

## A Patient-level Analysis of Efficacy and Hypoglycaemia Outcomes Across Treat-to-target Trials with Insulin Glargine Added to Oral Antidiabetes Agents in People with Type 2 Diabetes

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### Abstract

**Background:** A better understanding of hypoglycaemia risk when insulin is used in combination with one or more oral antidiabetes agents may assist in the treatment decision-making process for the clinician and address concerns regarding hypoglycaemia when initiating or intensifying insulin therapy. The objective of this study was to analyse efficacy and hypoglycaemia outcomes in people with type 2 diabetes receiving insulin glargine (IG) with metformin (MET), sulphonylurea (SU) or MET+SU. **Methods:** Patient-level data were pooled from 15 randomised, treat-to-target trials (fasting plasma glucose [FPG] targets <5.6 mmol/l) with a duration ≥24 weeks. Efficacy outcomes included glycated haemoglobin (HbA<sub>1c</sub>), FPG and HbA<sub>1c</sub> target achievement. Overall hypoglycaemia events were assessed by a confirmed PG value of <3.9, <3.1 and <2.8 mmol/l or assistance required; daytime, nocturnal (00:01–05:59 AM); and severe (assistance required or with confirmed PG <2.0 mmol/l). **Results:** Overall, 2,837 IG patients were analysed, with either MET (634), SU (906) or MET+SU (1,297) as background oral antidiabetes agents. Endpoint HbA<sub>1c</sub> in IG+MET and IG+MET+SU-treated patients was significantly lower than in IG+SU-treated patients (adjusted difference –0.32 %; p=0.0001 and –0.33 %; p=0.0002, respectively). Fewer patients achieved endpoint HbA<sub>1c</sub> <7.0 % with IG+SU (32 %) versus IG+MET (57 %) or IG+MET+SU (49 %). IG+SU and IG+MET+SU led to significant increases in overall, daytime and nocturnal hypoglycaemia versus IG+MET; severe hypoglycaemia was rare. Weight gain was lowest in IG+MET patients (adjusted difference –1.51 kg versus IG+SU; p<0.0001; –0.78 kg versus IG+MET+SU; p=0.0037) despite higher insulin doses (0.51 U/kg versus 0.43 and 0.42 U/kg, respectively). **Conclusions:** Better glycaemic goal achievement and reduced risk of hypoglycaemia and weight gain were observed with IG+MET versus IG+SU and IG+MET+SU, albeit with an increased insulin dose requirement.

### Keywords

Insulin therapy, type 2 diabetes, metformin, sulphonylurea

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Maintaining appropriate glycaemic control in type 2 diabetes can prevent or delay the development and progression of diabetes

complications.<sup>1–3</sup> Initial pharmacological treatment usually begins with metformin (MET), with a second agent being added once monotherapy

**Table 1: Summary of 15 Treat-to-target Trials Included in the Pooled Analyses**

Study	Phase	Treatment <sup>a</sup>	Number of Patients	Treatment Period (Weeks)	Goal Blood Glucose for Insulin Glargine (mmol/l)	Insulin Titration Schedule
<b>IG+MET Studies</b>						
LANTU_C_02761 (EASIE) <sup>1</sup>	IIIb/IV	IG+MET vs. SITA+MET	515	24	≤5.6	Twice weekly
4020 <sup>2</sup>	IIIb	IG+SU or MET vs. PIO+SU or MET	389	24 extended to 48	≥3.9 and ≤5.6 (weeks 0–24) ≥3.9 and ≤5.2 (weeks 25–48)	Weekly
4022 <sup>3</sup>	IIIb	IG+SU or MET vs. TZD+SU+MET	337	24 extended to 48	≥4.0 and ≤5.6 (weeks 0–24) ≥3.9 and ≤5.2 (weeks 25–48)	Weekly
LANTU_C_00579 (L2T3) <sup>4</sup>	IV	IG+OADs vs. DET+OADs	973	24	≤5.6	Every 2 days
3502 (INSIGHT) <sup>5,6</sup>	IIIb	IG+current OADs vs. current OADs	405	24	≤5.6	Daily
<b>IG+SU Studies</b>						
4001 <sup>6</sup>	IIIb	IG+GLI vs. NPH insulin+GLI	695	24	≤5.6	Weekly
4009 <sup>7</sup>	IIIb	Morning vs. bedtime IG+morning GLI	624	24	≤5.6	Weekly
4013 <sup>8</sup>	IIIb	IG+GLI vs. NPH insulin+GLI	481	24	≤5.6	Weekly
<b>IG+MET+SU Studies</b>						
4002 (TTT) <sup>9</sup>	IIIb	IG+OADs vs. NPH insulin+OADs	764	24	≤5.6	Weekly
4014 (TRIPLE) <sup>10</sup>	IIIb	IG+SU+MET vs. ROS+SU+MET	219	24	≤5.6	Weekly
4021 <sup>11</sup>	IIIb	IG+SU+MET vs. LIS 75/25+SU+MET	212	24	≤5.6	Weekly
4027 (LAPTOP) <sup>12</sup>	IIIb	IG+GLI+MET vs. premixed NPH insulin 30/70	371	24	≤5.6	Weekly for first 8 weeks, then at 2-week intervals
4040 (APOLLO) <sup>13</sup>	IV	IG+OADs vs. LIS+OADs	415	44	≤5.6	Weekly
4041 (INITIATE) <sup>14</sup>	IV	IG with group education+OADs vs. IG with individual education+OADs	121	24	4.0–5.5	Self-titration, then investigator-reviewed at each visit
4042 (TULIP) <sup>15</sup>	IV	IG+OADs vs. hygienic and dietary measures+OADs	215	40	3.9–5.6	Every 2 days

<sup>a</sup>From the insulin glargine (IG) arms of each of the considered studies, the pool for analysis was composed of patients treated with IG+metformin (MET), IG+sulphonylurea (SU) or IG+MET+SU. <sup>b</sup>Also included in the analysis of IG+SU studies. <sup>c</sup>Also included in the analysis of IG+MET+SU studies. DET = insulin detemir; GLI = glimepiride; LIS = insulin lispro; NPH = neutral protamine hagedorn (intermediate-acting insulin); OAD = oral antidiabetic drugs; PIO = pioglitazone; ROS = rosiglitazone; SITA = sitagliptin; TZD = thiazolidinedione.

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is insufficient to provide adequate glycaemic control.<sup>3</sup> Over time, a substantial proportion of patients will ultimately require insulin therapy to maintain glucose control.<sup>3–5</sup> MET is usually maintained and whether sulphonylurea (SU) should be discontinued or maintained at the start of insulin therapy is an unresolved matter.<sup>6</sup>

When selecting glucose-lowering agents to achieve glycaemic targets, several factors should be taken into consideration, including the glucose-lowering potential of the agent, the risk of hypoglycaemia, weight gain, tolerability and costs. Hypoglycaemia can influence well-being, quality of life and cause anxiety.<sup>7</sup> Fear of hypoglycaemia may represent a barrier to some physicians who might be reluctant to prescribe insulin<sup>8</sup> or delay initiating insulin.<sup>9,10</sup> It is also a commonly quoted reason for patient reluctance to accept insulin<sup>11</sup> or intensify their insulin regimen.<sup>12,13</sup>

The definition of hypoglycaemia in clinical trials is based on symptoms (including severity), blood glucose levels and the timing of the event. In symptomatic events, the patient displays one or more symptoms of hypoglycaemia; in confirmed events, a 'low' blood glucose measurement is documented; and severe events usually require 'third-party assistance' with or without blood glucose measurements and prompt recovery on

countermeasures.<sup>14</sup> In addition, hypoglycaemic events can be classified as daytime or nocturnal events. Reporting of data on hypoglycaemia across randomised controlled trials investigating the use of basal insulin analogues in type 2 diabetes has not been standardised, with various definitions and blood glucose cutoffs utilised within the literature.<sup>15</sup> In addition, the collection of hypoglycaemia data is often incomplete and relies on patient reporting and transcription of events. This can make the interpretation of data on hypoglycaemia problematic.<sup>16</sup>

The use of standardised endpoints to define clinical hypoglycaemia could enable physicians to make informed treatment decisions based on the risks and benefits of therapy. A better understanding of the hypoglycaemia risk when insulin is used in combination with one or more glucose-lowering agents may further inform the treatment decision-making process for the clinician, and address concerns regarding hypoglycaemia when initiating or intensifying insulin therapy.

The aim of this pooled analysis of patient-level data was to investigate efficacy (glycated haemoglobin [HbA<sub>1c</sub>], responder rate, fasting plasma glucose [FPG]) and safety outcomes (hypoglycaemia, weight) of insulin-naïve people with type 2 diabetes included in treat-to-target randomised

**Table 2: Demographics and Baseline Characteristics of Study Population**

	IG+MET	IG+SU	IG+MET+SU	Pooled	IG+MET vs. IG+SU p value	Comparison IG+MET vs. IG+MET+SU p value	IG+SU vs. IG+MET+SU p value
<b>n</b>	<b>634</b>	<b>906</b>	<b>1,297</b>	<b>2,837</b>			
Age, years	54.7±9.6	59.1±10.2	58.2±9.3	57.7±9.8	<0.0001	<0.0001	0.03
Male sex, n (%)	330 (52.1)	488 (53.9)	708 (54.6)	1,526 (53.8)	0.50	0.31	0.74
Type 2 diabetes duration, years	7.3±5.7	9.5±6.6	9.5±6.3	9.0±6.4	<0.0001	<0.0001	0.99
Weight, kg	88±19.7	82.2±18	88.9±17.4	86.6±18.4	<0.0001	0.29	<0.0001
BMI, kg/m <sup>2</sup>	31.5±5.8	29.1±5.2	31.2±5.0	30.6±5.3	<0.0001	0.25	<0.0001
HbA <sub>1c</sub> , %	8.7±1.1	9.0±1.1	8.7±1.0	8.8±1.1	<0.0001	0.11	<0.0001
FPG, mmol/l	10.5±3.2	11.4±3.2	10.7±2.9	10.9±3.1	<0.0001	0.10	<0.0001

Values are mean ± standard deviation unless otherwise noted. p values are from analysis of variance models including treatment group as a factor and for gender variable; p value is from a logistic model including treatment group as a factor. BMI = body mass index; FPG = fasting plasma glucose; HbA<sub>1c</sub> = glycated haemoglobin; IG = insulin glargine; MET = metformin; SU = sulphonylurea.

controlled studies who received insulin glargine (IG) once-daily at bedtime in combination with different oral antidiabetes drugs (OADs). We compared the profile and outcomes of patients treated with IG and MET (IG+MET) with those treated with IG and a SU (IG+SU) and those treated with IG+MET+SU.

## Methods

### Study Selection and Population

Eligibility criteria were prospective, randomised, controlled, treat-to-target trials with protocol-driven titration algorithms targeting FPG levels <5.6 mmol/l (<100 mg/dl) with a duration ≥24 weeks. Studies enrolled insulin-naïve adult patients with type 2 diabetes, who all initiated IG in combination with their current OADs according to the study protocols. For the analysis of IG+MET, studies had to include an arm or predefined subpopulation that was treated with only IG+MET. Similarly, for the analyses of IG+SU and IG+MET+SU, the studies had to include an arm or predefined subpopulation who received only these treatments for the entire study period. Comparator controls included either OAD combination therapy, other insulin treatment with OADs or lifestyle interventions only. The analysis considered only studies conducted by the manufacturer of IG (i.e., Sanofi or its predecessor companies) and those in accordance with Good Clinical Practice (GCP) guidelines where detailed information based on individual patient-level data for efficacy and hypoglycaemia were available.

Overall, 15 studies fulfilled all of the inclusion criteria, of which 13 have been published (see Table 1). Two studies were eligible for both the analysis of IG+MET and IG+MET+SU, two studies for the analysis of IG+MET and IG+SU and one study for the analysis of IG+SU and IG+MET+SU. The analysis of IG+MET included patients previously treated with MET who were subsequently treated with IG+MET for the 24-week treatment period. Moreover, patients who received antidiabetes treatments other than IG+MET from the point of randomisation up to and including the day after the end of the 24-week treatment period, or who did not receive both IG and MET were excluded from the analysis pool. Similarly, the analyses of IG+SU and IG+MET+SU only included patients who were previously treated with these OAD combinations, and those who were subsequently treated with only these OADs in combination with IG during the randomised treatment period.

### Efficacy Outcomes

Efficacy was evaluated using the following outcomes: endpoint and change from baseline to endpoint in HbA<sub>1c</sub> level, the percentage of patients achieving an HbA<sub>1c</sub> level <7.0 % at week 24 and endpoint and the change from baseline to endpoint in FPG level. Endpoint was

**Table 3: Efficacy Outcomes and Insulin Dose at Endpoint**

	IG+MET	IG+SU	IG+MET+SU	Pooled
<b>n</b>	<b>593</b>	<b>867</b>	<b>1,268</b>	<b>2,728</b>
Week 24 HbA <sub>1c</sub> (%)	7.0±1.0	7.6±1.2	7.1±0.9	7.2±1.0
Change in HbA <sub>1c</sub> from baseline to endpoint (%)	-1.7±1.2	-1.4±1.2	-1.6±1.0	-1.6±1.2
Patients with HbA <sub>1c</sub> <7.0 % at endpoint, n (%) <sup>a</sup>	336 (56.8)	270 (31.5)	620 (49.3)	1,226 (45.3)
<b>n</b>	<b>583</b>	<b>884</b>	<b>1,252</b>	<b>2,719</b>
Week 24 FPG (mmol/l)	6.2±2.0	6.8±2.2	6.7±2.1	6.6±2.2
Change in FPG from baseline to endpoint (mmol/l)	-4.1±3.2	-4.6±3.6	-4.0±3.2	-4.2±3.4
<b>n</b>	<b>634</b>	<b>906</b>	<b>1,297</b>	<b>2,837</b>
Week 24 insulin dose (U/kg)	0.51±0.27	0.43±0.24	0.42±0.25	0.44±0.26
Change in insulin dose from baseline to endpoint (U/kg)	0.35±0.28	0.23±0.23	0.29±0.25	0.28±0.25

Values are mean ± standard deviation unless otherwise noted. <sup>a</sup>Limited to patients with baseline glycated haemoglobin (HbA<sub>1c</sub>) ≥7.0 %. FPG = fasting plasma glucose; IG = insulin glargine; MET = metformin; SU = sulphonylurea.

defined as the last on-treatment measurement up to and including week 24 plus 14 days for HbA<sub>1c</sub> and plus 1 day for FPG.

### Hypoglycaemia Outcomes

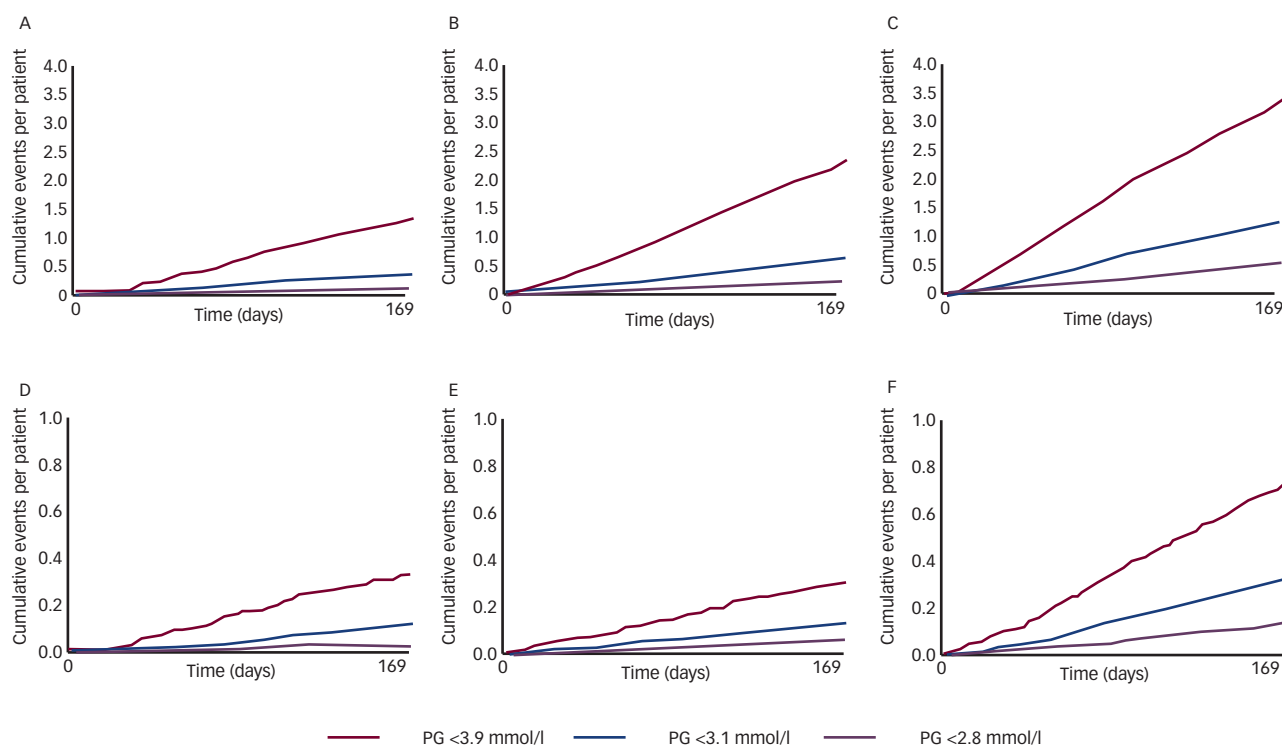
Numbers of confirmed hypoglycaemic events were determined by using several PG cutoffs : PG <3.9 mmol/l (<70 mg/dl), <3.1 mmol/l (<56 mg/dl) and <2.8 mmol/l (<50 mg/dl), respectively. These categories were also analysed by time of occurrence during the day: at any time of the day (defined as PG-confirmed events over 24 hours), daytime (PG-confirmed events occurring between 06:00 and midnight) and nocturnal (PG-confirmed events between 00:01 and 05:59). In addition, a severe hypoglycaemic event was assessed using two definitions irrespective of time of occurrence: events requiring third-party assistance) and events requiring third-party assistance with documented PG <2.0 mmol/l (<36 mg/dl).

Overall hypoglycaemia occurring at any time of the day included PG-confirmed events or severe events requiring third-party assistance (without a documented PG value). Daytime and nocturnal hypoglycaemia analysis excluded any severe events.

### Composite Outcomes and Body Weight

The percentage of patients achieving an HbA<sub>1c</sub> level <7.0 % at week 24 without overall or nocturnal hypoglycaemia with PG <3.9 mmol/l and

**Figure 1: Cumulative Numbers of Overall and Nocturnal Hypoglycaemia Events per Patient Over Time for IG+MET (A and D, Respectively), IG+SU (B and E, Respectively) and IG+MET+SU (C and F, Respectively) Treatment Groups**



Plasma glucose (PG)  $<3.9\text{ mmol/l} = <70\text{ mg/dl}$ ;  $PG <3.1\text{ mmol/l} = <56\text{ mg/dl}$ ;  $PG <2.8\text{ mmol/l} = <50\text{ mg/dl}$ . IG = insulin glargine; MET = metformin; SU = sulphonylurea.

$<3.1\text{ mmol/l}$  over the treatment period are reported. Weight data were analysed for patients treated with IG+MET, IG+SU or IG+MET+SU.

retained in the final model as appropriate. A p value of  $\leq 0.05$  was considered to be statistically significant.

## Statistical and Analytical Procedures

Baseline and week 24 patient-level data for patients treated with IG+MET, IG+SU and IG+MET+SU were pooled and analysed from all patients who were randomised and who subsequently received  $\geq 1$  dose of IG and the OADs as defined for the subpopulation of interest. Continuous efficacy endpoints of HbA<sub>1c</sub>, dose and weight at endpoint were analysed using generalised linear models with adjustments for OAD treatment group, study, duration of diabetes, body mass index (BMI), age and baseline value. For the outcome of achievement of HbA<sub>1c</sub>  $<7.0\%$  at endpoint, odds ratios (ORs) for pairs of OAD treatment groups were derived from a logistic model, adjusting for the same factors as in the continuous model.

All hypoglycaemic events experienced up to and including 1 day after the end of the treatment period (day of last dose or week 24, whichever came first) were considered for analysis. Hypoglycaemic events were summarised by categories using descriptive statistics, including the number and percentage of patients with  $\geq 1$  event (incidence), the total number of episodes and the annualised rate (events/patient-year). The incidence and annualised rate of hypoglycaemic events for each OAD treatment group were estimated and analysed using logistic and negative binomial regression, respectively. In both cases, BMI and duration of diabetes were pre-specified factors and were included for all hypoglycaemia categories for which there were sufficient data. Other potential prognostic factors (including age, gender, HbA<sub>1c</sub> at baseline, OAD treatment group, study and interaction of duration of diabetes and OAD treatment group) were considered for inclusion in the model using univariate analyses and multivariate model selection and were

The cumulative number of hypoglycaemia events per patient over time (by study day) was also determined. The relationship between hypoglycaemia and glycaemic outcomes at study end was also investigated using binomial meta-regression techniques.<sup>17</sup> Regression coefficients for HbA<sub>1c</sub> and FPG at endpoint were used to model event rates per patient-year for HbA<sub>1c</sub> and FPG values reported at endpoint.

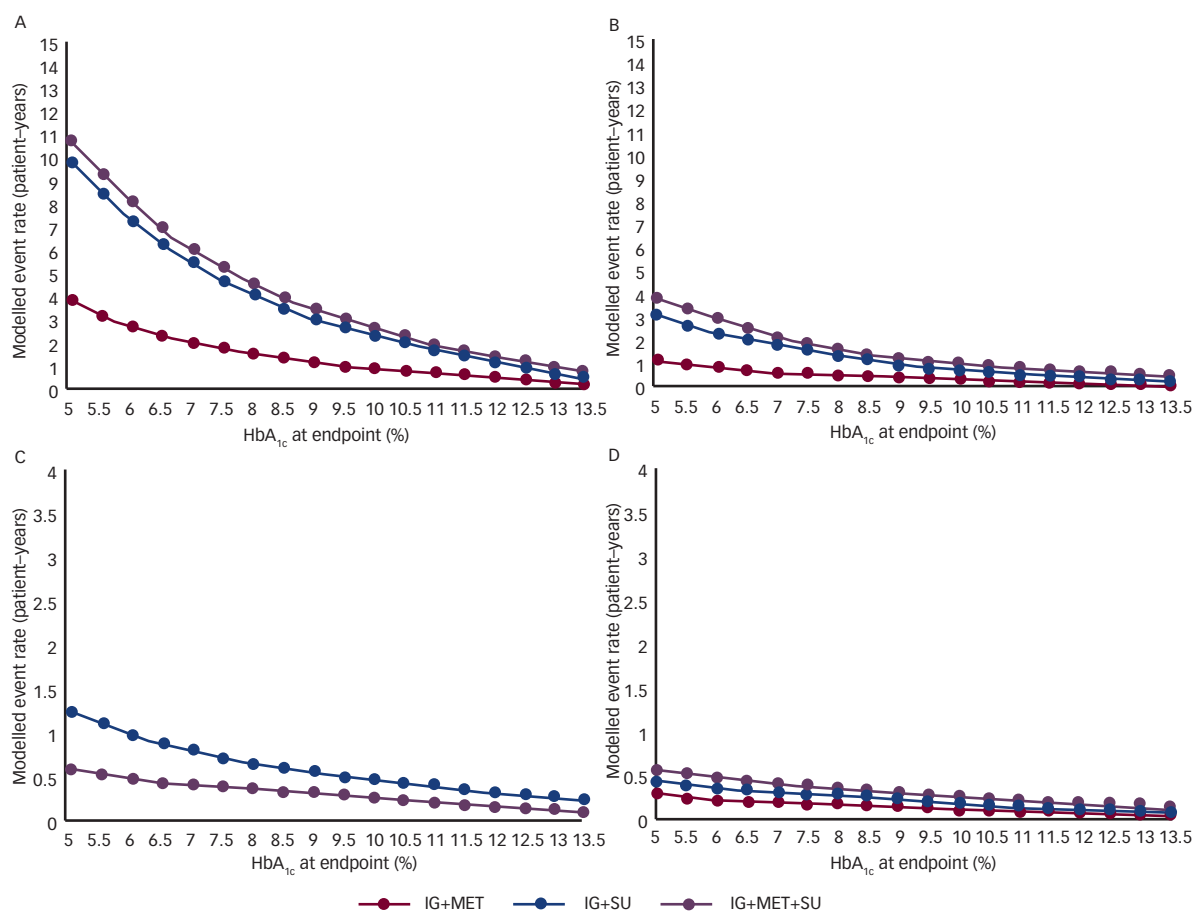
## Results Patients

Out of the patients who were treated with IG, 44 patients were excluded from analysis as they did not receive any of the prespecified background OAD medication. Another 34 patients were also excluded from the analysis as they referred to four study sites that were non-compliant to GCP guidelines. As a result, a total of 2,837 patients treated with IG were eligible for analysis according to OAD background medication: 634 patients treated with IG+MET, 906 patients treated with IG+SU and 1,297 patients treated with IG+MET+SU. Patients in the latter two treatment groups were significantly older ( $p < 0.0001$  for both;  $p = 0.0302$  for IG+SU versus IG+MET+SU) and had a longer duration of type 2 diabetes ( $p < 0.0001$  for both). In IG+SU-treated patients, baseline HbA<sub>1c</sub> and FPG levels were significantly higher (all  $p < 0.0001$ ), and weight and BMI significantly lower (all  $p < 0.0001$ ) compared with the other two treatment groups (see Table 2).

## Efficacy

Efficacy outcomes are summarised in Table 3. The IG+MET and IG+MET+SU treatment groups had similar endpoint HbA<sub>1c</sub> levels (7.0% and 7.1%, respectively) and a similar change in HbA<sub>1c</sub> level

**Figure 2: Modelled Adjusted Overall (PG <3.9 mmol/l [A] and PG <3.1 mmol/l [B]) and Nocturnal (PG <3.9 mmol/l [C] and PG <3.1 mmol/l [D]) Hypoglycaemia Event Rates for HbA<sub>1c</sub> Values Reported at Endpoint**



PG <3.9 mmol/l = <70 mg/dl; PG <3.1 mmol/l = <56 mg/dl. IG = insulin glargine; MET = metformin; PG = plasma glucose; SU = sulphonylurea.

from baseline to endpoint ( $-1.7\%$  and  $-1.6\%$ , respectively). Patients in the IG+SU treatment group had an endpoint HbA<sub>1c</sub> level of  $7.6\%$  and a change in HbA<sub>1c</sub> level from baseline to endpoint of  $-1.4\%$ . In the adjusted model, taking into account baseline HbA<sub>1c</sub>, endpoint HbA<sub>1c</sub> levels in the IG+MET and IG+MET+SU treatment groups were significantly lower and change from baseline to endpoint HbA<sub>1c</sub> levels significantly higher than in the IG+SU treatment group (difference for both:  $-0.32\%$ , 95% confidence interval [CI]  $-0.48$  to  $-0.16$ ;  $p=0.0001$  and  $-0.33\%$ ; 95% CI  $-0.51$  to  $-0.16$ ;  $p=0.0002$ , respectively). The proportion of patients with HbA<sub>1c</sub> <7.0% at week 24 was 57%, 32% and 49% in the IG+MET, IG+SU and IG+MET+SU treatment groups, respectively. Patients in the IG+MET treatment group were significantly more likely to achieve an HbA<sub>1c</sub> <7.0% at week 24 than patients in the IG+SU treatment group (OR 2.00, 95% CI 1.29–3.12). For the comparison of HbA<sub>1c</sub> achievement between patients treated with IG+MET+SU versus IG+SU, the OR was 1.66, 95% CI 0.99–2.80. Endpoint FPG levels were 6.2, 6.7 and 6.7 mmol/l in the IG+MET, IG+SU and IG+MET+SU treatment groups, respectively. In the adjusted model, taking into account baseline FPG, endpoint FPG level was significantly lower and change from baseline to endpoint in FPG level significantly higher in the IG+MET treatment group than in the IG+SU and IG+MET+SU treatment groups (difference for both:  $-0.82$  mmol/l, 95% CI  $-1.17$  to  $-0.47$ ;  $p<0.0001$  and  $-0.53$  mmol/l, 95% CI  $-0.83$  to  $-0.23$ ;  $p=0.0005$ , respectively). The insulin dose at endpoint was 0.51, 0.43 and 0.42 U/kg in the IG+MET, IG+SU and IG+MET+SU treatment groups, respectively.

In the adjusted model, insulin dose at endpoint was significantly greater in the IG+MET treatment group compared with the IG+MET+SU treatment group (difference in adjusted endpoint dose: 0.06 U/kg, 95% CI 0.02–0.09;  $p=0.0026$ ) and numerically greater compared with the IG+SU group (0.01 U/kg, 95% CI  $-0.03$  to 0.06;  $p=0.5067$ ).

### Hypoglycaemia Rates and Incidence

Adjusted pooled incidences and event rates of overall, daytime, nocturnal and severe hypoglycaemia are shown in Table 4a and 4b. IG+SU and IG+MET+SU showed significant observed increases in overall, daytime and nocturnal hypoglycaemia rates (up to threefold compared with IG+MET). Daytime and nocturnal hypoglycaemia incidence was also increased in patients treated with IG+MET+SU and IG+SU compared with patients treated with IG+MET. Severe hypoglycaemia with IG was rare, with no significant differences observed in event rate or incidence between the three treatment groups (see Table 4a and 4b). A similar pattern of increased hypoglycaemia with IG+SU and IG+MET+SU compared with IG+MET was observed in the unadjusted data. The cumulative numbers of overall and nocturnal hypoglycaemia events per patient over time for the IG+MET, IG+SU and IG+MET+SU treatment groups are shown in Figure 1.

Binomial meta-regression revealed that, in patients treated with IG+MET, IG+SU and IG+MET+SU, both overall and nocturnal hypoglycaemia event rates increased in patients who achieved lower endpoint HbA<sub>1c</sub> levels



**Table 4a: Adjusted Pooled Incidence of Overall, Daytime, Nocturnal and Severe Hypoglycaemia**

Hypoglycaemia Category	Adjusted Mean Incidence ± SE, %				Difference					
	IG+MET	IG+SU	IG+MET+SU Pooled	2,837	IG+MET vs. IG+SU	IG+MET vs. IG+MET+SU	IG+SU vs. IG+MET+SU			
n	634	906	1,297	2,837	Odds Ratio (95 % CI)	Odds Ratio (95 % CI)	Odds Ratio (95 % CI)	p value	p value	
Overall, <sup>a</sup> PG <3.9 mmol/l	37.0±3.0	52.0±4.4	50.7±2.6	46.5±1.4	0.54 (0.35–0.83)	0.57 (0.41–0.81)	1.06 (0.64–1.75)	0.005	0.001	0.832
Overall, <sup>a</sup> PG <3.1 mmol/l	16.3±2.3	30.1±4.5	34.1±2.7	26.0±1.3	0.45 (0.26–0.80)	0.38 (0.25–0.57)	0.83 (0.45–1.54)	0.006	<0.001	0.554
Overall, <sup>a</sup> PG <2.8 mmol/l	11.8±2.0	15.8±3.6	20.7±2.4	15.8±1.1	0.71 (0.36–1.40)	0.51 (0.32–0.83)	0.72 (0.34–1.53)	0.326	0.007	0.392
Daytime, <sup>a</sup> PG <3.9 mmol/l	30.8±2.9	46.3±4.5	45.0±2.6	40.5±1.4	0.52 (0.33–0.81)	0.55 (0.38–0.78)	1.05 (0.63–1.76)	0.004	<0.001	0.843
Daytime, <sup>a</sup> PG <3.1 mmol/l	11.8±2.0	23.8±4.3	27.2±2.6	20.0±1.2	0.43 (0.23–0.80)	0.36 (0.22–0.57)	0.83 (0.42–1.64)	0.008	<0.001	0.600
Daytime, <sup>a</sup> PG <2.8 mmol/l	7.0±1.6	11.9±3.2	15.4±2.2	10.9±0.9	0.56 (0.25–1.24)	0.41 (0.22–0.76)	0.74 (0.31–1.77)	0.152	0.004	0.496
Nocturnal, <sup>b</sup> PG <3.9 mmol/l	11.5±1.8	15.0±3.5	17.5±2.1	14.5±1.0	0.74 (0.37–1.47)	0.61 (0.40–0.94)	0.83 (0.39–1.77)	0.384	0.026	0.628
Nocturnal, <sup>b</sup> PG <3.1 mmol/l	4.8±1.2	5.4±2.3	11.3±2.1	6.7±0.7	0.88 (0.29–2.73)	0.40 (0.22–0.72)	0.45 (0.13–1.49)	0.830	0.003	0.189
Nocturnal, <sup>b</sup> PG <2.8 mmol/l	4.0±1.2	2.2±1.3	6.4±1.6	3.8±0.6	1.88 (0.38–9.28)	0.61 (0.30–1.25)	0.33 (0.06–1.72)	0.438	0.178	0.187
Severe, <sup>c</sup> (third-party assistance required)	2.2±0.6	2.2±0.5	1.9±0.4	2.1±0.3	0.99 (0.49–1.99)	1.15 (0.59–2.25)	1.17 (0.64–2.12)	0.966	0.683	0.611
Severe, <sup>c</sup> (third-party assistance required and PG <2.0 mmol/l)	0.4±0.3	0.3±0.2	0.07±0.1	0.2±0.1	1.49 (0.28–7.80)	5.75 (0.58–56.68)	3.86 (0.39–38.16)	0.638	0.134	0.247

**Table 4b: Adjusted Pooled Event Rates of Overall, Daytime, Nocturnal and Severe Hypoglycaemia**

Hypoglycaemia Category	Adjusted Mean Event Rate ± SE, Events/Patient-Year				Difference					
	IG+MET	IG+SU	IG+MET+SU Pooled	2,837	IG+MET vs. IG+SU	IG+MET vs. IG+MET+SU	IG+SU vs. IG+MET+SU			
n	634	906	1,297	2,837	Rate Ratio (95 % CI)	Rate Ratio (95 % CI)	Rate Ratio (95 % CI)	p value	p value	
Overall, <sup>a</sup> PG <3.9 mmol/l	2.05±0.24	5.03±0.84	5.78±0.55	3.90±0.21	0.41 (0.27–0.61)	0.35 (0.26–0.48)	0.87 (0.54–1.40)	<0.001	<0.001	0.572
Overall, <sup>a</sup> PG <3.1 mmol/l	0.64±0.10	1.60±0.34	2.16±0.26	1.30±0.09	0.40 (0.23–0.68)	0.29 (0.20–0.44)	0.74 (0.40–1.36)	<0.001	<0.001	0.331
Overall, <sup>a</sup> PG <2.8 mmol/l	0.34±0.07	0.57±0.15	1.04±0.15	0.59±0.05	0.60 (0.31–1.19)	0.33 (0.20–0.54)	0.55 (0.26–1.17)	0.144	<0.001	0.119
Daytime, <sup>a</sup> PG <3.9 mmol/l	1.55±0.20	3.55±0.65	4.84±0.50	2.99±0.17	0.44 (0.28–0.67)	0.32 (0.23–0.45)	0.73 (0.44–1.24)	<0.001	<0.001	0.244
Daytime, <sup>a</sup> PG <3.1 mmol/l	0.40±0.07	1.00±0.24	1.72±0.23	0.88±0.07	0.40 (0.22–0.73)	0.23 (0.14–0.37)	0.58 (0.29–1.15)	0.003	<0.001	0.116
Daytime, <sup>a</sup> PG <2.8 mmol/l	0.21±0.05	0.41±0.13	0.68±0.12	0.39±0.04	0.51 (0.23–1.13)	0.30 (0.16–0.56)	0.60 (0.24–1.47)	0.096	<0.001	0.264
Nocturnal, <sup>b</sup> PG <3.9 mmol/l	0.37±0.07	0.75±0.21	0.79±0.12	0.60±0.05	0.48 (0.24–0.98)	0.46 (0.29–0.73)	0.96 (0.44–2.10)	0.045	<0.001	0.916
Nocturnal, <sup>b</sup> PG <3.1 mmol/l	0.18±0.04	0.25±0.10	0.36±0.07	0.25±0.03	0.71 (0.25–2.06)	0.49 (0.27–0.86)	0.68 (0.22–2.15)	0.529	0.013	0.513
Nocturnal, <sup>b</sup> PG <2.8 mmol/l	0.11±0.04	0.05±0.03	0.24±0.07	0.11±0.02	2.30 (0.43–12.22)	0.44 (0.21–0.95)	0.19 (0.03–1.12)	0.327	0.038	0.067
Severe, <sup>c</sup> (third-party assistance required)	0.07±0.03	0.10±0.03	0.10±0.03	0.09±0.02	0.71 (0.28–1.81)	0.76 (0.29–1.95)	1.07 (0.46–2.48)	0.470	0.565	0.870
Severe, <sup>c</sup> (third-party assistance required and PG <2.0 mmol/l)	0.010±0.006	0.007±0.004	0.002±0.002	0.005±0.002	1.35 (0.26–6.90)	6.05 (0.62–59.45)	4.49 (0.47–43.21)	0.721	0.123	0.193

Hypoglycaemia incidences and event rates estimated and analysed using negative binomial regression. Plasma glucose (PG) <3.9 mmol/l = <70 mg/dl; PG <3.1 mmol/l = <56 mg/dl; PG <2.8 mmol/l = <50 mg/dl; PG <2.0 mmol/l = <36 mg/dl. <sup>a</sup>Adjusting for baseline body mass index (BMI), duration of diabetes, age, oral antidiabetes drug (OAD) treatment group, study and interaction of duration of diabetes and OAD treatment group. <sup>b</sup>Adjusting for baseline BMI, duration of diabetes, age, OAD treatment group and study. <sup>c</sup>Adjusting for baseline BMI, duration of diabetes, age and OAD treatment group. <sup>d</sup>Adjusting for duration of diabetes, age and OAD treatment group. IG = insulin glargine; MET = metformin; SE = standard error; SU = sulphonylurea.

(see Figure 2). A similar pattern was observed for overall and nocturnal hypoglycaemia event rates according to FPG levels achieved at endpoint. Modelled hypoglycaemia event rates were consistently higher in patients treated with IG+MET+SU and IG+SU compared with IG+MET. This was observed regardless of the hypoglycaemia definition and PG cutoff used, but increased rates were most marked for overall and nocturnal hypoglycaemia event rates with documented PG <3.9 mmol/l.

### Glycated Haemoglobin <7.0 % without Hypoglycaemia

In the group of patients treated with IG+MET, 36.0 % and 44.9 % achieved an HbA<sub>1c</sub> <7.0 % without overall hypoglycaemia with PG <3.9 mmol/l and <3.1 mmol/l, respectively. This rate was higher than that observed in patients treated with IG+SU (17.5 % and 24.2 %, respectively) and patients treated with IG+MET+SU (17.4 % and 26.5 %, respectively). A similar pattern was observed when examining achievement of HbA<sub>1c</sub> <7.0 % without nocturnal hypoglycaemia with PG <3.9 mmol/l and <3.1 mmol/l (IG+MET: 48.0 % and 52.9 %, respectively; IG+SU: 27.0 % and 29.4 %, respectively; and IG+MET+SU: 35.8 % and 40.0 %, respectively).

### Body Weight

Weight increased from baseline to week 24 in all three treatment groups (0.8±4.0 kg for IG+MET, 2.8±3.9 kg for IG+SU and 2.0±3.4 kg for IG+MET+SU). In the adjusted model, weight gain was significantly lower in patients treated with IG+MET compared with IG+SU and IG+MET+SU (difference in adjusted change from baseline weight: -1.51 kg, 95 % CI -2.13 to -0.88; p<0.0001; and -0.78 kg, 95 % CI -1.30 to -0.25; p=0.0037, respectively) and also in patients treated with IG+MET+SU compared with IG+SU (-0.73 kg, 95 % CI -1.40 to -0.06; p=0.0329).

### Discussion

Hypoglycaemia is a substantial complication in the treatment of type 2 diabetes. The risk and severity of hypoglycaemia increase with disease duration and intensification or duration of insulin treatment.<sup>1,18-20</sup> Severe hypoglycaemia can lead to seizures and coma, and has been reported to be associated with an increased risk of macrovascular events, microvascular events and all-cause death.<sup>21,22</sup> Non-severe hypoglycaemia is also associated with a significant reduction in quality of life and accounts for a substantial reduction in work productivity.<sup>23-25</sup>

The current pooled, post hoc analysis of patient-level data from 15 randomised, controlled, treat-to-target studies of IG with OADs illustrates that in this patient population, regimens where a SU is utilised are associated with a reduced proportion of patients reaching target HbA<sub>1c</sub> levels and a greater risk of overall, daytime and nocturnal hypoglycaemia, along with greater weight gain. The insulin dose at endpoint was significantly greater in the IG+MET treatment group, which could indicate that a SU limits the amount of insulin added, possibly due to the resulting hypoglycaemia and associated weight gain. Rates of severe hypoglycaemia associated with IG+MET, IG+SU and IG+MET+SU were low (0.07, 0.10 and 0.10 events/patient-year, respectively), and not statistically different. Patients treated with IG+SU, who were older, had a higher HbA<sub>1c</sub> and FPG and a lower body weight and BMI at baseline than the other two groups, experienced less correction of HbA<sub>1c</sub> and FPG levels, possibly indicating that patients in this treatment group had more advanced beta-cell deficiency than in the other two treatment groups. Patients in the IG+MET treatment group had a significantly shorter duration of diabetes compared with patients who received a SU in their treatment regimen. Thus, more favorable efficacy and safety results seen in patients treated with MET only may reflect somewhat better beta-cell

function in the MET only group. Moreover, our analysis indicates that treatment with basal insulin soon after MET only failure leads to a better glycaemic control compared with the often-delayed insulin treatment in patients failing SU or MET+SU therapy. Such patients may need a more intensified insulin treatment either by more aggressive up-titration of basal insulin dose or earlier addition of a prandial insulin supplement, thereby replacing SU medication.

The results of this analysis do, however, support earlier findings regarding the overall efficacy of adding IG to prior therapy with MET, SU or MET+SU in terms of HbA<sub>1c</sub> reduction and achievement of an HbA<sub>1c</sub> target level of <7.0 %, <sup>5,26-30</sup> and provide important epidemiological data on the risk of hypoglycaemia with different OAD regimens, which may be a useful reference point for physicians when comparing hypoglycaemia rates in other studies. A higher rate of hypoglycaemia with IG+SU and IG+MET+SU compared with IG+MET was anticipated based on the mode of action of SUs.<sup>3</sup> A previous pooled analysis of data from 11 IG clinical studies also showed that treatment with IG+MET was associated with a higher proportion of patients achieving the HbA<sub>1c</sub> target of ≤7.0 % (68.1 % versus 50.4 % and 56.4 %, respectively; p=0.0006) and significantly lower rates of confirmed symptomatic hypoglycaemia (1.81 versus 4.88 and 7.30 events/patient-year, respectively; p<0.0001) compared with IG+SU and IG+MET+SU, respectively.<sup>31</sup> The current analysis includes more patients in the IG+MET treatment group (n=634) compared with the study by Fonseca et al. (n=185), and therefore represents a more balanced comparison versus IG+SU and IG+MET+SU (current analysis: n=906 and n=1,297; Fonseca study<sup>31</sup> n=792 and n=1,084, respectively). In addition, the previous study only reported symptomatic hypoglycaemia (including confirmed symptomatic and severe symptomatic),<sup>31</sup> whereas the current analysis provides additional information regarding rates of overall, daytime, nocturnal and severe hypoglycaemia.

Comparison of data on hypoglycaemia across clinical studies is challenging for several reasons. First, reporting of hypoglycaemia data across studies is inconsistent,<sup>15</sup> reducing the pool of data available for comparison. Variations in study design, such as the insulin titration algorithm, FPG targets and the insulin dosing times utilised, can also have an effect on the risk of hypoglycaemia. Second, several patient-related factors are associated with an increased risk of hypoglycaemia in type 2 diabetes. These include younger age, lower BMI, previous hypoglycaemic events, presence of individual micro- and macrovascular complications, duration of diabetes, duration of insulin treatment, type of insulin and number of insulin injections.<sup>32-37</sup> Finally, and as shown in the current study, the type of OAD administered as background therapy and the characteristics of the patients administered these different combinations can also impact on the risk of hypoglycaemia. In agreement with our results, a previous investigation showed that use of a SU in addition to MET, rather than MET alone, increased the risk of symptomatic hypoglycaemia by up to 88 %.<sup>37</sup> Thus, the ability to compare the incidences and event rates of hypoglycaemia from this analysis with those reported in other published studies is limited and problematic. Comparison would only be appropriate if the study methodology, the definitions of hypoglycaemia utilised, the study populations and the background oral therapy were identical.

This analysis benefits from the inclusion of data from prospective, randomised, controlled clinical trials and the large patient population evaluated (n=2,837). The large number of centres and geographic regions included (Asia, Australia, Eastern and Western Europe and North and South America), although liable to introduce variability

in the implementation of the treatment regimens, provides an advantage in terms of the translatability of the results. Standardised protocol-driven titration regimens and treatment targets were used in the studies included in the analysis and, in addition, the analysis only considered IG administered at bedtime. Derived data were also standardised, allowing consistent endpoint definitions to be applied across the studies. Furthermore, the patient-level analysis allowed for the inclusion of patient-level baseline characteristics as covariates. The analysis is, however, limited by the fact that only five IG+MET, six IG+SU and nine IG+MET+SU treat-to-target studies were evaluated from which relevant patient-level data were available and that the findings are limited to IG and therefore not applicable to other basal insulins. Although the post hoc nature of the analysis can be considered as a limitation, the analyses were conducted using a pre-specified statistical

analysis plan. In order to fully evaluate the various combinations of oral agents and insulin, specifically differences in HbA<sub>1c</sub> between MET and SU, randomised comparative trials are required.

## Conclusion

In summary, the results of this pooled, post hoc, analysis of patient-level data from treat-to-target randomised trials illustrate that differences in glycaemic control, hypoglycaemia risk, weight change and dose can be seen in patients with type 2 diabetes, depending on the background OAD therapy that is combined with IG. A greater proportion of patients treated with IG+MET achieved target glycaemic control and the overall risk of hypoglycaemia and weight gain was lower with this regimen compared with IG+SU and IG+MET+SU, despite an increased insulin dose requirement. ■

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