A semimechanistic and mechanistic population PK–PD model for biomarker response to ibandronate, a new bisphosphonate for the treatment of osteoporosis

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Aims

Ibandronate, a highly potent nitrogen-containing bisphosphonate, is the subject of an ongoing clinical development programme that aims to maximize the potential of simplified, less frequent oral and intravenous (i.v.) administration in osteoporosis. A modelling and simulation project was undertaken to characterize further the clinical pharmacology of ibandronate and identify convenient intermittent oral and i.v. regimens for clinical evaluation.

Methods and results

Using selected data from clinical studies involving 174 women with postmenopausal osteoporosis (PMO), a classical multicompartmental pharmacokinetic-pharmacodynamic (PK-PD) model was developed that accurately described the PK of i.v. ibandronate in plasma and urine and urinary excretion of the C-telopeptide of the α chain of type I collagen (uCTX), a sensitive biomarker of PD response to ibandronate. To reduce processing times, the classical PK-PD model was simplified using a 'kinetics of drug action' or kinetic (K)-PD model (i.e. a dose-response model as opposed to a dose-concentration-response model). The performance of the K-PD model was evaluated by fitting data simulated with the PK-PD model under various dosing regimens. The simplified model produced a virtually indistinguishable fit of the data from that of the PK-PD model. The K-PD model was extended to consider the influence of supplemental therapy (calcium with or without vitamin D) on the PD response and validated by retrospectively simulating the uCTX response in a prior Phase III and Phase II/III study of i.v. ibandronate, given once every 3 months, in 3380 women with PMO. The observed median uCTX responses at the scheduled assessment points in the completed studies were within the distribution of the simulated responses. The K-PD model for i.v. ibandronate was extended further to allow simultaneous fitting of uCTX responses after i.v. and oral administration in 676 postmenopausal women with osteoporosis, and validated by retrospectively simulating the data observed in a Phase I study of oral daily ibandronate in 180 women with PMO. The K-PD model adequately described the uCTX response after oral dosing.

Conclusions

This validated K-PD model is currently being used to evaluate a range of novel intermittent oral and i.v. ibandronate regimens in an ongoing clinical development programme.

Introduction

Osteoporosis is a chronic disease characterized by low bone mass and microarchitectural deterioration of bone tissue, resulting in increased bone fragility and susceptibility to fracture [1]. In women, osteoporosis is most commonly associated with the menopause, with declining oestrogen concentrations resulting in subtle changes in bone metabolism [2]. Most notably, oestrogen depletion is thought to result in the dysregulation of osteoclast activity, causing an imbalance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation. Bone resorption exceeds bone formation, resulting in a net loss of bone mineral and the progressive loss of bone strength.

Bisphosphonates are potent antiresorptive agents that possess high affinity for bone mineral [3]. Following administration, bisphosphonates accumulate rapidly at bone mineral surfaces, from where they are released slowly (with a half-life of months to years). At sites of active bone resorption, surface-bound bisphosphonates interfere with the action of osteoclasts, and potentially osteoclast precursor cells, resulting in reduced resorptive activity. In this way, bisphosphonates are able to correct the imbalance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation associated with oestrogen depletion. This prevents further bone loss and, in many cases, induces a net gain in bone mineral density. Accordingly, bisphosphonates are considered by many as agents of first choice for the management of postmenopausal osteoporosis (PMO).

Although highly effective, current oral bisphosphonates for the treatment and prevention of osteoporosis must be administered continuously (daily or weekly) [4], and in accordance with stringent dosing recommendations. However, the inconvenience of frequent dosing and need for compliance with rigid dosing guidelines is believed to compromise long-term patient adherence, potentially jeopardizing therapeutic outcomes. Indeed, studies suggest that compliance with daily regimens is low and less than that reported in clinical trials [5]. A strong patient preference for less frequent than daily regimens has also been reported [6]. Accordingly, novel treatment options that enhance patient convenience through less frequent dosing are predicted to promote long-term adherence to therapy. Alternative dosing regimens that avoid the stringent recommendation associated with oral administration, such as intravenous (i.v.) injection, may also be preferred by some patients.

Ibandronate, a highly potent nitrogen-containing bisphosphonate, is the subject of an ongoing clinical development programme that aims to exploit the potential of less frequent dosing in PMO. To date, ibandronate has

been shown to provide lasting efficacy when administered as a continuous oral daily [7, 8] and weekly [9] regimen, and as a novel intermittent regimen with a between-dose interval of more than 2 months [8, 10]. Moreover, the efficacy and favourable tolerability of ibandronate when administered as a novel and convenient i.v. injection given once every 3 months has also been demonstrated [11–13].

In light of these positive findings, additional clinical studies are planned, which will evaluate novel intermittent oral and i.v. dosing regimens, the aim of which is to identify schedules offering optimal efficacy, tolerability and patient convenience. These factors are of critical importance, given the unlimited number of dosage combinations and the extended duration of study required for the clinical evaluation of osteoporosis drugs [6–12 months for the assessment of bone mineral density (BMD) response *vs.* 3–5 years for the assessment of antifracture efficacy). Clearly, the ability to predict and evaluate a physiological response to a 'virtual' ibandronate regimen prior to clinical assessment would be of significant value.

Modelling and simulation techniques are routinely used in areas other than the pharmaceutical industry to design and develop products more efficiently and safely [14, 15]. Recent years have seen the implementation of modelling and simulation techniques in the drug development process [16–20]. Such an approach focuses on the development of a pharmacostatistical model which consists of two parts: a mathematical model based on a pharmacokinetic-pharmacodynamic (PK–PD) hypothesis related to the underlying physiological process and the presumed pharmacological action(s) of the drug concerned, and a superimposed nonlinear mixed-effects model for the characterization of between-subject variability in model parameters and residual error in the response [21–23]. Validation of the model is then achieved by external validation, *i.e.* by retrospectively simulating the data from completed clinical studies but without using these data for model development. These simulations are based on Clinical Trial Simulation, a process for combining premises/assumptions to generate large numbers of replications of 'virtual' (representations of actual) clinical studies. Notably, each replicate of a computer-simulated trial is viewed as one realization from a probability distribution of all possible study outcomes with the same design properties (or system parameters). The emphasis is on forecasting expected study outcomes, exploring the sensitivity of the outcome to system parameters and covariates, and understanding the influence of the premise and model on the study outcome.

Here, we describe a modelling and simulation project that was performed to assist the identification of novel intermittent oral and i.v. dosing regimens for ibandronate. The principle aim of the project was to develop and validate a pharmacologically realistic mathematical model for ibandronate in osteoporosis, capable of describing its PK in serum and urine, and the urinary excretion of the C-telopeptide of the α chain of type I

collagen (uCTX), a sensitive PD biomarker of osteoclast-mediated bone resorption.

Methods

Sources of data

Tables 1 and 2 summarize the studies whose data were used in the development and validation, respectively, of the pharmacostatistical model for ibandronate in

Table 1

Details of the studies used in the development of the pharmacostatistical model for ibandronate in osteoporosis

Study	MF9853	Thiebaud <i>et al.</i> [11]	Delmas <i>et al.</i> [8]
Objectives	Phase I evaluation of the PK and PD of i.v. ibandronate injections, given once every 3 months	Phase I dose-finding study of i.v. ibandronate injections, given once every 3 months	Phase III evaluation of the fracture efficacy of oral daily ibandronate
Subjects	Postmenopausal (Japanese) women with osteopenia ($n = 50$)	Postmenopausal (Caucasian) women with osteoporosis ($n = 124$)	Postmenopausal (Caucasian) women with osteoporosis ($n = 676$)
Regimen	Two consecutive i.v. injections of ibandronate (0.25 mg, 0.5 mg, 1 mg, 2 mg) or placebo, given once every 3 months,	Four consecutive i.v. injections of ibandronate (0.25 mg, 0.5 mg, 1 mg, 2 mg) or placebo, given once every 3 months, plus oral daily calcium and vitamin D	Oral daily ibandronate (2.5 mg) or placebo plus oral daily calcium and vitamin D
PK sampling [parent drug in plasma and urine (h)]	Dose 1: 0.083, 0.5, 1, 2, 4, 12, 24, 36, 48 Dose 2: 0.083, 12, 24, 36, 48	Not collected	Not collected
PD sampling [uCTX excretion (days)]	Dose 1: 0, 1, 4, 8, 15, 29, 57 Dose 2: 0, 1, 2, 3, 4, 8, 15, 29, 57, 92	0, 30, 60, 90, 180, 270, 300, 330, 360, 450	0, 90, 180, 360, 720, 1080

Table 2

Details of the studies used in the validation of the pharmacostatistical model for ibandronate in osteoporosis

Study	Adami <i>et al.</i> [13]	Recker <i>et al.</i> [12]	Ravn <i>et al.</i> [7]
Objectives	Phase II/III evaluation of the dose-response relationship and efficacy of i.v. ibandronate injections, given once every 3 months, for 1 year	Phase III evaluation of i.v. ibandronate injections, given once every 3 months, for 3 years	Phase II dose-finding study of oral daily ibandronate
Subjects	Postmenopausal (Caucasian) women with osteoporosis ($n = 520$)	Postmenopausal (Caucasian) women with osteoporosis ($n = 2860$)	Postmenopausal (Caucasian) women with osteopenia ($n = 180$)
Regimen	I.v. injections of ibandronate (1 mg, 2 mg) or placebo, given once every 3 months, plus oral daily calcium and vitamin D	I.v. injection of ibandronate (0.5 mg, 1 mg) or placebo, given once every 3 months, plus oral daily calcium and vitamin D	Oral daily ibandronate (0.25 mg, 0.5 mg, 1 mg, 2 mg, 5 mg) or placebo, plus oral daily calcium and vitamin D
PK sampling	Not collected	Not collected	Not collected
PD sampling [uCTX excretion (days)]	0, 90, 180, 270, 360	0, 30, 60, 90, 180, 270, 300, 330, 360, 450	0, 90, 180, 270, 360, 450

osteoporosis. All subjects who participated in these studies provided written informed consent. The institutional review board at each site approved the relevant study protocol.

Analytical procedures

Ibandronate A validated ELISA assay for ibandronate in serum (data on file [24]); and urine (data on file) was used. The between-run coefficient of variation (CV) for the assay was between 5.9% and 8.7% in the concentration range 150–1000 pg ml⁻¹. The corresponding within-run CV was between 3.8% and 4.3%. The lower limit of quantification was 50 pg ml⁻¹.

Serum concentrations of ibandronate were also assayed using GC-MS methodology (details on file). The between-run CV was between 3.9% and 6.9% in the concentration range 10–5000 ng ml⁻¹. The corresponding within-run CV was 3.5–5.4%. The lower limit of quantification was 1 ng ml⁻¹.

uCTX uCTX excretion was measured using a standard ELISA assay (Crosslaps[®], Osteometer, Denmark). All measurements were corrected for variation in urine volume using creatinine concentrations measured at the same time. The intra- and interassay CV was 5.1% and 4.0%, respectively, and the detection limit was 0.2 µg ml⁻¹.

Data analysis

Model development and simulation were performed using nonlinear mixed-effect modelling within the program NONMEM, version 5, level 1. Double precision and first-order estimation were used [25]. All NONMEM data files were prepared using SAS version 6.12 (SAS Institute, Cary, NC, USA), whereas postprocessing of the NONMEM output (e.g. diagnostic graphics) used S-Plus (Insightful Corporation, Seattle, WA, USA). Simulation of clinical trials was conducted using Pharsight Trial Simulator version 2.1.1 (Pharsight Corporation, Mountain View, CA, USA). The hardware platform comprised 800-Mhz Pentium III processors with 320 Mb RAM running under Microsoft Windows NT4.0.

Results

A four-compartment PK model was combined with an indirect response PD model (Figure 1) [26]. A three-compartment model was adequate to describe the serum and urine concentration *vs.* time profile of ibandronate. A fourth PK compartment was introduced into the model to allow a link to the PD response that was not

where:
 Dose = ibandronate dose
 v_1 – v_4 = volumes of PK distributional compartments 1–4, respectively
 CL = renal clearance
 Ae = amount excreted in urine
 uCTX = urinary CTX
 KS = uCTX formation rate
 KD = uCTX degradation rate constant

Figure 1

Schematic representation of the four-compartment pharmacokinetic (PK) and indirect response pharmacodynamic (PD) model with the appropriate equations

identifiable (because of inadequate duration of PK sampling and/or the drug concentration likely to be below the lower limit of quantification of the assay) from the PK alone. This fourth compartment is labelled 'Bone' in Figure 1. Ibandronate clearance (CL) was assumed to be *via* a single route. Ibandronate was assumed to inhibit osteoclast activity and, hence, the rate of synthesis (KS) and the urinary excretion of CTX. The time-dependence in KS, which was noted from the raw data (especially for the 1-mg and 2-mg doses), was incorporated by allowing this parameter to reach a target value (R_{tar}) at a rate governed by a first order rate constant (k_{qq} ; see Appendix for equations relating to Figure 1).

The complex 'physiological' PK-PD model adequately described the PK of intravenously administered ibandronate in serum (Figure 2) and urine (not shown) and the time course of uCTX in study MF9853 (Figure 3). For the 3-monthly regimen, the population estimate for the new target synthesis rate (R_{tar}) was 16% lower than the baseline KS and the half-life for its attainment ($\ln 2/k_{qq}$) approximately 40 weeks (Table 3). Inter-individual variability in k_{qq} was large (475%) and was estimated with a degree of uncertainty (39%). Examination of long-term data from a Phase III study of i.v. ibandronate [13] indicated a rapid attainment of the new target rate of uCTX synthesis. Thus, since the time-dependent change in KS was highly variable, poorly estimated and of limited magnitude, this function was not included in its current form in subsequent stages of model development.

Figure 2

Population prediction and observed serum ibandronate concentration vs. time profiles for the four-compartment pharmacokinetic-pharmacodynamic (PK-PD) model in the four dose groups (study MF9853). Observation after dose one (*), observation after dose two (○), prediction after dose one (—), prediction after dose two (---)

Although the complex 'physiological' PK-PD model described the data well, its major disadvantages were the long computer run-times (~ 5 days on a Pentium 800-MHz PC) and the numerical difficulties associated with solving a rather stiff problem, i.e. where rate constant values for the PK and PD time courses varied over a wide range. Attempts were therefore made to simplify the model.

Several authors have suggested methods for analysing dose-response time data in certain defined situations, where it may be convenient to 'abstract' the PK [27, 28]. The features of the ibandronate PK-PD system, with the large difference in the time course of ibandronate PK (hours) and the PD (weeks) response, suggested that an 'abstraction' of the PK might be appropriate. Thus, to reduce the computer run-times associated with the PK-PD model, a 'kinetics of drug action' or K-PD model, as described by Jacqmin *et al.* [28], was employed.

A schematic representation of the K-PD model is presented in Figure 4. The reduction in the uCTX formation rate (KS) in response to i.v. ibandronate is modelled with a sigmoid $E_{\max}$ model, in which the independent variable is a virtual dose-driving rate (DODR). This is defined as the product of the first order equilibration rate (KDE) from a virtual compartment (into which the drug is administered) and the amount in this compartment. The KDE is analogous to the KEO in the link model [29]. EKD_{50} represents the DODR that leads to a 50% inhibition of KS. The K character in EKD_{50} indicates that, besides variability in PD, the apparent potency of the drug is also influenced by the dosing form and PK variability (see Appendix for equations relating to Figure 4).

The K-PD model has considerably fewer parameters than the complex four-compartment PK-PD model. Therefore, the estimated PD parameters from the two

Figure 3

Population prediction and observed uCTX excretion vs. time profiles for the four-compartment pharmacokinetic-pharmacodynamic (PK-PD) model (study MF9853). Observation after dose one (*), observation after dose two (○), prediction after dose one (—), prediction after dose two (---)

Figure 4

Schematic representation of the kinetic-pharmacodynamic (K-PD) model used to describe the time course of uCTX excretion in the absence of pharmacokinetic data with the appropriate equations

models are not directly comparable with regards to their numerical values. The better comparison is that between the ability of the models to describe the data. The K-PD model resulted in a fit to the data from study MF9853 that was virtually indistinguishable from that of the PK-PD model (Figure 5). Moreover, this result was achieved with a significant saving in terms of computer run-times. Thus, the K-PD model converged in ~ 2 h, whereas a single run of the complex PK-PD model converged in ~ 5 days.

To increase confidence in the simplified model, the K-PD model was subjected to a validation procedure, in which data simulated with the PK-PD model were fitted with the K-PD model. The objective was to confirm the invariance of the parameters of the K-PD model in conditions where the total-dose exposure was kept constant but where the schedule of administration was varied. This was of particular importance, as a primary objective of this *in numero* study was to develop a model that could evaluate the PD response associated with different dosing schedules for ibandronate.

In the validation procedure, data from 100 subjects were simulated in NONMEM using the complex PK-

Table 3

Parameters of the 'classical' four-compartment pharmacokinetic-pharmacodynamic (PK-PD) model for the urine and serum PK of ibandronate and uCTX response to i.v. administration of ibandronate

	Estimate	BSV (CV %)	RSE (CV %)
<i>PK parameters</i>			
V1 (l)	4.30	17	4
CL (l day ⁻¹)	57.00	20	5
V2 (l)	2.80	–	4
Q2 (l day ⁻¹)	69.43	–	13
V3 (l)	8.70	–	5
Q3 (l day ⁻¹)	18.57	Small	5
V4 (l)	609.00	–	9
Q4 (l day ⁻¹)	51.71	3	4
<i>PD parameters</i>			
KS (µg mmolCR ⁻¹ day ⁻¹)	231.43	84	10
IC ₅₀ (µg l ⁻¹)	0.37	40	8
uCTX _{ss} (µg mmolCR ⁻¹)	339	34	5
R _{tar} (µg mmolCR ⁻¹ day ⁻¹)	194.29	–	15
k _{qq} (1 day ⁻¹)	0.0024	475	39
Hill coefficient	1.92	–	9
<i>Derived parameters</i>			
KS at 26 weeks (µg mmolCR ⁻¹ day ⁻¹)	218.00		
uCTX at 26 weeks (µg mmolCR ⁻¹)	319		
k _{qq} half-life (weeks)	40		
KD (1 day ⁻¹)	0.68		
k _{qq} (1 day ⁻¹)	0.0024		
<i>Residual error</i>			
Plasma ibandronate concentration (% CV)		16	
Urine ibandronate amount (% CV)		44	
uCTX concentration (% CV)		27	
NONMEM objective function		–2221	

BSV, Between-subject variability; CV, coefficient of variation; RSE, relative standard error; V1-V4, volumes of PK distributional compartments 1-4, respectively; Q2-Q4, intercompartmental clearance between compartment 1 and the PK distributional compartments 2-4, respectively; KS, synthesis rate (uCTX); uCTX_{ss}, steady-state uCTX concentration; KD, degradation rate constant (uCTX); IC₅₀, ibandronate concentration in 'bone' compartment producing half maximum inhibition of uCTX formation; CL, renal clearance of ibandronate; HILL, shape factor; uCTX, urinary CTX; R_{tar}, limit value for uCTX formation rate (T→); k_{qq}, rate constant by which R_{tar} is attained.

PD model for a total cumulative dose of ~ 8 mg (i.v.) ibandronate per year, given as follows: 2 mg given once every 3 months; 0.667 mg given once monthly; 0.167 mg given once weekly; and 0.0222 mg given once daily. The K-PD model was fitted to the simulated data under two conditions: using a sigmoidal $E_{\max}$ model (EKD₅₀ = 0.4; Hill coefficient = 2.27) and using a simple $E_{\max}$ model (EKD₅₀ = 0.04; Hill coefficient = 1). $E_{\max}$ model parameters (EKD₅₀ = 0.4; Hill coefficient = 2.27) were taken from a fit of MF9853 by the four-compartment PK-PD model NONMEM run, as described above. A 10-fold lower EKD₅₀ value was also chosen to explore the sensitivity of the model with respect to potency.

These analyses indicated that the K-PD model for ibandronate is stable under both modelling assumptions (sigmoidal $E_{\max}$ and simple $E_{\max}$) for dosing intervals of up to 1 week. However, with once-daily administrations, the model appeared to be over-parameterized, as reducing the number of parameters to be estimated (by fixing KD) also resulted in stable estimates for once-daily dosing. This is because the offset was not contained in the simulated once-daily dosing data, unlike other regimens. Thus, our conclusion from this exercise was that, in addition to providing a satisfactory fit of the data, the simplification offered by the K-PD model was likely to result in stable analyses for the drug given once weekly or even less frequently.

Figure 5

Typical fits for the kinetic-pharmacodynamic (K-PD) and the pharmacokinetic-pharmacodynamic (PK-PD) models in arbitrarily chosen subjects from each dose group in study MF9853. Observation in MF9853 (○), individual prediction (—), population prediction (----)

Figure 6a,b indicates that the PD response to i.v. ibandronate was different in study MF9853 and the Phase I dose-finding [11], especially with respect to the rate of uCTX excretion. This was probably due to the administration of supplementary calcium in the Phase I dose-finding study. A combined fit to the data from these two studies was considered important, since they separately provided complementary information that could be exploited within the population mixed-effects analysis paradigm. The schedule of uCTX assessments in study MF9853 provided detailed information on the onset and nadir of the uCTX response, whereas the relatively sparse data from the Phase I dose-finding study gave information on the influence of daily oral calcium supplementation. As the administration of supplemental therapy is indicated in clinical studies of antiresorptive agents [30], it was essential to consider the influence of this variable in model development.

The effect of supplemental therapy was introduced as a covariate effect on the KDE parameter of the K-PD model, since evaluation of systematic parameter variation revealed that this parameter was the most sensitive in our reference parameter space. For all subjects, a linear change in uCTX excretion over time was assumed to be a measure of disease progression. The 'pure' placebo arm in study MF9853 was used to provide an estimation of this parameter. An additive interindividual error model was used for this 'pure' placebo effect to account for the positive and negative changes in uCTX excretion from baseline noted from the raw data from MF9853 (Figure 6b) and in other clinical studies (on file). In the Phase I dose-finding study, the uCTX response associated with supplemental therapy in the 'placebo' arm was measured over a longer time period and could be described using an exponential decrease in uCTX over time.

Figure 6

Time course of the mean change in uCTX (%) after (a) four consecutive i.v. ibandronate doses, once every 3 months, plus calcium and vitamin D [11] and (b) after two consecutive i.v. ibandronate doses, once every 3 months (MF9853). Placebo (○), 0.25 mg (△), 0.5 mg (+), 1.0 mg (×), 2.0 mg (◇)

The model developed for uCTX response after coadministration of i.v. ibandronate and supplemental therapy was validated by retrospectively simulating uCTX response observed in a Phase III [12] and Phase II/III [13] study of i.v. ibandronate (Table 2; Figure 7). As the data from these two studies were not used in model development, this procedure represents a rigorous external validation of the model.

In Figure 7, each circle represents one replicate of a clinical trial and is the median uCTX concentration observed in 250 simulated subjects expressed as the change (%) from baseline. The trial was replicated 100 times and it is reassuring that the median uCTX responses observed at the scheduled assessment points in the completed studies for the 0.5-mg, 1-mg and 2-mg intermittent (once every 3 months) i.v. ibandronate regimens lie within the distribution of the simulated

responses. However, in the case of the placebo arm, the model predictions were less satisfactory, being higher at three, lower at two and within the range at two of the observation points.

Population PK analysis of Phase I and Phase II data estimated the oral bioavailability of ibandronate to be between 0.7 and 0.8% [31], with an interindividual CV of 52–67%, depending on the dose. The model developed for uCTX response after i.v. administration of ibandronate was extended to allow simultaneous fitting of i.v. and oral data using this estimate of oral bioavailability (Figure 4, Appendix).

The parameters of the final K-PD model for the uCTX response after i.v. and oral administration of ibandronate, with and without supplemental therapy, are shown in (Table 4). These had acceptable precision, as shown by the small estimates of relative standard error (all $\leq 22\%$).

Figure 8 depicts the simulated and observed response to uCTX after oral daily ibandronate and supplemental therapy [7]. Each circle represents one replicate of a clinical trial and is the median uCTX concentration observed in 250 simulated subjects expressed as the change (%) from baseline after oral ibandronate administration. The simulated trials were replicated 100 times, and the observed median response for all dose arms lies within the distribution of responses simulated using the model. Thus, the K-PD model for i.v. ibandronate is also able to predict the response after oral administration of the drug by correcting the dose for oral bioavailability.

Discussion

Biochemical markers of bone turnover provide a rapid and accessible means of evaluating physiological responses to antiresorptive therapies. Recent evidence also suggests an association between the magnitude of biomarker suppression and likely response in terms of BMD change and fracture risk reduction [32–34]. This association suggests that these biomarkers are on the causal pathway for prevention of fracture following administration of bisphosphonates. As such, biochemical markers of bone turnover can offer a timely indication of the likely efficacy associated with nominal dosing regimens, be they continuous (e.g. daily or weekly) or intermittent (beyond once weekly).

As an extended duration of study and large number of patients are required to demonstrate fracture efficacy with antiresorptive agents, methods for evaluating nominal treatment regimens prior to clinical assessment may be of considerable value in optimizing study outcomes, shortening the clinical development process and safeguarding often substantial investments. An ability to

Figure 7

Simulated uCTX response after i.v. ibandronate administration with calcium and vitamin D. Each circle represents one replicate of a clinical trial and is the median uCTX concentration observed in 250 simulated subjects. Simulated median (○), observed median in Recker *et al.*, 2000 (*), observed median in Adami *et al.*, 2002 (#) solid line shows simulated profile for the typical individual

simulate biomarker responses to novel intermittent bisphosphonate regimens prior to clinical evaluation would be likely to assist in identifying the most suitable regimens for clinical assessment.

In the current study, a mathematical model, representing a simplified abstraction of the underlying physiological process and drug effect, was developed to describe the time course of the change in uCTX, a sensitive biomarker of bone turnover and the action of ibandronate, in response to oral and i.v. intermittent ibandronate regimens in women with PMO. A classical PK-PD model was developed that described accurately the PK of intravenously administered ibandronate and the effect on uCTX PD. By ‘abstracting’ the PK of ibandronate, the PK-PD model was simplified to form a ‘kinetics of drug action’ or K-PD model, giving an essentially identical performance to the PK-PD model. However, as a consequence of reduced computation times, results could be obtained in a much shorter time

period (~ 2 h with K-PD model *vs.* ~ 5 days with PK-PD model). The model was subsequently extended to consider the influence of supplemental therapy on the PD response and subjected to ‘external validation’ by retrospectively simulating the time course of uCTX change reported in a Phase III study [12] and Phase II/III study [13] of i.v. ibandronate. The median uCTX responses observed at the scheduled assessment points were within the distribution of the simulated responses. By correcting the dosing rate for oral bioavailability, the model was extended further to allow the simultaneous fitting of i.v. and oral data, and validated by retrospectively simulating biomarker responses observed in a Phase I dose-finding study of oral ibandronate [7]. The final K-PD model adequately described the uCTX response following oral dosing in women with PMO.

In general, model parameters were estimated with good precision (Table 4), reflecting the rich information content of the data. The estimate for the linear slope for

Table 4

Parameters of the kinetic-pharmacodynamic (K-PD) model for the uCTX response to i.v. and oral administration of ibandronate, with and without calcium coadministration

	Estimate	BSV (CV %)	RSE (CV %)
KS ($\mu\text{g mmolCR}^{-1} \text{ day}^{-1}$)	255.00	26	7
KD (1 day^{-1})	1.06	34	7
EKD ₅₀ ($\mu\text{g day}^{-1}$)	17.20	83	8
KDE (MF9853; 1 day^{-1})	0.112	30	13
KDE (MF4361/MF4411; 1 day^{-1})	0.014	139	11
Hill coefficient	0.913	—	10
SLOPE for placebo (1 day^{-1})	2.32E-04	3.16E-07*	22
VIT ($\mu\text{g mmolCR}^{-1} \text{ day}^{-1}$)	0.314	50	8
KVIT (1 day^{-1})	0.012	192	20
F (2.5 mg)	0.008	52	—
F (20 mg)	0.007	67	—
Residual error (%)	33		
NONMEM objective function	-2951		

BSV, Between-subject variability; CV, coefficient of variation; RSE, relative standard error; KS, synthesis rate (uCTX); KD, degradation rate constant (uCTX); EKD₅₀, dose rate resulting in 50% inhibition of KS; KDE, first-order equilibration rate of the 'virtual' effect compartment—different values for studies with [8, 11] and without (MF9853) supplemental calcium and vitamin D therapy; VIT, effect elicited by calcium and vitamin D supplementation; SLOPE, relative increase in uCTX per day following placebo treatment (disease progression); KVIT, first-order rate constant for attainment of VIT; F, oral bioavailability of ibandronate obtained from a separate NONMEM analysis of an absolute bioavailability study [30]. *BSV for slope is modelled as additive and reported as variance.

Figure 8

Simulated uCTX response after oral daily ibandronate administration with calcium and vitamin D. Each circle represents one replicate of a clinical trial and is the median uCTX concentration observed in 250 simulated subjects. Simulated median (○), observed median in Ravn *et al.*, 1996 (△)

the effect of 'pure' placebo ('disease progression') was small (0.7% per month). This effect was also observed in long-term studies of i.v. [11] and oral [8] ibandronate. This estimate for mean disease progression is likely to be reasonably accurate, as at the end of the growth period of life in humans, bone mass, and hence osteoclast activity, are very stable over much of the remaining lifespan. However, there is an increase in the loss of bone mass after menopause that lasts for varying periods of time in different patients. In the model, the random effect (BSV) on the slope parameter was additive, i.e. individual subjects could have either a positive or a negative value. Whereas the majority of patients showed an increase in uCTX from baseline values at the end of the observation period, 89 patients (~ 11%) experienced a small decrease in uCTX. This accounts for the high between-subject variance in the slope parameter and might reflect the inclusion of patients in our population both within and after the period of accelerated bone loss that occurs during menopause. The high BSV seen with KVIT probably reflects varying degrees of compliance with the calcium and vitamin D supplementation regimen. In our model we assumed full compliance. KDE showed much lower variability in the MF9853 study,

which was relatively small and well controlled and not influenced by the potentially variable compliance with different supplementation regimens.

Several studies have described the influence of supplemental therapy in patients with and without osteoporosis. Notably, calcium and vitamin D supplementation has been shown to decrease the rate of bone turnover, increase bone mass and decrease the risk of fractures [35–38]. In the present analysis, the contribution of supplemental therapy to the suppression of uCTX was estimated to be relatively large (~ 30%) [11].

Although the simulated uCTX response observed with the K-PD model for i.v. ibandronate was similar to the observed values in the Phase III and Phase II/III study, placebo simulations do not appear to predict the observed data in the Phase III study. However, the simulated placebo data fall well within the observed responses in the Phase II/III study (median – 24.71% and – 17.42% at 6 and 12 months, respectively) [13], the Phase I dose-finding study (mean – 15.0 to – 22.9% over 15 months) [11] and an additional study of ibandronate in the prevention of PMO (median – 7% at 12 months) [39]. The observed differences among these studies are likely to be the result of differences between the placebo medications, such as calcium (e.g. 500–1000 mg) and coadministration of vitamin D, and between the study populations (e.g. early vs. late postmenopausal women, with or without osteoporosis). For active treatment, the simulated values correspond well with the values and patterns of uCTX suppression observed with i.v. ibandronate therapy at 0.5 mg (– 16 to – 52%) [11], 1 mg (– 26.0 to – 63.1% [11]; – 42.0% at 12 months [13]) and 2 mg (– 25.7 to – 66.1% [11]; – 61% at 12 months [13] and – 50% at 12 months [39]).

Cremers *et al.* [40] recently presented a PK–PD model for i.v. pamidronate that had three compartments, with a central compartment representing serum, a second compartment representing bone surface and a third compartment representing deep bone. An $E_{\max}$ model was used to describe the time course of urinary hydroxyproline (a biomarker for osteoclastic bone resorption) after 3-monthly i.v. infusions of pamidronate in 22 osteoporotic women. The time course of change was found to be dependent on the amount of pamidronate attached to the bone and the amount buried in bone. The PK components of this model were simulated, in part, from a related compound and/or were fixed to population mean values using data from a separate group of patients. However, this model has yet to be tested prospectively. The model described in the present study has distinct advantages over that described by Cremers *et al.* [40]. First, in that it was developed from a large and

heterogeneous clinical dataset, and second, it was externally validated using data from independent studies that were not used for model development.

Studies of hormone replacement therapy and alendronate therapy suggest that a 'threshold' level of suppression of biochemical markers of bone turnover is required for a clinically meaningful response in BMD. For example, a suppression range of – 45 to – 65% for uCTX and urinary cross-linked N-terminal telopeptides of type I collagen is associated with a 90% certainty of a positive BMD response [33]. For serum CTX, a predictive range of – 35 to – 55% is recognized, whereas for serum osteocalcin and bone-specific alkaline phosphatase, the predictive range is – 20 to – 40%. Thus, treatment regimens that fulfil certain criteria with respect to threshold biomarker suppression or fluctuation may be identified and explored using clinical trial simulations.

In summary, a pharmacostatistical model was developed and validated that adequately described the time course of uCTX change after oral and i.v. ibandronate therapy for osteoporosis. This model is currently being used to aid in the development of novel intermittent oral and i.v. regimens for ibandronate.

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Appendix

PK–PD model equations: Figure 1

$$\begin{aligned}
 dA1/dt &= -(CL/V1 + k12 + k13 + k14) \\
 &\quad \times A1 + k21 \times A2 + k31 \times A3 + k41 \times A4 \\
 dA2/dt &= k12 \times A1 - k21 \times A2 \\
 dA3/dt &= k13 \times A1 - k31 \times A3 \\
 dA4/dt &= k14 \times A1 - k41 \times A4 \\
 INH &= 1 - (A4/V4)^{HILL} / [IC_{50}^{HILL} + (A4/V4)^{HILL}] \\
 FUN &= 1 + (R_{tar} - KS)/KS \times [1 - \exp(-k_{qq} \times T)] \\
 duCTX/dt &= KS \times FUN \times INH - KD \times uCTX \\
 dAe/dt &= CL/V1 \times A1
 \end{aligned}$$

Dose, Ibandronate dose; T , time after drug intake; $V1$ – $V4$, volumes of PK distributional compartments 1–4, respectively; $A1$ – $A4$, amounts of ibandronate in PK compartments 1–4, respectively; k_{ij} , rate constant for

ibandronate transport from compartment i to compartment j ; Rate constants were re-parameterized to inter-compartmental clearances (Q) by $k_{ij} = Q_j/V_i$; CL , renal clearance; Ae , amount excreted in urine; IC_{50} , ibandronate concentration in ‘bone’ compartment producing half maximum inhibition of uCTX formation; $HILL$, shape factor; uCTX, urinary CTX; KS , uCTX formation rate; KD , uCTX degradation rate constant; R_{tar} , limit value for uCTX formation rate ($T \rightarrow$); k_{qq} , rate constant by which R_{tar} is attained.

K–PD model equations: Figure 4

$$\begin{aligned}
 dA1/dt &= -KDE \times A1 \\
 DODR &= KDE \times A1 \times F \\
 INH &= 1 - DODR^{HILL} / [EKD_{50}^{HILL} + DODR^{HILL}] \\
 PBO &= (1 + SLOPE \times TIME) \\
 VITD &= 1 - VIT \times [1 - \exp(-KVIT \times TIME)] \\
 duCTX/dt &= (KS \times INH - KD \times uCTX) \\
 uCTX \text{ (composite)} &= uCTX \times PBO \times VITD
 \end{aligned}$$

Dose, Ibandronate dose; KDE, equilibration rate constant; DODR, dose-driving rate; EKD_{50} , DODR that leads to 50% inhibition of KS; PBO, placebo treatment effect on uCTX (disease progression); SLOPE, relative change in uCTX per day following placebo treatment; VITD, effect elicited by calcium and vitamin D supplementation; VIT, relative decrease in baseline uCTX due to calcium and vitamin D supplementation; KVIT, first-order rate constant for attainment of VIT; uCTX, urinary CTX; KS, uCTX formation rate; KD, uCTX degradation rate constant.