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One-year sustained glycemic control and weight reduction in type 2 diabetes after addition of liraglutide to metformin followed by insulin detemir according to HbA_{1c} target☆☆,★

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ABSTRACT

Aim: To investigate durability of efficacy and safety over 1 year of the sequence of liraglutide added to metformin followed by add-on insulin detemir if glycated hemoglobin (HbA_{1c}) remains ≥7.0%.
Methods: Patients previously uncontrolled on metformin ± sulfonylurea with HbA_{1c} ≥7.0% after 12 weeks of adding liraglutide 1.8 mg to metformin (run-in; sulfonylurea discontinued) were randomized 1:1 to 52 weeks' open-label add-on detemir (randomized treatment [RT] group; $n = 162$) or continuation without detemir (randomized control [RC] group; $n = 161$). Patients with HbA_{1c} <7.0% continued 52 weeks' unchanged treatment (observational group; $n = 498$).
Results: Run-in HbA_{1c} improvement from 8.3% to 7.6% (–0.6%) was further enhanced in the RT group (–0.50%) and maintained in the RC group (+0.01%) over 52 weeks; estimated treatment difference (ETD)[95%CI]: −0.51 [−0.70;−0.31]; $P < 0.0001$. More RT (52%) than RC patients (22%) achieved HbA_{1c} <7.0% at 52 weeks ($P < 0.0001$). Run-in weight loss (–3.5 kg) was maintained in the RT (–0.05 kg) and enhanced in the RC group (−1.02 kg) after 52 weeks; ETD [95%CI]: 0.97 [0.04;1.91]; $P = 0.04$. No major hypoglycemia occurred; minor hypoglycemia rates were low across groups (0.034–0.228 events/patient-year).

☆☆ Conflict of interest: JR has participated in advisory panels for Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly & Co, GlaxoSmithKline, Johnson&Johnson, Lexicon, MannKind Corporation, Novartis, Novo Nordisk A/S, Pfizer, Roche, Sanofi, Merck, Takeda; and has received research support from Amylin, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Eli Lilly & Co, GlaxoSmithKline, Johnson&Johnson, Lexicon, MannKind Corporation, Merck, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda. HR has attended advisory panels for Amylin, AstraZeneca, Biodel, Bayer, Novo Nordisk, Roche Diagnostics, and sanofi-aventis; has acted as consultant for Biodel, and Roche Diagnostics; has received research support from AstraZeneca, Biodel, Boehringer Ingelheim, Eli Lilly & Co, Merck, Novartis, Novo Nordisk, Roche Diagnostics, and sanofi-aventis; and has attended speaker's bureaux for Amylin, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly & Co, Merck, and Novo Nordisk. SB has attended advisory panels for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Diartis, Eli Lilly & Co, Merck, Sharp & Dohme, Novo Nordisk, Omnia-Med, and Sanofi; and is a board member for GlycosMedia. DDA has acted as consultant for Eli Lilly & Co, Novo Nordisk Inc, Amylin Pharmaceuticals Inc, Takeda Global Research and Development Center, Inc, Zealand Pharma A/S, Merck & Co; and has received research support from sanofi-aventis, Ethicon, MannKind Corporation, and Johnson&Johnson. JS has attended speaker's bureaux for Takeda, Bayer, Novartis, Merck Sharp & Dohme, AstraZeneca/Bristol Myers-Squibb, Novo Nordisk, Sanofi-Aventis, Berlin Chemie, Eli Lilly & Co, Merck, Roche, Ipsen, Pfizer, Janssen, Lifescan; has attended advisory panels for Takeda, Bayer, Novartis, Merck Sharp & Dohme, AstraZeneca/Bristol Myers-Squibb, Novo Nordisk, sanofi-aventis, Berlin Chemie, Eli Lilly & Co, Roche, Ipsen, Pfizer, Janssen, Lifescan; and has received research support from Takeda, Novartis, Merck Sharp & Dohme, sanofi-aventis, Ipsen, and Pfizer. AT and CS are both full-time employees of, and shareholders in, Novo Nordisk A/S. JHDV is a Board Member for Eli Lilly & Co, Johnson&Johnson, Novo Nordisk A/S, Roche Diagnostics; has received research support from GluMetrics Inc, Novartis Pharmaceuticals Corporation and Novo Nordisk A/S; and has attended speaker's bureaux for Dexcom Inc, Eli Lilly & Co and Novo Nordisk A/S.

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Conclusions: Supplementing metformin + liraglutide with detemir for 52 weeks improved glycemic control with sustained weight loss and low hypoglycemia rate.

1. Introduction

Metformin is a well-established pharmacologic agent for patients with type 2 diabetes (T2D) and, contraindications notwithstanding, is generally the first-line treatment of choice (Inzucchi et al., 2012; Rodbard et al., 2009). Selecting the optimal treatment intensification option(s) for individual patients after metformin failure tends to be more challenging. The 2012 position statement from the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) includes general recommendations for five classes of anti-hyperglycemic agents in second- and third-line treatment combinations (i.e. sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 [DPP-4] inhibitors, glucagon-like peptide-1 receptor agonists [GLP-1RAs], and basal insulin), albeit without prioritization due, in the authors' view, to limited comparative effectiveness data (Inzucchi et al., 2012). Certainly, diabetes clinical trials are typically conducted in selected populations and controlled conditions, with study designs based primarily on meeting regulatory requirements (Inzucchi et al., 2012). Thus, more translational trials prospectively testing different treatment sequences in a randomized design are needed. Here, we present data from one such translational trial, which examines the efficacy and safety of one particular intensification sequence – the addition of a GLP-1RA (liraglutide) to metformin for 12 weeks (run-in) (approximately one-third discontinued sulfonylureas at inclusion), followed by randomization of patients with glycated hemoglobin (HbA_{1c}) ≥7.0% after run-in to either further addition of a basal insulin (insulin detemir) or continued metformin + liraglutide treatment. We previously published the results observed 26 weeks after randomization (DeVries et al., 2012). Now, we describe the results of pre-specified analyses 52 weeks after randomization (i.e. the main 26-week treatment period plus the pre-specified 26-week extension) to assess the durability of glucose-lowering effects and weight loss, and also the longer-term safety of this intensification treatment sequence. To our knowledge, this is the first longer-term investigation of sequential combination therapy with a once-daily GLP-1RA and basal insulin in T2D.

2. Materials and methods

2.1. Study design and patients

Details of study design and patients enrolled have been reported previously (DeVries et al., 2012). In brief, this multinational study investigated the efficacy and safety of an antihyperglycemic treatment intensification sequence in insulin naïve T2D patients. At study start, patients had been receiving metformin (≥1500 mg/day for ≥3 months; HbA_{1c} 7.0–10.0%) or metformin (≥1500 mg/day) + sulfonylurea (≤half maximum approved dose; HbA_{1c} 7.0–8.5%). In the run-in, sulfonylureas were discontinued and metformin + liraglutide 1.8 mg administered for 12 weeks. Patients with HbA_{1c} ≥7.0% at the end of run-in were randomly allocated to either continued metformin + liraglutide 1.8 mg (randomized control [RC] group) or metformin + liraglutide 1.8 mg + insulin detemir (randomized treatment [RT] group) (Fig. 1). Patients with HbA_{1c} <7.0% at run-in end continued treatment with metformin + liraglutide 1.8 mg as an observational group. The subsequent main treatment period (weeks 0–26) corresponded to the assessment of the primary endpoint (change in HbA_{1c}); the primary endpoint and supporting efficacy and safety data for this period were reported previously (DeVries et al., 2012). In a pre-defined extension, patients continued treatment for a further 26 weeks (no separate re-enrollment step) except that, for ethical reasons, patients in the RC and observational groups with HbA_{1c} ≥8.0% at weeks 26 or 38 could opt to intensify treatment with insulin detemir (in which case, data from the last visit before intensification were carried forward). The study started (beginning of run-in) on March 3, 2009 and completed on November 1, 2010. Protocol amendments are noted in the Supplementary Appendix. Protocol, amendments, and informed consent documents were approved by independent local ethics committees and implemented according to Good Clinical Practice and the Declaration of Helsinki. The trial is registered with ClinicalTrials.gov (NCT00856986).

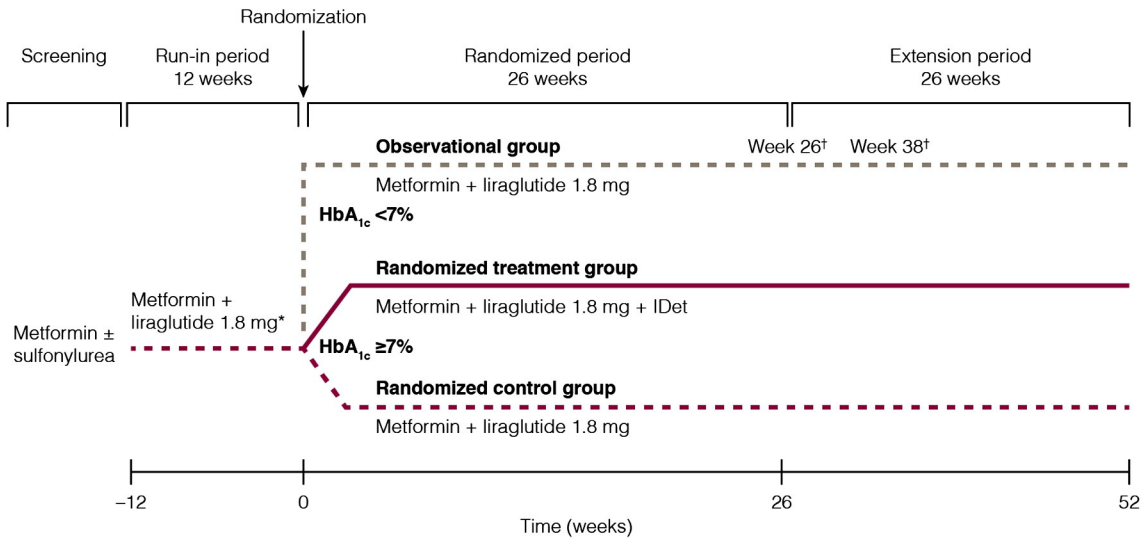

Fig. 1. Study design. *Liraglutide initiated at 0.6 mg/day and titrated in weekly increments of 0.6 mg/day to final dose of 1.8 mg/day; †patients in the observational and the randomized control group with HbA_{1c} values ≥8.0%, and giving consent, could intensify treatment with IDet. IDet, insulin detemir. ©2012 American Diabetes Association; adapted with permission from DeVries et al. Diabetes Care 2012;35:1446–54.

2.2. Outcomes

The pre-specified primary outcome (change from randomization [week 0] to week 26) was reported previously (DeVries et al., 2012). Efficacy outcomes for the extension study reported here comprised: changes from randomization to week 52 in HbA_{1c}, fasting plasma glucose (FPG), postprandial plasma glucose (PPG) from self-measured seven-point plasma glucose (PG) profiles, body weight, blood pressure (BP), and lipids; proportions of patients at week 52 reaching HbA_{1c} <7.0% and ≤6.5% and the composite endpoint of HbA_{1c} <7.0% without weight gain and major or minor hypoglycemia (i.e. no hypoglycemia during weeks 0–52). Minor hypoglycemic episodes were defined as those with a confirmed PG <3.1 mmol/l and were self-treated; major hypoglycemia required third-party assistance, irrespective of PG level. Pre-specified safety outcomes included adverse events (AEs), hypoglycemic episodes, vital signs, and biochemical and hematological measures. Serum samples were tested for liraglutide antibodies at weeks –12 (run-in start), 0, 26, 52, and 53 for all patients and positive samples were characterized in vitro for cross-reactivity to native GLP-1 as described previously (Buse, Garber,

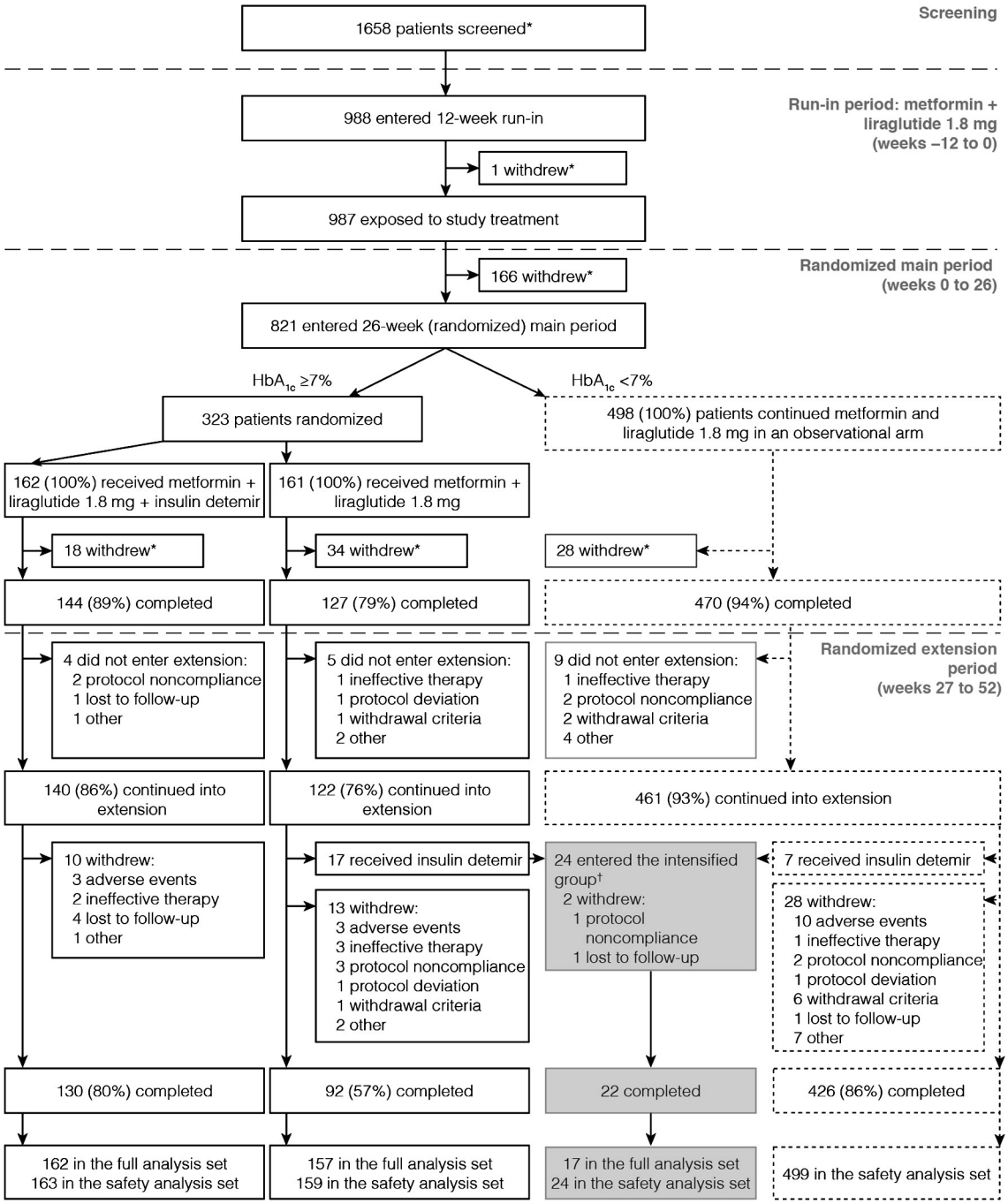

Fig. 2. Flow of patients through the study. *Full details of patient withdrawals during screening, run-in and the 26-week main period have been published previously (DeVries et al., 2012); †Patients with HbA_{1c} ≥8.0% and giving consent at weeks 26/38 intensified treatment with insulin detemir. Two patients who had been randomly allocated to the metformin + liraglutide control group received the wrong treatment: one was supplied with insulin detemir but withdrew before administering the treatment; the other should not have been randomized as her glycated hemoglobin level at week 0 was <7.0%. For efficacy analyses, data for these patients appear in the group to which they were randomized; for safety analyses, their data were analyzed according to treatment received. ©2012 American Diabetes Association; adapted with permission from DeVries et al. Diabetes Care 2012;35:1446–54.

et al., 2011). Serum samples were tested for antibodies specific to insulin detemir and antibodies cross-reacting to human insulin (Bartley, Bogoev, Larsen, & Philotheou, 2008) at week 0 in all patients, and at weeks 26, 52, and 53 in patients receiving insulin detemir. The neutralizing effect of liraglutide and insulin antibodies was evaluated using scatter plots of antibody response vs. change in HbA_{1c}.

The full analysis set (all randomized patients with at least one efficacy value) was used for efficacy parameters, unless noted otherwise, with missing values imputed (last observation forward [LOCF]). As noted earlier, for observational/RC-group patients intensifying treatment with insulin detemir during the extension, pre-intensification values were carried forward (i.e. LOCF). Statistical analyses on efficacy parameters were conducted for RT and RC groups only. Changes from randomization to week 52 were analyzed using an ANCOVA model with treatment, country, and previous oral antidiabetic (OAD) therapy as fixed effects and randomization (week 0) value as covariate. Proportions of patients reaching HbA_{1c} <7% or ≤6.5% were analyzed by logistic regression with treatment and previous OAD therapy as fixed effects and randomization HbA_{1c} value as covariate. The logistic regression model used for the composite endpoint included treatment, country, and previous OAD therapy as fixed effects and randomization HbA_{1c} and weight values as covariates. All tests were two-sided with 5% significance level and with no adjustment applied for multiplicity. The safety analysis set comprised all patients exposed to at least one dose of trial drug. AEs were included in the treatment group to which patients belonged when the AE occurred; AEs that increased in severity after intensification were included in both groups. Hypoglycemic episodes were analyzed using a generalized linear model. Descriptive statistics were calculated for other safety data from randomized groups and for all efficacy and safety data from the observational group.

3. Results

3.1. Patient characteristics: randomized and observational groups

Information regarding patient flow through screening, run-in, and the 26-week main treatment period was published previously (DeVries et al., 2012) and is outlined in Fig. 2 alongside patient flow through the 26-week extension. In brief, of 821 patients completing run-in, 648 (79%) from across the RT, RC, and observational treatment groups completed 52 weeks' further therapy (Fig. 2). Overall, 18 patients withdrew between completing the 26-week main treatment period and starting the extension. A total of 51 patients withdrew during the extension and 24 patients were transferred to the intensification group during the extension. Demographics and disease characteristics are shown in Table 1 (DeVries et al., 2012).

3.2. Efficacy: randomized groups

HbA_{1c} decreased from 8.3% to 7.6% (−0.6%) in the randomized groups during the initial 12-week run-in (Fig. 3A). Thereafter, a further decrease (−0.5%) occurred in the RT group (i.e. with add-on insulin detemir) up to week 12, after which HbA_{1c} remained relatively stable up to study end (i.e. week 52). In contrast, HbA_{1c} was relatively stable in the RC group from randomization (week 0) to study end, confirming adequate duration of the run-in. The range of HbA_{1c} values also shifted more over time (towards lower HbA_{1c} levels) for the RT group than RC group (Figure S1). Mean ± S.E. change in HbA_{1c} from week 0 to week 52 was significantly greater for the RT group (−0.50% [0.09]) than the RC group (+0.01 [0.09]; estimated treatment difference [ETD], −0.51%; 95% CI [−0.70; −0.31]; $P < 0.0001$), and the changes were similar in magnitude to those for weeks 0–26 (DeVries et al., 2012). At week 52, significantly more RT than RC patients achieved an HbA_{1c} <7.0% (52% vs. 22%, respectively; $P < 0.0001$) or HbA_{1c} ≤6.5% (22% vs. 7%, respectively; $P < 0.0001$) (see also Table S1). Proportions of patients achieving HbA_{1c} targets were slightly higher at week 52 than week 26 (Figure S1).

FPG decreases up to 26 weeks (DeVries et al., 2012) were sustained in both randomized groups during the extension (Fig. 3B); the mean ± S.E. reduction from week 0 to week 52 for the RT group was significantly greater than that for the RC group (−1.91 [0.21] vs. −0.14 [0.21] mmol/l, respectively; ETD: −1.77 mmol/l; 95% CI [−2.24; −1.30]; $P < 0.0001$). Mean self-measured PG levels decreased between week 0 and week 52 in both randomized groups (Fig. 3C). The mean reductions in postprandial values were significantly greater in the RT group than the RC group for breakfast (ETD −1.74 mmol/l; 95% CI [−2.32; −1.16]; $P < 0.0001$) and lunch (ETD −0.63 [−1.21; −0.04]; $P = 0.04$).

The 3.5-kg weight loss during run-in with metformin + liraglutide 1.8 mg was basically maintained over the subsequent 52 weeks in the RT group (Fig. 3D). Weight loss continued in the RC group over

Table 1
Demographics and disease characteristics at run-in start (week −12) and randomization (week 0).

	Randomized treatment group (metformin + liraglutide 1.8 mg + insulin detemir) ($n = 162$)	Randomized control group (metformin + liraglutide 1.8 mg) ($n = 161$)	Observational group (metformin + liraglutide 1.8 mg) ($n = 498$)
At run-in (week −12)			
Age (years)	56.8 ± 9.4	57.3 ± 9.8	56.5 ± 9.7
Male:female (%)	54.3:45.7	55.3:44.7	56.6:43.4
BMI (kg/m^2)	34.9 ± 6.3	33.9 ± 6.0	34.4 ± 6.7
Weight (kg)	99.5 ± 21.2	98.6 ± 21.3	99.0 ± 20.8
Duration of diabetes (years)	8.6 ± 5.8	8.5 ± 6.0	6.6 ± 5.7
Previous treatment (metformin: metformin + sulfonylurea)	50.0:50.0	50.3:49.7	74.5:25.5
HbA_{1c} (%)	8.2 ± 0.7	8.3 ± 0.8	7.7 ± 0.7
Fasting plasma glucose (mmol/l)	10.2 ± 2.4	10.3 ± 2.5	9.2 ± 1.8
HOMA-B	59.0 ± 50.8	51.2 ± 34.9	63.7 ± 46.1
Systolic blood pressure (mmHg)	134.0 ± 16.9	135.7 ± 16.8	134.4 ± 15.3
Diastolic blood pressure (mmHg)	80.1 ± 9.7	80.8 ± 9.8	81.5 ± 9.2
At randomization (week 0)			
Weight (kg)	96.0 ± 20.9	95.3 ± 21.1	94.7 ± 20.5
HbA_{1c} (%)	7.6 ± 0.6	7.6 ± 0.7	6.4 ± 0.4
Fasting plasma glucose (mmol/l)	9.2 ± 1.9	8.8 ± 2.1	7.2 ± 1.3
Systolic blood pressure (mmHg)	132.2 ± 16.3	131.7 ± 14.9	128.9 ± 15.2
Diastolic blood pressure (mmHg)	79.6 ± 9.8	80.9 ± 9.4	79.4 ± 9.5

Data are means ± S.D. unless otherwise noted. Data for patients whose treatment was intensified with insulin detemir during the extension period are included in their original treatment groups (see also Table S2). BMI, body mass index; HbA_{1c}, glycated hemoglobin; HOMA-B, homeostasis model assessment of beta-cell function.

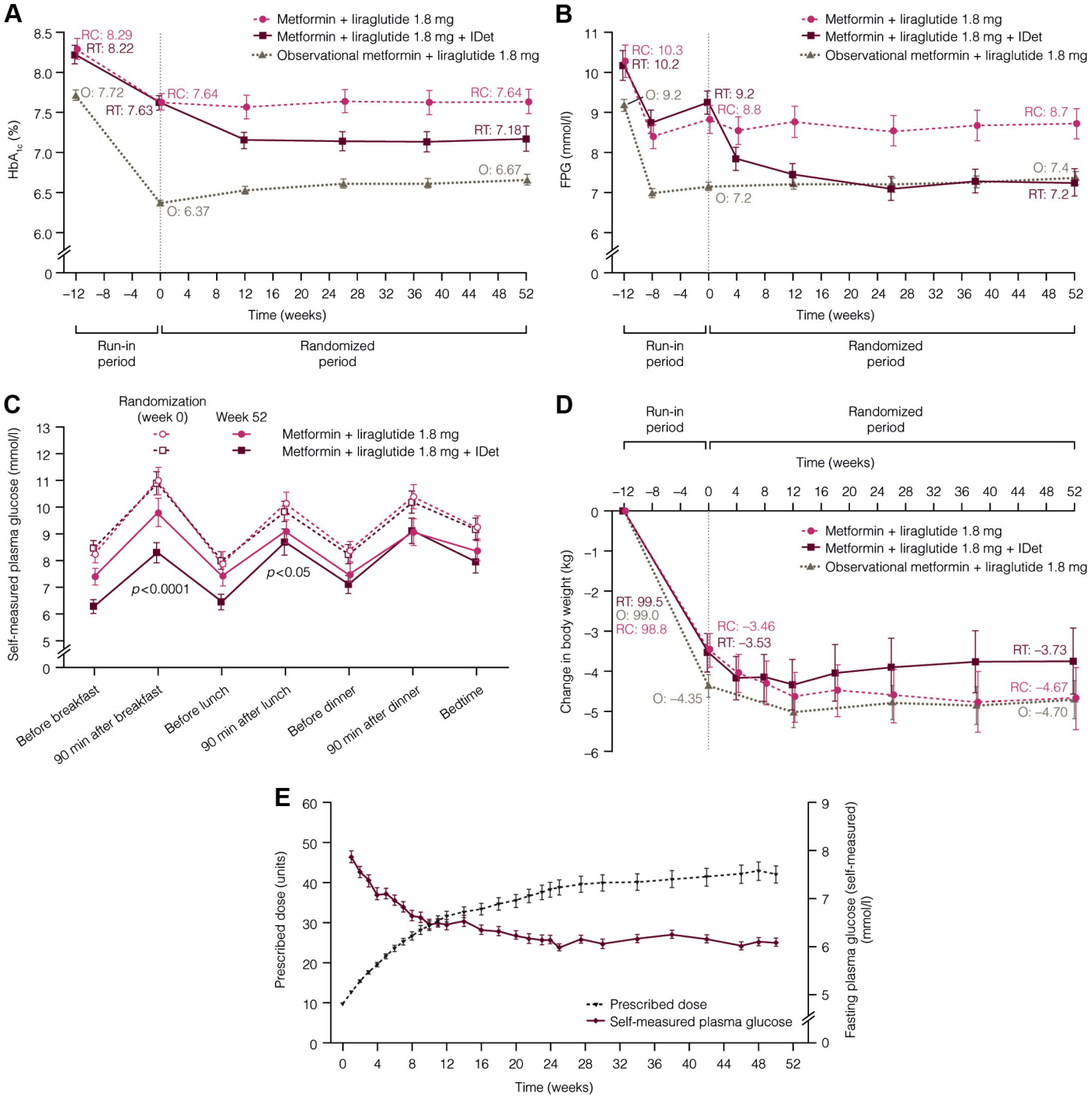

Fig. 3. Glycemic efficacy, body weight and insulin detemir doses. Results from run-in to study end are depicted for (A) glycated hemoglobin (HbA_{1c}) levels, (B) fasting plasma glucose and (D) change in body weight; data are means ± 2 S.E. from the full analysis set with last observation carried forwards. Figure (C) depicts self-monitored plasma glucose profiles before and after breakfast, lunch, dinner, and at bedtime for the randomized treatment and control groups at weeks 0 and 52; data are means ± 2 S.E. from the full analysis set (no imputation) and *P*-values refer to differences between randomized groups in the change in postprandial plasma glucose levels from randomization (week 0) to week 52 for each meal. Figure (E) depicts mean ± S.E. insulin detemir doses (left ordinate) and mean ± S.E. self-measured fasting plasma glucose levels (right ordinate) during the randomized period for patients randomly allocated to receive IDet. IDet, insulin detemir; RT: randomized treatment group; RC: randomized control group; O: observational group.

the same period, and the mean ± S.E. weight change for weeks 0–52 was significantly greater for the RC group than RT group (−1.02 [0.41] vs. −0.05 [0.42] kg, respectively; ETD: 0.97 kg; 95% CI [0.04; 1.91]; $P = 0.04$). The proportion of patients achieving the composite endpoint ($HbA_{1c} < 7.0\%$ without weight gain and major or minor hypoglycemia) at week 52 was greater for the RT group (26%) than RC group (17%) but the treatment difference was not significant ($P = 0.06$; Table S1). These proportions were nevertheless numerically increased over those at 26 weeks (DeVries et al., 2012).

Mean prescribed insulin doses increased from 10 U at week 0 to 39.5 U (0.41 U/kg) at week 26, and were then stable to study end (42 U [0.45 U/kg] at week 50) (Fig. 3E). Mean self-measured FPG decreased from 7.9 mmol/l at week 1 to 6.1 mmol/l at week 50. The titration algorithm was apparently followed, with mean prescribed insulin doses matching closely to recommended doses (Figure S2).

Lipid profile improvements during the 26-week main period (DeVries et al., 2012) were generally sustained or enhanced during weeks 27–52 (data not shown). Changes in lipid profiles for weeks 0–52

Table 2
Patients with adverse events (AEs) during weeks 0–52.

	Randomized treatment group (metformin + liraglutide 1.8 mg + insulin detemir) ($n = 163$)	Randomized control group (metformin + liraglutide 1.8 mg) ($n = 159$)	Observational group (metformin + liraglutide 1.8 mg) ($n = 499$)	Intensified group[§] (metformin + liraglutide 1.8 mg + insulin detemir) ($n = 24$)
Serious AEs[*]	17 (10.4)	10 (6.3)	51 (10.2)	1 (4.2)
Deaths[†]	0	1 (0.6)	1 (0.2)	0
AEs (of any severity) reported by ≥5% of patients				
Nasopharyngitis	32 (19.6)	38 (23.9)	64 (12.8)	3 (12.5)
Diarrhea	21 (12.9)	14 (8.8)	35 (7.0)	1 (4.2)
Increased lipase	20 (12.3)	7 (4.4)	39 (7.8)	4 (16.7)
Headache	13 (8.0)	15 (9.4)	41 (8.2)	2 (8.3)
Upper respiratory tract infection	12 (7.4)	7 (4.4)	21 (4.2)	0
Vomiting	10 (6.1)	9 (5.7)	21 (4.2)	0
Nausea	9 (5.5)	12 (7.5)	25 (5.0)	1 (4.2)
Oropharyngeal pain	4 (2.5)	10 (6.3)	13 (2.6)	0
Back pain	3 (1.8)	8 (5.0)	17 (3.4)	1 (4.2)

Data are number (%) of patients.
[*] Serious AEs for the extension period are detailed in Table S3; serious AEs for the main 26-week trial period are detailed in DeVries et al., 2012.
[†] Two deaths occurred in the extension: one death (randomized control group) was due to pulmonary mass and CNS metastases that had occurred in the main period [see DeVries et al., 2012]; the other death (observational group) followed a serious AE in the extension (see Table S3).
[§] AEs for patients intensifying treatment with insulin detemir during the extension are tabulated with the initial treatment group if the adverse event occurred before intensification; AEs that increased in severity after intensification are tabulated in both treatment groups. N/A, not applicable.

were not significantly different between randomized groups, except for a greater increase in high-density lipoprotein cholesterol levels for the RT group than RC group (0.07 [0.02] vs. 0.02 [0.02] mmol/l, respectively; ETD: 0.05 mmol/l; 95% CI [0.01; 0.08]; $P = 0.01$). Decreases from run-in start to 52 weeks occurred in both randomized groups for mean systolic BP (SBP) (RT group, −2.07 mmHg; RC group, −4.89 mmHg) and mean diastolic BP (DBP) (RT group, −0.54 mmHg; RC group, −1.44 mmHg). Differences between the two randomized groups for changes in SBP or DBP for weeks 0–52 were not statistically significant (SBP, ETD: 0.90 mmHg, 95%CI [−1.85; 3.64]; $P = 0.52$; DBP, ETD: 0.77 mmHg [−1.02; 2.55]; $P = 0.40$).

3.3. Efficacy: observational group

The group comprised patients reaching $HbA_{1c} < 7.0\%$ at run-in end. Fifty-two weeks later, 73% had an $HbA_{1c} < 7.0\%$. Over the whole study, the group experienced a mean change of −1.05% in HbA_{1c} (7.7% at run-in start; 6.7% at week 52; Fig. 3A). The group also showed reductions in FPG (−1.8 mmol/l; 9.2 mmol/l at run-in start; 7.4 mmol/l at week 52), seven-point PG, and weight (−4.7 kg; 99.0 kg at run-in start; 94.4 kg at week 52) (Figs. 3B–D).

3.4. Intensified group

Sixty-three patients (RC group, 45/161 [28%]; observational group, 18/498 [4%]) met the criterion for treatment intensification ($HbA_{1c} \geq 8.0\%$) with insulin detemir during the extension; of these, 24 patients (RC group, $n = 17$; observational, $n = 7$) agreed to intensify treatment (intensified group). Compared with the other groups at run-in start (Table 1), the intensified group was younger (mean ~2 years younger than the overall study population), had higher body mass index (BMI) and weight values (mean weight almost 10 kg higher), and a greater proportion (58%) were previously treated with metformin + sulfonylurea than metformin monotherapy (42%) (Table S2). Reductions were apparent in HbA_{1c} (mean change from run-in start to week 52, −1.0% [$n = 22$]; 8.4% at run-in start to 7.4% at week 52), FPG (−3.33 mmol/l [$n = 21$]; from 10.4 mmol/l to 7.1 mmol/l) and weight (−3.86 kg [$n = 22$]; from 108.6 kg to 101.8 kg at week 52).

3.5. Safety

Similar proportions of RT and observational groups reported at least one AE over weeks 0–52 (72.4% [$n = 118$] vs 73.7% [$n = 368$], respectively); somewhat smaller proportions reported AEs in the other groups (RC group, 64.2% [$n = 102$]; intensified group, 58.3% [$n = 14$]). Nasopharyngitis was the most common AE over this period in randomized and observational groups (12.8–23.9%); increased lipase levels was the most common AE in the intensified group (16.7%; $n = 4$; Table 2). Although nausea, vomiting, and diarrhea were reported in ≥5% of patients over weeks 0–52, there was a clear decrease in the proportions reporting these gastrointestinal symptoms from run-in start to study end. Thus, nausea frequencies over the run-in ranged from 14.1 to 24.2% across groups (DeVries et al., 2012); these fell to 3.2–5.7% over the 26-week main period (DeVries et al., 2012) and then to 1.9–4.2% over the subsequent 26-week extension (see also Figure S3). The incidence (number of new nausea events) fell to <7% in all groups after the initial 3 weeks of treatment (DeVries et al., 2012). For vomiting, the frequencies over run-in, the 26-week main period, and subsequent 26-week extension for the groups were 5.5–8.0%, 3.0–4.9% (DeVries et al., 2012), and 0.0–2.5%, respectively. For diarrhea, the frequencies were 6.7–9.8%, 3.8–11.7% (DeVries et al., 2012), and 2.5–4.2%, respectively.

No deaths occurred in weeks 0–26 (DeVries et al., 2012). Two deaths occurred in weeks 27–52; one was due to gallbladder cancer with liver metastases (observational group) and one to a pulmonary mass with central nervous system (CNS) metastases (RCT group; Table 2, Table S3). The proportion of patients reporting serious AEs (SAEs) was low in all groups for weeks 0–52 with no observed pattern or clustering (Table 2).

No major hypoglycemia occurred during weeks 0–52. Minor hypoglycemia rates were low in all groups (RT group, 0.23 events/patient-year [33 episodes during 145 patient-years of exposure]; RC group, 0.03 events/patient-year [4 episodes during 118 patient-years]; observational group, 0.12 events/patient-year [53 episodes during 462 patient-years]; intensified group, 0.10 events/patient-year [1 episode during 10 patient-years]). Minor hypoglycemia rates were significantly lower for the RC group than the RT group using the pre-specified analysis (i.e. excluding one outlier in the RC group with 37 minor and symptoms-only hypoglycemic episodes; rate ratio, 6.80; 95%CI [2.14; 21.60]; $P = 0.0011$). With outlier included, the difference between randomized groups was not significant.

Four pancreatitis cases occurred during the entire study: one occurred during run-in and one during weeks 0–26 as described previously (DeVries et al., 2012; Steinberg et al., 2012); two cases occurred during the extension (RC group, acute pancreatitis; observational group, 'pancreatitis' [not defined further]). A total of 20.4% (199/977) of patients had lipase values above the upper limit of

normal (ULN) before treatment started (week −12) and 19.0% (156/821) had lipase elevations to ≥2 × ULN at some point during the trial; however, only one of these elevations preceded a case of pancreatitis (observational group). More 'increased lipase' AEs were reported in the RT group than the other groups (Table 2). Minor increases in median lipase levels (but still remaining below the ULN) were observed with no apparent difference between groups from run-in to week 26 (DeVries et al., 2012), followed by no further change or a trend towards a decrease during weeks 27–52 (Figure S4).

Heart rate increases were observed in all groups during run-in (Figure S5). These were followed by a gradual decrease during weeks 0–52 such that, at study end, mean heart rates were still increased compared with run-in start (RT group, 2.80 beats/min; RC group, 2.54 beats/min; observational group, 2.72 beats/min; intensified group, 1.27 beats/min).

At the start of run-in, none of the patients had positive tests for anti-liraglutide antibodies (Table S4). At week 53 (for patients discontinuing liraglutide at week 52), 21 of the 596 patients tested (3.5%) had anti-liraglutide antibodies; 20 of these 21 patients showed GLP-1 cross-reactive effects but only seven (1.2% of patients tested) showed neutralizing effects. Mean titers for anti-detemir antibodies were generally low throughout the trial (Table S5), while mean titers for anti-insulin antibodies cross-reacting to insulin detemir increased slightly over time. There were no correlations between titer changes (either specific to or cross-reacting with insulin detemir) and changes in HbA_{1c}, and no indication that co-treatment with liraglutide and insulin detemir influenced antibody formation.

4. Discussion

Sequential intensification of metformin with the long-acting GLP-1RA liraglutide, followed by 26 weeks of add-on insulin detemir was previously shown to be safe and efficacious in T2D (DeVries et al., 2012). The present report provides the first longer-term evaluation of the liraglutide–basal insulin combination. Improvements in glycemic control and weight reductions were sustained for a further 26 weeks, with no evidence of declining efficacy, and with low rates of hypoglycemia, nausea, and other AEs. Co-treatment with basal insulin did not affect the development of anti-liraglutide antibodies or vice versa. The low anti-liraglutide antibody frequency was, in fact, smaller than previously observed in liraglutide phase 3 clinical trials (Buse, Garber, et al., 2011) and there was no adverse effect on glycemic efficacy.

Modest weight gain and an increased risk of mild hypoglycemia typically accompany basal insulin treatment (Hermansen et al., 2006 Inzucchi et al., 2012; Riddle, Rosenstock, Gerich, & Insulin Glargine 4002 Study Investigators, 2003), such that there may be reluctance to initiate or intensify insulin therapy (Peyrot, Rubin, & Khunti, 2010). It is noteworthy that in the present trial, the 3.5-kg mean weight loss with 12 weeks of metformin + liraglutide 1.8 mg was maintained with 52 weeks of add-on insulin detemir. Moreover, although the confirmed minor hypoglycemia rate reported previously for patients receiving insulin detemir for 26 weeks was already very low (0.29 events/patient-year [22 episodes during 77 patient-years of exposure] (DeVries et al., 2012), the data suggest a slightly lower rate in the 27–52-week period because the overall 52-week rate was 0.23 events/patient-year (33 episodes during 145 patient-years of exposure). The lower rate during the extension likely resulted from stabilization of insulin doses during the previous 26-week treatment period. Minor hypoglycemia rates in this study also compared favorably with those from other trials with insulin detemir added to OADs: 1.6 events/patient-year for insulin detemir + metformin (Swinnen et al., 2010) and 0.52 events/patient-year for insulin detemir + sitagliptin + metformin (Hollander, Raslova, Skjoth, Rastam, & Liutkus, 2011). GLP-1RAs may be associated with low hypoglycemia rates by perhaps preserving pancreatic defenses against hypoglycemia (Kielgast, Asmar, Madsbad, & Holst, 2010; Nauck et al., 2002). Moreover, in liraglutide–basal insulin combination therapy, using liraglutide is likely to reduce the insulin dosage needed to achieve the target HbA_{1c} and may mitigate the need for prandial insulin to control PPG levels at all three meals. Similar additive effects have been shown for twice-daily exenatide, which may have more exclusive PPG effects as it is administered like a bolus treatment before meals due to its shorter half-life (2.4 h) (Arnolds et al., 2010; Buse, Bergenstal, et al., 2011). The longer-term findings in the present study for weight and hypoglycemia may reassure those concerned about insulin initiation, and may facilitate improved patient adherence to their treatment regimens.

In the RC and observational groups (receiving metformin + liraglutide 1.8 mg), HbA_{1c} decreases were generally stable after run-in, and very few patients (28 and 4%, respectively) were eligible for add-on insulin detemir (i.e. HbA_{1c} ≥8.0% at weeks 26/38). Even though approximately one-third of patients overall were switching from metformin + sulfonylurea (rather than adding to previous metformin monotherapy), HbA_{1c} reductions over the 64-week study ranged from 0.66% to 1.05%. These are comparable to the reduction (0.6%) in another 2-year switch study of patients receiving liraglutide 1.8 mg after failure of OAD monotherapy or combination therapy (Nauck et al., 2012). As expected, in a true add-on study, a greater reduction (1.5%) was observed for metformin + liraglutide 1.8 mg after 52 weeks (Pratley et al., 2011). Mean weight losses were similar for RC and observational groups in the present study, although weight loss was achieved more quickly in the latter group (Fig. 3). Overall weight loss (4.7 kg in both groups) was greater than observed previously (2.9 kg (Nauck et al., 2012) and 3.7 kg, respectively (Pratley et al., 2011)), again, likely due to sulfonylurea termination for many patients.

Sequential intensification clearly effected considerable improvements in HbA_{1c} for the majority of patients during the 64-week period (Figure S1). In fact, extrapolating from data in the present study, we might predict that approximately 75% of individuals uncontrolled on metformin ± sulfonylurea in clinical practice could achieve glycemic control (HbA_{1c} <7.0%) with the stepwise treatment intensification employed here (Figure S6). Importantly, of the patients who had been receiving metformin + sulfonylurea previously (approximately one-third), a smaller proportion achieved the HbA_{1c} target compared with those previously receiving metformin monotherapy (45 vs. 70%, respectively) (Bain, Seufert, Thomsen, Furber, & D'Alessio, 2010). While the prediction can apply only to patients with the same clinical profile as those in the study, the study inclusion criteria do correspond well with patients encountered in daily clinical practice.

While good glycemic control remains an important goal in T2D, it remains unclear whether or not even mild hypoglycemia may induce harm. In a recent large nationwide observational cohort study from Taiwan, even mild symptomatic hypoglycemia was significantly associated with an increased risk of cardiovascular events, all-cause hospitalization, and all-cause mortality (Hsu et al., 2012). In addition, Zhao and colleagues reported recently that patients with hypoglycemia had significantly higher risks of cardiovascular events (hazard ratio, 2.00) and microvascular complications (hazard ratio, 1.76) (Zhao, Campbell, Fonseca, & Shi, 2012). Hence, physicians need to carefully balance the risks and benefits of tight glycemic control for individual patients. In the present study, notwithstanding the absolute low rates of hypoglycemia with liraglutide + insulin detemir treatment, this RT group did have a higher rate of minor hypoglycemia than the RC group. However, comparing the hypoglycemic rates between the observational and RT groups (with quite similar glycemic levels), the difference in the absolute risk of hypoglycemia was very small and probably not clinically relevant, implying that addition of insulin detemir to liraglutide could be undertaken without an additional significant increase in hypoglycemia risk.

Post-marketing reports of pancreatitis in patients with T2D treated with incretin therapies (US Food and Drug Administration, 2008, 2009) have prompted routine monitoring of pancreatic enzymes in clinical trials involving these agents. Elevated pancreatic enzyme levels (≥3 × ULN) are considered markers of pancreatic inflammation, but are not diagnostic for pancreatitis by themselves (at least two

features are required from: serum amylase and/or lipase ≥3 × ULN; characteristic abdominal pain; characteristic findings of acute pancreatitis with contrast-enhanced computed tomography (Banks et al., 2013)). In the present study, 20.4% of patients had lipase values > ULN before treatment started and many experienced large serum lipase fluctuations throughout the trial. In fact, 156 (19.0%) patients exhibited a lipase elevation to ≥2 x ULN at some time during the study, but pancreatitis was reported for only one of these patients. The positive predictive value of lipase elevations ≥2 × upper limit of the normal range for the diagnosis of acute pancreatitis was thus very low (<1%), and the cause of lipase fluctuations is presently unknown. Importantly, in this trial of approximately 900 patient-years of exposure, the four pancreatitis cases are probably in line with the background pancreatitis incidence in T2D (~4 cases/1000 patient-years) (Noel, Braun, Patterson, & Bloomgren, 2009). Moreover, in an independent post-hoc adjudication of pancreatitis cases occurring during T2D clinical trials with liraglutide, the majority did not meet diagnostic criteria (Steinberg et al., 2012). Nevertheless, vigilance for pancreatitis remains a prudent approach for clinicians prescribing GLP-1 RAs until a robust answer is hopefully obtained from the large long-term safety outcomes trials being undertaken with these compounds (e.g. ClinicalTrials.gov, 2012a [NCT01179048]; (ClinicalTrials.gov, 2012b [NCT01144338]).

The strengths of the present study include the longer term (>1 year) investigation period and use of pre-defined protocol endpoints/analyses. Additionally, the stepwise treatment intensification mirrors the approach used in clinical practice: the addition of a second, typically non-insulin, anti-hyperglycemic agent after metformin failure, followed by a third-line therapy (in this case, basal insulin) in patients failing to meet glycemic targets using two-agent combinations. Moreover, with the particular treatment sequence employed here, patients are able to adapt to the requirements of a once-daily injectable treatment before initiating further (insulin) injections. Liraglutide treatment also does not require frequent self-monitoring of blood glucose and does not carry the same hypoglycemia risk as prandial insulin therapy. By avoiding the weight gain usually associated with initiating insulin, improved treatment compliance and duration of glycemic control might be anticipated. Trial limitations include the absence of placebo or active comparators in the RC group. As the first investigation of liraglutide in combination with insulin in T2D, the emphasis was on safety and no active comparator was included. However, as safety was confirmed to be good and the hypoglycemia risk very low, future investigations need to include an active comparator for higher prioritization of efficacy. A trial investigating the addition of liraglutide to basal insulin is already underway (ClinicalTrials.gov, 2012c [NCT01617434]). Studies analyzing the cost–benefit outcomes could also be very valuable. Ideally, such studies should include not only medication costs, but also the overall, long-term savings in medical and hospital costs that may result from a lower risk of hypoglycemia and potentially a lower risk of complications associated with sustained treatment adherence and glycemic control.

In summary, intensification of metformin treatment with the once-daily GLP-1RA liraglutide enabled the majority of patients previously inadequately controlled with metformin ± sulfonylurea to reach the ADA/EASD target HbA_{1c} of 7.0% after 12 weeks, with glycemic and weight reductions sustained over the subsequent 52 weeks of continued treatment. Further treatment intensification with insulin detemir for patients with HbA_{1c} remaining ≥7.0% after 12 weeks of metformin + liraglutide 1.8 mg resulted in additional sustained improvement in glycemic control with a very low hypoglycemia rate and maintenance of pre-intensification weight reduction over 52 weeks.

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Appendix A. Supplementary data

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