INVESTIGATIONS OF INTER- AND INTRA-INDIVIDUAL RELATIONSHIPS BETWEEN ABSORPTION OF ORAL SALMON CALCITONIN AND A SURROGATE MARKER OF PHARMACODYNAMIC EFFICACY

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Purpose: The aim of the study was to compare inter- and intra-individual bioavailability of 0.8 mg of oral salmon calcitonin (sCT) given once before or after food intake to assess the relationship between bioavailability and levels of the bone resorption biomarker, serum C-terminal telopeptide of collagen type I (CTX-I).

Methods: Participants were from two randomized, double-blind, placebo-controlled studies. Study I was a cross-over trial including healthy postmenopausal women receiving a single dose of 0.8 mg of oral sCT or placebo pre-breakfast at 08:00 (n=42), pre-dinner at 17:00 (n=20), or post-dinner at 22:00 (n=19). Blood samples were taken before drug intake, and at 5, 10, 15, 30, 45 minutes, 1, 1½, 2, 2½, 3 hours, and every subsequent hour until 24 hours after dosing. Study II investigated the pharmacokinetics and pharmacodynamics of oral sCT administered on days 1 and 14 to postmenopausal women and men (n=73) suffering from osteoarthritis (OA). In one treatment arm, 0.8 mg of oral sCT was given twice daily with one dose in the morning at 08:00 and one dose given pre-dinner at 17:00 (n=26). On treatment day 1 and day 14, blood samples were taken before drug intake, and at 10, 15, 30, 45 minutes, and 1, 2, and 4 hours post-dose. In both studies the absorption of calcitonin was assessed by plasma sCT concentrations, and bone resorption by the biochemical marker of serum CTX-I.

Results: Irrespective of dosing time, a single dose of 0.8 mg oral sCT was rapidly absorbed, reaching Cmax between 15 to 30 minutes in both low and high absorbers. Following Cmax, sCT was eliminated from plasma with a half-life of between 9 and 15 minutes. Overall, a single dose of 0.8 mg oral sCT resulted in significant suppression of serum CTX-I compared with placebo irrespective of the level of absorption of sCT. At all three dosing times a significantly higher suppression of sCTX-I was observed in subjects with the highest intestinal absorption of sCT. The effect of increased absorption of sCT was a marked prolongation of serum CTX-I suppression whereas acute suppression 1 to 2 hours after dosing was unaffected. A high degree of correlation between the level of absorption of sCT and the suppression of serum CTX-I was observed at all three dosing times, i.e. a Pearson correlation coefficient of r = -0.74, r = -0.94, and r = -0.78, was found at the dose times 08:00, 17:00, and 22:00. A weak association of borderline significance was found in the intra-individual absorption of sCT on dosing days 1 and 14 with r = 0.40 and r = 0.38 at the dose times 08:00 and 17:00. As expected, the intra-individual response in serum CTX-I levels was statistically non-significantly associated on dosing days 1 and 14 with r = 0.34 and r = 0.27 at the dose times 08:00 and 17:00.

Conclusions: Increased bioavailability of orally administered 0.8 mg sCT is highly correlated with suppression of the bone resorption marker, serum CTX-I. Moreover, the effect is highly controlled with a minimum of individual variability in serum CTX-I. The variable absorption of the drug demonstrates the importance of determining the optimal conditions for ensuring a most beneficial drug uptake.