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Awadhesh Kumar Singh[1–4], Akriti Singh[5], Ritu Singh[3], Jayshree Swain[4]
[1]G. D Hospital & Diabetes Institute, Kolkata, West Bengal, India
[2]Sun Valley Hospital & Diabetes Research Center, Guwahati, Assam, India
[3]Horizon Life Line Multispecialty Hospital, Kolkata, West Bengal, India
[4]Institute of Medical Science & SUM Hospital, Bhubaneswar, Odisha, India
[5]KPC Medical College & Hospital, Jadavpur, West Bengal, India

# Reality of Real-World Experience with Oral Semaglutide in Type 2 Diabetes

Oral semaglutide is the first oral glucagon-like-peptide-1 receptor agonist (GLP-1RA) approved for the treatment of type 2 diabetes (T2D) since the United States Food Drug Administration (US-FDA) approval in 2019, based on extensive phase 3 randomized Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) clinical developmental program. Indeed, in people with T2D, oral semaglutide 14 mg has not shown only superior efficacy (HbA1c and weight reduction) against placebo but also demonstrated a significant superiority against other active comparators, including sitagliptin 100 mg (PIONEER-3, PIONEER-7), empagliflozin 25 mg (PIONEER-2), injectable liraglutide 1.8 mg once daily (PIONEER-4), and injectable dulaglutide 0.75 mg once weekly (PIONEER-10) [1]. Following the approval of oral semaglutide worldwide, including in India in 2022, many real-world studies have been conducted and published to date.

In this issue of "Clinical Diabetology", Ray and Colleagues [2] present an 18-month follow-up of a real-world retrospective survey conducted with oral semaglutide as adjunctive therapy in T2D from three centers in India based on electronic health/medical records (EHR/EMR). This study of 60 Indian patients of T2D (mean 5.8-year duration) with a mean baseline HbA1c of 8.7% and body weight of 82.3 kg showed a significant reduction in HbA1c (Δ –1.9 to –1.6% at 6 and 18 months, respectively) and body weight (Δ –6.0 to –4.7 kg at 6 and 18 months, respectively) with oral semaglutide 3–14 mg once daily over 6 to 18 months duration, while some plateau effect observed between 12 and 18 months. This reduction in HbA1c appears to be more prominent even though more than 50% were on a submaximal dose of 7 mg oral semaglutide, likely due to tolerance issues. However, two other recent retrospective studies [3, 4] done with oral semaglutide on Indian patients with T2D had both convergent and divergent results compared with this study. For example, a retrospective EHR-based Semaglutide OraL In Indian T2D (SOLID) patients study [3] conducted with oral semaglutide in 209 patients from eight centers in India showed a significant reduction in HbA1c (Δ –2.0%) and body weight (Δ –5.3 kg) at 3 months, with a mean baseline HbA1c of 9.2% and body weight of 92 kg. Even in the SOLID study, HbA1c reduction appears very prominent despite less than 45% of patients being on the maximal approved dose of 14 mg oral semaglutide primarily due to tolerability issues. However, the duration of T2D was unknown in the SOLID study. Other single-center retrospective EMR survey of 6 months consisting of 46 Indian patients with T2D (median base-

Address for correspondence:
Awadhesh Kumar Singh,
Department of Diabetes & Endocrinology, G.D Hospital & Diabetes Institute, 139A, Lenin Sarani, Kolkata – 700013, India
E-mail: drawadheshkumarsingh@gmail.com
Phone: 919831020428
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**Table 1. Baseline Characteristics and Key Results from Six PIONEER REAL Studies of Mean/Median 38 Weeks Duration**

| Trial Eponyms | N (FAS) | Duration of T2D, Yrs (mean) | Male (%) | Age, Yrs (mean) | Weight, kg (mean) | BMI, kg/m$^2$ (mean) | HbA1c, % (mean) | HbA1c change at EOS, % | Weight change at EOS, kg | HbA1c < 7% at EOS, % | Composite of ≥ 1% HbA1c reduction and ≥ 5% weight loss, % | Dose of oral SEMA at EOS, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PIONEER REAL, Canada [6] | 182 | 8.1 | 64.3 | 58.6 | 93.7 | 32.5 | 8 | –1.1 | –7.2 | 53.7 | 31.6 | 3 mg: 11.7<br>7 mg: 32.8<br>14 mg: 55.5 |
| PIONEER REAL, Switzerland [7] | 185 | 6.4 | 63.7 | 62 | 95.6 | 33.2 | 7.7 | –0.9 | –4.7 | 64.2 | 28.3 | 3 mg: 7.0<br>7 mg: 26.8<br>14 mg: 66.2 |
| PIONEER REAL, UK [8] | 333 | 7.4 | 61.3 | 58.5 | 102.8 | 35.5 | 8.6 | –1.1 | –4.8 | 46.3 | 27.1 | 3 mg: 5.3<br>7 mg: 21.6<br>14 mg: 73.1 |
| PIONEER REAL, Netherlands [9] | 187 | 8.7 | 54 | 58.8 | 103.1 | 35.1 | 8.6 | –1.2 | –5.8 | 47.5 | 35.5 | 3 mg: 4.1<br>7 mg: 42.2<br>14 mg: 53.7 |
| PIONEER REAL, Sweden [10] | 187 | 6.8 | 64.7 | 62.5 | 96.9 | 32.4 | 7.7 | –0.9 | –4.6 | 64.6 | 22.9 | 3 mg: 6.4<br>7 mg: 39.7<br>14 mg: 53.2 |
| PIONEER REAL, Japan [11] | 624 | 10.7 | 56.9 | 64.1 | 72.4 | 27.5 | 7.7 | –0.7 | –2.8 | 55.3 | 16.5 | 3 mg: 26.6<br>7 mg: 61.8<br>14 mg: 11.2 |

BMI — body mass index; EOS — end of study; FAS — full analysis set; HbA1c — glycated hemoglobin; SEMA — semaglutide; T2D — type 2 diabetes; Yrs — years

line HbA1c of 8% and mean body weight of 81.8 kg) receiving oral semaglutide showed a significant HbA1c (Δ –0.7%) and body weight (Δ –2.7 kg) reduction, even though 43% were receiving 14 mg of oral semaglutide [4]. However, the duration of T2D is also unknown in this study. Interestingly, most of the other retrospective EHR/EMR surveys from the USA, Spain, Japan, Italy, and Croatia showed an HbA1c reduction from –0.3 to –1.4%, while body weight reduction varied from –1.4 to –5.9 kg [5]. Only the United Kingdom (UK) retrospective study showed an HbA1c and body weight reduction of –1.8% and -9.0 kg with a mean baseline HbA1c and body weight of 9.3% and 110 kg, respectively [5]. Notwithstanding, these varying degrees of HbA1c and body weight reduction are partly related to differences in baseline characteristics and partly to the associated bias inherent with retrospective studies. This requires a high-quality, well-planned, prospective, control-armed, real-world study.

To this end, thirteen Phase 4 prospective real-world studies, PIONEER REAL, were initiated and completed [5]. However, full data from only six PIONEER REAL studies are currently available [6–11]. The baseline characteristics and key findings from these six PIONEER REAL studies are summarized in Table 1. The PIONEER REAL INDIA is the fourteenth prospective study initiated in 2022 and is currently underway [5]. Overall, there was an average –1.0% reduction in HbA1c and –5 kg weight loss across five PIONEER REAL, where the majority (> 50%) tolerated the 14 mg dose of oral semaglutide [6–10]. In PIONEER REAL Japan, there was –0.7% HbA1c and –3 kg weight reduction, with the majority on a 7 mg dose of oral semaglutide [11]. Notably, adding oral semaglutide to pre-existing pharmacotherapy allowed nearly 55% of patients with T2D to achieve the target HbA1c of < 7%, while more than one-fourth of the proportion had a composite reduction of HbA1c of ≥ 1% and weight loss of ≥ 5%. Figure 1 captures the impact of oral semaglutide on HbA1c and body weight, while Figure 2 summarizes its effect on the composite of both HbA1c and body weight lowering and the proportion of patients achieving the target of HbA1c of < 7% across six PIONEER REAL studies [6–11]. Indeed, a pooled analysis of seven PIONEER REAL studies (including those of unpublished results from PIONEER REAL Italy and Denmark but excluding PIONNER Japan) showed a mean HbA1c reduction of –1% and –5 kg weight loss with oral semaglutide in T2D in addition with other pharmacotherapies [12]. Nevertheless, the absence of a control arm remains

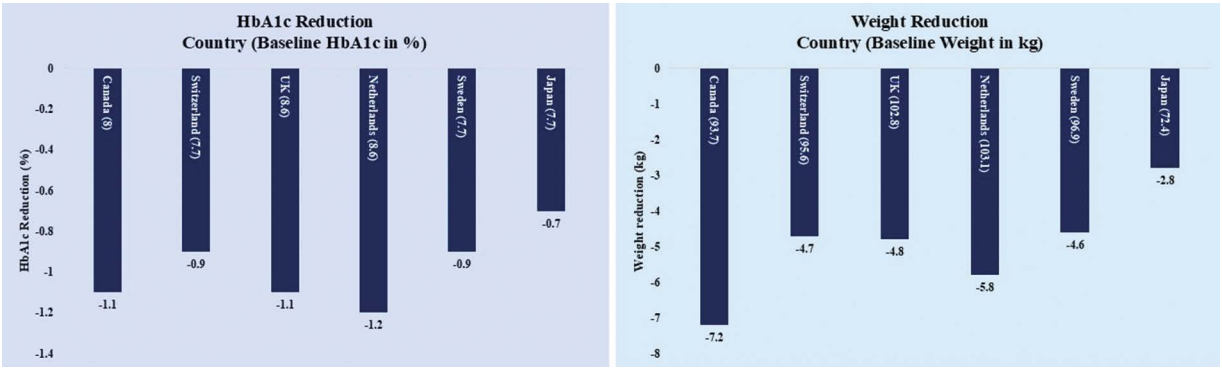


**Figure 1.** PIONEER REAL: Real-World-Evidence with Oral Semaglutide on HbA1c and Weight
HbA1c — glycated hemoglobin

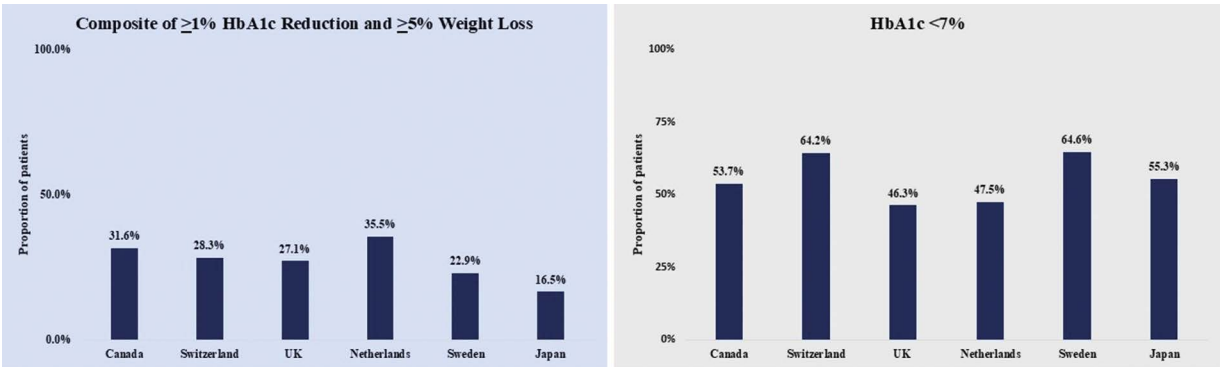


**Figure 2.** PIONEER REAL: Real-World-Evidence with Oral Semaglutide on Composite of HbA1c plus Weight and HbA1c Target < 7%
HbA1c — glycated hemoglobin

the main limitation of all PIONEER REAL studies. Additionally, most retrospective studies have limited data on safety issues.

Summarily, the HbA1c and body weight-lowering ability of oral semaglutide, as demonstrated in Phase 4 real-world studies, complement the findings from eight global and 2 Japanese PIONEER programs. The 14% relative risk reduction in the composite of major adverse cardiovascular outcome data as reported in top-line results [13] of SOUL (Semaglutide cardiOvascular oUtcomes trial) will be an additional milestone for oral semaglutide, even though the non-inferiority PIONEER 6 trial did show a non-significant positive trend on cardiovascular endpoints including mortality outcomes. Full results of SOUL and a deep dive into cardiovascular (primary) and renal outcomes (secondary) are eagerly awaited in the first quarter of 2025.

## Article information

### Author's contribution

AKS conceptualized and searched the literature; AKS and RS did the statistical interpretation; AS wrote the first draft; AKS, AS, RS, and JS edited the final draft. All authors agreed mutually to submit for publication.

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### Conflict of interest

The authors declare no conflict of interest.

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