Pharmacokinetic and Pharmacodynamic Assessments with ITCA 650, Continuous Subcutaneous Delivery of Exenatide, in Type 2 Diabetes

J. Dahms 1, Y. Chandrasekher 1, R. Fielding 1, R. Zhou 1, R. Henry 4, J. Rosenstock 5, T. Alessi 1, K. Luskey 1

Abstract

Background and Aim

ITCA 650 is a subcutaneous slow-release pump that provides continuous zero-order delivery of exenatide. Dosing for up to 12 months with a single placement; 3-month ITCA 650s used in these studies. Placebo/device was a 3-month in-office procedure.

Methods

PK and PD data were collected from type 2 diabetes in a 28-day Phase 1 study, 4 weeks follow-up, and in a 48-week Phase 2 study in 155 metformin-treated subjects. PK/PD data were collected from type 2 diabetics in a 28-day Phase 1b study (44 subjects) and a 24-week Phase 2 study (155 metformin-treated subjects) with a 24-week extension period. PK and PD data were collected from type 2 diabetics in a 28-day Phase 1b study and a 24-week Phase 2 study. PK and PD data were collected from type 2 diabetics in a 28-day Phase 1b study and a 24-week Phase 2 study. PK and PD data were collected from type 2 diabetics in a 28-day Phase 1b study and a 24-week Phase 2 study. PK and PD data were collected from type 2 diabetics in a 28-day Phase 1b study and a 24-week Phase 2 study.

Pharmacodynamics of ITCA 650

Day 1

- Plasma exenatide detected at 12 hr in Phase 2 subjects in all dose groups.
- Steady state concentrations achieved within 24 hrs of treatment.
- Reductions in HbA1c observed within 6-12 hrs.
- FPG and 3-m postprandial glucose signify benefits.
- Reductions maintained over 48 weeks of treatment.

Weeks 1 through 12

- Significant decrease in HbA1c were observed in the first 12 weeks. Further decreases seen with longer times and higher concentrations.

Weeks 13 through 48

- Effects on FPG were seen in Weeks 1-12. Effect was maintained with longer times.

Comparison to Infusion, Injection

- ITCA 650 produced plasma levels and dose durations similar to or better than
- Activity observed at exenatide levels < 30 pg/mL
- Activity observed at exenatide levels 30-60 pg/mL
- Activity observed at exenatide levels > 60 pg/mL

PK/PD Conclusions

- All doses of ITCA 650 were active
- Higher exenatide concentrations tended to produce larger reductions in HbA1c, weight and FPG
- Activity observed at exenatide levels > 60 pg/mL
- Activity observed at exenatide levels > 60 pg/mL
- Activity observed at exenatide levels > 60 pg/mL

Conclusion

- Provides continuous exposure with consistent plasma exenatide levels for up to 48 weeks.
- Higher exenatide concentrations were associated with larger reductions in HbA1c.

Pharmacokinetics / Pharmacodynamics of ITCA 650

- Consistent with its 2.4 hr half-life, exenatide was not measurable in any subject 24 hrs after ITCA 650.
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Change in Body Weight Over Time

- Baseline HbA1c played a major role in determining magnitude of response to ITCA 650. The relationship between exenatide exposure and glycemic control was dose dependent.
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PK Conclusions

- Basal propranoid appears
- Response rates similar to injection
- Following removal of ITCA 650, plasma exenatide levels drop rapidly to baseline levels within 24 hrs.

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Materials and methods:

Bioavailability of exenatide by ITCA 650 was similar to that observed with immediate release delivery and extended release delivery of exenatide. ITCA 650 has been shown to reduce FPG, HbA1c and body weight in type 2 diabetes patients. ITCA 650 has been shown to reduce FPG, HbA1c and body weight in type 2 diabetes patients.

Results:

Data were analyzed using linear and tobit regression models, and graphically explored with LOESS (locally weighted scatterplot smoothing) techniques.

Conclusion:

- Exposures with ITCA 650 were consistent with exposures provided continuous exposure for the duration of each placement (up to 12 weeks) and for the duration of treatment (up to 48 weeks). Exposures with ITCA 650 were consistent with exposures provided continuous exposure for the duration of each placement (up to 12 weeks) and for the duration of treatment (up to 48 weeks).
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Change in Exenatide Concentration

The relationship between the PK and PD of ITCA 650 was examined. The effects of ITCA 650 were assessed from 24 hrs after placement through end of treatment. Exposures with ITCA 650 were consistent with exposures provided continuous exposure for the duration of each placement (up to 12 weeks) and for the duration of treatment (up to 48 weeks).

Methods

- PK and PD data were collected from type 2 diabetes in a 28-day Phase 1 study; 4 weeks follow-up, and in a 48-week Phase 2 study in 155 metformin-treated subjects.
- Fasting plasma exenatide concentrations were measured using an inulin-based assay, along with C-peptide and ACTH to assess exenatide delivery.

Pharmacokinetics / Pharmacodynamics of ITCA 650

- PK/PD relationship of exenatide exposure relative to changes in HbA1c and BW was examined.
- Higher exenatide concentrations were associated with linear and hold downregulator responses, and typically explored with LOESS (locally weighted scatterplot smoothing) techniques.

Conclusions

- Exposures with ITCA 650 were consistent with exposures provided continuous exposure for the duration of each placement (up to 12 weeks) and for the duration of treatment (up to 48 weeks). Exposures with ITCA 650 were consistent with exposures provided continuous exposure for the duration of each placement (up to 12 weeks) and for the duration of treatment (up to 48 weeks).
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Change in HbA1c from Baseline to Week 12 (%)

- Higher exenatide concentrations were associated with a greater reduction in HbA1c.
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Change in FPG from Baseline to Week 48 (mg/dL)

- Reductions in FPG observed within 6-12 hrs of treatment.
- Reductions maintained over 48 weeks of treatment.
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Change in Weight from Baseline to Week 48 (kg)

- Baseline HbA1c played a major role in determining magnitude of response to ITCA 650. The relationship between exenatide exposure and glycemic control was dose dependent.
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