Review Article

Pharmacotherapy for Type 2 Diabetes Mellitus: What's Up and Coming in the Glucagon-Like Peptide-1 (GLP-1) Pipeline?

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Mary J. Elder, PharmD[1] and Emily J. Ashjian, PharmD, BCPS, BCACP, CDCES[2]

Abstract

Glucagon-like peptide-1 (GLP-1), an incretin hormone, is known to lower glucose levels, suppress glucagon secretion, and slow gastric emptying. These properties make GLP-1 an ideal target in treating type 2 diabetes mellitus (T2DM). There are many FDA-approved GLP-1 agonists on the market today, several of which have demonstrated benefit beyond improving glycemic control. Given the beneficial effects of GLP-1 agonists in patients with T2DM, new drugs are in development that combine the mechanism of action of GLP-1 receptor agonism with novel mechanisms and with drugs that promote GLP-1 secretion. These agents are designed to improve glycemic control and target greater body weight reduction. This article discusses new GLP-1 drugs in the pipeline for the treatment of T2DM.

Keywords

diabetes mellitus, glucagon-like peptide-1 receptor agonist, gastric inhibitory polypeptide, G protein-coupled receptor 119 agonist, glucagon receptor agonist

Introduction

Type 2 diabetes mellitus (T2DM) affects 34.2 million people in the United States, and the numbers continue to rise.[1] T2DM is characterized by progressive insulin resistance and beta-cell dysfunction which can lead to complications including blindness, kidney failure, cardiovascular events, and lower limb amputation.[2] The goal of treatment is to control blood glucose as measured by glycated hemoglobin (A1c) and prevent micro- and macrovascular complications.[2] Due to the progressive nature of T2DM and ongoing deterioration of beta-cell function, glycemic control can be difficult to obtain for many patients. Thus, the development of novel treatments is of utmost importance.

For patients with T2DM, metformin in combination with lifestyle changes is recommended.[3] When choosing a second-line agent, a patient-centered approach is suggested with consideration of whether the patient has been diagnosed with or is at a high risk for atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), or chronic kidney disease (CKD), if the patient needs to lose weight, or if the patient is at a high risk for hypoglycemia.[3] Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RA) with proven cardiovascular (CV) benefit or sodium-glucose cotransporter-2 (SGLT2) inhibitors with proven CV benefit are recommended as a preferred treatment option for patients with ASCVD or if they have indicators of high risk, whereas SGLT2 inhibitors with proven benefit are recommended preferentially in patients with HF with reduced ejection fraction and in patients with CKD. GLP-1 RA offer weight loss benefits with a low risk of hypoglycemia when used as monotherapy or as an add-on to metformin.[3]

GLP-1 is an incretin hormone that is produced in the intestine in response to food.[4] GLP-1 is known to lower glucose levels, suppress glucagon secretion, and slow gastric emptying, making it a target of interest in treating diabetes.[4] There are currently 7 GLP-1 RA that are FDA approved for the treatment of diabetes.[5-11] Benefits of these medications include decreased glucagon concentrations, increased insulin secretion, decreased A1c, delayed gastric emptying leading to increased satiety, decreased bodyweight, and cardioprotection.[4] When considering use of a GLP-1 RA, these benefits should be weighed against potential adverse effects (AE) including gastrointestinal

[1]Pharmacy Innovations and Partnerships, Michigan Medicine, Ann Arbor, MI, USA.
[2]Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, MI, USA

Corresponding Author:
Mary J. Elder, PharmD, Pharmacy Innovations and Partnerships, Michigan Medicine, 2500 Green Road, Suite 100, Ann Arbor, MI 48105, USA.
Email: elmaryjo@med.umich.edu

upset with slowing of gastric emptying. Patients should also be assessed for any contraindications (personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2) and precautions (e.g., pancreatitis) and counseled to monitor for injection site reactions.[4-11]

As GLP-1 RA have shown benefit in the treatment of diabetes, new medications are under development with novel mechanisms of action used in combination with GLP-1 receptor agonism.[12-15] There are also medications in development that promote GLP-1 secretion and new medications within the GLP-1 class.[16-18] All of these agents aim to further improve glycemic control in T2DM and reduce bodyweight. The objective of this article is to discuss medications in development in the GLP-1 agonist pipeline and ongoing clinical trials.

Methods

An English-language literature search was conducted of all articles in PubMed through October 28, 2019 using the filter Adult 19+ years. Search terms included Type 2 Diabetes Mellitus or Diabetes Mellitus, or body weight in combination with each of the following terms: Glucagon-Like Peptides, Glucagon-Like Peptide-1 Receptor, Gastric Inhibitory Polypeptide, dulaglutide, efpeglenatide, liraglutide and drug-therapy, treatment, treatment outcome, and not insulin.

A total of 1008 articles resulted from the search; these articles were reviewed for inclusion. Inclusion criteria consisted of medications that are not currently FDA-approved and are still in development for the treatment of T2DM. Medications were excluded if they were FDA-approved or if clinical trials had been discontinued. It was determined there was 1 medication that did not result in our PubMed search, efpeglenatide. A Google Scholar search was completed for this medication.

Dual GLP-1 and Glucose-Dependent Insulinotropic Polypeptide (GIP) Receptor Agonists

LY3298176 (Tirzepatide)

Tirzepatide combines the mechanism of action of GLP-1 and GIP. GIP is an incretin hormone that is secreted from intestinal K cells in response to food. GIP induces insulin secretion under hyperglycemic conditions and glucagon secretion under hypoglycemic conditions. GIP receptors are also expressed in adipose tissue, leading to additional activity in regulating glucose uptake and lipolysis suggesting a role in fat accumulation and weight regulation. Tirzepatide has been formulated as a once weekly subcutaneous injection.[12,19]

Coskun et al conducted a three-part randomized, placebo-controlled, double-blind study of tirzepatide.[12] The first part was a single-ascending dose (SAD) protocol in healthy subjects, followed by a multiple-ascending dose (MAD) protocol done over 4 weeks in healthy subjects. Part 3 was a four-week multiple-dose Phase 1b proof-of-concept (POC) protocol completed in patients with T2DM. Patients in the SAD study were randomized to tirzepatide (.25 mg, .5 mg, 1 mg, 2.5 mg, 5 mg, 8 mg) or placebo and those in the MAD study were randomized to tirzepatide (.5 mg, 1.5 mg, 4.5 mg or titration of 5 mg, 5 mg, 8 mg, 10 mg up-titrated weekly), dulaglutide (1.5 mg), or placebo. Patients in the POC study were randomized to either one of two fixed doses of tirzepatide (.5 mg or 5 mg) or 1 of 2 titration schedules up to 10 mg (5 mg, 5 mg, 10 mg, 10 mg) or 15 mg (5 mg, 5 mg, 10 mg, 15 mg) which were both up-titrated weekly. A total of 146 patients were enrolled across the three study parts, with 142 patients included in the final analysis. The primary objective was to investigate safety and tolerability of tirzepatide in healthy patients (SAD and MAD) and patients with T2DM (POC). Secondary outcomes included changes in fasting plasma glucose (FPG), A1c, and bodyweight. The most frequent AE reported across all 3 parts of the study were gastrointestinal in nature and mild to moderate in severity (Table 1). The gastrointestinal AE were dose limiting at 8 mg in the SAD study; however, higher doses were tolerated in the MAD and POC studies, but were still limiting in patients who did not have dose titrations. Patients in the POC study who had T2DM tolerated higher doses and had fewer gastrointestinal AE overall. Incidence of other AE including hypoglycemia was low, without any cases of acute pancreatitis. Change in FPG was only significant for the tirzepatide 4.5 mg dose compared with placebo in the MAD trial on day 29. In the POC study, only the 5/5/10/10 mg and 5/5/10/15 mg titrations were significant for change in FPG and A1c from baseline to day 29 with −1% and −.74% decreases in A1c, respectively. In both the MAD and POC studies, bodyweight decreased in a dose- and time-dependent manner. In the MAD study, all treatment groups had statistically significant decreases in weight except for the .5 mg group. In the POC study, the two titration doses up to 10 mg and 15 mg were significant for weight decrease compared to placebo. The authors concluded that greater titration optimization was needed to improve tolerability, but the efficacy was promising and warranted further studies.[12]

Frias et al conducted a double-blind, randomized, placebo- and active-comparator controlled study to determine safety and efficacy of tirzepatide in patients with T2DM.[19] A total of 318 adults with T2DM uncontrolled with lifestyle changes or on a stable dose of metformin were randomized to receive tirzepatide (1 mg, 5 mg, 10 mg, or 15 mg), dulaglutide (1.5 mg), or placebo for 26 weeks. Average A1c at baseline in all groups was 8.1% and average weight at baseline was 92.8 kg. The primary outcome was change in A1c from baseline to week 26 compared to placebo and dulaglutide; secondary endpoints included change in FPG, mean bodyweight, and waist circumference from baseline to weeks 12 and 26. Mean change in A1c for all doses of tirzepatide was greater than that of placebo, −.7% for 1 mg ($P = .0004$), −1.6% for 5 mg ($P < .0001$), −2.0% for 10 mg ($P < .0001$), −2.4% for

Table 1. Common Adverse Effects.[a]

	Gastrointestinal Effects n (%)			Injection site Reaction n (%)	Pancreatitis Incidence n (%)
Tirzepatide					
Coskun et al[12]	Vomiting	Diarrhea	Nausea		
LY3298176 .5 mg (n = 9)	1 (11.1)	1 (11.1)	1 (11.1)	None reported across all doses and placebo	None reported across all doses and placebo
5 mg (n = 9)	0	1 (11.1)	1 (11.1)		
5/5/10/10 mg (n = 12)	1 (8.3)	3 (25.0)	1 (8.3)		
5/5/10/15 mg (n = 12)	9 (75.0)	5 (41.7)	6 (50.0)		
Placebo (n = 11)	0	1 (9.1)	0		
Frias et al[19]					
LY3298176 1 mg (n =52)	12 (23.1)			1 (1.9)	0
5 mg (n = 55)	18 (32.7)			3 (5.5)	2 (3.6)
10 mg (n = 51)	26 (51.0)			4 (7.8)	0
15 mg (n = 53)	35 (66.0)			1 (1.9)	0
Dulaglutide 1.5 mg (n = 54)	23 (42.6)			6 (11.1)	0
Placebo (n = 51)	5 (9.8)			2 (3.9)	0
NNC0090-2746 (RG7697)					
Portron et al[13 b]	Vomiting		Nausea		
RG7697 .03 mg (n = 6)	1 (17)		1 (17)	None reported across all doses and placebo	Not reported
.07 mg (n = 7)	0		1 (14)		
.2 mg (n = 6)	0		1 (17)		
.6 mg (n = 6)	0		0		
1.8 mg (n = 5)	0		1 (20)		
3.6 mg (n = 6)	0		2 (33)		
5 mg (n = 2)	1(50)		2 (100)		
Placebo (n = 13)	0		1 (8)		
Schmitt et al[20 c]	Diarrhea		Nausea		
RG7697 .25 mg (n = 8)	2 (25.0)		2 (25.0)	2 (25)	Not reported
.75 mg (n = 9)	1 (11.1)		1 (11.1)	0	
1.1 mg (n = 5)	3 (60.0)		2 (40.0)	1 (20)	
1.5 mg (n = 9)	0		2 (22.2)	2 (22.2)	
2 mg (n = 4)	2 (50.0)		1 (25.0)	0	
2.5 mg (n = 7)	4 (57.1)		4 (57.1)	1 (14.3)	
Placebo (n = 14)	3 (21.4)		3 (21.4)	2 (14.3)	
Frias et al[21]					
NNC0090-2746 1.8 mg (n = 37)	13 (35.1)			4 (10.8)	None reported across all doses and placebo
Placebo (n = 36)	6 (16.7)			0	
SAR425899					
Tillner et al[14]	Vomiting	Diarrhea	Nausea		
MAD1—SAR425899 .025-.05-.075 mg (n = 6)	0	1 (16.7)	2 (33.3)	None reported across all doses and placebo	Not reported
.05-.075-.1 mg (n = 6)	0	0	0		
.05-.1-.15 mg (n = 6)	0	0	0		
.06-.12-.18 mg (n = 6)	2 (33.3)	2 (33.3)	3 (50.0)		
.05-.1-.2 mg (n = 6)	3 (50.0)	2 (33.3)	5 (83.3)		
Placebo (n = 10)	0	1 (10.0)	0		
MAD2—SAR425899 .03-.06-.09 mg (n = 9)	0	2 (22.2)	1 (11.1)		
.06-.12-.18 mg (n = 18)	3 (16.7)	5 (27.8)	6 (33.3)		
Placebo (n = 9)	0	4 (44.4)	0		

(continued)

Table 1. (continued)

	Gastrointestinal Effects n (%)	Injection site Reaction n (%)	Pancreatitis Incidence n (%)
MEDI0382			
MEDI0382 5 μg (n = 6)	0	0	Not reported
10 μg (n = 6)	1 (16.7)	0	
30 μg (n = 6)	0	1 (16.7)	
100 μg (n = 6)	1 (16.7)	0	
150 μg (n = 6)	5 (83.3)	0	
300 μg (n = 6)	5 (83.3)	0	
Placebo (n = 12)	1 (8.3)	0	
Ambery et al[22]			
MAD study—MEDI0382 cohort a (n = 6)	3 (50)	Not specifically reported	Not reported
Cohort B (n = 6)	5 (83)		
Cohort C (n = 7)	6 (86)		
Cohort D (n = 11)	8 (73)		
Cohort E (n = 12)	9 (75)		
Placebo (n = 19)	6 (32)		
Phase 2a study—MEDI0382 (n = 25)	18 (72)		
Placebo (n = 26)	13 (50)		
DS-8500a			
Yamada et al[16]	Not reported	Oral administration	Not reported
JNJ-38431055			
Katz et al[17]			
Single dose—JNJ-38431055 100 mg (n = 23)	1 (4)	Oral administration	Not reported
500 mg (n = 24)	0		
Sitagliptin 100 mg (n = 24)	1 (4)		
Placebo (n = 23)	2 (9)		
Multiple dose—JNJ-38431055 500 mg (n = 15)	4 (27)		
Placebo (n = 17)	2 (12)		
Efpeglenatide			
Rosenstock et al[18]			
Efpeglenatide .3 mg (n = 37)	8 (22)	4 (10.8)	Not reported
1 mg (n = 37)	6 (16)	6 (16.2)	
2 mg (n = 33)	12 (36)	4 (12.1)	
3 mg (n = 36)	15 (42)	6 (16.7)	
4 mg (n = 36)	19 (53)	0	
Liraglutide 1.8 mg (n = 36)	16 (44)	10 (27.8)	
Placebo (n =37)	11 (30)	4 (10.8)	
Pratley et al[24]			
Efpeglenatide 4 mg weekly (n = 59)	43 (72.9)	11 (18.6)	None reported across all doses and placebo
6 mg weekly (n = 59)	49 (83.1)	7 (11.9)	
6 mg every 2 weeks (n = 59)	38 (64.4)	5 (8.5)	
8 mg every 2 weeks (n = 58)	44 (75.9)	8 (13.8)	
Placebo (n = 60)	28 (46.7)	13 (21.7)	

[a]Total incidence by dose unless otherwise noted.
[b]Incidence of diarrhea not reported.
[c]Incidence of vomiting not reported.

15 mg ($P < .0001$), and .1% for placebo. The 5 mg, 10 mg, and 15 mg doses of tirzepatide demonstrated greater reductions in A1c than dulaglutide whose mean change in A1c was −1.1% ($P = .0152$ for 5 mg, $P = .0001$ for 10 mg, and $P < .0001$ for 15 mg). Bodyweight was reduced in a dose-dependent manner for all doses of tirzepatide relative to placebo (−.9 kg for 1 mg ($P = .6548$), −4.8 kg for 5 mg ($P < .0001$), −8.7 kg for 10 mg ($P < .0001$), −11.3 kg for 15 mg ($P < .0001$), and −.4 kg for placebo). The 10 mg and 15 mg doses of tirzepatide demonstrated statistically significantly greater reductions in bodyweight than dulaglutide whose mean change was −2.7 kg ($P < .0001$ for 10 mg, and $P < .0001$ for 15 mg). AE related to tirzepatide increased in a dose-dependent manner. The incidence of AE in the 5 mg and 10 mg tirzepatide groups (72.7% and 78.4%, respectively) were similar to that of the dulaglutide group (74.1%). The authors concluded that all doses of tirzepatide resulted in reductions in A1c and bodyweight in a dose-dependent manner when compared with placebo and active-comparator, dulaglutide, with a safety profile consistent with dulaglutide.[19]

NNC0090-2746 (RG7697)

NNC0090-2746 also combines the mechanism of GIP and GLP-1. It is administered as a once-daily subcutaneous injection.

Portron et al conducted a double-blind, randomized, placebo-controlled, single ascending-dose study to determine the pharmacokinetics, pharmacodynamics, and safety of NNC0090-2746 in healthy patients.[13] In this study, 51 participants with a BMI of 22 to 32 kg/m^2 were randomized to one of seven doses (.03 mg, .07 mg, .2 mg, .6 mg, 1.8 mg, 3.6 mg, or 5 mg) of the study drug or placebo. Titration occurred up to a maximum of 5 mg daily with escalation based on safety, tolerability, and pharmacokinetic values at the previous dose. Due to unanticipated gastrointestinal AE with the .03 mg dose in the first cohort, the dosing scheme was changed from the original planned .03 mg, .1 mg, .3 mg, 1 mg, 3 mg, and 6 mg doses to those mentioned above. The study drug was generally well tolerated up to doses of 3.6 mg, with the majority of AE being gastrointestinal (nausea and vomiting), dizziness, and vasovagal episodes. Gastrointestinal AE were observed at all doses of the study drug except for the .6 mg dose and with placebo. Incidence of nausea increased with higher doses of the study drug. No further dose escalation was done beyond 3.6 mg after 1 patient had nausea and vomiting related to the drug at this dose. Increased heart rates were observed in participants on doses ≥1.8 mg. At the 3.6 mg and 5 mg doses, increases in heart rate of 6 to 20 beats per minute were seen compared with placebo. No effect of NNC0090-2746 was seen on FPG and fasting plasma insulin levels; however, after a meal, maximum plasma glucose concentrations decreased in the 1.8 mg (−25%) and 3.6 mg (−46%) dose groups compared with placebo. The 1.8 mg and 3.6 mg doses of NNC0090-2746 also decreased the maximum plasma insulin levels by 38% and 64%, respectively, after a meal tolerance test. The authors concluded that NNC0090-2746 was safe and well tolerated up to doses of 3.6 mg and that larger clinical trials were warranted to confirm its efficacy on glycemic control in patients with T2DM.[13]

Schmitt et al conducted a randomized, double-blind, placebo-controlled, dose-escalation study to determine the pharmacodynamics, pharmacokinetics, and safety of NNC0090-2746 in patients with T2DM.[20] Fifty-six patients with T2DM were randomized to one of six doses of the study drug (.25 mg, .75 mg, 1.1 mg, 1.5 mg, 2 mg, or 2.5 mg) or placebo for 14 days. The dosing scheme was changed due to nonlinear pharmacokinetics predicting over-exposure at the 3 mg dose. Titration occurred up to the higher doses with escalation occurring based on safety, tolerability and pharmacokinetic values from the previous dose. The average A1c across all study groups was 7.75% and average baseline BMI was 33.8 kg/m^2. NNC0090-2746 lowered glucose in a dose-related manner compared with placebo. FPG levels were reduced with time and lowest at 2 weeks. In the placebo group, FPG decreased by 18.5 mg/dL and in the NNC0090-2746 group a decrease of 16.4 mg/dL for .25 mg; 42.6 mg/dL for .75 mg; 66.1 mg/dL for 1.1 mg; 32.9 mg/dL for 1.5 mg; 36.6 mg/dL for 2 mg; and 64.2 mg/dL for the 2.5 mg dose was seen. Postprandial glucose levels were reduced with doses ≥.75 mg and post-prandial insulin levels were reduced with doses ≥1.1 mg. There was a dose-dependent decrease in A1c seen with reductions greater than placebo with doses ≥.75 mg. All doses of the study drug except the .25 mg dose demonstrated a decrease in bodyweight. The most common AE across all groups were hypoglycemia (31.0%), diarrhea (28.6%), nausea (28.6%), headache (26.2%), and decreased appetite (23.8%). There was a higher incidence of gastrointestinal AE in the NNC0090-2746 group than placebo and incidence increased as doses increased. The authors concluded that NNC0090-2746 demonstrated safety and efficacy in this study and further studies were warranted for longer time periods.[20]

Frias et al conducted a randomized, double-blind, multicenter, parallel-group, placebo-controlled study of NNC0090-2746 to determine effects on glycemic control and bodyweight in patients with T2DM.[21] A total of 108 patients were randomized to 1.8 mg of NNC0090-2746, placebo, or liraglutide titrated up to 1.8 mg according to the manufacturer's labeling, for 12 weeks. Average A1c at baseline was 8.3% and average weight at baseline was 90.9 kg across all groups. The primary endpoint was change in A1c from baseline to week 8. Secondary and exploratory endpoints included change in A1c, bodyweight, and total cholesterol from baseline to week 12 (A1c and bodyweight) or week 13 (cholesterol). Patients who were in the NNC0090-2746 group had significant reductions in A1c, bodyweight, and total cholesterol compared to baseline and placebo. Change from baseline in A1c was −.63% and −.96% in patients treated with NNC0090-2746 at weeks 8 and 12, respectively, vs placebo ($P < .0001$ for both). Change in

bodyweight was significant compared to placebo at week 8 (−1.80%; $P = .0141$) but not at week 12 (−1.67%; $P = .0621$) in patients treated with NNC0090-2746. Patients on the study drug had a decrease of 8% in their total cholesterol relative to placebo at week 13 ($P = .0214$). More AE were reported with the study drug than with placebo (64.9% vs 41.7%, respectively). Liraglutide was included as a qualitative reference, and no comparison was done with the study drug. Thirty-five percent of patients reported at least one gastrointestinal AE. The authors concluded that NNC0090-2746 is beneficial in improving glycemic control, weight loss, and lowering cholesterol, but further studies are needed for dose-finding, to determine dose escalation schedule, and the long-term effect of the study drug.[21]

Dual GLP-1 and Glucagon Receptor Agonists

SAR425899

SAR425899 combines the mechanism of a GLP-1 agonist and a glucagon receptor (GCR) agonist. The combination of agonism of GLP-1 and GCR was designed for greater weight loss and greater glycemic control. The mechanism of the drug is based off of the naturally occurring peptide hormone, OXM, which activates both GLP-1 and GCR. This peptide has been shown to cause weight-loss through reducing energy intake using GLP-1 agonism and increasing energy expenditure using GCR agonism.[14,15] SAR425899 is formulated as a once daily subcutaneous injection.

Tillner et al conducted a phase 1, randomized, placebo-controlled, double-blind study comprised of a single-ascending-dose trial and two MAD trials to assess the safety, pharmacokinetic, and pharmacodynamic profiles of SAR425899.[14] In the single-ascending-dose trial, 32 healthy overweight patients were randomized to receive one of five doses of SAR425899 (.01 mg, .03 mg, .05 mg, .075 mg, or .1 mg) or placebo for one dose. In part 1 of the multiple-ascending-dose trial, 40 healthy overweight patients were randomized to one of five dosing regimens of SAR425899 or placebo over 21 days (A: .025 mg, .05 mg on day 5, .075 mg on day 9; B: .05 mg, .075 mg on day 5, .1 mg on day 9; C: .05 mg, .1 mg on day 7, .2 mg on day 14; D: .05 mg, .1 mg on day 7, .15 mg on day 14, and E: .06 mg, .12 mg on day 7, .18 mg on day 14). In the second part of the multiple-ascending-dose trial, 36 patients with T2DM were randomized to one of two dosing regimens of SAR425899 or placebo over 28 days (Y: .03 mg, .06 mg, .09 mg and Z: .06 mg, .12 mg, .18 mg with dose titrations occurring on days 7 and 14 of treatment).

In the SAD trial, a decrease in post-prandial glucose and insulin-levels was seen for doses ≥.03 mg after mixed-meal test (change from baseline to day 1). No change was noted in the placebo group. In the first part of the MAD trial, a decrease in FPG was seen across all dosing regimens from baseline to day 22; regimen E had the greatest effect with a −.47 mmol/L decrease. Weight loss was seen across all dosing regimens from baseline to day 22; regimen C had the greatest effect (−5.32 kg). The second part of the MAD trial showed a significant decrease in FPG for both regimens compared with placebo (Y: −1.93 mmol/L [$P = .025$]; Z: −2.47 [$P = .002$]). Both regimens also demonstrated a significant decrease in A1c from baseline compared with placebo (Y: −.75% ($P < .001$); Z: −.74% ($P < .001$)) Gastrointestinal AE were the most common AE across all three trials. Eructation and dyspepsia were the most common AE in part 2 of the MAD trial. The authors concluded that further trials would be needed to confirm the results with larger, better powered studies and comparisons of safety and efficacy of currently approved GLP-1 RA.[14]

MEDI0382

MEDI0382 also combines the mechanism of GLP-1 and GCR agonism. It has been formulated as a once-daily subcutaneous injection.

Ambery et al conducted a randomized, placebo-controlled, double-blind SAD phase 1 study to evaluate safety, tolerability, pharmacokinetic, and pharmacodynamic properties of MEDI0382 in healthy patients.[15] The primary endpoint was safety and tolerability. In the study, 48 patients were randomized to one of six doses of MEDI0382 (5 μg, 10 μg, 30 μg, 100 μg, 150 μg, or 300 μg) or placebo. The study was originally designed to titrate MEDI0382 to 2000 μg, but the 300 μg dose was not tolerated, and 150 μg became the maximum dose. Incidence of AE was higher in the MEDI0382 groups with highest incidence occurring in the 150 μg and 300 μg groups compared to placebo. Nausea and vomiting were the most frequent AE, starting 3–4 hours post-dose and subsiding around 12 hours post-dose. Of the 10 patients who experienced vomiting, 5 were receiving 300 μg of the study drug. There were no serious AE related to the study drug and no withdrawals from the study due to AE. The authors concluded that MEDI0832 is safe and further multi-dose clinical studies are warranted for MEDI0382 starting with doses of up to 150 μg and up-titration to higher doses.[15]

Ambery et al conducted a Phase 2a randomized, double-blind, placebo-controlled, MAD study to determine the optimal dosing regimen and assess the efficacy and safety of MEDI0382 in patients with T2DM.[22] Patients were assigned to one of five cohorts, with each cohort receiving once daily injections to a specified dose with an up-titration occurring to the desired dose. Cohort A took 100 μg for 7 days; cohort B: 100 μg for 4 days, then 150 μg for 7 days; cohort C: 100 μg for 4 days, then 150 μg for 4 days, then 220 μg for 7 days; cohort D: 100 μg for 5 days, 150 μg for 5 days, 200 μg for 5 days, then 300 μg for 7 days; cohort E: 100 μg for 5 days, 200 μg for 5 days, then 300 μg for 7 days. In the phase 2 trial, patients received 100 μg for 4 days, then 150 μg for 4 days, then 200 μg for 33 days. The primary outcome was percent change in glucose area under the curve at 0–4 ($AUC_{0\text{-}4}$) hours after a

mixed meal tolerance test (MMTT) and change in bodyweight from baseline to day 41 in the phase 2 trial. These same endpoints for the MAD trial were assessed as secondary outcomes from baseline to the end of treatment. Change from baseline to end of treatment in A1c in cohorts D and E of the MAD trial and all cohorts in the phase 2 trial were assessed as secondary outcomes.

Sixty-one patients were assigned to the MAD trial and 51 patients were assigned to the phase 2 trial. Percentage glucose $AUC_{0\text{-}4}$ after an MMTT was significantly decreased from baseline to day 41 for the study drug vs placebo in the phase 2 trial (least squares mean −32.78% vs −10.16%; $P < .0001$). Bodyweight was also significantly decreased from baseline to day 41 with the study drug vs placebo in the phase 2 trial (least squares mean −3.84 kg vs −1.70 kg; $P = .0008$). In the MAD trial, all cohorts had a significant decrease in percentage glucose $AUC_{0\text{-}4}$ after an MMTT from baseline to end of treatment. All cohorts had numerical decreases in bodyweight from baseline to end of treatment with the study drug vs placebo, with only cohort D showing a significant reduction in bodyweight (−3.4 kg vs −.7 kg; $P < .05$). There was a significant decrease in A1c from baseline to end of treatment in the phase 2 trial (−.9% for the study drug and −.6% for placebo ($P = .004$)). For cohort D in the MAD trial, there was a significant decrease in A1c from baseline vs placebo (−.6% vs −.1%; $P < .05$). There was not a significant decrease in A1c from baseline vs placebo in cohort E (−.4% vs −.2%). AE incidence was similar between all treatment groups. Gastrointestinal disorders occurred more often in the MEDI0382 cohorts than with placebo, specifically nausea and vomiting. These effects did not appear to be dose-related as cohorts D and E (titration up to 300 μg) had the lowest incidence of gastrointestinal disorders out of all cohorts other than cohort A (73% vs 75% vs 50% incidence of gastrointestinal disorders, respectively, with 83% incidence in cohort B and 86% incidence in cohort C). The authors concluded that MEDI0382 improved glycemic control and assisted with weight loss, but noted that further studies are warranted to evaluate longer-term therapy.[22]

G Protein-Coupled Receptor 119 Agonists

DS-8500a

DS-8500a is a G protein-coupled receptor 119 (GPR119) agonist formulated as a once daily oral medication. GPR119 is a novel target for the treatment of T2DM. GPR119 is expressed in L-cells in the small intestine and beta-cells in the pancreas which secretes incretin hormones, including GLP-1, which helps to regulate glucose levels. Targeting this receptor promotes insulin secretion and may preserve beta-cell function, reducing blood glucose levels.[16,17]

Yamada et al conducted a randomized, double-blind, parallel-group comparison study to determine the safety and efficacy of DS-8500a in 368 patients with T2DM.[16] Patients were assigned to one of three doses of DS-8500a (25 mg, 50 mg, or 75 mg), placebo, or sitagliptin 50 mg daily for 12 weeks. Change in A1c from baseline to week 12 was the primary endpoint. Secondary endpoints included change in A1c at weeks 4 and 8, patients who reached A1c <7% at week 12, change in FPG and 2-hour post-prandial plasma glucose. All three doses of the study drug demonstrated a statistically significant decrease in A1c in a dose-dependent manner compared with placebo from baseline to week 12 (−.23% ($P = .0173$) for the 25 mg dose of DS-8500a, −.37% ($P = .0001$) for the 50 mg dose, and −.44% ($P < .0001$) for the 75 mg dose compared with the placebo group which had an increase in A1c of .17%). DS-8500a did not demonstrate greater A1c lowering when compared to sitagliptin which demonstrated a −.97% decrease in A1c at week 12 vs placebo ($P < .001$). No serious AE related to DS-8500a occurred, and it was well tolerated at all doses. The authors concluded that DS-8500a has a lesser blood glucose lowering effect than sitagliptin, but still may be a viable treatment option for T2DM in patients whose beta-cells are not yet exhausted.[16] An additional study was completed by Terauchi and colleagues assessing DS-8500a in combination with sitaglipitin.[23] This study found that at 25 mg and 75 mg doses, DS-8500a did show additive glycemic benefits compared with placebo and a decrease in total cholesterol, LDL, and triglycerides when used in combination with sitagliptin.[23]

JNJ-38431055

JNJ-38431055 is a GPR119 agonist, formulated as a once daily oral suspension.

Katz et al conducted a randomized, double-blind, placebo-controlled study consisting of two parts.[17] The first part was a placebo and positive-controlled, single-dose cross-over study, the second part was a multiple-dose parallel design study. In the single-dose study, patients were randomized to one of four treatment sequences where they received 1 dose of treatment (100 mg or 500 mg of JNJ-38431055, sitagliptin 100 mg, or placebo) in varying orders every 7 days. For the multiple-dose study, patients were randomized to either 500 mg of JNJ-38431055 or placebo once daily for 14 days. Study outcomes included pharmacokinetic parameters (plasma drug levels), pharmacodynamic parameters (plasma glucose and insulin levels), safety, and tolerability. The primary endpoint for the multiple-dose study was 24-hour weighted mean glucose (WMG) on day 14. Twenty-five and 32 patients were randomized to the single-dose and multiple-dose study, respectively. In the single-dose study, after an oral glucose tolerance test, both doses of the study drug and sitagliptin significantly decreased plasma glucose AUC compared with placebo. For JNJ-38431055 100 mg, there was a 12.5% decrease ($P = .03$) in plasma glucose AUC, for the 500 mg dose there was a 16.6% decrease ($P = .007$) and for sitagliptin there was a 24.6% decrease ($P < .001$) when compared to placebo. In the multiple-dose study, there was a −3.6% decrease in 24-hour

Table 2. GLP-1 Receptor Agonists Currently in Development.

						Results		
Drug and description	Reference	n	Design	Duration	Treatment	Change in A1c	Change in FPG	Other
Polyethylene glycol loxenatide (PEX 168) Polyethylene glycol-conjugated glucagon-like peptide-receptor agonist Once weekly injection	Yang et al[25]	50	R, DB, PC, multiple-dose	8 weeks	PEX168 100 μg weekly PEX168 200 μg weekly PEX168 300 μg weekly Placebo	−.0% −.2% −.6% (P < .05) −.9% (P < .05) +.4%		
	Chen et al[26]	118	R, DB, PC	12 weeks		−1.05% (P < .01) −1.41% (P < .01) +.15%	−37.8 mg/dL −40.9 mg/dL −4.9 mg/dL (P = .0171)	
Recombinant Exendin-4 (rE-4) Lyophilized recombinant glucagon-like peptide-1 receptor agonist Twice-daily subcutaneous injection	Zang et al[27]	12	PK study	12 weeks	rE-4 5 μg twice daily[a]			PK data only, drug follows two-compartment model with first-order absorption and elimination
	Wang et al[28]	29	R, OL, PG	12 weeks	rE-4 10 μg twice daily[b] Exenatide 10 μg twice daily rE-4 10 μg twice daily[a] with metformin 500 mg twice	−1.19% −1.13% −.84% (P = .708)	−41.2 mg/dL −33.8 mg/dL −41.9 mg/dL (P = .858)	
Recombinant GLP-1 (rGLP-1) Subcutaneous glucagon-like peptide-1	Torekov et al[29]	47	R, DB, PC, PG	8 weeks	rGLP-1 1.25 pmol/kg/min rGLP-1 2.5 pmol/kg/min rGLP-1 5.0 pmol/kg/min rGLP-1 8.5 pmol/kg/min Placebo		−22.7 mg/dL (P = .27) −37.0 mg/dL (P = .064) −53.9 mg/dL (P = .005) −76.2 mg/dL (P = .0002) −1.1 mg/dL	
	Torekov et al[30]	95	R, DB, PC, PG	12 weeks	rGLP-1 1.25 pmol/kg/min rGLP-1 2.5 pmol/kg/min rGLP-1 5.0 pmol/kg/min Placebo	No value (P = .020) No value (P = .001) −1.3% (P < .001) No value	No value (P = .02) No value (P = .01) −26 mg/dL (P = .02) No value	

Abbreviations: R, randomized; DB, double-blind; PC, placebo-controlled; OL, open-label; PG, parallel-group; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; PK, pharmacokinetic; PF, PF-04603629.

[a]rE-4 increased to 10 μg twice daily at day 29 if glycated albumin ≥17%.

[b]rE-4 and exenatide increased to 10 μg twice daily at day 29 after rE-4 or exenatide 5 μg twice daily for 28 days.

plasma glucose for the study drug group and 1.4% increase in the placebo group. This 5% difference in 24–hour plasma glucose translated to a −10 mg/dL change in WMG that was not statistically significant ($P = .38$). No serious AE occurred. The authors concluded that JNJ-38431055 did not produce the meaningful decreases in plasma glucose after 14 days of treatment necessary to be used as a therapeutic agent; thus, further studies are warranted to determine if JNJ-38431055 may have use as an adjunctive agent.[17]

Efpeglenatide

Efpeglenatide is a long-acting GLP-1 receptor agonist that is currently in development. It has been formulated as a single amino-acid-modified exendin conjugated to a fragment crystallizable region of human immunoglobulin 4 which allows for administration as a once-weekly subcutaneous injection.

Rosenstock et al conducted a randomized, placebo-controlled, double-blind, parallel-group, dose-ranging study to assess the efficacy, safety, and tolerability of efpeglenatide once weekly in patients with T2DM.[18] A total of 254 patients were randomized to one of five doses of efpeglenatide once weekly with no titration (.3 mg, 1 mg, 2 mg, 3 mg, or 4 mg), placebo, or open-label liraglutide 1.8 mg once daily (with titration of .6 mg for 7 days, then 1.2 mg for 7 days, then 1.8 mg) over 12 weeks. The primary outcome was change in A1c from baseline to week 13 for efpeglenatide vs placebo. Change in baseline A1c for efpeglenatide vs liraglutide was an exploratory endpoint. Secondary outcomes included the percentage of patients achieving A1c <7% or ≤6.5% at week 13 and change in FPG from baseline to week 13. Efpeglenatide led to dose-dependent reductions in A1c from baseline to week 13 with doses ≥1 mg resulting in significantly greater reductions compared to placebo. Differences in least squares mean changes were −.16% for .3 mg ($P = .30$); −.55% for 1 mg, ($P < .05$); −.79% for 2 mg ($P < .05$); −1.01% for 3 mg ($P < .05$); and −1.21% for 4 mg ($P < .05$) compared with placebo. Compared with liraglutide in the exploratory analysis, only the 4 mg dose of efpeglenatide was non-inferior with a least squares mean change in A1c of −.23%. AE were reported in all treatment groups including the placebo group. The most common AE across all efpeglenatide groups were nausea (20.1%), vomiting (9.5%), and headache (8.9%); nausea (33.3%) and vomiting (13.9%) were also common in the liraglutide group. The authors concluded that efpeglenatide demonstrated dose-dependent reductions in A1c similar to those achieved with liraglutide.[18] Further studies are warranted to refine the treatment dose of efpeglenatide over a longer duration.

Pratley et al conducted a multinational, double-blind, randomized, placebo-controlled, parallel-group study to assess safety and tolerability of efpeglenatide once weekly or once every 2 weeks and its potential to reduce bodyweight in patients without diabetes.[24] Patients were randomized to one of two doses of efpeglenatide (4 mg or 6 mg) once weekly without titration, one of two doses of efpeglenatide (6 mg or 8 mg) once every 2° weeks with a 2-week titration of 4 mg once weekly, or placebo for 20 weeks. The primary outcome was change in bodyweight from baseline to week 21. Secondary outcomes were percent change in: bodyweight, BMI, FPG, and A1c from baseline. A total of 297 patients were randomized to either the study drug or placebo. All doses of efpeglenatide led to a significant reduction in bodyweight compared to placebo from baseline to week 21. Efpeglenatide 4 mg once weekly had a least square mean change of −6.5 kg compared to placebo, for 6 mg once weekly it was −7.2 kg, for 6 mg every 2 weeks it was −6.3 kg, and for 8 mg every 2 weeks it was −6.9 kg ($P < .0001$ for all comparisons). All efpeglenatide groups had significant decreases in A1c compared to placebo ($P < .0001$). Gastrointestinal AE were the most common (72.9% for 4 mg once weekly, 83.1% for 6 mg once weekly, 64.4% for 6 mg every 2 weeks, and 75.9% for 8 mg every 2 weeks). The authors concluded that treatment benefits appear to be dose related with 6 mg once weekly and 8 mg once every 2 weeks having the greatest benefit on weight loss with benefit on glycemic control.[24] Further studies are needed to assess safety and efficacy of higher doses over longer periods of time.

Several other GLP-1 RA are currently in development (Table 2).

Conclusion

GLP-1 RA are often used as second-line treatments for diabetes as an add-on to metformin. The success of GLP-1 RA in improving glycemic control while promoting weight loss and offering cardiovascular and renal benefit has led to continued interest in further developing this pipeline. Medications that combine the mechanism of GLP-1 RA with a complementary mechanism such as glucose-dependent insulinotropic polypetide agonism and GCR agonism (tirzepatide and NNC0090-2746) are promising for T2DM. Clinical trials for both medications show meaningful improvements in glycemic control and weight loss. SAR425899 and MEDI0382 combine the mechanism of GLP-1 RA and GCR agonism, designed for greater weight loss and glycemic control. Trials for both medications indicate safety, few AE, and benefits on glycemic control and weight loss. With their novel mechanism, GPR119 agonists DS-8500a and JNJ-38431055 were hopeful treatments for T2DM. Completed clinical trials were not as promising due to weaker blood glucose lowering effects. Further studies are warranted to determine their role as adjunctive agents. Efpeglenatide also shows promise as a future treatment. Similar to currently approved GLP-1 RA, there is the potential for AE (gastrointestinal upset, pancreatitis, and injection site reactions). All of the studies of pipeline agents demonstrate glucose-lowering effects; however, it is difficult to determine real-world clinical significance based on available studies. Future studies comparing

these pipeline medications to currently available GLP-1 RA, including cardiovascular and renal outcomes, are warranted to determine place in therapy of these medications. Depending on the results of ongoing studies, these agents and others may soon be added to the armamentarium of options for T2DM.

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ORCID iDs

Mary J. Elder, PharmD https://orcid.org/0000-0001-8061-0201
Emily J. Ashjian, PharmD, BCPS, BCACP, CDCES https://orcid.org/0000-0001-5746-0233

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