

An Open-Label, Multicenter Trial of Viaject vs. Regular Human Insulin in Patients with Type 1 Diabetes: Impact of Regional Differences on Efficacy Analyses

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Abstract

Viaject is a novel formulation of human insulin which is absorbed more rapidly than insulin lispro or regular human insulin (RHI) after subcutaneous injection. Preliminary analyses of a 6-month randomized, open-label study comparing the efficacy and safety of Viaject vs. RHI as prandial insulin in patients with type 1 diabetes were previously reported. Final results and additional analyses of regional differences in results are presented here. The study was conducted in the US (n=307), Germany (n=50) and India (n=106). HbA1c decreased similarly in both treatment groups in the US and Germany [-0.20 in the Viaject arm vs. -0.30 in the RHI group, LSM difference 0.10, 95% CI (-0.07, 0.27)]; however, significant heterogeneity (p=0.0008) in the treatment group difference was observed in India. This was due to atypically robust HbA1c lowering seen with RHI in India (-0.20 with Viaject vs. -1.09 with RHI). Several factors may have contributed to the RHI response in India, including a greater pre-trial use of regular insulin (90.5% in India vs. < 19% in US/Germany), differences in dose change frequencies and baseline glycemic control. In addition, a large subset of baseline HbA1c blood samples in India were shipped under conditions in which stability could not be ensured, contributing to overall variability. Advantages in two key secondary endpoints were seen in the Viaject arm in the US/Germany cohort. Significantly less weight gain was observed in patients treated with Viaject compared to RHI (-0.11 kg vs. +1.36, LSM difference -1.47 (-2.11, -0.83), p<0.0001). A trend toward fewer Viaject-treated patients experiencing severe hypoglycemia (4.4% with Viaject compared to 8.6%* with RHI) was also seen. The prevalence of injection site reactions, most commonly pain and irritation, was higher with Viaject, although this declined over the course of the study. Insulin antibodies and other safety laboratory tests were similar between treatment groups. This study confirms that insulin titration trials are susceptible to regional differences but that Viaject represents a valuable therapeutic option for patients with type 1 diabetes.

* number corrected post abstract publication

Introduction

- Viaject is a novel formulation of **recombinant human insulin** that results in more rapid absorption and more rapid onset of action than insulin lispro or Regular Human Insulin (RHI)¹.
- Viaject contains EDTA, which de-stabilizes insulin hexamers by chelating zinc. Citric acid is used to mask surface charges on the insulin molecules, facilitating absorption and preventing re-aggregation of monomers.
- More rapidly absorbed insulin may better simulate first phase insulin responses to meals, better matching insulin delivery to meal-related glucose peaks. This could allow for optimization of meal time insulin dosing and minimization of postprandial hyper- and hypoglycemia while minimizing insulin therapy associated weight gain.

Study Purpose

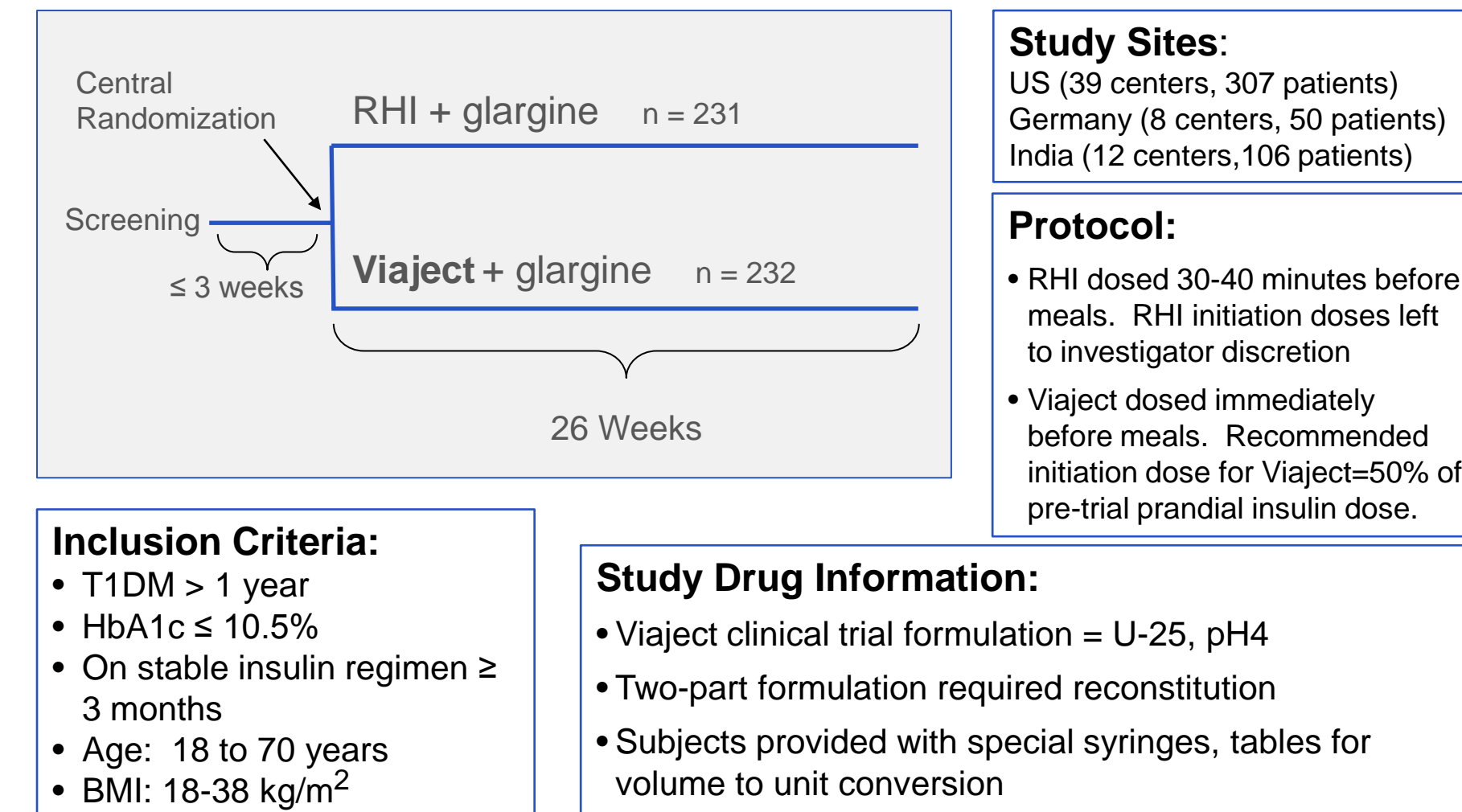
- To investigate whether an insulin regimen consisting of pre-meal Viaject plus basal insulin glargine can provide glycemic control similar to a regimen consisting of pre-meal RHI plus basal glargine in patients with type 1 diabetes as measured by change from baseline of HbA1c.
- To assess the safety and tolerability of Viaject over a period of 6 months.
- Preliminary results have been previously reported. This poster presents finalized analyses, including analyses by region.

References

- Steiner S, et al. A novel insulin formulation with a more rapid onset of action. *Diabetologia*. 2008;51(9):1602-6.
- Little R, et al. Effects of sample storage conditions on glycated hemoglobin measurement: evaluation of five different high performance liquid chromatography methods. *Diabetes Technology & Therapeutics*. 2007;9(1):36-42.

Methods and Study Design

Open-Label, Parallel Group Study Design



Statistical Analyses

- Primary objective:** Evaluate treatment group difference in change from baseline HbA1c
- Analysis of Covariance (ANCOVA) model with baseline HbA1c as covariate
 - Non-inferiority defined by upper bound of 95% CI ≤ 0.4%
 - Missing data imputed using Last Observation Carried Forward (LOCF) analysis
- Secondary objectives: Weight and dose:** ANCOVA with baseline values as covariate. **Hypoglycemia:** Fisher's exact test on the number of subjects with at least one event.

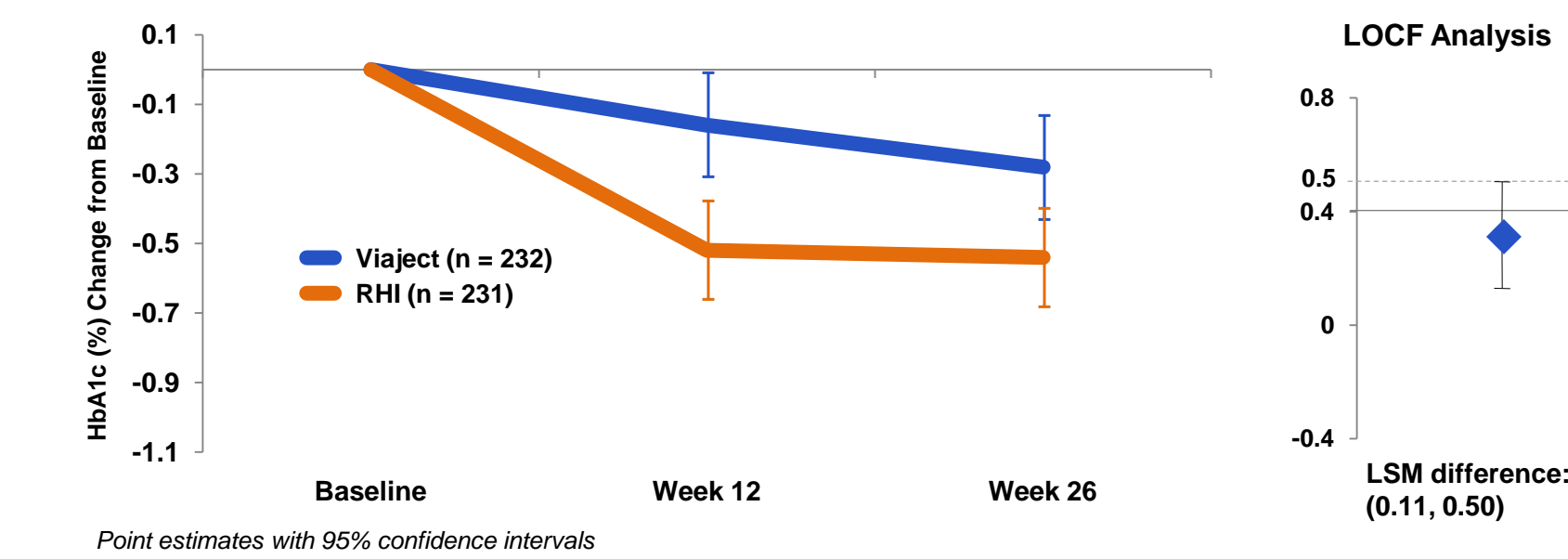
Subject Characteristics at Baseline

| | US/Germany | | India | |
|--------------------------------------|--------------|--------------|--------------|--------------|
| | Viaject | RHI | Viaject | RHI |
| Mean Age (± SD) | 45.0 (12.33) | 43.1 (13.00) | 27.4 (9.04) | 27.7 (8.19) |
| Gender (% M/F) | 60/40 | 65/35 | 46/54 | 46/54 |
| Mean Baseline HbA1c (± SD) | 7.88 (1.214) | 7.90 (1.290) | 8.99 (1.644) | 9.21 (1.281) |
| Mean Disease Duration (Y) (± SD) | 20.1 (11.80) | 19.7 (12.44) | 9.2 (7.74) | 11.6 (8.82) |
| Mean BMI (kg/m ²) (± SD) | 26.9 (4.40) | 27.5 (4.90) | 21.4 (2.50) | 21.5 (3.20) |

| | US/Germany | India |
|--|------------|-------|
| % of subjects taking ≥ 3 prandial insulin injections per day pre-trial | 85.9 | 43.4 |
| % of subjects taking RHI pre-trial | 18.5 | 90.5 |

Center and Country Interactions

Mean HbA1c: All Countries



Center and Country Interactions

- A pre-specified analysis to assess a treatment-by-center interaction yielded a highly significant interaction (p=0.0002).
- It was determined that the treatment-by-center interaction was due to a highly significant treatment-by-country interaction (p=0.0008).
- The treatment-by-country interaction reflected both greater variability and a differential effect in India.

| LS Mean Change from Baseline HbA1c at Endpoint (LOCF) (mean change, SD) | Viaject | RHI |
|---|---------------|---------------|
| US and Germany | -0.20 (0.759) | -0.30 (0.762) |
| India | -0.20 (1.515) | -1.09 (1.514) |

Multifactorial Origins of Geographic Heterogeneity

- Differences in baseline use of RHI and intensive insulin regimens, in baseline HbA1c, and in other demographic measures are noted in **Subject Characteristics at Baseline** section.
- HbA1c sample shipping differences contributed to greater intra-subject variability**
- At the start of the study in India, HbA1c samples were shipped to a local laboratory where they were stored prior to shipment to the central laboratory in Singapore. Subsequent samples were shipped overnight directly from sites in India to the central laboratory in Singapore.
- An analysis of baseline HbA1c levels drawn less than three weeks apart (screening and day of randomization) by laboratory shipping pattern is shown at right. It is noted that the local laboratory shipping step affected central laboratory HbA1c results.

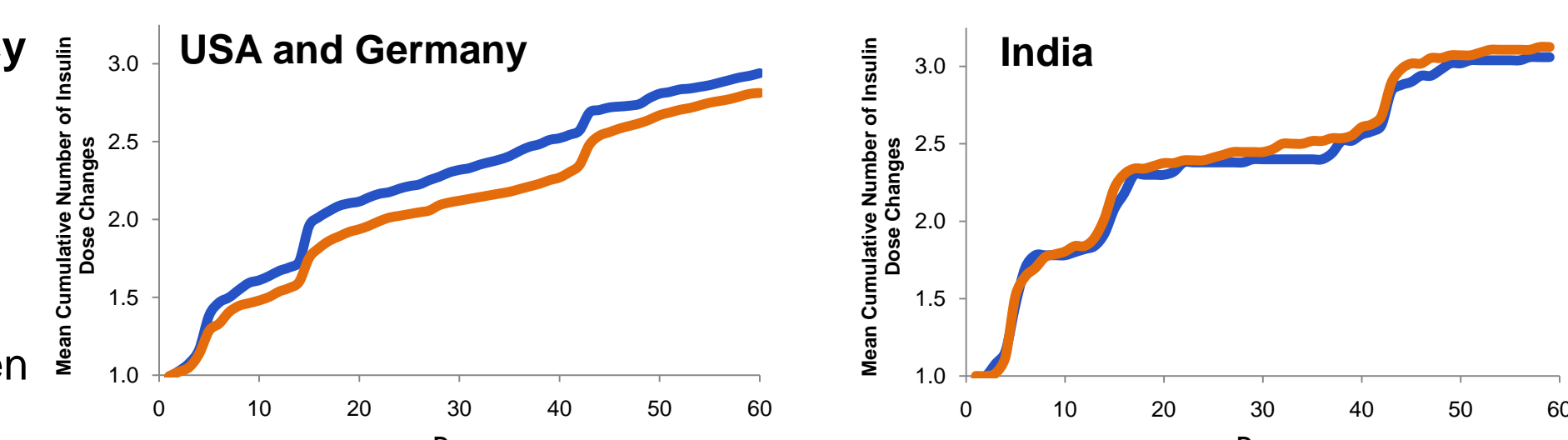
| Day 1 HbA1c value relative to Screening value (both measured in central laboratory) | Both samples initially shipped to local laboratory in India | Screening sample initially shipped to local laboratory in India, Day 1 sample shipped directly to central laboratory | Both samples initially shipped directly to central laboratory |
|---|---|--|---|
| Increased | 7 (35%) | 23 (79%) | 177 (45%) |
| No difference | 5 (25%) | 2 (7%) | 50 (13%) |
| Decreased | 8 (40%) | 4 (14%) | 164 (42%) |

When evaluating all subjects in US, Germany and India except those with blood specimens shipped through the local laboratory in India, the difference between treatment groups in change from baseline HbA1c at Endpoint/LOCF was 0.20 (95% CI: 0.01, 0.39).

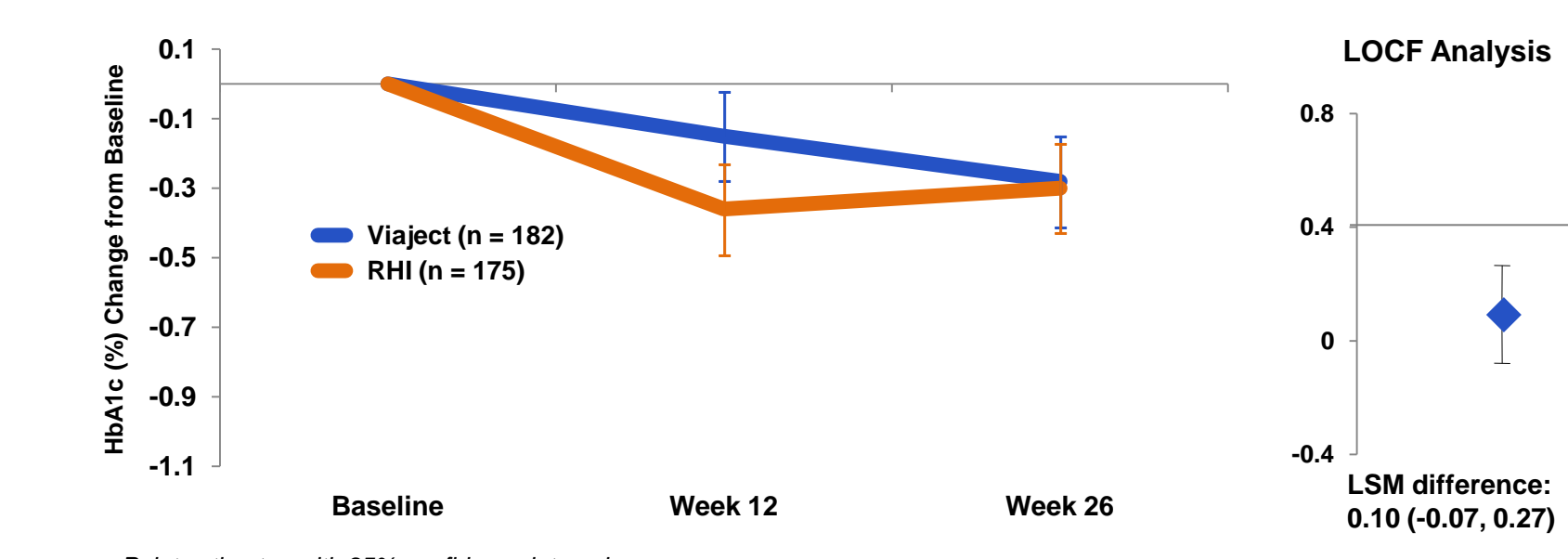
Excessive heat exposure en route to the central laboratory in India may have caused this shipping effect (Little et al)².

Regional differences in dose titration frequency

Because recommended initiation doses in the Viaject arm were lower than RHI at the outset of the study, a higher frequency of dose changes compared to comparator early in the study would be expected. The expected increased titration frequency in the first 60 days of the study was seen in the US and Germany, but not India.

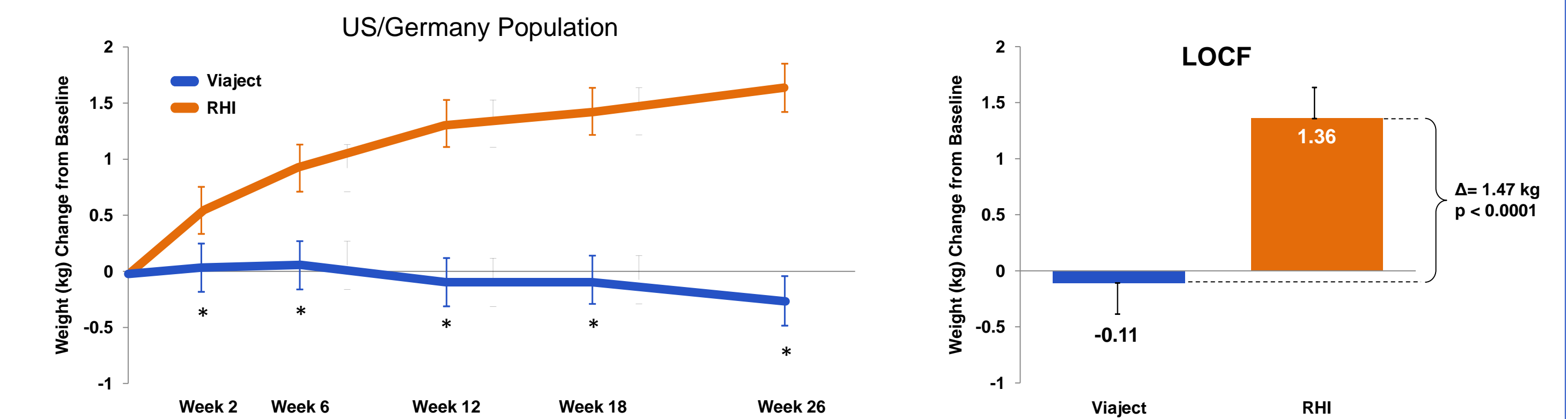


Mean HbA1c: US and Germany Population



- Because of anomalous data from India, analyses are also presented for the US/Germany population.
- HbA1c decreased similarly in both treatment groups in the US and Germany [-0.20 in the Viaject group, -0.30 in the RHI group, LSM difference 0.10, 95% CI (-0.07, 0.27)]. This indicates non-inferiority in treatment response, despite the smaller sample size in the US/Germany cohort.
- Similar results were seen in the completer population set.

Mean Body Weight



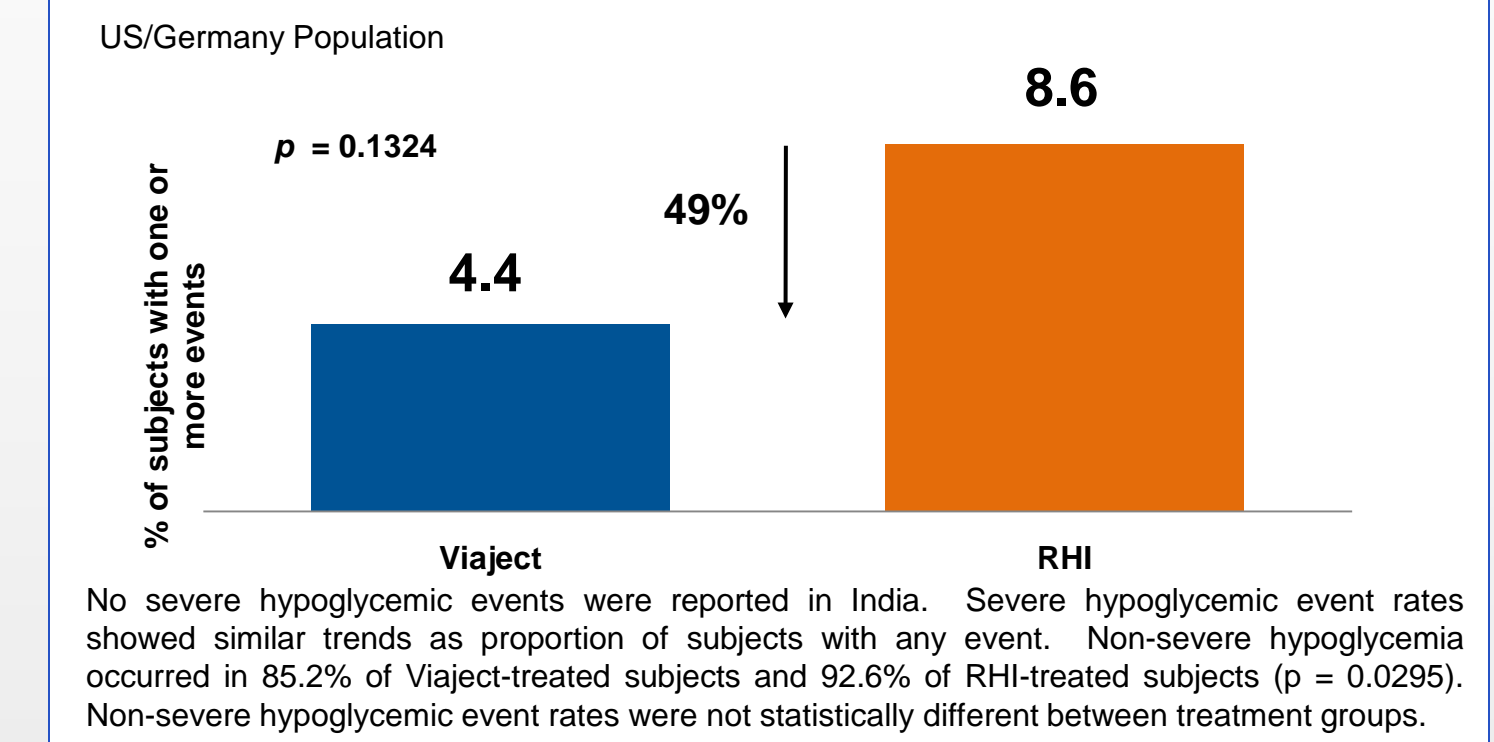
*Statistically significant (p < 0.001) difference in weight between Viaject and RHI. Error bars represent one standard error. ITT Population shown, completer population results consistent. All-country analysis (including India) showed consistent results.

Mean Insulin Doses (U/kg)

| US/Germany Population | | Week 0 (Starting Dose) | Week 12 | Week 26 |
|-----------------------|--------------------|------------------------|--------------|--------------|
| Viaject | Prandial Mean (SE) | 0.20 (0.010) | 0.30 (0.019) | 0.33 (0.022) |
| | Basal Mean (SE) | 0.34 (0.009) | 0.36 (0.013) | 0.36 (0.013) |
| RHI | Prandial Mean (SE) | 0.28 (0.012) | 0.32 (0.014) | 0.34 (0.015) |
| | Basal Mean (SE) | 0.35 (0.014) | 0.34 (0.013) | 0.34 (0.015) |

Similar dose trends in India

Severe Hypoglycemic Events (% of subjects with ≥ 1 event)



Adverse Events, Toleration and Safety Laboratory Tests

- The safety analysis population consisted of all treated subjects from all three countries. Overall, the frequency and nature of adverse events were comparable between treatment groups
- The U-25, pH4 clinical formulation was associated with injection site discomfort more so than RHI:
 - Most commonly described as "stinging"
 - Prevalence highest after initiation and then declined with time
 - < 5% of subjects discontinued for this reason
 - A neutral pH, U-100 formulation is intended for commercial use
- Insulin antibodies: mean endpoint (LOCF) change from baseline was -0.601 U/mL in the Viaject group and -1.335 U/mL in the RHI group (normal range for ELISA assay < 10 U/ml)
- Results of general safety laboratory tests were comparable between treatment groups

Summary

- Mean HbA1c reductions from baseline were demonstrated in both treatment arms
- Similar HbA1c reduction (non-inferiority) was demonstrated in US/Germany population in the Viaject arm compared to RHI
- HbA1c data from India was found to be significantly anomalous related to regional differences in blood sample processing, baseline subject characteristics and differences in insulin dose titration
- Injection site discomfort associated with initiation of phase 3 formulation (U-25, pH4) subsided with time and infrequently resulted in discontinuation
- Compared to RHI, Viaject was associated with
 - Significantly less weight gain
 - Trend toward reduced incidence of severe hypoglycemia