ORIGINAL ARTICLE doi: 10.1111/j.1463-1326.2009.01056.x

Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial

M. Jadzinsky,[1] A. Pfützner,[2] E. Paz-Pacheco,[3] Z. Xu,[4] E. Allen[5] and R. Chen[6] for the CV181-039 Investigators*

[1]Durand Hospital, Buenos Aires, Argentina
[2]Research and Development, Institute for Clinical Research and Development, Mainz, Germany
[3]The Medical City, Pasig City, Philippines
[4]Global Biometric Sciences, Bristol-Myers Squibb, Princeton, NJ, USA
[5]Global Medical Affairs, Research and Development, Bristol-Myers Squibb, Princeton, NJ, USA
[6]Global Clinical Research, Research and Development, Bristol-Myers Squibb, Princeton, NJ, USA

Aim: The study aim was to evaluate the efficacy and safety of initial combination therapy with saxagliptin + metformin vs. saxagliptin or metformin monotherapy in treatment-naïve patients with type 2 diabetes (T2D) and inadequate glycaemic control.

Methods: In this multicentre, randomized, double-blind, active-controlled phase 3 trial, 1306 treatment-naïve patients with T2D ≥18 to ≤77 years, glycosylated haemoglobin (HbA1c) ≥8 to ≤12%, fasting C-peptide concentration ≥1.0 ng/ml, body mass index ≤40 kg/m^2 were randomized to receive saxagliptin 5 mg + metformin 500 mg, saxagliptin 10 mg + metformin 500 mg, saxagliptin 10 mg + placebo or metformin 500 mg + placebo for 24 weeks. From weeks 1–5, metformin was uptitrated in 500-mg/day increments to 2000 mg/day maximum in the saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin and metformin + placebo treatment groups. The main outcome measure was HbA1c change from baseline to week 24. Selected secondary outcomes included change from baseline to week 24 in fasting plasma glucose (FPG), proportion of patients achieving HbA1c <7% and postprandial glucose area under the curve (PPG-AUC).

Results: At 24 weeks, saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin demonstrated statistically significant adjusted mean decreases vs. saxagliptin 10 mg and metformin monotherapies in HbA1c (−2.5 and −2.5% vs. −1.7 and −2.0%, all $p < 0.0001$ vs. monotherapy) and FPG (−60 and −62 mg/dl vs. −31 and −47 mg/dl, both $p < 0.0001$ vs. saxagliptin 10 mg; $p = 0.0002$ saxagliptin 5 mg + metformin vs. metformin; $p < 0.0001$ saxagliptin 10 mg + metformin vs. metformin). Proportion of patients achieving an HbA1c <7% was 60.3 and 59.7%, respectively, for saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin (all $p < 0.0001$ vs. monotherapy). PPG-AUC was significantly reduced [−21 080 mg·min/dl (saxagliptin 5 mg + metformin) and −21 336 mg·min/dl (saxagliptin 10 mg + metformin) vs. −16 054 mg·min/dl (saxagliptin 10 mg) and −15 005 mg·min/dl (metformin), all $p < 0.0001$ vs. monotherapy]. Adverse event occurrence was similar across all groups. Hypoglycaemic events were infrequent.

Conclusion: Saxagliptin + metformin as initial therapy led to statistically significant improvements compared with either treatment alone across key glycaemic parameters with a tolerability profile similar to the monotherapy components.

Keywords: DPP-4, metformin, saxagliptin, type 2 diabetes
Received 12 January 2009; returned for revision 20 February 2009; revised version accepted 02 March 2009

Correspondence:
Roland Chen, MD, Bristol-Myers Squibb, Route 206 and Province Line Road, Princeton, NJ 08540, USA.
E-mail:
roland.chen@bms.com

Introduction

Initial antihyperglycaemic monotherapy is frequently insufficient to enable patients with type 2 diabetes (T2D) to achieve or sustain glycaemic targets [1–3]. An approach based on initial combination therapy has the potential to enable more patients to reach glycaemic targets earlier in the disease course and may minimize the need for subsequent treatment changes based on a stepwise approach. Furthermore, with the availability of newer agents that differ in their mechanisms of action (MOA) and side-effect profiles, treatments may be combined to address the variety of pathophysiological abnormalities in T2D. Achieving specific glycaemic goals can substantially reduce morbidity, making early aggressive treatment particularly important for

Conflicts of interest:
M. J. reported that he had served on advisory boards and received honoraria and consulting fees from GlaxoSmithKline, Novo Nordisk, Merck Sharp & Dohme, Eli Lilly, Bristol-Myers Squibb and AstraZeneca. During the past 5 years, A. P., or his private institute, Institute for Clinical Research and Development, has received grants, consultancy fees, speaker fees and travel support from the following companies and organizations: Aerogen, Mountain View, CA, USA; AK Study Nurse, Hamburg, Germany; American Diabetes Association; Arbeitsgemeinschaft Diabetes und Endokrinologie Rheinland-Pfalz; Alkermes, Cambridge, UK; Allpresan, Emsdetten, Germany; Alsitan, Greifenberg, Germany; AstraZeneca, Wedel, Germany; sanofi-aventis, Berlin, Germany; Becton Dickinson, Heidelberg/München, Germany; Berlin Chemie, Berlin, Germany; Biocon Ltd, Bangalore, India; Biodel, Danbury, CT, USA; Biopheresis, Heidelberg, Germany; Boehringer Ingelheim, Ingelheim, Germany; Bristol-Myers Squibb, München, Germany; Bundesministerium für Bildung und Forschung, Berlin, Germany; Bundeswirtschaftsministerium, Berlin, Germany; Clinical Trial Operation, Al Oss, The Netherlands; Ergomed, Frankfurt, Germany; Fraunhofer Institut, St Ingbert, Germany; Forum Salutare, Gieben, Germany; GlaxoSmithKline, München, Germany; Halozyme, San Diego, CA, USA; Hexal, Holzkirchen, Germany; Hoffmann-La Roche, Grenzach, Germany; Hoffmann-La Roche, USA; Home Diagnostics, Fort Lauderdale, FL, USA; IME, Selb, Germany; Immundiagnostik AG, Bensheim, Germany; ImVision, Hannover, Germany; IPF Pharmaceuticals, Hannover, Germany; Johnson & Johnson, New Brunswick, NJ, USA; Kirchheim-Verlag, Mainz, Germany; Kreussler-Pharma, Wiesbaden, Germany; Lilly, Indianapolis, MN, USA; Lilly, GB, Lilly Deutschland, Bad Homburg, Germany; Linco Research, USA; McCann Healthcare, Frankfurt, Germany; Medacorp, Boston, MA, USA; Medisense, Abingdon, UK; MediTech Media, London, UK; Medizinische Gesellschaft Mainz; Medtronic, Northridge, LA, USA; Medtronic Minimed, Düsseldorf, Germany; Medtrust, Lichtenwörth, Austria; Merck, Darmstadt, Germany; Merz, Frankfurt, Germany; Molecular Light Technology, Cardiff, UK; Florian Müller, Hamburg, Germany; Novartis, Nürnberg, Germany; Nova Biomedical, Waltham, MA, USA; Novo Nordisk, Mainz, Germany; Novo Nordisk, Bagsvaerd, Denmark; Ortho Clinical Diagnostics, Raritan, NJ, USA; OsteoMedical-Tecomed AG, sanofi-aventis, Berlin, Germany; TecoMedical, Sissach, Switzerland; Mannkind, Danbury, CT, USA; Pfizer, New London, CT, USA; Profil GmbH, Neuss, Germany; Profil Chula Vista, USA; Quintiles, Neu-Isenburg, Germany; Rahn-Minimed, Zürich, Switzerland; Roche Diagnostics, Mannheim, Germany; Roche Diagnostics, Welwyn, GB, UK; Sankyo Pharma GmbH, München, Germany; schwa-medico, Ehringshausen, Germany; Takeda, IL, USA; Takeda, Aachen, Germany; Terumo, Eschborn, Germany; Unomedical, Roskilde, Denmark. Urgo. E. P.-P. reports that she has served on advisory boards and received honoraria from AstraZeneca and is involved in clinical trial work with Bristol-Myers Squibb. Drs R. C., Z. X. and E. A. are employees of Bristol-Myers Squibb.
*Study Investigators: *Argentina*: Antunez P., Baccaro C., Bertone R., Bragagnolo J., Cordo C. S., Dieuzeide G., Fideleff H. L., Hermida S., Herrera J., Issa C., Jadzinsky M., Kraft M., Maffei L., Man Z., Marcucci G., Oviedo A., Sanchez J. M., Vines G., Zambon F.; *Brazil*: Chacra A., Farias F., Felicio J., Forti A., Gross J. L., Hissa M. N., Rassi N., Sgarbi J. A.; *Germany*: Barakat A., Böhm G. F., Hanefeld M., Illies G., Kellner A., Klausmann G., Klein C., Molle A., Nauck M., Pfützner A., Sauter J., Schaller J., Wachter J.; *Hungary*: Deák G., Dudás M., Foldesi I., Harcsa E., Salamon C.; *India*: Agarwal R. P., Aravind S. R., Dharmalingam M., Jugal Bihari G., Kale S., Kalra S., Kumar P., Mahadevan S., Mohan V., Rao P., Shah S., Thomas N., Wangnoo S. K.; *Italy*: Bosi E., Cocchi R., Cordera R., Perriello G., Squatrito S.; *Mexico*: Arechavaleta Granell M. D. R., Galvez Correa G., Garcia Hernandez P. A., Hernandez N., Jerjes Sanchez C., Jimenez Ramos S. A., Lozano F., Reyes C., Robles Torres F. J., Sauque Reyna L., Tamez Perez H. E., Velazquez M. V., Villegas E. M.; *Philippines*: Cimafranca K., Denopol M., Jimeno C., Lim-Abrahan M., Liwag A., Panelo A. A., Paz-Pacheco E., Tan G. H.; *Poland*: Derezinski T., Galczak W., Jasieniak-Pinis G., Mrozek J., Petryka R., Skokowska E., Stasinska T., Strojek K.; *Puerto Rico*: Abreu-Feshold F., Barranco E., Claudio J., Sosa-Padilla M., Vazquez-Tanus J., Velazquez-Navarro S.; *Russian Federation*: Antciferov M., Arutunov G., Balabolkin M., Barbarash O., Bokarev I., Bondar I., Bova E., Dreval A., Grineva E., Gurieva I., Ivanova L., Ivleva A., Khalimov Y., Kobalava Z., Kotelnikov M., Lantseva O., Marasaev V., Nedogoda S., Nosova N., Ponomareva A., Radygina E., Ragozin A., Rakov A., Rebrov A., Reshedko G., Reshetko O., Rodionova T., Rodoman G., Ruyatkina L., Semenova O., Sherenkov A., Shustov S., Shvarts Y., Smirnova E., Solovyev O., Strongin L., Suplotova L., Trusov V., Vorobyev S., Vorokhobina N., Voychik E., Yakusevich V., Zagrebelnaya O., Zalevskaya A., Zanozina O., Zhavoronkova N., Zhukova L.; *Ukraine*: Bazylevych A., Girina O., Levchenko O., Netiazhenko V., Perepelytsya M., Pertseva T., Rudyk Y., Slyvka Y., Vlasenko M., Yagensky A.; *USA*: Ashley R., Atiee G., Bleser S. D., Bright D. K., Bueso G., Buth D. K., Cabasares H., Campolo M. E., Chappel C., Conard S. E., Constantine J., Dayon D. L., Dionne D., Fenton I. F., Garcia R., George A., Gilman R., Glaser L., Gollapudi M., Gray J., Henry III W. J., Iranmanesh A., Ison R., Jacks R. K., Jacks W., Jain M., Johnson Jr G., Kaplan R., Khairi R. A., LaBuda J., LaSalle J., Lawrence M. K., Lipetz R. S., Miller S., Montoro R., Mora Y., Poindexter III A., Quigley J. F., Raad G. L., Rawtani P., Schneider A., Shah S., Spence J., Stanton D., Sugimoto D., Thomas F. L., Weiss D., Weissman P., Woodward W. R.

patients with a high baseline glycosylated haemoglobin (HbA1c) [4].

Incretin hormones play a critical role in the regulation of blood glucose [5,6]. One treatment option for patients with T2D is enhancement of incretin concentrations through the inhibition of dipeptidyl peptidase-4 (DPP-4) activity. DPP-4 inhibitors have been studied in monotherapy and in combination therapy and may be particularly efficacious if used early in the course of T2D due to potential beneficial effects on the islet dysfunction that characterizes T2D [5,7–9]. DPP-4 inhibitors are generally well tolerated, carry a low propensity for hypoglycaemia as monotherapy and, secondary to their physiological-based MOA, are weight neutral, all features lending additional support to their early use in combination with other oral antidiabetic drugs (OADs) [10].

Metformin is the most commonly used OAD both as monotherapy and in combination with other OADs [11]. Metformin reduces hepatic glucose production [3] and works through pathways complementary to DPP-4 inhibitors as metformin preferentially targets fasting plasma glucose (FPG) [12]. A recent randomized controlled trial evaluating the effects of metformin and sitagliptin on the incretin axis demonstrated that each agent alone increased postmeal active glucagon-like peptide-1 concentrations by 1.5–2 times and in combination by four times [13]. This additive effect suggests that initial combination therapy with metformin and a DPP-4 inhibitor may improve glycaemic control to a greater degree than the monotherapy components. The 2007 American Association of Clinical Endocrinologists (AACE) guidelines recommend metformin in combination with a DPP-4 inhibitor for patients with HbA1c levels between 7 and 8% and intensification of combination therapy when HbA1c levels are 8–10% to address FPG and PPG levels [14]. The 2008 Canadian Diabetes Association Clinical Practice Guidelines also support use of such initial combination therapy in patients with marked hyperglycaemia and recommend combining agents that differ in their MOA to maximize efficacy [15]. The newly issued American Diabetes Association/European Association for the Study of Diabetes guidelines note that when HbA1c levels are high (>8.5%), earlier initiation of combination therapy or use of OAD classes that have greater or more rapid glucose-lowering effect is appropriate [16].

Saxagliptin is a potent, selective DPP-4 inhibitor specifically designed for extended inhibition of the DPP-4 enzyme [17]. Proof of concept for saxagliptin was previously established in a 12-week trial across a dose range of 2.5–40 mg [18]. This current 24-week study assessed the efficacy and safety of initial combination therapy with saxagliptin plus immediate-release (IR) metformin compared with saxagliptin or metformin monotherapy in treatment-naïve patients with T2D and higher HbA1c values at baseline, reflecting a patient population less likely to achieve glycaemic targets with monotherapy.

Methods

Study Design and Patients

The present study (CV181-039) was a phase 3, multicentre, randomized, four-group, double-blind, active-controlled international trial. Patients were recruited from outpatient settings, advertisements, postings and referrals. Eligible patients entered a 1-week, single-blind, dietary and exercise placebo lead-in period. Good compliance (80–120%) with placebo was required to be eligible for the short-term treatment period. Patients were followed up for 24 weeks on double-blind study medication, during which diet and exercise management continued.

Study inclusion criteria included patients aged 18–77 years with T2D, HbA1c $\geq$8 and $\leq$12% at screening, fasting C-peptide concentration $\geq$1.0 ng/ml and body mass index $\leq$40 kg/m^2. Patients also had to be treatment naïve, defined as never having received medical treatment for diabetes or having received medical treatment for diabetes for a total period of <1 month since original diagnosis and not having received antihyperglycaemic therapy for more than three consecutive days or for a total of seven non-consecutive days during 8 weeks before screening. Exclusion criteria included symptoms of poorly controlled diabetes; history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; insulin therapy within 1 year of screening; cardiovascular event within 6 months before study entry or New York Heart Association stage III/IV congestive heart failure and/or known left ventricular ejection fraction $\leq$40%; significant renal, liver or psychiatric history; history of alcohol or drug abuse within the previous year; treatment with potent CYP3A4 inhibitors or inducers; immunocompromised individuals; active liver disease or clinically significant abnormal hepatic, renal, endocrine, metabolic or haematological screening tests.

The study protocol was approved by the institutional review board or independent ethics committee for each participating site and carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Patients were informed of the study purpose, potential risks and other critical issues, and they provided written informed consent.

At screening, an interactive voice response system (IVRS) assigned each patient a unique numeric identifier used throughout the study. Following the lead-in period, eligible patients were randomized (1 : 1 : 1 : 1) by IVRS using a blocked randomization schedule (block size 4) to one of four treatment groups: saxagliptin 5 mg/day + metformin IR 500 mg, saxagliptin 10 mg/day + metformin IR 500 mg, saxagliptin 10 mg/day + placebo (saxagliptin 10 mg) or metformin 500 IR mg + placebo (metformin). At week 1, all patients randomized to metformin, either as monotherapy or in combination with saxagliptin, were titrated to 1000 mg/day of metformin. From weeks 2–5, metformin was uptitrated based on predefined FPG levels (FPG >110 mg/dl) in 500-mg/day increments as tolerated to 2000 mg/day maximum in the saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin and metformin + placebo arms. Throughout the study, saxagliptin was to be taken daily before the morning meal. Metformin was to be taken in two divided doses with morning and evening meals. Study medication was not to be taken the morning of a scheduled visit; the assigned dose for that day was administered at the study site post-study visit procedures. Patients were eligible for rescue therapy based on progressively strict glycaemic control criteria over 24 weeks if FPG levels were as follows: >240 mg/dl (week 6); >220 mg/dl (week 8) and >200 mg/dl (weeks 12, 16, 20 and 24). Patients who met rescue criteria were entered directly into the long-term extension period, where they were administered open-label pioglitazone 15 mg, which could be uptitrated to 45 mg, in addition to blinded study medication. Long-term extension results will be reported in a future communication.

Study Measurements

The primary end-point was HbA1c change from baseline to week 24; subgroup analyses for baseline HbA1c were prespecified. Secondary efficacy end-points assessed at week 24 and listed in tested order were change from baseline in FPG, proportion of patients achieving HbA1c <7.0%, change from baseline in area under the curve (AUC) from 0 to 180 min for PPG response to an oral glucose tolerance test (OGTT), proportion of patients achieving HbA1c ≤6.5% and proportion of patients requiring rescue for failing to achieve prespecified glycaemic targets or discontinuing for lack of efficacy at week 24. Other efficacy end-points included change from baseline to week 12 in FPG; change from baseline to week 24 in fasting and postprandial insulin, C-peptide and glucagon; β-cell function [measured by homeostatic model assessment (HOMA)-2β]; insulin resistance (measured by HOMA-2IR) and proportion of patients achieving a glycaemic response at week 24 based on prespecified criteria. Changes from baseline to week 24 in body weight, lipid parameters, insulinogenic index, Matsuda index [19] and oral glucose insulin sensitivity [20] were also examined. Safety and tolerability end-points included incidence of adverse events (AEs), serious adverse events (SAEs), discontinuation due to AEs, physical and electrocardiographic examinations, vital signs and results of clinical laboratory tests.

Statistical Analysis and Sample Size

Efficacy analyses were conducted utilising data collected at baseline and postbaseline in the randomized patients data set comprising all randomized patients who took at least one dose of double-blind study medication. The primary efficacy analysis was performed using analysis of covariance (ANCOVA) with treatment group as an effect and baseline value as the covariate. Because of the large number of sites and small number of patients enrolled at most sites, site was not included as a factor in the ANCOVA model. Within the framework of the ANCOVA model, point estimates and 95% confidence intervals were calculated for mean changes within each treatment group and for differences in mean changes between saxagliptin 5 mg + metformin relative to saxagliptin 10 mg and relative to metformin and differences in mean changes between saxagliptin 10 mg + metformin relative to saxagliptin 10 mg and relative to metformin. Each combination treatment group was compared with each individual component (i.e. saxagliptin 10 mg and metformin); each comparison was performed at the 0.027 alpha level from Dunnett's adjustment so that the overall (family-wise) type I error rate was controlled at the 0.05 significance level. Sequential testing methodology was utilized for secondary efficacy end-points. At each step in the testing sequence, only the combination treatment group significantly superior to both controls was tested at the subsequent step. The percentage of patients achieving a therapeutic glycaemic response at week 24 and the proportion of patients requiring rescue/discontinuation because of lack of glycaemic control at week 24 were compared between each combination group and the monotherapy group using the Fisher exact test. Demographic and other baseline characteristics were summarized using descriptive statistics by treatment group. Last observation carried forward methodology was utilized to handle missing data. Systeme International (SI) conversion from mg/dl to mmol/l of glucose can be calculated with the equation: mg/dl × 0.0555.

All other SI conversions pertaining to data presented for this study are noted in the online appendix, table S1. Estimated average glucose (eAG) values were calculated *post hoc* based on HbA1c values using the linear regression: $eAG_{mg/dl} = 28.7 \times HbA1c - 46.7$ [21].

Safety analyses were performed in the treated patient population, consisting of patients who received at least one dose of study medication. Hypoglycaemia symptoms and confirmed hypoglycaemia were recorded and analysed separately from other AEs. Hypoglycaemic event intensity was graded according to the investigator's discretion. Efficacy and safety measurements obtained after rescue were not included in analyses.

Based on the primary end-point, the sample size afforded at least 90% power for both the combination comparisons and the individual components based on the min test by Laska and Meisner [22] for normal case.

Results

Patient Disposition and Clinical Characteristics

A total of 1306 patients were randomized and treated with double-blind therapy; 991 patients completed the 24-week treatment period (figure 1). Demographic and baseline clinical characteristics were generally balanced

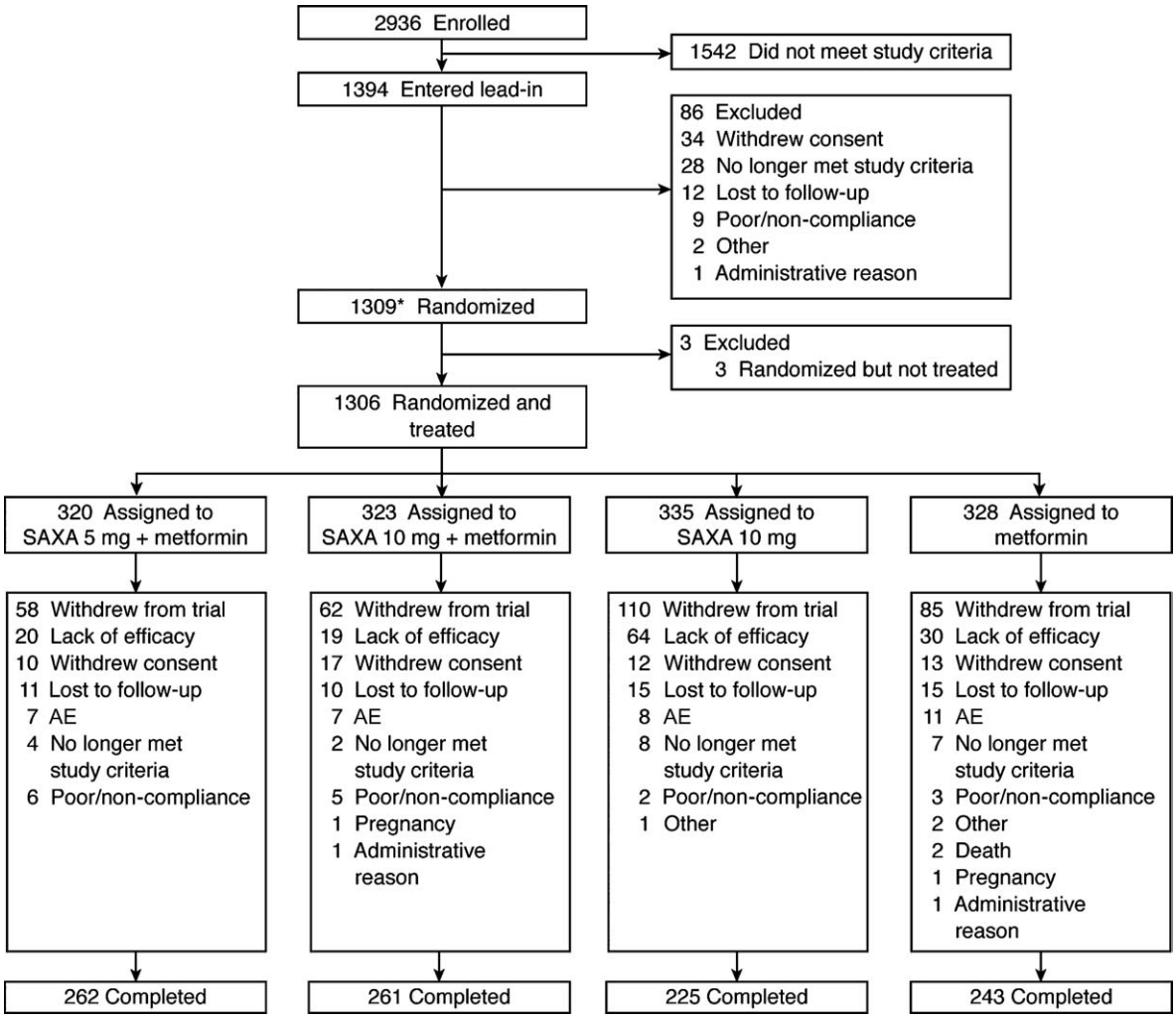

Fig. 1 Patient flow through the study. Recruitment period was from 30 May 2006 through 1 June 2007 with follow-up ending on 27 November 2007. AE, adverse event; SAXA, saxagliptin. *One patient was randomized directly after enrolment. This patient did not enter the lead-in period. Patients who discontinued prematurely were required to have brief safety visits performed every 2 weeks until completing a total of 24 weeks of exposure to double-blind or open-label study medication. The number of patients who discontinued and who were rescued are not mutually exclusive.

across treatment groups (table 1). Of the total study population, 98.4% had not been previously treated with antihyperglycaemic medication before enrolment. Discontinuations were higher in the monotherapy [32.8% (saxagliptin 10 mg), 25.9% (metformin)] vs. the combination therapy groups [18.1% (saxagliptin 5 mg + metformin), 19.2% (saxagliptin 10 mg + metformin)]. Consequently, mean duration of exposure to metformin was longer in the combination therapy vs. monotherapy groups (152, 151 and 144 days for saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin and metformin respectively). Mean daily metformin doses at week 24 were 1790, 1776 and 1817 mg for saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin and metformin respectively.

Efficacy Outcomes

At 24 weeks, patients randomized to saxagliptin 5 mg + metformin or saxagliptin 10 mg + metformin demonstrated statistically significant reductions in HbA1c, FPG and PPG from baseline compared with either monotherapy group. Baseline vs. week 24 HbA1c means were 9.4 vs. 6.9%, 9.5 vs. 7.0%, 9.6 vs. 7.9% and 9.4 vs. 7.5% for saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin, saxagliptin 10 mg and metformin respectively. Corresponding eAG values were 223 vs. 151 mg/dl (saxagliptin 5 mg + metformin), 226 vs. 154 mg/dl (saxagliptin 10 mg + metformin), 229 vs. 180 mg/dl (saxagliptin 10 mg) and 223 vs. 169 mg/dl (metformin). Adjusted mean change in HbA1c from baseline was −2.5% in both the saxagliptin 5 mg + metformin and the saxagliptin 10 mg + metformin groups vs. −1.7% for saxagliptin 10 mg and −2.0% for metformin respectively (all $p < 0.0001$ vs. monotherapy) (figure 2A). Greater HbA1c mean reductions were observed for combination therapy vs. monotherapy at week 4, the earliest time point assessed for HbA1c and continued for all subsequent time points. Beginning at week 8, fewer patients were rescued or discontinued because of lack of efficacy in the combination vs. the monotherapy groups. Time to discontinuation or rescue was later for the combination vs. the monotherapy groups.

Statistically significantly greater mean reductions in FPG at week 24 were observed for saxagliptin 5 mg + metformin vs. saxagliptin 10 mg ($p < 0.0001$) and vs. metformin ($p = 0.0002$) and for saxagliptin 10 mg + metformin vs. saxagliptin 10 mg and vs. metformin (both $p < 0.0001$ vs. monotherapy). Adjusted mean change from baseline was −60 mg/dl (saxagliptin 5 mg + metformin)

Table 1 Baseline demographic and clinical characteristics by randomized group

Characteristics	SAXA 5 mg + metformin (n = 320)	SAXA 10 mg + metformin (n = 323)	SAXA 10 mg (n = 335)	Metformin (n = 328)
Age (years)*	52.0 (10.4)	52.1 (11.6)	52.1 (10.2)	51.8 (10.7)
Age ≥65 (years)†	33 (10.3)	54 (16.7)	43 (12.8)	36 (11.0)
Sex†				
Men	165 (51.6)	146 (45.2)	169 (50.4)	163 (49.7)
Women	155 (48.4)	177 (54.8)	166 (49.6)	165 (50.3)
Race†,‡				
White	246 (76.9)	243 (75.2)	255 (76.1)	251 (76.5)
Asian	51 (15.9)	54 (16.7)	56 (16.7)	52 (15.9)
Black/African American	7 (2.2)	7 (2.2)	6 (1.8)	4 (1.2)
Other	16 (5.0)	19 (5.9)	18 (5.4)	21 (6.4)
Weight (kg)*	82.1 (16.3)	82.5 (16.9)	83.1 (16.9)	82.8 (17.5)
BMI (kg/m^2)*	29.9 (4.5)	30.3 (5.0)	30.2 (4.9)	30.2 (4.9)
Diabetes duration (years)*	2.0 (3.6)	1.4 (2.5)	1.7 (2.8)	1.7 (3.1)
HbA1c (%)*	9.4 (1.2)	9.5 (1.2)	9.6 (1.3)	9.4 (1.3)
<8†	31 (9.7)	33 (10.2)	27 (8.1)	37 (11.3)
≥8 to <9†	92 (28.8)	74 (22.9)	87 (26.0)	98 (29.9)
≥9 to <10†	85 (26.6)	97 (30.0)	89 (26.6)	75 (22.9)
≥10†	110 (34.4)	119 (36.8)	129 (38.5)	117 (35.7)
FPG (mg/dl)§	199 (56.6)	204 (59.7)	201 (54.8)	198 (58.7)

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin; SAXA, saxagliptin.
*Values are expressed as mean (s.d.).
†Values are expressed as n (%).
‡Race/ethnicity were self-reported.
§Systeme International conversion to mmol/l: mg/dl × 0.0555.

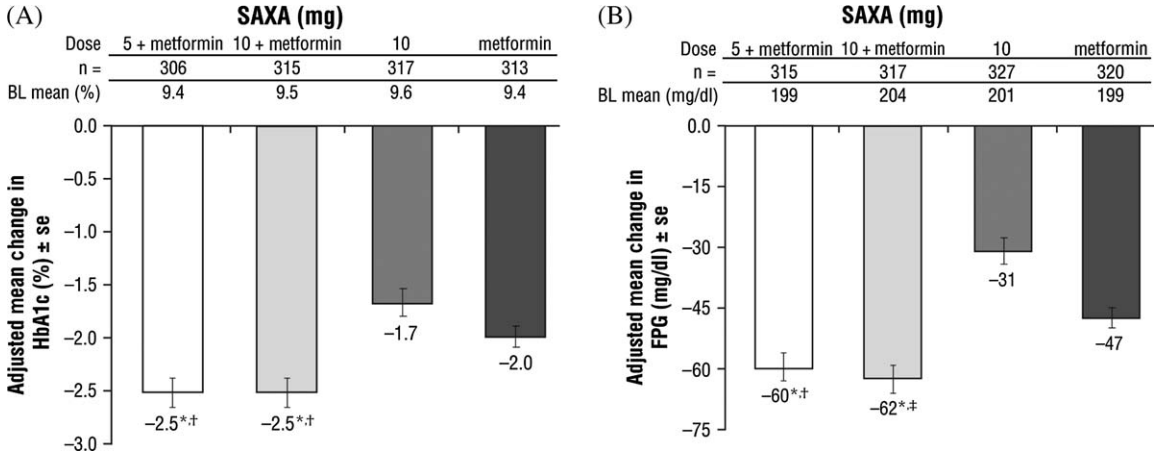

Fig. 2 Changes in glycaemic variables during 24-week treatment period: saxagliptin + metformin vs. monotherapy. (A) HbA1c-adjusted mean change from BL to week 24. *$p < 0.0001$ vs. SAXA 10 mg. †$p < 0.0001$ vs. metformin. (B) FPG adjusted mean change from BL to week 24. *$p < 0.0001$ vs. SAXA 10 mg. †$p = 0.0002$ vs. metformin. ‡$p < 0.0001$ vs. metformin. Systeme International conversion to mmol/l: mg/dl × 0.0555. BL, baseline; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin; SAXA, saxagliptin.

and −62 mg/dl (saxagliptin 10 mg + metformin) vs. −31 mg/dl (saxagliptin 10 mg) and −47 mg/dl (metformin) (figure 2B). FPG concentrations reached a nadir at week 8 and remained level for the remainder of the study.

The proportion of patients achieving a therapeutic glycaemic response (HbA1c <7 or ≤6.5%) was statistically significantly greater for the combination vs. the monotherapy groups. The proportion of patients with an HbA1c <7% at week 24 was statistically significantly greater for saxagliptin 5 mg + metformin (60.3%) and saxagliptin 10 mg + metformin (59.7%) vs. saxagliptin 10 mg (32.2%) and metformin (41.1%) (all $p < 0.0001$ vs. monotherapy). The proportion of patients with an HbA1c ≤6.5% at week 24 was 45.3, 40.6, 20.3 and 29.0% for saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin, saxagliptin 10 mg and metformin, respectively, and statistically significantly greater for saxagliptin 5 mg + metformin vs. saxagliptin 10 mg and metformin (all $p < 0.0001$) and for saxagliptin 10 mg + metformin vs. saxagliptin 10 mg ($p < 0.0001$) and vs. metformin ($p = 0.0026$). For all treatment groups, greater HbA1c reductions occurred in patients with higher baseline HbA1c levels, with HbA1c lowering up to −3.3% in patients with a baseline HbA1c ≥10% (figure 3).

A statistically significant reduction in glucose exposure from baseline to week 24 was seen in postprandial glucose area under the curve (PPG-AUC) during the OGTT for saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin vs. saxagliptin 10 mg and metformin (−21 080 and −21 336 vs. −16 054 and −15 005 mg·min/dl, respectively, all $p < 0.0001$ vs. monotherapy). An overall decrease from baseline in mean glucose concentration at all time points of the OGTT occurred in all treatment groups at week 24 (figure 4). At the 120-min time point of the OGTT, PPG-adjusted mean changes from baseline were −138 mg/dl (saxagliptin 5 mg + metformin) and −137 mg/dl (saxagliptin 10 mg + metformin) relative to −106 mg/dl (saxagliptin 10 mg) and −97 mg/dl (metformin) ($p = 0.0001$, saxagliptin 5 mg + metformin vs. saxagliptin 10 mg; $p = 0.0002$, saxagliptin 10 mg + metformin vs. saxagliptin 10 mg; all $p < 0.0001$ vs. metformin).

The proportion of patients discontinued or rescued for lack of glycaemic control at week 24 was statistically significantly lower for saxagliptin 5 mg + metformin (7.5%)

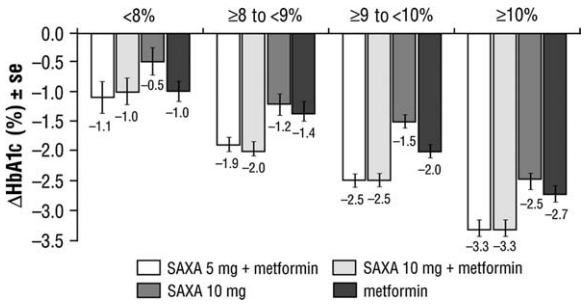

Fig. 3 HbA1c-adjusted mean change: subgroup analysis by baseline HbA1c. HbA1c, glycosylated haemoglobin; SAXA, saxagliptin.

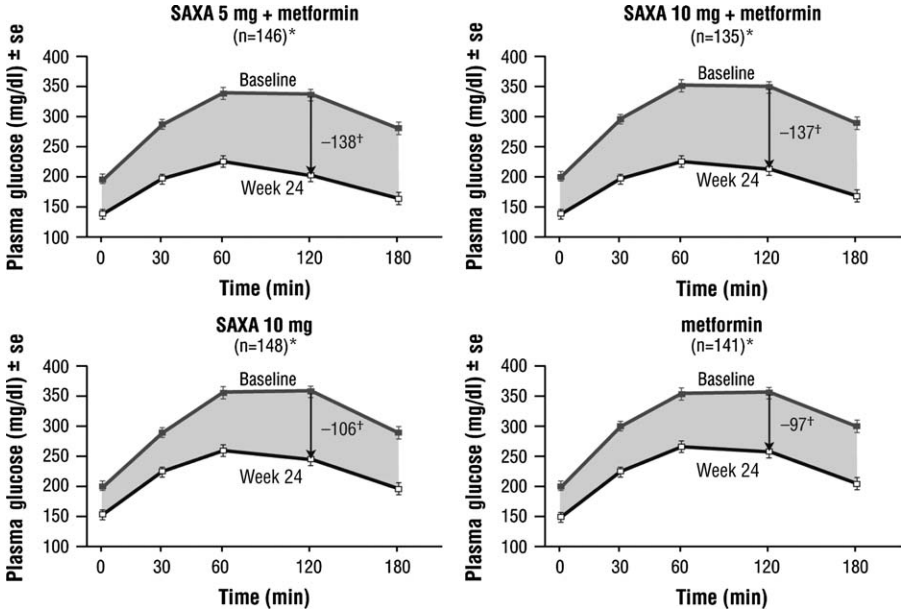

Fig. 4 Postprandial glucose (PPG) response to 3-h oral glucose tolerance test: baseline vs. week 24. *Sample size at 120-min time point. †Adjusted mean change in 120-min PPG. Systeme International conversion to mmol/l: mg/dl × 0.0555.

vs. saxagliptin 10 mg (21.2%) ($p < 0.0001$) but not vs. metformin (10.1%) ($p = 0.2693$). Similarly, the proportion of patients discontinued or rescued for lack of glycaemic control at week 24 was statistically significantly lower for saxagliptin 10 mg + metformin (5.9%) vs. saxagliptin 10 mg ($p < 0.0001$) but not vs. metformin ($p = 0.0597$).

Changes in other efficacy assessments are listed in online appendix, table S2. At week 24, saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin had numerically greater increases in postprandial insulin AUC vs. metformin but not vs. saxagliptin 10 mg. Early insulin response to a glucose load as determined by the insulinogenic index was numerically higher for combination treatment vs. monotherapy. There was little or no effect on postprandial glucagon AUC at week 24 in all treatment groups. Statistically significant improvements in β-cell function (HOMA-2β assessment) from baseline to week 24 were demonstrated for saxagliptin 5 mg + metformin vs. saxagliptin 10 mg ($p < 0.0001$) and metformin ($p = 0.0004$) and for saxagliptin 10 mg + metformin vs. saxagliptin 10 mg and metformin (all $p < 0.0001$). Weight loss occurred in all treatment groups. Mean changes from baseline at week 24 were −1.8, −1.4, −1.1 and −1.6 kg for saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin, saxagliptin 10 mg and metformin respectively. Modest numerical improvements from baseline to week 24 in total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides were demonstrated in all treatment groups (online appendix, table S2).

Safety and Tolerability

Overall, saxagliptin given as initial combination therapy with metformin was generally well tolerated. The proportion of patients reporting any AE (excluding hypoglycaemia) and SAEs was similar across all treatment groups (table 2). Three deaths occurred, all in the metformin group, and were considered by the respective investigators to be unrelated to the study drug. AEs leading to study discontinuation were 8 (2.5%), 7 (2.2%), 8 (2.4%) and 11 (3.4%) for saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin, saxagliptin 10 mg and metformin respectively. Discontinuations due to SAEs were one (0.3%) for saxagliptin 5 mg + metformin, three (0.9%) for saxagliptin 10 mg + metformin, zero for saxagliptin 10 mg and one (0.3%) for metformin. The majority of AEs were mild or moderate in intensity. Most commonly reported AEs (≥5%, any treatment group) were headache (up to 9.9%), diarrhoea (up to 9.6%), nasopharyngitis (up to 6.9%) and hypertension (up to 5.3%). Of note, mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) decreased in

Table 2 Safety and tolerability during 24-week treatment period by randomized group

	SAXA 5 mg + metformin (n = 320)	SAXA 10 mg + metformin (n = 323)	SAXA 10 mg (n = 335)	Metformin (n = 328)
AEs (%)*				
≥1 AE	177 (55.3)	185 (57.3)	179 (53.4)	192 (58.5)
≥1 related AE	33 (10.3)	61 (18.9)	40 (11.9)	59 (18.0)
Deaths	0	0	0	3 (0.9)
≥1 SAE†	8 (2.5)	12 (3.7)	6 (1.8)	8 (2.4)
≥1 related SAE	1 (0.3)	3 (0.9)	0	0
Discontinuations due to SAEs	1 (0.3)	3 (0.9)	0	1 (0.3)
Discontinuations due to AEs	8 (2.5)	7 (2.2)	8 (2.4)	11 (3.4)
AEs (≥5%)‡				
Nasopharyngitis	22 (6.9)	8 (2.5)	14 (4.2)	13 (4.0)
Headache	24 (7.5)	32 (9.9)	21 (6.3)	17 (5.2)
Diarrhoea	22 (6.9)	31 (9.6)	10 (3.0)	24 (7.3)
Hypertension	15 (4.7)	17 (5.3)	15 (4.5)	11 (3.4)
Reported hypoglycaemia (%)§	11 (3.4)	16 (5.0)	5 (1.5)	13 (4.0)
Confirmed hypoglycaemia (%)¶	0 (0)	2 (0.6)	0 (0)	1 (0.3)

AE, adverse event; SAE, serious adverse event; SAXA, saxagliptin.

*AE defined as any new or worsening illness, sign, symptom or clinically significant laboratory test abnormality as noted by the investigator during the course of the study, regardless of the investigator's attribution of the event to study treatment.

†SAE defined as an AE that was fatal, life threatening, required in-patient hospitalization or prolonged an existing hospitalization, resulted in persistent or significant disability or incapacity, a cancer, a congenital anomaly/birth defect, resulted in the development of drug dependency or drug abuse or was an important medical event that jeopardized the patient or required intervention to prevent a serious outcome.

‡Excludes hypoglycaemia.

§Reported hypoglycaemia was defined as events consistent with signs or symptoms of hypoglycaemia with or without documented blood glucose levels.

¶Confirmed hypoglycaemia was defined by a fingerstick glucose value ≤50 mg/dl with associated symptoms.

all treatment groups by approximately 5.0 mmHg (SBP) and 3.0 mmHg (DBP) at week 24.

Of special interest, the proportion of patients with skin-related AEs was similar: 3.4% (saxagliptin 5 mg + metformin), 4.3% (saxagliptin 10 mg + metformin), 4.2% (saxagliptin 10 mg) and 2.7% (metformin). No events of Stevens–Johnson syndrome or angioedema were reported. Cardiac disorder events were 7 (2.2%) for saxagliptin 5 mg + metformin, 8 (2.5%) for saxagliptin 10 mg + metformin, 10 (3.0%) for saxagliptin 10 mg and 16 (4.9%) for metformin. Small numerical decreases in mean absolute lymphocyte count were observed with saxagliptin 10 mg + metformin and saxagliptin 10 mg from baseline to week 24 (-0.10 and -0.16×10^3 cells/μl for saxagliptin 10 mg + metformin and saxagliptin 10 mg, respectively, vs. 0.03 and 0.07×10^3 cells/μl for saxagliptin 5 mg + metformin and metformin respectively). However, mean lymphocyte counts remained within normal limits across all treatment groups, with no evidence of clinical sequelae. There were no clinically meaningful drug effects on any other laboratory safety parameter.

Overall frequency of hypoglycaemic events was very low (table 2). One patient in the saxagliptin 10 mg + metformin group experienced an AE of confirmed hypoglycaemia that was easily managed by the patient. No hypoglycaemic event was judged by the study investigator to be serious or led to a discontinuation of study therapy.

Discussion

The overall therapeutic goal of T2D treatment is to achieve and maintain target HbA1c, FPG and PPG levels without compromising safety and tolerability [11]. The present study demonstrated that saxagliptin, given in combination with metformin as initial therapy for 24 weeks, led to clinically relevant improvements that were statistically significantly greater than either treatment alone across key glycaemic parameters, with a tolerability profile similar to that of the monotherapy components. Reductions observed in HbA1c with co-administration of saxagliptin and metformin corresponded with substantial improvements in FPG and PPG. The additional glycaemic benefit observed in the saxagliptin + metformin combination therapy groups is likely to be a consequence of each component's different MOA working in concert [12,13].

Patients with T2D should be managed early in the course of their disease to delay the onset and progression

of complications [4,23]. A statistically significantly greater proportion of patients receiving combination therapy with saxagliptin and metformin achieved the American Diabetes Association-recommended HbA1c goal of <7% [24] and the AACE-recommended HbA1c goal of ≤6.5% [14] than those receiving either agent as monotherapy. Despite high baseline HbA1c values, approximately 60% of patients who received initial combination therapy achieved an HbA1c target of <7%. Patients receiving initial combination treatment achieved HbA1c targets of <7 and ≤6.5% more rapidly than those receiving either monotherapy. Notably, over half of patients receiving initial combination therapy achieved the HbA1c goal of <7% by week 12 of the study, thereby reducing the harmful impact of glucotoxicity on β-cell function earlier in the disease course [25]. As is frequently observed with antihyperglycaemic agents, greater reductions in HbA1c were seen in patients with higher HbA1c values at baseline; in this study, the greatest reductions were achieved with combination therapy in the subgroup of patients with HbA1c ≥10% at baseline (−3.3% in both combination groups), with relatively similar reductions between the saxagliptin 5 mg + metformin and the saxagliptin 10 mg + metformin groups across all baseline HbA1c levels. These results are of particular importance, given the inadequate glycaemic control observed in a high proportion of patients with T2D in real-world settings. While questions frequently arise regarding the applicability of clinical trial results beyond the research setting, this study was large, multinational and enrolled treatment-naïve patients across a wide range of higher HbA1c values. The consistency of effect, overall and across various subgroups, suggests the generalizability of these results to the broader real-world setting.

Initial combination therapy with saxagliptin and metformin provided added efficacy without additional tolerability issues. Combination therapy is often associated with an increased risk for hypoglycaemia, particularly combinations that use sulphonylureas or insulin. Hypoglycaemic events with saxagliptin + metformin combination therapy were similar to monotherapy, even with significantly greater glycaemic efficacy achieved with combination therapy. Although weight gain has been observed with intensive glycaemic control, similar degrees of weight loss were observed in both combination treatment and monotherapy groups [26].

Of the patients in this trial, almost all (98.4%) had never received any antihyperglycaemic therapy despite more than one-third having an HbA1c ≥10.0% and median duration of diabetes was only 0.4 years. This study enrolled a patient population almost entirely treatment naïve, in contrast to the withdrawal of monotherapy prior to randomization embedded in the designs of other studies examining DPP-4 inhibitors or other agents given as initial combination therapy [7,27]. The glycaemic lowering of saxagliptin given in combination with metformin as initial therapy demonstrated in this patient population, combined with a tolerability profile similar to that of monotherapy components, is indicative of the benefits of earlier aggressive treatment for patients with T2D and higher HbA1c values at baseline.

Although firm conclusions cannot be drawn from comparisons between studies performed in different patient populations with different designs, the efficacy of saxagliptin and metformin initial combination therapy was within the range of results of a similar study by Goldstein *et al.* of initial combination therapy utilising a DPP-4 inhibitor (sitagliptin) and metformin. Mean changes from baseline in HbA1c, FPG, PPG-AUC and PPG at 120 min for the sitagliptin 100 mg + metformin 2000 mg group and the sitagliptin 100 mg + metformin 1000 mg group were statistically significant vs. placebo and vs. the monotherapy components. There was a low incidence of hypoglycaemia, and the incidence of AEs was generally similar across treatment groups, with the highest incidence in the high-dose metformin monotherapy group and the lowest incidence in the placebo group [7]. These results, in addition to those demonstrated in the current study, support the utility of initial combination therapy with a DPP-4 inhibitor and metformin.

Study limitations included differences in exposure to blinded study medication for the saxagliptin + metformin combination groups vs. monotherapy treatment groups. Specifically, the greater time of exposure to blinded study medication in the combination treatment groups led to a greater mean duration of time in which a patient could experience an AE. Despite these differences in mean exposure to study medication, AE rates were generally similar in all treatment groups. Only data collected prior to rescue were used for efficacy and safety analyses. This approach was adopted to minimize potential confounding of rescue therapy. However, only approximately 6–20% of patients across the four treatment groups required rescue for failing to achieve prespecified glycaemic targets or discontinued for lack of efficacy.

Failure to achieve and maintain adequate glycaemic control is due to the progressive nature of T2D and limitations of current therapies. Achieving specific glycaemic goals can substantially reduce morbidity, making effective treatment of hyperglycaemia a top priority, particularly for individuals with a high HbA1c. By using agents

that differ in their MOA and side-effect profiles, combination regimens can begin to address the numerous pathophysiological abnormalities that characterize T2D. Initial combination therapy with saxagliptin and metformin represents such an option for the management of patients with T2D.

Acknowledgements

Unfortunately, M. J. passed away prior to final preparation and publication of this manuscript. The authors gratefully acknowledge the study participants and site staff who assisted this research. The authors would also like to thank Ian Wyglendowski, BA, for overall operational management of the study. Technical and editorial assistance for this manuscript was provided by Jennifer Ciafullo, MPH, Innovex Medical Communications. This study was funded, designed and supervised by scientists at Bristol-Myers Squibb and AstraZeneca, discoverer and developer of saxagliptin. This trial (NCT00327015) is registered with http://www.clinicaltrials.gov.

References

1 Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999; **281:** 2005–2012.

2 Stonehouse A, Okerson T, Kendall D, Maggs D. Emerging incretin-based therapies for type 2 diabetes: incretin mimetics and DPP-4 inhibitors. Curr Diabetes Rev 2008; **4:** 101–109.

3 Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. JAMA 2002; **287:** 360–372.

4 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10 year follow-up of intensive glucose control in type 2 diabetes. UKPDS 80. N Engl J Med 2008; **359:** 1577–1589.

5 Drucker DJ. Dipeptidyl peptidase-4 inhibition and the treatment of type 2 diabetes: preclinical biology and mechanisms of action. Diabetes Care 2007; **30:** 1335–1343.

6 Pospisilik JA, Martin J, Doty T *et al.* Dipeptidyl peptidase IV inhibitor treatment stimulates beta-cell survival and islet neogenesis in streptozotocin-induced diabetic rats. Diabetes 2003; **52:** 741–750.

7 Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes Care 2007; **30:** 1979–1987.

8 Rosenstock J, Baron MA, Camisasca RP, Cressier F, Couturier A, Dejager S. Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with component monotherapy in patients with type 2 diabetes. Diabetes Obes Metab 2007; **9:** 175–185.

9 Deacon CF, Carr RD, Holst JJ. DPP-4 inhibitor therapy: new directions in the treatment of type 2 diabetes. Front Biosci 2008; **13:** 1780–1794.

10 Levetan C. Oral antidiabetic agents in type 2 diabetes. Curr Med Res Opin 2007; **23:** 945–952.

11 Nathan DM, Buse JB, Davidson MB *et al.* Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2006; **49:** 1711–1721.

12 Mannucci E, Ognibene A, Cremasco F *et al.* Effect of metformin on glucagon-like peptide 1 (GLP-1) and leptin levels in obese nondiabetic subjects. Diabetes Care 2001; **24:** 489–494.

13 Migoya EM, Miller J, Larson P *et al.* Sitagliptin, a selective DPP-4 inhibitor, and metformin have complementary effects to increase active GLP-1 concentrations. Abstract 0286-OR. *Diabetes Abstract Book, American Diabetes Association 67th Scientific Sessions*. Chicago, IL, USA, 22–26 June 2007.

14 Rodbard HW, Blonde L, Braithwaite SS *et al.* American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract 2007; **13:** 1–68.

15 Canadian Diabetes Association. Clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2008; **32:** S1–S215.

16 Nathan DM, Buse JB, Davidson MB *et al.* Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009; **32:** 193–203.

17 Augeri DJ, Robl JA, Betebenner DA *et al.* Discovery and preclinical profile of saxagliptin (BMS-477118): a highly potent, long-acting, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. J Med Chem 2005; **48:** 5025–5037.

18 Rosenstock J, Sankoh S, List JF. Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naive patients with type 2 diabetes. Diabetes Obes Metab 2008; **10:** 376–386.

19 Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999; **22:** 1462–1470.

20 Mari A, Pacini G, Murphy E, Ludvik B, Nolan JJ. A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. Diabetes Care 2001; **24:** 539–548.

21 Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008; **31:** 1473–1478.
22 Laska EM, Meisner MJ. Testing whether an identified treatment is best. Biometrics 1989; **45:** 1139–1151.
23 Stratton IM, Adler AI, Neil HA *et al*. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; **321:** 405–412.
24 American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2007; **30:** S4–S41.
25 Marchetti P, Dotta F, Lauro D, Purrello F. An overview of pancreatic beta-cells defects in human type 2 diabetes: implications for treatment. Regul Pept 2008; **146:** 4–11.
26 UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; **352:** 837–853.
27 Rosenstock J, Rood J, Cobitz A, Biswas N, Chou H, Garber A. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. Diabetes Obes Metab 2006; **8:** 650–660.

Supporting Information

The following supporting information is available for this article:

Table S1 Conversion chart: conventional to Systeme International units.

Table S2 Other efficacy assessments at 24 weeks.

Additional Supporting Information may be found in the online version of this article.

Please note: Willey-Blackwell Publishing is not responsible for the content or functionality of any supplementary materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

