Drugs of the Future 2022, 47(6): 407-418

e-ISSN: 2013-0368
DOI: 10.1358/dof.2022.47.6.3373535

Clarivate™

Monograph

Danuglipron

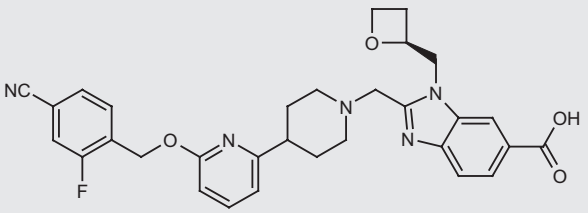
Rec INN; USAN

Glucagon-like peptide 1 receptor agonist
Treatment of type 2 diabetes
Treatment of obesity

Alexander J. Sperry[1], Jennifer Hardy[1], Rebecca F. Goldfaden[1], Amber Hurst[1], Andrea Ashchi[2], David Sutton[3], Mae Sheikh-Ali[3], Jessica Huston[4] and Rushab Choksi[1]

[1]East Coast Institute for Research, Jacksonville, Florida, USA; [2]Emory University, Atlanta, Georgia, USA; [3]Northeast Florida Endocrine & Diabetes Associates, Jacksonville, Florida, USA; [4]University of Florida, College of Pharmacy, Jacksonville, Florida, USA

Contents



PF-06882961
DN9IUI24GP (UNII)

2-[(4-[6-[(4-Cyano-2-fluorophenyl)methoxy]pyridin-2-yl]piperidin-1-yl)methyl]-1-[[(2*S*)-oxetan-2-yl]methyl]-1*H*-benzimidazole-6-carboxylic acid

$C_{31}H_{30}FN_5O_4$; Mol wt: 555.599

Cortellis Drug Discovery Intelligence Entry Number: 979681

Summary

Type 2 diabetes mellitus (T2DM) is one of the most diagnosed conditions in the United States. Antihyperglycemic medications are a mainstay in the treatment of T2DM to prevent complications such as cardiac and renal death. One class of antihyperglycemic medication that has shown benefit for hemoglobin A_{1c} (A_{1c}) lowering, weight loss, renal protection, as well as cardiac protection are the glucagon-like peptide 1 receptor agonists (GLP-1RAs). These agents bind to the glucagon-like peptide 1 receptor (GLP-1R) promoting β-cell production of insulin, prevent apoptosis and promote proliferation. One limitation with these medications is the method of administration being subcutaneous due to the long peptide chains required. This changed when Rybelsus (semaglutide) was approved as an oral peptide GLP-1RA. Growing evidence has suggested that oral small molecule GLP-1RAs may be a new therapeutic alternative with comparable safety and efficacy for both A_{1c} lowering and weight loss when compared to current subcutaneous GLP-1RAs and Rybelsus. This review aims to present and discuss the current clinical and scientific evidence pertaining to danuglipron, a novel oral small molecule GLP-1RA.

Key words: Danuglipron – PF-06882961 – GLP-1 receptor agonist – Type 2 diabetes – Obesity

Correspondence: Rebecca F. Goldfaden, PharmD, East Coast Institute for Research, Jacksonville, FL, USA. Rg@eastcoastresearch.net.

Background

Type 2 diabetes mellitus (T2DM) is one of the most commonly diagnosed conditions in the United States with 1 in 10—approximately 34 million—individuals currently being diagnosed with the condition (1). The International Diabetes Federation reported that 537 million adults (ages 20-79) were living with T2DM (2). Diabetes mellitus is rarely the direct cause of death in those who are diagnosed, but death is more often due to the microvascular and macrovascular complications that arise from the progression of the condition (3). These complications present as retinopathy, neuropathy, diabetic kidney disease (DKD) and atherosclerotic cardiovascular diseases (ASCVD) (3-5). Of those complications and associated conditions, DKD and ASCVD

are the most common indirect causes of death in patients with uncontrolled T2DM (4, 6). Management of T2DM is patient-centered and incorporates lifestyle modifications as well as antidiabetic pharmacotherapy. The American Diabetes Association (ADA) recommends for T2DM to be initially managed with lifestyle modifications alone, or in combination with metformin; however, intensive double, triple, or insulin therapy can be initiated based on the severity of glycated hemoglobin (A_{1c}) (e.g., $A_{1c} > 9\%$) (7). McGovern et al. showed that 30% of patients prescribed metformin did not take their prescribed dose resulting in required adjunctive therapy for disease state management, and Tucker et al. showed that 50% of patients stopped taking metformin after 1 year due to the gastrointestinal side effects (8, 9).

Adjunctive treatment for the management of T2DM is patient-specific and is based on cost, comorbidities and preference (7). Patients who have established or are at high risk for ASCVD and/or DKD are recommended to receive agents with proven benefits. Agents that can be used to reduce ASCVD risk and/or DKD progression include 3 glucagon-like peptide-1 receptor agonists (GLP-1RAs)—dulaglutide, liraglutide and semaglutide—while also showing a class-based effect on weight loss (7). By targeting the GLP-1 receptor (GLP-1R), the pancreas can preserve, repair and induce growth of the β cells through increased production of GLP-1, preventing early β-cell death (10). In turn, β cells are able to naturally produce insulin, reducing the need for insulin analogue use (11, 12). In addition to this, natural incretins are released which have shown a positive impact on cardiovascular risk reduction (11, 12). One common limitation with this medication class is the route of administration. The GLP-1RAs are known for being administered subcutaneously (s.c.) due to their 30 amino-acid-long peptide chain being difficult to preserve when given orally. This has since changed with the development of the first oral GLP-1RA called semaglutide (Rybelsus), which led to a shift in research for further development of oral GLP-1RAs (13, 14). Oral GLP-1RAs provide the benefits of increased patient compliance and adherence due to the oral dosage formulation, while having a comparable A_{1c}-lowering effect as an injectable formulation. One such product in development that has shown potential is an oral small molecule GLP-1RA called danuglipron (PF-06882961), and it is the focus of this review.

Molecular Properties of Danuglipron

Danuglipron is a first of its kind, small molecule oral GLP-1RA that is currently being developed for the treatment of obesity and T2DM (15). A promising phase I study demonstrated an efficacious A_{1c}-lowering effect in addition to weight loss as early as 4 weeks (15, 16). Danuglipron has a molecular weight of 555.6 Daltons. In comparison, s.c. GLP-1RAs such as liraglutide and albiglutide have a relative weight range of 3751-72,970 Daltons, and the oral peptide agent semaglutide weighs 4,114 Daltons (16, 17).

Mechanism of Action

Danuglipron utilizes the same receptor as semaglutide, the G protein-coupled receptor (GPCR) on the GLP-1R. The main site of action for the activation of GLP-1 is the class B1 GPCR. A study by Zhang et al. determined that the class B1 GPCR is the specific site of action, and validated the stability of the complex binding required for danuglipron (18). The activation of these GPCRs results in a signaling cascade in the body when activated, allowing for GLP-1 secretion. These GPCRs are composed of 463 amino acid residues, which are responsible for peptide binding. The binding capabilities are facilitated through N-terminal extracellular domains (ECD) and C-terminal transmembrane domains (TMD) (18-21).

The mechanism through which danuglipron works is through binding to the N-terminal ECD of Trp33 ($Trp33^{ECD}$). The binding to $Trp33^{ECD}$ causes activation of the canonical GPCR signaling cascade. This is the critical binding site on the GLP-1R required for the binding of small GLP-1RA molecules but is not critical for the activation of the receptor in native GLP-1R activation. Danuglipron interacts at the $Trp33^{ECD}$ through van der Waal interactions and hydrogen bonding with both extracellular loop (ECL) 1 and ECL2, while GLP-1RA peptides only interact with ECL2. This interaction with danuglipron promotes stabilization to the binding pocket of the GLP-1R, and in turn activation of the class B1 GPCR. The activation of the class B1 GPCR results in the production of cyclic AMP (cAMP), leading to an increase in Ca^{2+} levels, promoting GLP-1 secretion. The increase in GLP-1 allows for an increase in the mass of β cells in the pancreas through neogenesis and proliferation (20, 22). Additionally, danuglipron can also act as a partial agonist in the β-arrestin (βArr) pathway, more specifically βArr2, by binding to the C-terminal TMD in the helices of kink 6 resulting in exocytosis of insulin-filled vesicles in the cell and reduction of apoptosis (20, 22-24). The clinical presentation of these effects results in β-cell preservation and insulin secretion allowing for an A_{1c}-lowering effect. The increase in GLP-1 secretion also helps suppress glucagon secretion and inhibits gastric emptying, in turn, lowering exogenous glucose in the blood. These effects also result in the feeling of satiety and reduction of food intake (25).

Preclinical Studies

Limited preclinical data on danuglipron have been published; however, Griffith et al. studied the molecular activity of danuglipron through the cAMP and βArr pathways and compared it to those of 2 peptide-based GLP-1RAs, exenatide and liraglutide (26). In vitro, the potency of danuglipron on the cAMP pathway was determined to have a maximal EC_{50} of 13 nM. Data on recruiting βArr2 indicated an EC_{50} of 490, 9.0 and 20 nM, for danuglipron, exenatide and liraglutide, respectively. The maximal effect of these drugs at high concentrations when all receptors were occupied (E_{max}) was 36%, 75% and 99%, respectively. It was calculated that

danuglipron has an ~5-fold increase in the selectivity of the binding to N-terminal $Trp33^{ECD}$, the cAMP pathway, relative to C-terminal TMD helices at kink 6, the βArr pathway (20, 22-24). Binding affinity to the GLP-1R was tested using radioligand binding and found to have an inhibition constant (K_i) of 360 nM, which was 3900- and 82-fold lower than those of exenatide and liraglutide, respectively (26).

Saxena et al. discussed the physiological effects of the small molecule GLP-1RA in mice. Mice with the human GLP-1R (hGLP-1R) gene underwent an intraperitoneal glucose tolerance test where they were administered a single fixed dose (3 mg/kg) of a 5% dextrose vehicle or danuglipron, followed by a post-dose of 40% dextrose (2 g/kg). It was determined that danuglipron displayed improved glucose tolerance, reduced blood glucose area under the curve (AUC) from 0-120 min, and improved plasma insulin. The initial blood glucose of the mice was ~125 mg/dL, with a spike of ~175 mg/dL at the time of administration of the 40% dextrose. The blood glucose $AUC_{0\text{-}120}$ in the hGLP-1R mice given the 5% dextrose vehicle was ~50,000 (mg/dL)·min, with the danuglipron group having an $AUC_{0\text{-}120}$ of ~15,000 (mg/dL)·min. The plasma insulin level for all mice was ~1.5-2 mg/dL, and the only change observed was in the group that received danuglipron having a plasma insulin of ~8 mg/dL at the time of the 40% dextrose administration, and a return to baseline at 120 min (27).

Griffith et al. also conducted studies of danuglipron in cynomolgus monkeys. The therapeutic effects of danuglipron on serum insulin and blood glucose were assessed using an i.v. glucose tolerance test. Four cynomolgus monkeys were placed into 2 separate cohorts to receive either a 1 mg/kg i.v. dose of danuglipron or formulation vehicle. The baseline plasma glucose for both cohorts before administration was ~50 ng/mL. A 250 mg/kg dose of 50% dextrose was administered to both cohorts with a plasma glucose spike to ~180 mg/dL at ~2.5 min which decreased to ~50 mg/dL after 30 min for both groups. The pharmacokinetics were further studied with 6 cynomolgus monkeys that received either 1 mg/kg i.v. danuglipron, 5 mg/kg oral danuglipron or 100 mg/kg oral danuglipron. This test was done to determine the plasma concentrations of danuglipron after administration of different doses and formulations. The results were dose-dependent in the plasma concentrations for oral administration of danuglipron. Plasma concentrations peaked at 3 h with the 100 mg/kg oral dose having a plasma concentration of ~1000 ng/mL with a subsequent decrease to ~250 ng/mL after 24 h, while the 5 mg/kg oral dose had a peak plasma concentration at 3 h of ~80 ng/mL, and a subsequent decrease to ~1.5 ng/mL at 24 h (26).

Clinical Studies

Phase I

A total of 11 phase I clinical studies with danuglipron have been completed by Pfizer (Table I), and only 1 of these has results published. Seven studies assessed the safety, pharmacokinetics, pharmacodynamics, adverse events and dose assessments in healthy individuals with or without comorbidities. Four studies evaluated the effects of danuglipron in participants with hepatic impairment, renal impairment, obesity and T2DM.

Completed phase I studies in healthy participants

The first-in-human study of danuglipron was conducted to evaluate the safety, tolerability and pharmacokinetic profile of single doses of danuglipron in healthy participants. This was a randomized, double-blind, placebo-controlled study that included 25 participants (ClinicalTrials.gov Identifier NCT03309241) (28). The follow-up to this study (NCT03492697) was a single-dose crossover study evaluating different formulations of danuglipron. This study was conducted by administering fixed doses of danuglipron as either an immediate release tablet, a short controlled-release (CR) tablet, a long CR tablet or an immediate-release (IR) solution (29).

Additionally, a bioavailability and pharmacokinetic study was conducted where participants received a single oral dose of 50 mg danuglipron or a single oral dose of 50 mg danuglipron followed by a 100-μg i.v. infusion of danuglipron 3 h later. The purpose of this study was to determine the absolute bioavailability and the route of excretion of danuglipron through the recovery of radioactivity in the urine and feces in a 14-day period (NCT04495140) (30).

Completed phase I studies in participants with comorbidities

There are 7 completed studies that have assessed danuglipron in participants with various comorbidities such as obesity, renal impairment and hepatic impairment. The first study of danuglipron in participants with T2DM was conducted in Japanese adults assessing the safety, tolerability, pharmacokinetics and pharmacokinetics of danuglipron. This study was conducted with 4 treatment arms. Participants received 1 of the following: placebo, danuglipron titrated to 40 mg over 2 weeks, danuglipron titrated to 80 mg over 4 weeks, or danuglipron titrated to 120 mg over 6 weeks (NCT04552470) (31).

Another study was conducted where otherwise healthy adult participants who were overweight or had obesity were given single doses of 4 different oral formulations of danuglipron at a fixed dose of 100 mg. The study was open-label and contained a 4-period crossover design where each participant received a different formulation during each period (NCT04616339) (32).

A concurrent study was completed analyzing the effect of 2 steady-state doses of danuglipron on the pharmacokinetics of rosuvastatin and midazolam in participants with obesity. Participants received either 120 mg twice daily (b.i.d.), or 200 mg b.i.d. of danuglipron with a subsequent single dose

Table I. *Summary of completed phase I clinical trials using danuglipron (28-38).*

ClinicalTrials.gov Identifier	Study population	Results being analyzed	Study intervention
NCT03309241	Overall healthy adults	Number of TEAEs	**Arm A**: Placebo **Arm B:** Single ascending doses of danuglipron starting at 3 mg
NCT03492697	Overall healthy adults	C_{max}, t_{max}, AUC_{last}, AUC_{∞}, plasma concentration, clearance rate and peak/trough ratio	**Arm A:** Single danuglipron IR tablet **Arm B:** Single danuglipron long CR tablet **Arm C:** Single danuglipron short CR tablet **Arm D:** Single danuglipron solution
NCT04495140	Overall healthy adult males	Recovery of danuglipron in urine and feces post dose	**Arm A:** A single 50 mg oral liquid danuglipron **Arm B:** A single 50 mg oral liquid danuglipron followed by 100 μg i.v. danuglipron 3 h later
NCT04552470	Overall healthy Japanese adults with T2DM treated only with diet and exercise	Number of TEAEs	Each treatment arm receives an initial dose titration **Arm A:** Placebo; titration schedule based on matching danuglipron dose **Arm B:** 40 mg danuglipron 3 tablets b.i.d. for 8 weeks; 2-week titration **Arm C:** 80 mg danuglipron 3 tablets b.i.d. for 8 weeks; 4-week titration **Arm D:** 120 mg danuglipron 3 tablets b.i.d. for 8 weeks; 6-week titration
NCT04616339	Overall healthy adults	C_{max}, AUC_{last} and AUC_{∞}, for Formulations A and B	Single doses of 100 mg danuglipron formulations (a, b, c, d). **Arm A:** Period 1 – a; Period 2 – b; Period 3 – c; Period 1 – d **Arm B:** Period 1 – a; Period 2 – b; Period 3 – d; Period 1 – c **Arm C:** Period 1 – b; Period 2 – a; Period 3 – c; Period 1 – d **Arm D:** Period 1 – b; Period 2 – a; Period 3 – d; Period 1 – c
NCT04621227	Overall healthy but obese/overweight	Effects of danuglipron on rosuvastatin and midazolam on AUC_{last}, and AUC_{∞}	Each participant will cycle through 8 dosing periods **Period 1:** 10 mg rosuvastatin **Period 2:** 2 mg midazolam **Period 3:** 120 mg b.i.d. danuglipron **Period 4:** 120 mg b.i.d. danuglipron with 10 mg rosuvastatin **Period 5:** 120 mg danuglipron with 2 mg midazolam **Period 6:** 200 mg danuglipron **Period 7:** 200 mg danuglipron with 10 mg rosuvastatin **Period 8:** 200 mg danuglipron with 2 mg midazolam
NCT04604496	Overall healthy adults with or without hepatic impairment	C_{max}, AUC_{last}, AUC_{∞} and fraction of unbound drug in plasma	Each treatment arm receives 20 mg danuglipron. Treatment arms are divided based on hepatic impairment **Arm A:** Without hepatic impairment **Arm B:** Mild hepatic impairment **Arm C:** Moderate hepatic impairment **Arm D:** Severe hepatic impairment

(Continued)

Table I. *Summary of completed phase I clinical trials using danuglipron (28-38). (Cont.)*

ClinicalTrials.gov Identifier	Study population	Results being analyzed	Study intervention
NCT04616027	Overall healthy patients with or without T2DM and renal impairment	C_{max}, AUC_{last}, AUC_{∞}, and fraction of unbound drug in plasma	Each treatment arm receives 20 mg danuglipron. Treatment arms are divided based on presence of T2DM and renal function **Arm A:** Normal renal function without T2DM **Arm B:** Normal renal function with T2DM **Arm C:** Mild renal function with T2DM **Arm D:** Moderate renal function with T2DM **Arm E:** Severe renal function with T2DM
NCT04839393	Overall healthy but obese/overweight	C_{max} and AUC_{24} for each arm and sequence	**Arm A, Sequence 1**: Danuglipron followed by danuglipron with ervogastat **Arm A, Sequence 1:** Danuglipron with ervogastat followed by danuglipron **Arm B:** Danuglipron with ervogastat
NCT04889157	Overall healthy Chinese adults with T2DM	C_{max} and AUC	Total run time of 8 weeks with 6-week titration period **Arm A**: Placebo **Arm B:** Target dose of 120 mg danuglipron
NCT03538743	Overall healthy adults with T2DM	Number of TEAEs	Intervention ran over 28 days **Arm A:** Placebo **Arm B:** 10 mg danuglipron b.i.d. **Arm C:** 15 mg danuglipron b.i.d. **Arm D:** 50 mg danuglipron b.i.d. **Arm E:** 70 mg danuglipron b.i.d. **Arm F:** 120 mg danuglipron b.i.d. **Arm G:** Slow titration to 120 mg danuglipron once daily **Arm H:** 120 mg danuglipron once daily **Arm I:** 200 mg CR danuglipron once daily

AUC, area under the curve; AUC_{24}, area under the curve from time zero to 24 h; AUC_{∞}, area under the curve from time zero to extrapolated infinite time; AUC_{last}, area under the curve at end of observation period; C_{max}, maximum plasma concentration; CR, controlled release; IR, immediate release; T2DM, type 2 diabetes mellitus; TEAEs, treatment-emergent adverse events; t_{max}, time to maximum observed plasma concentration.

of 10 mg rosuvastatin and/or a single dose of 2 mg midazolam. There were 2 control groups: 1 group receiving a single 10-mg rosuvastatin dose and the other receiving a single 2-mg midazolam dose (NCT04621227) (33).

A nonrandomized, open-label, single-dose, parallel cohort study in patients with varying degrees of hepatic impairment was recently completed. The study analyzed pharmacokinetic parameters of a 1-time 20-mg dose of danuglipron including AUC, C_{max} and unbound drug in the plasma over 3 days, and any treatment-emergent adverse events (TEAEs) over 30 days (NCT04604496) (34).

A study evaluated renal impairment with respect to danuglipron and pharmacokinetic parameters of a 1-time, 20-mg dose of danuglipron including AUC, C_{max}, unbound drug in the plasma over 3 days, and any TEAEs over 30 days (NCT04616027) (35).

A drug–drug interaction study enrolled participants who were then split into 3 treatment arms, with the first 2 arms receiving either a 20-mg single dose of danuglipron or a 20- and 300-mg dose of danuglipron, 320 mg total. These 2 arms then underwent a 3-day washout and received the opposite treatment arm. The third treatment arm had participants receive a 300-mg dose of danuglipron on day 1, followed by a titration from 10 to 200 mg b.i.d. over days 3-46. This arm then received another 300-mg dose on day 47, followed by 200 mg b.i.d. on days 47-48, and lastly 500 mg b.i.d. for days 49-62 (NCT04839393) (36).

A phase I randomized, double-blind, placebo-controlled study was also recently completed, in which participants with type 2 diabetes received an undisclosed dose of danuglipron beginning with 3 tablets b.i.d. and titrated over 6 weeks to a target dose of 120 mg and a treatment duration of 8 weeks (NCT04889157) (37).

Published phase I clinical study

A phase I randomized, placebo-controlled, multiple-ascending-dose study (NCT03538743) assessed the pharmacokinetic and pharmacodynamic properties of danuglipron. The study enrolled 98 participants who were randomized to receive placebo, IR or CR danuglipron. The IR doses studied included 10 mg b.i.d., 15 mg b.i.d., 50 mg b.i.d., 70 mg b.i.d., 120 mg b.i.d., 120 mg b.i.d. with an initial dose titration from 5 mg, 120 mg once daily; and the CR dose studied was a 200-mg once-daily tablet (Table II) (38, 39). At baseline, patient A_{1c} was 8.3%; after 28 days the placebo group showed an average decrease in A_{1c} of 0.4%. Participants receiving the 10-mg b.i.d. dose of danuglipron had a decrease in A_{1c} of 0.8%, while those receiving the 15-mg b.i.d. dose had a decrease in A_{1c} of 0.9%, and those receiving 50-mg b.i.d., 70-mg b.i.d. and 120-mg b.i.d. doses saw a decrease in A_{1c} of 1.2%. It was predicted that the steady-state A_{1c} would have an actual decrease by ~1.7% for the 120-mg b.i.d. dose if the study was extended beyond 28 days. There was a dose-dependent effect on weight loss with the danuglipron group with a baseline of 92.5 kg; weight loss ranged 2.4 to 7.9 kg in those treated with danuglipron while the placebo group showed an average weight loss of 1.9 kg. The effect of danuglipron on fasting plasma glucose (FPG) also showed a dose-dependent decrease. Baseline FPG was 178.7 mg/dL and exhibited a decrease ranging from 34.5 to 89.7 mg/dL in the danuglipron arms, and a decrease of 24.8 mg/dL for those who received placebo (40). Saxena et al. discussed the pharmacokinetic parameters on the plasma exposure of danuglipron after 28 days by measuring C_{max}, t_{max} and the AUC_{24}. Results showed that danuglipron exhibits a dose-dependent effect on AUC_{24}, C_{max} and t_{max} for the IR formulations. At day 28, t_{max} was between 3 and 10 h for all formulations except the CR formulation which exhibited a

Table II. *Summary of clinical data reported from trial NCT03538743 of danuglipron (27).*

Treatment arm	Placebo	Danuglipron						
		15 mg b.i.d.	50 mg b.i.d.	70 mg b.i.d.	120 mg b.i.d.	120 b.i.d. ST	120 mg q.d.	200 mg q.d. CR
Age range (years)	41-70	37-68	48-68	46-65	40-64	50-69	43-66	45-69
Males (%)[a]	48	34	50	45	78	45	50	50
Latino (%)[a]	72	45	70	67	45	45	75	60
Caucasian (%)[a]	72	56	80	78	67	45	100	70
AUC day 28 (ng·h/mL)[a]	N/A	1653	3171	8368	5973	2723	4372	2723
C_{max} day 28 (ng/mL)[a]	N/A	82	134	329	686	438	192	304
Headache (%)[a]	32	12	50	23	0	0	50	30
Constipation/diarrhea (%)[a]	32	56	30	56	56	78	38	60
Nausea/vomiting (%)[a,b]	24	23	90	56	167	178	125	110
Decreased appetite (%)[a]	4	0	10	12	67	23	38	50

[a]Value rounded up to nearest whole digit.
[b]Combined data between side effects.
ST, slow titration; CR, controlled release.

t_{max} at 14 h. The C_{max} was seen to be largest for the 120-mg IR b.i.d. dose with a plasma concentration of ~500 ng/mL, and lowest for the 10 mg IR b.i.d. dose with a C_{max} of about 30 ng/mL. The 200-mg CR formulation had a similar C_{max} to that of the 70 mg IR b.i.d. dose at ~250 ng/mL but had a shallower decline and mimicked the 120-mg IR b.i.d. plasma level decline. Danuglipron was seen to be unchanged in the urine with < 0.1% being excreted suggesting that the primary form of excretion is not in the urine (27).

Phase II

There is currently 1 active phase II study for danuglipron and 2 completed phase II studies. There are no preliminary results posted for these studies at this time (Table III).

Completed phase II clinical studies in participants with comorbidities

A 16-week study that evaluated the efficacy and safety of danuglipron in T2DM enrolled 412 patients aged 18-75 years old, BMI 24.5-45.4 kg/m^2, and A_{1c} 7-10.5% who were inadequately treated with metformin alone. This phase IIb, randomized, double-blind, placebo-controlled, parallel-group study began on June 13, 2019, and closed on August 12, 2021, but has not released any anticipated dates for a preliminary data readout. Participants were randomized to placebo, 2.5 mg danuglipron, or 10 mg danuglipron without a titration, or 40 mg, 80 mg, 120 mg with a titration schedule of 2, 4 and 6 weeks, respectively. The primary endpoint of this study was analyzing the change in A_{1c} over 16 weeks (NCT03985293) (41).

A 12-week, phase IIa, randomized, double-blind, placebo-controlled, parallel study evaluated the safety, tolerability and pharmacodynamic properties of danuglipron titration in adults 18-75 years old with T2DM treated with metformin, as well as nondiabetic adults with obesity. There is no disclosed value that defines obesity for this second group analyzed. This 12-week study began November 5, 2020, and enrolled 151 participants before the close date of November 17, 2021. Participants with T2DM received either placebo, or a starting dose of 5 mg danuglipron b.i.d. titrated to 80 mg b.i.d., 10 mg b.i.d. titrated to 80 mg b.i.d., 5 mg b.i.d. titrated to 120 mg b.i.d., 10 mg b.i.d. titrated to 100 mg b.i.d., or 10 mg b.i.d. titrated to 200 mg b.i.d. of danuglipron, while obese patients received either placebo or 10 mg b.i.d. titrated to 200 mg b.i.d. of danuglipron. The primary endpoint is to determine the incidence and severity of TEAEs over 112 days for each treatment arm (NCT04617275) (42).

Active phase II clinical study

Another phase II study is a 26-week, phase IIb, randomized, double-blind, placebo-controlled, parallel-group, dose-range study evaluating the efficacy and safety in adults with obesity. It is active but no longer recruiting. A total of 444 patients 18-75 years old, with a stable weight that has not changed by more than 5 kg over 90 days, and a BMI ≥ 30 kg/m^2 were enrolled. The study began January 13, 2021, and has an expected completion date of January 14, 2023. Patients are administered either placebo, or 40 mg b.i.d., 80 mg b.i.d., 120 mg b.i.d., 160 mg b.i.d., 200 mg b.i.d. of danuglipron, where the patients treated with danuglipron will be further divided to receive either a standard titration over 1 week or a slow titration schedule over 2 weeks. The primary endpoint of this study is the change in overall body weight from baseline until week 26 as well as the safety in these patients with the various treatment arms (NCT04707313) (43).

Safety

Saxena et al. reported a compilation of all side effects from their danuglipron study (NCT03538743) and did not distinguish side effects based on dose received. It was seen that all-causality adverse effects were nausea (49%), dyspepsia (32.7%), vomiting (26.5%), diarrhea (24.5%), headache (23.5%) and constipation (20.4%) (27). In contrast, the rates for placebo were 16% for nausea, 16% for dyspepsia, 8% for vomiting, 20% for diarrhea, 32% for headache, and 12% for constipation (27). There was an increase in the overall heart rate of patients which is seen as a potential side effect across the entire class of GLP-1RA medications. This side effect was not determined to be clinically significant. On average, the heart rate of patients increased by 11.8 beats per minute over 24 h compared to placebo. There was no observable change in diastolic blood pressure for both the placebo arm and the treatment arms; however, there was an observable decrease in systolic blood pressure, defined as ≥ 30 mmHg while supine. This in 36% of the participants in the placebo group, 55.6% in those receiving 15 mg IR b.i.d. and 70 mg IR b.i.d., and as much as 62.5% in the 120-mg IR once-daily group (27, 38).

Discussion

Preliminary results show that danuglipron has the potential to be an effective oral GLP-1RA agent to reduce A_{1c} in T2DM and aid in weight loss for obese patients. While danuglipron is not the first oral GLP-1RA, it is the first small molecule oral GLP-1RA with a unique mechanism of action that provides a promising area of drug discovery other than oral semaglutide, which is a small oral peptide (20, 22).

It is important to evaluate danuglipron performance in comparison to Rybelsus due to the latter being the only FDA-approved oral GLP-1RA on the market (44). A phase II study evaluated oral semaglutide compared to injectable semaglutide and placebo. All doses of oral semaglutide (2.5 to 40 mg) showed an A_{1c}-lowering effect, with the 2.5-mg dose decreasing A_{1c} by 0.7% and the 40-mg dose lowering A_{1c} by 1.9%. The oral 40-mg dose of semaglutide was seen to have the same A_{1c}-lowering effect as 1 mg of injectable semaglutide. A_{1c} decreased by 0.7% for the oral 2.5-mg

Table III. *Summary of phase II clinical trials using danuglipron (41-43).*

ClinicalTrials.gov Identifier	Status	Study population	Results being analyzed	Study Intervention
NCT03985293	Completed	Overall healthy adults with T2DM	Change from baseline in A_{1c}	Trial was ran over the course of 16 weeks. Arms D-F received an initial dose titration **Arm A:** Placebo **Arm B:** 2.5 mg danuglipron 4 tablets b.i.d. **Arm C:** 10 mg danuglipron 4 tablets b.i.d. **Arm D:** 40 mg danuglipron 4 tablets b.i.d.; 2-week titration **Arm E:** 80 mg danuglipron 4 tablets b.i.d.; 4-week titration **Arm F:** 120 mg danuglipron 4 tablets b.i.d.; 6-week titration
NCT04617275	Completed	Overall healthy adults with T2DM and/or are obese	Number of TEAEs	Each treatment arm titrated for a total of 12 weeks to receive a desired dose **Arm A:** Placebo **Arm B:** Starting dose 5 mg b.i.d. titrated to 120 mg b.i.d. in T2DM **Arm C:** Starting dose 10 mg b.i.d. titrated to 120 mg b.i.d. in T2DM **Arm D:** Starting dose 5 mg b.i.d. titrated to 80 mg b.i.d. in T2DM **Arm E:** Starting dose 10 mg b.i.d. titrated to 80 mg b.i.d. in T2DM **Arm E:** Starting dose 10 mg b.i.d. titrated to 200 mg b.i.d. in T2DM **Arm G:** Starting dose 10 mg b.i.d. titrated to 200 mg b.i.d. in obesity
NCT04707313	Active, not recruiting	Overall healthy adults with obesity	Percent change from baseline in body weight	Each treatment arm receives a titration over 1-2 weeks for a total 26 weeks of treatment **Arm A:** Placebo **Arm B:** Target dose of 40 mg b.i.d.; 1-week titration **Arm C:** Target dose of 80 mg b.i.d.; 1-week titration **Arm D:** Target dose of 120 mg b.i.d.; 1-week titration **Arm E:** Target dose of 160 mg b.i.d.; 1-week titration **Arm F:** Target dose of 200 mg b.i.d.; 1-week titration **Arm G:** Target dose of 120 mg b.i.d.; 2-week titration **Arm H:** Target dose of 160 mg b.i.d.; 2-week titration **Arm I:** Target dose of 200 mg b.i.d.; 2-week titration

A_{1c}, hemoglobin A_{1c}; T2DM, type 2 diabetes mellitus; TEAEs, treatment-emergent adverse events.

semaglutide dose and decreased by as much as 1.9% for the oral 40-mg dose. Body weight decreased by 2.1 kg for the oral 2.5-mg semaglutide dose, and 6.9 kg for the oral 40-mg dose, while the s.c. 1-mg dose had a decrease of 6.4 kg (45). The follow-up to this study, PIONEER 1, was a 26-week, phase IIIa study with 703 patients with T2DM (14, 44, 46). This study assessed the A_{1c}-lowering effect of 3, 7 and 14 mg semaglutide in T2DM, and found that A_{1c} decreased by 0.9%, 1.2% and 1.1%, respectively (14, 46). From these data it can be inferred that the maximum approved oral dose of 14 mg Rybelsus may not be as efficacious as 1 mg s.c. semaglutide (Ozempic) (45).

It is difficult to make a direct comparison for the reduction in A_{1c} and body weight between danuglipron and oral semaglutide due to the participant population for danuglipron's phase I trial only having 98 patients followed for 28 days, while PIONEER 1 had 703 participants who were followed for 26 weeks (27, 46). The moderate intensity dose of Rybelsus, 14 mg, had an observed A_{1c} reduction of 1.2% over 26 weeks, while danuglipron's reduction was 0.8-1.2% between the 10- and 120-mg b.i.d. doses administered for only 28 days. This would suggest that doses above 50 mg b.i.d. of danuglipron may be similar or greater in terms of efficacy but it is inconclusive with the data reported at this time. It is anticipated that the 120-mg b.i.d. dose of danuglipron would be able to have an A_{1c} reduction of ~1.7% if extended beyond the 28-day period, which would be comparable to the oral 40-mg dose of semaglutide (15, 45). The side effect profile of danuglipron shows higher rates of nausea (49% vs. 16%), diarrhea (24.5% vs. 9%), vomiting (26.5% vs. 6.9%) and headache (23.5% vs. 5.1%) when compared to Rybelsus. One potential reason for this discrepancy is that danuglipron was administered without titration, unlike oral semaglutide which was titrated, and may be the contributing factor for why many studies for danuglipron are including titrations to avoid these side effects (15, 46). The side effects of mild tachycardia in patients treated with danuglipron were similar to other GLP-1RAs and are shown to be a class-based effect (47).

T-0632, CHU-128, LY-3502970 and TT-OAD2 are 4 other small molecule oral GLP-1R-modulating agents that have been studied (Table IV) (48-50). T-0632 had preclinical testing performed by Mitsubishi Tanabe Pharma, but is a GLP-1R antagonist, unlike danuglipron, which is an agonist. Another key difference between these agents is that T-0632 only effects the cAMP production, while danuglipron also works on the βArr pathway (26, 48). T-0632 has the same target site for the $Trp33^{ECD}$ of the GLP-1R affecting the class B GPCR, which allows it to express its effect in the body (48). T-0632 was studied in vivo in the COS-7 cell line and showed a 100-fold increase in the EC_{50} for cells that expressed the hGLP-1R gene compared to cells that had rat GLP-1R gene, but cannot be compared to danuglipron with danuglipron being tested in vitro (48).

CHU-128 is a patented product from the Chugai patent series that is a small molecule GLP-1RA but differs in its effects compared to danuglipron, which mimics the actions of natural GLP-1, while CHU-128 does not. CHU-128 has minimal ligand binding affinity, but results show it may not be suitable for use in human models. CHU-128, however, exhibited an equivalent potency to danuglipron and both were full agonists for cAMP production with an ~30-fold lower potency compared to natural GLP-1. The last major difference between these 2 agents is that CHU-128 has a bias to only the cAMP pathway and no other pathway in the recruitment of GLP-1 (51, 52).

LY-3502970, originally OWL-833, is being studied by Eli Lilly and Company in phase II studies. This product was originally part of the Chugai patent series like CHU-128 before Eli Lilly and Company obtained the rights. LY-3502970 is a partial agonist to GLP-1R that has a similar agonist property to danuglipron but does not affect the βArr pathway like danuglipron, and has higher potency to the activation of class B1 GPCR resulting in the cAMP pathway. This agent also targets the $Trp33^{ECD2}$ similarly to danuglipron, but danuglipron stabilized the TMD helices kink 6 in the GLP-1R, while LY-3502970 does this stabilization at the TMD helices kinks 1, 2, 3 and 7. Four phase I clinical trials have been completed with LY-3502970 in healthy male participants, healthy male and female participants, and patients with T2DM that are otherwise healthy (53-56). There are currently no posted results to allow for comparison to danuglipron (16, 20, 26).

Table IV. *Oral small molecule GLP-1R modulators (48-52).*

Molecule name	Molecule owner	Molecular weight (Daltons)	$Trp33^{ECD}$ binding site	TMD helices kinks	cAMP agonism	βArr agonism
Danuglipron	Pfizer	555.6	ECL1; ECL2	6	Full	Partial
T-0632	Mitsubishi Tanabe Pharma	502.2	ECL; ECL2	6	N/A; works through antagonism	N/A
CHU-128	Chugai Pharmaceutical	161.0	ECL1; ECL3	7	Full	Partial
LY-3502970	Eli Lilly and Company	883.0	ECL2	1; 2; 3; 7	Partial	N/A
TT-OAD2	vTv Therapeutics	929.7	ECL1; ECL2	1; 6; 7	Partial	N/A

βArr, β-Arrestin; cAMP, cyclic AMP; ECL, extracellular loop; TMD, C-terminal transmembrane domain; $Trp33^{ECD}$, N-terminal extracellular domain of tryptophan residue 33.

TT-OAD2 is an agent from vTv Therapeutics that has been studied for the way it binds to the GLP-1R allowing for its action. It works on the class B GPCR at the Trp33 residue; however unlike danuglipron, it also works on ECL3 at the top of the TMD helices at kinks 1, 6 and 7. TT-OAD2 does share a similarity to danuglipron by also working on ECL2 at the TMD helices at kink 6. TT-OAD2 was tested in the HEK-293 cell line with overexpressed GLP-1R, and it was found that it had low-potency partial agonism for the cAMP pathway with week Ca^{2+} responses. No clinical trials have been done on this agent (49).

One other small molecule from Eli Lilly and Company is LSN-3160440, which is a positive allosteric modulator of GLP-1R and does not target GPCR. LSN-3160440 binds to the tyrosine-kinase MET, causing an allosteric conformational change and causes the ECD of the GLP-1R to change and allowing for the cAMP to begin (57). This agent has limited data available and could be a potential competitor to danuglipron with it having a different mechanism of action (52, 57).

Conclusions

Danuglipron has demonstrated that small molecule oral GLP-1RAs have a place in the treatment of obesity and T2DM. Danuglipron is the first small molecule GLP-1RA to be evaluated and has a unique multifactorial mechanism of action that may be a protentional agent to improve the health outcomes of patients with both T2DM and obesity, but is still unknown. Current and future studies will assist in evaluating the place in patient therapy for dosing, potential TEAEs, effects in patients with renal and hepatic impairment, potential weight loss, and A_{1c}-lowering benefits.

Author Contributions

All authors contributed to the review. Rebecca Goldfaden had the idea for the article, Alexander J. Sperry, PharmD, and Jennifer Hardy, PharmD, performed the literature search and data analysis, and all authors drafted and/or critically revised the review. All authors read and approved the final manuscript.

Disclosures

The authors state no conflicts of interest. No external funding was used in the preparation of this manuscript.

Submitted: September 28, 2021. Revised: February 16, 2022. Accepted: February 23, 2022.

References

1. *Type 2 diabetes*. Centers for Disease Control and Prevention (CDC) Website. Dec 16, 2021. https://www.cdc.gov/diabetes/basics/type2.html. Accessed May 5, 2022.
2. *IDF Diabetes Atlas*. International Diabetes Federation (IDF). https://diabetesatlas.org/. Accessed May 5, 2022.
3. Zimmerman, R.S. *Diabetes mellitus: management of microvascular and macrovascular complications*. Cleveland Clinic Center for Continuing Education. Sept 2016. https://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/endocrinology/diabetes-mellitus/. Accessed Aug 21, 2021.
4. *Complications*. American Diabetes Association. https://www.diabetes.org/diabetes/complications. Accessed Aug 12, 2021.
5. American Diabetes Association Professional Practice Committee. *10. Cardiovascular disease and risk management: standards of medical care in diabetes-2022.* Diabetes Care 2022, 45(Suppl 1): S144-S74.
6. American Diabetes Association. *10. Cardiovascular disease and risk management: standards of medical care in diabetes-2021.* Diabetes Care 2021, 44(Suppl 1): S125-S50.
7. American Diabetes Association. *9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2021.* Diabetes Care 2021, 44(Suppl 1): S111-S24.
8. McGovern, A., Tippu, Z., Hinton, W., Munro, N., Whyte, M., de Lusignan, S. *Comparison of medication adherence and persistence in type 2 diabetes: A systematic review and meta-analysis.* Diabetes Obes Metab 2018, 20(4): 1040-3.
9. Tucker, M.E. *Half abandon metformin within a year of diabetes diagnosis*. Medscape. Aug 3, 2021.
10. Shaefer, C.F., Jr., Kushner, P., Aguilar, R. *User's guide to mechanism of action and clinical use of GLP-1 receptor agonists.* Postgrad Med 2015, 127(8): 818-26.
11. Wysham, C., Shubrook, J. *Beta-cell failure in type 2 diabetes: mechanisms, markers, and clinical implications.* Postgrad Med 2020, 132(8): 676-86.
12. Marchetti, P., Bugliani, M., De Tata, V., Suleiman, M., Marselli, L. *Pancreatic beta cell identity in humans and the role of type 2 diabetes.* Front Cell Dev Biol 2017, 5: 55.
13. Hughes, S., Neumiller, J.J. *Oral semaglutide.* Clin Diabetes 2020, 38(1): 109-11.
14. Rodbard, H.W., Dougherty, T., Taddei-Allen, P. *Efficacy of oral semaglutide: overview of the PIONEER clinical trial program and implications for managed care.* Am J Manag Care 2020, 26(16 Suppl): S335-S43.
15. *Pfizer Investor Day features significant number of pipeline advances for COVID-19 programs and across numerous therapeutic areas* [news release]. Pfizer, Inc. Sept 15, 2020. Accessed Aug 21, 2021.
16. Nauck, M.A., Quast, D.R., Meier, J.J. *Another milestone in the evolution of GLP-1-based diabetes therapies.* Nat Med 2021, 27(6): 952-3.
17. Taylor, S.I. *GLP-1 receptor agonists: differentiation within the class.* Lancet Diabetes Endocrinol 2018, 6(2): 83-5.
18. Zhang, X., Johnson, R.M., Drulyte, I. et al. *Evolving cryo-EM structural approaches for GPCR drug discovery.* Structure 2021, 29(9): 963-74 e6.
19. Wu, F., Yang, L., Hang, K. et al. *Full-length human GLP-1 receptor structure without orthosteric ligands.* Nat Commun 2020, 11(1): 1272.
20. Choe, H.J., Cho, Y.M. *Peptidyl and non-peptidyl oral glucagon-like peptide-1 receptor agonists.* Endocrinol Metab (Seoul) 2021, 36(1): 22-9.
21. Ruozi, G., Bortolotti, F., Recchia, F.A. *Chapter 6 - Gut-derived hormones—cardiac effects of ghrelin and glucagon-like peptide-1*.

In: Endocrinology of the Heart in Health and Disease. J.C. Schisler, C.H. Lang, M.S. Willis (Eds.). Academic Press: 2017, 139-66.
22. Drucker, D.J. *Mechanisms of action and therapeutic application of glucagon-like peptide-1.* Cell Metab 2018, 27(4): 740-56.
23. Jean-Charles, P.Y., Kaur, S., Shenoy, S.K. *G protein-coupled receptor signaling through beta-arrestin-dependent mechanisms.* J Cardiovasc Pharmacol 2017, 70(3): 142-58.
24. Wen, Y., He, J., Xue, X. et al. *beta-Arrestin2 inhibits apoptosis and liver inflamation induced by ischemia-reperfusion in mice via AKT and TLR4 pathway.* Arch Med Res 2019, 50(7): 413-22.
25. Fletcher, M.M., Halls, M.L., Christopoulos, A., Sexton, P.M., Wootten, D. *The complexity of signalling mediated by the glucagon-like peptide-1 receptor.* Biochem Soc Trans 2016, 44(2): 582-8.
26. Griffith, D.A., Edmonds, D.J., Fortin, J.-P. et al. *A small-molecule oral agonist of the human glucagon-like peptide-1 receptor.* bioRxiv 2020.09.29.319483.
27. Saxena, A.R., Gorman, D.N., Esquejo, R.M. et al. *Danuglipron (PF-06882961) in type 2 diabetes: a randomized, placebo-controlled, multiple ascending-dose phase 1 trial.* Nat Med 2021, 27(6): 1079-87.
28. *First In human, single escalating oral dose study of PF-06882961 in healthy adult subjects (NCT03309241)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
29. *A single dose crossover study in healthy subjects to evaluate different formulations of PF-06882961 (NCT03492697)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
30. *Study to characterize mass balance, absolute bioavailability, fraction absorbed and pharmacokinetics of 14C PF-06882961 (NCT04495140)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
31. *A study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of PF-06882961 in Japanese adults with type 2 diabetes mellitus (NCT04552470)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
32. *Study to compare pharmacokinetics (PK) of single oral doses of different PF-06882961 formulations in participants who are overweight or have obesity (NCT04616339)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
33. *Study to evaluate the effect of two steady state doses of PF 06882961 on rosuvastatin and midazolam pharmacokinetics in otherwise healthy adult participants with obesity (NCT04621227)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
34. *Study of PF-06882961 in participants with and without varying degrees of hepatic impairement (NCT04604496)* ClinicalTrials.gov Website. Accessed May 12, 2022.
35. *Study of PF-06882961 in participants with type 2 diabetes mellitus with varying degrees of renal impairment and participants without renal impairment (NCT04616027)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
36. *A drug-drug interaction study between PF-06882961 and PF-06865571 in healthy adult participants and overweight adults or adults with obesity who are otherwise healthy (NCT04839393)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
37. *A study to evaluate the pharmacokinetics, pharmacodynamics, safety and tolerability of PF-06882961 in Chinese adults with type 2 diabetes mellitus (NCT04889157)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
38. *4-Week, multiple-dose, dose-escalating study in patients with type 2 diabetes (NCT03538743)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
39. Saxena, A., Gorman, D., Chidsey, K., Buckeridge, C., Kim, A.M., Bergman, A. *Oral small molecule GLP-1R agonist PF-06882961 robustly reduces plasma glucose and body weight after 28 days in adults with T2DM*. 80th Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 12-16, Virtual) 2020, Abst 353-OR.
40. *Analyst and investor call to review presentations of hemophilia A gene therapy at WFH and oral GLP-1R agonist at ADA*. Pfizer. June 18, 2020. https://s21.q4cdn.com/317678438/files/doc_presentations/2020/06/Full-Slide-Deck_InvestorCall_FINAL_06172020.pdf.
41. *A 16 week study to evaluate the efficacy and safety of PF-06882961 in adults with type 2 diabetes mellitus (NCT03985293)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
42. *A 12-week titrate study to evaluate safety, tolerability and pharmacodynamics of PF-06882961 in adults with type 2 diabetes mellitus and in non-diabetic adults with obesity (NCT04617275)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
43. *A 26-week, 2-part study to evaluate the efficacy and safety of PF-06882961 in adults with obesity (NCT04707313)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
44. *Rybelsus Product Monograph*. Novo Nordisk Canada Inc. April 2020. https://www.novonordisk.ca/content/dam/Canada/AFFILIATE/www-novonordisk-ca/OurProducts/PDF/Rybelsus-PM-EN-monograph.pdf.
45. Davies, M., Pieber, T.R., Hartoft-Nielsen, M.L., Hansen, O.K.H., Jabbour, S., Rosenstock, J. *Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: a randomized clinical trial.* JAMA 2017, 318(15): 1460-70.
46. Aroda, V.R., Rosenstock, J., Terauchi, Y. et al. *PIONEER 1: randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes.* Diabetes Care 2019, 42(9): 1724-32.
47. Nauck, M.A., Kemmeries, G., Holst, J.J., Meier, J.J. *Rapid tachyphylaxis of the glucagon-like peptide 1-induced deceleration of gastric emptying in humans.* Diabetes 2011, 60(5): 1561-5.
48. Tibaduiza, E.C., Chen, C., Beinborn, M. *A small molecule ligand of the glucagon-like peptide 1 receptor targets its amino-terminal hormone binding domain.* J Biol Chem 2001, 276(41): 37787-93.
49. Zhao, P., Liang, Y.L., Belousoff, M.J. et al. *Activation of the GLP-1 receptor by a non-peptidic agonist.* Nature 2020, 577(7790): 432-6.
50. Kawai, T., Sun, B., Yoshino, H. et al. *Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist.* Proc Natl Acad Sci U S A 2020, 117(47): 29959-67.
51. Zhang, X., Belousoff, M.J., Zhao, P. et al. *Differential GLP-1R binding and activation by peptide and non-peptide agonists.* Mol Cell 2020, 80(3): 485-500 e7.
52. Cong, Z., Chen, L.N., Ma, H. et al. *Molecular insights into ago-allosteric modulation of the human glucagon-like peptide-1 receptor.* Nat Commun 2021, 12(1): 3763.

53. *A study of LY3502970 in healthy male participants (NCT04680767)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
54. *A study of LY3502970 in participants with type 2 diabetes (NCT04426474)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
55. *A study of LY3502970 in healthy participants (NCT03929744)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
56. *A multiple dose study of LY3502970 in healthy participants (NCT05051566)*. ClinicalTrials.gov Website. Accessed May 12, 2022.
57. Bueno, A.B., Sun, B., Willard, F.S. et al. *Structural insights into probe-dependent positive allosterism of the GLP-1 receptor.* Nat Chem Biol 2020, 16(10): 1105-10.