2. GHFA Synopsis

Clinical Study Report Synopsis: Study I2Y-MC-GHFA

Title of Study: A Phase 2 Study for Transdermal Application of Teriparatide	
Number of Investigators: This multicenter study included 23 principal investigators.	
Study Centers: This study was conducted at 23 study centers in 5 countries	
Publication(s) Based on the Study: None at this time.	
Length of Study: Date of first patient enrolled: 16 November 2009 Date of last patient completed: 06 September 2011	**Phase of Development:** 2

Objectives: The primary objective of this study was to assess if one or more of the transdermally (TD)- delivered teriparatide doses is noninferior to subcutaneous (SQ)-delivered teriparatide 20 µg/day - based on mean percent change of bone mineral density (BMD) at 12 months. The primary variable was the percent change from baseline in lumbar spine bone mineral density (BMD) in 12 months.

The secondary objectives were to:

- Evaluate differences between SQ and each TD dose in lumbar spine BMD at 6 months.
- Evaluate differences between SQ and each TD dose in procollagen type 1 N-terminal propeptide (P1NP) and C-terminal telopeptide (CTX).
- Evaluate differences between SQ and each TD dose in C-terminal propeptide (C1CP) (converted to serum procollagen type 1 C-propeptide [P1CP] for comparison to prior SQ studies).
- Determine the safety of TD-delivered teriparatide for a range of doses.
- Evaluate the population pharmacokinetics (PK) of teriparatide and explore the relationship between teriparatide plasma concentrations and pharmacodynamic (PD) endpoints.
- Evaluate the immunogenic response to TD-administered teriparatide.
- Evaluate data collected from patients via questionnaire on ease of use of the TD and SQ delivery experiences. This was a device-related outcome.

Study Design: Study GHFA was designed as a Phase 2, 12-month, noninferiority trial (TD-delivered teriparatide versus SQ-delivered teriparatide), and as a dose-ranging trial for TD teriparatide delivery. Postmenopausal women with osteoporosis and restricted osteoporosis treatment were randomized to receive open-label teriparatide SQ (20 µg) or double-blind teriparatide TD (30, 50, or 80 µg). All patients received daily open-label calcium (1000 mg) and vitamin D supplementation (800 to 1200 IU).

Number of Patients:

Planned: 432 (108 per treatment group)
Treated (at least 1 dose): 57 SQ20, 56 TD30, 54 TD50, and 64 TD80
Completed: 52 SQ20, 48 TD30, 45 TD50, and 52 TD80

Diagnosis and Main Criteria for Inclusion: Patients must have been ambulatory, postmenopausal women aged 45 to 85 years whose last menstrual period occurred at least 2 years prior to entry into the trial. Patients must have had a centrally confirmed lumbar spine or femoral neck BMD T-score as measured by densitometry (using dual-energy X-ray absorptiometry [DXA]) of ≤-2.5; 3 of 4 vertebrae (L1 through L4) must have been evaluable for BMD by DXA.

Study Drug, Dose, and Mode of Administration:

Double-blind administration of teriparatide in doses of:

- 30 µg/day given TD by ViaDerm shPTH(1-34) patch.
- 50 µg/day given TD by ViaDerm shPTH(1-34) patch.
- 80 µg/day given TD by ViaDerm shPTH(1-34) patch.

Reference Therapy, Dose, and Mode of Administration: Open-label administration of teriparatide 20 µg/day by SQ injection (Forteo®/Forsteo®).
Duration of Treatment: 12 months
Variables: Efficacy: Lumbar spine BMD as measured by densitometry (using dual-energy X-ray absorptiometry [DXA]) and bone marker measurements. Safety: Visual examination of the site of study drug administration; laboratory testing; blood pressure and pulse; adverse events; and parathyroid hormone antibody assessments. Pharmacokinetic/Pharmacodynamic: Population PK parameters
Statistical Methods: All analyses were conducted according to the intention-to-treat (ITT) principle, where the patient's treatment group was determined only by the group to which the patient was randomly allocated, even if the patient received an incorrect treatment. All analyses were performed on the Full Analysis Set (FAS). Supportive efficacy analyses were conducted on the Per Protocol (PP) set. Baseline was defined as the latest non-missing measurement taken prior to study drug administration. Unless otherwise specified, all hypothesis tests were performed at a two-sided alpha level of 0.05. No adjustments were made for multiple comparisons.

Summary: In this study, none of the doses of TD-delivered teriparatide (30, 50, or 80 µg) was noninferior to approved SQ-delivered teriparatide 20 µg with respect to primary efficacy. The 90% CIs for the difference in LS mean percentage change in lumbar spine BMD at 12 months from baseline for each pair-wise comparison shows that none of the three lower bounds (maximum lower bound of the 3 CIs was -7.4%) of the 90% CI for the difference between treatment groups met the noninferiority margin of -3.5%. The profiles of the bone turnover markers PINP and CTX at most TD doses were different than the profiles with SQ teriparatide. Overall, transdermal teriparatide exposure was low and variable. There were no safety concerns with TD-delivered teriparatide at doses of 30, 50, and 80 µg compared to the safety profile of SQ-delivered teriparatide 20 µg.

Conclusions:

- None of the doses of TD-delivered teriparatide was noninferior to SQ-delivered teriparatide 20 µg with respect to percent change from baseline in lumbar spine BMD.
- There were no new safety concerns with TD-delivered teriparatide compared to the known safety profile of SQ-delivered teriparatide.
- LY333334 PK in the SQ cohort was consistent with Lilly's historical result. High variability in LY333334 exposure was observed from dose to dose in all three TD cohorts