Efficacy and safety of linagliptin in type 2 diabetes patients with self-reported hepatic disorders: a retrospective pooled analysis of 17 randomized, double-blind, placebo-controlled clinical trials

Nobuya Inagaki[a,*], Wayne H.-H. Sheu[b], David R. Owens[c], Susanne Crowe[d], Amit Bhandari[e], Yan Gong[d], Sanjay Patel[f,†]

[a]*Department of Diabetes, Endocrinology and Nutrition, Kyoto University Graduate School of Medicine, Kyoto, Japan*

[b]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan*

[c]*Institute of Life Sciences, Swansea University, Swansea, Wales, UK*

[d]*Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany*

[e]*Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA*

[f]*Boehringer Ingelheim Ltd, Bracknell, UK*[†]

*Corresponding author: Professor Nobuya Inagaki, Department of Diabetes, Endocrinology and Nutrition, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. Tel.: +81-75-751-3562; fax: +81-75-771-6601.

E-mail address: inagaki@metab.kuhp.kyoto-u.ac.jp

[†]Present address: Daiichi Sankyo Developments Ltd, Gerrards Cross, Buckinghamshire, UK

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Abstract (200 words – limit of 200)

Aims: Liver disease is highly prevalent among people with type 2 diabetes mellitus (T2DM). We evaluated the dipeptidyl peptidase-4 inhibitor linagliptin in subjects with T2DM and hepatic disorders.

Methods: Data were pooled from 17 randomized, double-blind, placebo-controlled clinical trials of linagliptin in T2DM subjects that included individuals with self-reported history of hepatic disorders at baseline. The primary endpoint was change in HbA1c from baseline to week 24.

Results: Of the 7009 participants (56% white, 39% Asian), 574 had hepatic disorders, most commonly hepatic steatosis (60%). At week 24, adjusted mean ± standard error (SE) change in HbA1c from baseline in those with hepatic disorders was −0.75% ± 0.05 with linagliptin and −0.20% ± 0.08 with placebo [treatment difference: −0.54% (95% confidence interval −0.72 to −0.36); $P<.0001$]. There was no significant difference in HbA1c reduction between subjects with and without baseline hepatic disorders ($P=.4042$). Among patients with hepatic disorders, 13.5% and 14.8% of the linagliptin and placebo groups, respectively, reported drug-related adverse events while 10.4% and 15.9%, respectively, reported hypoglycemia. Overall, adverse event rates were similar to individuals without hepatic disorders.

Conclusions: This large pooled analysis suggests that linagliptin is effective and well tolerated in people with T2DM and liver disease.

Keywords: Linagliptin, DPP-4 inhibitor, Type 2 diabetes, Liver disease, Pooled analysis, Efficacy, Safety

1. Introduction

Diabetes is a leading cause of liver disease, and non-alcoholic fatty liver disease (NAFLD), in particular, may be one of its sequelae (Tolman et al., 2007; Yki-Järvinen, 2014). Conversely, liver disease may be a cause of diabetes (Tolman et al., 2007; Yamazaki et al., 2015; Yki-Järvinen, 2014). Consequently, liver disease is prevalent amongst people with type 2 diabetes mellitus (T2DM). It is estimated that NAFLD affects approximately 70% (Cusi, 2009), and cirrhosis is a common cause of diabetes-related death (de Marco et al., 1999). Of note, more than 50% of people with diabetes live in the Western Pacific region (including China) and Southeast Asia (including India) (International Diabetes Federation) – where liver disease is already highly prevalent (e.g., viral hepatitis, cirrhosis, hepatocellular carcinoma) (Bosetti et al., 2014) with NAFLD becoming increasingly common (Wong, 2013).

The presence of liver disease complicates clinical decision-making in T2DM because the liver is essential to both glucose homeostasis and the metabolism and elimination of several glucose-lowering drugs. Consequently, a number of antihyperglycemic agents must be used cautiously, depending on the severity of hepatic impairment (Khan et al., 2012; Scheen, 2014a). Historically, the pharmacokinetics, efficacy and safety of older orally administered glucose-lowering drugs (i.e., sulfonylureas, meglitinides, metformin and thiazolidinediones) have not been extensively studied in the presence of liver disease (Khan et al., 2012; Scheen, 2014a). However, dosage reduction and/or cautious use in individuals with hepatic impairment is recommended for most of these agents due to the potential for lactic acidosis (metformin), hypoglycemia (sulfonylureas, meglitinides) or liver injury (with pioglitazone, the remaining widely used thiazolidinedione). Because of these potential limitations, the efficacy and safety of new glucose-lowering agents in patients with T2DM and liver disease are of interest, including dipeptidyl peptidase (DPP)-4 inhibitors.

Linagliptin is a DPP-4 inhibitor that is excreted mainly in feces via enterohepatic pathways; i.e., bile and direct excretion into the gut (Blech et al., 2010; Fuchs et al., 2012). However, hepatic metabolism plays only a minor role in the enterohepatic excretion of linagliptin, with over 80% of the administered dose excreted as parent compound (Graefe-Mody et al., 2012a). Despite the involvement of the liver in excretion of linagliptin, hepatic impairment does not have clinically relevant effects on its pharmacokinetics, even severe hepatic impairment based on Child–Pugh classification (Graefe-Mody et al., 2012b). This may be because of the very high affinity of linagliptin for DPP-4, which is present in plasma, resulting in high plasma protein binding (99% at concentrations below 1 nmol/l in *in vitro* assays (Fuchs et al., 2009)) and, therefore, very low plasma concentrations of free/unbound drug (~0.7 nmol/l) (Graefe-Mody et al., 2012b). Even subjects with severe hepatic impairment may have sufficient residual liver function to eliminate this small amount of free linagliptin from the blood, and dose adjustment of linagliptin is not advocated for hepatic impairment (Boehringer Ingelheim International GmbH & Co. KG, 2013a; McGill et al., 2013). As linagliptin is not substantially excreted by the kidneys, no dose adjustment is required in individuals with chronic kidney disease (Boehringer Ingelheim International GmbH & Co. KG, 2013a; Graefe-Mody et al., 2011; McGill et al., 2013), in contrast to other members of this class of drugs.

No randomized controlled study of the glycemic efficacy and tolerability of linagliptin, or any other DPP-4 inhibitor, has been conducted exclusively in people with both T2DM and liver disease; however, such individuals participated in several late-stage clinical trials of linagliptin. We have therefore conducted a retrospective pooled analysis of T2DM patients with known liver disease at baseline from these studies in order to examine the efficacy and tolerability of linagliptin in this population.

2. Methods

2.1. Study design and patient population

This was a retrospective pooled analysis of participant-level data from all randomized, double-blind, placebo-controlled Phase II or III clinical trials of linagliptin that lasted for at least 12 weeks, included individuals with pre-existing hepatic disorders, and had results available by January 2013. Subjects with T2DM were defined as having hepatic disorders if they had a concomitant diagnosis or adverse event at baseline that was classified within the Standardized Medical Query (SMQ) "hepatic disorders" from the Medical Dictionary for Regulatory Activities (MedDRA) version 15.1. Seventeen studies met these criteria (Bajaj et al., 2014; Barnett et al., 2013; Barnett et al., 2012; Chen et al., 2015; Del Prato et al., 2011; Gomis et al., 2011; Haak et al., 2012; Kawamori et al., 2012; Laakso et al., 2015; Lewin et al., 2012; McGill et al., 2013; Owens et al., 2011; Ross et al., 2012; Taskinen et al., 2011; Thrasher et al., 2014; Wang et al., 2015; Yki-Järvinen et al., 2013); these had compared linagliptin with placebo as monotherapy or added to other glucose-lowering drugs in a variety of patient populations (Table S1), with study durations ranging from 12 to 52 weeks.

In general, these studies included T2DM subjects aged ≥18 years with inadequate glycemic control, typically glycated hemoglobin (HbA1c) ≥7.0 to ≤10.0% (≥53 to ≤86 mmol/mol). Subjects who had experienced a recent myocardial infarction, stroke or transient ischemic attack were excluded. Also excluded were those with impaired hepatic function at screening, which was defined as serum concentration of alanine transaminase (ALT), aspartate transaminase (AST) or alkaline phosphatase (ALP) more than three times the upper limit of normal (ULN). However, individuals known to have liver disease were permitted to participate provided their hepatic function at screening satisfied the above criteria.

The primary endpoint in these studies was change from baseline in HbA1c, usually after 24 weeks, with other parameters such as changes from baseline in fasting plasma glucose (FPG), body weight, and tolerability assessed as secondary endpoints.

2.2. Assessments

In this pooled analysis, the primary efficacy parameter was change from baseline in HbA1c after 24 weeks. Other parameters evaluated were change from baseline in HbA1c over time, change from baseline in HbA1c at week 24 in subgroups according to duration of T2DM, renal function and race, and change from baseline in FPG at week 24. Changes in postprandial glucose, homeostasis model assessment of pancreatic β-cell function (HOMA-%B), disposition index and body weight were also evaluated. Safety and tolerability assessments included the incidence of reported adverse events, which were classified using MedDRA version 15.1. A serious adverse event was defined as an event that was fatal, life-threatening, required hospitalization or prolonged existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was deemed serious for any other reason. Hypoglycemia was defined by investigators as a blood glucose concentration of ≤3.9 mmol/l (≤70 mg/dl) or an event requiring the assistance of another person to administer carbohydrate, glucagon or other resuscitative action. Pancreatitis was defined as the MedDRA preferred term of chronic pancreatitis or any preferred term within the Standardized MedDRA Query for pancreatitis from MedDRA version 17.0 (Table S2). Pancreatic cancer was defined based on a customized MedDRA query for pancreatic cancer-related preferred terms from MedDRA version 17.0 (Table S2). The results of laboratory tests in the individual studies, conducted by central laboratories, were also pooled and analyzed.

2.3. Statistical analyses

Efficacy analyses were performed on the full-analysis set (FAS): all randomized subjects who received at least one dose of study drug and had a baseline HbA1c measurement and at least one on-treatment HbA1c measurement. Efficacy endpoints were compared between linagliptin and placebo using analysis of covariance (ANCOVA). Changes in HbA1c from baseline to week 24 and over time in the FAS were evaluated using a general ANCOVA model containing terms for treatment, study, continuous baseline HbA1c, prior use of oral anti-diabetes drugs, hepatic disorders, and hepatic disorders-by-treatment interaction. Efficacy measurements after start of glycemic rescue treatment were set to missing; those and other missing data were imputed using the last-observation-carried-forward (LOCF) method.

Change from baseline in HbA1c for FAS (LOCF) subgroups for T2DM duration, renal function and race were analyzed using the general ANCOVA model but with additional terms: subgroup, hepatic disorders-by-subgroup-by-treatment interaction. Change from baseline in FPG at week 24 was analyzed for the FAS (LOCF) using the general ANCOVA model with an additional term for continuous baseline FPG. Change from baseline in postprandial glucose was analyzed using descriptive statistics for the subset of subjects who had undergone meal-tolerance tests at baseline and at week 24 in four of the reference studies. Changes from baseline in HOMA-%B and disposition index were measured in nine and eight of the reference studies, respectively; data were pooled and analyzed for participants in the FAS of this subset who had available data (observed cases) using the general ANCOVA model with an additional term for continuous baseline HOMA-%B or continuous baseline disposition index, respectively. The disposition index was calculated as the ratio of HOMA-%B over HOMA of insulin resistance: i.e., disposition index = 450/[FPG (mmol/l) × [FPG (mmol/l) − 3.5]]. Change from baseline in body weight at week 24 was

analyzed for subjects in the FAS with available data (observed cases); the general ANCOVA model was used with the addition of continuous baseline body weight.

The incidence of participants with adverse events was summarized with descriptive statistics for the treated set: all randomized subjects who received at least one dose of study drug. In addition, data were adjusted for time exposed to study drug as the trials included had different durations. Laboratory data from liver function tests were also analyzed using descriptive statistics.

3. Results

3.1. Baseline characteristics and demographics

This pooled analysis comprised 574 T2DM subjects with baseline hepatic disorders and 6435 without. Most subjects were white or Asian, and baseline characteristics were generally similar between the linagliptin and placebo groups, with or without baseline hepatic disorders (Table 1). Among the former, hepatic steatosis was the most common condition, affecting approximately 60% of both the linagliptin and placebo groups (Table S3). Seventeen patients (3.0%) had hepatitis C.

3.2. Efficacy

Linagliptin was significantly more efficacious than placebo in reducing HbA1c. At week 24, the adjusted mean ± standard error (SE) change from baseline in subjects with baseline hepatic disorders was −0.75% ± 0.05 (−8.16 ± 0.60 mmol/mol) and −0.20% ± 0.08 (−2.24 ± 0.84 mmol/mol) with linagliptin and placebo, respectively, a treatment difference of −0.54% [95% confidence interval (CI) −0.72 to −0.36; $P<.0001$]. The placebo-adjusted HbA1c reduction with linagliptin was not significantly different between subjects with or without

hepatic disorders (*P*=.4042) (Fig. 1). The largest HbA1c reductions occurred during the first 12 weeks, after which time glycemic control remained stable (Fig. 2).

Furthermore, linagliptin generally had significantly greater efficacy than placebo in reducing HbA1c irrespective of T2DM duration, renal function or race (Fig. 3). Although the placebo-adjusted reduction in HbA1c at week 24 was not significant in black subjects with hepatic disorders, this is likely a consequence of low statistical power in this subgroup because of the small number of subjects (*n*=14). In all subgroups, the magnitude of HbA1c reduction was not significantly affected by the presence or absence of hepatic disorders (*P*>.05 for all three-way interactions between treatment, hepatic disorders and T2DM duration, kidney disease or race) (Fig. 3).

Linagliptin was also significantly more effective than placebo in reducing FPG. At week 24, the adjusted mean ± SE change from baseline in FPG in subjects with hepatic disorders was −0.60 ± 0.13 mmol/l and 0 ± 0.19 mmol/l with linagliptin and placebo, respectively, a treatment difference of −0.60 mmol/l (95% CI −1.04 to −0.16; *P*=.0071). In subjects without hepatic disorders, the adjusted mean ± SE change from baseline was −0.73 ± 0.05 mmol/l and 0.09 ± 0.06 mmol/l with linagliptin and placebo, respectively, a treatment difference of –0.82 mmol/l (95% CI −0.95 to −0.69; *P*<.0001).

Within the subset of subjects who underwent meal-tolerance testing, linagliptin treatment was associated with a reduction in 2-hour postprandial glucose whereas placebo treatment was associated with increased 2-hour postprandial glucose. At week 24 in subjects with hepatic disorders, mean ± standard deviation (SD) change from baseline in 2-hour postprandial glucose was −1.75 ± 3.67 mmol/l with linagliptin (*n*=17) compared with +3.98 ± 1.17 mmol/l in those receiving placebo (*n*=3). In subjects without hepatic disorders, mean ± SD change in 2-hour postprandial glucose was −2.20 ± 3.63 mmol/l and +0.85 ± 3.62 mmol/l in those receiving linagliptin (*n*=149) or placebo (*n*=55), respectively.

Among subjects whose pancreatic β-cell function was estimated by HOMA-%B, improvement at 24 weeks was greater with linagliptin than placebo, but the difference was significant only in those without hepatic disorders: placebo-adjusted mean change from baseline in HOMA-%B with linagliptin of 5.51 (95% CI –21.62 to 32.63; *P*=.6905) in subjects with hepatic disorders (*n*=248), and 14.80 (95% CI 6.51 to 23.09; *P*=.0005) in those without hepatic disorders (*n*=2678). Similarly, the disposition index improved from baseline to week 24 to a greater extent in subjects receiving linagliptin compared with those receiving placebo, with the treatment difference significant only in patients without hepatic disorders: placebo-adjusted mean change from baseline in disposition index with linagliptin of 1.13 (95% CI –11.94 to 14.21; *P*=.8651) in patients with hepatic disorders (*n*=274), and 4.87 (95% CI 0.83 to 8.92; *P*=.0183) in those without hepatic disorders (*n*=3005).

Mean changes in body weight were minimal. In subjects with hepatic disorders, the adjusted mean change from baseline in body weight at week 24 was 0.21 ± 0.19 kg and –0.23 ± 0.28 kg in the linagliptin and placebo groups, respectively; a treatment difference of 0.44 kg (95% CI –0.20 to 1.08; *P*=.1753). In subjects without hepatic disorders, the adjusted mean change from baseline in body weight at week 24 was –0.03 ± 0.07 kg and –0.21 ± 0.09 kg in the linagliptin and placebo groups, respectively; a treatment difference of 0.18 kg (95% CI –0.01 to 0.36; *P*=.0637).

3.3. Tolerability and safety

Approximately 70% of subjects with baseline hepatic disorders reported adverse events compared with ~60% of those without baseline hepatic disorders, with little numerical difference between the linagliptin and placebo groups in the proportions affected. Similarly, there was little difference between groups in the incidence of drug-related adverse events, treatment discontinuation because of adverse events, and serious adverse events (Table 2).

The incidence of investigator-defined hypoglycaemia was lower with linagliptin than with placebo in patients with hepatic disorders, as well as those without (Table 2). Pancreatitis occurred in three (0.78%) linagliptin-treated subjects and none receiving placebo among those with hepatic disorders, and in one (0.02%) linagliptin patient and one (0.05%) placebo patient in those without hepatic disorders (Table 2). Increases in serum amylase or lipase during treatment did not occur in any subjects with baseline hepatic disorders. Among those without baseline hepatic disorders, amylase increased in 13 (0.31%) and four (0.18%) subjects receiving linagliptin and placebo, respectively, and lipase increased in three (0.14%) placebo-treated subjects but no linagliptin-treated subjects. No cases of pancreatic cancer occurred (Table 2).

After adjusting for time exposed to study drugs, incidence rates of affected subjects were similar between the linagliptin and placebo groups except for hypoglycemia, which occurred at a higher rate with placebo than linagliptin (Table 2).

3.4. Hepatic safety and function

During treatment with linagliptin or placebo, adverse events related to the liver (hepatobiliary disorders) occurred in 11 of 574 (1.9%) subjects with baseline hepatic disorders and 53 of 6435 (0.8%) patients without baseline hepatic disorders. In neither group was the incidence of on-treatment hepatobiliary disorders substantially different between linagliptin- and placebo-treated subjects (Table 2). Liver cancer occurred in one subject, an individual with a hepatic disorder who was receiving placebo (0.53% of that treatment group). Acute liver failure did not occur in any patient.

Among subjects with baseline hepatic disorders, elevations in transaminases (AST, ALT) during treatment were rare, with the proportion affected similar for the linagliptin and placebo groups (Table S4). Similarly, ALP, gamma-glutamyl transferase, lactate

dehydrogenase, and bilirubin were only rarely elevated during treatment with study drug, with few discernible differences between linagliptin and placebo subjects (Table S4). No Hy's Law cases were observed.

Mean values for serum lipid levels (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides) did not change substantially in any treatment group (data not shown).

4. Discussion

This retrospective pooled analysis suggests that linagliptin elicits clinically meaningful improvements in glycemic control and is well tolerated in people with T2DM and co-existing liver disease, a prevalent yet understudied patient population. The improvements in HbA1c, FPG and postprandial glucose in patients with baseline hepatic disorders were of similar magnitudes to those in patients without baseline hepatic disorders.

The liver is one of the main organs involved in glucose metabolism, and there appears to be a bidirectional relationship between diabetes and liver disease. It is estimated that the majority of people with T2DM also have NAFLD, the most common type of liver disease (Firneisz, 2014; Fruci et al., 2013). Furthermore, in a large population-based cohort study (the Verona Diabetes Study), cirrhosis was more than twice as common in people with T2DM compared with the general population, and was the fourth leading cause of mortality (de Marco et al., 1999). Conversely, it has been estimated that approximately one-third of people with cirrhosis also have T2DM (Tolman et al., 2007). Due to this complex two-way relationship, which may be explained by a common etiology previously suggested to be insulin resistance (Leite et al., 2014), people with both T2DM and liver disease comprise a highly prevalent population.

The presence of liver disease complicates treatment selection for those with T2DM, given the role played by the liver in both glucose homeostasis and metabolism of many glucose-lowering drugs. However, relatively few studies of glucose-lowering drugs have been conducted exclusively in T2DM subjects with concomitant liver disease, particularly with older agents. Almost no pharmacokinetic studies of metformin, sulfonylureas, meglitinides or thiazolidinediones in subjects with hepatic impairment have been published (Scheen, 2014a). While metformin does not undergo either hepatic metabolism or excretion, caution with its use in patients with liver disease is recommended to mitigate the risk of lactic acidosis arising from impaired lactate metabolism (Khan et al., 2012). Most sulfonylureas are metabolized by the liver and, in the absence of pharmacokinetic studies in subjects with hepatic impairment, caution is advised for their use in the presence of liver disease in order to reduce the risk of hypoglycemia (Scheen, 2014a). Meglitinides are extensively metabolized by the liver and consequently their pharmacokinetics are altered by hepatic impairment, with caution therefore advised for their use in those with liver disease (Scheen, 2014a). Pioglitazone is also extensively metabolized and excreted by the liver; therefore, it is recommended to obtain liver function tests prior to commencing treatment with pioglitazone and to use it cautiously in the presence of liver disease (Khan et al., 2012). Caution, and possible dose reduction, is also advised when using insulin in those with hepatic dysfunction because of the risk of hypoglycemia (Khan et al., 2012; Scheen, 2014a).

In contrast to the general lack of published pharmacokinetic data for older glucose-lowering drugs in hepatic impairment, the newer DPP-4 inhibitors, glucagon-like peptide-1 receptor agonists and sodium glucose co-transporter 2 inhibitors have been extensively characterized in this setting (Scheen, 2014a; Scheen, 2014b). Of the other globally available DPP-4 inhibitors, sitagliptin, vildagliptin, saxagliptin and alogliptin are excreted by the kidney with vildagliptin and saxagliptin metabolized extensively by the liver, unlike

sitagliptin and alogliptin which undergo minimal hepatic metabolism (Scheen, 2014a; Scheen, 2014b). Pharmacokinetic studies conducted in subjects with hepatic impairment indicate that dose adjustment of these DPP-4 inhibitors is generally not required in the presence of hepatic impairment (Scheen, 2014a; Scheen, 2014b) although vildagliptin is not recommended for such use (Novartis Pharmaceuticals UK Ltd, 2012). In contrast to other DPP-4 inhibitors, linagliptin is excreted extensively by the liver, albeit with only minimal hepatic metabolism (Blech et al., 2010; Fuchs et al., 2012). Despite this, a pharmacokinetic study in subjects with hepatic impairment found no clinically relevant changes in linagliptin exposure, even in those with severely impaired liver function (Graefe-Mody et al., 2012b) – the possible reasons for this were discussed earlier. Consequently, dose adjustment of linagliptin is not required for any degree of hepatic impairment (Boehringer Ingelheim International GmbH & Co. KG, 2013a; McGill et al., 2013).

For older and newer glucose-lowering drugs alike, there is little published data from randomized clinical trials on their glycemic efficacy and tolerability in individuals with liver disease (Scheen, 2014a). The pooled analysis of linagliptin reported here addresses this evidence gap. This analysis suggests that linagliptin in people with both T2DM and liver disease is efficacious and well tolerated across the treatment continuum; i.e., as monotherapy, combined with other oral glucose-lowering drugs, or added to insulin. In addition, the glucose-lowering efficacy of linagliptin in T2DM patients with liver disease was evident across different populations, including various racial/ethnic groups, the elderly, those with renal impairment and those intolerant of metformin. Importantly, the presence of liver disease did not affect the glycemic response to linagliptin treatment. Linagliptin was also well tolerated, with similar proportions of the linagliptin and placebo groups experiencing adverse events. Notably, hypoglycemia affected fewer linagliptin-treated subjects than placebo-treated subjects. There is growing recognition that hypoglycemia in individuals with T2DM

is not a trivial complication, and that preventing or minimizing hypoglycemic events may be as important as achieving tight glycemic control in vulnerable individuals (Seaquist et al., 2013; Slomski, 2013).

Importantly, there was no indication that linagliptin adversely impacted pre-existing liver disease. There were no cases of acute liver failure, and the incidence of new-onset hepatobiliary disorders was low in both the linagliptin and placebo groups (~2%) – albeit slightly higher than in subjects without liver disease (~1%). Furthermore, during linagliptin treatment, abnormal liver function tests were rare in subjects with baseline hepatic disorders as well as those without such disorders.

This pooled analysis has certain strengths and limitations. Notably, it included data for a large number of participants from rigorously controlled clinical trials. However, its *post-hoc* nature introduces the potential for confounding bias, as subjects were not randomized specifically for the analysis. Nevertheless, the baseline clinical and demographic characteristics of subjects were similar between treatment groups. Importantly, the presence or absence of hepatic disorders at baseline was identified by self-reporting with no formal assessment for liver disease, and subjects with active hepatic disease (serum transaminases >3 times ULN) were excluded. Of note, the study population had a heterogenous group of liver disorders. Moreover, linagliptin was compared only with placebo and not with other glucose-lowering drugs, and the demographic and clinical characteristics of the subjects in this analysis may not be identical to those with T2DM and liver disease elsewhere in clinical practice.

In conclusion, this large retrospective pooled analysis of 17 randomized clinical trials provides evidence that linagliptin – an enterohepatically excreted DPP-4 inhibitor that does not require dose adjustment for hepatic impairment – is efficacious and well tolerated in individuals with T2DM and liver disease. In addition, there was no evidence that liver disease

either affected the glycemic response to linagliptin or was adversely impacted by linagliptin. Linagliptin, therefore, may be a useful option within the therapeutic armamentarium for people with T2DM and liver disease, given the constraints on other glucose-lowering drugs in this under-recognised and prevalent population.

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Conflict of Interest

N.I. has received speaker fees from Sanofi, Astellas Pharma and Boehringer Ingelheim; clinical research grants from MSD, Mitsubishi Tanabe Pharma, Eli Lilly, Roche Diagnostics and Shiratori Pharmaceutical; and scholarship grants from Sanofi, Takeda Pharmaceutical, Japan Tobacco, Mitsubishi Tanabe Pharma, MSD, AstraZeneca, Daiichi Sankyo, Boehringer Ingelheim, Ono Pharmaceutical, Taisho Toyama Pharmaceutical, and Sumitomo Dainippon Pharma. W.H.-H.S. has no conflicts of interest to declare. D.R.O. has received consultancy fees, speaker fees and/or travel grants from Boehringer Ingelheim. A.B. and Y.G. are employees of Boehringer Ingelheim. S.C. was an employee of Boehringer Ingelheim at the time of the study. S.P. was an employee of Boehringer Ingelheim at the time of the study, but is now an employee of Daiichi Sankyo Developments Ltd.

N.I., W.H.-H.S. and D.R.O. participated in the design of the study, interpretation of data and preparation of the manuscript. S.C. performed the statistical analysis, and participated in interpretation of data and preparation of the manuscript. A.B., Y.G. and S.P.

participated in the design and conduct of the study, interpretation of data and preparation of the manuscript. All authors approved the final version of the manuscript.

Tables and Figures

Table 1

Baseline demographic and clinical characteristics

	Hepatic disorders		No hepatic disorders	
	Linagliptin	Placebo	Linagliptin	Placebo
Treated set, *n*	385	189	4240	2195
Male, *n* (%)	219 (56.9)	119 (63.0)	2240 (52.8)	1174 (53.5)
Age, years	57.5 ± 10.3	57.6 ± 10.0	58.4 ± 10.7	58.8 ± 10.7
<65 years, *n* (%)	286 (74.3)	144 (76.2)	2976 (70.2)	1512 (68.9)
65 to 74 years, *n* (%)	87 (22.6)	38 (20.1)	1011 (23.8)	537 (24.5)
≥75 years, *n* (%)	12 (3.1)	7 (3.7)	253 (6.0)	146 (6.7)
Race, *n* (%)				
White	192 (49.9)	100 (52.9)	2356 (55.6)	1243 (56.6)
Asian	185 (48.1)	81 (42.9)	1700 (40.1)	780 (35.5)
Black	8 (2.1)	8 (4.2)	184 (4.3)	172 (7.8)
BMI, kg/m^2	29.3 ± 5.2	29.7 ± 5.4	29.0 ± 5.2	29.6 ± 5.3
Renal function (eGFR, ml/min/1.73 m^2)*, *n* (%)				
Normal (≥90)	150 (39.0)	78 (41.3)	1690 (39.9)	801 (35.6)
Mild impairment (60 to <90)	191 (49.6)	79 (41.8)	1976 (46.6)	997 (45.4)
Moderate impairment (30 to <60)	37 (9.6)	21 (11.1)	460 (10.8)	281 (12.8)

	Hepatic disorders		No hepatic disorders	
	Linagliptin	Placebo	Linagliptin	Placebo
Severe impairment (<30)	7 (1.8)	11 (5.8)	104 (2.5)	101 (4.6)
Missing data	0 (0)	0 (0)	10 (0.2)	15 (0.7)
Liver function, median (interquartile range)				
AST (GOT)[†], units/l	24 (15−42)	27 (19−39)	18 (11−27)	18 (12−27)
ALT (SGPT)[‡], units/l	32 (20−59)	34 (20−54)	23 (14−36)	22 (14−34)
ALP[§], units/l	138 (105−181)	149 (112−189)	135 (103−176)	137 (103−181)
GGT[II], units/l	50 (27−98)	50 (23−92)	28 (15−51)	27 (13−51)
LDH[¶], units/l	169 (142−190)	166 (140−197)	169 (144−192)	171 (144−196)
Bilirubin**, mg/dl	0.4 (0.3−0.6)	0.4 (0.2−0.6)	0.4 (0.2−0.5)	0.3 (0.2−0.5)
Full-analysis set, *n*	378	188	4154	2138
HbA1c, %	8.23 ± 0.85	8.25 ± 0.91	8.17 ± 0.87	8.22 ± 0.89
(mmol/mol)	(66.49 ± 0.48)	(66.65 ± 0.73)	(65.82 ± 0.15)	(66.28 ± 0.21)
Fasting plasma glucose, mmol/l	9.15 ± 2.37	9.21 ± 2.63	9.06 ± 2.47	9.05 ± 2.59
Diabetes duration, *n* (%)				
≤1 year	46 (12.2)	23 (12.2)	549 (13.2)	244 (11.4)
>1 to ≤5 years	118 (31.2)	43 (22.9)	1231 (29.6)	553 (25.9)
>5 years	214 (56.6)	122 (64.9)	2374 (57.1)	1341 (62.7)

	Hepatic disorders		No hepatic disorders	
	Linagliptin	Placebo	Linagliptin	Placebo
Glucose-lowering drugs at screening, *n* (%)				
0	78 (20.6)	34 (18.1)	645 (15.5)	332 (15.5)
1	108 (28.6)	58 (30.9)	1622 (39.0)	809 (37.8)
≥2	192 (50.8)	96 (51.1)	1887 (45.4)	997 (46.6)

Data are mean ± SD unless otherwise stated. AST, aspartate transaminase/aspartate aminotransferase; ALP, alkaline phosphatase; ALT, alanine transaminase/alanine aminotransferase; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; GOT, serum glutamic oxaloacetic transaminase; LDH, lactate dehydrogenase; SGPT, serum glutamate-pyruvate transaminase/serum glutamic-pyruvic transaminase.

*According to the Modification of Diet in Renal Disease study equation.

[†]Data are for subjects in the treated set with available baseline measurements. Hepatic disorders: 372 linagliptin, 185 placebo; no hepatic disorders: 4090 linagliptin, 2099 placebo.

[‡]Hepatic disorders: 372 linagliptin, 185 placebo; no hepatic disorders: 4091 linagliptin, 2100 placebo.

[§]Hepatic disorders: 373 linagliptin, 186 placebo; no hepatic disorders: 4106 linagliptin, 2105 placebo.

[II]Hepatic disorders: 368 linagliptin, 184 placebo; no hepatic disorders: 4004 linagliptin, 1987 placebo.

[¶]Hepatic disorders: 363 linagliptin, 182 placebo; no hepatic disorders: 3966 linagliptin, 1970 placebo.

**Hepatic disorders: 367 linagliptin, 178 placebo; no hepatic disorders: 4038 linagliptin, 2044 placebo.

Table 2

Adverse events

	Hepatic disorders		No hepatic disorders	
	Linagliptin (*n*=385)	Placebo (*n*=189)	Linagliptin (*n*=4240)	Placebo (*n*=2195)
Subjects, *n* (%)				
Any AE	269 (69.9)	130 (68.8)	2413 (56.9)	1376 (62.7)
Drug-related AE	52 (13.5)	28 (14.8)	492 (11.6)	303 (13.8)
Serious AE	29 (7.5)	16 (8.5)	200 (4.7)	149 (6.8)
Death	0 (0)	0 (0)	10 (0.2)	9 (0.4)
Requiring hospitalization	29 (7.5)	14 (7.4)	184 (4.3)	125 (5.7)
AE leading to discontinuation	16 (4.2)	5 (2.6)	116 (2.7)	86 (3.9)
Hepatobiliary disorders*	8 (2.1)	3 (1.6)	33 (0.8)	20 (0.9)
Gastrointestinal disorders*	57 (14.8)	32 (16.9)	472 (11.1)	281 (12.8)
Hypoglycemia (investigator-defined)	40 (10.4)	30 (15.9)	513 (12.1)	332 (15.1)
Severe hypoglycemia[†]	2 (0.5)	0 (0)	19 (0.4)	13 (0.6)
Pancreatitis[‡]	3 (0.78)	0 (0)	1 (0.02)	1 (0.05)
Pancreatic cancer[§]	0 (0)	0 (0)	0 (0)	0 (0)
AEs with incidence ≥5.0% in any treatment group[II]				

	Hepatic disorders		No hepatic disorders	
	Linagliptin (*n*=385)	Placebo (*n*=189)	Linagliptin (*n*=4240)	Placebo (*n*=2195)
Headache	14 (3.6)	10 (5.3)	127 (3.0)	66 (3.0)
Hyperglycemia	27 (7.0)	33 (17.5)	291 (6.9)	290 (13.2)
Nasopharyngitis	31 (8.1)	17 (9.0)	242 (5.7)	125 (5.7)
Upper respiratory tract infection	16 (4.2)	12 (6.4)	142 (3.4)	96 (4.4)
Incidence rate (subjects affected per 100 subject-years)[¶]				
Any AE	283.43	251.84	195.10	210.84
Drug-related AE	29.36	27.01	24.23	25.07
Serious AE	15.16	14.14	9.21	11.43
Death	0	0	0.45	0.66
Requiring hospitalization	15.14	12.32	8.46	9.57
AE leading to discontinuation	7.99	4.20	5.20	6.35
Hepatobiliary disorders*	4.08	2.55	1.48	1.48
Gastrointestinal disorders*	31.72	30.95	23.12	22.83
Hypoglycemia (investigator-defined)	22.66	29.23	26.16	28.83
Severe hypoglycemia[†]	1.00	0	0.85	0.96
Pancreatitis[‡]	1.51	0	0.04	0.07

	Hepatic disorders		No hepatic disorders	
	Linagliptin (*n*=385)	Placebo (*n*=189)	Linagliptin (*n*=4240)	Placebo (*n*=2195)
Pancreatic cancer[§]	0	0	0	0
AEs with incidence ≥5.0% in any treatment group[II]				
Headache	7.13	8.91	5.82	4.96
Hyperglycemia	14.04	31.76	13.64	23.53
Nasopharyngitis	15.93	14.75	11.32	9.66
Upper respiratory tract infection	8.24	10.50	6.48	7.26

Data are for the treated set of patients.

AE, adverse event.

*System organ class from the Medical Dictionary for Regulatory Activities (MedDRA) version 15.1.

[†]Requiring assistance from another person to administer carbohydrate, glucagon, or other resuscitative action.

[‡]Defined in Table S2.

[§]Defined in Table S2.

[II]Preferred terms from MedDRA.

[¶]Calculated by dividing the number of subjects with the event by the time at risk expressed as

	Hepatic disorders		No hepatic disorders	
	Linagliptin (*n*=385)	Placebo (*n*=189)	Linagliptin (*n*=4240)	Placebo (*n*=2195)

100 subject-years.

Figure captions

Fig. 1. Adjusted mean change from baseline in HbA1c at week 24. Data are for the full-analysis set of participants (LOCF).

Fig. 2. Change from baseline in HbA1c over time. Data are for the full-analysis set of participants (LOCF).

Fig. 3. Change from baseline in HbA1c at week 24 by (A) duration of T2DM, (B) renal function and (C) race. eGFR, estimated glomerular filtration rate. Data are for the full-analysis set of participants (LOCF).

Figures

Fig. 1. Adjusted mean change from baseline in HbA1c at week 24. Data are for the full-analysis set of participants (LOCF).

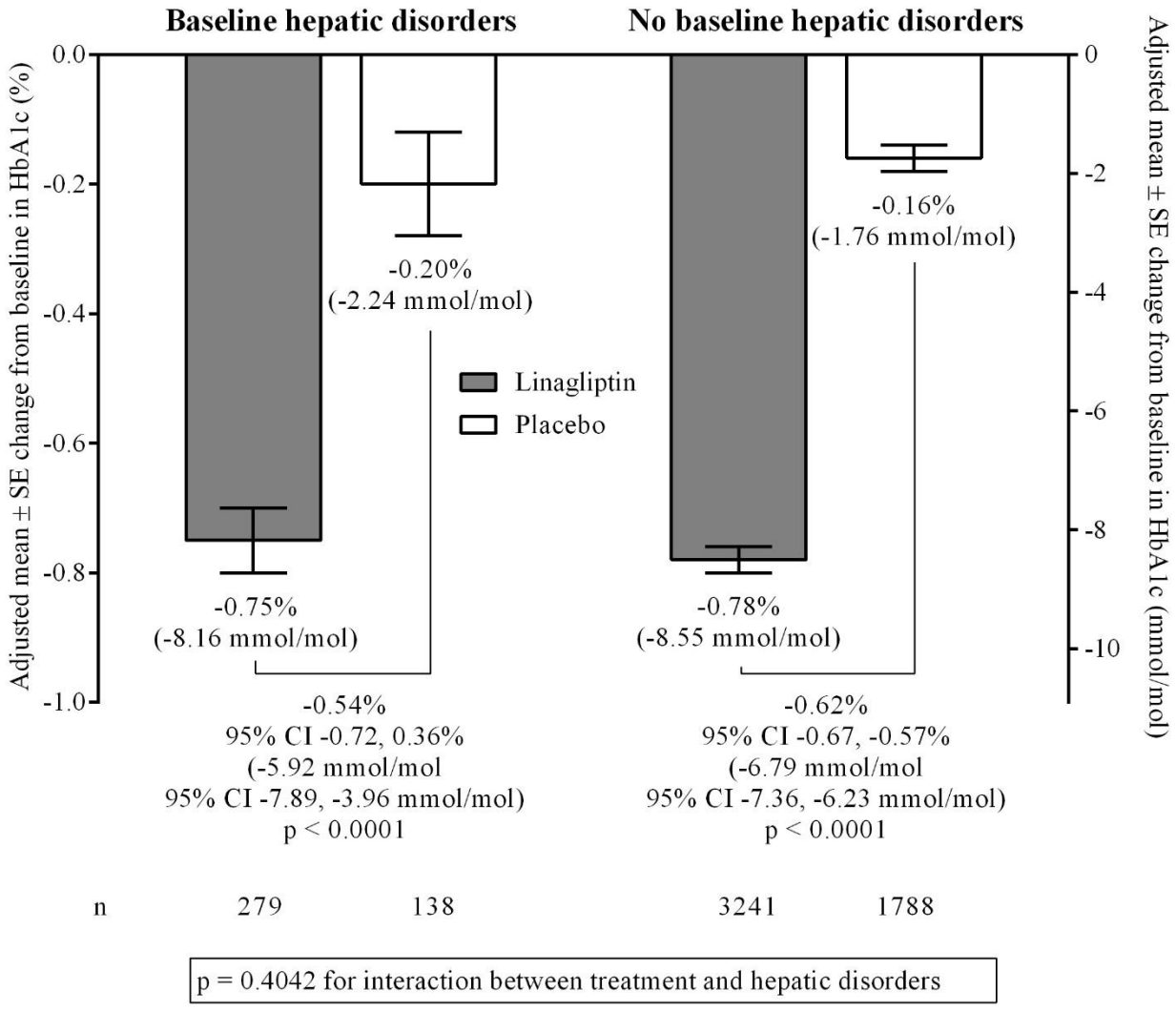
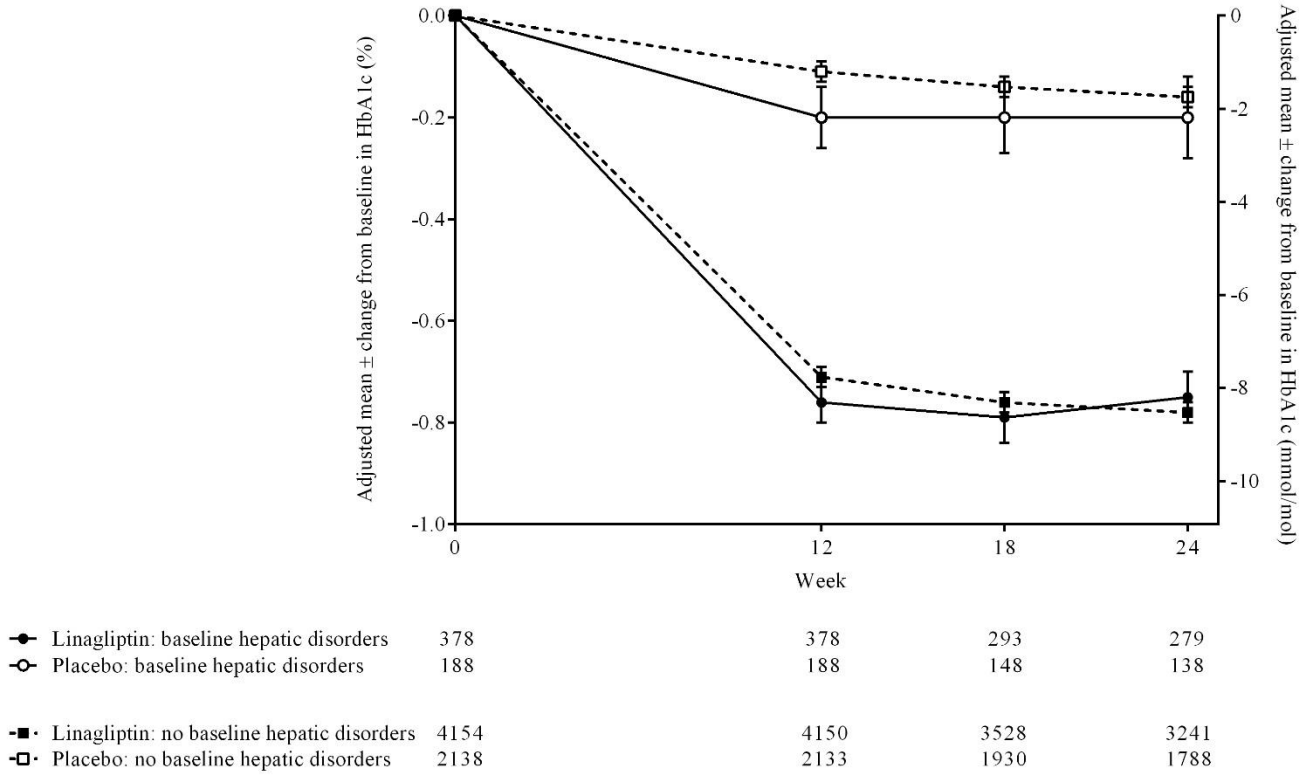
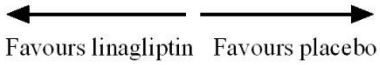


Fig. 2. Change from baseline in HbA1c over time. Data are for the full-analysis set of participants (LOCF).

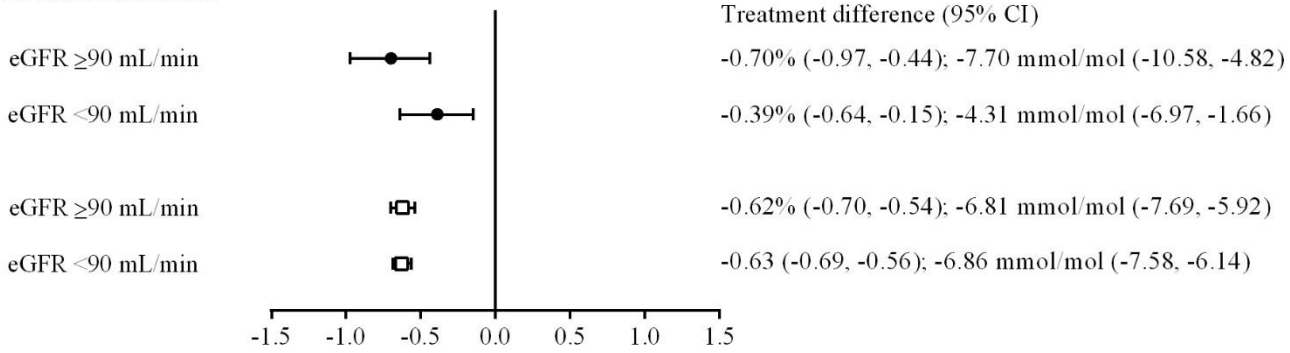


(adjusted mean change from baseline in HbA1c (%): linagliptin minus placebo)

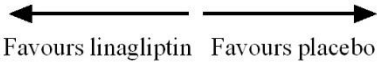


p = 0.4240 for interaction between treatment, hepatic disorders and duration of T2DM

B. Renal function

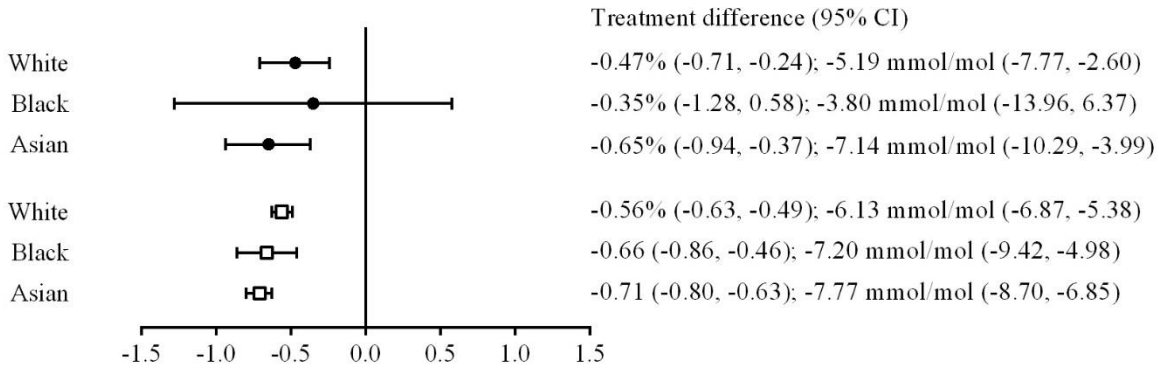


Treatment difference
(adjusted mean change from baseline in HbA1c (%): linagliptin minus placebo)

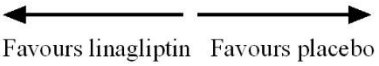


p = 0.0981 for interaction between treatment, hepatic disorders and eGFR

C. Race



Treatment difference
(adjusted mean change from baseline in HbA1c (%): linagliptin minus placebo)



p = 0.8836 for interaction between treatment, hepatic disorders and race

Online-Only Supporting Information

Table S1

Randomized, double-blind, placebo-controlled Phase II or III clinical trials of linagliptin that included partici
baseline

ClinicalTrials.gov number	Participant population	Treatment regimen (linagliptin or placebo)	Primary endpoint (week)	B disor
				Yes
NCT00621140	Aged 18–80 years	Monotherapy	24	29
NCT00641043	Aged 18–80 years	Initial combination with pioglitazone	24	47
NCT00601250	Aged 18–80 years	Added to metformin	24	34
NCT00602472	Aged 18–80 years	Added to metformin and a sulfonylurea	24	126

ClinicalTrials.gov number	Participant population	Treatment regimen (linagliptin or placebo)	Primary endpoint (week)	B disord
				Yes
NCT00654381	Aged 20–80 years in Japan	Monotherapy	12	72
NCT00819091	Aged 18–80 years	Added to a sulfonylurea	18	13
NCT00954447	Aged ≥18 years	Added to basal insulin	24	114
NCT00800683	Aged 18–80 years with severe renal impairment	Added to other glucose-lowering drugs	12	9
NCT00798161	Aged 18–80 years	Initial combination with metformin	24	21
NCT00740051	Aged 18–80 years with metformin intolerance/contraindication	Monotherapy	18	12
NCT00996658	Aged 18–79 years	Added to metformin and pioglitazone	24	12

ClinicalTrials.gov number	Participant population	Treatment regimen (linagliptin or placebo)	Primary endpoint (week)	B disord
				Yes
NCT01012037	Aged 18–80 years	Added to metformin	12	30
NCT01084005	Aged ≥70 years	Added to metformin and/or a sulfonylurea and/or basal insulin	24	4
NCT01087502	Aged ≥18 years with moderate/severe renal impairment	Added to other glucose-lowering drugs or monotherapy	12	24
NCT01215097	Aged 18–80 years in Asia	Added to metformin	24	7
NCT01214239	Aged 18–80 years in Asia	Monotherapy	24	14
NCT01194830	Black/African American subjects aged 18–80 years	Monotherapy or added to one glucose-lowering drug	24	6

Table S2

Definition of pancreatic adverse events

Adverse event	Definition
Pancreatitis	Either the MedDRA preferred term of “chronic pancreatitis” or any of the prefe MedDRA Query for pancreatitis based on MedDRA version 17.0: Cullen’s sign pancreatitis, edematous pancreatitis, pancreatic abscess, pancreatic hemorrhage, phlegmon, pancreatic pseudocyst, pancreatic pseudocyst drainage, pancreatitis, hemorrhagic, pancreatitis necrotizing, pancreatitis relapsing, pancreatorenal syn
Pancreatic cancer	Any of the following preferred terms from MedDRA version 17.0: acinar cell ca pancreas, benign neoplasm of islets of Langerhans, benign pancreatic neoplasm, ductal adenocarcinoma of pancreas, glucagonoma, insulinoma, intraductal papil papillary mucinous carcinoma of pancreas, malignant neoplasm of islets of Lang cystadenocarcinoma of pancreas, multiple endocrine neoplasia, multiple endocri endocrine neoplasia type 2, multiple endocrine neoplasia type 2a, multiple endo

Adverse event	Definition
	neuroendocrine carcinoma, neurotensinoma, pancreatic carcinoma, pancreatic ca
	carcinoma recurrent, pancreatic carcinoma stage 0, pancreatic carcinoma stage I
	pancreatic carcinoma stage III, pancreatic carcinoma stage IV, pancreatic neopla
	pancreatic neuroendocrine tumor metastatic, pancreatic sarcoma, Peutz–Jeghers
	cystadenocarcinoma of pancreas, solid pseudopapillary tumor of the pancreas, s

MedDRA, Medical Dictionary for Regulatory Activities

Table S3

Participants with hepatic disorders at baseline

	Linagliptin (*n*=385)	Placebo (*n*=189)
Concomitant diagnosis at baseline	**374 (97.1)**	**183 (96.8)**
Hepatic steatosis	230 (59.7)	113 (59.8)
Liver disorder	22 (5.7)	13 (6.9)
Hepatic enzyme increased	14 (3.6)	7 (3.7)
Gamma-glutamyl transferase increased	12 (3.1)	3 (1.6)
Hepatomegaly	14 (3.6)	5 (2.6)
Chronic hepatitis	10 (2.6)	4 (2.1)
Hepatitis B	9 (2.3)	7 (3.7)
Hepatitis C	9 (2.3)	5 (2.6)
Hepatitis A	9 (2.3)	2 (1.1)
Alcoholic liver disease	8 (2.1)	2 (1.1)
Hepatic cyst	7 (1.8)	3 (1.6)
Hepatic function abnormal	6 (1.6)	2 (1.1)
Alanine aminotransferase increased	6 (1.6)	1 (0.5)
Non-alcoholic steatohepatitis	5 (1.3)	6 (3.2)
Liver function test abnormal	5 (1.3)	5 (2.6)
Chronic hepatitis B	5 (1.3)	0 (0)

	Linagliptin (*n*=385)	Placebo (*n*=189)
Hemangioma of liver	4 (1.0)	1 (0.5)
Viral hepatitis carrier	4 (1.0)	0 (0)
Aspartate aminotransferase increased	4 (1.0)	0 (0)
Jaundice	3 (0.8)	2 (1.1)
Hypoalbuminemia	3 (0.8)	0 (0)
Hepatitis alcoholic	3 (0.8)	0 (0)
Chronic hepatitis C	3 (0.8)	0 (0)
Blood alkaline phosphatase increased	2 (0.5)	2 (1.1)
Liver injury	2 (0.5)	1 (0.5)
Hepatitis infectious	2 (0.5)	1 (0.5)
Fatty liver alcoholic	2 (0.5)	0 (0)
Autoimmune hepatitis	2 (0.5)	0 (0)
Hepatitis	1 (0.3)	3 (1.6)
Hepatic cirrhosis	1 (0.3)	2 (1.1)
Ascites	1 (0.3)	1 (0.5)
Hepatic fibrosis	1 (0.3)	1 (0.5)
Hepatitis viral	1 (0.3)	1 (0.5)
Hepatosplenomegaly	1 (0.3)	1 (0.5)

	Linagliptin (*n*=385)	Placebo (*n*=189)
Cirrhosis alcoholic	1 (0.3)	0 (0)
Hepatic echinococciasis	1 (0.3)	0 (0)
Hepatic enzyme abnormal	1 (0.3)	0 (0)
Liver abscess	1 (0.3)	0 (0)
Hepatic mass	1 (0.3)	0 (0)
Hepatitis neoplasm	1 (0.3)	0 (0)
Hepatitis neoplasm malignant	1 (0.3)	0 (0)
Transaminases increased	1 (0.3)	0 (0)
Yellow skin	1 (0.3)	0 (0)
Blood bilirubin increased	0 (0)	1 (0.5)
Glycogen storage disease type 1	1 (0.3)	0 (0)
Hepatectomy	0 (0)	1 (0.5)
Hepatic adenoma	0 (0)	1 (0.5)
Hepatitis chronic active	0 (0)	1 (0.5)
Hyperbilirubinemia	0 (0)	1 (0.5)
Cryptogenic cirrhosis	0 (0)	2 (1.1)
Varices esophageal	0 (0)	2 (1.1)
Adverse event at baseline*	**15 (3.9)**	**9 (4.8)**

	Linagliptin (*n*=385)	Placebo (*n*=189)
Alanine aminotransferase increased	7 (1.8)	2 (1.1)
Aspartate aminotransferase increased	4 (1.0)	0 (0)
Blood bilirubin increased	2 (0.5)	0 (0)
Hepatic enzyme increased	1 (0.3)	1 (0.5)
Blood alkaline phosphatase increased	1 (0.3)	0 (0)
Hemangioma of liver	1 (0.3)	0 (0)
Hepatomegaly	1 (0.3)	0 (0)
Hypoalbuminemia	1 (0.3)	0 (0)
Liver injury	1 (0.3)	0 (0)
Gamma-glutamyl transferase increased	0 (0)	3 (1.6)
Jaundice cholestatic	0 (0)	1 (0.5)
Hepatic neoplasm	0 (0)	1 (0.5)
Hepatocellular injury	0 (0)	1 (0.5)

Data are *n* (%) of the treated set of participants. Categories are not mutually exclusive (participants could have had both a concomitant diagnosis and adverse event at baseline, and could have had more than one hepatic disorder within each category). Disorders shown are preferred terms in the Standardized Medical Query "hepatic disorders" from the Medical Dictionary for Regulatory Activities version 15.1.

*Adverse events reported at screening prior to initiation of study drug.

Table S4

On-treatment changes in levels of hepatic enzymes and bilirubin in subjects with hepatic disorders

Baseline	Last value on treatment			Minimum value on treatment		Maxim tr
	<LLN	LLN–ULN	>ULN	≥LLN	<LLN	≤ULN
AST (GOT)						
Placebo (*n*=189)						
<LLN	0	**1 (100.0)**	0	0	0	1 (100.0)
LLN–ULN	0	153 (95.0)	**8 (5.0)**	161 (100.0)	0	161 (100.0
>ULN	0	**10 (43.5)**	13 (56.5)	23 (100.0)	0	0
Total	0	164 (88.6)	21 (11.4)	184 (99.5)	0	162 (87.6
Linagliptin (*n*=385)						
<LLN	0	0	0	0	0	0

Baseline	Last value on treatment			Minimum value on treatment		Maxim tr
	<LLN	LLN–ULN	>ULN	≥LLN	<LLN	≤ULN
LLN–ULN	0	292 (94.8)	**16 (5.2)**	308 (100.0)	0	308 (100.0
>ULN	0	**27 (42.2)**	37 (57.8)	64 (100.0)	0	0
Total	0	319 (85.8)	53 (14.2)	372 (100.0)	0	308 (82.8
ALT (SGPT)						
Placebo (*n*=189)						
<LLN	0	**1 (100.0)**	0	0	0	1 (100.0)
LLN–ULN	0	130 (92.2)	**11 (7.8)**	141 (100.0)	0	141 (100.0
>ULN	0	**21 (48.8)**	22 (51.2)	43 (100.0)	0	0
Total	0	152 (82.2)	33 (17.8)	184 (99.5)	0	142 (76.8
Linagliptin (*n*=385)						

Baseline	Last value on treatment			Minimum value on treatment		Maxim tr
	<LLN	LLN–ULN	>ULN	≥LLN	<LLN	≤ULN
<LLN	0	0	0	0	0	0
LLN–ULN	0	254 (93.0)	**19 (7.0)**	273 (100.0)	0	273 (100.0
>ULN	0	**38 (38.4)**	61 (61.6)	99 (100.0)	0	0
Total	0	292 (78.5)	80 (21.5)	372 (100.0)	0	273 (73.4
ALP						
Placebo (*n*=189)						
<LLN	1 (100.0)	0	0	0	0	1 (100.0)
LLN–ULN	1 (0.6)	163 (95.9)	**6 (3.5)**	170 (100.0)	1 (0.6)	170 (100.0
>ULN	0	**3 (20.0)**	12 (80.0)	15 (100.0)	0	0
Total	2 (1.1)	166 (89.2)	18 (9.7)	185 (99.5)	1 (0.5)	171 (91.9

Baseline	Last value on treatment			Minimum value on treatment		Maxim tr
	<LLN	LLN–ULN	>ULN	≥LLN	<LLN	≤ULN
Linagliptin (*n*=385)						
<LLN	4 (44.4)	5 (55.6)	0	0	0	9 (100.0)
LLN–ULN	5 (1.5)	332 (97.6)	**3 (0.9)**	340 (100.0)	7 (2.1)	340 (100.0
>ULN	0	**10 (41.7)**	14 (58.3)	24 (100.0)	0	0
Total	9 (2.4)	347 (93.0)	17 (4.6)	364 (97.6)	7 (2.1)	349 (93.6
GGT						
Placebo (*n*=189)						
<LLN	0	0	0	0	0	0
LLN–ULN	1 (0.8)	116 (89.2)	**13 (10.0)**	130 (100.0)	1 (0.8)	130 (100.0
>ULN	0	**16 (29.6)**	38 (70.4)	54 (100.0)	0	0

Baseline	Last value on treatment			Minimum value on treatment		Maxim tr
	<LLN	LLN–ULN	>ULN	≥LLN	<LLN	≤ULN
Total	1 (0.5)	132 (71.7)	51 (27.7)	184 (100.0)	1 (0.5)	130 (70.7
Linagliptin (*n*=385)						
<LLN	1 (100.0)	0	0	0	0	1 (100.0)
LLN–ULN	0	236 (92.2)	**20 (7.8)**	256 (100.0)	2 (0.8)	256 (100.0
>ULN	0	**14 (12.6)**	97 (87.4)	111 (100.0)	0	0
Total	1 (0.3)	250 (67.9)	117 (31.8)	367 (99.7)	2 (0.5)	257 (69.8
LDH						
Placebo (*n*=189)						
<LLN	8 (61.5)	5 (38.5)	0	0	0	13 (100.0
LLN–ULN	6 (3.9)	141 (92.8)	**5 (3.3)**	152 (100.0)	21 (13.8)	152 (100.0

Baseline	Last value on treatment			Minimum value on treatment		Maxim tr
	<LLN	LLN–ULN	>ULN	≥LLN	<LLN	≤ULN
>ULN	0	**5 (29.4)**	12 (70.6)	17 (100.0)	0	0
Total	14 (7.7)	151 (83.0)	17 (9.3)	169 (92.9)	21 (11.5)	165 (90.7
Linagliptin (*n*=385)						
<LLN	14 (35.9)	25 (64.1)	0	0	0	39 (100.0
LLN–ULN	15 (4.9)	284 (92.5)	**8 (2.6)**	307 (100.0)	25 (8.1)	307 (100.0
>ULN	0	**4 (23.5)**	13 (76.5)	17 (100.0)	0	0
Total	29 (8.0)	313 (86.2)	21 (5.8)	324 (89.3)	25 (6.9)	346 (95.3
Bilirubin						
Placebo (*n*=189)						
<LLN	1 (33.3)	2 (66.7)	0	0	0	3 (100.0)

Baseline	Last value on treatment			Minimum value on treatment		Maxim tr
	<LLN	LLN–ULN	>ULN	≥LLN	<LLN	≤ULN
LLN–ULN	3 (1.8)	156 (95.7)	**4 (2.5)**	163 (100.0)	11 (6.7)	163 (100.0
>ULN	0	**4 (33.3)**	8 (66.7)	12 (100.0)	0	0
Total	4 (2.2)	162 (91.0)	12 (6.7)	175 (98.3)	11 (6.2)	166 (93.3
Linagliptin (*n*=385)						
<LLN	1 (20.0)	4 (80.0)	0	0	0	5 (100.0)
LLN–ULN	7 (2.0)	326 (95.0)	**10 (2.9)**	343 (100.0)	20 (5.8)	343 (100.0
>ULN	0	**10 (52.6)**	9 (47.4)	19 (100.0)	0	0
Total	8 (2.2)	340 (92.6)	19 (5.2)	362 (98.6)	20 (5.4)	348 (94.8

Data are *n* (%) of the treated set of subjects. Bolded data indicate shifts between categories of reference range

transaminase/aspartate aminotransferase; ALP, alkaline phosphatase; ALT, alanine transaminase/alanine ami

Baseline	Last value on treatment			Minimum value on treatment		Maxim tr
	<LLN	LLN–ULN	>ULN	≥LLN	<LLN	≤ULN

glutamyl transferase; GOT, serum glutamic oxaloacetic transaminase; LDH, lactate dehydrogenase; LLN, lov

serum glutamate-pyruvate transaminase/serum glutamic-pyruvic transaminase; ULN, upper limit of normal.

References

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