

Urinary C-terminal telopeptide of type 1 collagen concentration as a possible biomarker for osteoporosis treatment: a direct comparison of modelling and simulation data with those actually obtained in Japanese patients with osteoporosis following a 3-year treatment with ibandronic acid

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SUMMARY

- Modelling and simulation is a well-recognised and useful tool to simulate values related to certain endpoints in clinical trials. However, only a limited number of reports are available in which direct comparative analyses have been conducted between simulated values prospectively and those actually obtained in patients.
- To examine the validity of prospective modelling and simulation methods, we conducted direct comparative analyses between prospective simulated data and real-life data obtained in a phase III trial of ibandronic acid (IBN) in Japanese patients with osteoporosis.

INTRODUCTION

- IBN is a potent, nitrogen-containing bisphosphonate that provides significant increases in vertebral and non-vertebral bone mineral density (BMD) when administered as an intravenous (i.v.) injection to patients with osteoporosis.^{1–3}
- In a randomised, double-blind, phase II trial in Japanese women with postmenopausal osteoporosis, 6 months of treatment with i.v. IBN substantially increased lumbar spine BMD and significantly reduced bone turnover markers compared with placebo.⁴
- Furthermore, 3 years of treatment with monthly i.v. IBN was found to be non-inferior to risedronate (the licensed Japanese daily oral dose) in terms of vertebral fracture risk reduction in a randomised, double-blind, phase III trial (MOVER study) in Japanese patients with primary osteoporosis.⁵
- We present the results of an analysis of simulated data based on the randomised phase II study⁴ compared with real-life data, obtained in the phase III trial described above,⁵ with the aim of optimising the response to IBN therapy in patients with osteoporosis.

METHODS

- Modelling and simulation were performed based on urinary C-terminal telopeptide of type 1 collagen concentration (uCTX) and lumbar spine (L2–L4) BMD responses obtained in a randomised, phase II, clinical trial in which i.v. IBN was administered monthly or bimonthly for 6 months to Japanese patients with osteoporosis (Figure 1).⁴

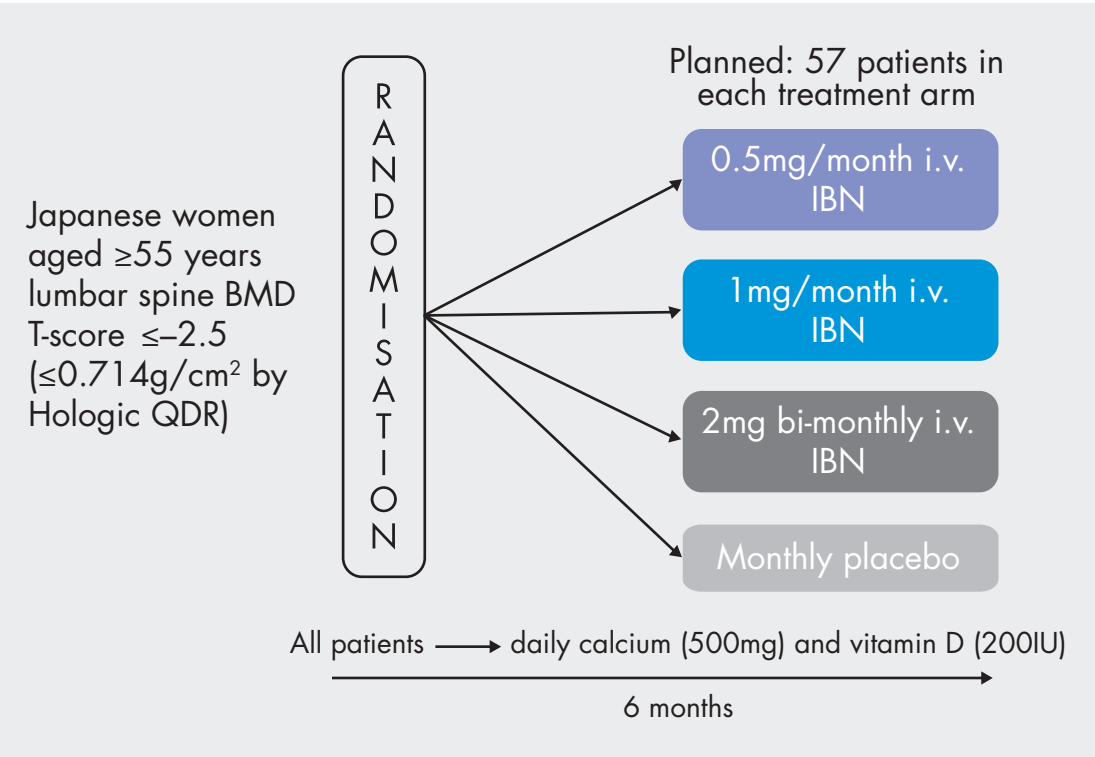


Figure 1. Randomised, double-blind, placebo-controlled phase II clinical trial in Japanese patients with osteoporosis.⁴

- The parameters in the modelling and simulation included the dosage of IBN and the uCTX and BMD values (Table 1); the association between each of these parameters was analysed as previously described (Figure 2).⁶

Table 1. Number of uCTX and BMD values obtained from the phase II clinical trial used for the modelling.

Group	Patients, n	uCTX		BMD	
		Sampling time	Samples, n	Sampling time	Samples, n
0.5mg/month IBN	52	Predose, 1, 2, 3, 4, 5 and 6 months	341	Predose, 4 and 6 months	147
1mg/month IBN	56		384		165
2mg/2months IBN	49		334		143
Placebo	55		371		159
Total	212		1430		614

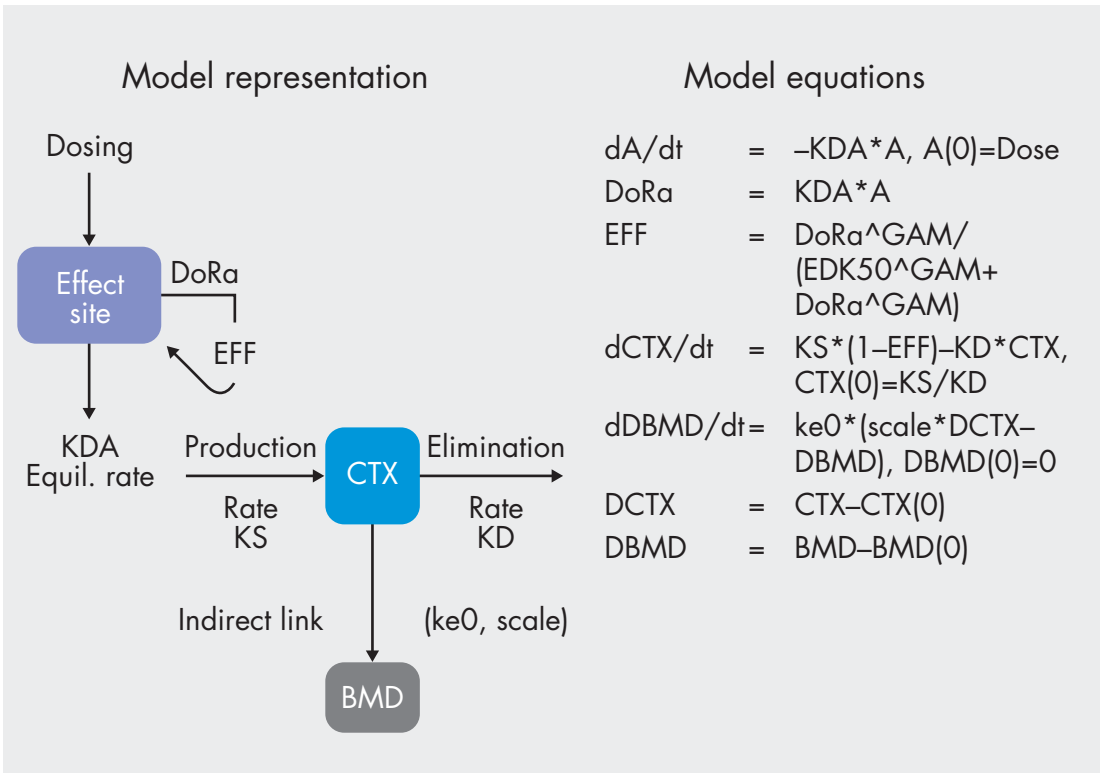


Figure 2. Schematic representation of the uCTX-BMD model for IBN.⁶

- The estimated model parameter values are shown in Table 2.
- The uCTX-BMD model accurately captured the BMD values obtained in the phase II clinical trial (Figure 3).

Table 2. Model parameter values estimated.

Model parameters	Population mean
uCTX	
KDA (1/day)	0.014
KS (µg/mmol cre/day)	255
KD (1/day)	1.06
EKD50 (µg/day)	17.2
GAM	0.916
SLOPE (1/day)	0.000232
VIT (µg/mmol cre/day)	0.314
KVIT (1/day)	0.012
BMD	
Scale (g/cm ²)/(µg/mmol cre/day)/10 ^{−4}	2.96
ke0 (1/day)	0.00338

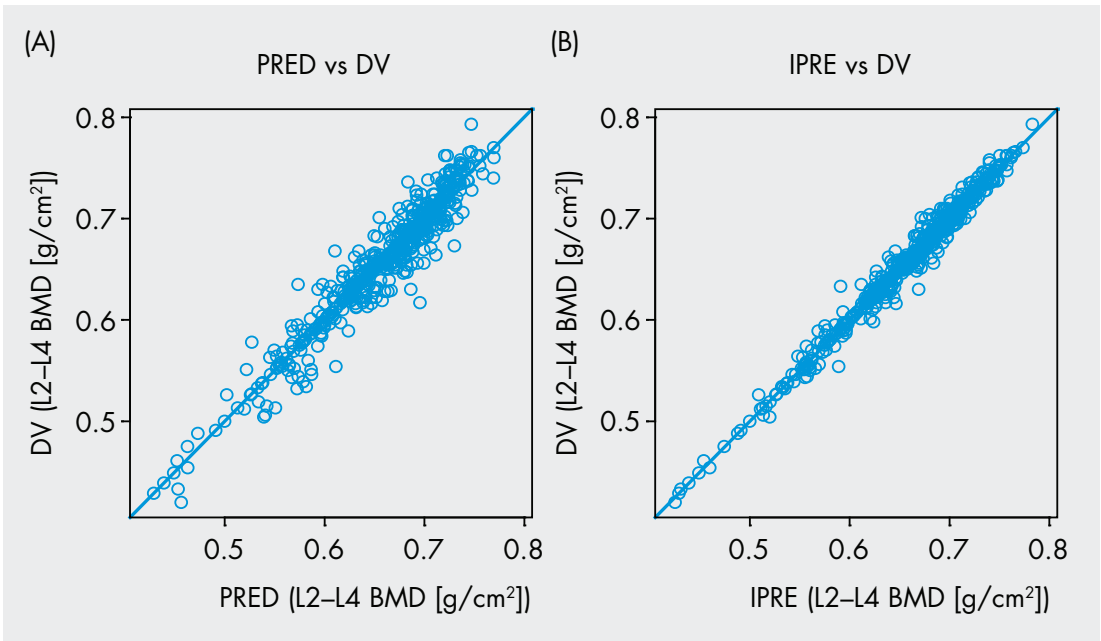


Figure 3. Observed and predicted lumbar spine BMD responses in the phase II clinical trial.

- Using the described model, simulation was performed to determine the BMD response achievable in a randomised, double-blind, phase III clinical trial, in which Japanese patients with primary osteoporosis received i.v. IBN (0.5mg or 1mg) for up to 3 years.

RESULTS

- Clear dose response of BMD at 3 years was simulated between 0.5mg/month and 1mg/month i.v. IBN (Figure 4).
- The design of the phase III clinical trial is shown in Figure 5.

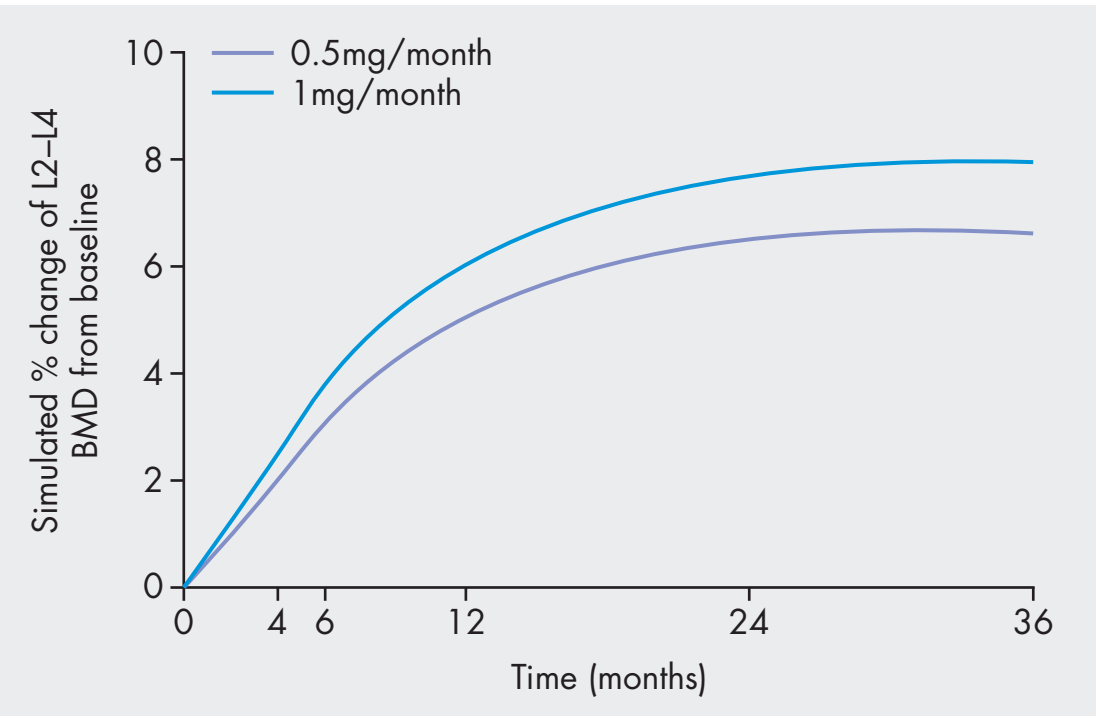


Figure 4. Prospectively simulated mean lumbar spine BMD responses in the phase III clinical trial.

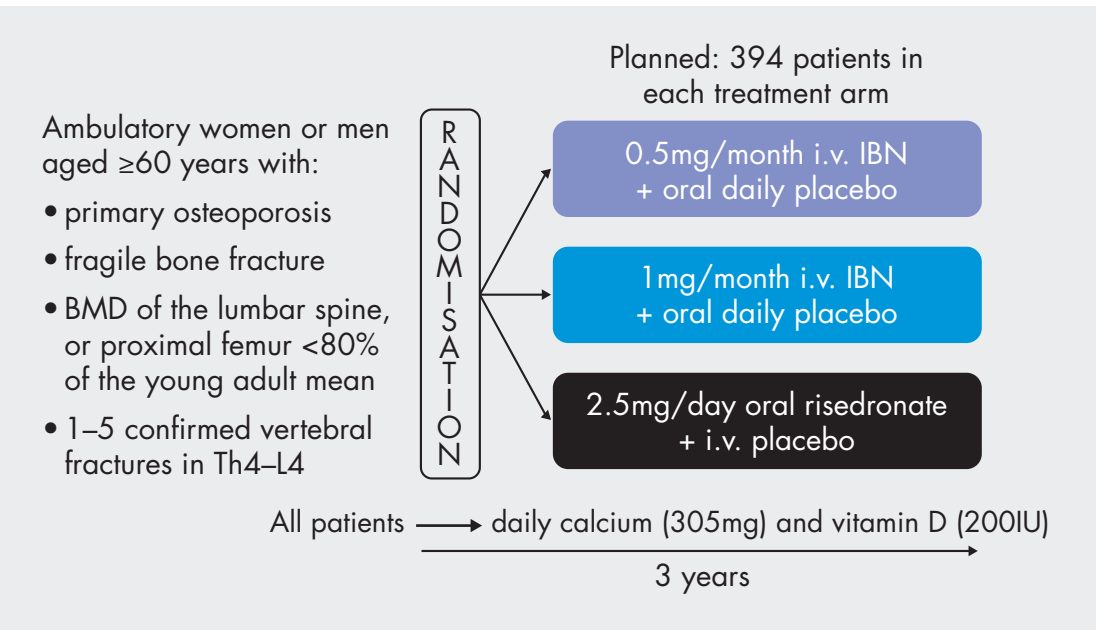


Figure 5. Randomised, double-blind phase III trial in Japanese patients with primary osteoporosis.⁵

- At a dose level of 1mg/month i.v. IBN, the simulated median BMD changes from baseline at the lumbar spine in the phase III trial were 3.70%, 6.60%, 7.66% and 7.91%, after 6, 12, 24 and 36 months, respectively (Table 3).

Table 3. Similarity of prospectively simulated and observed lumbar spine BMD changes.

Time, months	Change from baseline in L2–L4 BMD, %					
	0.5mg/month IBN			1mg/month IBN		
	Simulated	Observed	Mean	Simulated	Observed	Mean
6	3.02	3.74	4.44	3.70	4.46	5.11
12	5.09	4.54	5.57	6.60	5.69	6.51
24	6.48	5.66	6.47	7.66	6.87	7.96
36	6.60	6.87	7.68	7.91	8.01	9.02

- Thus, there was good agreement between simulated and actual median BMD values obtained in the phase III trial (<20% difference between the two).

Conclusions

- This study verified the merits of modelling and simulation for predicting clinical effects of IBN in patients with osteoporosis.
- Beneficial lumbar spine BMD gains achieved following IBN treatment were simulated in a quantitative manner.
- Modelling and simulation has the ability to significantly shorten drug development times, particularly for osteoporosis treatments.

Acknowledgements

- The phase II study was sponsored by Chugai Pharmaceutical Co. Ltd, Japan. The phase III study was jointly sponsored by Chugai Pharmaceutical Co. Ltd and Taisho Pharmaceutical Co. Ltd, Japan. Support for third-party writing assistance for this poster was provided by Chugai Pharmaceutical Co. Ltd.

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