, month, and date of the continued treatment period are missing, the following date is defined as the last date of Nesina treatment. (1) First date of Nesina treatment + 3 years (same month and date), if Nesina treatment is continued based on the survey sheet (electronic) after 36 months of treatment* (2) For other than the above, the first date of Nesina treatment + 1 year (same month and date), if Nesina treatment is continued based on the survey sheet (electronic) after 12 months of treatment**

Term	Definition
	<p>For the continued treatment of Nesina, the following is considered as the “treatment to be continued:”</p> <ul style="list-style-type: none"> ● [End of Nesina tablet treatment] <ul style="list-style-type: none"> * If “No” for “Did you discontinue Nesina tablets by 12 to 36 months after the start of treatment?” ** If “No” for “Did you discontinue Nesina tablets by 12 months after the start of treatment?”
Adverse drug reactions, etc.	<p>Abbreviation of “adverse drug reactions / infections”</p> <p>Of the adverse events, events for which causal relationship to Nesina was assessed as “Not related” by the Investigator.</p> <p>In this statistical analysis plan, “adverse drug reactions / infections” is used in the headings, while “adverse drug reactions, etc.” is used in the sentences and tables.</p>
Serious adverse events	<p>Adverse events assessed as “serious” by the Investigator.</p> <p>Events described in the MedDRA coding list in the Takeda Medically Significant AE List will be handled as serious even if the Investigator assesses as “Not serious.”</p>
Serious adverse drug reactions	<p>Abbreviation of “serious adverse drug reactions / infections”</p> <p>Of the “serious adverse events,” the events for which causal relationship to Nesina was assessed as “Not related” by the Investigator</p>
Number of patients with events	Number of patients with adverse events or adverse drug reactions, etc.
Number of events	Number of adverse events or adverse drug reactions, etc.
Percent of patients with events	<p>[For safety analysis calculation in the Safety Analysis Set]</p> <p>The formula is: Number of patients with events / Number of Safety Analysis Set × 100.</p> <p>[For safety analysis calculation in the Not Safety Analysis Set]</p> <p>The formula is: Number of patients with events / Number of Not Safety Analysis Set × 100.</p>
Percent of events	<p>[For safety analysis calculation in the Safety Analysis Set]</p> <p>The formula is: Number of events / Number of the Safety Analysis Set × 100.</p> <p>[For safety calculation in the Not Safety Analysis Set]</p> <p>The formula is: Number of events / Number of Not Safety Analysis Set × 100.</p>
Onset period	The formula is: Onset date of adverse events (or adverse drug reactions, etc.) – start date of Nesina treatment + 1.

Term	Definition
	For unknown onset date of adverse events (or adverse drug reactions, etc.), the onset period will be calculated as 1 day. However, if the start month and date of Nesina treatment are same as the onset month and date of adverse events (or adverse drug reactions, etc.), the onset period will be calculated as the start date of Nesina treatment.
Mild type 2 diabetes mellitus	Patients who have type 2 diabetes mellitus with HbA1c (NGSP value) of \leq 7.4% at the start date of Nesina treatment
Patients with diabetic complication	Patients with any of the following complications: diabetic nephropathy, diabetic retinopathy, or diabetic neuropathy.
Patients with diabetic nephropathy	Patients with complication of PT Code 10012660 (diabetic end stage renal disease) or 10061835 (diabetic nephropathy).
Patients with diabetic retinopathy	Patients with complication of PT Code 10012688 (diabetic retinal oedema) or 10012689 (diabetic retinopathy).
Patients with diabetic neuropathy	Patients with complication of PT Code 10012645 (diabetic autonomic neuropathy), 10012676 (diabetic mononeuropathy), or 10012680 (diabetic neuropathy).
Patients with concurrent hypertension	Patients with concurrent disease of the Standardised MedDRA Query (hereinafter SMQ) Code 20000147 (hypertension (SMQ) narrow).
Patients with concurrent dyslipidemia	Patients with concurrent disease of the SMQ Code 20000026 (dyslipidaemia (SMQ) narrow).
Patients with concurrent hyperuricemia	Patients with concurrent disease of the PT code meeting the Takeda MedDRA Query 20.1 (hereinafter, TMQ 20.1) (blood uric acid increased).
Patients with concurrent liver disorder	Patients with concurrent disease of the SMQ Code 20000005 (hepatic disorders (narrow)).
Patients with concurrent hepatic steatosis	Patients with concurrent disease of the PT Code 10019708 (hepatic steatosis).
Patients with concurrent alcoholic hepatitis	Patients with concurrent disease of the PT Code 10019728 (hepatitis alcoholic).
Patients with concurrent chronic hepatitis	Patients with concurrent disease of the PT Code 10008909 (chronic hepatitis).
Patients with concurrent hepatic cirrhosis	Patients with concurrent disease of the PT Code 10019641 (hepatic cirrhosis).
Patients with concurrent renal disorder	Patients with concurrent disease of the TMQ 20.1 (renal disease).
Patients with concurrent nephrotic syndrome	Patients with concurrent disease of the PT Code 10029164 (nephrotic syndrome).
Patients with concurrent glomerulonephritis	Patients with concurrent disease of the PT Code 10018364 (glomerulonephritis) or the PT Code 10018367 (glomerulonephritis chronic).

Term	Definition
Patients with concurrent chronic renal failure	Patients with concurrent disease of the PT Code 10064848 (chronic kidney disease) or the PT Code 10038435 (renal failure).
Patients with concurrent heart disease	Patients with concurrent disease of the SOC Code 10007541 (cardiac disorders).
Patients with concurrent cardiac failure	Patients with concurrent disease of the SMQ Code 20000004 (cardiac failure (SMQ) narrow).
Patients with concurrent myocardial infarction	Patients with concurrent disease of the SMQ Code 20000047 (myocardial infarction (SMQ) narrow).
Patients with concurrent angina pectoris	Patients with concurrent disease of the SOC Code 10007541 (cardiac disorders) and the PT Code 10036759 (prinzmetal angina), PT Code 10002383 (angina pectoris), PT Code 10058144 (postinfarction angina), PT Code 10002388 (angina unstable), or LLT Code 10065566 (microvascular angina).
Patients with concurrent stroke-related disease	Patients with concurrent disease of cerebral infarction, cerebral haemorrhage, subarachnoid haemorrhage, or transient ischaemic attack, described below.
Patients with concurrent disease cerebral infarction	Patients with concurrent disease of the SOC Code 10029205 (nervous system disorders) and the PT Code 10006147 (brain stem infarction), PT Code 10008118 (cerebral infarction), PT Code 10008119 (cerebral infarction foetal), PT Code 10008034 (cerebellar infarction), PT Code 10019005 (haemorrhagic cerebral infarction), PT Code 10051078 (lacunar infarction), PT Code 10056237 (migrainous infarction), PT Code 10058571 (spinal cord infarction), PT Code 10060839 (embolic cerebral infarction), PT Code 10060840 (ischaemic cerebral infarction), PT Code 10064961 (thalamic infarction), PT Code 10067347 (thrombotic cerebral infarction), or PT Code 10069020 (basal ganglia infarction).
Patients with concurrent cerebral hemorrhage	Patients with concurrent disease of the SOC Code 10029205 (nervous system disorders) and the PT Code 10006145 (brain stem haemorrhage), PT Code 10008111 (cerebral haemorrhage), PT Code 10008112 (cerebral haemorrhage neonatal), PT Code 10008030 (cerebellar haemorrhage), PT Code 10018985 (haemorrhage intracranial), PT Code 10022840 (intraventricular haemorrhage), PT Code 10022841 (intraventricular haemorrhage neonatal), PT Code 10042365 (subdural haemorrhage neonatal), PT Code 10049236 (spinal epidural haemorrhage), PT Code 10048992 (spinal cord haemorrhage), PT Code 10050157 (cerebral haemorrhage foetal), PT Code 10052593 (meningorrhagia), PT Code 10058939 (thalamus haemorrhage), PT Code 10058940 (putamen haemorrhage), PT Code 10067057 (basal ganglia haemorrhage), PT Code 10067277 (cerebral microhaemorrhage), PT Code 10071205 (brain stem microhaemorrhage), PT Code 10071206 (cerebellar microhaemorrhage), PT Code 10072043 (central nervous system haemorrhage),

Term	Definition
	or PT Code 10073563 (Spinal subdural haemorrhage).
Patients with concurrent subarachnoid hemorrhage	Patients with concurrent disease of the SOC Code 10029205 (nervous system disorders) and the PT Code 10042316 (subarachnoid haemorrhage), PT Code 10042317 (subarachnoid haemorrhage neonatal), PT Code 10073564 (spinal subarachnoid haemorrhage), LLT Code 10072201 (Asymptomatic subarachnoid haemorrhage).
Patients with concurrent transient ischemic attack	Patients with concurrent disease of the SOC Code 10029205 (nervous system disorders) and the PT Code 10044390 (transient ischaemic attack).
Patients with concurrent allergic disease	Patients with concurrent disease of bronchial asthma, pollinosis, allergic rhinitis, or allergic dermatitis, described below.
Patients with concurrent bronchial asthma	Patients with concurrent disease of the SOC Code 10038738 (respiratory, thoracic and mediastinal disorders) and the PT Code 10003553 (asthma), PT Code 10075084 (aspirin-exacerbated respiratory disease), PT Code 10003557 (asthma exercise induced), PT Code 10003559 (asthma late onset), PT Code 10041961 (status asthmaticus), PT Code 10001890 (alveolitis allergic), PT Code 10049585 (infantile asthma), PT Code 10070836 (occupational asthma), or PT Code 10064823 (asthmatic crisis).
Patients with concurrent pollinosis	Patients with concurrent disease of the PT Code 10048908 (seasonal allergy).
Patients with concurrent allergic rhinitis	Patients with concurrent disease of the PT Code 10039085 (rhinitis allergic).
Patients with concurrent allergic dermatitis	Patients with concurrent disease of the PT Code 10012434 (dermatitis allergic).
Patients with concurrent malignant tumor	Patients with concurrent disease of the SOC Code 10029104 (neoplasms benign, malignant and unspecified (incl cysts and polyps)).
Patients with concurrent malignant tumor (narrow sense)	Patients with concurrent disease of the SMQ Code 20000194 (malignant tumour (SMQ) narrow).
Patients with other concurrent disease	Patients with concurrent disease other than the above (diabetic complication, hypertension, dyslipidaemia, hyperuricaemia, liver disease, renal disease, heart disease, stroke-related disease, allergic disease, malignant tumor, or malignant tumor (narrow sense)).
Severity of renal impairment	Severity of renal impairment in the patient demographic section

Term	Definition
Age	If the start month and date of Nesina treatment is earlier than the birth month and date, calculate using the following formula: Start year of Nesina treatment – birth year – 1. If the birth month and date is earlier than or equal to the start month and date of Nesina treatment, calculate using the following formula: Start year of Nesina treatment – birth year. For unknown birth date, the birth date will be calculated as the 1st day of the birth month.
BMI	Calculate using the following formula: Weight (kg) / (0.0001 × Height (cm) × Height (cm)). Indicate to one decimal place rounded from two decimals.
Disease duration of type 2 diabetes mellitus (year)	Calculate using the following formula: (start date of Nesina treatment – diagnosis period of type 2 diabetes mellitus + 1) / 365.25. For unknown diagnosis month, calculate as January. Indicate to one decimal place rounded from two decimals.
Prior medication	Medications that patients were taking within 3 months before initiation of Nesina therapy.
Concomitant medication	Medications that patients were taking after the start date of Nesina treatment.
Start date of other diabetic drug and concomitant medication (other than diabetic drug)	Calculate as the start date of survey sheet (electronic).
End date of other diabetic drug and concomitant medication (other than diabetic drug)	Calculate as the end date of survey sheet (electronic).
Diabetic drugs	Drugs of the National Health Insurance (NHI) Drug List Code starting with 3969, 3961, 3962, 2492, 2499410, 2499411, 2499415, or 2499416.
α-glucosidase inhibitors	Drugs of the NHI Drug List Code starting with 3969003, 3969004, 3969009, or 3969102.
Thiazolidines	Drugs of the NHI Drug List Code starting with 3969005, 3969007, 3969100, 3969101, or 3969103.
Sulfonylureas	Drugs of the NHI Drug List Code starting with 3961 or 3969101.
Biguanides	Drugs of the NHI Drug List Code starting with 3962, 3969100, 3969104, or 3969105.
Rapid-acting insulin secretagogues	Drugs of the NHI Drug List Code starting with 3969006, 3969008, 3969013, or 3969102.
Insulin preparations	Drugs of the NHI Drug List Code starting with 2492.
DPP-4 inhibitors	Drugs of the NHI Drug List Code starting with 3969010, 3969011, 3969012, 3969014, 3969015, 3969016, 3969017, 3969024, 3969025, 3969103, 3969104, or 3969105.

Term	Definition
GLP-1 receptor agonists	Drugs of the NHI Drug List Code starting with 2499410, 2499411, 2499415, or 2499416.
SGLT2 inhibitors	Drugs of the NHI Drug List Code starting with 3969018, 3969018, 3969019, 3969020, 3969021, 3969022, or 3969023.
Combination of diabetic drugs	Drugs of the NHI Drug List Code starting with 3969100, 3969101, 3969102, 3969103, 3969104, or 3969105.
Other diabetic drugs	Other diabetic drugs not classified into the above diabetic drug categories (α -glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, insulin preparations, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, or combination of diabetic drugs).
Hypertension drugs	<p>ARB Drugs of the NHI Drug List Code starting with the following 7 numbers: 2149039, 2149040, 2149041, 2149042, 2149044, 2149046, 2149048, 2149100, 2149110, 2149111, 2149112, 2149113, 2149114, 2149115, 2149116, 2149117, 2149118, 2149119, 2149120, 2149121, 2149122</p> <p>Ca antagonists Drugs of the NHI Drug List Code starting with the following numbers: 2149019, 2149022, 2149027, 2149030, 2149034, 2149035, 2149037, 2149038, 2149043, 2149400, 2171006, 2171014, 2171019, 2171020, 2171021, 2171022, 2171405, 2190001, 2149114, 2149115, 2149116, 2149117, 2149118, 2149120, 2149121, 2149122</p> <p>ACE inhibitors Drugs of the NHI Drug List Code starting with the following 4 numbers: 2144</p> <p>Diuretics Drugs of the NHI Drug List Code starting with numbers 213 or the following 7 numbers: 2149003, 2149007, 2149012, 2149110, 2149111, 2149112, 2149113, 2149119, 2149122</p> <p>α blockers Drugs of the NHI Drug List Code starting with the following numbers: 1234400, 214200210, 2149002, 2149015, 2149023, 2149026, 1152, 1149107, 1149114, 1149115, 2531001, 2149020</p> <p>$\alpha\beta/\beta$ blockers Drugs of the NHI Drug List Code starting with the following numbers: 2149032, 2149018, 2123014, 2149009, 2123013, 2123003, 2149008, 2149016, 2442001, 2123011, 2149036, 2123016, 2149700, 2149031, 2149010, 2123001, 2123F01, 2149029, 2123008, 2149014, 2149021, 2149028, 2123015, 2123005, 2149025, 2123009, 2123403, 2149033, 2149011</p>

Term	Definition
	<p>Complication of hypertension drugs Drugs of the NHI Drug List Code starting with the following numbers: 2149110, 2149111, 2149112, 2149113, 2149114, 2149115, 2149116, 2149117, 2149118, 2149119, 2149120, 2149121, 2149122, 2190101, 2190102, 2190103, 2190104</p> <p>Other Drugs of the NHI Drug List Code starting with the following numbers: 2149047, 2142004, 2149001, 2149017, 2145</p>
Dyslipidaemia drugs	<p>Statins Drugs of the NHI Drug List Code starting with the following numbers: 2189010, 2189011, 2189012, 2189013, 2189015, 2189016, 2189017, 2190101, 2190102, 2190103, 2190104</p> <p>Fibrates Drugs of the NHI Drug List Code starting with the following numbers: 2183001, 2183002, 2183003, 2183004, 2183005, 2183006</p> <p>EPA/DHA Drugs of the NHI Drug List Code starting with the following numbers: 2189019, 3399004</p> <p>Other Drugs of the NHI Drug List Code starting with the following numbers: Dugs, other than the above, of the NHI Drug List Code starting with 218, 2900002, or 3133001.</p>
Concomitant medication (other)	Drugs other than the above (diabetic drugs, hypertension drugs, or dyslipidaemia drugs).
Protease Inhibitor	Use the results of the drug name in the survey sheet (electronic) coded with the NHI Drug List (Appendix 1. List of Protease Inhibitors).
Renal excretory drugs	Use the results of the drug name in the survey sheet (electronic) coded with the NHI Drug List (Appendix 2. List of Renal Excretory Drugs).
Nesina treatment period (days)	<p>Actual treatment period from the start date to the end date of Nesina treatment. However, the washout period is excluded from the treatment period.</p> <p>Calculate using the following formula: End of Nesina treatment – start date of Nesina treatment + 1 (grand total). (Consider the washout period.)</p>
Mean daily dose of Nesina	<p>Calculate using the following formula: Total of “daily dose of Nesina × Nesina treatment period at the relevant dose” / Nesina treatment period. For the calculation of Nesina treatment period, refer to the above.</p> <p>If the daily dose of Nesina is a number outside specification in the survey sheet (electronic) and is actual number, use the relevant number.</p>
HbA1c (NGSP value)	<p>The NGSP value only will be used in this analysis.</p> <p>For the HbA1c (JDS value), calculate using the following formula: NGSP value (%) = 1.02 × JDS value (%) + 0.25%</p> <p>The HbA1c (international standard value) will be handled as the NGSP value.</p>

Term	Definition
Change in HbA1c	For HbA1c converted to the NGSP value, calculate using the following formula: Laboratory value at each testing time point – Laboratory value at the start of Nesina treatment.
Glycemic control achievement rate	Divide the following two categories for the Glycemic control achievement rate: HbA1c (NGSP converted value) [Unit %] NGSP (%): < 6.0, ≥6.0 / < 7.0, ≥ 7.0
non-HDL cholesterol	Calculate using the following formula: “Total cholesterol” – “HDL cholesterol.”
Summary statistics	Number of patients, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum.

1.2 Important Identified Risks, Potential Risks, and Missing Information

Term	Definition
Important identified risk	
Hypoglycemia	Adverse events of the following PT Codes (term) are defined as hypoglycemia. 10020994(Hypoglycaemia neonatal) 10040576(Shock hypoglycaemic) 10021000(Hypoglycaemic coma) 10020993(Hypoglycaemia) 10065981(Hypoglycaemic unconsciousness) 10021002(Hypoglycaemic encephalopathy) 10048803(Hypoglycaemic seizure) 10020997(Hypoglycaemia unawareness) 10077216(Hyperinsulinaemic hypoglycaemia) 10059035(Postprandial hypoglycaemia)
Acute pancreatitis	Adverse events of the SMQ Code 20000022 (acute pancreatitis (SMQ) narrow scope are defined as acute pancreatitis.
Hepatic impairment / jaundice	Adverse events of the SMQ Code 20000005 (hepatic disorders (SMQ) broad) are defined as hepatic impairment / jaundice.
Skin disorder including oculomucocutaneous syndrome (Stevens-Johnson syndrome) / erythema multiforme	Adverse events of the SMQ Code 20000020 (severe skin adverse reactions (SMQ) narrow) are defined as skin disorder including oculomucocutaneous syndrome (Stevens-Johnson syndrome) / erythema multiforme.
Rhabdomyolysis	Adverse events of the SMQ Code 20000002 (rhabdomyolysis/myopathy (SMQ) narrow) are defined as rhabdomyolysis.
Intestinal obstruction	Adverse events of the SMQ Code 20000105 (gastrointestinal obstruction (SMQ) narrow) or the HLGT Code 10018008 (gastrointestinal stenosis and obstruction) or HLT Code 10052736 (non-mechanical ileus) are defined as intestinal obstruction.
Interstitial pneumonia	Adverse events of the SMQ Code 20000042 (interstitial lung disease (SMQ) narrow) are defined as interstitial pneumonia.
Angioedema	Adverse events of the SMQ Code 20000024 (angioedema (SMQ) narrow) are defined as angioedema.
Important potential risk	
Infection	Adverse events of SOC Code 10021881(infections and infestations) are defined as infection.
Malignant tumor	Adverse events of the SOC Code 10029104 (neoplasms benign, malignant and unspecified (incl cysts and polyps)) are defined as malignant tumor.

Malignant tumor (narrow sense)	Adverse events of the SMQ Code 20000194 (malignant tumors (SMQ) narrow) are defined as malignant tumor (narrow sense).
Pemphigoid	Adverse events of the PT Code 10067776 (ocular pemphigoid) or 10034277 (pemphigoid) are defined as pemphigoid.

Term	Definition
Important missing information	
Cardiovascular system risk	<p>Adverse events of the SMQ Code 20000047 (myocardial infarction (SMQ) broad) or SMQ Code 20000061 (central nervous system haemorrhages and cerebrovascular conditions (SMQ) broad) are defined as cardiovascular system risk.</p> <p>“Central nervous system haemorrhage and cerebrovascular conditions (SMQ) broad” includes the following SMQ classes.</p> <ul style="list-style-type: none"> ➤ 20000166(Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ) broad) ➤ 20000064(Cerebrovascular disorder haemorrhagic (SMQ) broad) ➤ 20000063(Cerebrovascular disease ischaemic (SMQ) broad)

1.3 Display digit

Term	Definition
Percentage (%)	<p>Percent of patients with adverse events or adverse drug reactions, etc. or percent of adverse events or adverse drug reactions, etc. :</p> <p>Indicate to two decimal places rounded from three decimals.</p> <p>Other than the above:</p> <p>Indicate to one decimal place rounded from two decimals.</p>
Summary statistics	<p>Mean, median, first quartile, and third quartile:</p> <p>Indicate one lower digit rounded from two lower digits than the digit of the to-be evaluated data.</p> <p>Standard deviation:</p> <p>Indicate two lower digits rounded from three lower digits of the to-be evaluated data.</p> <p>Minimum and maximum</p> <p>Indicate the same digit number as that of the to-be evaluated data (refer to Section 1.6).</p>
p-value	Indicate to three decimal places rounded down from four decimals.

Term	Definition
	If the data is rounded down from four decimal places and less than 0.001, display as $p < 0.001$.

1.4 Level of Significance and Confidence Coefficient

Two-sided 5%, two-sided 95%.

1.5 Handling of Laboratory/Measured Data

- VISIT as described in the survey sheet will be used for data other than 12 months and 36 months after Nesina treatment.
- 12 months after Nesina treatment: data at 12 months after Nesina treatment will be used for the 12 months survey sheet (electronic) for patients who continued treatment.
For patients who discontinued treatment, data at 12 months after Nesina treatment will not be used for the 12 months survey sheet (electronic).
- 36 months after Nesina treatment: data at 36 months after Nesina treatment will be used for the 36 months survey sheet (electronic) for patients who continued treatment.
For patients who discontinued treatment, data at 36 months after Nesina treatment will not be used for the 36 months survey sheet (electronic).
- At the last evaluation: The last VISIT data within the evaluation period will be used.

1.6 Display Data Digit

Display digits are described as below.

Term	Display digit	Unit
HbA1c	0.1	%
Fasting blood glucose level	1	mg/dL
Fasting insulin level	0.1	μ U/mL
Fasting triglyceride	1	mg/dL
Total cholesterol	1	mg/dL
HDL-cholesterol	1	mg/dL
LDL-cholesterol	1	mg/dL
Non-HDL cholesterol	1	mg/dL
Systolic blood pressure	1	mmHg
Diastolic blood pressure	1	mmHg
Weight	0.1	kg
BMI	0.1	kg/m^2
Age	1	Year

Disease duration of type 2 diabetes mellitus	0.1	Year
Height	1	cm
Week of pregnancy	1	Week
Nesina treatment period	1	Day
Mean daily dose of Nesina	0.01	mg

2.0 Disposition of Patients (Patient Diagram)

(1) Patients to be tabulated and analyzed

Registered patients

(2) Details of tabulation and analysis

The following will be tabulated: the number of registered patients, number of medical site at which patients is registered, number of patients whose survey sheets (electronic) are collected, number of patients whose survey sheets (electronic) are not collected, number of patients in the Safety Analysis Set, number of patients in the Not Safety Analysis Set, number of patients in the Efficacy Analysis Set, and number of patients in the Not Efficacy Analysis Set.

For the number of medical sites at which patients are registered, do not duplicate the same medical site with different departments.

For patients whose survey sheets (electronic) are not collected, tabulate the number of patients for each reason for not collected survey sheets.

For the Not Safety Analysis Set and Not Efficacy Analysis Set, the number of patients will be tabulated for each reason for exclusion to create the list.

The following is the handling of the decision whether patients who meet the following criteria should be evaluated:

Criterion	Safety evaluation	Efficacy evaluation
Pre-agreement administration [found after administration]	×	×
Registration 15 days after the start of Nesina treatment [found after registration]	×	×
Nesina taking not confirmed [after the end of patient registration period]	×	×
No data for post-administration of Nesina	×	×
No efficacy data at two time points equivalent to the start of Nesina treatment and 3 months after Nesina treatment	○	×
Other than patients with mild type 2 diabetes mellitus	○	×

○ Included, × Excluded or not evaluated

(3) Number of tables and figures

Figure 2.0-1 and Table 2.0-1

3.0 Patient Demographics

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Each parameter will be classified by the categories described below to tabulate the number of patients and frequency.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Category
Sex	Male, Female
Age	Summary statistics
	< 65 years, ≥ 65 years
	< 75 years, ≥ 75 years
	< 20 years, 20 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, 70 to 79 years, ≥ 80 years
Disease duration of type 2 diabetes mellitus (year)	Summary statistics
	< 2 years, 2 to < 5 years, 5 to < 10 years, ≥ 10 years, Unknown
Height	Summary statistics
Category of clinical practice	Outpatient, Inpatient
Pregnancy (only females)	No, Yes
Severity of renal impairment	Normal, Mild, Moderate, Severe
	Normal + Mild, Moderate + Severe
Concurrent disease	No, Yes
Diabetic complication	No, Yes
Details of diabetic complication (overlapped)	Diabetic nephropathy, diabetic retinopathy, diabetic neuropathy For the proportion, the number of patients with diabetic complication will be denominator.
Concurrent hypertension	No, Yes
Concurrent dyslipidemia	No, Yes
Concurrent hyperuricemia	No, Yes
Concurrent liver disorder	No, Yes
Details of concurrent	Hepatic steatosis, alcoholic hepatitis, chronic hepatitis, hepatic

Parameter	Category
liver disorder (overlapped)	cirrhosis, or other For the proportion, the number of with concurrent liver disorder will be denominator.
Concurrent renal disorder	No, Yes
Details of concurrent renal disorder (overlapped)	Nephrotic syndrome, glomerulonephritis, chronic glomerulonephritis, other For the proportion, the number of with concurrent renal disorder will be denominator.
Concurrent heart disease	No, Yes
Details of concurrent heart disease (overlapped)	Cardiac failure, myocardial infarction, angina pectoris, other For the proportion, the number of with concurrent heart disease will be denominator.
Concurrent cardiac failure	No, Yes
Severity classification of cardiac failure (NYHA classification)	Classes NYHA I, NYHA II, NYHA III, and NYHA IV, Unknown For the proportion, the number of with concurrent cardiac failure will be denominator.
Concurrent stroke-related disease	No, Yes
Details of concurrent stroke-related disease (overlapped)	Cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, transient ischaemic attack For the proportion, the number of with concurrent stroke-related disease will be denominator.
Concurrent allergic disease	No, Yes
Concurrent malignant tumour	No, Yes
Concurrent malignant tumour (narrow sense)	No, Yes
Other concurrent disease	No, Yes
Past medical history	No, Yes, Unknown
Hypersensitivity predisposition	No, Yes, Unknown
Alcohol history (drinking alcoholic)	Yes, No, Unknown

Parameter	Category
drinks almost on a daily basis)	
Smoking history	Never, Smoking, Smoked, Unknown
HbA1c(NGSP value) (at the start of Nesina treatment)	Summary statistics < 6.0%, 6.0% to < 7.0%, 7.0% to < 8.0%, ≥ 8.0%, Unknown ≥7.4%, > 7.4%, Unknown
Weight	Summary statistics
BMI	Summary statistics < 18.5 kg/m ² , 18.5 to < 25 kg/m ² , 25 to < 30 kg/m ² , ≥ 30 kg/m ² , Unknown < 25 kg/m ² , ≥25 kg/m ² , Unknown
Dietary intervention (at the start of Nesina treatment)	Yes, No
Exercise intervention (at the start of Nesina treatment)	Yes, No

(3) Number of tables and figures

Table 3.0-1

4.0 Details of Treatment

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Each parameter will be classified by the categories described below to tabulate the number of patients and frequency.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Category
Initial dose of Nesina	25 mg, 12.5 mg, 6.25 mg, or other
Mean daily dose of Nesina	> 25 mg, 25 to >12.5 mg, 12.5 to > 6.25 mg, or ≤6.25 mg
Nesina treatment period	Summary statistics
	1 to 60 days, 61 to 136 days, 137 to 273 days, 274 to 455 days, ≥456 days
Administration of prior medication (diabetic drug)	No, Yes
Prior medications (diabetic drugs)	<p>α-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, insulin preparations, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, combination of diabetic drugs, or other diabetic drugs</p> <p>For the proportion, the number of patients with “Yes” for administration of prior medication (diabetic drug) will be denominator.</p>
Administration of prior medication (other than diabetic drug)	No, Yes
Administration of concomitant medication (diabetic drug)	No, Yes
Concomitant medications (diabetic drugs) (overlapped)	<p>α-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, insulin preparations, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, combination of diabetic drugs, or other diabetic drugs</p> <p>For the proportion, the number of patients with “Yes” for administration of concomitant medication (diabetic drug) will be denominator.</p>

Parameter	Category
Administration of concomitant medication (hypertension drug)	No, Yes
Concomitant medications (hypertension drugs) (overlapped)	ARB, Ca antagonists, ACE inhibitors, diuretics, α blockers, $\alpha\beta/\beta$ blockers, Complication of hypertension drugs, or other For the proportion, the number of patients with “Yes” for administration of concomitant medication (hypertension drug) will be denominator.
Administration of concomitant medication (dyslipidaemia drug)	No, Yes
Concomitant medications (dyslipidaemia drugs) (overlapped)	Statins, fibrates, EPA/DHA, or other For the proportion, the number of patients with “Yes” for administration of concomitant medication (dyslipidaemia drug) will be denominator.
Administration of concomitant medication (protease drug)	No, Yes
Administration of concomitant medication (combined with renal excretory drug)	No, Yes
Administration of concomitant medication (other)	No, Yes

(3) Number of tables and figures

Table 4.0-1

4.1 Initial Dose of Nesina and Mean Daily Dose of Nesina, by Severity of Renal Impairment

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Cross tabulation will be used for the initial dose of Nesina and the mean daily dose of Nesina, by severity of renal impairment.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Category
Severity of renal impairment	Normal, Mild, Moderate, Severe
	Normal + Mild, Moderate + Severe
Initial dose of Nesina	25 mg, 12.5 mg, 6.25 mg, or other
Mean daily dose of Nesina	> 25 mg, 25 to >12.5 mg, 12.5 to > 6.25 mg, or \leq 6.25 mg

(3) Number of tables and figures

Tables 4.1-1 and 4.1-2

5.0 Safety Tabulation and Analysis

5.1 Occurrence of adverse events and adverse drug reactions / infections

5.1.1 Occurrence of adverse events

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

The following will be tabulated for adverse events.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Details of analysis
Number of patients with adverse events	Number of patients who experienced adverse events.
Number of adverse events	Number of adverse events. Count as an event if the same adverse event (LLT) occur multiple times in a patient. Count as different events for different LLTs even if they have the same PT.
Percent of patients with adverse events	Described in Section 1.1.
Type of adverse events	Will be broadly divided into the SOCs and tabulated by PT in the SOCs. In case of the laboratory test-related events, type of adverse events will be broadly divided into the SOCs and HLGTs for tabulation by PT. For the SOCs, the number of patients with adverse events and percent of patients with events will be described in the order of SOCs agreed internationally. For the PTs, the number of adverse events and percent of events will be described in the ascending order of PT codes. Count as an event if the same adverse event (LLT) occur multiple times in a patient. Count as different events for different LLTs even if they have the same PT.

(3) Number of tables and figures

Table 5.1.1-1

5.1.2 Occurrence of adverse drug reactions / infections

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

The following will be tabulated for adverse drug reactions, etc. and serious adverse drug reactions, etc.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Details of tabulation and analysis
Number of patients with adverse drug reactions, etc.	Number of patients who experienced adverse drug reactions, etc.
Number of adverse drug reactions, etc.	Number of adverse drug reactions, etc. Count as an event if the same adverse drug reactions, etc. (LLT) occur multiple times in a patient. Count as different events for different LLTs even though they have the same PT.
Percent of patients with adverse drug reactions, etc.	Described in Section 1.1.
Type of adverse drug reactions, etc.	Will be broadly divided into the SOCs and tabulated by PT in the SOCs. In case of the laboratory test-related events, type of adverse events will be broadly divided into the SOCs and HLGTs for tabulation by PT. For the SOCs, the number of patients with adverse drug reactions, etc. and percent of patients with adverse drug reactions, etc. will be described in the order of SOCs agreed internationally. For the PTs, the number of adverse drug reactions, etc. and percent of adverse drug reactions, etc. will be described in the ascending order of PT codes. Count as an event if the same adverse drug reactions, etc. (LLT) occur multiple times in a patient. Count as different events for different LLTs even though they have the same PT.

(3) Number of tables and figures

Tables 5.1.2-1 and 5.1.2-2

5.1.3 Important Identified Risks, Important Potential Risks, and Important Missing Information

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

The following will be tabulated for important identified risks, important potential risks, and important missing information (described in Section 1.2).

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Details of tabulation and analysis
Number of patients with adverse events (or adverse drug reactions,	Number of patients who experienced adverse events (or adverse drug reactions, etc.) with important identified risks, important potential risks, and important missing information.

Parameter	Details of tabulation and analysis
etc.)	
Number of adverse events (or adverse drug reactions, etc.)	Number of adverse events (or adverse drug reactions, etc.) with important identified risks, important potential risks, and important missing information. Count as an event if the same adverse event (or adverse drug reaction, etc.) (LLT) occur multiple times in a patient. Count as different events for different LLTs even if they have the same PT.
Percent of patients with adverse events (or adverse drug reactions, etc.)	Described in Section 1.1.
Type of adverse events (or adverse drug reactions, etc.)	Will be broadly divided into the important identified risks, important potential risks, and important missing information and tabulated by PT in them. For the PTs, the number of adverse events (or adverse drug reactions, etc.) and percent of adverse events (or adverse drug reactions, etc.) will be described in the ascending order of PT codes. Count as an event if the same adverse event (or adverse drug reaction, etc.) (LLT) occur multiple times in a patient. Count as different events for different LLTs even though they have the same PT.

- (3) Number of tables and figures
Tables 5.1.3-1 and 5.1.3-2

5.2 Occurrence of Adverse Events and Adverse Drug Reactions / Infections in the Not Safety Analysis

Set

5.2.1 Occurrence of Adverse Events

- (1) Patients to be tabulated and analyzed

Not Safety Analysis Set

- (2) Details of tabulation and analysis

The following will be tabulated.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Details of tabulation and analysis
Number of patients with adverse events	Number of patients who experienced adverse events.
Number of adverse	Number of adverse events. Count as an event if the same adverse

Parameter	Details of tabulation and analysis
events	event (LLT) occur multiple times in a patient. Count as different events for different LLTs even if they have the same PT.
Percent of patients with adverse events	Described in Section 1.1.
Type of adverse events	Will be broadly divided into the SOCs and tabulated by PT in the SOCs. In case of the laboratory test-related events, type of adverse events will be broadly divided into the SOCs and HLGTS for tabulation by PT. For the SOCs, the number of patients with adverse events and percent of patients with events will be described in the order of SOCs agreed internationally. For the PTs, the number of adverse events and percent of events will be described in the ascending order of PT codes. Count as an event if the same adverse event (LLT) occur multiple times in a patient. Count as different events for different LLTs even though they have the same PT.

(3) Number of tables and figures

Table 5.2-1

5.2.2 Occurrence of adverse drug reactions / infections

(1) Patients to be tabulated and analyzed

Not Safety Analysis Set

(2) Details of tabulation and analysis

The following will be tabulated.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Details of tabulation and analysis
Number of patients with adverse drug reactions, etc.	Number of patients who experienced adverse drug reactions, etc.
Number of adverse drug reactions, etc.	Number of adverse drug reactions, etc. Count as an event if the same adverse drug reactions, etc. (LLT) occur multiple times in a patient. Count as different events for different LLTs even if they have the same PT.
Percent of patients with adverse drug reactions, etc.	Described in Section 1.1.

Type of adverse drug reactions, etc.	<p>Will be broadly divided into the SOCs and tabulated by PT in the SOCs. In case of the laboratory test-related events, type of adverse events will be broadly divided into the SOCs and HLGs for tabulation by PT.</p> <p>For the SOCs, the number of patients with adverse drug reactions, etc. and percent of patients with adverse drug reactions, etc. will be described in the order of SOCs agreed internationally.</p> <p>For the PTs, the number of adverse drug reactions, etc. and percent of adverse drug reactions, etc. will be described in the ascending order of PT codes. Count as an event if the same adverse drug reactions, etc. (LLT) occur multiple times in a patient. Count as different events for different LLTs even though they have the same PT.</p>
--------------------------------------	--

(3) Number of tables and figures

Table 5.2-2

5.3 Occurrence of Adverse Drug Reactions / Infections by Severity, Onset Period, and Outcome

5.3.1 Occurrence of Adverse Drug Reactions / Infections by Severity, Onset Period, and Outcome

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Each parameter will be categorized by the categories described below to tabulate the type of adverse drug reactions, etc.

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Category
Severity	Serious, Not serious
Onset period	1 to 14 days, 15 to 28 days, 29 to 84 days, 85 to 168 days, 169 to 336 days, 337 to 504 days, 505 to 672 days, 673 to 840 days, 841 to 1008 days, ≥1009 days, or Unknown
Outcome	Resolved, Resolving, Not resolved, Resolved with sequelae, Death, or Unknown

The method for tabulation of type adverse drug reactions, etc. is described below:

Parameter	Details of tabulation and analysis
Type of adverse drug reactions, etc.	<p>Will be broadly divided into the SOCs and tabulated by PT in the SOCs. In case of the laboratory test-related events, type of adverse events will be broadly divided into the SOCs and HLGs for tabulation by PT.</p> <p>For the SOCs, the number of patients with adverse drug reactions,</p>

Parameter	Details of tabulation and analysis
	<p>etc. will be described in the order of SOCs agreed internationally.</p> <p>For the PTs, the number of adverse drug reactions, etc. will be described in the ascending order of PT codes. Count as an event if the same adverse drug reactions, etc. (LLT) occur multiple times in a patient. Count as different events for different LLTs even if they have the same PT. However, evaluate an event for the same LLT in accordance with the following order of priority:</p> <p>Onset period: earlier event</p> <p>Severity: Serious → Not serious</p> <p>Outcome: Death → Resolved with Sequelae → Not resolved → Resolving → Resolved → Unknown</p>

(3) Number of tables and figures

Tables 5.3-1 to 5.3-3

5.4 Patient Demographics and Frequency of Adverse Drug Reactions / Infections by Treatment

5.4.1 Patients demographics and Frequency of Adverse Drug Reactions / Infections by Treatment

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Each parameter will be categorized by the categories described below to tabulate the percent of patients with adverse drug reactions, etc.

The Fischer exact test will be used for parameters without rank data. The Mann-Whitney U test will be used for parameters with rank data. (The tests will be used for parameters with asterisk [*].)

Total and mild type 2 diabetes mellitus patients will be tabulated.

Parameter	Category
Sex*	Male, Female
Age*	< 65 years, ≥65 years
	< 75 years, ≥75 years
Severity of renal impairment*	Normal + Mild, Moderate + Severe
Concurrent liver disorder*	No, Yes
Concurrent renal disorder*	No, Yes
Concurrent heart disease*	No, Yes

Parameter	Category
Details of concurrent heart disease (overlapped)	Cardiac failure, myocardial infarction, or angina pectoris
Concurrent cardiac failure*	No, Yes
Severity classification of cardiac failure (NYHA classification)*	Classes NYHA I, NYHA II, NYHA III, and NYHA IV
Concurrent stroke-related disease*	No, Yes
Mean daily dose of Nesina	> 25 mg, 25 to >12.5 mg, 12.5 to > 6.25 mg, or ≤6.25 mg
Administration of concomitant medication (diabetic drug)	No, Yes
Concomitant medications (diabetic drugs) (overlapped)	α-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, or insulin preparations
Administration of concomitant medication (protease drug)*	No, Yes
Administration of concomitant medication (combined with renal excretory drug)*	No, Yes

(3) Number of tables and figures

Table 5.4.1-1

5.5 Occurrence of Adverse Drug Reactions / Infections by Age

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Age will be classified into < 65 years, ≥65 years and < 75 years, and ≥75 years for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Tables 5.5-1 to 5.5-2

5.6 Occurrence of Adverse Drug Reactions / Infections by Sex

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Sex will be classified into male or female for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.6-1

5.7 Occurrence of Adverse Drug Reactions / Infections by Liver Disorder

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Concurrent liver disorder will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.7-1

5.8 Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Renal Disorder

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Concurrent renal disorder will be classified into yes or no for tabulation of type of adverse

drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.8-1

5.9 Occurrence of Adverse Drug Reactions / Infections by Severity of Renal Impairment

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Severity of renal impairment will be classified into normal + mild or moderate + severe for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.9-1

5.10 Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Heart Disease

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Concurrent heart disease will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.10-1

5.11 Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Heart Failure

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Concurrent heart failure will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section

5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.11-1

5.12 Occurrence of Adverse Drug Reactions / Infections by Severity of Heart Failure

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Severity of heart failure will be classified into Class NYHA I, NYHA II, NYHA III, or NYHA IV for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.12-1

5.13 Occurrence of Adverse Drug Reactions / Infections by Presence of Concurrent Stroke-related Disease

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Concurrent stroke-related disease will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.13-1

5.14 Occurrence of Adverse Drug Reactions / Infections by Mean Daily Dose of Nesina

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

The mean daily dose of Nesina will be classified into > 25 mg, 25 to > 12.5 mg, 12.5 to > 6.25 mg, or ≤6.25 mg for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section

5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.14-1

5.15 Occurrence of Adverse Drug Reactions / Infections by Mean Daily Dose of Nesina in Patients with Special Demographics (Patients with Moderate or Higher Renal Impairment)

(1) Patients to be tabulated and analyzed

Patients with moderate or higher renal impairment in the Safety Analysis Set

(2) Details of tabulation and analysis

The mean daily dose of Nesina will be classified into > 25 mg, 25 to > 12.5 mg, 12.5 to > 6.25 mg, or ≤6.25 mg for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.15-1

5.16 Occurrence of Adverse Drug Reactions / Infections by Administration of Concomitant Medication (Diabetic Drug)

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Administration of concomitant medication (diabetic drug) will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.16-1

5.17 Occurrence of Adverse Drug Reactions / Infections by Concomitant Medication (Diabetic Drug)

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Concomitant medications (diabetic drugs) will be classified into the following drugs: α -glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin

secretagogues, or insulin preparations, for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.17-1

5.18 Occurrence of Adverse Drug Reactions / Infections by Presence of Concomitant Protease Inhibitors

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Concomitant protease inhibitor will be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.18-1

5.19 Occurrence of Adverse Drug Reactions / Infections by Presence of Concomitant Renal Excretory Drug

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

Concomitant renal excretory drug be classified into yes or no for tabulation of type of adverse drug reactions, etc.

The method for tabulation of adverse drug reactions, etc. is same as that described in Section 5.1.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.19-1

5.20 Change in Laboratory/Measured Data

5.20.1 Vital Signs

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

For blood pressure (systolic/diastolic) and weight, summary statistics will be calculated at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation). For changes from the start of Nesina treatment, summary statistics and the mean 95% confidence intervals will be calculated.

Measured values (mean and standard deviation) of blood pressure (systolic/diastolic) and weight will be plotted. For the changes, the mean changes will be created using a bar graph.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.20.1-1 and Figures 5.20.1-1 to 5.20.1-6

5.20.2 Laboratory Values

(1) Patients to be tabulated and analyzed

Safety Analysis Set

(2) Details of tabulation and analysis

For laboratory values of fasting triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, and non-HDL cholesterol, summary statistics will be calculated at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation). For changes from the start of Nesina treatment, summary statistics and the mean 95% confidence intervals will be calculated.

The individual laboratory values described above (mean and standard deviation) will be plotted. For the changes, the mean changes will be created using a bar graph.

Total and mild type 2 diabetes mellitus patients will be tabulated.

(3) Number of tables and figures

Table 5.20.2-1 and Figures 5.20.2-1 to 5.20.2-10

6.0 Efficacy Tabulation and Analysis

6.1 Changes in HbA1c

(1) Patients to be tabulated and analyzed

Efficacy Analysis Set

(2) Details of tabulation and analysis

For HbA1c (NGSP values), summary statistics will be calculated at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation). For changes, summary statistics and the mean 95% confidence intervals will be calculated and the paired t-test will be performed.

Measured values of HbA1c (NGSP values) will be plotted and for the changes a bar graph will be created excluding the unknown category at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation).

(3) Number of tables and figures

Table 6.1-1 and Figure 6.1-1

6.2 Glycemic control achievement rate (HbA1c)

(1) Patients to be tabulated and analyzed

Efficacy Analysis Set

(2) Details of tabulation and analysis

The Glycemic control achievement rate for HbA1c (NGSP value) will be tabulated ($< 7.0\%$, $\geq 7.0\%$ / $< 6.0\%$, $\geq 6.0\%$) and a bar graph will be created ($< 7.0\%$, $\geq 7.0\%$ / $< 6.0\%$, $\geq 6.0\%$) at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation) (the unknown category will be excluded for the bar graph).

(3) Number of tables and figures

Table 6.2-1 and Figure 6.2-1

6.3 Changes in Fasting blood glucose level and Fasting insulin level

(1) Patients to be tabulated and analyzed

Efficacy Analysis Set

(2) Details of tabulation and analysis

For fasting blood glucose level and fasting insulin level, summary statistics will be calculated at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation). For changes, summary statistics and the mean 95% confidence intervals will be calculated and the paired t-test will be performed.

Measured values of fasting blood glucose level and fasting insulin level will be plotted and for the changes a bar graph will be created excluding the unknown category at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months after Nesina treatment and last evaluation).

(3) Number of tables and figures

Tables 6.3-1 and 6.3-2 and Figures 6.3-1 and 6.3-2

6.4 Changes in HbA1c, etc. by Factor Probably Affecting Efficacy

(1) Patients to be tabulated and analyzed

Efficacy Analysis Set

(2) Details of tabulation and analysis

For changes in HbA1c (NGSP values), summary statistics and the mean 95% confidence intervals will be calculated and the paired t-test will be performed at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 24 months, and 36 months after Nesina treatment and last evaluation).

The Glycemic control achievement rate for HbA1c ($< 7.0\%$, $\geq 7.0\%$ / $< 6.0\%$, $\geq 6.0\%$) at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 24 months, and 36 months after Nesina treatment and last evaluation) will be tabulated at the following parameters:

i Sex (Male, Female)

ii Age (< 65 years, ≥ 65 years)

iii Age (< 75 years, ≥ 75 years)

iv Concurrent renal disorder (No, Yes)

v HbA1c (NGSP value) at the start of Nesina treatment ($< 6.0\%$, 6.0% to $< 7.0\%$, 7.0% to $< 8.0\%$, $\geq 8.0\%$)

vi Mean daily dose of Nesina (> 25 mg, 25 to > 12.5 mg, 12.5 to > 6.25 mg, or 6.25 mg)

vii Concomitant diabetic drugs (α -glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, rapid-acting insulin secretagogues, or insulin preparations)

(3) Number of tables and figures

Tables 6.4-1 to 6.4-14

6.5 Changes in HbA1c, etc. in Patients with Special Demographics

(1) Patients to be tabulated and analyzed

Efficacy Analysis Set.

However, patients will be evaluated for Parameter (ii) in (2) Details of tabulation and analysis.

Patients with moderate or higher renal impairment in the Efficacy Analysis Set.

(2) Details of tabulation and analysis

For changes in HbA1c (NGSP values), summary statistics and the mean 95% confidence

intervals will be calculated and the paired t-test will be performed at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 24 months, and 36 months after Nesina treatment and last evaluation).

The Glycemic control achievement rate for HbA1c ($< 7.0\%$, $\geq 7.0\%$ / $< 6.0\%$, $\geq 6.0\%$) at each testing time point (start of Nesina treatment, 3 months, 6 months, 12 months, 24 months, and 36 months after Nesina treatment and last evaluation) will be tabulated at the following parameters:

- i. Severity of renal impairment (Normal + Mild, Moderate + Severe)
- ii. Mean daily dose of Nesina (> 25 mg, 25 to > 12.5 mg, 12.5 to > 6.25 mg, or 6.25 mg)

(3) Number of tables and figures

Tables 6.5-1 to 6.5-4