ACTUALITIES IN ENDOCRINE PHARMACOLOGY: ADVANCES IN THE DEVELOPMENT OF ORAL FORMULATIONS FOR CALCITONIN AND SEMAGLUTIDE

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Abstract

As the medical utility of injectable therapeutic peptides is expanding, so is the challenge of developing technologies that allow the administration of such molecules via alternative routes, considering that chronic patients requiring treatment with parenteral formulations are less adherent and compliant to the therapeutic regimens. Hence, substantial efforts have been made to develop technologies that allow the oral formulation of peptides.

Due to their importance in the field of pharmaceutical technology, we describe the latest advancements made in the development of oral salmon calcitonin and oral semaglutide, in co-formulation with absorption enhancers such as 8-[(5-chloro-2-hydroxybenzoyl) amino] octanoic acid (or 5-CNAC) and N-[8-(2-hydroxybenzoyl) amino] caprylate (or SNAC). Oral semaglutide is considered to be a landmark for oral peptide delivery technology, as it is one of the very few successful examples of peptides that can be administered orally. Unlike semaglutide, oral calcitonin is still not approved by the regulatory authorities because it failed to demonstrate the anticipated effects in phase III clinical trials conducted so far. However, the efforts for obtaining an oral form of calcitonin have significantly contributed to the development of technologies that facilitate the absorption of peptide-structure macromolecules.

Keywords: oral semaglutide, oral calcitonine, permeation enhancers, pharmaceutical technology, diabetes.

INTRODUCTION

Patient preference is one of the most important factors that require integration in the therapeutic decision, in order to optimize the results of long-term treatments and the oral administration of drugs is by far the most popular route of administration. The majority (84%) of 50 most-sold pharmaceutical products in the US and European markets are given orally (1). Besides, oral pharmaceutical forms do not require

specific sterility conditions and other precautions against possible contamination with microorganisms, which may also have cost implications (2). Altogether, the preference for oral administration represents a major challenge from the drug delivery perspective, as macromolecular peptides have very low bioavailability when administered orally and thus, substantial efforts are being made to research and develop technologies which allow the administration of such molecules via oral, nasal and even transdermal routes.

In this review, we will only focus on describing the advancements made in developing two orally administered peptides, both developed by using the strategy of co-formulation with absorption enhancers: calcitonin, that currently has no approved label for the oral form, even though it is a benchmark molecule for oral peptide delivery systems, with intensive efforts made for its development and semaglutide, because it is the first glucagon-line peptide one receptor agonist and an analog of the endogenous glucagon-like peptide 1, first approved as an injectable form, by both FDA and EMA in the treatment of type 2 diabetes and it is considered to be a landmark in the field, that could energize the development of oral peptide therapeutics.

Calcitonin

Calcitonin (CT) is a human hormone produced in the thyroid gland, by the parafollicular cells (C cells). Calcitonin acts as a calcium and bone regulator and it is involved in the phosphocalcic and bone metabolism (3). In human adults, the physiological role of calcitonin is not entirely clear, as people with very low CT levels have no alteration of the bone mineral density or phosphocalcic profile, however we well know that calcitonin is a very specific marker for the diagnosis and prognosis of medullary thyroid carcinoma (3). Calcitonin (CT) is a 32 amino acid polypeptide disposed in a single chain with a C-terminal amidated

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proline and an N-terminal bridge between position one and position two (4).

CT was found in birds, mammals, reptiles and fish. Having a higher affinity for the human calcitonin receptor, salmon calcitonin (sCT) has a very high potency (up to 100 times higher than human calcitonin), has stronger analgesic effects (5) and is currently being used for medicinal purposes (6). Salmon calcitonin inhibits osteoclasts and promotes osteoblast-induced bone tissue formation, increases bone mass, reduces the serum calcium concentration, and, by inhibiting the reabsorption process in the nephrons, it promotes renal excretion of calcium, sodium, magnesium, and potassium (7). Salmon calcitonin is recommended in the treatment of Paget disease, in emergency settings, when it is necessary to rapidly decrease the blood calcium concentration, in the treatment of hypercalcemia, in the treatment of osteoporosis for women who have been experiencing menopause for at least five years (7). Salmon calcitonin (sCT) is approved in two pharmaceutical forms: parenteral (subcutaneous and intramuscular) and nasal (7). Considering that injectable therapies are usually associated with pain and discomfort for the patients, the long term and frequent administration of such therapies is very problematic, as it negatively affects both adherence (8) and persistence to treatment (9). Intranasal administration of calcitonin has also many downsides, as it can cause epistaxis, rhinitis, and ulcerations of the nasal mucosa (7). The development of an oral form of calcitonin has the potential to increase the addressability of this treatment among patients (10). To date, two forms of oral calcitonin have been tested, however none has been approved yet by the U.S. Food and Drug Administration (6).

Salmon calcitonin in co-formulation with citric acid

One such oral formulation of calcitonin was initially developed by Unigen under the trade name of TBRIA®, later acquired by Enteris Biopharma, and in 2019 it was sold to Osteon Therapeutics (11). Each tablet contains 200 mg of calcitonin, co-formulated with citric acid and is covered with a polymeric coating agent, which starts to dissolve when the pH increases above 5.5. The role of citric acid is to protect the salmon calcitonin molecules from the gastric proteolytic enzymes by increasing local acidity which ensures the integrity of calcitonin upon contact with the intestinal wall (11). Citric acid has a minimal effect on increasing the permeability of the intestinal

epithelium. This technology was patented by the brand name Peptelligence® (by Enteris Biopharma) (12). Despite the positive results of the ORACAL trial (6), which evaluated the efficacy and safety of oral calcitonin in comparison with nasal calcitonin in postmenopausal women with osteoporosis, showing that oral calcitonin significantly increases the lumbar spine bone mineral density, FDA did not approve the label because there were no differences on bone mineral density between oral calcitonin and placebo, observed at other sites (11). In 2014, the results of another clinical trial on post-menopausal, osteopenic women (13) were published, showing a significant effect of oral calcitonin on the increase of lumbar spine bone mineral density and suppression of collagen type 1 C-Telopeptide (CTx-1). Pharmacokinetic data have not been published yet, however, considering the comparator, the bioavailability of oral calcitonin is assumed to be 1%, which could be sufficient to achieve a therapeutic effect.

Salmon calcitonin in co-formulation with 5-CNAC

SMC021 is another form of oral salmon calcitonin, using in co-formulation the 8-[(5-chloro-2-hydroxybenzoyl) amino] octanoic acid (5-CNAC) as an absorption enhancer, together with vitamin D and calcium (11). The absorption enhancer 5-CNAC is reversibly linked to the active substance by non-covalent bonds, forming a stable complex at gastric pH, which protects the active substance from the action of proteolytic enzymes. This complex ensures the transportation of calcitonin through the gastric membrane by the transcellular route (14). The evaluation of efficacy and safety of SMC021 in the phase III clinical trial (NCT00525798) proved to be disappointing, as the primary objective of preventing new fractures was not reached (15). According to limited pharmacokinetic data, plasma concentrations of salmon calcitonin are at the detection limit (11). Following these results, the pharmaceutical company Novartis abandoned the project, but Nordic Biosciences started two additional clinical trials that investigated the efficacy and safety of SMC021, on patients with osteoarthritis of the knee (11). In both studies, SMC021 failed to demonstrate a statistically significant effect *vs.* placebo on joint space narrowing and improving pain scores (16). Based on the known relationship between the plasma concentration of salmon calcitonin and CTx-1 and the determinations made in phase I and II studies, it was concluded that the reason for the failures observed in

phase III studies was the insufficient gastric absorption of oral salmon calcitonin (11). Additionally, calcitonin receptors are distributed in non-skeletal tissues as well, leading to a limited availability of calcitonin at the bone tissue via a competitive absorption of sCT (17). Thus, a novel calcitonin analogue with increased specificity for bone minerals while retaining the function of sCT was developed: hexapeptide (Asp6)-conjugated sCT (sCT-Mal-Asp6) (17). In animal studies, it was shown that sCT-Mal-Asp6 had a 5.4 times higher absorption in bone minerals, a 3 times higher accumulation in the femur and a prolonged circulation time in comparison with sCT (17). Also, it is worth mentioning that calcitonin molecules have a tendency to associate and fibrilize, leading to a loss of potency (5). However, the tendency of calcitonin to self-associate was used to develop a supramolecular form of calcitonin which was proven to act as a prolonged release both *in vitro* as well as *in vivo* studies. Indeed, the Supramolecular Calcitonin Assembly (SCA-I) releases calcitonin for a period of at least 3 weeks (5).

As several other therapeutical options were developed for the treatment of osteoporosis, such as anabolic hormones and anti-resorptive agents, the enthusiasm in the development of oral calcitonin seems to have faded (8), despite *in vitro* data showing that other permeation enhancers such as sodium taurodeoxycholate, sodium caprate and coco-glucoside might be used further to increase the bioavailability of oral calcitonin (18). Also, novel controlled release delivery systems for the sustained delivery of calcitonin are currently being developed. One such experimental system uses the thermosensitive triblock copolymers monomethoxy poly (ethylene glycol) -poly lactico-glycolic acid (mPEG-PLGA-mPEG) which releases calcitonin with the slow and controlled breakdown of the polymer, in a diffusion-dependent manner (19). The hydrophobicity of the polymer is increased by increasing the lactico-glycolic acid ratio, which determines a decreased rate of the polymer breakdown, in turn extending the release of calcitonin over a period of 60 to 70 days, after subcutaneous administration (19), which will significantly increase patient's adherence, as the frequency of administration will be drastically reduced.

Semaglutide

Glucagon-like peptide 1 (GLP- 1) is an endogenous hormone produced by the L-cells from the intestines after food intake, first as proglucagon (20) which is proteolytically cleaved, in four different forms

of GLP- 1 (21). GLP-1 stimulates insulin secretion in a glucose-dependent manner, has protective effects on pancreatic β -cells, cardioprotective effects and induces weight loss by suppressing appetite and delaying gastric emptying (20). The endogenous GLP-1 hormone has a very short half-life, varying from 2 to 11 minutes (22) due to a rapid enzymatic metabolism by the dipeptidyl-peptidase IV (DPP IV) (31).

Semaglutide is a glucagon-like receptor agonist, sharing 94% of structural homology with the human endogenous glucagon-like peptide one, as it has two amino acid substitutions: alanine was substituted by alpha-aminoisobutyric acid in position 8 in order to obtain resistance to systemic degradation by dipeptidyl peptidase-IV (DPP-IV) and lysine was substituted by arginine in position 34 of the peptide backbone, a substitution which is believed to act as an enhancer of the molecule's stability, by enabling site-specific acylation of lysine in the 26th position (23). It is also derivatized in the 26th position, with a C-18 di-acid with high albumin affinity, attached to GLP-1 via a water-compatible chemical linker to ensure that the derivatized peptide has high GLP-1R potency in the presence of albumin (24). By subcutaneous administration, semaglutide has a bioavailability of 94% and a reported half-life of 165 hours (in human subjects) (25). Semaglutide was developed by Novo Nordisk, as a once-weekly injectable formulation, under the brand name Ozempic®. Injectable semaglutide was intensively investigated in "The Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes" (SUSTAIN) clinical trial program. Semaglutide proved to be superior *versus* all comparators (including sitagliptin, exenatide extended-release, dulaglutide, and insulin glargine U100) on both the reduction of HbA1c as well as weight reduction (26).

As it is believed that the development of an oral GLP1-RA agent would promote medication adherence and quality of life, there is a high interest in developing orally delivered non-peptide drugs (27). Danuglipron (PF 06882961) is a non-peptide GLP-1 receptor agonist developed by Pfizer and is currently investigated in clinical trials for the treatment of type 2 diabetes (27). However, not all GLP-1 peptide analogs require parenteral administration, semaglutide being the exception, as it is the most potent GLP-1 RA (28) and has a 4,11kD (29) molecular weight. Indeed, Novo Nordisk developed the orally administered semaglutide, receiving FDA approval in September 2019, for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes

(30). Rybelus® is the trade name for oral semaglutide in co-formulation with the absorption enhancer N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC or salcaprozate sodium) (31, 32). SNAC protects semaglutide from the proteolytic enzymes in the stomach, by forming a complex around the molecule and increasing the local pH (33). By allowing the active substance to be in close contact with the epithelium, SNAC facilitates the absorption of semaglutide via the transcellular pathway (33) in a concentration-dependent manner (34). Indeed, following the oral administration of semaglutide in co-formulation with SNAC in dogs and rats, it was revealed that semaglutide was found in the basal cytoplasm of mucus cells and not in the extracellular spaces between the cells, indicative of transcellular absorption (33). Phase II clinical trials have revealed that the bioavailability of oral semaglutide is approximately 1% (24). However, due to the high potency, oral semaglutide, administered daily, proved to have the same glucose lowering and weight lowering efficacy as once weekly injectable semaglutide (24). Orally administered semaglutide has also been intensively investigated in the phase III “Peptide Innovation for Early Diabetes Treatment” (PIONEER) clinical trial program and was associated with significantly higher reductions of HbA1c compared to other GLP-1 RAs and higher numerical reductions compared to injectable semaglutide (33) and dulaglutide (35). Oral semaglutide is one of the most effective GLP – 1 RA in terms of glycemic control and weight loss, while also being well tolerated and having a safety profile representative for GLP-1 RA class (35).

Responding to the 2008 US Food and Drug Administration (FDA) guidance for evaluating the cardiovascular safety in new glucose-lowering therapies, Novo Nordisk conducted the PIONEER 6 trial to evaluate the cardiovascular safety of oral semaglutide (36). PIONEER 6 was an event-driven, randomized, double-blind, placebo-controlled trial that included patients with type 2 diabetes, the majority being at high risk for cardiovascular disease. The patients were randomized to once-daily oral semaglutide or placebo, and the primary outcome was the time to first major cardiovascular event (death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) (36). Fewer major adverse cardiovascular events were reported in the subjects randomized to semaglutide (3.8%) than with placebo (4.8%), but the difference was not statistically significant (hazard ratio, 0.79; 95% confidence interval [CI], 0.57 to 1.11, $P < 0.001$

for noninferiority) (36). The rates of cardiovascular death and all-cause mortality were also lower with semaglutide and a network meta-analysis indirectly comparing GLP-1 RAs (liraglutide, exenatide once daily, exenatide once weekly, albiglutide, dulaglutide, injectable and oral semaglutide) places oral semaglutide as having the highest probability of being ranked first, in regards to cardiovascular death reduction and all cause death reduction. (37)

In conclusion, The PIONEER clinical trials program showed that oral semaglutide is at least as effective as dulaglutide (26) and injectable semaglutide in lowering HbA1c and weight for type 2 diabetes patients (35). Oral semaglutide also demonstrated cardiovascular safety (36) and has the highest probability of being ranked first, in regards to cardiovascular death reduction and all cause death reduction, in indirect comparison with other GLP-1 RAs (37). It is also worth mentioning that oral semaglutide opens new perspectives in the development of fixed-dose combinations with other oral agents such as SGLT2-inhibitors.

Unlike semaglutide, oral calcitonin is still not approved by the regulatory authorities (6) due to the disappointing results of the phase III clinical trials conducted so far (6, 11, 13, 15, 16). The primary reason for this is the insufficient gastric absorption of salmon calcitonin (9), leading to a very low bioavailability after oral administration. Additionally, the limited availability of calcitonin at the bone tissue due to the distribution of calcitonin receptors in non-skeletal tissues as well (17), combined with the tendency of calcitonin molecules to associate and fibrilize, leading to a loss of potency (5) might also have significantly contributed to the failure of oral calcitonin development.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Lennernäs H, Abrahamsson B. The use of biopharmaceutic classification of drugs in drug discovery and development: current status and future extension. *J Pharm Pharmacol*. 2005; 57(3):273-285.
2. Chung SW, Hil-lal TA, Byun Y. Strategies for non-invasive delivery of biologics. *J Drug Target*. 2012; 20(6):481–501.
3. Danila R, Livadariu R, Branisteanu D. Calcitonin revisited in 2020. *Acta Endocrinol (Buchar)*. 2019; 15(4):544-548.
4. Wimalawansa SJ. Physiology of Calcitonin and Its Therapeutic Uses. *Encyclopedia of Endocrine Diseases (Second Edition)*, Academic Press, 2018:178-191.

5. Manglani K, Vijayan V, Pathak C, Khandelwal M, Singh P, Chellappa S, Yadav VK, Surolia A, Gupta S. Development and characterization of supramolecular calcitonin assembly and assessment of its interactions with the bone remodeling process. *Bone*. 2019; 122:123-135.
6. Bandeira L, Lewiecki EM, Bilezikian JP, Pharmacodynamics and pharmacokinetics of oral salmon calcitonin in the treatment of osteoporosis. *Expert Opinion on Drug Metabolism & Toxicology*. 2016; 12(6):681-689.
7. McLaughlin MB, Jialal I. *Calcitonin*. StatPearls Treasure Island, Florida: StatPearls Publishing, 2020.
8. Drucker DJ. Advances in oral peptide therapeutics. *Nat Rev Drug Discov*. 2020; 19(4):277-289.
9. Yu M, Xie J, Fernandez LL, Kabul S, Swindle RW. Liraglutide Versus Exenatide Once Weekly: Persistence, Adherence, and Early Discontinuation, *Clinical Therapeutics*. 2016; 38(1): 149-160.
10. Hamdy RC, Daley DN. Oral calcitonin. *Int J Womens Health*. 2012; 4:471-479.
11. Brayden DJ, Hill TA, Fairlie DP, Maher S, Mrsny RJ. Systemic delivery of peptides by the oral route: Formulation and medicinal chemistry approaches. *Advanced Drug Delivery Reviews*. 2020.
12. Enteris Biopharma Peptelligence®. (Accessed October 29, 2020, at site <<https://enterisbiopharma.com/peptelligence/>>).
13. Binkley N, Bone H, Gilligan JP, Krause DS. Efficacy and safety of oral recombinant calcitonin tablets in postmenopausal women with low bone mass and increased fracture risk: a randomized, placebo-controlled trial. *Osteoporos Int*. 2014; 25(11):2649-2656.
14. Maher S, Mrsny RJ, Brayden DJ. Intestinal permeation enhancers for oral peptide delivery. *Adv. Drug Deliv. Rev*. 2016; 106(part B): 277-319.
15. Henriksen K, Byrjalsen I, Andersen JR, Bihlet AR, Russo LA, Alexandersen P, Valter I, Qvist P, Lau E, Riis BJ, Christiansen C, Karsdal MA. SMC021 investigators. A randomized, double-blind, multicenter, placebo-controlled study to evaluate the efficacy and safety of oral salmon calcitonin in the treatment of osteoporosis in postmenopausal women taking calcium and vitamin D. *Bone*. 2016; 91:122-129.
16. Karsdal MA, Byrjalsen I, Alexandersen P, Bihlet A, Andersen JR, Riis BJ, Bay-Jensen AC, Christiansen C. CSMC021C2301/2 investigators. Treatment of symptomatic knee osteoarthritis with oral salmon calcitonin: results from two phase 3 trials. *Osteoarthritis Cartilage*. 2015; 23(4):532-543.
17. Liu Y, Yu P, Peng X, Huang Q, Ding M, Chen Y, Jin R, Xie J, Zhao C, Li J. Hexapeptide-conjugated calcitonin for targeted therapy of osteoporosis. *J Control Release*. 2019; 304:39-50.
18. Aguirre TAS, Rosa M, Coulter I, Brayden, DJ. *In vitro* and *in vivo* preclinical evaluation of a minisphere emulsion-based formulation (SmPill®) of salmon calcitonin. *Eur J Pharm Sci*. 2015; 15(79):102-111.
19. Lipp L, Sharma D, Banerjee A, Singh J. Controlled Delivery of Salmon Calcitonin Using Thermosensitive Triblock Copolymer Depot for Treatment of Osteoporosis. *ACS Omega*. 2019; 4(1):1157-1166.
20. Cheang JY, Moyle PM. Glucagon-Like Peptide-1 (GLP-1)-Based Therapeutics: Current Status and Future Opportunities beyond Type 2 Diabetes. *Chem Med Chem*. 2018; 13(7):662-671.
21. Smith NK, Hackett TA, Galli A, Flynn CR. GLP-1: Molecular mechanisms and outcomes of a complex signaling system. *Neurochem Int*. 2019; 128:94-105.
22. Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Holst JJ. Both subcutaneously and intravenously administered glucagon-like peptide I are rapidly degraded from the NH2-terminus in type II diabetic patients and in healthy subjects. *Diabetes* 1995; 44(9):1126-1131.
23. Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, Kofoed J, Madsen K, Knudsen LB, McGuire J, Steensgaard DB, Strauss HM, Gram DX, Knudsen SM, Nielsen FS, Thygesen P, Reedtz-Runge S, Kruse T. Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide. *J Med Chem*. 2015; 58(18):7370-80.
24. Knudsen LB, Lau J. The Discovery and development of liraglutide and semaglutide. *Front Endocrinol (Lausanne)*. 2019; 12:1055.
25. Kapitza C, Nosek L, Jensen L, Hartvig H, Jensen CB, Flint A. Semaglutide, a once-weekly human GLP-1 analog, does not reduce the bioavailability of the combined oral contraceptive, ethinylestradiol/levonorgestrel. *J Clin Pharmacol*. 2015; 55(5):497-504.
26. Aroda VR, Ahmann A, Cariou B, Chow F, Davies MJ, Jódar E, Mehta R, Woo V, Lingvay I. Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: Insights from the SUSTAIN 1-7 trials. *Diabetes Metab*. 2019; 45(5):409-418.
27. Zhang X, Belousoff MJ, Zhao P, Kooistra AJ, Truong TT, Ang SY, Underwood CR, Egebjerg T, Šenel P, Stewart GD, Liang YL, Glukhova A, Venugopal H, Christopoulos A, Furness SGB, Miller LJ, Reedtz-Runge S, Langmead CJ, Gloriam DE, Danev R, Sexton PM, Wootton D. Differential GLP-1R Binding and Activation by Peptide and Non-peptide Agonists. *Mol Cell*. 2020; 80(3):485-500. e7.
28. Peter R, Bain SC. Safety of injectable semaglutide for type 2 diabetes. *Expert Opin Drug Saf*. 2020; 19(7):785-798.
29. Teva catalog: semaglutide. (Accessed October 30, 2020, at site <<https://www.teva-api.com/products/semaglutide/>>).
30. Hughes S, Neumiller JJ. Oral Semaglutide. *Clin Diabetes* 2020; 38(1):109-111.
31. U.S. Food and Drug Administration approves first oral GLP-1 treatment for type 2 diabetes (Accessed October 30, 2020, at site <<https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-glp-1-treatment-type-2-diabetes>>).
32. European Medicines Agency, First oral GLP-1 treatment for type 2 diabetes (Accessed October 30, 2020, at site <<https://www.ema.europa.eu/en/news/first-oral-glp-1-treatment-type-2-diabetes>>).
33. Buckley ST, Bækdal TA, Vegge A, Maarbjerg SJ, Pyke C, Ahnfelt-Rønne J, Madsen KG, Schéele SG, Alamentalo T, Kirk RK, Pedersen BL, Skygebjerg RB, Benic AJ, Strauss HM, Wahlund PO, Bjerregaard S, Farkas E, Fekete C, Søndergaard FL, Borregaard J, Hartoft-Nielsen ML, Knudsen LB. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. *Sci Transl Med*. 2018; 10(467):eaar7047.
34. Twarog C, Fattah S, Heade J, Maher S, Fattal E, Brayden DJ. Intestinal Permeation Enhancers for Oral Delivery of Macromolecules: A Comparison between Salscaprozate Sodium (SNAC) and Sodium Caprate (C10). *Pharmaceutics*. 2019; 11(2):78.
35. Nuho S, Gupta J, Hansen BB, Fletcher-Louis M, Dang-Tan T, Paine A. Orally Administered Semaglutide Versus GLP-1 RAs in Patients with Type 2 Diabetes Previously Receiving 1-2 Oral Antidiabetics: Systematic Review and Network Meta-Analysis. *Diabetes Ther*. 2019; 10(6):2183-2199.
37. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, Jeppesen OK, Lingvay I, Mosenzon O, Pedersen SD, Tack CJ, Thomsen M, Vilsbøll T, Warren ML, Bain SC, PIONEER 6 Investigators. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2019; 381(9):841-851.
37. Alfayez OM, Almohammed OA, Alkhezi OS, Almutairi AR, Al Yami MS. Indirect comparison of glucagon like peptide-1 receptor agonists regarding cardiovascular safety and mortality in patients with type 2 diabetes mellitus: network meta-analysis. *Cardiovasc Diabetol*. 2020; 19(1):96.