[2004] [SAT0227] CLINICAL UTILITY OF A PHARMACOSTATISTICAL MODEL FOR IBANDRONATE IN OSTEOPOROSIS

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Background: Ibandronate is a potent, nitrogen-containing bisphosphonate with proven antifracture efficacy when administered intermittently with a dosing interval of >2 months. An ongoing clinical development program is exploring the efficacy and safety of novel intermittent oral and i.v. (injection) ibandronate regimens in postmenopausal osteoporosis (PMO). To assist the selection of regimens likely to provide sustained efficacy, a pharmacostatistical model was developed using data from prior studies of ibandronate involving >700 patients, capable of describing the time course of uCTX change with oral and i. v. ibandronate.[1] The model was validated by retrospectively simulating the outcomes of additional studies of ibandronate. The model accurately described the time course of uCTX change with continuously and intermittently administered oral and i.v. ibandronate regimens.Objectives: To assist the selection of dose regimens for clinical assessment in the phase I, dose-ranging, Monthly Oral Pilot Study (MOPS) by simulating uCTX responses with oral monthly ibandronate regimens in postmenopausal women. To demonstrate the clinical utility of mathematical modelling and clinical trial simulation in the drug development process.Methods: The residual magnitude (i.e. one month after dosing) of median uCTX suppression observed with 12 cycles of several oral monthly ibandronate regimens was simulated. Simulations were replicated 100 times (per individual) in 250 'virtual' patients.Results: The predicted magnitude of residual median uCTX suppression with 100mg and 150mg oral monthly ibandronate after 3, 6, 9 and 12 months, in 100 simulated clinical trials, is reported below (table). At the studied doses, the simulations predict: a substantial magnitude of residual biomarker suppression; a strong dose-response relationship. Using the model, the following regimens were identified for clinical assessment in MOPS: 50mg, 100mg and 150mg. The recently reported findings from MOPS confirm that 3 cycles of 100mg and 150mg oral monthly ibandronate provide significant and substantial residual suppression of uCTX in postmenopausal women.[2]

Predicted median residual uCTX suppression (%) with oral monthly ibandronate

Dose	Month 3	Month 6	Month 9	Month 12
100mg	52.3–60.9	56.4–66.8	58.9–67.7	58.8–66.3
150mg	62.0–71.6	67.2–75.4	66.7–76.4	67.1–75.8

ld]Conclusion: The model was able to adequately predict the residual magnitude of uCTX suppression observed with oral monthly ibandronate. These data demonstrate the clinical utility of a pharmacostatistical model in the development of a bisphosphonate in PMO. The long-term (1 and 2 year) efficacy and safety of 100mg and 150mg oral monthly ibandronate regimens in women with PMO is being evaluated in an ongoing multinational study (Monthly Oral iBandronate In LadiEs: MOBILE).References: 1. Gieschke R, et al. Osteoporos Int 2002; 13 (Suppl. 3): S23 (Abstract P36).2. Reginster J-Y et al. Osteoporos Int 2003; 14 (Suppl. 7): S5 (Abstract OC15).

Osteoporosis Clinical aspects and treatment

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