A bioequivalence study of two formulations of oral semaglutide in healthy participants

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Independent Ethics Committee Institutional Review Boards

- ADVARRA, 372 Hollandview Trail, Suite 300, Aurora, Ontario L4G 0A5, Canada
- WCG IRB, 1019 39th Avenue SE, Suite 120, Puyallup, Washington 98734-2115, USA

Table S1 Inclusion and exclusion criteria

Inclusion criteria

Participants were eligible to be included in the study only if all of the following criteria applied:

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Male or female, aged 18–64 years (both inclusive) at the time of signing informed consent.
3. Body mass index between 21.0 and 32.0 kg/m^2 (both inclusive).
4. Considered to be generally healthy based on the medical history, physical examination, and the results of vital signs, electrocardiogram and clinical laboratory tests performed during the screening visit, as judged by the investigator.

Exclusion criteria

Participants were excluded from the study if any of the following criteria applied:

1. Known or suspected hypersensitivity to study intervention(s) or related products.
2. Previous randomisation in this study or more than one re-screening for the study.
3. Females who were pregnant, breast-feeding or intended to become pregnant or were of childbearing potential and not using adequate contraceptive methods.
4. Participation (i.e., signed informed consent) in any interventional, clinical study with the last study intervention being within 30 days (or five half-lives of the investigational medicinal product, whichever is greater) before randomisation.
5. Any laboratory safety parameter at screening outside the below extended laboratory ranges:
   - Alanine transaminase above upper limit normal (ULN) +10%
   - Aspartate transaminase above ULN +20%
   - Bilirubin outside lower limit normal and ULN +20%
   - Creatinine above ULN +10%.
6. HbA_{1c} ≥6.5% (48 mmol/mol) at screening.
7. Supine blood pressure at screening outside the range of 90−139 mmHg for systolic or 50−89 mmHg for diastolic.
8. Pulse outside the range of 50–89 beats/minute at screening.

9. Use of prescription medicinal products or non-prescription drugs or herbal products (including St John's wort), except for highly effective contraceptive methods, routine vitamins, topical medication not reaching the systemic circulation and occasional use of paracetamol (acetaminophen) within 14 days prior to the day of screening.

10. Use of any medication with unknown or unspecified content within 90 days before screening.

11. Diagnostic test results positive for human immunodeficiency virus 1 (HIV-1) or HIV-2 infection.

12. Diagnostic test results positive for hepatitis B or hepatitis C infection.

13. Mental incapacity, language barriers or unwillingness to comply with the requirements of the protocol, which may have precluded adequate understanding or cooperation during the study as judged by the investigator.

14. Use of tobacco and nicotine products, defined as any of the below:

    - Smoking more than five cigarettes or the equivalent per day

    - Not willing to refrain from smoking and use of nicotine substitute products within 48 hours prior to and during the inpatient periods.

15. Abuse or intake of alcohol, defined as any of the below:

    - Known or suspected alcohol abuse within 1 year prior to the day of screening (defined as regular intake of more than an average intake of 24 g of alcohol daily for men or 12 g of alcohol daily for women).

    - Positive alcohol test at screening.

16. Abuse or intake of drugs defined as any of the below:

    - Known or suspected drug/chemical substance abuse within 1 year prior to the day of screening.

    - Positive drug of abuse test at screening.

17. Blood donation, plasma donation or blood draw, of either of the below[a]:

    - In excess of 400 mL within the past 56 days prior to the day of screening.

    - In excess of 50 mL within the past 30 days prior to the day of screening.

18. Presence of clinically significant gastrointestinal disorders potentially affecting absorption of drugs and/or nutrients, as judged by the investigator.

19. Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma[a].

20. Presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, in-situ carcinomas of the cervix or in-situ prostate cancer) within 5 years before screening[a].

21. History of major surgical procedures involving the stomach potentially affecting absorption of study products (e.g., subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery) or current presence of gastrointestinal implant[a].

22. Participant was the investigator or other staff or relative thereof directly involved in the conduct of the study.

23. Participant had clinical signs and symptoms consistent with COVID-19, e.g., fever, dry cough, dyspnoea, sore throat, fatigue or confirmed infection by an appropriate laboratory test within the last 4 weeks prior to screening[a].

24. Participant who had previously had a severe course of COVID-19 (hospitalised due to COVID-19)[a].

[a]As declared by the participant or reported in the medical records.

Table S2 Additional bioequivalence acceptance limits guidance per European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) guidelines

EMA

As the within-participant coefficient of variation (CV) of the reference (first generation oral semaglutide [1G]) was >30% for $C_{max,\ 0–24\ h,\ SS}$, the acceptance interval for C_{max} was extended. For this the limits were scaled by $[\mathrm{U}, \mathrm{L}] = \exp[\pm \mathrm{k} \cdot \mathrm{s}_{\mathrm{WR}}]$ where U and L denote the upper and lower limit, respectively, k is the regulatory constant set to 0.760 and s_{WR} is the within-participant standard deviation of the log-transformed values of C_{max}. Second generation (2G) oral semaglutide and 1G oral semaglutide were confirmed as bioequivalent if the 90% confidence (CI) of C_{max} was completely within $[\mathrm{U}, \mathrm{L}]$ as defined above, the point estimate of the ratio lay within 0.8000–1.2500 and the 90% CI of $AUC_{0–24\ h}$ was completely within the standard acceptance interval of 0.8000–1.2500. The range could not be extended beyond the range determined by a within-participant standard deviation corresponding to a within-participant CV of 50%.

FDA

As the observed within-participant variability of the reference (1G oral semaglutide), s_{WR}, was ≥0.294 for C_{max} and AUC, the reference scaled average bioequivalence (RSABE) were utilised for both endpoints. This approach evaluates the endpoint by $\frac{(\mu_{\mathrm{T}}-\mu_{\mathrm{R}})^2}{\sigma^2_{\mathrm{WR}}} \leq \theta_{\mathrm{S}}$ where $(\mu_{\mathrm{T}} - \mu_{\mathrm{R}})^2$ is the treatment difference, σ^2_{WR} is the within-participant variation and $\theta_{\mathrm{S}} = \frac{(\ln(1.25))^2}{\sigma^2_{\mathrm{W0}}}$ is the bioequivalence limit where σ^2_{W0} is a regulatory constant set to 0.25 by the FDA. This can be rewritten as $(\mu_{\mathrm{T}} - \mu_{\mathrm{R}})^2 - \theta_{\mathrm{S}}\sigma^2_{\mathrm{WR}} \leq 0$. The implied limits using Howe's approximation are $\pm\left[\ln(1.25)\frac{\sigma_{\mathrm{WR}}}{\sigma_{\mathrm{W0}}}\right]$, which constitutes the acceptance interval for bioequivalence.

Table S3 Summary of treatment-emergent adverse events

	1G oral semaglutide		2G oral semaglutide		Total	
	n (%)	E	*n* (%)	E	*n* (%)	E
Group 1						
Number of participants	213		210		222	
TEAEs related to study product						
Probable	111 (52.1)	282	101 (48.1)	239	163 (73.4)	521
Possible	75 (35.2)	142	72 (34.3)	115	118 (53.2)	257
Unlikely	39 (18.3)	59	46 (21.9)	67	72 (32.4)	126
Outcome						
Fatal	1 (0.5)	1	0	0	1 (0.5)	1
Not recovered	0	0	3 (1.4)	3	3 (1.4)	3
Recovered with sequelae	0	0	0	0	0	0
Recovering	0	0	3 (1.4)	3	3 (1.4)	3
Recovered	135 (63.4)	474	141 (67.1)	403	181 (81.5)	877
Unknown	5 (2.3)	8	5 (2.4)	12	9 (4.1)	20

Group 2						
Number of participants	193		195		199	
TEAEs related to study product						
Probable	78 (40.4)	292	68 (34.9)	288	114 (57.3)	580
Possible	69 (35.8)	174	55 (28.2)	120	92 (46.2)	294
Unlikely	50 (25.9)	93	58 (29.7)	120	81 (40.7)	213
Outcome						
Fatal	0	0	0	0	0	0
Not recovered	0	0	3 (1.5)	6	3 (1.5)	6
Recovered with sequelae	0	0	1 (0.5)	1	1 (0.5)	1
Recovering	4 (2.1)	4	3 (1.5)	3	7 (3.5)	7
Recovered	111 (57.5)	554	107 (54.9)	511	144 (72.4)	1065
Unknown	1 (0.5)	1	3 (1.5)	7	4 (2.0)	8
Group 3						
Number of participants	122		120		123	
TEAEs related to study product						
Probable	1 (0.8)	1	2 (1.7)	2	3 (2.4)	3

Possible	33 (27.0)	70	25 (20.8)	47	49 (39.8)	117
Unlikely	29 (23.8)	39	26 (21.7)	42	45 (36.6)	81
Outcome						
Fatal	0	0	0	0	0	0
Not recovered	0	0	0	0	0	0
Recovered with sequelae	0	0	0	0	0	0
Recovering	0	0	0	0	0	0
Recovered	47 (38.5)	110	38 (31.7)	89	63 (51.2)	199
Unknown	0	0	2 (1.7)	2	2 (1.6)	2

Safety analysis set: all randomised participants who were exposed to at least 1 dose of study product.

1G first generation, *2G* second generation, *E* number of events, *n* number of participants, *TEAE* treatment-emergent adverse event.