Clinical Benefits of Treating Adults with Type 2 Diabetes Mellitus With iGlarLixi: A Patient-Level Simulation Study

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BACKGROUND AND OBJECTIVE

- About 37.3 million people in the U.S. have T2DM [1], accounting for more than 95% of all diabetes cases [2]
- Metformin is a commonly prescribed first-line therapy for T2DM [3]; however, treatment intensification is needed for adults with T2DM who fail to achieve optimal glycemic targets [4,5]
- The *Standard of Care in Diabetes – 2023* by ADA recommends SGLT2 and/or GLP-1RA or GIP /GLP-1RA as first-lines of therapy and addition of basal insulin as a free or FRC for those unable to achieve A1C goals with GIP/GLP-1RA [6]
- Compared to basal insulin alone, therapy with titratable FRCs, a combination of basal insulin and GLP-1RAs, improves glycemic control [7]
- The efficacy and safety profiles of iGlarLixi were demonstrated in the LixiLan-L and LixiLan-O phase III trials which included adults with T2DM who were not treated successfully on basal insulin +/- OADs or metformin alone at randomization, respectively [7]
- However, there is limited evidence of its benefits in diverse, real-world adults with T2DM present in routine clinical practice
- The objective of this study was to identify two real-world cohorts of individuals with T2DM from an integrated claims and EHR database who meet the criteria for treatment with iGlarLixi and apply a Monte Carlo simulation to mirror the treatment arms in the LixiLan-O and LixiLan-L trials, thus evaluating the clinical benefits of iGlarLixi in these patients

METHODS

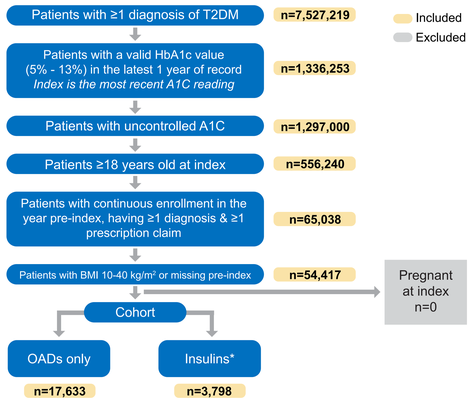
Identification of real-world cohorts

- Optum Humedica was used to identify two real-world cohorts (aged ≥18) with T2DM who were eligible for treatment with iGlarLixi
- At baseline, the first cohort (insulin cohort) received insulin with or without OADs, and the second (OAD only cohort) received OADs only
- A threshold for A1C goals of ≤7% was used for ages <65 years and ≤8% for ages ≥65 years, which is aligned with the standard of care
- The consort diagram is shown in Figure 1

Simulation

- A Monte Carlo patient-level simulation was applied to each cohort based on treatment strategies and efficacies from the LixiLan-L and -O trials [7] to estimate reductions in A1C and percentage achieving age-based A1C goals at 30 weeks
- Bootstrapping with replacement was first used to generate 1,000,000 replicates for each of the two cohorts [8]
- Separate models, following a patient-specific probabilistic path and the logic shown in Figure 2, were then applied to each bootstrap-sampled cohort to emulate the treatment strategy and the treatment efficacy from the Lixilan-L and -O trials
- Background therapies like DPP4, TZD, SGLT2i, etc. were removed to align with the treatment strategies from LixiLan-L and -O trials, and the patient-specific baseline A1C was adjusted according to the efficacies of the background therapies
- At baseline, an increment or reduction in A1C due to OAD/insulin treatment was applied to each cohort, based on estimates from the literature assuming a normal distribution of efficacy estimates for each treatment and applying instantaneous A1C change
- For the insulin cohort simulation, two clones were created for each sampled patient, mirroring treatment with iGlarLixi vs. iGlar. Efficacy at 30 weeks was estimated for each clone, drawing from a normal distribution defined by parameters reported in the LixiLan-L trial [7], stratified by index A1C value
- For the OAD only cohort simulation, three clones were created for every sampled patient, mirroring treatments with iGlarLixi, lixisenatide, and iGlar, respectively. Efficacy at 30 weeks was simulated for each clone drawing from a normal distribution informed by parameters reported in the Lixilan-O trial [7]
- Model based estimates were summarized by calculating average change in A1C levels and proportion of adults achieving age-based A1C goals at 30 weeks

Figure 1. Consort diagram



*≤60 units daily insulin, with/without OADs

Figure 2. Simulation logic

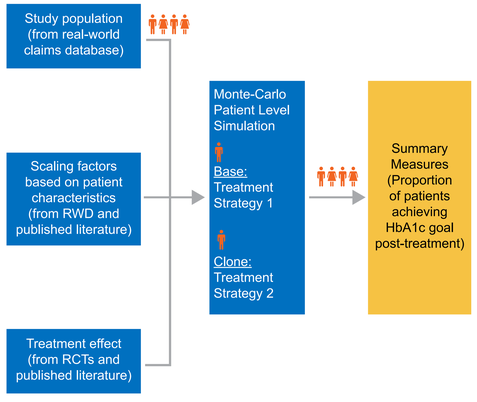


Table 1. Baseline characteristics of patients in the insulin and the OAD only cohorts

	Insulin cohort						OAD only cohort					
	Overall Cohort N=3,798		<65 years N=1,549		≥65 years N=2,249		Overall Cohort N=17,633		<65 years N=8,429		≥65 years N=9,204	
	Mean / n	Std / %	Mean / n	Std / %	Mean / n	Std / %	Mean / n	Std / %	Mean / n	Std / %	Mean / n	Std / %
Age, mean (std)	65.8	13.0	53.2	9.8	74.5	6.1	64.2	11.8	54.3	8.1	73.3	5.9
Baseline A1C %, mean (std)	8.9	1.4	9.0	1.5	8.5	1.2	8.3	1.2	8.4	1.3	8.1	1.1
BMI kg/m²												
Mean (std)	29.8	5.3	30.2	5.2	29.6	5.2	30.8	4.8	31.8	4.6	30.0	4.8
BMI category, n (%)												
Not available	293	7.71%	130	8.39%	163	7.25%	1,339	7.59%	698	8.28%	641	6.96%
[10, 20)	100	2.63%	32	2.07%	68	3.02%	146	0.83%	28	0.33%	118	1.28%
[20, 30)	1,697	44.68%	661	42.67%	1,036	46.06%	6,771	38.40%	2616	31.04%	4,155	45.14%
[30, 40]	1,708	44.97%	726	46.87%	982	43.66%	9,377	53.18%	5087	60.35%	4,290	46.61%
Sex, n (%)												
Male	1,909	50.26%	845	54.55%	1,064	47.31%	9,940	56.37%	4999	59.31%	4,941	53.68%
Female	1,887	49.68%	704	45.45%	1,183	52.60%	7,687	43.59%	3424	40.62%	4,263	46.32%
Unknown	2	0.05%	0	0.00%	2	0.09%	6	0.03%	6	0.07%	0	0.00%
Race, n (%)												
Asian	75	1.97%	34	2.19%	41	1.82%	739	4.19%	450	5.34%	289	3.14%
African American	562	14.80%	248	16.01%	314	13.96%	2,074	11.76%	1083	12.85%	991	10.77%
Caucasian	2,727	71.80%	1,077	69.53%	1,650	73.37%	12,686	71.94%	5667	67.23%	7,019	76.26%
Other/Unknown	434	11.43%	190	12.27%	244	10.85%	2,134	12.10%	1229	14.58%	905	9.83%
Comorbidities, n (%)												
Depression	758	19.96%	303	19.56%	455	20.23%	2,495	14.15%	1127	13.37%	1,368	14.86%
Hyperlipidemia	2,690	70.83%	1,027	66.30%	1,663	73.94%	12,505	70.92%	5703	67.66%	6,802	73.90%
Chronic Kidney Disease	1,162	30.60%	268	17.30%	894	39.75%	2,690	15.26%	561	6.66%	2,129	23.13%
Hypertension	2,970	78.20%	1,043	67.33%	1,927	85.68%	13,194	74.83%	5716	67.81%	7,478	81.25%
Myocardial Infarction	473	12.45%	144	9.30%	329	14.63%	1,267	7.19%	440	5.22%	827	8.99%
Ischemic Stroke	217	5.71%	65	4.20%	152	6.76%	458	2.60%	148	1.76%	310	3.37%
Complications, n (%)												
Diabetic Nephropathy	369	9.72%	92	5.94%	277	12.32%	979	5.55%	295	3.50%	684	7.43%
Diabetic Neuropathy	1,257	33.10%	446	28.79%	811	36.06%	3,137	17.79%	1128	13.38%	2,009	21.83%
Diabetic Retinopathy	43	1.13%	22	1.42%	21	0.93%	67	0.38%	30	0.36%	37	0.40%
Hypoglycemia	403	10.61%	162	10.46%	241	10.72%	336	1.91%	122	1.45%	214	2.33%
Gastrointestinal Disease	366	9.64%	178	11.49%	188	8.36%	1,085	6.15%	547	6.49%	538	5.85%

Table 2. Results from a patient-level simulation applied to the insulin cohort

	A1C goal		
	Age-based[1]	≤7%	≤8%
A1C before intensification	8.77	8.67	8.81
A1C at intensification	10.13	9.94	10.21
iGlarLixi treated A1C - week 30	7.78	7.68	7.82
iGlar treated A1C - week 30	8.44	8.33	8.48
Difference iGlarLixi vs. iGlar [95% CI]	-0.66 [-0.665, -0.655]	-0.65 [-0.655, -0.645]	-0.66 [-0.665, -0.655]
% Achieving goal on iGlarLixi	52.57%	31.09%	68.93%
% Achieving goal on iGlar	31.62%	4.98%	49.95%
Difference iGlarLixi vs. iGlar [95% CI]	20.95% [20.90%, 21.01%]	26.11% [26.05%, 26.17%]	18.97% [18.92%, 19.03%]

[1]. ≤7% for ages <65 years and ≤8% for ages ≥65 years

Table 3. Results from a patient-level simulation applied to the OAD only cohort

	A1C goal		
	Age-based[1]	≤7%	≤8%
A1C before intensification	8.61	8.40	8.88
A1C at intensification	9.19	8.83	9.62
iGlarLixi treated A1C - week 30	7.39	7.10	7.74
iGlar treated A1C - week 30	7.76	7.45	8.12
Lixisenatide treated A1C - week 30	8.26	7.94	8.65
Difference iGlarLixi vs. iGlar [95% CI]	-0.36 [-0.360, -0.360]	-0.35 [-0.350, -0.350]	-0.38 [-0.380, -0.380]
Difference iGlarLixi vs. lixisenatide [95% CI]	-0.87 [-0.870, -0.870]	-0.84 [-0.840, -0.840]	-0.91 [-0.910, -0.910]
iGlarLixi treated: % achieving goal	59.91%	57.29%	68.22%
Lixisenatide treated: % achieving goal	49.31%	45.96%	57.84%
iGlar treated: % achieving goal	32.82%	29.17%	40.11%
Difference iGlarLixi vs. iGlar [95% CI]	10.61% [10.58%, 10.64%]	11.33% [11.30%, 11.36%]	10.38% [10.35%, 10.41%]
Difference iGlarLixi vs. lixisenatide [95% CI]	27.09% [27.06%, 27.12%]	28.12 [28.09%, 28.15%]	28.12 [28.09%, 28.16%]

[1]. ≤7% for ages <65 years and ≤8% for ages ≥65 years
*Lixisenatide is no longer marketed in the US, but was during the time of study conduct

LIMITATIONS

- The study cohorts were identified from a large integrated claims and EHR dataset, which may not be fully representative of the U.S. population
- Treatment side effects were excluded due to limited availability of data in the claims database (e.g., hypoglycemia, gastrointestinal side effects)
- Baseline intensification and effectiveness at 30 weeks were obtained from the literature; additional research is needed to support iGlarLixi's overall clinical benefits, risks, and impact on costs
- Background therapies were limited to metformin to emulate LixiLan trial treatments at randomization, which might not always be routine clinical practice for patients initiating iGlarLixi
- Because of some missing data on dosage, caution needs to be exercised in the interpretation and generalization of the study results

RESULTS

Sample identification

- A total of n=7,525,219 individuals with at least one diagnosis of T2DM were initially identified in the Optum data
- After applying selection criteria, there were n=3,798 and n=17,633 individuals in the insulin and the OAD only cohorts, respectively (Figure 1)

Sample characteristics

- The real-world insulin and OAD only cohorts differed considerably in demographics, age, clinical characteristics, baseline A1C levels, and background OAD therapies compared to the populations in the Lixilan-L and Lixilan-O trials (Table 1)
- In the insulin cohort, 32.6% of patients were on metformin, (18.8% on monotherapy), and 15.9% on sulfonylurea as monotherapy or in combination with other OADs
- In the OAD only cohort, 69.7% were on metformin (36.7% on monotherapy), 38% of the patients were on sulfonylurea, 16% on SGLT2i, and 14.4% on DPP4 as monotherapy or in combination with other OADs

Insulin cohort simulation estimates

- In the insulin cohort simulation, A1C goals were achieved among 52.6% vs. 31.6% (p<0.001) of adults with T2DM in the iGlarLixi vs. the iGlar arms, respectively
- Average A1C levels at week 30 reduced by 0.66 when age-based goals were applied; a higher percentage of patients met age-based A1C goals, rising by 20.95%-points compared to iGlar
- Moreover, the proportion of patients who achieved age-based A1C goals rose by 18.97%-points and 26.11%-points when the ≤8% and ≤7% goals, respectively, were adopted for all patients
- The average A1C levels at week 30 were reduced by 0.66 and 0.65 compared to A1C levels at intensification using a threshold of ≤8% and ≤7%, respectively, for all patients (Table 2)

OAD only cohort simulation estimates

- In the OAD only cohort simulation, A1C goals were achieved among 59.9% vs. 49.3% and 32.8% (p<0.001) of adults with T2DM in the iGlarLixi vs. the iGlar and lixisenatide arms, respectively
- Average A1C levels at week 30 reduced by 0.36 when age-based A1C goals were applied, and the percentage of participants who met age-based A1C goals increased by 10.61%-points for iGlarLixi vs. iGlar
- Similar trends were observed when A1C ≤8% and ≤7% thresholds were used for all patients (Table 3)

CONCLUSIONS

- **Irrespective of treatment regimens at baseline (insulin vs. OAD only), this patient-level simulation demonstrated greater proportions of individuals achieving A1C goals with iGlarLixi compared to iGlar or lixisenatide alone**
- **These results persisted in separate analyses among adults <65 years as well as older individuals and when different A1C goals were used**
- **Findings suggest that the benefits of iGlarLixi extend to clinically diverse real-world populations**

REFERENCES:

1. https://diabetesatlas.org/data/en/country/211/us.html
2. https://www.who.int/news-room/fact-sheets/detail/diabetes
3. Baker C, Retzik-Stahr C, Singh V, et al. Ther Adv Endocrinol Metab. 2021
4. Pantalone KM, Wells BJ, Chagin KM et al. Diabetes Care. 2016;39(9):1527-34
5. Buysman EK, Fan T, Blauer-Peterson C, et al. Endocrinol Diabetes Metab. 2018;1(3):e00019.
6. ElSayed NA et al. Standards of Care in Diabetes Care-2023. Jan 1;46(Suppl 1):S5-S9
7. Rosenstock J et al. The LixiLan-O Randomized Trial. Diabetes Care. 2016;39(11):2026-35
8. Cannon CP. JAMA Cardiol. 2017;2(9):959-66

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AC, MS, JKO, SSSS, and AM are employees of Axtria, which received funding from Sanofi for this analysis. TD, SC, AR, and RP are employees of Sanofi and are stockholders of Sanofi stock.

ABBREVIATIONS:
A1C, Glycated hemoglobin; ADA, American Diabetes Association; BMI, Body Mass Index; CI, Confidence Intervals; DPP4, Dipeptidyl Peptidase-4; FRC, Fixed Ratio Combination; GIP, Gastric Inhibitory Peptide; GLP-1RA, Glucagon-Like Peptide 1 Receptor Agonists; HbA1c, Glycosylated Hemoglobin; RWD, Real World Data; SGLT2, Sodium/glucose cotransporter 2; T2DM, Type 2 Diabetes Mellitus; TZD, Thiazolidinedione; US, United States

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