SUNTEXT REVIEWS

SunText Review of Endocrine Care

ISSN: 2771-5469

Open Access
Commentary Article
Volume 2:1

Clinical Trials of Novel Perspectives on Semaglutide with Injectable and Oral Formulations

Bando H[1,2,*]

[1]*Medical research / Tokushima University, Tokushima, Japan*
[2]*Japan Low Carbohydrate Diet Promotion Association (JLCDPA), Kyoto, Japan*

[*]**Corresponding author:** Bando H, Tokushima University /Medical Research, Nakashowa 1-61, Tokushima 770-0943, Japan; E-mail: pianomed@bronze.ocn.ne.jp

Received date: 25 January 2022; **Accepted date:** 28 January 2022; **Published date:** 31 January 2022

Citation: Bando H (2022). Clinical Trials of Novel Perspectives on Semaglutide with Injectable and Oral Formulations. SunText Rev Endocrine Care 2(1): 107.

DOI: https://doi.org/10.51737/2771-5469.2022.007

Copyright: © 2022 Bando H. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Glucagon-Like Peptide 1 receptor agonists (GLP-1Ras) has been evaluated for its several positive effects in the treatment of type 2 diabetes mellitus (T2DM). Semaglutide has both of injectable and oral formulations, which is beneficial. Three clinical trials were conducted, which are Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN), Peptide Innovation for Early diabetes treatment (PIONEER) and Semaglutide Treatment Effect in People with Obesity (STEP). Among them, satisfactory clinical effects of reducing HbA1c and body weight have been observed. Oral semaglutide, Rybelsus has been effective oral hypoglycemic agent (OHA) and seems to be more prescribed widely.

Keywords: Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN); Peptide Innovation for Early Diabetes Treatment (PIONEER); Semaglutide Treatment Effect in People with Obesity (STEP); Sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC); Rybelsus

Commentary Article

Diabetes has been treated and managed for long worldwide by various association, such as International Diabetes Federation (IDF) and American Diabetes Association (ADA). ADA presented Standards of Medical Care in Diabetes-2022 as latest guideline in January, 2022 [1]. Among them, development for antidiabetic agents include Glucagon-Like Peptide 1 receptor agonists (GLP-1Ras) [2]. Several benefits of GLP-1Ras have been gradually clarified [3]. Authors et al. have continued clinical practice and research for diabetes, obesity, oral hypoglycemic agents (OHAs), and others [4]. In this article, recent topics of semaglutide (Rybelsus) will be described, as well as three clinical trials of SUSTAIN, PIONEER and STEP in this order.

The first is Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) studies [5]. Through 10 studies of SUSTAIN, semaglutide was found to be superior at reducing HbA1c and body weight compared with placebo and other antidiabetic agents [6,7], including insulin glargine, sitagliptin, exenatide extended release (ER), dulaglutide, canagliflozin, and liraglutide [8-10]. Further, the superiority of GLP-1 RAs was found for improving glycemic control and weight in some previous clinical trials [11]. Compared with other GLP-1 RAs, semaglutide was superior at promoting bodyweight reduction in the SUSTAIN clinical trials. Comparing other long-acting GLP-1 RAs of exenatide ER and dulaglutide [8], semaglutide showed superiority in overall weight loss and ratio of achieving more than 5% [11]. The important perspective would be semaglutide's place as weight reduction medication. In SUSTAIN 10 trials, semaglutide also showed the superiority over lilraglutide, which has been already currently marketed for weight reduction as Saxenda.

The second is Peptide InnOvatioN for Early diabEtes tReatment (PIONEER). PIONEER are a series of clinical trials, which were focused on weight loss and glucose variability in T2DM patients. The antidiabetic medical agent was oral semaglutide, which has been already introduced to actually clinical practice as Rybelsus. It has three kinds of tablets of 3mg, 7mg and 14mg. Comparison was conducted between semaglutide group and other comparators. Currently, semaglutide can have only oral agents,

while other GLP-Ras are all necessary for subcutaneous injection [12]. Oral semaglutide has been made as a co-formulation of semaglutide with an absorption enhancer, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) [13]. It requires larger amounts per tablet, because oral formation shows lower bioavailability.

According to the results of PIONEER trials, oral semaglutide 7-14mg/day revealed larger HbA1c decrease in comparison with that of sitagliptin. However, 3mg of semaglutide did not show clinically significant improvement [14]. These results were observed in other PIONEER clinical trials, and changes in HbA1c and weight were significantly greater than placebo group [15,16]. Oral semaglutide showed clinical superiority compared with other OHAs, including empagliflozin [17] and sitaglipitin [14]. The similar superiority was also observed in the compared studies of liraglutide [15,16] and dulaglutide [18]. After a series of SUSTAIN trials, PIONEER clinical trials showed the results of decreased body weight and glucose variability associated with add-on therapy to metformin mono-therapy [12,14,15].

From the comparative general results of semaglutide, dulaglutide and liraglutide, semaglutide showed the superior effects of weight reduction and glucose control [15,16]. In addition, other parameters of BMI and waist circumference were also improved. Cases provided semaglutide showed more effects of at least 5% weight reduction compared with other groups [15]. Semaglutide revealed weight reduction that was dose-dependent manner with maximum efficacy at 14mg [16]. Obesity cases given oral semaglutide tended to have remarkable weight reduction compared with that of liraglutide [15]. Most significant weight reduction was found in 28, 36, 52 weeks, while early significant difference was observed at 26 weeks [14,15].

As regards to safety, oral semaglutide showed non-inferiority to placebo for lowering the ratio of major adverse cardiovascular events (MACEs) [12]. Thus, clinical benefit of GLP-1RA would be cardioprotective and renoprotective properties. This is why semaglutide has been highly evaluated in the clinical practice, which can be also provided per os. In the case of renal dysfunction with 30-59% of glomerular filtration rate (GFR), safety of semaglutide was established for PIONEER 5 [19], associated with stable and no significant changes of GFR during the trial. Similar to the results of SUSTAIN clinical trials, oral semaglutide revealed no elevated risk incidence of hypoglycemia [14]. Gastrointestinal adverse effects (GIAEs) have been commonly found such as mild to moderate nausea and vomiting [14-18]. Further, a significant elevation of serum lipase value was noted [20].

The third is Semaglutide Treatment Effect in People with Obesity (STEP) trials. Primary goal of STEP was to evaluate the effect of semaglutide as the agent for weight reduction medication. Subjects were selected, that were based on body mass index (BMI) and were did not suffer from T2DM. The conditions were common for the clinical studies of STEP 1,3,4,5. In contrast, STEP 2 did not exclude T2DM, and analyzed the data of cases with T2DM [21]. Administered dose was 2.4mg subcutaneously with once a week. Among STEP 1-4, semaglutide showed significant weight reduction than 1.0mg of semaglutide. As to STEP2, comparison was conducted between 2.4mg vs 1.0mg, in which the result was -9.7kg vs -2.5kg, respectively [21]. STEP 4 applied the protocol switching from semaglutide to placebo at 20 weeks, and then 6kg weight gain was found afterward [22]. Regarding its safety profile, mild to moderate gastrointestinal (GI) symptoms of 2.4mg were similar to those of 10mg of oral semaglutide. Hypoglycemic episodes were rarely reported in the protocol, which suggest encouraging results for providing semaglutide to T2DM.

When various data of STEP 1-4 were analyzed, body weight change from baseline was -15.3kg, -9.7kg, -16.8kg, -7.1kg, respectively [21-24]. As regards to STEP 5, the detail analysis has been pending for summarized review at present [25]. During clinical trials during STEP 1-5, there were no direct comparison investigation of semaglutide 2.4 mg and other FDA-approved agents for weight reduction. Consequently, current results seem to be fruitful achievements for effective research on pharmacotherapeutics.

In summary, semaglutide has novel perspectives with jnjectable and oral formulations. It has beneficial evidence from clinical trials. Further development of research and practice will be expected.

References

1. American Diabetes Association. Introduction: Standards of Medical Care in Diabetes – 2022. Diabetes Care. 2022; 45: S1-S2.
2. Zhong P, Zeng H, Huang M, Fu W, Chen Z. Efficacy and safety of once-weekly semaglutide in adults with overweight or obesity: a meta-analysis. Endocrine. 2022.
3. ADA Professional Practice Committee; 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes. 2022. Diabetes Care. 2022; 45: S125-S143.
4. Iwatsuki N, Bando H, Okada M. Pharmacological Characteristic of Imeglimin (Twymeeg) For Dual Mechanism to Insulin Secretion and Resistance. SunText Rev Pharm Sci. 2022; 3: 113.
5. DeVries JH, Desouza C, Bellary S. Achieving glycaemic control without weight gain, hypoglycaemia, or gastrointestinal adverse events in type 2 diabetes in the SUSTAIN clinical trial programme. Diabetes Obes Metab. 2018; 20: 2426-2434.
6. Rodbard HW, Lingvay I, Reed J. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. J Clin Endocrinol Metab. 2018; 103: 2291-2301.
7. Zinman B, Bhosekar V, Busch R. Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. The Lancet Diabetes Endocrinol. 2019; 7: 356-367.

8. Pratley RE, Aroda VR, Lingvay I. Semaglutide versus dulaglutide onceweekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol. 2018; 6: 275-286.
9. Lingvay I, Catarig A-M, Frias JP. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. Lancet Diabetes Endocrinol. 2019; 7: 834-844.
10. Capehorn MS, Catarig A-M, Furberg JK. Efficacy and safety of onceweekly semaglutide 1.0 mg vs once-daily liraglutide 1.2 mg as add-on to 1–3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). Diabetes Metab. 2020; 46: 100-109.
11. Ahrén B, Atkin SL, Charpentier G. Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials. Diabetes Obes Metab. 2018; 20: 2210-2219.
12. Rodbard HW, Rosenstock J, Canani LH. Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial. Diabetes Care. 2019; 42: 2272-2281.
13. Thethi TK, Pratley R, Efficacy MJJ. Safety and cardiovascular outcomes of once-daily oral semaglutide in patients with type 2 diabetes: the PIONEER programme. Diabetes Obes Metab. 2020; 2020: 1-15.
14. Rosenstock J, Allison D, Birkenfeld AL. Effect of additional oral semaglutide vs sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea. JAMA. 2019; 321: 1466-1480.
15. Pratley R, Amod A, Hoff ST. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, doubleblind, phase 3A trial. Lancet. 2019; 394: 39-50.
16. Yamada Y, Katagiri H, Hamamoto Y. Dose-response, efficacy, and safety of oral semaglutide monotherapy in Japanese patients with type 2 diabetes (PIONEER 9): a 52-week, phase 2/3a, randomised, controlled trial. Lancet Diabetes Endocrinol. 2020; 8: 377-391.
17. Capehorn MS, Catarig A-M, Furberg JK. Efficacy and safety of once-weekly semaglutide 1.0 mg vs once-daily liraglutide 1.2 mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). Diabetes Metab. 2020; 46: 100-109.
18. Yabe D, Nakamura J, Kaneto H. Safety and efficacy of oral semaglutide versus dulaglutide in Japanese patients with type 2 diabetes (PIONEER 10): an open-label, randomised, active-controlled, phase 3A trial. Lancet Diabetes Endocrinol. 2020; 8: 392-406.
19. Mosenzon O, Blicher TM, Rosenlund S. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3A trial. Lancet Diabetes Endocrinol. 2019; 7: 515-527.
20. Aroda VR, Rosenstock J, Terauchi Y. 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: 1724-1732.
21. Davies M, Færch L, Jeppesen OK. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2021; 397: 971-984.
22. Rubino D, Abrahamsson N, Davies M. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: The STEP 4 randomized clinical trial. JAMA. 2021; 325: 1414-1425.
23. Wilding JPH, Batterham RL, Calanna S. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021; 384: 989-1002.
24. Wadden TA, Bailey TS, Billings LK. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: The STEP 3 randomized clinical trial. JAMA. 2021; 325: 1403-1413.
25. Kushner RF, Calanna S, Davies M. Semaglutide 2.4 mg for the treatment of obesity: key elements of the STEP trials 1 to 5. Obesity. 2020; 28: 1050-1061.