WILEY

ORIGINAL ARTICLE

Impact of delaying treatment intensification with a glucagon-like peptide-1 receptor agonist in patients with type 2 diabetes uncontrolled on basal insulin: A longitudinal study of a US administrative claims database

Liyue Tong MS[1] | Chunshen Pan PhD[1] | Hongwei Wang PhD[2] | Monica Bertolini MD[3] | Elisheva Lew MS[4] 🟢 | Luigi F. Meneghini MD[5]

[1]PRO Unlimited, Boca Raton, Florida

[2]Sanofi US, Inc., Bridgewater, New Jersey

[3]Sanofi, Paris, France

[4]Sanofi, Chilly-Mazarin, France

[5]University of Texas Southwestern Medical Center and Parkland Health & Hospital System, Dallas, Texas

Correspondence
Elisheva Lew, Health Economic and Outcomes Research (HEOR), Sanofi 1 Avenue Pierre Brossolette, 91 385 Chilly-Mazarin Cedex, France.
Email: elisheva.lew@sanofi.com

Aim: To evaluate the effect of delaying treatment intensification with a glucagon-like peptide-1 receptor agonist (GLP-1 RA) on clinical and economic outcomes in patients with type 2 diabetes (T2D).

Methods: We conducted a retrospective observational claims study using IMPACT (Impact National Managed Care Benchmark Database) in adult patients with T2D who initiated basal insulin between January 1, 2005 and December 31, 2012, with or without OADs, who remained uncontrolled (glycated haemoglobin [HbA1c] ≥7.0%). Patients were categorized into 3 groups: early, delayed, and no intensification with a GLP-1 RA. We evaluated changes from baseline to follow-up at 12 months for HbA1c level, rate of hypoglycaemic events, and healthcare costs, and we assessed the association between baseline patient characteristics and subsequent treatment intensification.

Results: A total of 139 patients (9.0% of 1552 eligible patients) met criteria for inclusion in the early intensification group, 588 patients (37.9%) met criteria for inclusion in the delayed intensification group, and 825 patients (53.2%) met criteria for inclusion in the no intensification group. Mean baseline HbA1c values were 9.16%, 9.07%, and 9.34%, respectively. At follow-up, delayed intensification was associated with significantly smaller decreases in HbA1c from baseline (−0.68%) compared with early intensification (−1.01%). Rates of overall hypoglycaemia were numerically greater in the delayed intensification group than in the early intensification group (0.26 vs 0.06 events/patient-years of exposure, respectively). Change in semi-annual total healthcare costs was greater in the no intensification group (+5266 USD) compared with the early intensification group (−560 USD) and the delayed intensification group (+1943 USD).

Conclusions: Timely addition of a GLP-1 RA to therapy for patients with T2D who were not adequately controlled with basal insulin is associated with better clinical and economic outcomes.

KEYWORDS
basal insulin, database research, GLP-1 receptor agonist, glycaemic control, type 2 diabetes

1 | INTRODUCTION

Guidelines jointly issued by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD),[1] and the more recent ADA guidelines,[2] recommend a timely stepwise approach to treatment intensification for patients with type 2 diabetes (T2D) who do not achieve or maintain glycaemic targets. Because of the progressive nature of T2D, many patients will eventually need to progress from

metformin monotherapy, through dual and/or triple therapies, to combination injectable therapy. Guidelines note that initial combination therapy using metformin plus a second agent may be better than sequential therapy, allowing patients to more rapidly achieve glycated haemoglobin (HbA1c) targets.[1,2] This approach is suggested to be appropriate for patients with more elevated HbA1c levels (eg, ≥9.0%) who are considered unlikely to achieve glycaemic targets using metformin monotherapy.

When injectable therapy is appropriate, the latest ADA guidelines recommend starting with a basal insulin replacement and, if needed, intensifying treatment by adding either a prandial insulin, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), or switching to a pre-mixed insulin.[2] The latest AACE/ACE guidelines also recommend starting with basal insulin and intensifying, if needed, with either prandial insulin or a GLP-1 RA, a sodium glucose co-transporter 2 - (SGLT2) inhibitor, or a dipeptidyl peptidase-4 (DPP-4) inhibitor.[3]

Recent studies have demonstrated the effectiveness of combining a GLP-1 RA (either shorter- or longer-acting weekly formulations) with basal insulin, where addition of a GLP-1 RA was associated with either equivalent or slightly better glycaemic control than that with the addition of prandial insulin, combined with weight loss and lower risk of hypoglycemia.[4–7] Available data suggest that either a GLP-1 RA or prandial insulin may be appropriate, and that a GLP-1 RA might be a safer option.[6,8,9]

For patients with T2D, there is evidence that early initiation of anti-hyperglycaemic therapy and prompt treatment intensification, when appropriate, reduce the risk of de novo or worsening micro- and macro-vascular complications.[10] Additionally, timely initiation and intensification of treatment are more likely to result in the desired glycaemic control, whereas delaying therapy until HbA1c is elevated (the so called "treat-to-fail" approach) predicts suboptimal response to treatment interventions.[11,12]

Despite guideline recommendations, only 52.5% of patients with T2D in the US reached a glycaemic target of HbA1c < 7.0% from 2007 to 2010.[13] Similarly, reports from around the world describe that glycaemic control (HbA1c <7.0%) was reported in 31.1% of urban and 30.8% of rural patients in India,[14] and in 39.7% of patients in China.[15] And, across 9 European countries (Belgium, France, Germany, Greece, Italy, Netherlands, Spain, Turkey, UK), 37.4% of patients had not achieved their glycaemic target of HbA1c < 7.0%.[16]

Despite general awareness of the disconnect between recommended treatment targets and achievement in clinical practice, clinical inertia or the failure to intensify treatment in a timely manner when patients do not reach recommended glycaemic targets, remains a global problem.[17] Numerous studies have shown that multiple complex factors can act as barriers to treatment intensification and contribute to clinical inertia. These include: physician reluctance to prescribe injectable agents for patients with uncontrolled T2D despite the use of multiple OADs,[18] poor communication between physicians and patients,[17] rudimentary patient understanding of the importance of maintaining good glycaemic control and of the risks of complications associated with poor control,[17] patient resistance to treatment escalation related to fears concerning therapy or the implications of treatment intensification concerning disease progression,[19] poor self-management skills,[19] and discontinuation of injectable therapy because of patient concerns such as fear of needles and associated pain.[20]

It has been suggested that clinical inertia is a factor that contributes to poor outcomes in patients with T2D, resulting in increased healthcare utilization and associated costs.[21,22] The incentive to develop effective strategies to overcome clinical inertia and improve management of T2D will require a deeper understanding of the drivers of, and contributors to, clinical inertia, as well as the effects of clinical inertia on clinical outcomes and the economic burden resulting from delayed treatment intensification.

The objective of this study was to evaluate the effect of delaying treatment intensification with a GLP-1 RA on longitudinal change in clinical outcomes and economic burden in patients with T2D who are inadequately controlled with basal insulin.

2 | RESEARCH DESIGN AND METHODS

2.1 | Study design and eligibility criteria

We conducted a retrospective observational study using the IMPACT™ (Impact National Managed Care Benchmark Database) health insurance database, a large US administrative claims database. Data from IMPACT provides information concerning paid medical and prescription claims and enrollment for national participants in commercial insurance plans of a large US managed care health insurance company (UnitedHealth Group and regional payers). It comprises approximately 50 US healthcare plans and contains medical claims (inpatient, outpatient and emergency department), pharmacy claims, and eligibility data, as well as laboratory results and associated costs, for 107 million patients, of whom 73% had pharmacy benefits and 18% had laboratory results.

The study design is shown in Figure 1. Adult patients ≥18 years of age at the time of basal initiation, with a diagnosis of T2D (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnosis codes 9 250.x0 or 250.x2)[23] were eligible for inclusion in the study. Eligible patients were insulin naïve, and initiated basal insulin between January 1, 2005 and December 31, 2012. This time span allowed for inclusion of a sufficient number of patients with up to 3 years of follow-up data after initiation of basal insulin. All included patients had continuous medical/pharmacy enrolment for at least 6 months prior to initiating basal insulin.

For the purpose of this analysis, patients whose glycaemic control remained inadequate (HbA1c ≥ 7.0%) following addition of basal insulin were selected, and were categorized into 3 groups: (1) the early intensification group underwent treatment intensification with a GLP-1 RA ≤ 6 months after basal insulin initiation; (2) the delayed intensification group underwent treatment intensification with a GLP-1 RA > 6–24 months after basal insulin initiation; and (3) the no intensification group had no reported use of any additional injectable treatments, including GLP-1 RAs, prandial insulin or premixed insulin, within 24 months after initiation of basal insulin. As routine, the last HbA1c value prior to GLP-1 RA initiation (or at 24 months for the no intensification group) was used as the representative HbA1c. If this HbA1c value was closest to the index date was still ≥7.0%, the patient was deemed to have uncontrolled T2D, and qualified for inclusion in the study.

To complement the main analysis, a subgroup analysis was performed by selecting patients receiving basal insulin who had HbA1c ≥ 8.0%
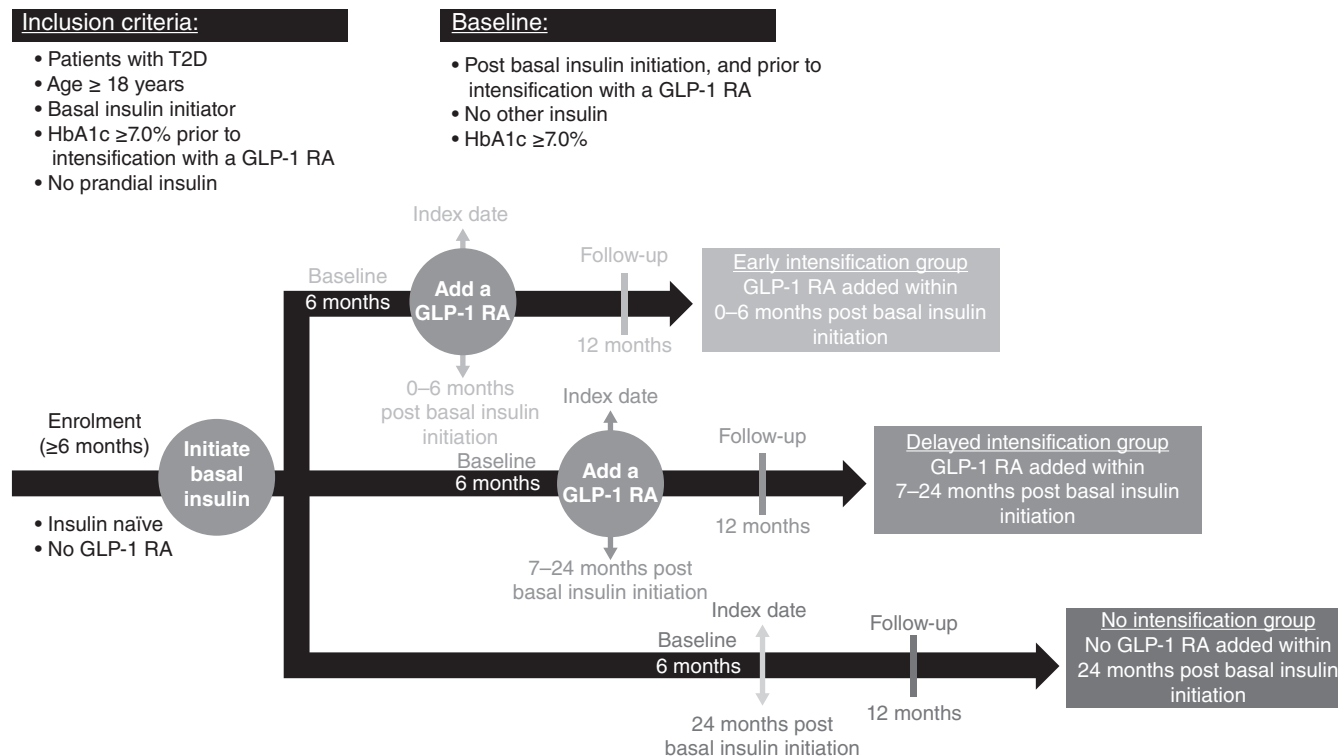
FIGURE 1 Study design. Abbreviations: GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; T2D, type 2 diabetes. A detailed explanation of the study design can be found in the main text (Research Design and Methods)

during the 6-month period prior to GLP-1 RA intensification. This was undertaken to ensure that the results are relevant in a real-world clinical setting where additional injectable therapy may not be initiated in patients with HbA1c < 8.0%. Results from the subgroup analysis are reported in Appendix S1.

In addition to injectables, patients could receive OADs. Changes in OAD therapy and use of injectable agents additional to GLP-1 RAs over the study period were not captured. The index date for early and delayed intensification groups was defined as the initiation date of GLP-1 RA treatment, whereas the index date for the no intensification group was defined as 24 months after basal insulin initiation. A 6-month cut-off point, to distinguish between early and delayed intensification groups, was chosen based on T2D guidelines that recommend evaluation of patients for treatment intensification every 3–6 months.[1–3,24,25] Baseline and follow-up periods were defined as the 6-month period pre-index date and the 12-month period post-index date, respectively. Additionally, patients were required to meet the following criteria: (1) no reported use of injectable T2D treatments prior to the index date, including use of GLP-1 RAs, prandial insulin or premixed insulin; and (2) ≥1 basal insulin prescription 12 months after the index date.

2.2 | Clinical outcomes

Patient characteristics at baseline, including demographics (age, gender), Charlson Comorbidity Index (CCI) score, comorbidities, OAD use, hypoglycaemia, and semi-annual healthcare costs, were described for the 3 groups. Time to treatment intensification was calculated from pharmacy records as the time from initiation of basal insulin to first claim for a GLP-1 RA. Factors associated with time to

treatment intensification during the 6-month period prior to basal insulin initiation were assessed.

Additionally, changes from baseline to follow-up were evaluated for HbA1c and the rate of hypoglycaemic events per patient-years of exposure (PYE). Hypoglycaemic events were identified by ICD-9-CM diagnosis codes 251.0, 251.1, 251.2, and 270.3 for hypoglycaemia, or an ICD-9-CM diagnosis code 9250.8x without diagnosis codes 259.8, 272.7, 681.xx, 682.xx, 686.9x, 707.1-707.9, 709.3, 730.0-730.2, or 731.8. The setting (outpatient or inpatient/emergency department) of a hypoglycaemic event was considered as a proxy for severity of the event (ie, severe event when medically attended and resulted in a healthcare encounter).

2.3 | Economic outcomes

Semi-annual healthcare costs (USD adjusted to the year 2011) were described at baseline for the 3 groups. Total healthcare costs consisted of claims-based actual costs captured from the IMPACT database. These included total inpatient, outpatient, emergency department, and prescription drug costs. Changes in semi-annual total healthcare costs and diabetes-related costs from baseline to follow-up were evaluated.

2.4 | Statistical analyses

Descriptive statistics were reported for patients' demographic and baseline characteristics, while univariate group comparisons were conducted using χ^2 tests for categorical variables and 2-sample t-tests for continuous variables. Multivariable generalized linear mixed models with patients as random effects were used to assess the effect of time to intensification on changes in clinical and economic outcomes from baseline to follow-up, accounting for patients'
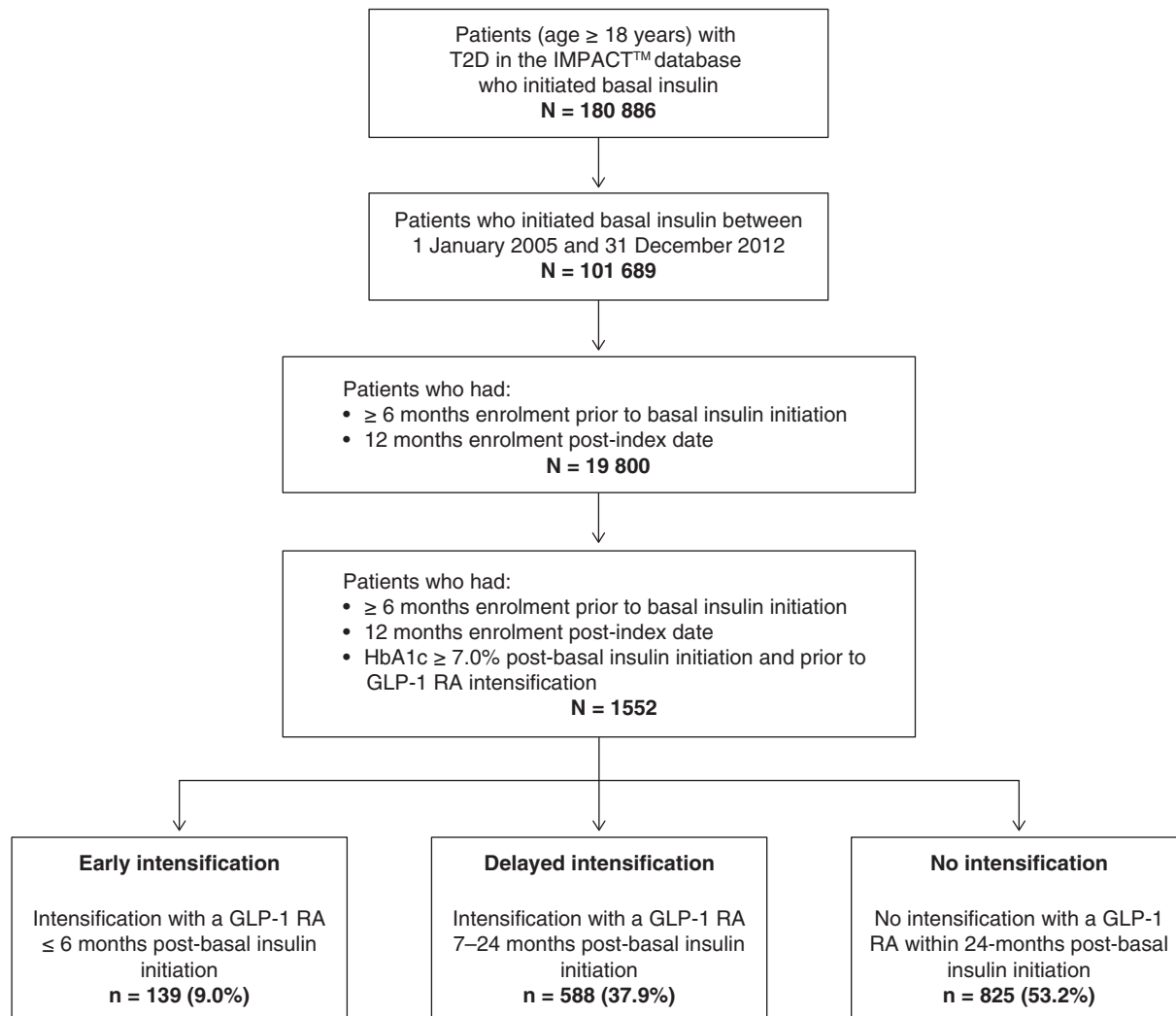
FIGURE 2 Patient disposition. Abbreviations: GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; T2D, type 2 diabetes

demographic and clinical characteristics. Variables with a *P* value <.1 in univariate analyses were entered into the multivariable model as covariates. Rates of hypoglycaemic events were assessed in a Poisson regression with log link function. Total healthcare costs were analysed using a generalized linear model, assuming a negative binomial distribution and log link function. A multivariable Cox proportional hazards regression model was used to evaluate the association between patients' characteristics and days to treatment intensification, adjusting for baseline characteristics.

3 | RESULTS

3.1 | Patient baseline demographics and clinical characteristics

Patient disposition is summarized in Figure 2. Of the 1552 patients who were eligible for inclusion in the study, 139 (9.0%) met criteria for inclusion in the early intensification group, 588 (37.9%) met criteria for inclusion in the delayed intensification group, and 825 (53.2%) met criteria for inclusion in the no intensification group.

Patient baseline demographics and clinical characteristics are summarized in Table 1. Mean HbA1c values were elevated at baseline in each of the groups (early intensification: 9.16%; delayed intensification: 9.07%; no intensification: 9.34%). Age, CCI score, diagnosis of obesity, number of OADs used, and total outpatient costs all differed significantly at baseline among the groups. Compared with the other groups, patients in the early intensification group were younger, had higher outpatient costs, had higher rates of hospitalization and endocrinology visits, were more likely to be obese, and were more likely to use a higher number of OADs during the baseline period. In the delayed intensification group, patients had a lower CCI score and a slightly lower mean HbA1c value. In the no intensification group, patients were older and more likely to use fewer OADs during the baseline period.

3.2 | Change in glycaemic control

At follow-up after 12 months, a significant reduction in HbA1c from baseline was seen in the intensification groups (Figure 3). The least squares (LS) mean HbA1c reduction from baseline was significantly greater (*P* < .001) in the early intensification group (from 9.16% to 8.01%; decrease of 1.01%) than in the delayed intensification group

TABLE 1 Patient baseline demographics and clinical characteristics

Patient profile	Baseline characteristics (6 months prior to GLP-1 RA initiation)			
	Early intensification (n = 139)	Delayed intensification (n = 588)	No intensification (n = 825)	Overall P value
Female, n (%)	66 (47.5)	272 (46.3)	349 (42.3)	.2445
Age in years, mean ± SD (median)	50.8 ± 9.4 (52.0)	53.5 ± 8.9 (54.0)	55.0 ± 10.0 (56.0)	.0018[a,b,c]
Baseline HbA1c, % mean ± SD (median)	9.16 ± 1.57 (8.70)	9.07 ± 1.67 (8.60)	9.34 ± 1.83 (9.00)	.015[b,c]
CCI score (excluding diabetes), mean ± SD (median)	0.6 ± 1.2 (0.0)	0.4 ± 0.8 (0.0)	0.6 ± 1.1 (0.0)	.04[a,c]
Comorbidities				
Obesity, n (%)	35 (25.1)	88 (14.9)	69 (8.3)	<.0001[a,b]
Gastrointestinal disease[d], n (%)	23 (16.5)	67 (11.3)	111 (13.4)	.2184
Macrovascular disease[e], n (%)	23 (16.5)	67 (11.3)	104 (12.6)	.2533
Microvascular disease[f], n (%)	40 (28.7)	201 (34.1)	236 (28.6)	.0709
Number of OADs, mean ± SD (median)	1.99 ± 1.04 (2.00)	1.9 ± 1.0 (2.0)	1.6 ± 1.03 (2.60)	<.0001[a,b,c]
Types of OAD, n (%)				
Metformin	105 (75.5%)	412 (70.0%)	519 (62.9%)	.0013[b,c]
TZD	47 (33.8%)	165 (28.0%)	197 (23.8%)	.0239[b,c]
Sulfonylureas	83 (59.7%)	322 (54.7%)	399 (48.3%)	.0089
DPP-4 inhibitors	35 (25.1%)	152 (25.8%)	147 (17.8%)	.0008[b,c]
Hypoglycaemia				
Any hypoglycaemia, n (%)	6 (4.3)	20 (3.4)	31 (3.7)	.8598
Hypoglycaemia, events per PYE, mean ± SD (median)	0.05 ± 0.250 (0.000)	0.17 ± 2.32 (0.000)	0.15 ± 1.5 (0.000)	.7659
Semi-annual healthcare costs[g], USD, mean ± SD (median)				
Total costs	10 851 ± 14 468 (5660)	8038 ± 13 361 (4776)	8460 ± 13 920 (4290)	.0945
Total inpatient costs	3023 ± 10 922 (0)	1755 ± 11 002 (0)	2336 ± 10 132 (0)	.3633
Total outpatient costs	4205 ± 8826 (1758)	2652 ± 5318 (1173)	2668 ± 4993 (907)	.0029[a,b]
Total ED department costs	296 ± 1256 (0)	267 ± 987 (0)	294 ± 1120 (0)	.8885
Total prescription drug costs	3327 ± 2672 (2737)	3364 ± 2682 (2825)	3162 ± 4708 (2308)	.6135
Healthcare utilization, mean ± SD (median)				
Hospitalization	0.13 ± 0.34 [0.00]	0.07 ± 0.36 [0.00]	0.10 ± 0.36 [0.00]	.1299
Diabetes related hospitalization	0.12 ± 0.33 [0.00]	0.06 ± 0.30 [0.00]	0.09 ± 0.32 [0.00]	.0563
Office visits	10.22 ± 7.49 [9.00]	7.89 ± 6.53 [6.00]	7.48 ± 9.96 [5.00]	.0024
Diabetes related office visits	5.48 ± 2.56 [5.00]	4.03 ± 3.17 [3.00]	3.50 ± 6.85 [3.00]	.0002
Endocrinologist visits	1.61 ± 1.83 [1.00]	0.95 ± 1.40 [0.00]	0.31 ± 0.81 [0.00]	<.0001
Diabetes related endocrinologist visits	1.59 ± 1.81 [1.00]	0.93 ± 1.37 [0.00]	0.29 ± 0.78 [0.00]	<.0001

Abbreviations: CCI, Charlson Comorbidity Index; DPP-4, dipeptidyl peptidase-4; ED, emergency department; OAD, oral antidiabetes drug; PYE, patient-year of exposure; SD, standard deviation; TZD, thiazolidinedione.

[a] P < .05 for early intensification vs delayed intensification.

[b] P < .05 for early intensification vs no intensification group.

[c] P < .05 for delayed intensification vs no intensification.

[d] Includes nausea, vomiting, diarrhoea, constipation, abdominal pain, and stomach disorders.

[e] Myocardial infarction, congestive heart failure, peripheral vascular disease, and stroke.

[f] Retinopathy, neuropathy, and nephropathy.

[g] Unadjusted semi-annual costs.

(from 9.07% to 8.39%; decrease of 0.68%) and the no intensification group (from 9.32% to 9.12%; decrease of 0.20%). In the early and delayed intensification groups, the LS mean reduction in HbA1c was significantly greater (P < .001) than in the no intensification group.

3.3 | Change in hypoglycaemia rate

The rates of hypoglycaemic events per PYE according to treatment group are shown in Table 2. In patients who underwent treatment

intensification with a GLP-1 RA, a trend towards decreased rates of overall hypoglycaemia and outpatient hypoglycaemia was seen from baseline to follow-up. Conversely, for patients in the no intensification group, there was a trend towards increased rates of overall hypoglycaemia and outpatient hypoglycaemia from baseline to follow-up.

Compared with the group who received delayed intensification with a GLP-1 RA, numerically lower rates of overall hypoglycaemia (−35%; relative risk ratio, 0.65; 95% Confidence interval [CI]; 0.35, 1.23) and of outpatient hypoglycaemia (−33%; relative risk ratio,
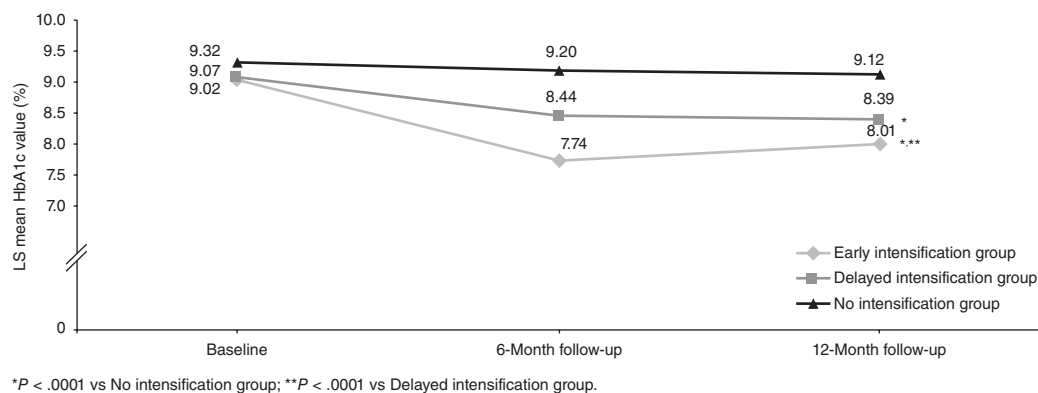
*P < .0001 vs No intensification group; **P < .0001 vs Delayed intensification group.

FIGURE 3 LS mean change in HbA1c value over time according to treatment intensification group. Abbreviations: HbA1c, glycated haemoglobin; LS, least squares

TABLE 2 Rates of hypoglycaemic events per PYE and relative risk ratios among groups

Outcome	Early intensification group (n = 139)		Delayed intensification group (n = 588)		No intensification group (n = 825)		Relative risk ratio (95% CI)		
	Baseline	12-month follow-up	Baseline	12-month follow-up	Baseline	12-month follow-up	Early intensification vs Delayed intensification	Early intensification vs No intensification	Delayed intensification vs No intensification
Overall hypoglycaemic events per PYE[a]	0.10 (0.50)	0.06 (0.52)	0.34 (4.60)	0.26 (1.83)	0.30 (2.98)	0.36 (3.66)	0.65 (0.35, 1.23)	0.84 (0.45, 1.87)	0.96 (0.79, 1.16)
Outpatient hypoglycaemic events per PYE[a]	0.08 (0.44)	0.04 (0.51)	0.30 (4.44)	0.24 (1.79)	0.26 (2.88)	0.32 (3.57)	0.67 (0.32, 1.39)	0.85 (0.41, 1.75)	0.94 (0.77, 1.15)
Inpatient/ED hypoglycaemic events per PYE[a]	0.02 (0.24)	0.02 (0.12)	0.02 (0.28)	0.02 (0.16)	0.02 (0.24)	0.04 (0.24)	n.a.	n.a.	n.a.

Abbreviations: CI, confidence interval; ED, emergency department; n.a., not available, as model did not converge because of small sample size; PYE, patient-years of exposure.

[a] Data are shown as mean ± SD.

0.67; 95% CI; 0.32, 1.39) were reported for the group that received early intensification with a GLP-1 RA. Comparing the early intensification group with the no intensification group, a similar trend towards lower overall hypoglycaemia and outpatient hypoglycaemia was observed.

3.4 | Change in semi-annual healthcare costs

The change in LS means semi-annual total healthcare costs over time, according to treatment group, is shown in Figure 4. From baseline to follow-up, the increase in LS mean semi-annual total healthcare costs was significantly greater in the no intensification group (+5260 USD; from 6926 USD to 12 192 USD) compared with the early intensification group (−560 USD; from 9581 USD to 9021 USD; P = .0011) and the delayed intensification group (+1943 USD; from 7780 USD to 9723 USD; P = .001).

3.5 | Factors associated with treatment intensification with a GLP-1 RA

We investigated baseline factors (ascertained from the 6-month period immediately prior to basal insulin initiation) that were associated with treatment intensification with a GLP-1 RA. Comparing the early and delayed intensification groups, factors associated with a significantly increased likelihood of early treatment intensification were: younger age (Odds Ratio [OR], 0.967 [CI; 0.947–0.987]), higher CCI score (OR, 1.253; [CI; 1.043–1.505]), and diagnosis of obesity (OR, 1.750 [CI; 1.113–2.751]). Comparing patients who underwent treatment intensification (early and delayed intensification groups) with patients in the no intensification group, baseline factors associated with a significantly greater likelihood of undergoing treatment intensification were: younger age (OR, 0.980 [CI; 0.969–0.990]), lower CCI score (OR, 0.892 [CI; 0.803–0.990]), higher OAD usage (OR, 1.374 [CI; 1.240–1.552]) and diagnosis of obesity (OR, 2.269 [CI; 1.645–3.130]).

3.6 | Factors associated with timing of intensification with a GLP-1 RA

The median time to treatment intensification with a GLP-1 RA was 111 days for the early intensification group and 540 days for the delayed intensification group. Results of the multivariable Cox regression analysis for time to treatment intensification are shown in Table 3. Time to treatment intensification with a GLP-1 RA was significantly longer in older patients (hazard ratio [HR], 0.98 [for each 1-year increase in age]; 95% CI; 0.97, 0.99) and was inversely
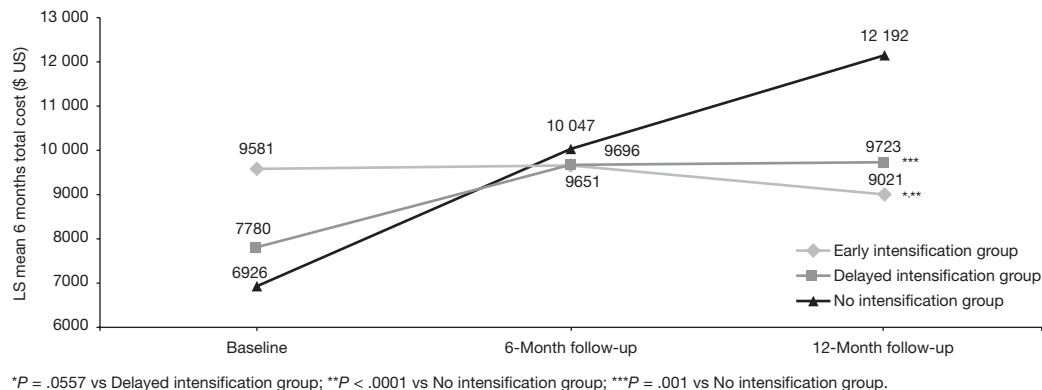
*P = .0557 vs Delayed intensification group; **P < .0001 vs No intensification group; ***P = .001 vs No intensification group.

FIGURE 4 LS mean change in semi-annual total healthcare costs over time according to treatment intensification group. Abbreviation: LS, least squares

TABLE 3 Multivariable Cox regression for time to intensification with a GLP-1 RA

Outcome	Hazard ratio	95% CI	P value
Age at index date	0.979	0.971, 0.986	<.0001
Number of OADs at baseline (ref = 0)			
1		1.253, 2.208	.0004
2		1.372, 2.335	<.0001
3		1.558, 2.754	<.0001
≥4		1.605, 3.893	<.0001
Diagnosis of obesity (Yes vs No)	1.434	1.179, 1.744	.0003

Abbreviations: CI, confidence interval; OAD, oral antidiabetes drug.

correlated with the number of OADs used at baseline. A diagnosis of obesity was significantly associated with a shorter time to treatment intensification (HR, 1.4; 95% CI; 1.2, 1.7).

4 | DISCUSSION

In patients with T2D who do not meet glycaemic goals, the importance of timely treatment intensification, when appropriate, has been emphasized by international clinical guidelines. Despite this, clinical inertia remains a major barrier to optimal diabetes care, contributing to poor outcomes and increased healthcare costs.

Using data from a large administrative claims database, representative of a large proportion of the US population, this study revealed that only 9.0% of patients who failed to meet HbA1c targets using basal insulin (with or without 1 or more OADs) underwent treatment intensification with a GLP-1 RA within 6 months of insulin initiation. The majority (53.2%) underwent no treatment intensification with any injectable therapy, and the remaining 37.9% of patients underwent delayed intensification with a GLP-1 RA between 7 and 12 months after basal insulin initiation.

At follow-up after 12 months, compared with early intensification, delayed intensification with a GLP-1 RA was shown to be associated with significantly smaller decreases in HbA1c from baseline, and numerically greater rates of overall and outpatient hypoglycaemia. Compared with treatment intensification with a GLP-1 RA (early or delayed), no treatment intensification was associated with significantly lower reduction in HbA1c, and a trend towards increased rates of hypoglycaemia. Because of their glucose-dependent mechanism of action, GLP-1 RAs are typically associated with low rates of minor hypoglycaemic events.[26-30] Furthermore, in clinical trials, the majority of hypoglycaemic events with GLP-1 RAs occurred with concomitant use of insulin or insulin secretagogues.[31] To avoid hypoglycaemia, it is recommended to lower the dose of these agents when adding a GLP-1 RA.[32]

At follow-up after 12 months, reduction in semi-annual total healthcare costs from baseline was significantly greater in the early intensification group than in the delayed or no intensification groups, despite addition of an expensive therapy, such as a GLP-1 RA. Considering data for 'factors associated with intensification' alongside 'total cost over time by intensification group,' younger age, lower CCI scores, and higher obesity are associated with a greater likelihood of intensification, which is in turn associated with lower costs. The association between obesity and a greater likelihood of treatment intensification with a GLP-1 RA might be expected. Most clinical trials and meta-analyses concerning the use of GLP-1 RAs, in patients with or without T2D, have demonstrated weight reduction as a primary or secondary treatment outcome.[33] It is possible that physicians are more likely to intensify therapy with a GLP-1 RA for obese and younger patients because of the added benefit of weight loss in addition to improved glycaemic control.

Patient selection for treatment intensification is known to be associated with an inherent bias, where, for example, younger patients tend to be treated more aggressively. Patients in the group who received early intensification with a GLP-1 RA had the lowest baseline overall and outpatient rates of hypoglycaemia, which may have contributed to their selection for prompt treatment intensification. Regarding the observed increase in healthcare costs from baseline to follow up in the no intensification group (5266 USD) compared with the decrease in the early intensification group (–560 USD), it is possible that the slightly older age and higher baseline comorbidities in the no intensification group may have indirectly played a role. However, age and general comorbidities were adjusted for in the generalized linear model used. At baseline, mean total prescription drug costs (for management of diabetes and other conditions) for patients in the early intensification group were not significantly higher than those for patients in the no intensification group. This may be explained by the

inclusion of antidiabetes treatments other than GLP-1 RA, as well as treatments for diabetes complications and comorbidities, in the total prescription drug costs of the no intensification group. Interestingly, in the early intensification vs delayed intensification comparison, higher comorbidities were found to be associated with earlier intensification, whereas, in the intensification vs no intensification comparison, higher comorbidities were associated with no intensification.

Results of the subgroup analysis of patients with HbA1c ≥ 8.0% were largely comparable to those obtained for the overall patient population with HbA1c ≥ 7.0%, with similar baseline characteristics and trends among the 3 groups. The differences in HbA1c reduction and rate of hypoglycaemic events between the groups who received early and delayed intensification with a GLP-1 RA were less evident in the subgroup analysis, compared with results from the overall patient population; however, a similar trend was observed in change in semi-annual healthcare costs among the 3 groups over time.

A major strength of this study is the use of data from clinical practice rather than from the controlled environment of a clinical trial, allowing for assessment of real-world practices and outcomes. Included patients were identified from a large health insurance claims database representative of a large proportion of the US population, and both descriptive and adjusted results were presented.

As with all studies, our analysis has certain limitations. As this retrospective study used data derived from a pre-existing database, only captured information was analysed. Consequently, the study may not be fully representative of differences observed in clinical practice (eg, data on hypoglycaemia may be an underestimation of the true rate of hypoglycaemic events). Data may be subject to possible coding errors, resulting in some diagnoses being missed or used incorrectly. Certain patient baseline demographic or clinical characteristics were not available from the claims data (eg, patient body weight). The 3 groups differed in sample size, with the early intensification group comprising considerably fewer patients than the other groups. This lack of parity in sample size may have had an impact on the results of comparisons among groups. The definition of "intensification" used in this study does not include intensification with therapies other than a GLP-1 RA. Thus, it is difficult to comment on clinical inertia other than where it concerns intensification with a GLP-1 RA. Baseline OAD use during the baseline period 6 months prior to GLP-1 initiation indicated a trend for fewer OADs among patients in the late and no intensification groups. This may indicate that patients in these 2 groups might have received "intensification" via the addition of other OADs during the study period. Dosing information for basal insulin is not available from claims databases and, therefore, could not be taken into account. The definitions of early and late intensification were based on a cut-off point of 6 months, which may have yielded biased estimations of the differences in clinical outcomes and healthcare costs among groups (eg, patients in the early intensification group may have a greater medical need for immediate treatment intensification). During the analysis, factors such as treatment switching, medication adherence or persistence, and suboptimal dosing of medication were not taken into account. This may confound the impact of treatment intensification in the real world. Analysis of factors associated with treatment intensification was largely exploratory, where the model fitting was not examined. It is possible that the direction of association may be affected by the small sample size of the early intensification group and distribution of the CCI score.

In conclusion, this study found that less than 10% of patients with T2D who are inadequately controlled with basal insulin underwent treatment intensification with a GLP-1 RA within 6 months of insulin initiation. Compared with early treatment intensification, delayed treatment intensification with a GLP-1 RA was associated with poorer glycaemic control, greater risk of hypoglycaemia, and higher total healthcare costs at the 12-month follow-up. Compared with patients who did not undergo treatment intensification during the 12-month follow-up period, healthcare costs for both the early and delayed intensification cohorts were significantly lower. Younger age, higher CCI score and a diagnosis of obesity at baseline were all positively associated with early treatment intensification with a GLP-1 RA. The identification of factors associated with early treatment intensification will be helpful in determining clinical practice patterns associated with clinical inertia.

Finally, for patients with T2D who are inadequately controlled with basal insulin, timely treatment intensification with a GLP-1 RA was associated with better glycaemic control and lower financial burden than that observed with delayed treatment intensification.

Conflict of interest

L. T. and C. P. were employees of PRO Unlimited, supporting Sanofi projects at the time of this analysis. H. W. was an employee of Sanofi US, Inc. at the time of this analysis. M. B. and E. L. are employees and stock-/shareholders of Sanofi France. L. M. is a consultant and member of scientific advisory boards for Sanofi and Novo Nordisk.

Author contributions

The study was designed by L.T., C.P., H.W., M.B. and E.L. and was conducted by L.T. C.P. and H.W. All authors contributed to the analysis and interpretation of the results, and to drafting and critically revising of the manuscript. All authors confirm that they meet the International Committee of Medical Journal Editors uniform requirements for authorship; they have read, reviewed and approved the final version and agree to be accountable for all aspects of the work.

ORCID

Elisheva Lew http://orcid.org/0000-0001-5097-0169

REFERENCES

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the

European Association for the Study of diabetes. *Diabetes Care*. 2015; 38:140–149.

2. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment. *Diabetes Care*. 2017;40(suppl 1):S64–S74.

3. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive type 2 diabetes management algorithm – 2017 executive summary. *Endocr Pract*. 2017;23:207–238.

4. Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med*. 2011;154:103–112.

5. Diamant M, Nauck MA, Shaginian R, et al. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. *Diabetes Care*. 2014;37:2763–2673.

6. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet*. 2014;384:2228–2234.

7. Rosenstock J, Guerci B, Hanefeld M, et al. Prandial options to advance basal insulin glargine therapy: testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: the Getgoal Duo-2 Trial. *Diabetes Care*. 2016;39:1318–1328.

8. Balena R, Hensley IE, Miller S, Barnett AH. Combination therapy with GLP-1 receptor agonists and basal insulin: a systematic review of the literature. *Diabetes Obes Metab*. 2013;15:485–502.

9. Charbonnel B, Bertolini M, Tinahones FJ, Domingo MP, Davies M. Lixisenatide plus basal insulin in patients with type 2 diabetes mellitus: a meta-analysis. *J Diabetes Complications*. 2014;28:880–886.

10. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577–1589.

11. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. *Diabetes Care*. 2004;27:1535–1540.

12. Karter AJ, Moffet HH, Liu J, et al. Glycemic response to newly initiated diabetes therapies. *Am J Manag Care*. 2007;13:598–606.

13. Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. *Diabetes Care*. 2013;36:2271–2279.

14. Unnikrishnan R, Anjana RM, Deepa M, et al. Glycemic control among individuals with self-reported diabetes in India—the ICMR-INDIAB Study. *Diabetes Technol Ther*. 2014;16:596–603.

15. Xu Y, Wang L, He J, et al. Prevalence and control of diabetes in Chinese adults. *JAMA*. 2013;310:948–959.

16. de Pablos-Velasco P, Parhofer KG, Bradley C, et al. Current level of glycaemic control and its associated factors in patients with type 2 diabetes across Europe: data from the PANORAMA study. *Clin Endocrinol (Oxf)*. 2014;80:47–56.

17. Strain WD, Cos X, Hirst M, et al. Time to do more: addressing clinical inertia in the management of type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2014;105:302–312.

18. Levin PA, Wei W, Zhou S, Xie L, Baser O. Outcomes and treatment patterns of adding a third agent to 2 OADs in patients with type 2 diabetes. *J Manag Care Spec Pharm*. 2014;20:501–512.

19. Ratanawongsa N, Crosson JC, Schillinger D, Karter AJ, Saha CK, Marrero DG. Getting under the skin of clinical inertia in insulin initiation: the Translating Research Into Action for Diabetes (TRIAD) Insulin Starts Project. *Diabetes Educ*. 2012;38:94–100.

20. Spain CV, Wright JJ, Hahn RM, Wivel A, Martin AA. Self-reported barriers to adherence and persistence to treatment with injectable medications for type 2 diabetes. *Clin Ther*. 2016;38:1653–1664.

21. Dunn JD. Diabetes pharmacy management: balancing safety, cost, and outcomes. *Am J Manag Care*. 2010;16(suppl 7):S201–S206.

22. Ziemer DC, Miller CD, Rhee MK, et al. Clinical inertia contributes to poor diabetes control in a primary care setting. *Diabetes Educ*. 2005;31:564–571.

23. Centers for Disease Control and Prevention. International Classification of Diseases, Ninth Revision (ICD-9). Available at: www.cdc.gov/nchs/icd/icd9.htm. Accessed July 10, 2016.

24. National Institute for Health and Care Excellence (2015). Type 2 diabetes in adults: management: NICE guidelines [NG28]. Available at: https://www.nice.org.uk/guidance/ng28/chapter/1-Recommendations#hba1c-measurement-and-targets. Accessed January 10, 2017.

25. International Diabetes Federation. 2012 Clinical guidelines task force. Global guideline for type 2 diabetes Available at: http://www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf. Accessed January 10, 2017.

26. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care*. 2005;28:1092–1100.

27. Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia*. 2009;52:2046–2055.

28. Drucker DJ, Buse JB, Taylor Kendall DM, Trautmann M, Zhaung D, Porter L. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet*. 2008;372:1240–1250.

29. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care*. 2009;32:84–90.

30. Rosenstock J, Reusch J, Bush M, Yang F, Stewart M, Albiglutide Study Group. Potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: a randomized controlled trial exploring weekly, biweekly, and monthly dosing. *Diabetes Care*. 2009;32:1880–1886.

31. Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ*. 2012; 344:d7771.

32. Cefalu WT, Buse JB, Del Prato S, et al. Beyond metformin: safety consideration in the decision making process for selecting a second medication for type 2 diabetes management. Reflections from a diabetes care editors' expert forum. *Diabetes Care*. 2014;37:2647–2659.

33. Isaacs D, Prasad-Reddy L, Srivastava SB. Role of glucagon-like peptide 1 receptor agonists in management of obesity. *Am J Health Syst Pharm*. 2016;73:1493–1507.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Tong L, Pan C, Wang H, Bertolini M, Lew E, Meneghini LF. Impact of delaying treatment intensification with a glucagon-like peptide-1 receptor agonist in patients with type 2 diabetes uncontrolled on basal insulin: A longitudinal study of a US administrative claims database. *Diabetes Obes Metab*. 2018;20:831–839. https://doi.org/10.1111/dom.13156