Natural history and real-world effectiveness of obesity management medications: REFLECT design/methods

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Objective

- To characterize multinational real-world cohorts aligned with KaiNETIC clinical trial populations, generating baseline and longitudinal real-world insights among individuals living with overweight or obesity and to provide context for populations enrolled in the KaiNETIC clinical trials.

Introduction

- Clinical obesity is a serious, complex, chronic, and relapsing disease with a prevalence that is projected to increase substantially over the next decade.[1-3]
- The progressive nature of overweight and obesity leads to an increased risk in development of metabolic and long-term complications, with higher body mass index (BMI) contributing to approximately 4 million global deaths annually.[1,4]
- Although current obesity management medications (OMMs) have undoubtedly advanced care, some people living with higher levels of obesity may require a greater magnitude of weight reduction to mitigate complication risks, while optimizing long-term health.[5-9]
- As next-generation OMMs become available, characterizing real-world populations living with higher levels of obesity will be critical for identifying individuals who are most likely to achieve optimal health benefits.
- Ribupatide* is an investigational once-weekly injectable glucagon-like peptide-1 (GLP-1)/glucose-dependent insulinotropic polypeptide (GIP) dual receptor agonist in development to treat people living with obesity or overweight in the KaiNETIC Phase 3 clinical trial program (NCT07284875, NCT07284901, and NCT07284979).[10-12]
- Establishing a real-world cohort aligned with KaiNETIC eligibility criteria may offer a framework to contextualize upcoming trial results.

Study design

- REFLECT (Real-World Evaluation of the Natural History and Long-Term Clinical Effects of GLP-1 and GLP-1/GIP Therapies in Adults Living with Obesity) is an ongoing, retrospective, and longitudinal observational cohort trial that utilizes three real-world data sources encompassing more than 200 million patients (**Figure 1**).
- The three cohorts comprising REFLECT will implement selected eligibility criteria used for the three KaiNETIC Phase 3 clinical trials of ribupatide (**Table 1**).†
- The time frame for participant inclusion in REFLECT is from January 1, 2018 to June 30, 2024,‡ with last observation follow-up on December 31, 2025.
- Patients ≥18 years of age during the time frame for participant inclusion‡ were selected on criteria of:† BMI ≥27 kg/m^2 on at least 2 visits, ≥12 months of data before the second qualifying BMI visit (index date§), and no instances of:
  - pregnancy during the 9 months before the index date
  - bariatric surgery during the 12 months before the index date
  - prescriptions for either semaglutide or tirzepatide within 3 months before the index date.
- Longitudinal observation is ongoing from March 2026 through 76 weeks, in parallel with enrollment for the KaiNETIC clinical program.

Figure 1. Data sources



CPRD
- ~55 million patients
- EHRs from >2400 GP practices
- Linked with datasets from hospitals and specialist centers

Truveta
- ~150 million patients
- 31 US healthcare systems
- >20,000 clinics and >900 hospitals
- Linked to Veritas (death data)

BIG-PAC®
- ~2.3 million patients
- 6 Spanish healthcare systems
- EHRs from primary care
- Linked with datasets from hospitals and specialist centers

CPRD=Clinical Practice Research Datalink; EHR=electronic health record; GP=general practitioner.

Table 1. Study cohorts

Cohort	BMI category	T2DM	Semaglutide or tirzepatide within 3 months of index	To mimic KaiNETIC clinical trial program
1	≥30 kg/m^2 or ≥27 to <30 kg/m^2 with ≥1 ORC present[a]	✗	✗	KaiNETIC-1 (NCT07284875)
2	≥27 kg/m^2	✓	✗	KaiNETIC-2 (NCT07284901)
3	≥35 kg/m^2	✗	✗[b]	KaiNETIC-3 (NCT07284979)

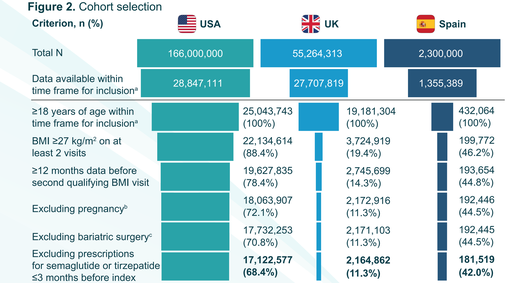
Only key eligibility criteria are shown; additional eligibility criteria apply.
The data in this presentation focus on the databases; data stratified by the KaiNETIC trial criteria will be presented elsewhere.

✓=criterion applies to the cohort; ✗=criterion does not apply to the cohort; BMI=body mass index; ORC=obesity-related complication; T2DM=type 2 diabetes mellitus. Patients may qualify for more than one cohort and will be included in any cohort for which they qualify. [a] ORCs include hypertension, dyslipidemia, obstructive sleep apnea, and cardiovascular disease. [b] A subset of the KaiNETIC-3 trial population will be treated with semaglutide; tirzepatide is not part of the KaiNETIC-3 clinical trial program.

Population overview

- Overall, 17,122,577 patients from USA, 2,164,862 patients from UK, and 181,519 patients from Spain were eligible for inclusion (**Figure 2**).
- Across all three countries, mean age ranged from 53.8 to 58.9 years, with more than half of patients being aged 55 years or older (**Table 2**).
- Among eligible patients in all three countries, more than half were women (**Table 2**).
- Mean BMI was 33.7, 32.8, and 32.2 kg/m^2 for USA, UK, and Spain, respectively. Note, there were more patients with BMI Class III in the US (14.2%) compared to the UK (9.7%) and Spain (6.6%) (**Table 3**).
- Cardiometabolic markers, obesity-related complications (ORCs), and medication use during the baseline period are described in **Table 3** and **Figure 3**

Figure 2. Cohort selection



BMI=body mass index.
[a] Time frames for participant inclusion were January 1, 2018 to June 30, 2024 for USA, January 2, 2019 to June 30, 2024 for UK, and June 1, 2019 to June 30, 2024 for Spain. [b] Patients without 9-month pre-index pregnancy codes. [c] Patients without 12-month pre-index surgical obesity treatment.

Table 2. Demographics

Variable	USA (N=17,122,577	UK (N=2,164,862)	Spain (N=181,519)
Age, years, mean (SD)	53.8 (17.5)	58.9 (14.5)	55.8 (17.9)
Age categories, years, %	18-34: 17.2; 35-44: 14.8; 45-54: 17.3; 55-64: 19.9; ≥65: 30.9	18-34: 7.4; 35-44: 8.9; 45-54: 17.8; 55-64: 24.8; ≥65: 41.0	18-34: 16.5; 35-44: 14.0; 45-54: 15.6; 55-64: 18.2; ≥65: 35.8
Sex, %	Male: 43.4; Female: 56.6; Other/undefined: 0.0	Male: 44.0; Female: 56.0; Other/undefined: 0.0	Male: 39.3; Female: 60.1; Other/undefined: 0.7
Race, %	Native American or Alaskan Native: 0.6; Asian: 0.4; Black: 4.9; White: 69.4; Native Hawaiian or Other Pacific Islander: 2.4; Other: 5.0; Mixed: 17.2; Unknown: 0.0	Native American or Alaskan Native: 3.8; Asian: 0.8; Black: 7.1; White: 81.2; Native Hawaiian or Other Pacific Islander: 0.5; Other: 6.6; Mixed: 0.0; Unknown: 0.0	*No information available*
Geographic region, %	Northeast – 11.3; Midwest – 22.2; West North Central –1. 4; South – 41.2; West – 16.8; Other or unknown - 7.1	North East – 4.3; North West – 23.4; Yorkshire and The Humber – 1.8; East Midlands – 1.5; West Midlands – 19.8; East of England – 3.4; London – 17.1; South East – 19.9; South West – 8.8	NA

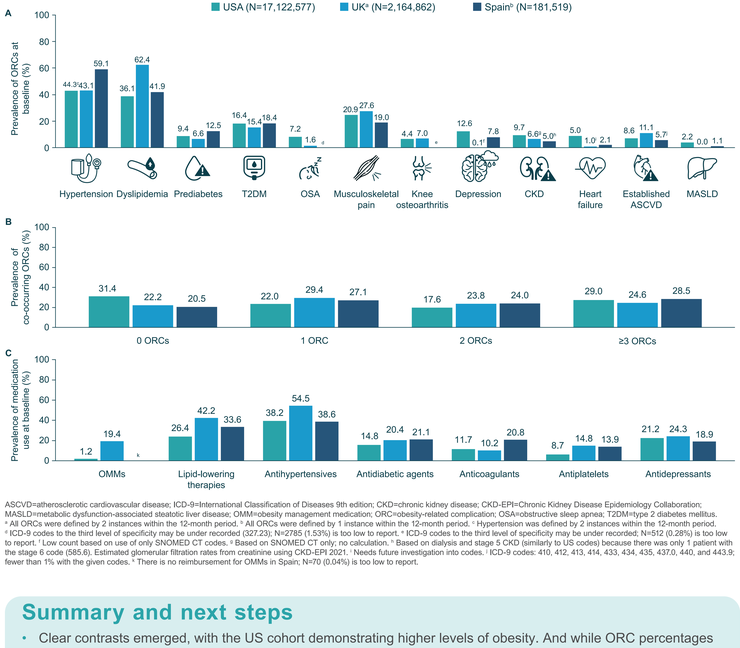
NA=not available; SD=standard deviation.

Table 3. Cardiometabolic markers

Variable, mean (SD)[a]	USA (N=17,122,577)	UK (N=2,164,862)	Spain (N=181,519)
Body weight, kg	92.6 (21.8)	90.5 (14.8)	85.9 (16.0)
BMI, kg/m^2	33.7 (6.4)	32.8 (5.5)	32.2 (4.7)
BMI category, %	Overweight: 34.2; Class I obesity: 34.5; Class II obesity: 17.0; Class III obesity: 14.2	Overweight: 36.7; Class I obesity: 37.8; Class II obesity: 15.7; Class III obesity: 9.7	Overweight: 40.4; Class I obesity: 38.5; Class II obesity: 14.5; Class III obesity: 6.6
Blood pressure, mmHg	SBP: 130.9 (18.0); DBP: 76.6 (12.7)	SBP: 131.5 (13.6); DBP: 78.7 (9.2)	SBP: 133.6 (19.6); DBP: 78.2 (11.5)
Lipids, mg/dL	Total cholesterol: 176.5 (40.2); LDL-C: 100.2 (34.2); HDL-C: 49.6 (13.2); Triglycerides: 134.3 (66.3)	Total cholesterol: 187.5 (39.8); LDL-C: 107.9 (34.8); HDL-C: 49.1 (11.6); Triglycerides: 145.3 (65.5)	Total cholesterol: 191.9 (42.2); LDL-C: 115.2 (36.4); HDL-C: 49.3 (12.7); Triglycerides: 136.0 (104.3)
Fasting glucose, mg/dL	114.9 (35.9)	98.2 (18.0)	94.3 (24.5)
HbA$_{1c}$, %	6.3 (1.3)	7.9 (2.3)	6.1 (1.5)

BMI=body mass index; DBP=diastolic blood pressure; HbA$_{1c}$=glycated hemoglobin; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; SD=standard deviation; SBP=systolic blood pressure.
Overweight was defined as BMI 27.0-29.9 kg/m^2; class I obesity was defined as BMI 30.0-34.9 kg/m^2; class II obesity was defined as BMI 35.0-39.9 kg/m^2; class III obesity was defined as BMI ≥40 kg/m^2.
[a] Unless stated otherwise.

Figure 3. ORCs and medication use



ASCVD=atherosclerotic cardiovascular disease; ICD-9=International Classification of Diseases 9th edition; CKD=chronic kidney disease; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; MASLD=metabolic dysfunction-associated steatotic liver disease; OMM=obesity management medication; ORC=obesity-related complication; OSA=obstructive sleep apnea; T2DM=type 2 diabetes mellitus.
[a] All ORCs were defined by 2 instances within the 12-month period. [b] All ORCs were defined by 1 instance within the 12-month period. [c] Hypertension was defined by 2 instances within the 12-month period. [d] ICD-9 codes to the third level of specificity may be under recorded (327.23); N=2785 (1.53%) is too low to report. [e] ICD-9 codes to the third level of specificity may be under recorded; N=512 (0.28%) is too low to report. [f] Low count based on use of only SNOMED CT codes. [g] Based on SNOMED CT only; no calculation. [h] Based on dialysis and stage 5 CKD (similarly to US codes) because there was only 1 patient with the stage 6 code (585.6). Estimated glomerular filtration rates from creatinine using CKD-EPI 2021. [i] Needs future investigation into codes. [j] ICD-9 codes: 410, 412, 413, 414, 433, 434, 435, 437.0, 440, and 443.9; fewer than 1% with the given codes. [k] There is no reimbursement for OMMs in Spain; N=70 (0.04%) is too low to report.

Summary and next steps

- Clear contrasts emerged, with the US cohort demonstrating higher levels of obesity. And while ORC percentages were similar between countries, patients with ≥3 ORCs represent ~5M patients in the US, ~500k patients in the UK, and ~50k patients in Spain, exponential differences in absolute magnitude.
- Although the present analysis encountered variation in capturing patient data from databases in USA, UK, and Spain, these differences may reflect both regional variation in populations and healthcare delivery, as well as differences in coding practices and data capture across databases.
- To contextualize the high clinical and economic burden attributable to obesity, forthcoming analyses from REFLECT will explore adverse health outcomes as well as healthcare resource utilization and treatment patterns.
- These findings may provide additional context for the interpretation of clinical trials evaluating ribupatide by describing real-world populations that meet selected KaiNETIC eligibility criteria.

*Ribupatide is an investigational drug and not approved for use in any region.

†Only key eligibility criteria are shown; in future specified analyses, patients will be identified against all eligibility criteria defined in the KaiNETIC Phase 3 clinical trials if mapping to each of the databases is feasible (directly, modified, or with additional specification), and specific BMI subgroup criteria will be implemented as necessary.

‡Time frames for participant inclusion were January 1, 2018 to June 30, 2024 for USA, January 2, 2019 to June 30, 2024 for UK, and June 1, 2019 to June 30, 2024 for Spain, with the first date for each country aligning with the date at which semaglutide became commercially available. Patients will be assessed for the number of outpatient visits for which they meet eligibility criteria. Patients must have at least 12 months of data before the index date to assess eligibility.

§Defined as the date the second BMI was recorded.

Abbreviations

ASCVD=atherosclerotic cardiovascular disease; BMI=body mass index; CPRD=Clinical Practice Research Datalink; CKD=chronic kidney disease; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; DBP=diastolic blood pressure; EHR=electronic health record; GIP=glucose dependent insulinotropic polypeptide; GLP-1=glucagon like peptide 1; GP=general practitioner; HbA$_{1c}$=glycated hemoglobin; HDL-C=high-density lipoprotein cholesterol; ICD-9=International Classification of Diseases 9th edition; LDL-C=low-density lipoprotein cholesterol; MASLD=metabolic dysfunction-associated steatotic liver disease; NA=not available; OMM=obesity management medication; ORC=obesity-related complication; OSA=obstructive sleep apnea; SBP=systolic blood pressure; SD=standard deviation; T2DM=type 2 diabetes mellitus.

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