Advancing therapy in suboptimally controlled basal insulin-treated type 2 diabetes

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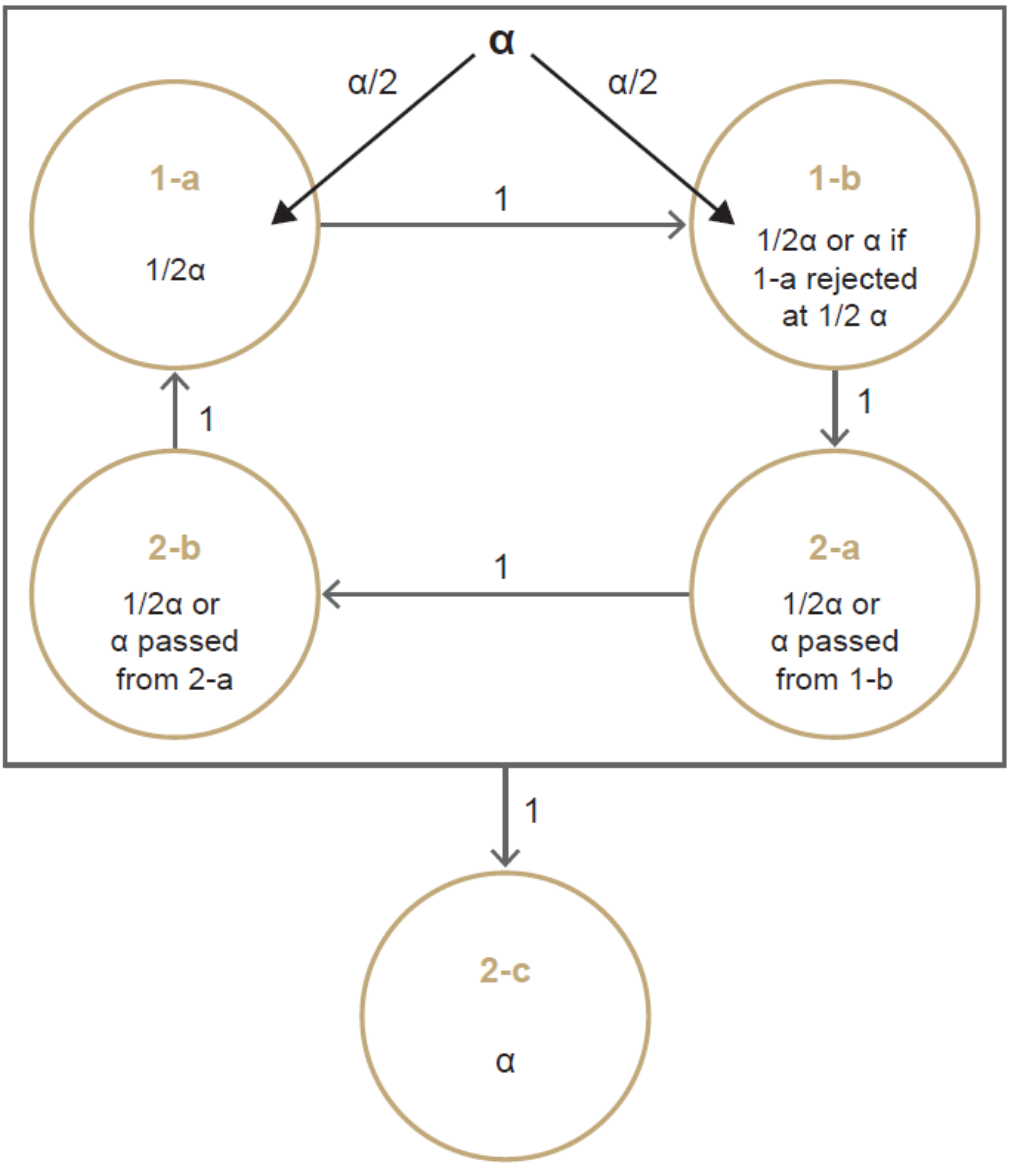
Supplementary Material

Supplementary Figure 1. Diagram of multiplicity testing approach.

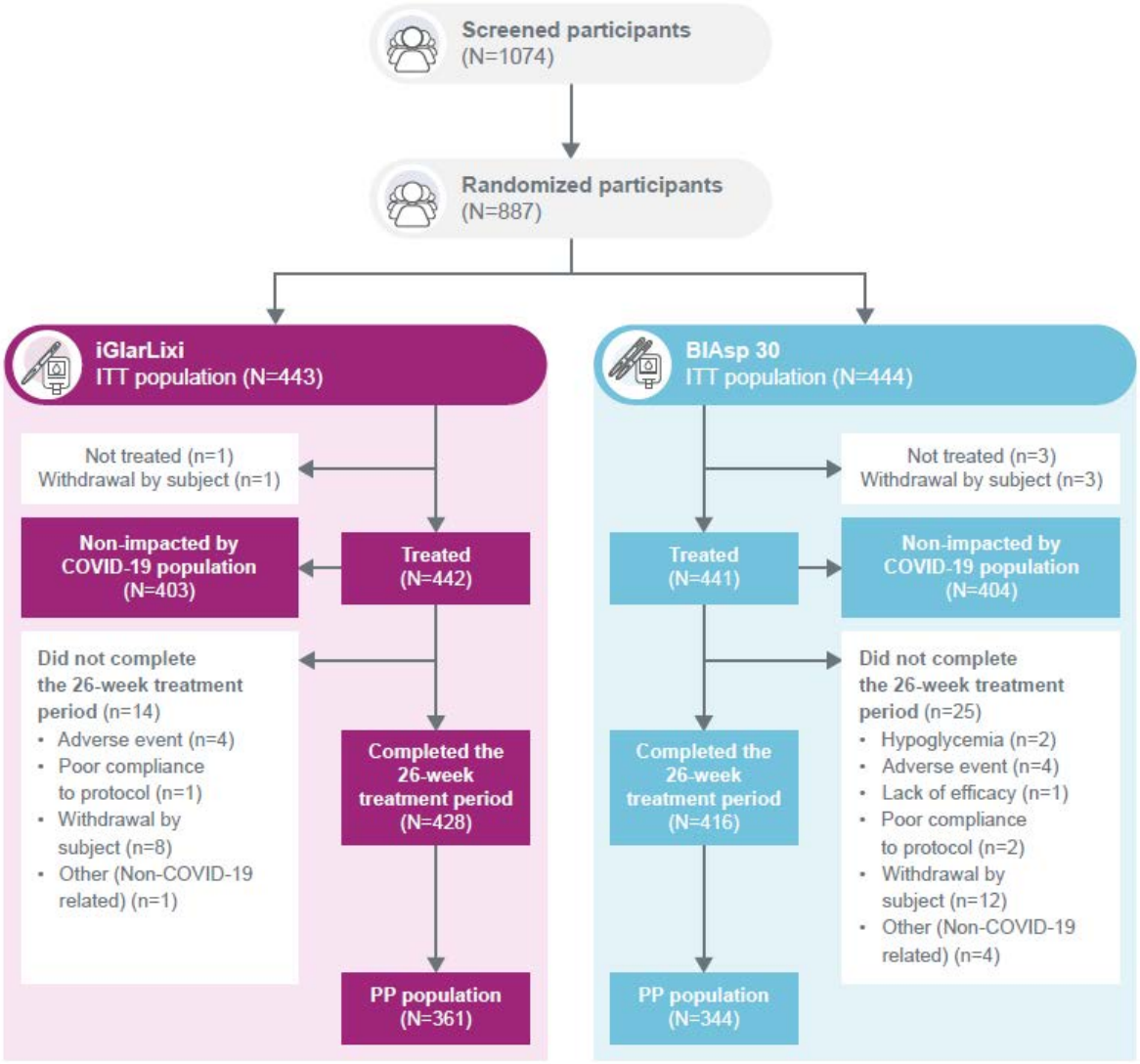


1-a: Non-inferiority of iGlarLixi versus BIAsp 30 on HbA_{1c} change from baseline to Week 26; 1-b: Superiority of iGlarLixi versus BIAsp 30 on bodyweight change from baseline to Week 26; 2a: Proportion of participants reaching HbA_{1c} target <7 % without weight gain at Week 26; 2b: Proportion of participants reaching HbA_{1c} target <7 % without hypoglycemia, and without weight gain at Week 26; 2-c: HbA_{1c} reduction from baseline at Week 26. Alpha will be allocated equally among both primary hypotheses (1-a and 1-b).
Test 1-a and 1-b at alpha/2 each;

a. If 1-a is significant, alpha/2 is passed from 1-a to 1-b and 1-b is tested at the full alpha level. If significant, the full alpha is passed to test hierarchically 2-a, 2-b and 2-c at full alpha, each.

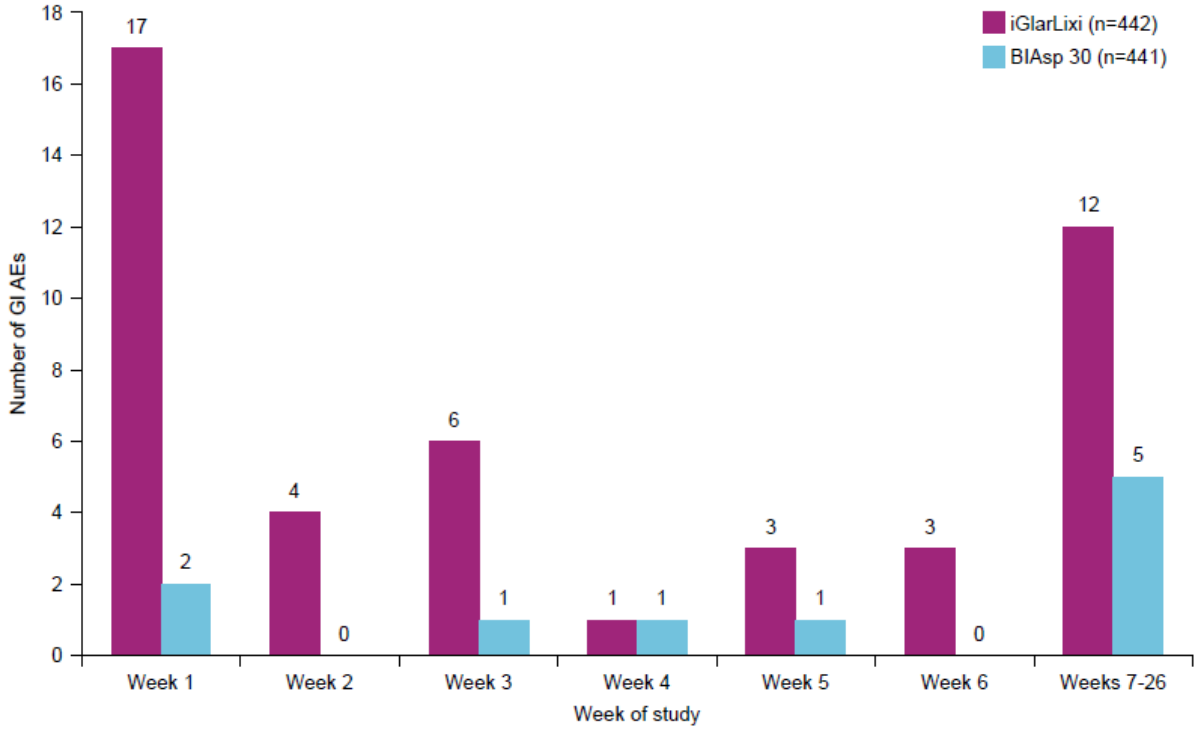
b. If 1-a is not rejected, but 1-b is rejected at alpha/2 level, test hierarchically 2-a, 2-b at alpha/2
    i. If significant, use a fallback procedure to pass alpha/2 back to 1-a and re-test 1-a at an alpha level.
    ii. If 1-a is rejected at the alpha level, test 2-c at the full alpha level. Essentially, 1-a, 1-b and 2-a and 2-b are put in a box as a gatekeeper for testing 2-c: 2-c can be tested only if 1-a, 1-b, 2-a and 2-b are all rejected.

Supplementary Figure 2. Participant disposition



BIAsp 30, biphasic aspart insulin 30 (30% insulin aspart and 70% insulin aspart protamine); iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and the glucagon-like peptide-1 receptor agonist, lixisenatide; ITT, intention-to-treat; PP, per protocol.

Supplementary Figure 3. Onset gastrointestinal adverse events reported over time (Safety population)



AE, adverse events; BIAsp 30, biphasic aspart insulin 30 (30% insulin aspart and 70% insulin aspart protamine); GI, gastrointestinal; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and the glucagon-like peptide-1 receptor agonist, lixisenatide.

Supplementary Table 1. Starting doses of iGlarLixi from iGlar*

		Previous therapy	
		iGlar ≥20 U to <30 U	**iGlar ≥30 U to ≤50 U**
Starting dose and pen	**iGlarLixi 10–40 pen†**	20 dose steps (20 U iGlar/10 μg Lixi)	
	iGlarLixi 30–60 pen†		30 dose steps (30 U iGlar/10 μg Lixi)

*If switching from twice-daily basal insulin or insulin glargine 300 U/mL, the total daily dose previously used should be reduced by 20% to choose the starting dose of iGlarLixi; for any other BI, the same dosing should be followed as shown above for iGlar.
†Suliqua®, Sanofi, Paris, France.
BI, basal insulin; GLP-1 RA, glucagon-like 1 receptor agonist; iGlar, insulin glargine 100 U/mL; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and the glucagon-like peptide-1 receptor agonist, lixisenatide; Lixi, lixisenatide; mcg, micrograms; OAD, oral antihyperglycemic drug; U, units.

Supplementary Table 2. Recommended dose adjustment algorithm for iGlarLixi

Median of fasting SMPG values from the last three measurements	**iGlarLixi* dose adjustments (U/day)**
>140 mg/dL (>7.8 mmol/L)	+4
>110 to ≤140 mg/dL (>6.1 to ≤7.8 mmol/L)	+2
Glycemic target: ≥80 to ≤110 mg/dL (≥4.4 to ≤6.1 mmol/L)	No change
≥60 and <80 mg/dL (≥3.3 to <4.4 mmol/L)	-2
<60 mg/dL (<3.3 mmol/L) or occurrence of ≥2 symptomatic hypoglycemic episodes or 1 severe hypoglycemic episode (requiring assistance) in the preceding week	-2 to -4 or at the investigator's discretion (or medically qualified designee)

*The U/day refers solely to the iGlar component of iGlarLixi.
iGlar, insulin glargine 100 U/mL; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and the glucagon-like peptide-1 receptor agonist, lixisenatide; SMPG, self-monitored plasma glucose; U, units.

Supplementary Table 3. Recommended dose adjustment algorithm for BIAsp 30

Premeal SMPG values*	**BIAsp 30 dose adjustments (U/day)**
<80 mg/dL (<4.4 mmol/L)	–2
Glycemic target: 80–110 mg/dL (4.4–6.1 mmol/L)	No change
111–140 mg/dL (6.2–7.8 mmol/L)	+2
141–180 mg/dL (7.9–10.0 mmol/L)	+4
>180 mg/dL (>10 mmol/L)	+6

*Titration was based on the lowest of pre-meal SMPG values of the previous 3 days, using pre-dinner SMPG values for breakfast dose adjustment and pre-breakfast SMPG values for the dinner dose adjustment. The dose was not to be increased if hypoglycemia occurred within these days.
BIAsp 30, biphasic aspart insulin 30 (30% insulin aspart and 70% insulin aspart protamine); SMPG, self-monitored plasma glucose; U, units.

Supplementary Table 4. Primary and secondary efficacy endpoints (ITT population)

	iGlarLixi (n=443)	**BIAsp 30 (n=444)**
Primary efficacy endpoints		
HbA_{1c}, %		
Baseline, mean ± SD	8.61 ± 0.67	8.57 ± 0.65
Week 26, mean ± SD	7.26 ± 1.06	7.48 ± 0.99
Change from baseline to Week 26, mean ± SD	-1.36 ± 1.06	-1.09 ± 1.02
LS mean change from baseline to Week 26 ± SE	-1.30 ± 0.06	-1.05 ± 0.06
LS mean difference (97.5% CI)*	-0.24 (-0.41, -0.08)	
p value for non-inferiority†	p<0.001	
LS mean difference (95% CI)‡	-0.24 (-0.39, -0.10)	
p value for superiority§	p<0.001	
HbA_{1c}, mmol/mol		
Baseline, mean ± SD	70.6 ± 7.3	70.2 ± 7.1
Week 26, mean ± SD	55.8 ± 11.5	58.2 ± 10.8
Change from baseline to Week 26, mean ± SD	-14.8 ± 11.6	-11.9 ± 11.1
LS mean change from baseline to Week 26 ± SE	-14.2 ± 0.7	-11.5 ± 0.7
LS mean difference (97.5% CI)*	-2.6 (-4.5, -0.9)	
p value for non-inferiority†	p<0.001	
LS mean difference (95% CI)‡	-2.6 (-4.3, -1.1)	
p value for superiority§	p<0.001	
Bodyweight, kg		
Baseline, mean ± SD	80.7 ± 16.5	82.2 ± 18.5
Week 26, mean ± SD	80.2 ± 16.6	83.4 ± 19.0
Change from baseline to Week 26, mean ± SD	-0.6 ± 3.1	+1.3 ± 3.1
LS mean change from baseline to Week 26 ± SE	-0.70 ± 0.20	+1.15 ± 0.20
LS mean difference (95% CI)‡	-1.86 (-2.28, -1.43)	
p value for superiority†	p<0.001	
Key secondary efficacy endpoints		
HbA_{1c} <7 % without weight gain‡§		

n (%)	122 (27.5)	55 (12.4)
Odds ratio (95% CI) p value for superiority	2.83 (1.98, 4.04) p<0.001	
HbA_{1c} <7 % without weight gain or hypoglycemia (plasma glucose <70 mg/dL [<3.9 mmol/L])‡§		
n (%)	86 (19.4)	31 (7.0)
Odds ratio (95% CI) p value for superiority	3.40 (2.19, 5.28) p<0.001	
Other secondary efficacy endpoints		
FPG, mmol/L		
Baseline, mean ± SD	8.37 ± 2.42	8.25 ± 2.28
Week 26, mean ± SD	7.22 ± 2.44	8.10 ± 2.84
Change from baseline to Week 26, mean ± SD	-1.12 ± 2.88	-0.16 ± 3.33
LS mean change from baseline to Week 26 ± SE	-1.07 ± 0.24	-0.16 ± 0.27
LS mean difference (95% CI)	-0.91 (-1.47, -0.34)	
Total insulin dose, U§		
Baseline, mean ± SD	26.4 ± 6.2	33.6 ± 11.0
Week 26, mean ± SD	39.7 ± 12.0	58.2 ± 23.6
Change from baseline to Week 26, mean ± SD	13.4 ± 10.3	24.5 ± 20.8
LS mean change from baseline to Week 26 ± SE	10.6 ± 1.2	22.9 ± 1.1
LS mean difference (95% CI)	-12.2 (-14.8, -9.7)	
HbA_{1c} <7 %§		
n (%)	187 (42.2)	141 (31.8)
Odds ratio (95% CI)	1.65 (1.25, 2.19)	

*Endpoint was assessed at the alpha 0.025 level. †Primary efficacy endpoints, non-inferiority of HbA_{1c} reduction was assessed using a margin of 0.3 %; ‡Endpoint was assessed at the alpha 0.05 level. §Secondary endpoint. BIAsp 30, biphasic aspart insulin 30 (30% insulin aspart and 70% insulin aspart protamine); CI, confidence interval; FPG, fasting plasma glucose; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and the glucagon-like peptide-1 receptor agonist, lixisenatide; ITT, intention-to-treat population; LS, least squares; SD, standard deviation; SE, standard error.

Supplementary Table 5. Sensitivity analyses of the primary and key secondary efficacy endpoints

	iGlarLixi	**BIAsp 30**
HbA_{1c}, %		
PP population	**n=361**	**n=344**
LS mean difference (95% CI)*†	-0.15 (-0.29, -0.01)	
MMRM analysis	**n=443**	**n=444**
LS mean difference (95% CI)*†	-0.20 (-0.33, -0.07)	
Penalized multiple imputation	**n=443**	**n=444**
LS mean difference (95% CI)*†	-0.24 (-0.38, -0.09)	
Multiple imputation for COVID-19 impacted participants	**n=443**	**n=444**
LS mean difference (95% CI)*†	-0.24 (-0.39, -0.09)	
ANCOVA during the on-treatment period	**n=443**	**n=444**
LS mean difference (95% CI)*†	-0.20 (-0.33, -0.07)	
Non-impacted by COVID-19 population	**(n=403)**	**(n=404)**
LS mean difference (95% CI)*†	-0.25 (-0.41, -0.10)	
Bodyweight, kg		
MMRM analysis	**n=443**	**n=444**
LS mean difference (95% CI) p value for superiority	-1.87 (-2.28, -1.46) p<0.001	
Multiple imputation for COVID-19 impacted participants	**n=443**	**n=444**
LS mean difference (95% CI) p value for superiority	-1.85 (-2.29, -1.41) p<0.001	
ANCOVA during the on-treatment period	**n=443**	**n=444**
LS mean difference (95% CI) p value for superiority	-1.89 (-2.31, -1.47) p<0.001	
Non-impacted by COVID-19 population	**(n=403)**	**(n=404)**
LS mean difference (95% CI) p value for superiority	-1.85 (-2.31, -1.40) p<0.001	
HbA_{1c} <7 % without weight gain		
Non-impacted by COVID-19 population	**(n=403)**	**(n=404)**

n (%)	110 (27.3)	53 (13.1)
Odds ratio (95% CI)	2.58 (1.79, 3.73)	
p value for superiority	p<0.001	
HbA_{1c} <7 % without weight gain or hypoglycemia (plasma glucose <70 mg/dL [<3.9 mmol/L])		
Not-impacted by COVID-19 population	**(n=403)**	**(n=404)**
n (%)	76 (18.9)	29 (7.2)
Odds ratio (95% CI)	3.16 (2.00, 5.00)	
p value for superiority	p<0.001	

All endpoints were assessed at the alpha 0.05 level. *Non-inferiority objective confirmed. †Superiority objective confirmed. PP: same ANCOVA model as described for the primary analysis in the PP population (no imputation necessary since patients with missing HbA_{1c} were excluded from PP). MMRM: MMRM under the missing at random framework was carried out using an adequate contrast at Visit 10 (Week 26), based on ITT population. Penalized multiple imputation: same ANCOVA model as described for the primary analysis with multiple imputation. A penalty of 0.3 % was added to missing HbA_{1c} values in the iGlarLixi group only. Missing related to COVID-19 were not penalized. Multiple imputation for COVID-19 impacted participants: same ANCOVA model as described for the primary analysis in the ITT population, with separate multiple imputation process for COVID-19 impacted and non-impacted patients. Missing data in COVID-19 non-impacted patients were imputed with the same approach as primary analysis (Missing Not At Random). COVID-19 impacted patients were imputed using multiple imputation under the Missing At Random framework. ANCOVA during the on-treatment period: same ANCOVA as primary analysis in the ITT population during the on-treatment period. Only assessments before IMP discontinuation or introduction of the rescue therapy were considered in this analysis. Non-impacted by COVID-19 population: analyzed using the same methodology as primary analysis in the ITT not impacted by COVID-19 population. ANCOVA, analysis of covariance; BIAsp 30, biphasic aspart insulin 30 (30% insulin aspart and 70% insulin aspart protamine); CI, confidence interval; iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL and the glucagon-like peptide-1 receptor agonist, lixisenatide; IMP, investigational medicinal product; ITT, intention-to-treat; LS, least squares; MMRM, mixed effect repeated measure; PP, per protocol.

Supplementary Materials

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