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ORIGINAL RESEARCH

GLP-1 Receptor Agonist Therapy in Older Adults with Diabetes: A Qualitative Analysis of Phase 4 ClinicalTrials.gov Studies

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Background: Type 2 diabetes mellitus is highly prevalent among older adults and often requires multidrug therapy to optimize glycemic control while minimizing adverse effects. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are among the most effective antihyperglycemic drugs with demonstrated cardiometabolic benefits. However, their real-world safety, tolerability, and long-term outcomes in geriatric populations remain under-explored.

Objective: To qualitatively analyze completed Phase 4 interventional trials evaluating GLP-1 RA therapy among older adults (≥65 years) with diabetes, as registered on ClinicalTrials.gov.

Methods: A descriptive qualitative review was performed using data from all completed Phase 4 interventional studies with posted results involving older adults and GLP-1 RA therapy for diabetes. Trials were identified through a structured search of ClinicalTrials.gov up to 10 November 2025. Extracted data included drug name, comparator type, outcome measures, and enrollment size. Descriptive qualitative analyses were conducted to summarize treatment trends and reported safety outcomes.

Results: Thirty-seven Phase 4 studies met inclusion criteria. Liraglutide (n = 12) and semaglutide (n = 8) were most frequently investigated, followed by dulaglutide (n = 7), exenatide (n = 5), and lixisenatide (n = 3). Across trials (median enrollment = 180, range = 23–1100), primary endpoints focused on glycated hemoglobin (HbA1c) reduction (45.9%), cardiovascular risk markers (27%), and safety (18.9%). Most studies demonstrated significant improvements in glycemic control and body weight, with frequent adverse effects of gastrointestinal intolerance (15–30%), injection-site reactions (≤5%), and low rates of hypoglycemia (<5%).

Conclusion: This qualitative synthesis highlights consistent clinical benefits of GLP-1 RAs in older adults with diabetes, though tolerability and adherence remain concerns. Post-marketing data underscore the need for individualized prescribing and further research on long-term safety, renal outcomes, and polypharmacy interactions in geriatric populations.

Keywords: diabetes mellitus, GLP-1 receptor agonist, phase 4 clinical trials, older adults, ClinicalTrials.gov

Introduction

Type 2 diabetes mellitus disproportionately affects the elderly, with global prevalence estimated at over 25% among adults aged ≥65 years.[1,2] Aging is associated with progressive insulin resistance, beta-cell dysfunction, and frequent comorbidities that complicate glycemic management.[3–5] Maintaining glycemic targets in this group requires balancing efficacy with safety, especially avoiding hypoglycemia and drug–drug interactions.

In Type 2 diabetes mellitus, therapeutic targets are directed toward correcting insulin resistance, progressive β-cell dysfunction, and dysregulated glucose flux across key organs.[6,7] First-line therapy commonly targets hepatic gluconeogenesis and peripheral insulin resistance, while additional agents are selected to enhance glucose-dependent insulin secretion, modulate incretin signaling, reduce intestinal glucose absorption, or increase renal glucose excretion.[8–10] Exogenous insulin is indicated when endogenous insulin production is inadequate or when oral therapies fail to achieve

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glycemic targets.[11–13] Therapeutic strategies are individualized according to disease severity, comorbidities, and risk of hypoglycemia, with the primary objective of achieving sustained glycemic control and preventing acute and chronic diabetic complications.[14,15]

In addition, emerging and adjunct therapeutic targets in Type 2 diabetes mellitus focus on addressing the multisystem nature of the disease and its cardiometabolic consequences. These include adipose tissue signaling pathways involved in lipotoxicity and inflammation, central nervous system mechanisms regulating appetite and energy balance, and β-cell preservation strategies aimed at slowing disease progression.[16–18] Activation of PPAR-γ improves insulin sensitivity at the transcriptional level, while amylin analogs modulate postprandial glucose excursions by delaying gastric emptying and suppressing glucagon secretion.[19–23]

In older adults, Type 2 diabetes mellitus accelerates the progression of microvascular complications such as nephropathy, retinopathy, and neuropathy, leading to higher rates of disability and functional decline.[24–27] It is also strongly associated with increased risks of cognitive impairment and dementia, driven in part by chronic hyperglycemia–induced vascular and neuroinflammatory pathways.[28–30] Additionally, older adults with diabetes experience a significantly higher incidence of cardiovascular events, including myocardial infarction and heart failure, which contributes to elevated morbidity and mortality in this population.[31–33] The disease further exacerbates frailty and sarcopenia, reducing mobility, impairing balance, and increasing the risk of falls and hospitalization.[34–37]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) mimic the incretin hormone GLP-1 to enhance glucose-dependent insulin secretion, suppress glucagon, delay gastric emptying, and promote satiety.[38,39] Agents such as liraglutide, semaglutide, dulaglutide and exenatide have demonstrated robust HbA1c reductions and cardiovascular protection in large-scale trials.[40–43]

Older adults enrolled in randomized controlled trials commonly exhibit higher polypharmacy exposure, altered pharmacokinetics, and increased susceptibility to adverse events such as dehydration and gastrointestinal intolerance.[44–46]

While numerous meta-analyses have examined GLP-1 RA efficacy in T2DM, few have focused on completed post-marketing interventional studies specifically targeting older adults. Phase 4 post-marketing interventional trials are uniquely important for older populations because they evaluate therapies under routine clinical conditions where polypharmacy, multimorbidity, and age-related physiological changes are most pronounced. Unlike pre-marketing trials, these studies better capture real-world tolerability, adherence, and safety outcomes that are critical for optimizing treatment in geriatric patients. ClinicalTrials.gov provides an opportunity to identify trends in study design, safety outcomes, and therapeutic focus. This analysis qualitatively synthesizes all completed Phase 4 interventional studies evaluating GLP-1 RAs among older adults with diabetes, aiming to clarify clinical trends and highlight future research directions.

Methods

Study Design and Data Source

This study was conducted as a registry-based descriptive qualitative synthesis of completed interventional Phase 4 clinical trials evaluating glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in older adults with diabetes. The analysis used data publicly available through the ClinicalTrials.gov registry, which provides standardized information on trial design, interventions, outcomes, and safety reporting. This approach was selected to characterize post-marketing research trends and reported outcomes under routine clinical conditions rather than to perform comparative effectiveness analyses.

Eligibility Criteria

Studies were eligible for inclusion if they were registered on ClinicalTrials.gov, classified as interventional Phase 4 trials, evaluated a glucagon-like peptide-1 receptor agonist as the primary intervention, included older adults defined as participants aged 65 years or older, and had a completed study status with posted results. Studies were excluded if they were observational in design, ongoing or terminated without available results, focused solely on behavioral or lifestyle interventions, or lacked age-specific information relevant to older adult populations.

Search Strategy

A structured search of the ClinicalTrials.gov database was performed using predefined keywords and filters, including combinations of "diabetes," "GLP-1," "Phase 4," "completed," "older adult," and "with results." Searches were limited to interventional studies with posted results. The final search was conducted on 10 November 2025. All retrieved records were screened for eligibility based on study phase, population characteristics, intervention type, and availability of results.

Data Extraction

Collected data included NCT number, study title, drug, comparator, primary outcomes, enrollment, design, and adverse events.

Data Analysis

A descriptive qualitative synthesis was employed because Phase 4 trials varied widely in study design, duration, comparator selection, outcome measures, and reporting practices. Extracted data were summarized descriptively and grouped into predefined outcome domains, including glycemic control, cardiovascular and metabolic outcomes, renal outcomes, weight-related measures, and safety and tolerability. Patterns and trends across studies were identified through structured comparison rather than formal thematic qualitative analysis.

Ethical Considerations

All analyzed data were publicly available from ClinicalTrials.gov; no ethics approval or consent was required.

Results

The included Phase 4 trials demonstrated marked heterogeneity in study design, duration, comparator selection, and outcome prioritization. Most studies focused on surrogate efficacy endpoints, particularly glycemic control, while substantially fewer trials examined renal outcomes or safety-specific endpoints. This distribution reflects prevailing post-marketing research priorities in diabetes care rather than a comprehensive assessment of geriatric-relevant outcomes.

A total of 37 completed interventional Phase 4 studies met eligibility criteria, all involving GLP-1 receptor agonist therapy among older adults with diabetes. Study characteristics, including the number of trials per agent, enrollment size, comparators, and primary outcomes, are summarized in Table 1. The distribution of primary outcome domains, grouped by efficacy, cardiovascular, renal, and safety measures, is presented in Table 2. As shown in Figure 1, liraglutide accounted for the largest proportion of studies (n = 12), representing almost one-third of all included trials. Semaglutide was the second most frequently evaluated agent (n = 8), followed by dulaglutide (n = 7). Exenatide and lixisenatide were less commonly studied, with 5 and 3 trials, respectively.

Table 1 Summary of Included Phase 4 GLP-1 RA Clinical Trials

Drug	Trials (n/37)	Enrollment	Comparator	Primary Outcomes	Adverse Events
Liraglutide	12	≈3,200	Placebo/Metformin	HbA1c, Weight	Nausea, diarrhea
Semaglutide	8	≈2,700	SGLT2i/DPP-4i	CV, Glycemic control	GI intolerance
Dulaglutide	7	≈1,800	Basal insulin	Safety, HbA1c	Constipation
Exenatide	5	≈950	Metformin	PPG, Beta-cell	Injection site pain
Lixisenatide	3	≈600	Insulin glargine	FPG, CV	Headache
Other Combo	2	≈300	Basal-bolus	Renal, Glycemic	GI intolerance

Table 2 Distribution of Primary Outcome Domains

Outcome Domain	Trials (n)	Representative Measures
Glycemic control	17	HbA1c, FPG, PPG
Cardiovascular/metabolic	10	BP, Lipids, CV events
Weight/body composition	5	BMI, Body weight, Epicardial fat
Renal outcomes	3	eGFR, UACR
Safety/tolerability	2	Adverse events, Withdrawal rate

The concentration of studies evaluating liraglutide and semaglutide suggests greater post-marketing clinical interest and wider real-world adoption of these agents in older adults compared with other GLP-1 receptor agonists. In contrast, the smaller number of trials investigating exenatide and lixisenatide, often with shorter durations and lower enrollment, may limit the robustness of safety and long-term outcome data for these therapies in geriatric populations. As shown in Table 1, liraglutide (n=12) and semaglutide (n=8) were the most frequently investigated GLP-1 receptor agonists, followed by dulaglutide (n=7), exenatide (n=5), and lixisenatide (n=3). Most trials compared GLP-1 RAs to metformin or insulin-based therapies. Reported adverse events were predominantly gastrointestinal, with nausea being the most common.

Outcome selection across trials was heavily skewed toward glycemic efficacy, with nearly half of studies prioritizing HbA1c-related endpoints. Cardiovascular and metabolic markers were assessed less frequently, while renal and safety-specific outcomes were rarely designated as primary endpoints, highlighting an important gap in post-marketing evidence relevant to older adults. Table 2 demonstrates that glycemic efficacy was the most common primary endpoint (46%), followed by cardiovascular markers (27%) and weight reduction (13%). Only a minority of studies focused on renal or safety-specific outcomes.

As indicated in Table 3, parallel-group randomized designs were dominant (70%), while open-label and crossover studies represented smaller proportions. Approximately two-thirds of trials utilized active comparators, reflecting real-world post-marketing evaluations.

Most trials were of moderate duration (24–52 weeks) with relatively small to medium sample sizes, reflecting typical post-marketing evaluation designs. Although longer-duration studies were present, they constituted a minority, limiting insight into long-term safety, adherence, and functional outcomes in older adults. Table 4 summarizes study durations and sample sizes, showing that nearly half of the studies lasted 24–52 weeks with median enrollment around 180 participants. Long-term trials (>1 year) constituted approximately one-quarter of the total dataset.

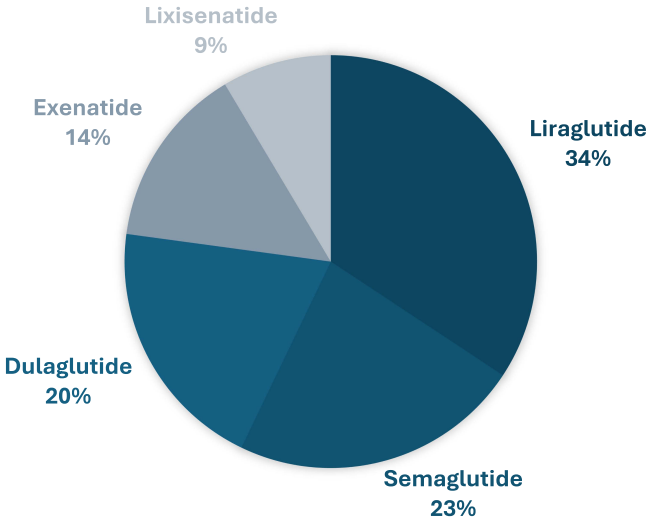

Figure 1 Distribution of Phase 4 clinical trials by GLP-1 receptor agonist.

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Table 3 Study Design and Comparator Type

Design Type	Number of Trials	Comparator Type
Parallel-group randomized	26	Placebo or active control
Open-label single-arm	7	None (self-controlled)
Crossover design	4	Within-subject comparison

Table 4 Study Duration and Sample Size Distribution

Duration Category	Number of Trials	Median Enrollment
<24 weeks	11	120
24–52 weeks	17	180
>52 weeks	9	260

Table 5 Reported Adverse Events by Frequency

Adverse Event	Frequency (%)	Notes
Nausea	25–30%	Transient, dose-dependent
Vomiting/Diarrhea	10–15%	Improves with titration
Hypoglycemia	<5%	Mainly with insulin co-use
Injection site reaction	≤5%	Mild erythema or pain
Headache/Dizziness	≤3%	Self-limiting

Adverse event reporting across studies was dominated by gastrointestinal symptoms, which were generally transient and dose-dependent. The consistently low incidence of hypoglycemia across trials is clinically relevant in older adults, given their increased vulnerability to hypoglycemia-related morbidity. As detailed in Table 5, gastrointestinal symptoms (nausea, vomiting, diarrhea) were the most frequently reported adverse events, occurring in up to 30% of participants. Hypoglycemia was rare, primarily when GLP-1 RAs were combined with insulin. Injection-site reactions were mild and transient.

Discussion

This qualitative synthesis of 37 completed Phase 4 interventional trials provides real-world insights into reported effectiveness and safety outcomes of GLP-1 receptor agonists in older adults with type 2 diabetes, a population characterized by a high burden of comorbidity, functional decline, and increased vulnerability to drug-related complications. Given the registry-based and descriptive nature of this synthesis, the findings should not be interpreted as evidence of comparative effectiveness or causal inference, but rather as an overview of reported outcomes and research patterns across completed Phase 4 trials.

Aging is associated with progressive insulin resistance, increased cardiovascular risk, and a heightened susceptibility to hypoglycemia in the context of polypharmacy and reduced physiological reserve.[47–49] The findings of the present analysis suggest that GLP-1 receptor agonists may help address several of these therapeutic challenges by offering

glycemic improvement, weight reduction, and cardiometabolic benefits, while maintaining a relatively low reported risk of hypoglycemia.[50–53]

Integration of data from Tables 1 and 4 indicates that studies evaluating liraglutide and semaglutide generally enrolled larger numbers of participants and more frequently extended beyond 24 weeks of follow-up, reflecting greater post-marketing research focus and availability of longer-term safety data for these agents. In contrast, trials assessing exenatide and lixisenatide were typically smaller and shorter in duration, which may limit the generalizability and robustness of long-term outcome assessment for these therapies in older populations.

Across the included Phase 4 trials, liraglutide and semaglutide were the most frequently studied agents, consistent with their widespread clinical use and established evidence base from earlier large-scale trials.[54–57] Consistent with earlier Phase 3 trials, nearly half of the studies in this analysis demonstrated significant HbA1c reductions, while over one-quarter focused on cardiovascular markers, aligning with cardiometabolic outcome patterns reported in landmark trials such as LEADER, SUSTAIN, and REWIND, while reflecting outcomes observed under routine clinical conditions. Importantly, similar outcome trends were reported among older adults, addressing a critical evidence gap regarding the under-representation of geriatric populations in pivotal randomized trials.[44–46] The safety profile observed in this study aligns with the known tolerability patterns of GLP-1 Ras.[58–60] Gastrointestinal symptoms particularly nausea and vomiting were the most common adverse events, occurring in up to 30% of participants.[61–63] However, these were generally transient and dose-dependent. Hypoglycemia rates remained low (<5%), which is clinically meaningful given the heightened vulnerability of older adults to severe hypoglycemic events and their associated risks of falls, cognitive impairment, and cardiovascular stress. Notably, only a small proportion of trials specifically evaluated renal outcomes or frailty-related parameters, despite their relevance to geriatric care.

Study design patterns revealed that most Phase 4 trials were randomized and ranged from 24 to 52 weeks, reflecting real-world treatment durations. Nonetheless, substantial heterogeneity existed in outcome measures, comparator types, and reporting of adverse events, limiting cross-study comparability. Additionally, the predominance of glycemic endpoints suggests that broader geriatric-focused outcomes such as functional status, quality of life, and polypharmacy interactions remain under-explored.

Overall, the findings of this descriptive synthesis indicate that GLP-1 receptor agonists are commonly reported as effective and generally well tolerated in older adults within post-marketing clinical trials. However, interpretation should remain cautious given the heterogeneity of included studies. Future Phase 4 research would benefit from standardized outcome frameworks, longer follow-up durations, and explicit incorporation of geriatric-relevant endpoints to enhance the clinical applicability of post-marketing evidence in this growing population.

Limitations

This study has several limitations. The analysis depended on data posted in ClinicalTrials.gov, where reporting quality varies and some trials provide incomplete outcome or adverse event information. Heterogeneity in study designs, sample sizes, and endpoints limited direct comparison across trials. Additionally, potential reporting and publication bias may exist, as some sponsors selectively post results or delay adverse event reporting. Finally, most studies did not include geriatric-specific outcomes such as frailty, functional status, or quality of life, which restricts the applicability of findings to the broader older adult population.

Conclusion

GLP-1 receptor agonists are commonly reported as effective and generally well tolerated in older adults across completed Phase 4 clinical trials. Post-marketing Phase 4 trials confirm improvements in glycemic control and cardiometabolic parameters. Future studies should standardize endpoints, include frailty measures, and assess adherence, cost, and long-term outcomes.

Data Sharing Statement

All data analyzed in this study are derived from publicly available records on ClinicalTrials.gov and are presented within the paper.

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Author Contributions

Nasser M. Alorfi contributed to Conceptualization, Methodology, Formal Analysis, Investigation, Data Curation, Writing – Original Draft, Visualization, and Funding Acquisition Project Administration. Nouf M. Alourfi contributed to Conceptualization, Methodology, Supervision, Validation, Resources, and Project Administration. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest related to this work.

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