ABCD Spring Meeting 2020
16 December
Virtual Meeting

Switching to iGlarLixi vs Continuation of Glucagon-Like Peptide-1 Receptor Agonist in Inadequately Controlled Type 2 Diabetes Mellitus: The Randomised LixiLan-G Trial

LixiLan-G

Lawrence Blonde[1], Julio Rosenstock[2], Stefano Del Prato[3], Robert Henry[4], Naim Shehadeh[5], Juan Frias[6], Elisabeth Niemoeller[7], Elisabeth Souhami[8], Junlong Wu[9], Chen Ji[9], Vanita R. Aroda[10]

[1]Ochsner Medical Center, New Orleans, LA, USA; [2]Dallas Diabetes Research Center at Medical City, Dallas, TX, USA; [3]University of Pisa School of Medicine, Pisa, Italy; [4]UC San Diego and Veterans Affairs San Diego Healthcare System, Center for Metabolic Research, San Diego, CA, USA; [5]Rambam Health Care Campus, Haifa, Israel; [6]National Research Institute, Los Angeles, CA, USA; [7]Sanofi, Frankfurt, Germany; [8]Sanofi, Paris, France; [9]Sanofi, Beijing, China; [10]MedStar Health Research Institute, Hyattsville, MD, USA, and Brigham and Women's Hospital, Boston, MA, USA

INTRODUCTION

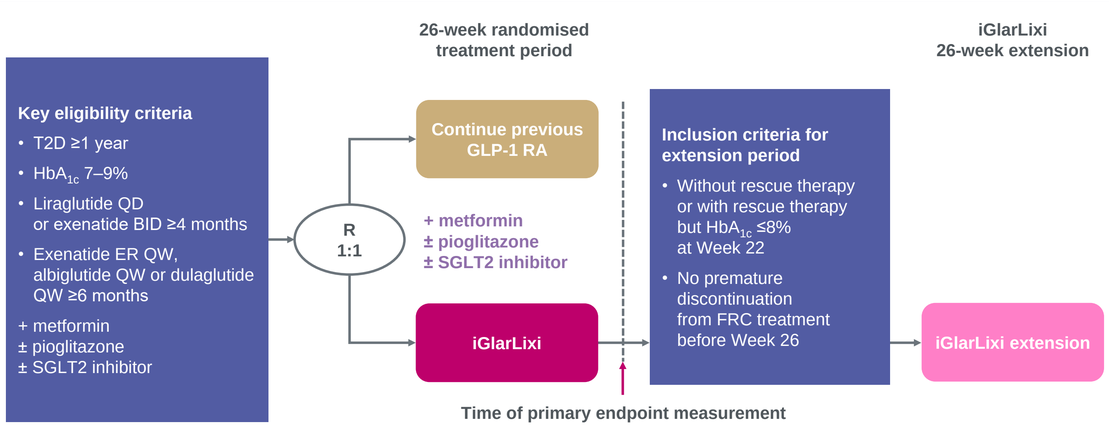
- The ADA/EASD management of hyperglycaemia in T2D consensus report states that GLP-1 RAs are the preferred first injectable antihyperglycaemic agents.[1,2]
- Fixed-ratio combinations (FRCs) of basal insulin plus a GLP-1 RA offer concomitant administration of complementary injectable therapies for individuals with T2D.
- iGlarLixi, a titratable FRC of insulin glargine plus lixisenatide, has been shown to be efficacious and well tolerated in patients with T2D uncontrolled by OADs in the LixiLan-O trial (NCT02058147) or by basal insulin in the LixiLan-L trial (NCT02058160).[3,4]
- Prior to the LixiLan-G trial, the efficacy and safety of treatment intensification to iGlarLixi in patients receiving either daily or long-acting GLP-1 RAs had not been studied.

OBJECTIVE

To compare the efficacy and safety of switching to iGlarLixi versus continuing treatment with prior GLP-1 RA therapy over 26 weeks, and to evaluate the durability of efficacy and safety of iGlarLixi over 52 weeks.

METHODS

Figure 1: LixiLan-G randomised, open-label trial design (NCT02787551)



RESULTS

Figure 2: LixiLan-G patient disposition

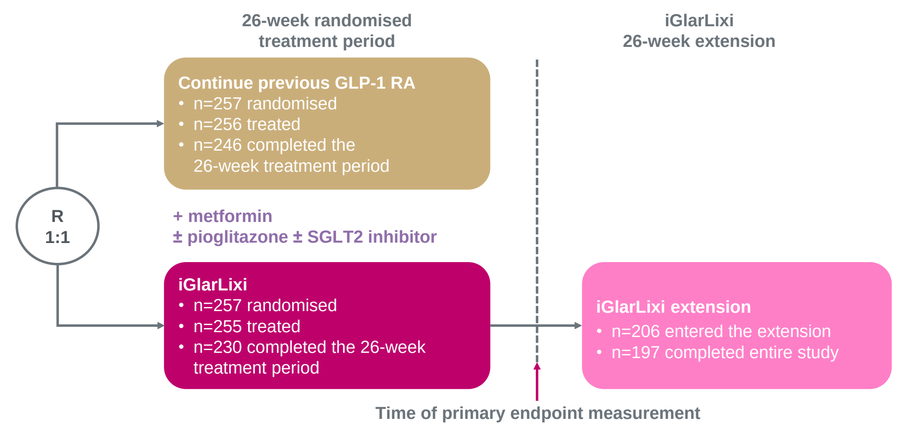
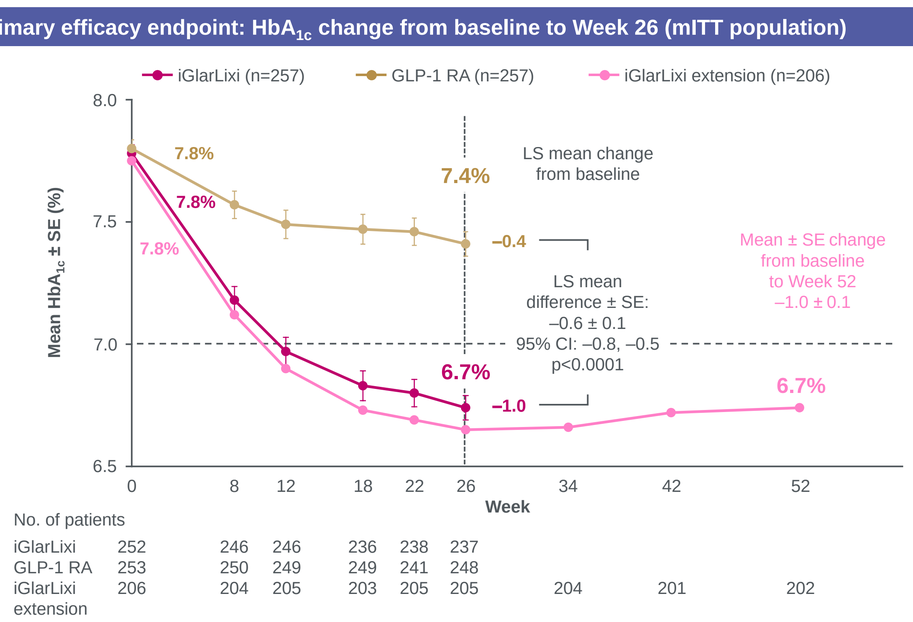


Table 1: Demographics and baseline characteristics (randomised population)

	26-week randomised population at screening		Randomised population who entered single-arm extension
	GLP-1 RA (n=257)	iGlarLixi (n=257)	iGlarLixi (n=206)
Age (years)	60.0 ± 10.3	59.2 ± 9.6	59.8 ± 9.1
Female, n (%)	113 (44.0)	131 (51.0)	106 (51.5)
BMI (kg/m²)	33.0 ± 4.4	32.8 ± 4.4	32.9 ± 4.4
Duration of diabetes (years)	11.0 ± 6.1	11.2 ± 7.4	11.5 ± 7.7
Duration of GLP-1 RA treatment (years)	1.9 ± 1.9	1.9 ± 1.8	1.9 ± 1.8
HbA1c (%) at screening	7.9 ± 0.5	7.9 ± 0.6	7.8 ± 0.5
GLP-1 RA use by type at screening, n (%)			
QD/BID formulation	**154 (59.9)**	**153 (59.5)**	**126 (61.2)**
Liraglutide QD	**145 (56.4)**	**135 (52.5)**	**112 (54.4)**
Exenatide BID	9 (3.5)	18 (7.0)	14 (6.8)
QW formulation	**103 (40.1)**	**104 (40.5)**	**80 (38.8)**
Dulaglutide	**51 (19.8)**	**54 (21.0)**	**43 (20.9)**
Exenatide ER	**48 (18.7)**	**45 (17.5)**	**33 (16.0)**
Albiglutide	4 (1.6)	5 (1.9)	4 (1.9)
Pioglitazone use at screening, n (%)	22 (8.6)	12 (4.7)	10 (4.9)
SGLT2 inhibitor use at screening, n (%)	26 (10.1)	26 (10.1)	19 (9.2)

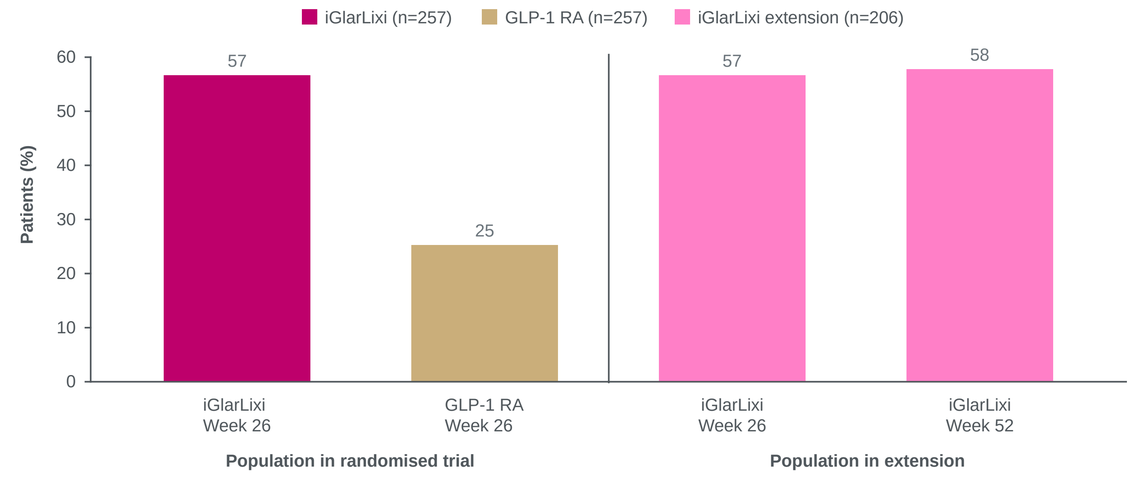
Data are mean ± SD unless otherwise noted. All patients were taking metformin at screening

Figure 3: Primary efficacy endpoint: HbA1c change from baseline to Week 26 (mITT population)



Switching to iGlarLixi reduced HbA1c significantly more than continuing prior GLP-1 RA, and the HbA1c reduction with iGlarLixi was maintained at Week 52 for patients who entered the extension.

Figure 4: Proportions of patients achieving HbA1c <7% without documented symptomatic hypoglycaemia



More iGlarLixi patients achieved the composite endpoint of HbA1c <7% without documented symptomatic hypoglycaemia (plasma glucose <3.0 mmol/L) at Week 26 compared with patients continuing on GLP-1 RA; this was sustained at Week 52 in patients in the iGlarLixi extension.

Table 2: Efficacy over 26 and 52 weeks (mITT population)

	26-week randomised population		Randomised population who entered single-arm extension	
	GLP-1 RA (n=253)	iGlarLixi (n=252)		iGlarLixi[a] (n=206)
Time period	**Week 0–26**	**Week 0–26**		**Week 0–52**
HbA1c (%) <7% n (%) at Week 26	65 (25.7)	156 (61.9)	n (%) at Week 52	132 (64.1)
Difference (95% CI)	36.1% (28.1, 44.0); p<0.0001			
FPG, mmol/L				
Baseline	9.5 ± 1.9	9.1 ± 2.1	Baseline	9.0 ± 2.2
Week 26	8.7 ± 2.0	6.9 ± 1.7	Week 52	6.8 ± 1.7
Change	–0.6 ± 0.1	–2.3 ± 0.1	Change	–2.3 ± 0.2
Difference (95% CI)	–1.7 ± 0.2 (–2.0, –1.3); p<0.0001			
2-hour PPG, mmol/L[b]				
Baseline	13.8 ± 3.3	13.6 ± 3.3	Baseline	13.5 ± 3.4
Week 26	12.6 ± 3.3	9.7 ± 3.1	Week 52	9.2 ± 2.9
Change	–1.1 ± 0.2	–4.0 ± 0.2	Change	–4.3 ± 0.3
Difference (95% CI)	–2.9 ± 0.3 (–3.4, –2.3); p<0.0001			
Body weight, kg				
Baseline	95.5 ± 16.9	93.0 ± 16.5	Baseline	92.8 ± 16.4
Week 26	94.5 ± 16.9	94.9 ± 16.4	Week 52	95.6 ± 16.5
Change	–1.1 ± 0.2	1.9 ± 0.2	Change	2.8 ± 0.3
Difference (95% CI)	3.0 ± 0.3 (2.4, 3.6)			

[a]Results presented for the entire 0–52-week study period for those patients (n=206) who received iGlarLixi, completed the first 26-week randomised period and entered the single-arm extension period. [b]LOCF. Unless otherwise noted, baseline, Week 26 and Week 52 values are mean ± SD; Week 26 and Week 52 change from baseline and between-treatment differences are LS mean ± SE. Two-hour PPG was recorded during a standardised meal test. mITT population was defined as all randomised patients with a baseline assessment and ≥1 post-baseline assessment of any primary or secondary efficacy variables

- Among patients treated with iGlarLixi who entered the extension, the proportions of patients who achieved HbA1c <7% were similar at 26 and 52 weeks, as were FPG and PPG levels.
- Mean body weight increased from baseline (2.78 kg) with iGlarLixi over the 52-week treatment period.

Table 3: Adverse and hypoglycaemic events (safety population)

Number of patients with adverse event, n (%)	26-week randomised population		Randomised population who entered single-arm extension
	GLP-1 RA (n=256)	iGlarLixi (n=255)	iGlarLixi[a] (n=206)
Time period	**Week 0–26**	**Week 0–26**	**Week 0–52**
Any TEAE, n (%)	121 (47.3)	163 (63.9)	150 (72.8)
Any serious TEAE, n (%)	9 (3.5)	10 (3.9)	21 (10.2)
GI disorders, n (%)	26 (10.2)	55 (21.6)	51 (24.8)
Diarrhoea	6 (2.3)	14 (5.5)	15 (7.3)
Nausea	6 (2.3)	22 (8.6)	19 (9.2)
Vomiting	2 (0.8)	8 (3.1)	8 (3.9)
Documented (<3.0 mmol/L) symptomatic hypoglycaemia, n (%)	1 (0.4)	24 (9.4)	37 (18.0)
Events/patient-year	<0.01	0.25	0.24

[a]Results presented for the entire 0–52-week study period for those patients (n=206) who received iGlarLixi, completed the first 26-week randomised period and entered the single-arm extension period

- One case of severe symptomatic hypoglycaemia was reported during the first 26-week period in the iGlarLixi group.
- Safety profiles for iGlarLixi over 52 weeks were comparable with those seen over 26 weeks.
- One post-treatment death was reported during the extension treatment period due to a glioblastoma and was assessed as not related to treatment.

CONCLUSIONS

- **Switching to iGlarLixi further improved glucose control in patients with T2D receiving the maximum tolerated GLP-1 RA dose with OADs, offering an efficacious and safe treatment intensification option.**
- **The efficacy and safety of iGlarLixi were maintained up to Week 52 in the extension phase of the study.**

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DISCLOSURE

LB — **Consultant:** AstraZeneca, Gilead, Janssen, Merck, Novo Nordisk, Sanofi; **Grant/research support (including institutional):** Janssen, Lexicon, Merck, Novo Nordisk, Sanofi; **Speaker:** Janssen, Novo Nordisk, Sanofi; JR — **Consultant:** Boehringer Ingelheim, Eli Lilly, Intarcia, Janssen, Novo Nordisk, Sanofi; **Grant/research support:** AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Genentech, GSK, Intarcia, Janssen, Lexicon, Merck, Novo Nordisk, Pfizer, Sanofi; SDP — **Grant/research support:** AstraZeneca, Boehringer Ingelheim, Merck, Novartis; **Honoraria:** Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Mundipharma, Novartis, Novo Nordisk, Sanofi, Servier, Takeda; RH — **Advisory panel:** AstraZeneca, Boehringer Ingelheim, Elcelyx, Intarcia, Johnson & Johnson, Merck, Sanofi-Aventis; **Consultant:** Abbott, Alere, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Intarcia, Ionis, Janssen, Ligand, Merck, Sanofi-Aventis; **Research support:** AstaReal, Eli Lilly, Hitachi, Lexicon, ViaCyte; NS — **Consultant:** Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi; **Grant/research support and honoraria:** AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Sanofi; JF — **Consultant:** Boehringer Ingelheim, Johnson & Johnson, Eli Lilly, Merck, Novo Nordisk, Sanofi; **Grant/research support:** AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, Novo Nordisk, Pfizer, Sanofi, Theracos; **Speaker:** Merck, Sanofi; EN, ES and CJ — **Employees:** Sanofi; JW — **Employee**: Former employee of Sanofi; VRA — **Clinical trial/research support:** Fractyl, Novo Nordisk, Sanofi; **Consultant:** AstraZeneca, BD, Novo Nordisk, Sanofi, Zafgen.

FUNDING

This study was sponsored by Sanofi. Editorial assistance was provided by Jennifer Steeber of Caudex (New York, NY), and was funded by Sanofi. Assistance with the layout of this encore poster was provided by Fishawack Communications Ltd, UK, and was funded by Sanofi.

CONTACT

Lawrence Blonde, Ochsner Medical Center, New Orleans, LA, USA; lblonde@ochsner.org

ACKNOWLEDGEMENTS

The authors would like to express their gratitude for the contributions of the LixiLan-G Steering Committee, including Dr Robert Henry, who sadly passed away prior to the presentation of this poster.

ABBREVIATIONS

ADA, American Diabetes Association; BID, twice daily; BMI, body mass index; CI, confidence interval; EASD, European Association for the Study of Diabetes; ER, extended release; FPG, fasting plasma glucose; FRC, fixed-ratio combination; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; iGlarLixi, insulin glargine and lixisenatide; LOCF, last observation carried forward; LS, least squares; mITT, modified intent-to-treat; OAD, oral antidiabetes drug; PPG, postprandial plasma glucose; QD, once daily; QW, once weekly; R, randomisation; SD, standard deviation; SE, standard error; SGLT2, sodium–glucose cotransporter 2; T2D, type 2 diabetes; TEAE, treatment-emergent adverse event

Previously presented at the 55th Annual Meeting of the European Association for the Study of Diabetes, 16–20 September 2019, Barcelona, Spain.