Assessment report

Tenelia® 20 mg

Teneligliptin

(Teneligliptin Hydrobromide Hydrate)

Submission number: 1C 15107/61(N)

Applicant: Mitsubishi Tanabe Pharma (Thailand) Co., Ltd.

Product team leader:	Worasuda yoongthong
Co-product team leader:	Kridiphol Janthranant
Start of the procedure:	26 September 2018
e-submission number and sequence number	e6100072 0001-0005
Date of this report:	4 March 2020

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Administrative information

Invented name of the medicinal product:	เทเนเลีย 20 มก. Tenelia® 20 mg
INN (or common name) of the active substance(s):	Teneligliptin (INN) Teneligliptin Hydrobromide Hydrate (JAN)
Applicant:	Mitsubishi Tanabe Pharma (Thailand) Co., Ltd.
Applied Indication(s):	**Monotherapy:** TENELIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus **Combination therapy:** TENELIA is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin, sulfonylureas, PPAR agonist (e.g., thiazolidinediones), rapid insulin secretagogues, alpha-glucosidase inhibitors, sodium glucose co-transporter 2 inhibitor, or insulin when the single agent alone, with diet and exercise, does not provide adequate glycemic control.
Pharmaco-therapeutic group (ATC Code):	Dipeptidyl peptidase 4 (DPP-4) inhibitors (A10BH)
Pharmaceutical form(s) and strength(s):	Transdermal patch 100 mg
Product team leader contact person: **Co-Product team leader contact person:**	**Name**: Worasuda yoongthong Email: worasuda302@gmail.com **Name**: Kridiphol Janthranant Email: kridipholjan.fda@gmail.com

Declaration

This application includes an Active Substance Master File (ASMF):

☐ Yes

☑ No

List of abbreviations

SU	Sulfonylurea
JP	Japanese Pharmacopoeia
JPE	Japanese Pharmaceutical Excipients
NOAEL	No Observe Adverse Effect Level
PK	Pharmacokinetic
OGTT	Oral glucose tolerance test
OCLT	Oral calcium-loading tes
q.d.	Once daily
t.i.d.	Three times a day

1. Recommendation

Based on the review of the data and the Applicant's response to the list of questions (LOQs) on quality, safety, efficacy, Thai FDA consider that the application for Tenelia 20 mg, a new medicinal product in the indications,

Monotherapy:
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Combination therapy:
TENELIA is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin, sulfonylureas, PPAR agonist (e.g., thiazolidinediones), rapid insulin secretagogues, alpha-glucosidase inhibitors, sodium glucose co-transporter 2 inhibitor, or insulin when the single agent alone, with diet and exercise, does not provide adequate glycemic control

is approvable provided that the applicant commits to perform a number of post authorisation measures to be reported back to Thai FDA within predefined timeframes. Preliminary lists of such post-authorisation measures are in section 5.1 of this report.

2. Executive summary

2.1. Problem statement

Type 2 Diabetes Mellitus (T2D) is a progressive chronic metabolic disease primarily characterised by abnormal glucose metabolism. Data support a heterogeneous pathogenesis that involves environmental, lifestyle, and genetic components leading to chronic hyperglycaemia caused by insulin resistance in the peripheral tissue, reduced insulin production in the pancreatic β-cells and increased hepatic glucose release.

The prevalence of diabetes is increasing rapidly worldwide especially in middle- and low-income countries. It can cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation. Due to the progressive nature of T2D, most patients will require treatment intensification, which can be in the form of additional anti-glycaemic oral agents or an injectable therapy.

Six types of oral anti-hyperglycemic drugs are commercially available for treatment of type 2 diabetes. The six types are sulfonylurea, Biguanides, α-Glucosidase inhibitors (α-GI), Thiazolidinedione, Rapid-acting insulin secretagogues and DPP-4 inhibitors. The drug to administer is selected on the basis of the individual patient's condition, taking into consideration the adverse drug reactions and specific activities of each drug.

There are risks of various types of adverse drug reaction by using oral anti-hyperglycemic drug, including hypoglycemia with SU drugs and rapid-acting insulin secretagogues; gastrointestinal disorders and lactic acidosis with BG; flatus and diarrhea with α-GI; and body weight gain, edema, and heart failure with TZD drugs.

In addition, the characteristic chronic complications of diabetes include retinopathy, nephropathy and neuropathy, which are classed as microangiopathy. During an early stage in the clinical course of diabetic nephropathy, the patient develops microalbuminuria, followed by macroproteinuria until hemodialysis finally becomes necessary. The incidence of both microalbuminuria and macroproteinuria are high and it has been reported that many type 2 diabetes patients even without microalbuminuria or macroproteinuria have impaired renal function.

2.2. About the product

Teneligliptin hydrobromide hydrate is a dipeptidyl peptidase-4 (DPP-4) inhibitor. DPP-4 inhibitors are therapeutic drugs for type 2 diabetes that increase the concentration of active glucagon-like peptide-1

(GLP-1) in the blood, thus promoting glucose-dependent insulin secretion, and inhibiting glucagon secretion, resulting in antihyperglycemic effects. The indication of Teneligliptin is

Monotherapy: TENELIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus

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2.3. The development programme/compliance with Thai FDA guidance/scientific advice

Not applicable.

2.4. General comments on compliance with GMP, GLP, GCP

The GMP certificate from Mitsubishi Tanabe Pharma Factory Ltd., is available accepted by Thai FDA. The information stated in the dossier that compliance of ICH guideline and GLP in non-clinical studies. The clinical studies were conducted with consideration given to ethical principles based on the Declaration of Helsinki, and compliance with GCP. All data were noted and acceptable.

2.5. Type of application and other comments on the submitted dossier

- Stand alone application

The overall assessment was conducted by collecting external expert comments with expert panel meeting.

3. Scientific overview and discussion

3.1. Introduction

Teneligliptin hydrobromide hydrate, the active ingredient of Tenelia 20 mg, is a dipeptidyl peptidase-4 (DPP-4) inhibitor synthesized by Mitsubishi Tanabe Pharma Corporation. A DPP-4 inhibitor is a therapeutic drug for type 2 diabetes mellitus, exerting its hypoglycemic effect by suppressing degradation of active glucagon-like peptide-1 to increase its blood concentration, resulting in glucose-dependent enhancement of insulin secretion and also suppression of glucagon secretion.

In the non-clinical studies, teneligliptin hydrobromide hydrate showed sustained DPP-4 inhibition.

In the clinical studies, Tenelia 20 mg or placebo was administered once a day for 12 weeks to type 2 diabetes patients with insufficient blood glucose control by diet therapy and exercise therapy, and the patients with insufficient blood glucose control by sulfonylurea or thiazolidine in addition to the diet therapy and exercise therapy. In these studies, Tenelia 20 mg decreased hemoglobin A1c (HbA1c), fasting blood glucose, and 2-h postprandial blood glucose levels significantly compared to the placebo group and the efficacy of once-daily administration for improving blood glucose control over 24 h was confirmed. Also, the efficacy and the safety of long term administration of Tenelia 20 mg with sulfonylurea, thiazolidine, glinide, biguanide, or α- glucosidase inhibitor were confirmed.

Based on the results of non-clinical and clinical studies, Tenelia 20 mg is thought to be a useful drug for type 2 diabetes mellitus.

3.2. Quality aspects

3.2.1. Introduction

Proprietary Name of drug Product: Tenelia

Nonproprietary Name of drug Product: Teneligliptin

Nonproprietary Name of drug substance: Teneligliptin Hydrobromide Hydrate

Company name: Mitsubishi Tanabe Pharma (Thailand) Co., Ltd.

Dosage form: Film coated tablet

Strength: 20 mg/tablet

Route of administration: oral

Proposed indication:

Monotherapy: Tenelia is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus

Combination therapy: Tenelia is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin, sulfonylureas, PPAR agonist (e.g., thiazolidinediones), rapid insulin secretagogues, alpha-glucosidase inhibitors, sodium glucose co-transporter 2 inhibitor, or insulin when the single agent alone, with diet and exercise, does not provide adequate glycemic control

3.2.2. Active Substance

General Information

International Nonproprietary Name (r-INN): teneligliptin

Manufacture, characterisation and process controls

Mitsubishi Tanabe Pharma Factory Ltd., Japan is responsible for manufacture of the active substance.
The active substance is manufactured according to current Good Manufacturing Practices.
For manufacturing process data, All steps have been described and explained in dossier.

Control of Materials

The applicant provided adequate information regarding the raw materials used during the manufacturing of the active substance. Compendial substances are released according to their pharmacopeial requirements. Acceptance criteria and test methods for non-compendial materials have been provided.

Controls of Critical Steps and Intermediates

(1) Critical step

The controls and acceptance criteria of critical steps are shown in dossier.

(2) Critical intermediate

The controls and acceptance criteria are shown in dossier.

Process Validation and/or Evaluation

Manufacturing process validation was performed using three consecutive process verification lots for the active substance manufactured with the commercial process. Results have been reported as supporting data.

Manufacturing Process Development

No significant modifications have been made excluding the change to the order of charging reagents in production since the manufacture of drug substance for toxicity testing. Manufacturing batch for toxicity testing, charging order of reagents was different from other batches. The modified order of charging reagents does not impact on the quality of teneligliptin hydrobromide hydrate.

Characterisation

Elucidation of structure and other characteristics

Elemental analysis, spectrometry (ultraviolet-visible absorption spectrum, infrared absorption spectrum, nuclear magnetic resonance spectrum, mass spectrum), and single-crystal X-ray structure analysis of teneligliptin hydrobromide hydrate were performed for determination of structure.

Impurity

Related substances that may be present in teneligliptin hydrobromide hydrate are listed in dossier.

Specification

The drug substance specification including control of identity, purity, and other general test has been provided.

Analytical Procedures

The analytical procedures of teneligliptin hydrobromide hydrate were conducted. Validation of analytical procedures was carried out in references to the ICH guideline, Q2A and Q2B. All the acceptance criteria on the validation characteristics were met, and the data confirmed that the proposed test methods are appropriate for the testing of teneligliptin hydrobromide hydrate.

Batch analyses

The batch analysis data for 3 batches of Teneligliptin hydrobromide hydrate are present in the dossier. All batch release data shown comply with the drug substance specification for teneligliptin.

Container closure system

Teneligliptin hydrobromide hydrate is placed in primary packaging and then in secondary packaging.

Stability Data of teneligliptin hydrobromide hydrate manufactured for performance qualification and process validation showed no significant changes for up to 36 months in the long-term stability studies and for up to 6 months in the accelerated test. The above container closure systems were therefore successfully qualified.

Stability

Stability studies of one lot of teneligliptin hydrobromide hydrate manufactured for the performance qualification at Mitsubishi Tanabe Pharma Factory Ltd. and 3 lots manufactured for process validation for the first time in commercial scale at Mitsubishi Tanabe Pharma Factory Ltd. have been completed.

The performance qualification lot of teneligliptin hydrobromide hydrate showed no significant changes for up to 36 months in the long-term stability study and for up to 6 months in the accelerated test.

The process validation lots of teneligliptin hydrobromide hydrate showed no significant changes for up to 36 months in the long-term stability study and for up to 6 months in the accelerated test.

Stress test

Results of stress tests including temperature test, humidity test and lights test are provided in dossier. All of tests are following the ICH guideline. The report had shown no significant changes at all periods in these stress tests.

Conclusions

Number of batch, condition, duration and parameters followed by ICH guideline are suitable. The stability results indicate that the active substance manufactured by the proposed suppliers sufficiently stable in the proposed container.

3.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The drug product, Tenelia 20 mg contains Teneligliptin 20 mg with others excipients to form film-coated tablet weight 125 mg.

Composition:

Specification	Component
In specification	Teneligliptin
JP	D-Mannitol
JP	Corn starch
JP	Hydroxypropylcellulose
JP	Light Anhydrous Silicic Acid
JP	Low Substituted Hydroxypropylcellulose
JP	Magnesium Stearate
JP	Hypromellose
JP	Macrogol 400
JP	Titanium Oxide
JPE	Red Ferric Oxide
JP	Hydrogenated Oil

JP: Japanese Pharmacopeia
JPE: Japanese Pharmaceutical Excipients

Information on Development studies

Teneligliptin hydrobromide hydrate is a compound discovered to have a long-acting DPP-4 inhibitory effect. For oral administration, tablet, the most common dosage form among oral formulations, was selected.

Component of the Drug product

The solubility of teneligliptin hydrobromide hydrate is freely soluble; showing the solubility of the drug substance is unlikely to affect dissolution of the drug product. Excipients are selected from common excipients based on the experience with oral solid formulations.

Finished product

The tablet is round having a diameter of about 7 mm and a thickness of about 3 mm. One tablet weight is 125 mg. The tablet is coated to give a vivid light red color.

The dissolution rate of Tenelia 20 mg produced in commercial scale was not less than 85% in 15 minutes in all the test solutions.

Manufacture of the product and process controls

Manufacturing and site responsibility

1. Mitsubishi Tanabe Pharma Factory Ltd., Yoshitomi Plant (955, Oaza-Koiwai, Yoshitomi-cho, Chikujou-gun, Fukuoka 871-8550, Japan): Site 1

Responsibility: Procurement (and acceptance test) and weighing of raw materials, manufacturing of bulk drug product, testing/inspection of bulk drug product

2. Site 2 (undisclosure information)

Responsibility: Confidential

3. PT Mitsubishi Tanabe Pharma Indonesia (JL. Rumah Sakit 104, Ujungberung, Bandung 40612, Indonesia): Site 3

Responsibility: Packaging, labeling, testing and inspection, storage of final product

Manufacturing process and in process control

The manufacturing process and in process control of Tenelia 20 mg drug product was described as flow diagram in the dossier.

Control of critical steps

The critical steps together with limits and actions for critical in-process controls for Tenelia 20 mg finished product are provided

Process validation and Evaluation

All the acceptance criteria were met in in-process tests, process analysis test, bulk tests and manufacturability of all 3 lots.

After process validation of the primary packaging process of Tenelia 20mg by using Blistering Machine and secondary packaging process by using Pillow Packaging Machines

a. Primary packaging processes meet the acceptance criteria. Secondary packaging processes meet the acceptance criteria.

It could be concluded that packaging process for blistering test and pillow packaging test of Tenelia 20 mg were meet the established specification with the optimum setting of machine. The settings of machine were validated and it could be implemented in routine packaging process.

Control of excipients

Specifications

The excipients are complied with JP and JPE that show formulation has standard and acceptable. Moreover, they have no use novel excipients in the formulation.

Product specification

The drug product specification including control of identity and other general test has been provided.

Analytical procedures

The analytical procedures which comply with JP are described.

Note: Unless otherwise specified, the specifications and test methods follow the General Notices section, the General Rules for Preparations section, and the General Tests, Processes and Apparatus section in the JP.

Validation of Analytical Procedures *(performed in Oct-Nov 2013)*

Based on the above result all of the validation characteristics were met the acceptance criteria of Tenelia 20 mg. It can be concluded that the Identification, Purity, Uniformity of dosage units, Dissolution and Assay method used for analyzing the Tenelia 20 mg has been validated.

Batch analysis

The results of the release testing of the Tenelia 20 mg three batches are provided. The manufacturing and packaging information for the batches is provided in the dossier.

Characterization of Impurities

A characterisation study was conducted to characterise the Tenelia 20 mg related impurities generated during the manufacture and storage of semaglutide finished product.

Justification of Specification

Tenelia 20 mg was approved in Japan, therefore the validity of the specification approved by Japanese authority was verified based on the stability data and was alresdy provided in dossier.

Reference Standards

Teneligliptin hydrobromide hydrate reference standard must meet the specifications for teneligliptin hydrobromide hydrate.

Container closure system

The drug products are contained into blister packs of 10 tablets. Each 3 blisters sheets and each 10 blisters sheets are packed in pillow pack and then in box.

Stability of the product

The stability testing of Tenelia 20 mg, the accelerated stability test at 40°C/75%RH and long term stability test at 30°C/75%RH were performed using the drug products manufactured at Yoshitomi Plant of Mitsubishi Tanabe Pharma Factory Ltd., and packaged at Bandung factory of PT Mitsubishi Tanabe Pharma Indonesia.

The results of the stability studies are summarized in table below. No significant change was observed until 6 months of the accelerated test and 42 months of long-term stability study.

Photostability study

In photostability study, Tenelia 20 mg without packaging were exposed to total illumination intensity of not less than 1.2 million lux · hr and near ultraviolet energy of not less than 200W · h/m2. As the result, test items except for impurity didn't have any change from initial. On the other hand, impurity of tablets without packaging increased. However, the value is not more than threshold value and met the planned specification.

Post-Approval stability protocol and stability commitments

On each subsequent year, at least one commercial batch of Tenelia 20 mg, packed into the approved packaging material, will be placed on stability test; the samples will be stored at 30°C/75% RH and tested yearly, during the product shelf life.

Conclusion of stability study

Test results for 3 stability batches, for up to 6 months at 40ºC/75% RH and up to 42 months at the 30ºC/75% RH storage conditions, are also provided in support of drug product stability. Condition of stability test is accordance with ASEAN stability guideline on drug product 2013. All results of the stability study are within the proposed specification acceptance criteria at all test intervals for all storage conditions. From the stability study, it can be concluded that Tenelia 20 mg tablet is stable at least 42 months in the temperature not more than 30°C/75%RH in the light proof container stated above.

Adventitious agents

N/A

GMO

N/A

3.2.4. Discussion on chemical, pharmaceutical and biological aspects

The lists of questions (LOQs) were raised by the external experts and the Co-PTL. Almost questions focused on the adequacy of the details in manufacturing process and quality control. The LOQs were summarized and adequate response in appendix 6.3.

3.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Tenelia 20 mg tablet contain Teneligliptin hydrobromide hydrate as the drug substance. The the information of drug substance and drug product were fully described and appropriate. The lists of questions (LOQs) were raised by external experts in quality part. LOQs were summarized and adequate response by the applicants. Based on the information in dossier and adequate response from the applicant, the quality part of Tenelia 20 mg is acceptable and appropriate.

3.3. Non clinical aspects

In the nonclinical studies, with the aim of clarifying the safety of the clinical dose predicted to be effective, the pharmacology, pharmacokinetics, and toxicity of teneligliptin and its metabolites predicted in humans were evaluated using various types of in vitro and in vivo studies. There are three stereoisomers of teneligliptin; however, the concentrations of these isomers were found to be below the limit of quantification in rat plasma and in human plasma in the Phase I clinical study, indicating that stereoconversion is not considered to take place within the human body, and therefore a decision not to evaluate the pharmacology and toxicity of the stereoisomers was made. The teneligliptin doses and teneligliptin concentrations in test samples are all expressed in terms of the free base. Details of the pharmacology, pharmacokinetics, and toxicity study protocols are shown below.

3.3.1. Pharmacology

In the in vitro studies, the DPP-4-inhibitory activities of teneligliptin were investigated using human recombinant DPP-4 and DPP-4 in human and rat plasma. In addition, the mode of inhibition was investigated using human recombinant DPP-4, and the mechanism of action was investigated using rat plasma. The DPP-4-inhibitory activities of the teneligliptin metabolites (M1, M2, M3, M4, M5) were also investigated. In addition, in the in vivo studies, DPP-4 inhibition and alleviation of abnormal glucose tolerance were investigated using normal animals (rats and cynomolgus monkeys) and animals models of diabetes mellitus (mice and rats), and effects on fasting-state blood glucose were investigated using normal rats.

Secondary pharmacodynamic studies were conducted to investigate the selectivity of teneligliptin for enzymes related to DPP-4 and for various enzymes and receptors in vitro. At the same time, M1, the most abundant metabolite present in human plasma, was also investigated.

Safety pharmacology studies were conducted to evaluate the effects of teneligliptin on the central nervous system, cardiovascular system, respiratory system, renal/urinarysystem, and gastrointestinal system. In addition, the effects of M1 on the human ether-a-go-go related gene (hERG) channel were evaluated in vitro. The core battery safety pharmacology studies were conducted in accordance with the S7A Guidelines, which are safety pharmacology guidelines published by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), other relevant ICH guidelines, and Good Laboratory Practice for safety evaluation of pharmaceuticals (Pharmaceutical GLP). The pharmacology studies were summarized in the table below:

Table: Summary of pharmacology studies of Teneligliptin

No.	**Title**	**Model**	**Results**
1	Inhibitory effects on human recombinant DPP-4 (including metabolites)	Human (In vitro) Dose (mg/kg): 0.01-1000 mmol/L	IC_{50} values: Teneligliptin: 0.889 nmol/L M1: 34.3 nmol/L M2: 35.7 nmol/L M3: >1000 nmol/L M4: 0.951 nmol/L M5: 5.06 nmol/L
2	Study of inhibition kinetics using human recombinant DPP-	Human (In vitro) Dose (mg/kg): 0.1-3	Inhibition kinetics of the competitive type with a Ki of

No.	Title	Model	Results
	4	mmol/L	0.406 nmol/L
3	Comparison with drugs in the same class with respect to effects on human recombinant DPP-4	Human (In vitro) Dose (mg/kg): 0.01-1000 mmol/L	IC_{50} values: Teneligliptin: 1.01 nmol/L Sitagliptin: 6.74 nmol/L Vildagliptin: 10.5 nmol/L Saxagliptin: 2.51 nmol/L
4	Inhibitory effects on human plasma DPP-4	Human (In vitro) Dose (mg/kg): 0.01-1000 mmol/L	IC_{50} value: 1.75 nmol/L
5	Comparison with drugs in the same class with respect to inhibitory effects on human plasma DPP-4	Human (In vitro) Dose (mg/kg): 0.01-1000 mmol/L	IC_{50} values: Teneligliptin: 1.45 nmol/L Sitagliptin: 4.88 nmol/L Vildagliptin: 7.67 nmol/L
6	Inhibitory effects on rat plasma DPP-4	Rat/Wistar (In vitro) Dose (mg/kg): 0.01-1000 mmol/L	IC_{50} values: Teneligliptin: 1.14 nmol/L Sitagliptin: 10.4 nmol/L Vildagliptin: 6.81 nmol/L
7	Suppressive effects on degradation of rat plasma GLP-1	Rat/Wistar (In vitro) Dose (mg/kg): 0.01-1000 mmol/L	IC_{50} values: Teneligliptin: 2.92 nmol/L Vildagliptin: 11.8 nmol/L
8	Inhibitory effects on plasma DPP-4 in normal rats after a single dose (comparison with drugs in the same class)	Rat/Wistar (p.o.) Dose (mg/kg):0.01-10 (Sitagliptin: 0.1-100 Vildagliptin: 0.1-100)	ED_{50} values: Teneligliptin: 0.41 mg/kg ED_{50} value at 12 h after administration: 1.39 mg/kg Sitagliptin: 27.28 mg/kg Vildagliptin: 12.77 mg/kg ED_{50} values of these drugs 12 h after administration: >100 mg/kg
9	Inhibitory effects on plasma DPP-4 in monkeys after a single dose	Cynomolgus monkey (p.o.) Dose (mg/kg): 0.13, 0.43, 1.3 (Vildagliptin: 0.3)	Maximum inhibition: Teneligliptin (0.13 mg/kg) and vildagliptin (0.3 mg/kg) were similar (approximately 65% inhibition) Duration of effect: The inhibitory effect of teneligliptin (0.13 mg/kg) lasted for 24 h after administration, whereas that of vildagliptin (0.3 mg/kg) disappeared 8 h after administration
10	Suppression of blood glucose increase in ZF rats during OGTT	Rat/(ZUC)-fa/fa(ZUC)-lean (p.o.) Dose (mg/kg): 0.01-3	Teneligliptin (≥0.03 mg/kg) alleviated glucose tolerance during OGTT 30 min after administration
11	Suppression of blood glucose increase in ZF rats during OCLT conducted twice at a 12-h interval	Rat/(ZUC)-fa/fa (ZUC)-lean (p.o.) Dose (mg/kg): 0.1, 0.3, 1	Teneligliptin (≥0.1 mg/kg) alleviated glucose tolerance during the first OCLT 15 min after administration and during the second OCLT 12 h 15 min after administration. Inhibition of plasma DPP-4 was sustained throughout the entire test period (up to 15 h 15 min after administration).

No.	Title	Model	Results
12	Effects on plasma active GLP-1 concentration in ZF rats during OCLT	Rat/(ZUC)-fa/fa (ZUC)-lean (p.o.) Dose (mg/kg): 0.01, 0.1, 1	Teneligliptin (≥0.1 mg/kg) increased plasma active GLP-1 concentration during OCLT 15 min after administration.
13	Suppression of blood glucose increase in KK-A^y mice during OGTT	Mouse/KK-A^y/Ta (p.o.) Dose (mg/kg): 0.1-10	Teneligliptin (≥0.3 mg/kg) alleviated glucose tolerance during OGTT 30 min after administration.
14	Effect on fasting blood glucose level in normal rats	Rat/Wista (p.o.) Dose (mg/kg): 0.01-100 (nateglinide: 10-300)	Teneligliptin (up to 100 mg/kg) did not affect fasting blood glucose levels. Nateglinide (≥30 mg/kg) decreased fasting blood glucose levels.
15	Selectivity to DPP-4-related enzymes (including metabolite M1)	Human (in Vitro) Concentration used (μmol/L): 0.01-10	IC_{50} values of teneligliptin DPP-8: 0.189 μmol/L DPP-9: 0.150 μmol/L FAP: >10 μmol/L IC_{50} values of metabolite M1 DPP-8: 6.96 μmol/L DPP-9: 2.72 μmol/L FAP: >10 μmol/L
16	Selectivity to various enzymes (including metabolite M1)	174 types of enzymes (in vitro) Concentration used (μmol/L): 10	Neither teneligliptin nor M1 inhibited any of the 174 enzymes other than DPP-4.
17	Selectivity to various receptors, ion channels, and transporters including metabolite M1)	164 types of receptors, ion channels, and transporters (in vitro) Concentration used (μmol/L): 10	IC_{50} values of teneligliptin Histamine H1 receptor: 0.775 μmol/L Sigma 1 receptor: 16.2 μmol/L IC_{50} values of metabolite M1 Histamine H1 receptor: 5.19 μmol/L M1 did not inhibit any of the others.
18	Effects on general symptoms and behavior (modified Irwin's method)	Rat/CD(SD)IGS (p.o.) Dose (mg/kg): 1, 10, 100	No effect
19	Effects on spontaneous locomotor activity	Rat/CD(SD)IGS (p.o.) Dose (mg/kg): 1, 10, 100	No effect
20	Proconvulsive effects (electroshock-induced convulsion)	Rat/CD(SD)IGS (p.o.) Dose (mg/kg): 1, 10, 100	No effect
21	Proconvulsive effects (pentylenetetrazole-induced convulsion)	Rat/CD(SD)IGS (p.o.) Dose (mg/kg): 1, 10, 100	No effect
22	Effects on motor-coordination (rota-rod method)	Rat/CD(SD)IGS (p.o.) Dose (mg/kg): 1, 10, 100	No effect
23	Effects on body temperature	Rat/CD(SD)IGS (p.o.) Dose (mg/kg): 1, 10, 100	No effect
24	Effects on the hERG current	HEK293 cell (in vitro) Dose (μmol/L): 1, 10, 100	IC50 value = 3.45 μmol/L
25	Effects on action potential	Isolated guinea pig	Teneligliptin (≥10 μmol/L)

No.	Title	Model	Results
		papillary muscle (in vitro) Dose (μmol/L): 1, 10, 100	prolonged APD_{50} and APD_{90}.
26	Effects on blood pressure, heart rate, and electrocardiogram	Monkey/cynomolgus (conscious) (p.o.) Dose (mg/kg): 3, 10, 30	Teneligliptin (30 mg/kg) prolonged QT and QTc intervals 1 h after administration.
27	Effects on monophasic action potential	Dog/beagle (under anesthesia) (i.v.) Dose (mg/kg): 1, 2, 7	Teneligliptin (7 mg/kg) prolonged the QTc, MAP duration (MAP90), and effective refractory period.
28	Effects on respiratory rate, tidal volume, and per-minute respiratory volume	Rat/CD(SD)IGS (p.o.) Dose (mg/kg): 1, 10, 100	No effect
29	Effects on urine volume and urinary electrolyte excretion	Rat/CD(SD)IGS (p.o.) Dose (mg/kg): 1, 10, 100	No effect
30	Effects on gastric emptying	Rat/CD(SD)IGS (p.o.) Dose (mg/kg): 1, 10, 100	Teneligliptin (100 mg/kg) decreased the gastric emptying rate (to 5% of the vehicle-control level).
31	hERG current (M1)	HEK293 cell (in vitro) Dose (μmol/L): 30, 100	IC_{50} value >100 μmol/L (2% and 19% inhibition at 30 and 100 μmol/L, respectively)

3.3.2. Pharmacokinetics

Pharmacokinetics of teneligliptin in rats and monkeys were investigated in vivo and in vitro, using unlabeled and 14C-labeled teneligliptin. Radioactivity was measured mainly using a liquid scintillation counter. In addition, the amounts of teneligliptin and its stereoisomers (2R4R, 2R4S, 2S4R forms) contained in biological samples were measured using liquid chromatography/tandem mass spectrometry (LC-MS/MS).

To evaluate the differences between species, the teneligliptin plasma protein-binding rate, blood/plasma concentration ratio, distribution rate in blood cells, metabolites in biological samples, and metabolism using liver microsomes were investigated. In addition, the molecular species of cytochrome P450 (CYP) and flavin-containing monooxygenase (FMO) involved in teneligliptin metabolism were identified.

In order to evaluate the potential for drug interactions in clinical use, the inhibitory effects of teneligliptin on CYP and FMO metabolic activities, and on the transport activities of P-glycoprotein (P-gp), organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), and organic cation transporter 2 (OCT2) were investigated, as were the inductive effects on CYP. The pharmacokinetics studies summarized in the table below:

Table: Summary of non-clinical pharmacokinetics studies of Teneligliptin

Item	Frequency of dosing	Animal species	Dosing route	Radioactive tracer	Dose (mg/kg/day)	Vehicle
Absorption	Single	SD rat	I.V.	-	0.3	Water for injection
			P.O.		0.1, 0.3, 1	0.5% CMC
			I.V.	[^{14}C]	1	Water for injection
			P.O.	[^{14}C]	1	0.5% CMC
		ZF rat[a)]	P.O.	-	0.1, 1	0.5% HPMC
		Cynomolgus	I.V.	-	0.3	Water for

Item	Frequency of dosing	Animal species	Dosing route	Radioactive tracer	Dose (mg/kg/day)	Vehicle
		monkey				injection
			P.O.	-	0.1, 0.3, 1	0.5% CMC
			I.V.	[^{14}C]	1	Water for injection
			P.O.	[^{14}C]	1	0.5% CMC
	Repeated	Wistar rat [b)] (TK)	P.O.	-	10, 30, 150	0.5% CMC
		SD rat	P.O.	[^{14}C]	1	0.5% CMC
		Cynomolgus monkey (TK)	P.O.	-	10, 30, 75/60	0.5% CMC
Distribution	Single	SD rat	P.O.	[^{14}C]	1	0.5% CMC
		Pigmented rat[c)]	P.O.	[^{14}C]	1	0.5% CMC
		F344 rat [d)]	P.O.	[^{14}C]	1	0.5% CMC
	Repeated	SD rat	P.O.	[^{14}C]	1	0.5% CMC
	Single	SD rat	P.O.	[^{14}C]	1	0.5% CMC
Metabolism	Single	SD rat	P.O.	[^{14}C]	1	0.5% CMC
		Cynomolgus monkey	P.O.	[^{14}C]	1	0.5% CMC
Excretion	Single	SD rat	I.V.	[^{14}C]	1	Water for injection
		SD rat	P.O.	[^{14}C]	1	0.5% CMC
		Cynomolgus monkey	I.V.	[^{14}C]	1	Water for injection
			P.O.	[^{14}C]	1	0.5% CMC
	Repeated	SD rat	P.O.	[^{14}C]	1	0.5% CMC
		SD rat	P.O.	[^{14}C]	1	0.5% CMC

Teneligliptin was rapidly absorbed by oral route in rats and monkeys, as in humans, and biphasic elimination took place after Cmax was reached. The Cmax and AUC increased with the increasing dose, and the bioavailability was favorable. No obvious differences between the sexes in Cmax or $AUC_{0\text{-}24h}$ were observed in rats and monkeys. In addition, no changes in pharmacokinetics were found when teneligliptin was administered repeatedly to rats, and in humans also the linearity of teneligliptin pharmacokinetics was maintained after repeated oral administration.
When [14C]-labeled teneligliptin was administered orally to rats, radioactivity was distributed rapidly to all tissues in the body, and the radioactivity concentrations in the liver and kidneys were higher than in other tissues. Even after repeated administration the tissue distribution pattern of radioactivity was similar to that observed after a single dose, and no tissues showed marked accumulation of radioactivity. In the investigation using pigmented rats, teneligliptin was shown to have an affinity for melanin. When [^{14}C]-labeled teneligliptin was administered to pregnant rats, no radioactivity was found in the fetuses. The in vitro plasma protein-binding rates in animals and humans were 62.5% to 88.5% and 77.6% to 82.2%, respectively, and the principal proteins binding to teneligliptin in human plasma were human serum albumin and α1-acid glycoprotein.
Five teneligliptin metabolites were identified in animals and humans. When [^{14}C]-labeled teneligliptin was administered to rats, monkeys, and humans, in all three species the main component in the plasma was the unchanged teneligliptin and the most abundant metabolite was M1. The elimination half-lives of M1, M2, M3, M4, and M5 from human plasma were similar to that of teneligliptin, and marked accumulation was therefore not considered to occur after repeated administration. The principal metaboliteformed using rat, monkey, and human liver microsomes was also M1, and no

human-specific metabolites were found. The principal molecules involved in teneligliptin metabolism were CYP3A4, FMO1, and FMO3, and numerous molecules were involved in the metabolism, so the probability of marked effects on drug interaction was judged to be low.
In rats and monkeys, the major excretion pathway for teneligliptin and its metabolites was judged to be the fecal route via biliary excretion. After oral administration tonursing rats, teneligliptin and/or its metabolites were rapidly transferred to the milk, and the concentration in bile decreased with decreasing concentration in plasma.
The outcome of investigation of drug interactions was that, taking into consideration the Cmax after administration to humans at 40 mg/day, it was judged that clinical administration of teneligliptin would not result in induction of CYP1A2 or CYP3A4, and that there was a low probability of teneligliptin affecting the metabolic activity of CYP2D6, CYP3A4, and FMO, which were found to be inhibited in the in vitro studies, and the transport activities of P-gp and OAT3.
On the basis of the results of human and animal pharmacokinetic studies, it was judged that the animal species used in the toxicity studies, rats and monkeys, were appropriate for evaluation of the safety of teneligliptin and its metabolites.

3.3.3. Toxicology

In single-dose toxicity studies, rats and monkeys were killed moribund and necropsied because of poor clinical conditions observed after administration of 2000 mg/kg teneligliptin, whereas no serious toxicity was found after administration of 1000 mg/kg teneligliptin, and therefore, the approximate lethal dose of teneligliptin in both species was 2000 mg/kg.

In repeated-dose toxicity studies, the NOAEL in the 26-week repeated-dose toxicity study in rats was 10 mg/kg/day, which gave an approximately three-fold safety margin in relation to the $AUC_{0\text{-}24h}$ when 40 mg/day was administered to humans. The NOAEL was determined based on a slight increase in white blood cell count in rats given 30 mg/kg/day, and the $AUC_{0\text{-}24h}$ at this dose was approximately 14 times that of the clinical exposure in humans given 40 mg/day. The NOAEL in the 52-week repeated-dose toxicity study in monkeys was 30 mg/kg/day, and the safety margin in this case was 14- to 24-fold with respect to the clinical exposure in humans given 40 mg/day. The NOAEL was determined based on skin lesions and QTc prolongation in monkeys given 75/60 mg/kg/day; however, these changes occurred at exposure levels atleast 44 times the clinical exposure in humans given 40 mg/day.

The genotoxicity of teneligliptin was evaluated in the bacterial reverse mutation test, chromosomal aberration test using CHL/IU cells, micronucleus test in rats, and unscheduled DNA synthesis test in rats. In the chromosomal aberration test, an increased incidence of structurally aberrant cells judged to be secondary changes due to severe cytotoxicity was noted, whereas the results of the other three tests were negative, and there was therefore considered to be no risk of genotoxicity. Metabolites M1 and M2 were evaluated in the bacterial reverse-mutation test, chromosomal aberration test using CHL/IU cells, and micronucleus tests in mice, and showed positive results at high exposure levels in the chromosomal aberration test. However, in the micronucleus test in mice, both metabolites were negative, and the maximum plasma concentrations of M1 and M2 were 520.3 and 474.0 μg/mL, respectively; these concentrations were approximately 67000 and 118500 times the Cmax observed after administration of 40 mg/day to humans, so there was judged to be no risk of genotoxicity with either of these metabolites.

In the carcinogenicity studies in rats and CB6F1-Tg rasH2 mice, teneligliptin was negative for carcinogenicity even at the maximum tolerated doses, which were 75, 100, and 600 mg/kg/day in male rats, female rats, and mice, respectively. With these maximum doses, the exposure levels in rats and CB6F1-Tg rasH2 mice were at least 65 and 118 times the clinical expose in humans given 40 mg/day. In addition, in CB6F1-Tg rasH2 mice, the M1 and M2 exposure levels were at least 108 and 30 times, respectively, those observed after administration of 40 mg/day to humans. The NOAEL for non-tumor lesions were 10 and 60 mg/kg/day in rats and CB6F1-Tg rasH2 mice, respectively, and in each species the safety margin was therefore approximately four-fold as compared with the exposure level after administration in humans given 40 mg/day.

In the reproductive toxicity studies in rats, the NOAELs for male and female fertility were 70 and 100 mg/kg/day, respectively, ensuring an 11- to 45-fold safety margin as compared with the exposure level after administration of 40 mg/day to humans. In the embryo-fetal development studies in rats

and rabbits, no signs of teratogenicity were found with either species, and the NOAEL for embryo-fetal development in both species was 30 mg/kg/day, ensuring an 11- to 16-fold safety margin compared with the exposure level after administration of 40 mg/day to humans. In the pre- and post-natal development including maternal function in rats, the NOAEL was found to be 30 mg/kg/day, ensuring an approximately 11-fold safety margin compared with the exposure level after administration of 40 mg/day to humans.

In other toxicity studies, antigenicity studies in rats and guinea pigs, tests of effects on lymphocyte proliferation, and immunotoxicity study in rats were conducted, and teneligliptin did not show antigenicity or immunotoxicity.

3.3.4. Discussion on non-clinical aspects

The standard of the pharmacology, pharmacokinetic and toxicology studies were completed and submitted. All pivotal toxicity studies, including the safety pharmacology and pharmacokinetics wre performed in accordance with GLP principles and ICH M3(R2) program, as declared by the applicant. Results have shown no safety concerns for Teneligliptin.

3.3.5. Conclusion on non-clinical aspects

Based on the information in dossier, the evaluation results from external evaluator, and the results of Expert Meeting on 24 Oct 2019, the non-clinical part of Tenelia 20 mg is acceptable and appropriate.

3.4. Clinical aspects

- ***Tabular overview of clinical studies***

Table: Overview on the clinical studies for Tenelia 20 mg in Japan

Study	design	Dosage and regimen	Duration of Tenelia	N	Subject details
Phase I, single-dose study	Single dose: Randomized, double- blind, placebocontrolled	Placebo, and 2.5, 5, 10, 20, 40, 80, 160, and 320 mg of Teneligliptin; fasting state; oral administration	Single dose	64	Healthy adult males
	Food effect: randomized, double-blind, placebo-controlled	Placebo, Teneligliptin: 40mg Fasting-state, and 1 min before start of breakfast, oral admistration	Single dose	8	Healthy adult males
Phase I repeated-dose study	Randomized, double-blind, placebo-controlled	Placebo, Teneligliptin: 20, 80 mg Once daily, before breakfast, oral administration	Single dose and 7 day	20	Healthy adult males
Phase II exploratory study	Randomized, double-blind, placebo-controlled	Placebo, Teneligliptin: 2.5, 10, 40 mg Once daily, before breakfast, oral administration	12 wk	186 Placebo: 45 2.5mg:49 10mg:45 40mg:47	Type 2 diabetes patients
Phase II confirmatory study	Randomized, double-blind, placebo-controlled	Placebo, Teneligliptin: 10, 20, 40 mg Once daily, before breakfast, oral administration	12wk	324 Placebo: 80 10mg: 84	Type 2 diabetes patients

Study	design	Dosage and regimen	Duration of Tenelia	N	Subject details
				20mg: 79 40mg: 81	
Phase III confirmatory study	Randomized, double-blind, placebo-controlled	Placebo, Teneligliptin: 20 mg Once daily, before breakfast, oral administration	12 wk	203 Placebo: 104 20mg:99	Type 2 diabetes patients
Phase III SU concomitant therapy study	Stage I: Randomized, double-blind, placebo-controlled Concomitant drug: Glimepiride: 1, 2, 3, 4 mg, once or twice daily, oral	Placebo, Teneligliptin: 20 mg Once daily, before breakfast, oral administration	12wk	194 Placebo: 98 20mg: 96	Type 2 diabetes patients
	Stage II: Unblinded Concomitant drug: Glimepiride, 1, 2, 3, 4 mg, once or twice daily, oral	Teneligliptin: 20 mg (after dose increase: 40 mg)* Once daily, before breakfast, oral administration	40 wk	190 Placebo: 95 20mg: 95	Type 2 diabetes patients
Phase III, TZD concomitant therapy study	Stage I: Randomized, double-blind, placebo-controlled Concomitant drug: Pioglitazone, 15, 30 mg, once daily, oral administration	Placebo, Teneligliptin: 20 mg Once daily, before breakfast, oral administration	12 wk	204 Placebo: 101 20 mg: 103	Type 2 diabetes patients
	Stage II: Unblinded Concomitant drug: Pioglitazone, 15, 30 mg, once daily, oral administration	Teneligliptin: 20 mg (after dose increase: 40 mg)* Once daily, before breakfast, oral administration * If the efficacy is insufficient after treatment for between 24 and 36 weeks, the dose is increased from 20 to 40 mg at the next scheduled hospital visit.	40 wk	196 Placebo: 98 20 mg: 98	Type 2 diabetes patients
Phase III SU concomitant therapy study	Stage I: Randomized, double-blind, placebo-controlled Concomitant drug: Glimepiride: 1, 2, 3, 4 mg, once or twice daily, oral	Placebo, Teneligliptin: 20 mg Once daily, before breakfast, oral administration	12 wk	194 Placebo: 98 20 mg: 96	Type 2 diabetes patients
	Stage II: Unblinded Concomitant	Teneligliptin: 20 mg (after doseincrease: 40 mg)* Once daily, before breakfast, oral	40 wk	190 Placebo: 95 40 wk	Type 2 diabetes patients

Study	design	Dosage and regimen	Duration of Tenelia	N	Subject details
	drug: Glimepiride, 1, 2, 3, 4 mg, once or twice daily, oral	administration * If the efficacy is insufficient after treatment for between 24 and 36 weeks, the dose is increased from 20 to 40 mg at the next scheduled hospital visit.		20 mg: 95	
Phase III, TZD Concomitant therapy study	Stage I: Randomized, double-blind, placebo-controlled Concomitant drug: Pioglitazone, 15, 30 mg, once daily, oral administration	Placebo, Teneligliptin: 20 mg Once daily, before breakfast, oral administration	12 wk	204 Placebo: 101 20mg:103	Type 2 diabetes patients
	Stage II: Unblinded Concomitant drug: Pioglitazone, 15, 30 mg, once daily, oral administration	Teneligliptin: 20 mg (after dose increase: 40 mg)* Once daily, before breakfast, oral administration * If the efficacy is insufficient after treatment for between 24 and 36 weeks, the dose is increased from 20 to 40 mg at the next scheduled hospital visit.	40 wk	196 Placebo: 95 20mg: 98	Type 2 diabetes patients
Phase III, long-term treatment study	Unblinded Concomitant SU drug: Glimepiride, 1, 2, 3, 4 mg, once to twice daily, oral administration	Teneligliptin: 20 mg (after dose increase:: 40 mg)* Once daily, before breakfast, oral administration * If the efficacy is insufficient after treatment for between 24 and 36 weeks, the dose is increased from 20 to 40 mg at the next scheduled hospital visit.	52 wk	240 Monotherapy: 151 Concomitant SU drugs: 89	Type 2 diabetes patients
Bioequivalence study	Randomized, unblinded, two-stage, cross-over	Teneligliptin: 20 mg (one 20-mg tablet, or two 10-mg tablets), fasting-state, oral administration	Single dose	22	Healthy adult males
Drug-drug interactions study with glimepiride	Group 1: Effects of glimepiride on teneligliptin pharmacokinetics, unblinded	Stage I: Teneligliptin, 40 mg Stage II: Days 1–4: Glimepiride, 1 mg Day 2: Teneligliptin, 40 mg Once daily, before breakfast, oral administration	Single dose	16	Healthy adult males
	Group 2: Effects of Teneligliptin on glimepiride pharmacokinetics ,unblinded	Stage I: Glimepiride, 1 mg Stage II: Days 1–7: Teneligliptin, 40 mg Day 7: Glimepiride, 1 mg Once daily, before breakfast, oral administration	7 days	19	Healthy adult males
Drug-drug interactions study with	Group 1: Effects of pioglitazone on teneligliptin pharmacokinetics ,unblinded	Stage I: Teneligliptin, 40 mg Stage II: Days 1–9: Pioglitazone, 30 mg Day 7: Teneligliptin, 40 mg	Single dose	16	Healthy adult males

Study	design	Dosage and regimen	Duration of Tenelia	N	Subject details
pioglitazone		Once daily, before breakfast, oral administration			
	Group 2: Effects of Teneligliptin on pioglitazone pharmacokinetics ,unblinded	Stage I: Pioglitazone, 30 mg Stage II: Days 1–9: Teneligliptin, 40 mg Day 7: Pioglitazone, 30 mg Once daily, before breakfast, oral administration	9 days	24	Healthy adult males
Clinical pharmacology study with type 2 diabetes patients	Randomized, double-blind, placebo-controlled	Placebo, Teneligliptin: 10, 20 mg Once daily, before breakfast, oral administration	4 wk	99 Placebo: 32 10 mg: 34 20 mg: 33	Type 2 diabetes patients
Food effect study	Randomized, unblinded, two-stage, cross-over	Teneligliptin: 20 mg Fasting-state and postprandial, oral administration	Single dose	14	Healthy adult males
Long-term concomitant treatment study	Unblinded Monotherapy Concomitant Glinide drug BG drug α-GI drug	Teneligliptin: 20 mg (after doseincrease:: 40 mg)* Once daily, before breakfast, oral administration	52 wk	462 Monotherapy: 212 Concomitant Glinide drug: 80 BG drug: 95 α-GI drug: 75	

Table: Overview on the overseas clinical studies for Tenelia 20 mg in Japan

Study	design	Dosage and regimen	No. of subject	Subject details
Phase I, single-dose study	Single dose: Randomized, double- blind, placebocontrolled	Placebo, and 2.5, 5, 10, 20, 40, 80, 160, and 320 mg of Teneligliptin; fasting state; oral administration	64	Healthy adult males
	Food effect: Randomized,unblinded, 3-stage cross-over	40 mg of Teneligliptin; fasting state, preprandial and postprandial; oral administration	15	Healthy adult males
Phase I, repeated-dose study	Part 1: Randomized, double-blind, placebocontrolled	Placebo, and 10, 20, and 80 mg of Teneligliptin; once-daily oral administration before breakfast	42	Healthy adult males, aged 18-45
	Part 2: Randomized, double-blind,	Placebo and 80 mg of Teneligliptin; once-daily oral administration before breakfast	16	Healthy adult males,

Study	design	Dosage and regimen	No. of subject	Subject details
	placebocontrolled			aged 46-64
Clinical pharmacology study with type 2 diabetes patients	Randomized, double-blind, placebo- controlled	Placebo, and 2.5, 10, and 40 mg of Teneligliptin; once-daily oral administration before breakfast	48	Type 2 diabetes patients
Male vs. female and elderly vs. non-elderly comparative pharmacokinetics study	Randomized, double-blind, placebo- controlled	Placebo, and 20 and 80 mg of Teneligliptin; once-daily oral administration before breakfast	40	Healthy adult males
Drug-drug interactions study with metformin	Group 1: Effects of metformin on teneligliptin pharmacokinetics; randomized; unblinded	Days 1–8: 40 mg of Teneligliptin Days 6–8: 1700 mg of metformin Teneligliptin: Once-daily, oral administration after breakfast Metformin: Twice-daily, oral administration after breakfast and supper	20	Healthy adult males and females
	Group 2: Effects of teneligliptin on metformin pharmacokinetics;randomized; unblinded	Days 1–8: 1700 mg of metformin Days 4–8: 40 mg of Teneligliptin Teneligliptin: Once-daily, oral administration after breakfast Metformin: Twice-daily, oral administration after breakfast and supper	20	Healthy adult males and females
Phase II, metformin concomitant therapy study	Stage I: Randomized, double-blind, placebocontrolled Concomitant drug: Metformin, ≥1500 mg, 1 to3 times per day, oral	Placebo, and 5, 10, 20, and 40 mg of Teneligliptin; once-daily oral administration before breakfast	448 Placebo: 55 5mg: 87 10mg:93 20mg:91 40mg:89	Type 2 diabetes patients
	Stage II: Unblinded Concomitant drug: Metformin, ≥1500 mg, 1 to 3 times per day, oral	20 mg of Teneligliptin; once-daily oral administration before breakfast	364 Placebo: 68 5mg: 81 20mg:71 40mg:74	Type 2 diabetes patients
Mass balance study	Unblinded	20 mg as ^{14}C-labeled teneligliptin hydrobromide hydrate free form (approx. 1.85 MBq); fasting state; oral administration	6	Healthy adult males
Pharmacokinetic study in subjects with renal impairment	Unblinded	20 mg of teneligliptin; oral; before breakfast (oral, preprandial administration to end-stage renal failure patients)	48	Healthy adult, patients with renal impairment, males and females
Pharmacokinetic study in subjects with hepatic impairment	Unblinded	20 mg of teneligliptin; oral administration before breakfast	24	Healthy adult, with hepatic

Study	design	Dosage and regimen	No. of subject	Subject details
				impairment ,males and females
Drug-drug interactions study with ketoconazole	Unblinded	Days 1 and 11: 20 mg of teneligliptin Days 8–13: 400 mg of ketoconazole Teneligliptin: Fasting state, oral Ketoconazole: Once-daily, oral administration at breakfast, or oral administration in fasting state when concomitant with teneligliptin	16	Healthy adult males and females
Thorough QT/QTc study	Randomized; double-blind; with positive and placebo controls	Placebo, 40 and 160 mg of teneligliptin, and 400 mg of moxifloxacin; once-daily, oral administration before breakfast	240 Placebo: 60 40mg: 59 160mg: 59 Moxifloxacin: 62	Healthy adult males and females

3.4.1. Pharmacokinetics

Absorption

Teneligliptin is absorbed rapidly after oral administration. The median tmax was approximately 1 h after both single and repeated doses. Although longer tmax and lower Cmax were found after postprandial administration, food consumption did not affect AUC.

Distribution

The principal teneligliptin-binding proteins in human plasma are serum albumin and α1-acid glycoprotein. The *in vitro* teneligliptin protein-binding rate was 77.6%–82.2%, and plasma protein-binding was reversible. Investigation of the plasma protein-binding rates of teneligliptin in healthy subjects, subjects with renal impairment, and subjects with hepatic impairment found that the proportion of plasma protein-unbound fraction was 30%–50%.

Metabolism

When single doses of 14C-labeled teneligliptin were administered to healthy adult male subjects in an overseas study, the $AUC_{0-\infty}$ values for teneligliptin, M1, M2, M3, M4, and M5 were 71.1%, 14.7%, 1.3%, 1.3%, 0.3%, and 1.1%, respectively, of the $AUC_{0-\infty}$ for plasma radioactivity up to 72 h after administration. The radioactivity in the plasma was thus mostly in the form of teneligliptin, and the principal metabolite was M1. In addition, because the terminal elimination half-life ($t_{1/2}$) of each metabolite was approximately the same as the teneligliptin $t_{1/2}$, it is not considered that there are any concerns of metabolite accumulation with repeated doses.

The M1 inhibited DPP-4 activity with approximately 1/39 potency of teneligliptin, but did not inhibit related enzymes, other class of enzymes, or receptors. Therefore, it is not considered that M1 pharmacokinetics affect the efficacy and safety of teneligliptin.

The principal enzymes involved with teneligliptin metabolism are considered CYP3A4, FMO1, and FMO3 in a study using microsomes expressing human CYP isoforms or human FMO isoforms. Teneligliptin was found to have mild inhibitory effects on CYP3A4, CYP2D6, and FMO, with IC50 values of 197.5, 489.4, and 467.2 μmol/L, respectively. No inhibitory effects on CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C8/9, CYP2C19, or CYP2E1 were found. M1 had no inhibitory effects on any isoforms. In addition, at doses of up to 10 μmol/L, teneligliptin did not induce CYP1A2 or CYP3A4.

Teneligliptin is the 2S4S form, and stereoisomers (2R4R, 2R4S, and 2S4R forms) also exist. However, none of these stereoisomers were detected in Japanese and overseas Phase I clinical studies.

Excretion

When single doses of 14C-labeled teneligliptin were administered to healthy adult male subjects in an overseas study, 45.4% and 46.5% of the administered radioactivity had been excreted in the urine and feces, respectively, by 216 h after administration. By 120 h after administration, teneligliptin, M1, M2, and M3 in urine made up 14.8%, 17.7%, 1.4%, and 1.9%, respectively, of the administered dose. M4 was not detected in urine, and M5 was detected in three of the six subjects, but in each case the cumulative excretion rate was <1% of the dose. With respect to excretion in feces, teneligliptin, M1, M3, M4 and M5 made up 26.1%, 4.0%, 1.6%, 0.3%, and 1.3% of the administered dose, respectively, by 120 h after administration. It is therefore considered that absorbed teneligliptin is eliminated by metabolism and by excretion via the kidneys.

Pharmacokinetics with Single and Repeated Doses

The dose proportionality was evaluated using a power model in Japanese healthy adult male subjects administered with single doses of 2.5 to 160 mg of teneligliptin. It was found that whereas teneligliptin Cmax increased slightly more than proportionally to dose, AUC_{0-t} and $AUC_{0-\infty}$ increased in proportion to dose. Similar results were found when single doses of 2.5 to 320 mg were administered to healthy adult male subjects in an overseas study.

In addition, when repeated doses of 20 or 80 mg of teneligliptin were administered once daily for 7 days to Japanese healthy adult male subjects, the cumulative coefficient (repeated doses/single dose) for teneligliptin AUC_{0-24h} was approximately 1.4, and the linearity index in repeated doses, i.e. the ratio between the geometric mean of the AUC_{0-24h} after repeated doses and the $AUC_{0-\infty}$ after a single dose, was approximately 1. It was thus confirmed that a steady state was reached within 7 days after repeated administration, and linearity was maintained with repeated administration. Similar results were found in the overseas study when repeated doses of 10 to 80 mg of teneligliptin were administered to healthy adult male subjects.

3.4.2. Pharmacodynamics

Pharmacodynamic Effects in Healthy Adult Subjects

When single doses of 2.5 to 160 mg of teneligliptin were administered to Japanese healthy adult male subjects, the maximum plasma DPP-4 inhibition rate (Emax) and the plasma DPP-4 inhibition rate 24 h after administration (E24h) increased dose-dependently. In addition, since the tmax for DPP-4 inhibition in plasma was between 1 and 2 h irrespective of whether single or repeated doses were administered, the inhibition rate was found to be reached the maximum rapidly after teneligliptin administration. In addition, the Emax and E24h were approximately the same irrespective of whether or not food was consumed. When 20 mg, the dose in the Japanese submission, was administered as a single dose, the E24h was 53.85%.

The Cmax of the in plasma and the AUC up to 2 h after meals of active GLP-1 concentration were higher when teneligliptin was administered, as either single or repeated doses, than those with placebo administration.

The plasma DPP-4 inhibition rate and plasma active GLP-1 concentration after administration of single and repeated doses to overseas healthy adult male subjects were similar to those with administration to Japanese healthy adult male subjects.

Pharmacodynamic Effects in Patients with Type 2 Diabetes

Since the tmax of the plasma DPP-4 inhibition rate with once-daily administration of 10 or 20 mg of teneligliptin for 4 weeks was approximately 1 h in both cases in Japanese patients with type 2 diabetes, it was confirmed that the Emax was reached rapidly after teneligliptin administration. The E24h was 53.1% and 61.8%, respectively. In addition, the change in AUC of the plasma active GLP-1 concentration increased significantly in comparison with placebo administration irrespective of whether 10 or 20 mg of teneligliptin was administered, and whether administration was after breakfast, lunch, or supper.

Investigation of Ethnic Differences in Pharmacokinetics and

Pharmacodynamics

On the basis of the results of Japanese and overseas Phase I clinical studies with healthy adult subjects and clinical pharmacology studies with type 2 diabetes patients, the similarity of teneligliptin pharmacokinetics and pharmacodynamics was analyzed with Japanese and non-Japanese subjects.

Teneligliptin AUC and Cmax were similar in Japanese and non-Japanese subjects. In addition, teneligliptin pharmacokinetics was similar in healthy adult subjects and type 2diabetes patients.

In addition, since teneligliptin pharmacodynamic parameters (plasma DPP-4 inhibition rate and plasma active GLP-1 concentration) were similar in Japanese and non-Japanese, irrespective of whether or not they had type 2 diabetes, there considered to be no ethnic differences in pharmacodynamics.

Drug-drug Interactions

Terminal elimination of teneligliptin involves a metabolic pathway with several metabolic enzymes (CYP3A4, FMO1, FMO3), and excretion pathway by the kidneys.

The results of nonclinical studies showed that teneligliptin is metabolized by CYP3A4, and is a substrate for P-glycoprotein (P-gp). In an overseas study (study MP-513-E11), drug-drug interaction was investigated with ketoconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, administered concomitantly with 20 mg of teneligliptin. Concomitant administration of ketoconazole increased the teneligliptin $AUC_{0-\infty}$ and Cmax 1.49- and 1.37-fold, respectively. However, since even concomitant administration of a potent inhibitor of CYP3A4 and P-gp, ketoconazole, did not double the teneligliptin $AUC_{0-\infty}$ or Cmax, and the safety of teneligliptin at doses of up to 40 mg was confirmed in clinical studies with type 2 diabetes patients, adjustment of the teneligliptin dosage and regimen is not considered to be necessary even with concomitant administration of a CYP3A4- or P-gp inhibitor.

In study MP-513-E06, the drug-drug interactions were investigated with concomitant administration of metformin and 40 mg of teneligliptin. For both AUC_{0-24h} and Cmax, the 90% confidence intervals for the ratios between the geometric least-squares mean (LSMean) with concomitant metformin administration and that with teneligliptin monotherapy were within the previously stipulated acceptable range (0.80–1.25). On the other hand, the 90% confidence interval for the ratio of the metformin AUC_{0-12h} geometric LSMean with concomitant teneligliptin administration was slightly above the upper limit of the previously stipulated acceptable range (0.80–1.25). The 90% confidence interval for the ratio of the metformin Cmax geometric LSMean was within the previously stipulated acceptable range (0.80–1.25). Because the AUC showed only slight increase and the Cmax showed no increase, and because whereas metformin is a substrate for organic cation-transporter (OCT2) teneligliptin was not an inhibitor of OCT2 in *in vitro* study, teneligliptin is unlikely to have a major effect on metformin pharmacokinetics. Although drug interaction studies of concomitant use of teneligliptin with glinide or α-GI have not been conducted, in an overseas Phase II metformin concomitant therapy study in patients with type 2 diabetes (study MP-513-E07) and long-term concomitant treatment therapy study (study 3000-A14), metformin was found to have no major effects on the safety of teneligliptin administration for up to 52 weeks.

Study 3000-A10 was conducted in Japan to evaluate the drug interactions when glimepiride, an SU drug in wide use in Japan, is administered concomitantly with 40 mg of teneligliptin. Because the 90% confidence intervals for the $AUC_{0-\infty}$ and Cmax geometric mean ratios with concomitant administration, in comparison with monotherapy, were within the previously stipulated acceptable range (0.80–1.25), no drug interactions with glimepiride were found. Since the metabolism of other SU drugs (glibenclamide, gliclazide, and tolbutamide) involves the same principal enzymes as that of glimepiride, it is not expected that these other drugs show clinically important drug interactions. In a Phase III SU concomitant therapy study (study 3000-A6), SU drugs posed no problems on the safety of teneligliptin administration for up to 52 weeks.

In addition, Study 3000-A11 was conducted in Japan to evaluate the drug interactions when pioglitazone, a TZD drug, is administered concomitantly with 40 mg of teneligliptin. With respect to teneligliptin and pioglitazone as well as its active metabolites (M-III and M-IV), the 90% confidence intervals for the $AUC_{0-\infty}$ and Cmax geometric mean ratios with concomitant administration, in comparison with monotherapy, were all within the previously stipulated acceptable range (0.80–1.25), with the exception of teneligliptin Cmax,. Although the 90% confidence interval for the teneligliptin Cmax geometric mean ratio with concomitant pioglitazone administration was slightly above the upper limit of the acceptable range (0.80–1.25), no consistent tendency in the direction of change in Cmax was found in individual participants, and there were no changes in AUC0-∞ or other pharmacokinetic parameters as a result of concomitant pioglitazone administration. Therefore, concomitant pioglitazone administration is not considered to affect teneligliptin pharmacokinetics. Although the adverse event and adverse drug reaction rates were significantly higher in the teneligliptin group than in the placebo

group in a Japanese Phase III TZD concomitant therapy study (study 3000-A7), the analysis stratified on the basis of renal function and other background factors that increase plasma teneligliptin concentration showed no consistent tendency in the adverse event and adverse drug reaction rates. In addition, evaluation of individual adverse events did not pose any marked safety-related problems with teneligliptin administration for up to 52 weeks. On the basis of the above findings, it is considered that, although concomitant administration of teneligliptin and pioglitazone in drug-drug interactions studies resulted in slight increase in teneligliptin Cmax, adjustment of the teneligliptin dosage and/or regimen is not required.

In summary although teneligliptin $AUC_{0-\infty}$ and Cmax increased as a result of concomitant administration with CYP3A4- and P-gp inhibitors, these $AUC0-_{\infty}$ and Cmax values did not exceed twice the respective values with teneligliptin monotherapy. Adjustment of the teneligliptin dosage and regimen is therefore not considered to be necessary. In addition, adjustment of the dosage and regimen is not considered to be necessary even with concomitant administration of oral hypoglycaemic agents, which is expected on the basis of the indications for teneligliptin.

Patients with Renal Impairment

The effects of renal impairment on the pharmacokinetics of a single 20-mg teneligliptin dose were evaluated in an overseas study (study MP-513-E09) in subjects with renal impairment. Teneligliptin Cmax and t1/2 showed no marked changes dependent upon severity of renal impairment, whereas the $AUC0-_{\infty}$ geometric LSMeans in patients with mild renal impairment (CCr: ≥50 mL/min and ≤80 mL/min), moderate renal impairment (CCr: ≥30 mL/min and <50 mL/min), or severe renal impairment (CCr: <30 mL/min) were approximately 1.25, 1.68, and 1.49 times, respectively, this value in healthy adults.

In addition, the AUC0–43h geometric LSMean in patients with end-stage kidney failure was approximately 1.16 times that in healthy adults. Nevertheless, as the AUC geometric LSMean in patients with renal impairment did not exceed twice that in healthy adults and the results of clinical studies with type 2 diabetes patients confirmed the safety of teneligliptin at doses of up to 40 mg, it is not considered necessary to adjust the teneligliptin dosage or regimen for subjects with renal impairment.

In addition, as the mean rate of removal of teneligliptin by hemodialysis was 15.6% in patients with end-stage kidney failure, teneligliptin administration is considered to be possible irrespective of the timing of hemodialysis.

Patients with Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics after a single 20-mg teneligliptin dose were evaluated in an overseas study (study MP-513-E10) in subjects with hepatic impairment. In subjects with mild hepatic impairment (total Child-Pugh score: 5–6) and moderate hepatic impairment (total Child-Pugh score: 7–9), the teneligliptin Cmax geometric LSMeans were approximately 1.25 and 1.38 times, respectively, the value in healthy adults; and the $AUC0-_{\infty}$ geometric LSMeans were approximately 1.46 and 1.59 times, respectively. Nevertheless, the geometric LSMean of neither Cmax nor $AUC0-_{\infty}$ in subjects with hepatic impairment exceeded twice the mean in healthy adults, and in clinical studies in type 2 diabetes patients the safety was confirmed at teneligliptin doses of up to 40 mg. It is, therefore, considered that adjustment of dosage and regimen for subjects with mild or moderate hepatic impairment is unnecessary. No investigation of the pharmacokinetics when teneligliptin is administered orally to subjects with severe hepatic impairment has been conducted.

Pediatric Patients

No study of oral administration of teneligliptin to pediatric patients has been conducted.

Elderly Patients

In an overseas pharmacokinetic study (study MP-513-E05), teneligliptin was administered to elderly subjects. As there were no changes due to aging, dosage and regimen adjustment on the basis of patient age is considered to be unnecessary.

Effects on QT/QTc Interval

An overseas study (study MP-513-A01) was conducted with healthy adult males and females in order to evaluate the effects on QT/QTc interval of once-daily administration of 40 or 160 mg of teneligliptin for 4 days. There was no clinically significant prolongation of the QTc interval occurred when the expected maximum clinical dose of teneligliptin, 40 mg, was administered. On the other hand, there is

the possibility of prolongation of the QTc interval occurring in the high-concentration range at tmax with 160 mg of teneligliptin. However, because a moderate correlation was found between the change from the baseline of the corrected QT interval (QTcI) using an individual correction method and the plasma teneligliptin concentration, and because the QTc interval prolongation by 160 mg of teneligliptin occurred transiently at approximately tmax, it is considered that this effect is linked to teneligliptin Cmax rather than AUC. Estimation at the steady state when 40 or 160 mg was administered repeatedly to Japanese and non-Japanese subjects showed that whereas the AUC0–24h was slightly higher in Japanese than non-Japanese subjects, the Cmax was approximately the same in the two groups. In addition, "Clinical Investigation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs" contains the following statement: "Although the data on ethnic differences are limited it is not considered that ethnic factors affect the results of QT/QTc evaluation studies". It was therefore possible to evaluate the effects of teneligliptin on QT/QTc interval in Japanese people on the basis of the results of the overseas thorough QT/QTc study.

3.4.3. Discussion on clinical pharmacology

Teneligliptin hydrobromide hydrate is a dipeptidyl peptidase-4 (DPP4) inhibitor. DPP-4 inhibitors are therapeutic drugs for type 2 diabetess that increase the concentration of active glucagon-like peptide-1 (GLP-1) inblood, thus promoting glucose-dependent insulin secretion, and inhibiting glucagon secretion, resulting in antihyperglycemic effect. Teneligliptin is absorbed rapidly after oral administration (tmax was approximately 1 hour after doses). The principal teneligliptin-binding proteins in human polasma are serum albumin and glycoprotein (rate was 77.6%-82.2%). The principal enzymes involved with teneligliptin metabolism are considered CYP3A4 FMO1, and FMO3. There was found to have mild inhibitory effects on CYP3A4, CYP2D6, and FMO, No inhibitory effects on CYP1A, CYP2A6, CYP2B6, CYP2C8, CYP2C8/9, CYP2C19, or CYP2E1. Absorbed teneligliptin is eliminated by metabolism and by excretion via the kidneys.

3.4.4. Conclusions on clinical pharmacology

Tenelia 20 mg was developed by a current demand for DPP-4 inhibitors that can be administered once daily, with which dose adjustment is not necessary in patients with hepatic and/or renal impairment, and that can be prescribed with other class of anti-hyperglycemic agents depending on patients' conditions. The clinical studies were designed rationally to support the pharmacology and pharmacokinetics. Based on the information in the dossier and data summarized in SmPC, the the clinical pharmacology of Tenelia 20 mg is acceptable and appropriate.

3.4.5. Clinical efficacy and safety

Summary of main efficacy results and safety

There were five main clinical studies in Phase III to prove the efficacy of Teneligliptin. The table below were summarized the results.

Table: Summary of clinical studies of Teneliglilptin

<table>
<tr><th>No.</th><th>Objective</th><th>Design</th><th>Result</th></tr>
<tr><td>1.

(300A-5)</td><td>To confirm efficacy and examine safety as compared to the placebo.</td><td>A Phase III, Double-blind, Placebo Controlled. (Confirmative Study)

Participants: 203 enrolled, Age 20-75 years old

Duration: 12 weeks

Interventions:

1)Teneligliptin placebo-matching tablets, orally, once daily (Placebo)

2)Teneligliptin 20 mg, orally, once daily</td><td><u>Efficacy</u>

<u>Primary outcome</u>

(1) Change From Baseline in HbA1c at Week 12:

<table>
<tr><th rowspan="2">Results</th><th rowspan="2">Topics</th><th colspan="2">Treatment group</th></tr>
<tr><th>Placebo

(SD)</th><th>Teneligliptin 20 mg

(SD)</th></tr>
<tr><td>HbA1c (%)</td><td>Change in HbA1C at the end of the treatment</td><td>0.17
(0.05)</td><td>-0.62

(0.05)</td></tr>
</table>
<u>Secondary outcome</u>

(1) Change from the baseline in fasting plasma glucose at week 12:

<table>
<tr><th rowspan="2">Results</th><th rowspan="2">Topics</th><th colspan="2">Treatment group</th></tr>
<tr><th>Placebo

(SD)</th><th>Teneligliptin 20 mg

(SD)</th></tr>
<tr><td>Fasting plasma glucose (mg/dL)</td><td>Change in Fasting plasma glucose at the end of the treatment</td><td>-0.2 (1.8)</td><td>-19.2 (1.8)</td></tr>
</table>
(2) Change From Baseline in the Areas Under the Curve From 0 to 2 h (AUC0-2h) for Postprandial Plasma Glucose at Week 12

<table>
<tr><th rowspan="2">Results</th><th rowspan="2">Topics</th><th colspan="2">Treatment group</th></tr>
<tr><th>Placebo

(SD)</th><th>Teneligliptin 20 mg

(SD)</th></tr>
<tr><td>AUC0-2h (mg*h/dL)</td><td>change from Baseline in AUC0-2h for Postprandial Plasma Glucose collected</td><td>0.224
(4.849)</td><td>-73.124
(4.824)</td></tr>
</table>
(3) Change From Baseline in 2-hour Postprandial Plasma Glucose at Week 12</td></tr>
</table>

<table>
<tr><th>No.</th><th>Objective</th><th>Design</th><th>Result</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><th>Results</th><th>Topics</th><th colspan="2">Treatment group</th></tr>
<tr><td></td><td></td><td>Placebo
(SD)</td><td>Teneligliptin 20 mg
(SD)</td></tr>
<tr><td>2-hour Postprandial Plasma Glucose (mg/dL)</td><td>hange From Baseline in 2-hour Postprandial Plasma Glucose at Week 12</td><td>-3.2 (3.6)</td><td>-47.9 (3.5)</td></tr>
</table>
</td></tr>
<tr><td>2
(300-A6)</td><td>To evaluate the safety and efficacy of Teneligliptin in combination with sulfonylurea in patients with DM type 2 for 12 weeks administration and an extension treatment for up to 52 weeks.</td><td>Phase III SU concomitant therapy study:
Period I: Randomized, double-blind, placebo-controlled
Concomitant agent: 1, 2, 3, and 4 mg of glimepiride, once to twice daily, oral
Participants: 194 enrolled, Age 20-75 year old
Duration: 12 weeks
Interventions:
1) Placebo / Teneli (Teneligliptin) + SU (Sulfonylurea)
2) Teneli / Teneli + SU
Period II: Open label
Concomitant agent: 1, 2, 3, and 4 mg of glimepiride, once to twice daily, oral
Participants: 190 enrolled, Age 20-75 year old
Duration: 40 weeks
Interventions:
1) Placebo / Teneli (Teneligliptin) + SU (Sulfonylurea)</td><td><u>Efficacy</u>
<u>Primary outcome</u>
(1) Change From Baseline in HbA1c at Week 12
<table>
<tr><th>Result</th><th>Topic</th><th colspan="2">Treatment group</th></tr>
<tr><td></td><td></td><td>Placebo (12wk) then Teneli + SU
(SD)</td><td>Teneli(12 wk) then Teneli + SU
(SD)</td></tr>
<tr><td>HbA1c (%)</td><td>Change From Baseline in HbA1c at Week 12</td><td>0.29 (0.06)</td><td>-0.71 (0.06)</td></tr>
</table>
<u>Secondary Outcome</u>
(1) Change From Baseline in Fasting Plasma Glucose at Week 12
<table>
<tr><th>Result</th><th>Topic</th><th colspan="2">Treatment group</th></tr>
<tr><td></td><td></td><td>Placebo (12wk) then Teneli + SU
(SD)</td><td>Teneli(12 wk) then Teneli + SU
(SD)</td></tr>
<tr><td>Fasting plasma glucose (mg/dL)</td><td>Change From Baseline in Fasting Plasma Glucose at Week 12</td><td>9.8 (2.2)</td><td>-17.3 (2.2)</td></tr>
</table>
(2) Change From Baseline in the Areas Under the</td></tr>
</table>

<table>
<tr><th>No.</th><th>Objective</th><th>Design</th><th>Result</th></tr>
<tr><td></td><td></td><td>2) Teneli / Teneli + SU</td><td>Curve From 0 to 2 h (AUC0-2h) for Postprandial Plasma Glucose at Week 12
<table><tr><th rowspan="2">Result</th><th rowspan="2">Topic</th><th colspan="2">Treatment group</th></tr><tr><th>Placebo (12wk) then Teneli + SU
(SD)</th><th>Teneli(12 wk) then Teneli + SU
(SD)</th></tr><tr><td>AUC0-2h (mg*h/ dL)</td><td>Change from Baseline in (AUC0-2h for Postprandial Plasma glucose at Week 12</td><td>15.514 (6.072)</td><td>-65.544 (6.072)</td></tr></table>(3)Change From Baseline in 2-hour Postprandial Plasma Glucose at Week 12
<table><tr><th rowspan="2">Result</th><th rowspan="2">Topic</th><th colspan="2">Treatment group</th></tr><tr><th>Placebo (12wk) then Teneli + SU
(SD)</th><th>Teneli(12 wk) then Teneli + SU
(SD)</th></tr><tr><td>2-hour Postprandial Plasma Glucose (mg/dL)</td><td>Change From baseline in 2-hour postprandial Plasma Glucose at Week 12</td><td>6.0 (4.4)</td><td>-43.1 (4.4)</td></tr></table></td></tr>
<tr><td>3
(300-A7)</td><td>To evaluate the efficacy and safety of Teneligliptin in combination with thiazolidinedione in patients with type 2 Diabetes for 12 weeks administration and to evaluate the safety and</td><td>Phase III TZD concomitant therapy study
Period I: Randomized, double-blind,placebo controlled
Concomitant agent: 15 and 30 mg of pioglitazone, once daily, oral
Participants: 204 enrolled, Age 20-75 year old</td><td><u>Efficacy</u>
<u>Primary outcome</u>
(1)Change From Baseline in HbA1c at Week 12
<table><tr><th rowspan="2">Result</th><th rowspan="2">Topic</th><th colspan="2">Treatment group</th></tr><tr><th>Placebo (12wk) then Teneli + Pio
(SD)</th><th>Teneli(12 wk) then Teneli + Pio
(SD)</th></tr><tr><td>HbA1c</td><td>Change From</td><td>-0.20</td><td>-0.94</td></tr></table></td></tr>
</table>

<table>
<tr><th>No.</th><th>Objective</th><th>Design</th><th>Result</th></tr>
<tr><td></td><td>efficacy of Teneligliptin in combination with thiazolidinedione with an extension treatment for up to 52 weeks.</td><td>Duration: 12 weeks

Interventions:

1) Placebo / Teneli (Teneligliptin) + pio (pioglitazone)

2) Teneli / Teneli + pio</td><td>
<table>
<tr><td>(%)</td><td>Baseline in HbA1c at Week 12</td><td>(0.05)</td><td>(0.04)</td></tr>
</table>
<u>Secondary Outcome</u>

(1)Change From Baseline in Fasting Plasma Glucose at Week 12
<table>
<tr><td>Result</td><td>Topic</td><td colspan="2">Treatment group</td></tr>
<tr><td></td><td></td><td>Placebo (12wk) then Teneli + Pio

(SD)</td><td>Teneli(12 wk) then Teneli + Pio

(SD)</td></tr>
<tr><td>Fasting plasma glucose (mg/dL)</td><td>Change From Baseline in Fasting Plasma Glucose at Week 12</td><td>-4.5 (2.0)</td><td>-21.0 (1.9)</td></tr>
</table>
(2) Change From Baseline in the Areas Under the Curve From 0 to 2 h (AUC0-2h) for Postprandial Plasma Glucose at Week 12
<table>
<tr><td>Result</td><td>Topic</td><td colspan="2">Treatment group</td></tr>
<tr><td></td><td></td><td>Placebo (12wk) then Teneli + Pio

(SD)</td><td>Teneli(12 wk) then Teneli + Pio

(SD)</td></tr>
<tr><td>AUC0-2h (mg*h/dL)</td><td>Change from Baseline in (AUC0-2h for Postprandial Plasma glucose at Week 12</td><td>-13.722 (5.134)</td><td>-85.031 (5.134)</td></tr>
</table>
(3)Change From Baseline in 2-hour Postprandial Plasma Glucose at Week 12
<table>
<tr><td>Result</td><td>Topic</td><td colspan="2">Treatment group</td></tr>
<tr><td></td><td></td><td>Placebo (12wk) then Teneli + Pio

(SD)</td><td>Teneli(12 wk) then Teneli + Pio

(SD)</td></tr>
<tr><td>2-hour Postpra</td><td>Change From</td><td>-5.6 (3.6)</td><td>-56.9 (3.6)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>No.</th><th>Objective</th><th>Design</th><th>Result</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>ndial Plasma Glucose (mg/dL)</td><td>baseline in 2-hour postprandial Plasma Glucose at Week 12</td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>4 (300-A8)</td><td>To evaluate the safety and efficacy of Teneligliptin as monotherapy or in combination with Sulfonylurea (glimepiride) in Japanese patients with T2DM for 52 weeks administration.</td><td>Non-rendomized, parallel assignment, open label treatment
Participants: 240 enrolled, Age 20-75 years old
Duration: 52 weeks
Interventions:
1)Teneligliptin
2)Teneligliptin + Sulfonylurea</td><td>
<u>Primary outcome</u>
(1)Number of participants with adverse events
<table>
<tr><td>Result</td><td>Topic</td><td colspan="2">Treatment group</td></tr>
<tr><td></td><td></td><td>Teneli</td><td>Teneli + SU</td></tr>
<tr><td rowspan="2">Number of participants with adverse events</td><td>Serious adverse event</td><td>6 (3.97%)</td><td>7 (7.86%)</td></tr>
<tr><td>Other adverse event</td><td>136 (90%)</td><td>84 (94.38%)</td></tr>
</table>
<u>Secondary outcome</u>
(1) Change From Baseline in HbA1c at Week 52
<table>
<tr><td>Result</td><td>Topic</td><td colspan="2">Treatment group</td></tr>
<tr><td></td><td></td><td>Teneli</td><td>Teneli + SU</td></tr>
<tr><td>HbA1c (%)</td><td>Change from baseline in HbA1c at Week 52</td><td>-0.63 (0.67)</td><td>-0.81 (0.76)</td></tr>
</table>
(2) Change From Baseline in Fasting Plasma Glucose at Week 52
<table>
<tr><td>Result</td><td>Topic</td><td colspan="2">Treatment group</td></tr>
<tr><td></td><td></td><td>Teneli</td><td>Teneli + SU</td></tr>
<tr><td>Fasting plasma glucose (mg/dL)</td><td>Change from baseline in Fasting plasma glucose at Week 52</td><td>-12.4 (22.9)</td><td>-17.0 (30.5)</td></tr>
</table>
</td></tr>
<tr><td>5
(300-A14)</td><td>To evaluate the safety and efficacy of Teneligliptin as monotherapy or in combination with oral antihyperglycaemic agent in</td><td>Long-term
concomitant treatment study
Participants: 462 enrolled, Age 20-75 years old
Duration: 52 weeks
Interventions:</td><td>
<u>Primary outcome</u>
(1) Number of Participants With Adverse Events
<table>
<tr><td>Result</td><td colspan="4">Treatment group</td></tr>
<tr><td>N</td><td>T (212)</td><td>T+Gli (80)</td><td>T+Bigu (95)</td><td>T+Alpha (75)</td></tr>
<tr><td>Serious adverse event</td><td>14</td><td>3</td><td>6</td><td>6</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>No.</th><th>Objective</th><th>Design</th><th>Result</th></tr>
<tr><td></td><td>patients with type 2 Diabetes for 52 weeks administration .</td><td>1) Teneligliptin
2) Teneligliptin + Glinide
3) Teneligliptin + Biguanide
4) Teneligliptin + alphaglucosidase</td><td>
<table>
<tr><td>Other adverse event</td><td>182</td><td>72</td><td>81</td><td>59</td></tr>
</table>
<u>Secondary outcome</u>
(1) Change from baseline in HbA1c at week 52
<table>
<tr><td>Result</td><td colspan="4">Treatment group</td></tr>
<tr><td>N</td><td>T (212)</td><td>T+Gli (80)</td><td>T+Bigu (95)</td><td>T+Alpha (75)</td></tr>
<tr><td>HbA1c % reduction</td><td>-0.63 (0.64)</td><td>-0.76 (0.70)</td><td>-0.78 (0.75)</td><td>-0.89 (0.64)</td></tr>
</table>
(2) Change From Baseline in Fasting Plasma Glucose at Week 52
<table>
<tr><td>Result</td><td colspan="4">Treatment group</td></tr>
<tr><td>N</td><td>T (212)</td><td>T+Gli (80)</td><td>T+Bigu (95)</td><td>T+Alpha (75)</td></tr>
<tr><td>Fasting plasma glucose (mg/dL)</td><td>-117 (25.5)</td><td>-13.7 (23.7)</td><td>-12.7 (27.1)</td><td>-19.5 (23.5)</td></tr>
</table>
(3) Change From Baseline in Fasting Glucagon at Week 52
<table>
<tr><td>Result</td><td colspan="4">Treatment group</td></tr>
<tr><td>N</td><td>T (212)</td><td>T+Gli (80)</td><td>T+Bigu (95)</td><td>T+Alpha (75)</td></tr>
<tr><td>Fasting plasma glucagon (pg/mL)</td><td>2.8 (12.5)</td><td>5.3 (13.7)</td><td>5.0 (14.4)</td><td>6.9 (15.2)</td></tr>
</table>
</td></tr>
</table>

3.4.6. Discussion on clinical efficacy and safety

Design and conduct of clinical studies

All clinical studies were conducted with consideration given to ethical principles based on the Declaration of Helsinki, and in compliance with criteria for performance of clinical studies on pharmaceuticals, termed Good Clinical Practice (GCP). The clinical data package for Teneligliptin is shown in table below.

Territory	Study category	Study name	Study no.	Document category
Japanese	Phase I	Phase I, single-dose study	3000-A1	Evaluation
		Phase I, repeated-dose study	3000-A2	Evaluation
	Phase II	Phase II, exploratory study	3000-A3	Evaluation
		Phase II, confirmatory study	3000-A4	Evaluation
	Phase III	Phase III, confirmatory study	3000-A5	Evaluation
		Phase III, SU concomitant therapy study	3000-A6	Evaluation
		Phase III, TZD concomitant therapy study	3000-A7	Evaluation
		Phase III, long-term treatment study	3000-A8	Evaluation
		Long-term concomitant treatment therapy study	3000-A14	Evaluation
	Clinical pharmaco-logy	Bioequivalence study	3000-A9	Evaluation
		Drug-drug interactions study with glimepiride	3000-A10	Evaluation
		Drug-drug interactions study with pioglitazone	3000-A11	Evaluation
		Clinical pharmacology study with type 2 diabetes patients	3000-A12	Evaluation
		Food effect study	3000-A13	Evaluation
Overseas	Phase I	Phase I, single-dose study	MP-513-E01	Reference
		Phase I, repeated-dose study	MP-513-E02	Reference
	Phase II	Phase II, metformin concomitant therapy study	MP-513-E07	Reference
	Clinical pharmaco-logy	Male vs. female, and elderly vs. non-elderly comparative pharmacokinetic study	MP-513-E05	Reference
		Clinical pharmacology study in type 2 diabetes patients	MP-513-E03	Reference
		Mass balance study	MP-513-E08	Reference
		Drug-drug interactions study with metformin	MP-513-E06	Reference
		Drug-drug interactions study with ketoconazole	MP-513-E11	Reference
		Pharmacokinetic study in subjects with renal impairment	MP-513-E09	Reference
		Pharmacokinetic study in subjects with hepatic impairment	MP-513-E10	Reference
		Thorough QT/QTc study	MP-513-A01	Evaluation

Efficacy data and additional analyses

The primary endpoint, changing in HbA1c, was significantly decreased in all teneligliptin groups in comparison with the placebo group in a Phase II exploratory study in which teneligliptin at doses of 2.5, 10, or 40 mg, or placebo, was administered once daily for 12 weeks to type 2 diabetes patients with insufficient blood glucose control by dietary and exercise therapy (study 3000-A3), and in a Phase II confirmatory study in which 10, 20, or 40 mg of teneligliptin, or placebo, was administered to similar patients with a similar regimen and duration (study 3000-A4).

Hypoglycemic activity was demonstrated after the supper, as well as after breakfast and lunch, and improved blood glucose control over 24 h was demonstrated with teneligliptin doses of 10 mg or higher, in a clinical pharmacology study in which the effects on blood glucose control over 24 h were evaluated with 10 or 20 mg of teneligliptin, or placebo once daily for 4 weeks to type 2 diabetes patients with insufficient blood glucose control by diet and exercise therapy (study 3000-A12). In addition, it is considered that slightly higher efficacy can be expected with 20 mg of teneligliptin after the supper, when the plasma teneligliptin concentration decreases, although no marked differences between 10 and 20 mg were found in blood glucose-related endpoints.

The HbA1c, fasting blood glucose, and 2-h postprandial blood glucose levels were significantly lower with 20 mg of teneligliptin than in the placebo group and the superiority of this teneligliptin dose over placebo was confirmed in a Phase III confirmatory study in which 20 mg of teneligliptin, or placebo, was administered once daily for 12 weeks to type 2 diabetes patients with insufficient blood glucose control by dietary and exercise therapy (study 3000-A5).

The HbA1c, fasting blood glucose, and 2-h postprandial blood glucose levels were significantly lower with 20 mg of teneligliptin than with placebo and the superiority of this teneligliptin dose over placebo was thus confirmed in concomitant therapy studies in which 20 mg of teneligliptin, or placebo, was administered once daily for 12 weeks to type 2 diabetes patients with insufficient blood glucose control by diet therapy, exercise therapy, and SU or TZD drugs (study 3000-A6 and study 3000-A7).

The decreases in HbA1c, fasting blood glucose, and 2-h postprandial blood glucose levels lasted for 52 weeks of administration when teneligliptin was administered once daily for 52 weeks, at a dose of 20 mg, and was increased to 40 mg if necessary in a Phase III long-term treatment study (study 3000-

A8), Phase III combination therapy studies (study 3000-A6 and study 3000-A7) and Long-term concomitant treatment therapy study (study 3000-A14). Some subjects achieved the glycemic control goal of HbA1c.

In summary, once-daily administration of 20 mg of teneligliptin to type 2 diabetes patients with insufficient blood glucose control by diet and exercise therapy, or diet therapy, exercise therapy, and SU, TZD, glinide, BG or α-GI drugs, improved blood glucose control and this effect lasted for 52 weeks of administration. In addition, when the once-daily dose of 20 mg of teneligliptin was increased to a once-daily dose of 40 mg in patients with insufficient efficacy, the HbA1c and fasting blood glucose levels were reduced, and the blood glucose control target of HbA1c was achieved with some patients after the dose increase. A teneligliptin dose increase to 40 mg, once daily, is therefore considered to be clinically significant.

Safety data and additional analyses

In the integrated analysis of all Japanese clinical studies with type 2 diabetes patients, the adverse events that occurred at ≥5% were as follows: (i) all teneligliptin-treated patients: "nasopharyngitis": 23.8% (281/1183 subjects); "upper respiratory tract inflammation": 7.0% (83/1183 subjects); and "glucose urine present", and "protein urine present": each 6.7% (79/1183 subjects); and (ii) 20-mg group: "nasopharyngitis": 27.5% (232/843 subjects); "glucose urine present": 8.8% (74/843 subjects); "protein urine present": 8.7% (73/843 subjects); "upper respiratory tract inflammation": 7.4% (62/843 subjects); "blood urine present" 5.9% (50/843 subjects); and "blood creatine phosphokinase increased": 5.7% (48/843 subjects). The adverse drug reaction that occurred at ≥2% was "hypoglycemia" at 3.0% (35/ 1183 subjects) in all teneligliptin-treated patients and 3.8% (32/843 subjects) in the 20-mg group.

In study 3000-A14, adverse events with an incidence of 5% or higher in any treatment group include influenza at 5.0% (4/80 subjects) in the glinide group; pharyngitis at 5.7% (12/212 subjects) in the monotherapy group, 5.0% (4/80 subjects) in the glinide group and 5.3% (5/95 subjects) in the BG group; bronchitis at 8.8% (7/80 subjects) in the glinide group and 5.3% (5/95 subjects) in the BG group; nasopharyngitis at 29.2% (62/212 subjects) in the monotherapy group, 23.8% (19/80 subjects) in the glinide group, 29.5% (28/95 subjects) in the BG group, and 28.0% (21/75 subjects) in the α-GI group; cystitis at 5.3% (5/95 subjects) in the BG group; hypoglycaemia at 5.0% (4/80 subjects) in the glinide group; upper respiratory tract inflammation at 9.4% (20/212 subjects) in the monotherapy group, 13.8% (11/80 subjects) in the glinide group, 10.5% (10/95 subjects) in the BG group, and 10.7% (8/75 subjects) in the α-GI group; gastroesophageal reflux at 6.7% (5/75 subjects) in the α-GI group; diarrhoea at 5.3% (4/75 subjects) in the α-GI group; constipation at 7.4% (7/95 subjects) in the BG group; eczema at 5.0% (4/80 subjects) in the glinide group, and 9.3% (7/75 subjects) in the α-GI group; arthralgia at 6.3% (5/80 subjects) in the glinide group; back pain at 6.1% (13/212 subjects) in the monotherapy group, and 5.3% (4/75 subjects) in the α-GI group; blood creatine phosphokinase increased at 5.7% (12/212 subjects) in the monotherapy group, 5.0% (4/80 subjects) in the glinide group, and 6.3% (6/95 subjects) in the BG group; urine ketone body present at 7.5% (6/80 subjects) in the glinide group, and 6.3% (6/95 subjects) in the BG group; glucose urine present at 7.4% (7/95 subjects) in the BG group; blood urine present at 7.1% (15/212 subjects) in the monotherapy group, 7.5% (6/80 subjects) in the glinide group, 9.5% (9/95 subjects) in the BG group, and 6.7% (5/75 subjects) in the α-GI group; protein urine present at 6.6% (14/212 subjects) in the monotherapy group, 7.5% (6/80 subjects) in the glinide group, and 6.7% (5/75 subjects) in the α-GI group; open wound at 5.3% (4/75 subjects) in the α-GI group; and contusion at 6.3% (5/80 subjects) in the glinide group.

The incidence of hypoglycemia as adverse events and adverse drug reactions in the teneligliptin groups were low, approximately the same as in the placebo groups, and no tendency of dose-dependent increase in all Japanese double-blind comparative studies. All cases of hypoglycemia in the teneligliptin groups were mild, and no cases of hypoglycemia as serious adverse events or adverse events leading to study drug discontinuation were reported.

All hypoglycaemic events in Japanese long-term treatment studies were mild in severity. Although one subject in the SU group discontinued the study treatment due to hypoglycaemia, none of the events were reported as an SAE. The incidence of AEs or ADRs of hypoglycaemia did not tend to increase with a prolonged treatment period.

The incidence of AEs and ADRs of hypoglycaemia between "Days 0 and 14" (immediately after start of the treatment with teneligliptin) was similar to that in the other timing of onset. Although serious hypoglycaemia did not occur, the incidences of AEs and ADRs of hypoglycaemia in the SU group were higher than those in the other treatment groups. Thus, it was considered that hypoglycaemia should be carefully monitored for the patients in combination use with SU continuously.

Both the incidence and numbers of cases of hypoglycaemia occurring as adverse events and adverse drug reactions in the SU concomitant groups were higher than in the monotherapy and TZD concomitant groups. However, there were no tendencies of dose-dependent increase in incidence of hypoglycemia as adverse events and adverse drug reactions to increase with the dose of glimepiride in the SU concomitant groups, and there was also no tendency of higher incidence in elderly patients or subjects with renal impairment. Nevertheless, as the incidence of hypoglycemia occurring as adverse events and adverse drug reactions were higher in the SU concomitant group than in the monotherapy

or TZD concomitant groups. It is considered necessary to raise caution to hypoglycemia when SU drugs are concomitantly administered.

In the overseas thorough QT/QTc study although QTc interval prolongation occurred within the high-concentration range close to tmax when 160 mg of teneligliptin was administered, no clinically significant QTc interval prolongation occurred when 40 mg of teneligliptin was administered. No clinically significant QTc interval prolongation was found in the Japanese and overseas clinical studies with type 2 diabetes patients. In addition, the only adverse event with symptoms related to QT interval prolongation observed in Japanese clinical studies was loss of consciousness (1 subject) in the 20 mg group during was judged to be due to decreased blood pressure. It is therefore considered that clinically significant QTc prolongation does not occur at teneligliptin doses up to the expected.

In Japanese double-blind comparative studies, although the incidence of skin and subcutaneous tissue disorders as adverse events and adverse drug reactions were slightly higher in the teneligliptin groups than the placebo groups, there was no tendency of increase with teneligliptin dose. The adverse events in the teneligliptin groups were mild or moderate in severity, with no severe adverse events or serious adverse drug reactions. In addition, in Japanese long-term treatment studies, the incidences of AEs and ADRs in skin and subcutaneous tissue disorders were almost comparable among all treatment groups. All of the events were mild or moderate in severity, and neither severe events nor serious ADRs were reported. The necrotic skin symptoms found in the monkey teneligliptin toxicity study did not occur in any of the clinical studies, and the NOAEL in the monkey toxicity study was 30 mg/kg/day, givinga 14- to 24-fold safety margin with respect to the AUC0–24h when the expected maximum clinical dose, 40 mg, is administered. The risk of the necrotic skin symptoms found in the monkey toxicity study is therefore considered to be low in humans.

In Japanese double-blind comparative studies, the incidence of gastrointestinal disorders as adverse events and adverse drug reactions were slightly higher in the 20-and 40-mg groups than in the placebo group, but in all dose groups the events were mild or moderate in severity, and there were no severe adverse events or serious adverse drug reactions. In addition, in Japanese long-term treatment studies, the incidences of AEs and ADRs in gastrointestinal disorders were almost comparable among all treatment groups. Serious ADRs included ileus in one subject in the glinide group, haemorrhoids in one subject in the BG group, and Mallory-Weiss syndrome in one subject in the α-GI group.

The incidences of AEs and ADRs in neoplasms benign, malignant and unspecified (including cysts and polyps) were low in any Japanese long-term treatment study and comparable among treatment groups. In the long-term concomitant treatment therapy study (Study 3000-A14), 7 SAEs in neoplasms benign, malignant and unspecified (including cysts and polyps) occurred in 7 subjects receiving teneligliptin, and 2 serious ADRs occurred in 2 subjects receiving teneligliptin.

In the Japanese and overseas double-blind comparative studies of cardiovascular adverse events investigated as an evaluation of the risk of cardiovascular diseases, the incidence of adverse events and adverse drug reactions were found to be similar to those in the placebo groups. In the Japanese long-term treatment studies, the incidence of cardiovascular AEs was low in any treatment group. It was concluded that in lipid-related parameters (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride), no clinically significant changes would occur due to teneligliptin. Because the body weight increase was slight, it was concluded that no clinically significant changes in body weight would occur.

In Japanese long-term treatment studies, the incidences of AEs and ADRs of symptoms related to intestinal obstruction were almost comparable among all treatment groups. However, Ileus (one in 1 subject) was reported as a serious ADR in the glinide group in the long-term concomitant treatment therapy study (Study 3000-A14). It was concluded that intestinal obstruction should be carefully monitored during teneligliptin treatment, and especially to patients with a history of abdominal operation or intestinal obstruction, adequate attention has to be paid.

For the safety of teneligliptin at the increased dose of 40 mg given once daily, the incidences of AEs and ADRs in subjects with a dose increase to teneligliptin 40 mg in any treatment group did not show any remarkable increasing trend in comparison with those with a dose maintained at teneligliptin 20 mg in any corresponding group. No increasing trend was observed in incidences of AEs and ADRs in SOCs of skin and subcutaneous tissue disorders, gastrointestinal disorders and neoplasms benign, malignant and unspecified or in PT of hypoglycaemia in the subjects with a dose increase to teneligliptin 40 mg in comparison with those with a dose maintained. For SAEs and AEs leading to

discontinuation of study treatment, the number of events was not increased after the dose increase to teneligliptin 40 mg in any treatment group.

No clinically significant changes due to teneligliptin treatment were observed in laboratory values. No considerable differences were observed among the treatment groups.

With respect to the safety of teneligliptin, no clear differences were found in any of the following parameters: sex, age, BMI, renal impairment, hepatic impairment, smoking status, or alcohol consumption status.

No cases of "acute pancreatitis" occurred in the Japanese clinical studies. However, one case of acute pancreatitis was reported as a serious adverse drug reaction in study MP-513-E07 conducted overseas. With sitagliptin phosphate hydrate, a related drug with DPP-4-inhibitory activity, there have been overseas post-marketing reports of hemorrhagic pancreatitis and necrotizing pancreatitis, and there have also been multiple reports of acute pancreatitis as an adverse drug reaction in Japan, so the Package Insert has a warning about the possibility of these conditions as important adverse drug reactions. It is therefore considered to be essential to take notice on the possibility of pancreatitis developing.

Postmarketing data from safety database

Teneligliptin was approved in Japan on June 29, 2012 and marketed on September 10, 2012. This drug has been approved for marketing in Korea in 2014.

In Japan, between marketing and June 28, 2017, 430 ADRs were observed in 364 of the 10532 cases for the safety analysis. One hundred and three serious ADRs were reported in 91 of the 10532 cases for the safety analysis.

In addition, between the approval and June 28, 2017, there were no safety actions on teneligliptin taken by the regulatory authority or marketing authorization holder that led to withdrawal or discontinuation of the marketing approval, restriction of the marketing, premature termination of the clinical studies, amendment of the dosage and administration, amendment of the indications or amendment of the formulation.

The MAHs submitted the complete PSUR report for the new prescription drug from June 29, 2016 – June 28, 2018. There are acceptable.

3.4.7. Conclusions on clinical efficacy and safety

Tenelia 20 mg was compared with other DPP-4 inhibitors in monotherapy or combination therapy. The results showed non-inferiority in efficacy and acceptable safety. The safety of Tenelia 20 mg is searched independently by the evaluator and is no seriously concerns. Based on the clinical studies provided in the dossier and independent information of safety, the clinical part of Tenelia 20 mg is acceptable and appropriate.

Pharmacovigilance system and risk management plan

Safety monitoring program

Risk-based Safety Monitoring Program (SMP) has to be applied with Tenelia 20 mg. According to the Thai FDA's Notification about the risk-based RMP (9 Oct 2017), the 2 level of risks were classified.

Pharmacovigilance and risk management system

The Pharmacovigilance system and Risk Management Plan were provided in the eCTD 1.8 Information relating to Pharmacovigilance. As routine pharmacovigilance activities, signal of the risk is monitored by gathering and analysing ADR reports, scientific and medical publications, and safety-related regulatory actions taken by regulatory authorities in other countries. No additional pharmacovigilance activity is planned. The risk management system details were summarized as the following tables:

Table Part V.1: Description of risk minimisation measures by safety concern

Safety concern	Routine measures	Additional Measures
Hypoglycaemia (hypoglycaemia associated with teneligliptin in combination use with insulin/glucose-independent insulin secretagogues)	Provide precaution to physicians, pharmacists and other health care professionals by SmPC (section 4.4, 4.5 and 4.8) and PIL (section 2.2 and 4).	None
Hypoglycaemia (hypoglycaemia associated with teneligliptin without concomitant use of insulin/glucose-independent insulin secretagogues)	Same with above SmPC (section 4.8) PIL (section 4 and 5.2)	None
Intestinal obstruction	Same with above SmPC (section 4.4 and 4.8) PIL(section 2.2 and 5.2)	None
Hepatic impairment	Same with above SmPC (section 4.4 and 4.8) PIL (section 4 and 5.2)	None
Interstitial lung disease	Same with above SmPC (section 4.8) PIL (section 5.2)	None

Table Part V.1: Continued

Safety concern	Routine measures	Additional Measures
Pemphigoid	Same with above SmPC (section 4.8) PIL (section 5.2)	None
Electrocardiogram QT prolonged	Same with above SmPC(section 4.4) PIL (section 2.2)	None
Acute pancreatitis	Same with above SmPC (section 4.4 and 4.8) PIL (section 5.2)	None
Important missing information		
Use in the elderly	Same with above SmPC (section 4.4)	None
Use in patients with hepatic impairment	Same with above SmPC (section 4.4 and 4.8)	None

4. Benefit risk assessment

Benefits

Clinical studies results confirmed the efficacy of Tenelia 20 mg as monotherapy and combination therapy with existing oral hypoglycemic drugs and the long-term treatment data for up to 52 weeks have demonstrated stable glycemic control in the prolonged treatment. The blood glucose control is possible with once-daily administration, improving compliance. Tenelia 20 mg is not considered to be necessary for dose adjustment in subject with renal and mild to moderated hepatic impairment also. Last but not least, tenelia 20 mg has the lower incidence of hypoglycaemia. However, using tenelia with SU group was increased hypoglycemic incidences than using in monotherapy or using with other oral hypoglycemic drugs.

Risks

On the basis of the results of Japanese and overseas clinical studies, it is necessary to consider the possibility of hypoglycemia developing in an SU concomitant therapy. The effect on QTc prolongation was found in increasing dosage to 40 mg per day. The relevant information is provided in the package leaflet. The non-clinical relevant information of Tenelia 20 mg found that there were risks of mecrotic skin symptoms in monkey toxicity studies. This information is to be provided in SmPC. Moreover, Tenelia 20 mg was considerd to be necessary to take notice on the occurrence of pancreatitis and intestinal obstruction with teneligliptin administration. However, the safety of Tenelia 20 mg was directly compared with the safety of placebo and other DPP-4 inhibitors.

Benefit-risk balance

Based on the data from quality, non-clinic, and clinical aspects, the benefit-risk balance is positive.

5. Conditions for marketing authorisation and product information

5.1. Conditions for the marketing authorisation

Tenelia 20 mg has the important conditions for the marketing authorisation:

1) Utilized under the health facility and specified on the label
2) Perform PIL usability testing within 12 months after authorisation and report to Thai FDA
3) Monitor the safety of medicine as the protocol in SMP
4) Complied to the risk management plan as the information in section 1.8.2 Risk management system in eCTD

5.2. Summary of product characteristics (SmPC)

The information in SmPC is concordance with the quality, non-clinical, and clinical data as submitted in the dossier. The information is correct, appropriate, and promotes the rationale to use. SmPC of Tenelia 20 mg is available as the attachment in Appendix 6.2.

5.3. Labelling

The labelling is met the requirement recommended by Thai FDA (2009), Annex 3, the labeling and documentation for drug registration. This labelling is also in accordance with ASEAN Harmonization and appropriate. The details of labelling are summarized as the following:

Blister/Strips

No.	Topic	Available	Appropriate
1	Product name	✓	✓
2	Name of active ingredients	✓	✓
3	Strength of active ingredients	✓	✓
4	Batch number	✓	✓
5	Expiration date	✓	✓
6	Name and address of market authorization holder/manufacturer	✓	✓
7	Countrys registration number	✓	✓

✓ Available or Appropriate
n/a Not relevant to the topic

UNIT CARTON (Box and Pouch)

No.	Topic	Available	Appropriate
1	Product name	✓	✓
2	Dosage form	✓	✓
3	Name of active ingredients	✓	✓
4	Strength of active ingredients	✓	✓
5	Batch number	✓	✓
6	Manufacturing date	✓	✓
7	Expiration date	✓	✓
8	Route of Administration	✓	✓
9	Storage condition	✓	✓
10	Countrys registration number	✓	✓
11	Name and address of market authorization holder	✓	✓
12	Name and address of manufacturer	✓	✓
13	Special labeling	✓	✓
14	Recommended daily allowance (for vitamins or minerals)	n/a	n/a
15	Warnings (according to the notifications of the Ministry of Public Health)	✓	✓
16	Pack sizes	✓	✓

✓ Available or Appropriate
n/a Not relevant to the topic

5.4. Patient information leaflet (PIL)

Patient Information Leaflet (PIL) is suitable and in accordance with the Sumary Product Characteristic (SmPC). The content and format are complied with Thai FDA guideline for leaflet development (3 Jul 2013), as well as the Guidelinde for Leaflet Development (May 2019) implemented by Division of Innovative Health Product and Services. However, the applicant has to commit for usability testing to ensure that PIL is legible, clear, and easy to use (see section 5.1).

6. Appendices

6.1. Risk management system

Risk management system was available as the attachment.

03_RMP_Tenelia_V1.pdf

6.2. PIL, SmPC, and labels

Patient information leaflet (PIL)

04_PIL_Tenelia_V1.pdf

Summary of Product Characteristic (SmPC)

05_SmPC_Tenelia_V1.pdf

Labels

06_Label_Tenelia_V1.pdf