OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 20-835/SE8-035	Submission Date(s): 01/26/2009; 04/03/2009; 04/17/2009
Brand Name	Actonel®
Generic Name	Risedronate Sodium
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology III
OND Division	Division of Reproductive and Urologic Products
Sponsor	Procter & Gamble Pharmaceuticals
Relevant IND(s)	31,029
Submission Type; Code	Priority; Pediatric Efficacy Supplement
Formulation; Strength(s)	Film-coated tablets (2.5 mg, 5 mg)
Indication	Osteogenesis Imperfecta; OI
	[Note: Sponsor is not seeking the indication]

An optional inter-divisional Clinical Pharmacology briefing was held on May 29, 2009 from 11 AM to noon [Room 3300, Building 51, White Oak]. Attendees were Drs. Dennis Bashaw, Hae Young Ahn, Myong Jin Kim, Sandhya Apparaju, Stephen Voss, Doanh Tran, Hyunjin Kim, Ting Eng Ong, Jang Ik Lee, and Pengfei Song.

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1.1 Recommendation

NDA 20-835/SE8-035 is acceptable from a Clinical Pharmacology perspective, provided an agreement can be reached with the sponsor related to the proposed labeling revisions.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Risedronate is an orally administered third generation pyridinyl bisphosphonate currently approved in Europe and the United States for use in the treatment of Paget's disease of bone and the treatment and prevention of osteoporosis in postmenopausal (PMO) women.

A pediatric written request (PWR) for Actonel was issued under the Best Pharmaceuticals for Children's Act (BPCA) for evaluation in children with Osteogenesis Imperfecta (OI), a disease characterized by increased bone fragility ("brittle bone disease"). Children with severe OI suffer recurrent fractures resulting in severe deformity and stunted growth and usually accompanied by chronic bone pain with loss of independent ambulation by the teenage years in over 50% of cases. Currently, there is no approved drug treatment in the U.S. for OI.

To fulfill the PWR, P&GP/s-a conducted two clinical studies in pediatric patients with Osteogenesis Imperfecta (OI). These include a pediatric single dose PK study 2002020 and a phase 3 efficacy and safety trial in pediatric OI patients (# 2003100).

The sponsor is not seeking an indication in pediatric OI patients given the long-term safety concerns with the bisphosphonate class. The decision not to seek approval for the indication was made with the consensus of the clinical division during a pre-NDA meeting held on September 18, 2008, when the division noted that from a regulatory perspective, the risk of osteonecrosis of the jaw (ONJ) following use of bisphosphonates in the OI population who are already prone to dentogenesis imperfecta is a major indication-specific concern. However, the overall concern for ONJ, atypical fracture, etc., with this class of drug applies to all pediatric indications at this time. Thus the sNDA review was solely for the purposes of pediatric exclusivity determination and to determine acceptability of the proposed labeling changes.

The sponsor has fulfilled the conditions of the PWR and therefore was granted pediatric exclusivity on April 24, 2009.

The first pediatric study 2002020 was an open-label, parallel group, randomized, single dose PK and safety/tolerability study in pediatric patients with OI (ages 5-15 years; n =28). Patients were stratified into two body weight (BW) strata (10-30 kg or > 30 kg). Within each BW group, the patients were then randomized to one of two doses: 1) 2.5 mg or 5 mg risedronate in 10-30 kg cohort and 2) 5 mg or 10 mg risedronate dose in > 30 kg BW cohort. N = 8 patients were enrolled in each of the dose subgroups.

Risedronate analyses in serum and urine samples were conducted using validated enzyme linked immunosorbent assays. The accuracy and precision values for the standards and quality controls (QCs) during sample analyses runs were within the acceptable range.

The mean absolute oral bioavailability (BA) of risedronate tablets as determined previously is 0.63% (90% CI: 0.54% to 0.75%). Due to this low BA, serum risedronate concentrations are typically very low and cannot be adequately detected at all time points using the currently available serum analytical methodology. Hence the sponsor has in the past relied upon simultaneous pharmacokinetic analyses of serum and urinary data instead of traditional non-compartmental analyses for pharmacokinetic characterization. In this pediatric PK study as well, the pharmacokinetic parameters of risedronate were obtained by simultaneous pharmacokinetic analysis of serum concentration-time and urinary excretion rate-time data from pediatric patients. A descriptive summary of pharmacokinetic parameters is shown for each of the doses studied:

Mean ± SD (% CV)	**10-30 Kg BW Cohort**		**>30 Kg BW Cohort**	
	2.5 mg (n = 5 - 7)	**5 mg (n = 5 - 7)**	**5 mg (n = 2 – 3)**	**10 mg (n = 2 – 3)**
Cmax (ng/ml)	0.85 ± 0.42 (48 %)	1.42 ± 0.38 (26 %)	1.47 ± 0.05 (13 %)	2.10 ± 0.56 (27 %)
Tmax (h); median(range)	0.35 (0.23-0.59)	0.26 (0.13-0.88)	0.45 (0.42-0.49)	0.66 (0.18-1.99)
AUC 0-∞ (ng.h/ml)	6.19 ± 2.45 (40 %)	5.82 ± 1.28 (22 %)	13.6 ± 1.51 (11 %)	14.67 ± 2.86 (19 %)
T1/2 (h)	322 ± 269 (83 %)	397 ± 332 (84 %)	264 ± 232 (88 %)	490 ± 224 (45 %)
Ae' (%)	0.37 ± 0.19 (50 %)	0.24 ± 0.16 (66 %)	0.21 ± 0.11 (50 %)	0.37 ± 0.26 (46 %)

Ae': Cumulative urinary excretion rate normalized by dose and expressed as %

Tmax in general occurred within an hour after dose administration. Peak risedronate concentrations (Cmax) increased in relation to dose within each of the body weight cohorts. Baseline covariates of interest including gender, age, body weight were not found to significantly influence the exposure of risedronate in pediatric patients.

2 Question-Based Review

2.1 General Attributes

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Risedronate is an orally administered third generation pyridinyl bisphosphonate. The initial FDA approval for Actonel (Risedronate Sodium) in adult indications was given on March 27, 1998. Actonel is a bisphosphonate currently indicated in adults for:

- Treatment and prevention of postmenopausal osteoporosis (5 mg qd; 35 mg once a week, 75 mg taken on two consecutive days each month or 150 mg once a month)
- Treatment to increase bone mass in men with osteoporosis (35 mg once a week)
- Treatment and prevention of glucocorticoid-induced osteoporosis (5 mg once daily)

- Treatment of Paget's disease (30 mg daily for 2 months)

A pediatric written request (PWR) for Actonel was issued under the Best Pharmaceuticals for Children's Act (BPCA) for evaluation in children with Osteogenesis Imperfecta (OI), a disease characterized by increased bone fragility ("brittle bone disease"). Children with severe OI suffer recurrent fractures resulting in severe deformity and stunted growth and usually accompanied by chronic bone pain with loss of independent ambulation by the teenage years in over 50% of cases. Currently, there is no approved drug treatment in the U.S. for OI.

The initial PWR was issued on April 19, 2002. It was subsequently amended on September 11, 2002, January 8, 2004, and May 7, 2004. With this sNDA submission (20-835/SE8-035) sponsor intends to demonstrate fulfillment of the terms of the PWR via completion of the two pediatric studies (2002020 and 2003100), and to request a determination of pediatric exclusivity under section 505A of the FDC act. In addition, sponsor is requesting labeling review to update the pediatric sections of the risedronate labeling.

It is important to note that the sponsor is not seeking the pediatric indication. The label will be updated to indicate that Actonel (Risedronate Sodium) is not indicated for children. This decision to not seek the pediatric indication was made by P&GP prior to the sNDA submission in consultation with the Division of Reproductive and Urologic Products (DRUP) given the long-term safety concerns with the bisphosphonate class.

Pediatric Exclusivity was granted to the applicant on April 24, 2009.

What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Risedronate sodium is a pyridinyl bisphosphonate drug with the empirical formula for the hemipentahydrate as C7H10NO7P2Na •2.5 H2O [MW 350.13]. The chemical name of risedronate sodium is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt.

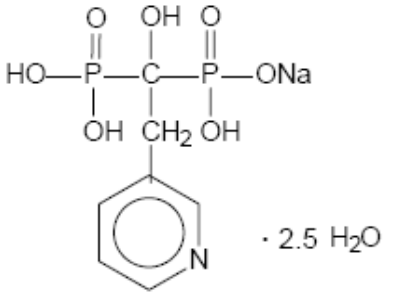


Figure 1: Structure of Risedronate sodium.

It is currently available in strengths of 5, 30, 35, 75 or 150 mg tablets.
Risedronate sodium is a fine, white to off-white, odorless, crystalline powder. It is soluble in water and in aqueous solutions and essentially insoluble in common organic solvents.

Risedronate sodium 2.5 mg and 5 mg tablets were supplied as cellulose-film-coated tablets. Excipients included microcrystalline cellulose, hydrous lactose, crospovidone, and magnesium stearate.

What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of action: Risedronate sodium is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. It has an affinity for hydroxyapatite crystals in bone and acts as an antiresorptive agent. At the cellular level, risedronate inhibits osteoclasts. The osteoclasts adhere normally to the bone surface, but show evidence of reduced active resorption (e.g., lack of ruffled border). Histomorphometry in rats, dogs, and minipigs showed that risedronate treatment reduces bone turnover (activation frequency, i.e., the rate at which bone remodeling sites are activated) and bone resorption at remodeling sites.

Indication: No pediatric indication is being sought by the sponsor.
The clinical trials in children have been done in the Osteogenesis Imperfecta (OI) population.

2.2 General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To fulfill the PWR, P&GP/s-a conducted two clinical studies in pediatric patients with osteogenesis imperfecta (OI).

Study 2002020: *An Open Label, Randomized, Multi-center, Parallel Group Study to Investigate the Safety, Tolerability and Pharmacokinetics of Risedronate Administered as a Single Oral Dose of 2.5 mg or 5 mg in Children 30 kg and 5 mg or 10 mg in Children> 30 kg with Osteogenesis Imperfecta*

This was a phase 1, open label, single dose, randomized, multi-center, parallel group study in children with OI. The objectives were to investigate safety, tolerability and pharmacokinetics of risedronate. Patients were initially stratified by body weight [10-30 kg or > 30 kg] and the risedronate doses were further randomized within each BW cohort as shown: single doses of 2.5 mg or 5 mg in the 10-30 kg BW group; and single doses of 5 mg or 10 mg in the > 30 kg BW group. 28 patients (13 male and 15 female) between the ages of 4-16 years were enrolled and all completed the study. Dose was administered as a tablet. In children who were unable to swallow the tablets (n =10), use of a dosing spoon to dissolve tablet into 10 ml of water was allowed. Although the solution dosage form was used in patients during the two pediatric studies, it is not clear whether the sponsor has sought the consensus in this regard from the Division of Metabolism and Endocrinology Products (DMEP), the clinical division where this indication was previously housed. In addition, there is no mention of the solution dosage form in the PWR.

Study 2003100: *A Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel Group Study of One year Duration Followed by 2 Years of Open-label Treatment to Determine the Safety and Efficacy of Orally Administered 2.5 mg or 5.0 mg Daily Risedronate, in Children 4 to < 16 Years Old with Osteogenesis Imperfecta.*

The primary objective of this study was to determine the efficacy of risedronate compared to placebo in children: 4 to < 16 years of age with OI as assessed by percent change from Baseline in lumbar spine bone mineral density (BMD) at Month 12. Secondary objectives of this study included assessing the incidence and rate of new vertebral fractures, and the incidence and rate of clinical vertebral and non-vertebral fractures. In addition, the safety and tolerability of risedronate treatment was evaluated in children with OI. No PK analyses were included in this trial. A total of 94 patients were randomized to risedronate (52 patients weighing between 10-30 kg on 2.5 mg dose and 42 patients weighing >30 kg on 5 mg dose); N = 49 were randomized to placebo. 37 patients used the dosing spoon (i.e. tablet dissolved in 10 ml water) at some time during the study. Of these 23 were randomized to receive risedronate. Sponsor notes that the dose selection for phase 3 was based on the exposure and safety results of the Phase I study 2002020.

See the clinical discipline review for additional details of this study.

Are the active moieties in the biological fluids appropriately identified and measured to assess pharmacokinetic parameters?

Yes. Serum and urine concentrations of the parent drug Risedronate were assessed in the pediatric PK study (2002020) using validated ELISA methodologies. Sample analysis involved isolation of risedronate from the matrix through cation exchange chromatography. The ELISA assay is based on the principle of competitive inhibition where the specific interaction of an antibody with the solid-phase analyte is competitively inhibited by the liquid-phase analyte found in a test sample. Quality control (QC) samples were analyzed to monitor the accuracy and precision of the analytical runs. The lower limit of quantitation for both the serum and urine assays was 0.200 ng/mL. The accuracy and precision of the QC samples during specimen analysis were in general comparable to the accuracy and precision of the QC samples observed during method validation.

Pharmacokinetics:

Study 2002020: This was an open-label, parallel group, randomized, single dose PK and safety/tolerability study in pediatric patients with OI (ages 5-15 years; n =28). Patients were grouped into two body weight strata (10-30 Kg or > 30 Kg) and within each group patients were randomized to one of two doses as shown: 1) 2.5 mg or 5 mg risedronate in 10-30 Kg cohort and 2) 5 mg or 10 mg risedronate dose in > 30 Kg BW cohort.

PK sampling: Blood samples were obtained pre-dose and at 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose and urine samples for risedronate analysis were obtained over the following collection intervals: pre-dose and 0-1, 1-4, 4-12, and 12-24 hours post-dose. Patients were discharged from the study centers 24 hours after dosing. Additional timed urine collections

(over 4 to 12 hours) were obtained on Days 4 and 6 post-dose and then twice a week for the next 3 weeks with a minimum of 2 days between each collection.

Pharmacokinetic analysis: Due to the low bioavailability of risedronate sodium (0.63 %), available serum bioanalytical methodology does not allow adequate characterization of serum concentration-time profiles at low doses to allow traditional non-compartmental analyses for PK. Serum concentrations were not detectable beyond 4 hours at the doses employed in the pediatric study. Therefore, the sponsor has employed simultaneous analyses of risedronate serum concentration-time and urinary excretion rate-time data using WinNonlin Professional (Version 4.1) for pharmacokinetic characterization. Decisions on appropriate weighting and number of exponents required to characterize the serum concentration-time and urinary excretion rate-time profiles were based on randomness of scatter of observed data about the fitted line, sum of weighted squared residuals, and precision of the estimated parameters. To assess the impact of baseline covariates such as age, weight, gender, and creatinine clearance on PK parameters, a multiple linear regression analysis was conducted by the sponsor for each PK parameter.

Pharmacokinetic Results: Of the 28 patients who entered the study, 25 were Caucasian, 1 was black (2.5 mg group), and 2 were Indian (Asian). There were 15 females and 13 males enrolled in this study. The age range at the time of first dose was 5-15 years old, inclusive.

A descriptive summary of pharmacokinetic parameters obtained by simultaneous pharmacokinetic analysis of serum and urine concentration data is shown.

Table 1: Pharmacokinetic data [mean ± SD (% CV)] for risedronate in pediatric OI patients in study 2002020. Data are from n = 5-7 individuals in the lower body weight cohorts (10-30 Kg) and n = 2-3 individuals in the higher body weight cohorts (>30 Kg).

Mean ± SD (% CV)	**10-30 Kg Cohort**		**> 30 Kg Cohort**	
	2.5 mg (n = 5– 7)	**5 mg (n = 5 – 7)**	**5 mg (n = 2 – 3)**	**10 mg (n = 2 – 3)**
Cmax (ng/ml)	0.85 ± 0.42 (48 %)	1.42 ± 0.38 (26 %)	1.47 ± 0.05 (13 %)	2.10 ± 0.56 (27 %)
Tmax (h); median(range)	0.35 (0.23-0.59)	0.26 (0.13-0.88)	0.45 (0.42-0.49)	0.66 (0.18-1.99)
AUC 0-∞ (ng.h/ml)	6.19 ± 2.45 (40 %)	5.82 ± 1.28 (22 %)	13.6 ± 1.51 (11 %)	14.67 ± 2.86 (19 %)
T1/2 (h)	322 ± 269 (83 %)	397 ± 332 (84 %)	264 ± 232 (88 %)	490 ± 224 (45 %)
Clo (L/h/kg)	25.3 ± 12.5 (49 %)	41 ± 13 (32 %)	9 ± 1 (11 %)	18 ± 3 (16 %)
CLR (L/h/kg)	0.1 ± 0.04 (44 %)	0.10 ± 0.09 (85 %)	0.019 (82 %)	0.085 (35 %)
Vz (L/kg)	8598 ± 4536 (53 %)	22138 ± 17936 (81 %)	3287 ± 2880 (87 %)	13307 ± 6828 (51 %)
Ae' (%)	0.37 ± 0.19 (50 %)	0.24 ± 0.16 (66 %)	0.21 ± 0.11 (50 %)	0.37 ± 0.26 (46 %)

Median Tmax occurred between 0.3 and 0.7 hours across all dose groups. Maximum serum risedronate concentrations (Cmax) increased as the dose of risedronate increased (0.85 to 2.1 ng/mL). Mean risedronate area under the serum concentration-time profile (AUC) ranged from 5.8 to 14.67 ng*h/mL across the 4 treatment groups. Within each of the body-weight cohorts, there was no trend for increasing AUC with increasing doses of risedronate.

Average serum concentration vs. time and urinary excretion rate vs. time profiles are shown below. Serum concentrations were in general not detectable beyond 4 hours post-dose due to the low bioavailability (0.63 %) of risedronate and the limitations of the serum analysis method.

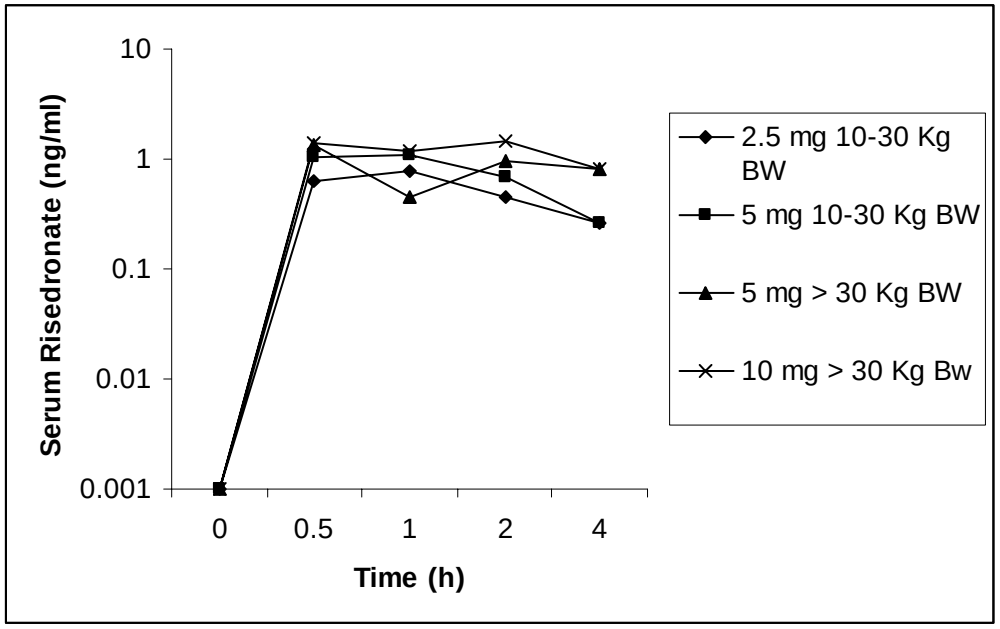


Figure 2: Mean serum risedronate concentration-time data following a single dose oral administration to pediatric patients with Osteogenesis Imperfecta (n = 7-8 in the 10-30 kg cohorts and N = 2-3 in the > 30 kg cohorts).

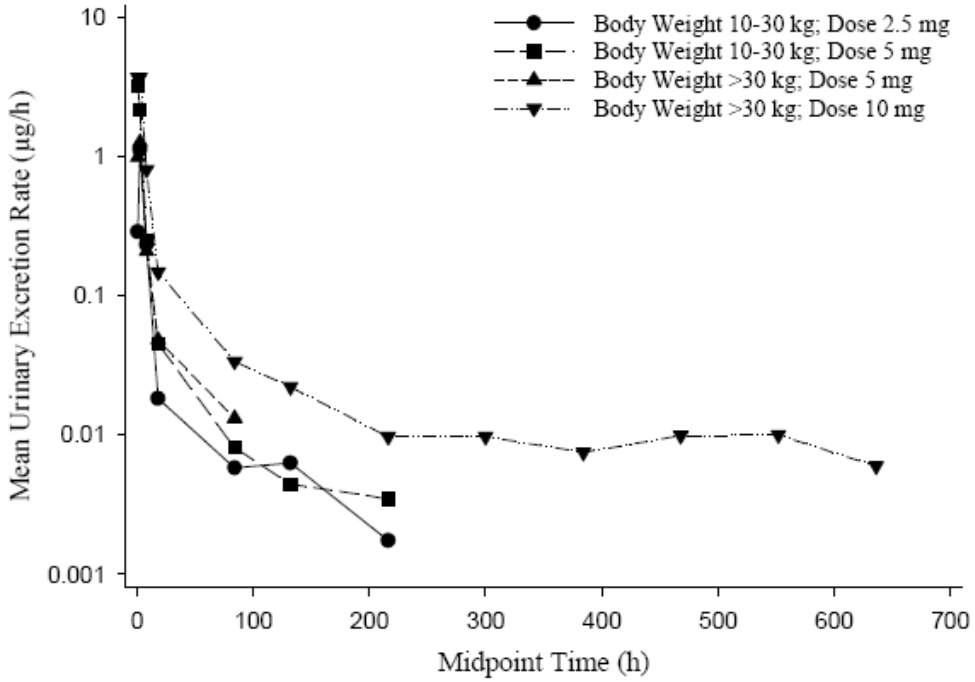
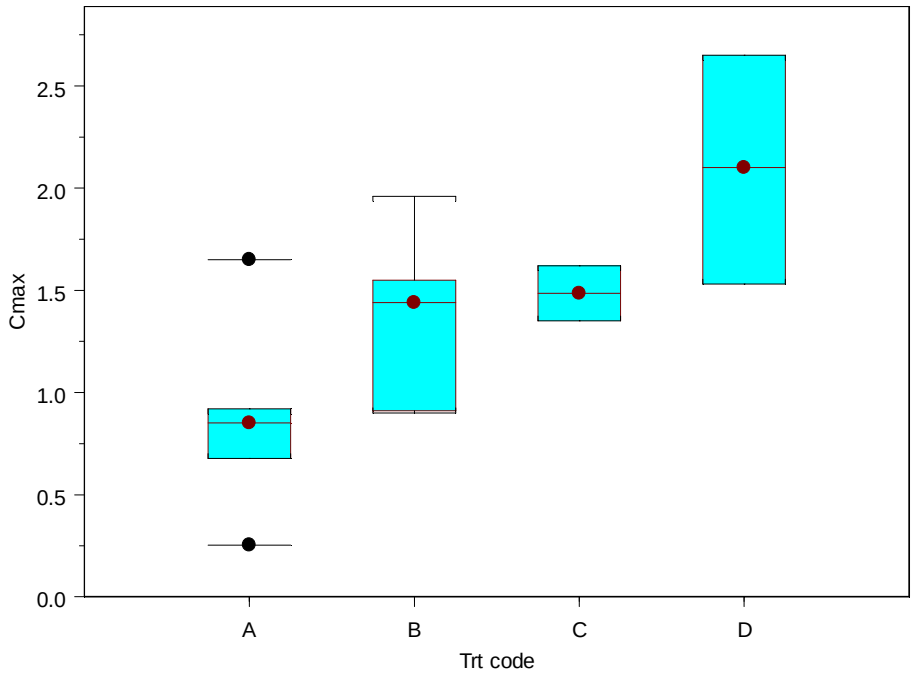


Figure 3: Mean risedronate urinary excretion rate-time profiles after single dose oral administration to pediatric patients with OI.

The distribution of the PK parameters and dose-related trends are shown in the plots below:



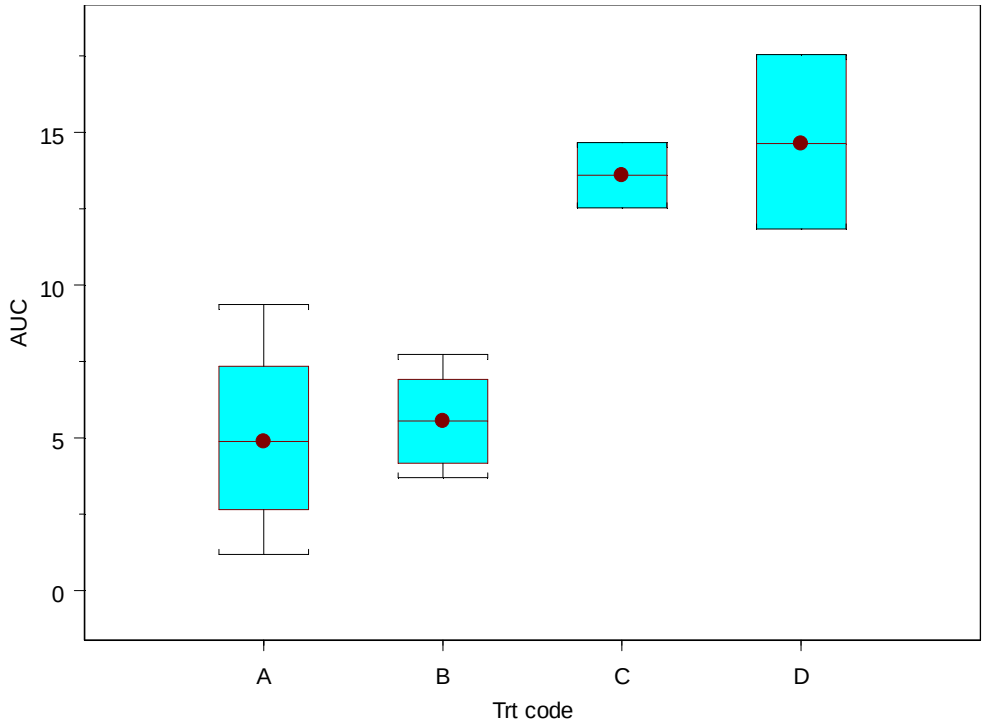


Figure 4: Box plots of Cmax and AUC of risedronate in pediatric patients of study 2002020; Trt: Treatment codes; A: 2.5 mg 10-30 Kg BW; B: 5 mg 10-30 Kg BW; C: 5 mg > 30 kg BW; D: 10 mg > 30 kg BW. PK parameters are from N = 5-7 patients in the 10-30 Kg cohorts and N = 2-3 in the > 30 kg cohorts.

PK comparability to that of adult Actonel data (historical data):

- Sponsor has used single and multiple dose PK data (table below) from previous adult risedronate studies to claim PK comparability to that of the pediatric OI population.

Table 2: Single and multiple dose PK data (historical) of risedronate (5 mg) in adults.

Risedronate Pharmacokinetic Parameters After Oral Administration to Adults

Treatment Group	Statistic	AUC (ng•h/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{½,z}$ (h)	CL_r (L/h/kg)	CL_o (L/h/kg)	A'_e (%)
RMD008894[a] 5 mg group	N	31	31	31	31	31	31	31
	Mean	6.601	1.025	0.734	478.657	0.06644	14.605	0.519
	CV (%)	58.5	47.8	15.9	42.1	22.9	40.9	36.9
	Median	5.13	0.8438	0.74	453.29	0.0674	14.36	0.460
	Minimum	(b) (4)						
	Maximum							
HMR 4003E/1001[b] 5 mg group	N	18	18	18	NA	18	18	18
	Mean	9.342	1.7274	0.6209	NA	0.04398	8.914	0.545
	CV (%)	31.9	52.3	55.4	NA	66	36.7	86.9
	Median	9.055	1.4915	0.672	NA	0.0353	8.185	0.414
	Minimum	(b) (4)						
	Maximum							
RSD005794[c] 5 mg group	N	22	22	22	22	22	22	22
	Mean	3.86	0.94	0.87	202.18	0.2236	22.03	1.259
	CV (%)	41.2	40.1	40.8	35.0	112.2	57.9	142.4
	Median	3.92	0.91	0.90	202.48	0.1592	17.13	0.767
	Minimum	(b) (4)						
	Maximum							

NA = not available

AUC for studies RMD008894 and HMR 4003E/1001 is the area under the dosing interval (24 hours) at steady state; for study RSD005794 it is area under the serum concentration-time profile from time 0 to ∞.

C_{max} and t_{max} for studies RMD008894 and HMR 4003E/1001 refers to Day 1.

[a] RMD008894: A Study to Determine the Linearity of Risedronate Pharmacokinetics Over Time, Upon Multiple Dose Administration of 2.5 or 5 mg to Postmenopausal Women.

[b] HMR 4003E/1001: Comparison of Daily (5 mg/day) versus Weekly (35 and 50 mg/week) Oral Dosing Regimens of Risedronate on Bone Turnover (Biochemical Markers) and Assessment of Pharmacokinetic Profiles in Postmenopausal Women.

[c] RSD005794: A Study to Determine the Dose Linearity and Safety of Risedronate After a Single Oral Dose of 2.5, 5, or 30 mg to Normal Healthy Volunteers.

Reviewer comments: Sponsor has not provided adequate information to support their conclusion of PK similarity across the adult and pediatric populations. Additional evidence in the form of plots comparing observed serum and urinary concentrations in adults vs. children, and/or statistical analysis of datasets merging necessary information from adult (historical) and pediatric data was not included.

2.3 Intrinsic Factors

Exploration of covariates in study 2002020: To assess the impact of baseline covariates such as age, weight, gender, and creatinine clearance on PK parameters, a multiple linear regression analysis ($p < 0.05$) was conducted by the sponsor for each PK parameter of the pediatric PK study 2002020.

Table 3: Relationship between baseline factors and PK parameters.

Relationship Between Baseline Factors and PK Parameters
(P-values from Analysis of Variance Model)

Pharmacokinetic Parameter	Dose	Sex	Age	Body Weight	CL_{cr}
A_e	0.0799	0.5134	0.3391	0.0115	0.0278
A_e(0-12h)	0.0493	0.9109	0.6769	0.0520	0.0205
A_e(0-24h)	0.0324	0.9970	0.6585	0.0591	0.0237
A'_e	0.3343	0.2213	0.3141	0.0586	0.0896
$AUC_{(0-\infty)}$	0.0273	0.9343	0.3466	0.0967	0.0618
CL_O	0.0873	0.7045	0.2454	0.0966	0.0569
CL_O; adjusted by body weight	0.2620	0.7318	0.6802	0.8882	0.1232
CL_r	0.3262	0.5538	0.2141	0.1995	0.1242
CL_r; adjusted by body weight	0.9918	0.4235	0.0972	0.9144	0.0622
C_{max}	0.0016	0.9664	0.5148	0.1871	0.5323
$t_{1/2,z}$	0.3147	0.3003	0.2051	0.3597	0.2735
t_{lag}	0.4333	0.7708	0.8850	0.3855	0.7773
t_{max}	0.7553	0.3775	0.7791	0.0430	0.2531
V_z/F	0.0602	0.4575	0.0501	0.0647	0.0280
V_z/F; adjusted by body weight	0.1234	0.5780	0.0814	0.2248	0.0389

A_e is the cumulative amount of drug excreted in urine from time 0 to ∞; A_e(0-12h) is the cumulative amount of drug excreted in urine from time 0 to 12 hours post-dose; A_e(0-24h) is the cumulative amount of drug excreted in urine from time 0 to 24 hours post-dose; A'_e is the cumulative amount of drug excreted in urine from time 0 to ∞, normalized for dose, and expressed as a percentage; $AUC_{0-\infty}$ is the area under the serum concentration-time profile from time 0 to ∞; CL_{cr} is creatinine clearance, estimated using the Traub & Johnson equation; CL_O is the oral clearance; CL_r is the renal clearance; C_{max} is the maximum serum concentration; $t_{1/2,z}$ is the half-life of the terminal exponential phase; t_{lag} is the lag time; t_{max} is the time of occurrence of C_{max}; and V_z/F is the terminal volume of distribution, uncorrected for bioavailability.
The 2 treatment groups of 5 mg were combined into one group for this model
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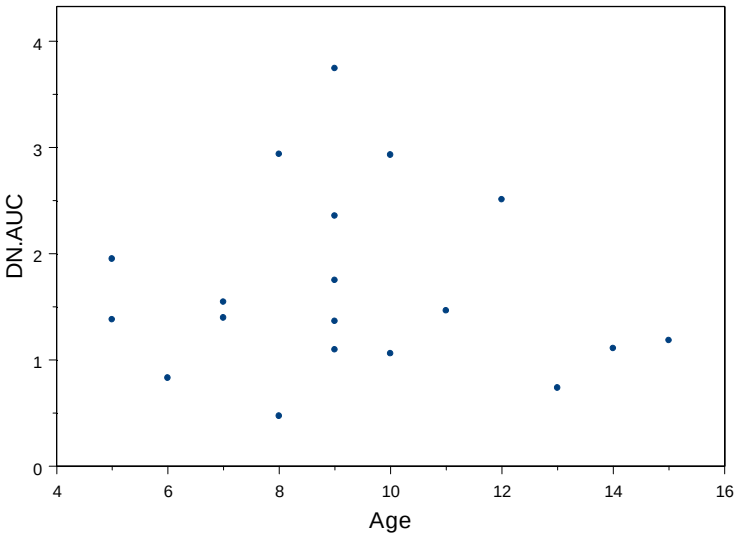
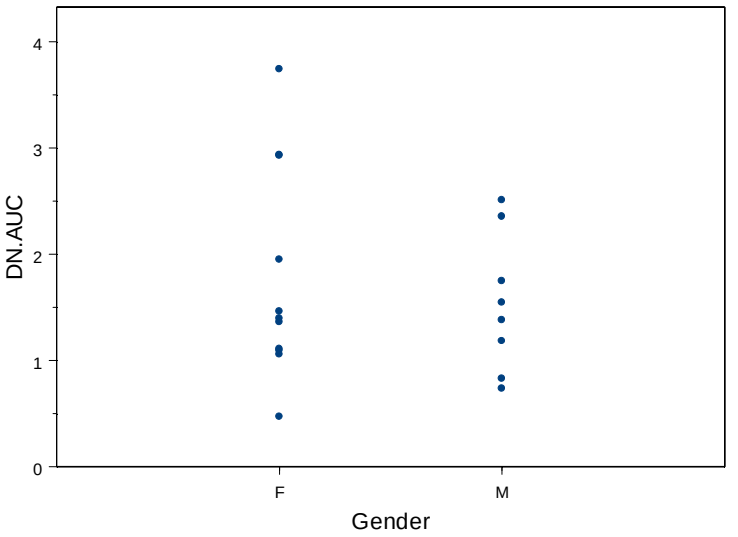
SAS 8.2 running HP-UX B.11.11 U on bdhp4368 for user ah5912, database hardlocked on 04mar04.
Corresponding data can be found in Appendix 2.3.

- Results show that none of the risedronate pharmacokinetic parameters was significantly affected by age or gender, although the relationship of age approached statistical significance with Vz prior to body weight adjustment.
- The relationship between drug dose and exposure parameters (Cmax, AUC) was statistically significant, while PK parameters such as T1/2, CLo, CLr did not show a relationship to dose, with the exception of Vz/F. The latter relationship became insignificant when Vz was adjusted to body weight.
- The relationship of CLo and CLr (adjusted to BW) with that of Clcr approached statistical significance. Clcr had an influence on the cumulative amount of drug excreted in urine, although this association was not statistically significant when the cumulative amount was normalized to dose (Ae').

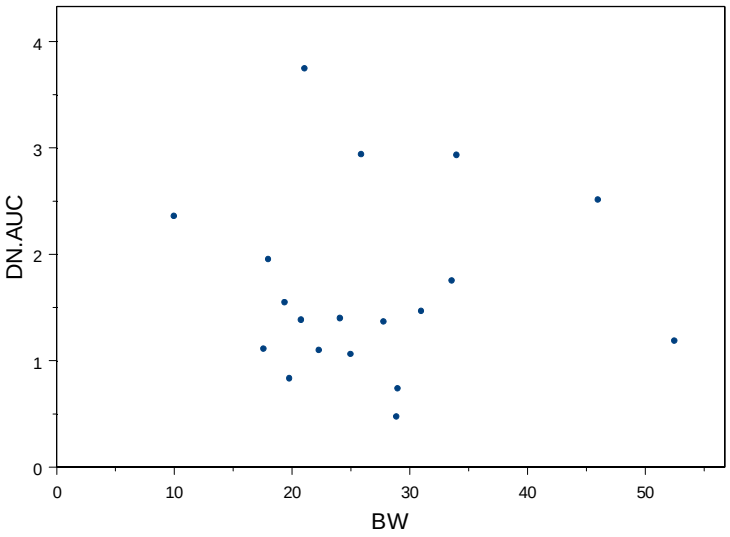
Age: The age range in the study was 5-15 years, with a mean age of 10 years. There was no correlation between age and dose-normalized (DN) Cmax or AUC.



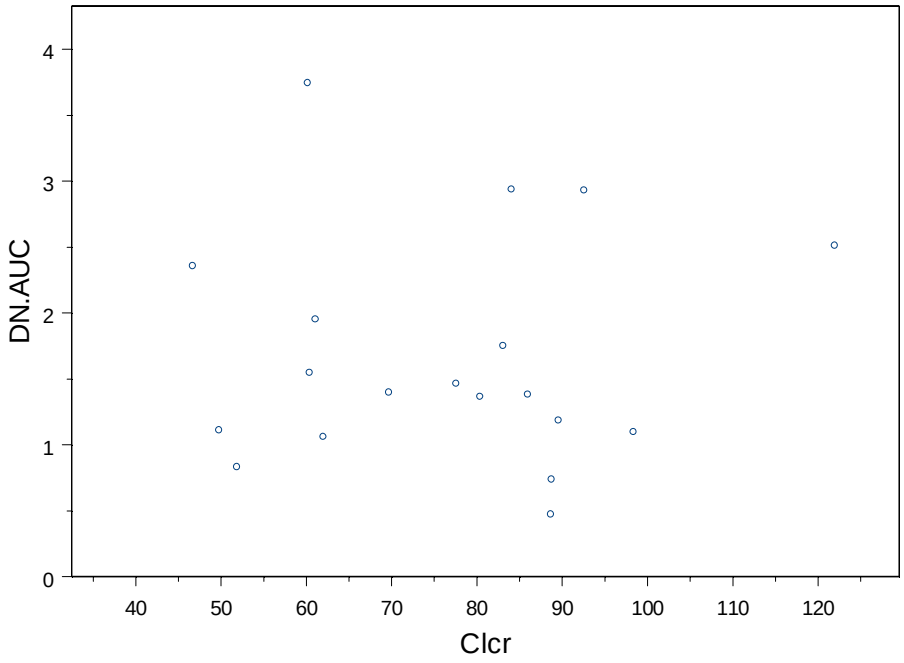
Gender: There were 15 females and 13 males in this study. PK parameters were available from 11 males and 9 females. With the exception of one female patient who demonstrated markedly higher AUC at the 2.5 mg dose, the range of dose normalized AUC values was comparable across genders.



Body weight: A significant effect of BW on AUC was observed as the higher body weight cohorts that received larger doses of the drug. This trend was not apparent when dose normalized AUC was used instead.



Creatinine Clearance: The range of Clcr in the study patients was 46.7-140.9 ml/min. Among the dose groups, the baseline Clcr values were variable (mean Clcr of 67.71, 72.54, 117.75 and 105.05 ml/min, at the 2.5 mg, 5 mg, 5 mgC2, and 10 mg dose cohorts), with the higher body weight cohorts demonstrating higher Clcr values. There was no significant effect of Clcr on dose-normalized AUC of risedronate in the pediatric patients.



Formulation: There were 10 patients who were allowed dosing of the dissolved tablet during this single dose study. It is not clear whether the sponsor had informed the previous review division (DMEP) of their intent to allow use of a

solution, nor was this formulation included in the PWR. Although no formal comparison was attempted by the sponsor (e.g. BA/BE study) to justify use of the two formulations interchangeably, during the pre-NDA meeting the division clarified to the sponsor that such information would not be required at this time as the sponsor is not seeking an indication.

Reviewer comments: Exploratory analysis of the baseline covariates and systemic exposure do not suggest a significant effect of age, gender, body weight, dosage

form (tablet or solution) or creatinine clearance on systemic exposure of risedronate in pediatric OI patients.

2.4 Analytical

The Bioanalytical analyses of risedronate in human serum and urine samples from study 2002020 were conducted using validated Enzyme-Linked Immunosorbent Assay (ELISA) techniques at (b) (4) . The ELISA assay is based on the principle of competitive inhibition where the specific interaction of an antibody with the solid-phase analyte is competitively inhibited by the liquid-phase analyte found in a test sample.

Validation: The ELISA methodology for serum and urine analyses of Risedronate in human PK samples was sufficiently validated. The validated range of the standard curves for both serum and urine analyses were 0.2-9.6 ng/ml. For QCs, the pre-specified acceptance criteria for accuracy (% nominal) was 80-120 % except at LLOQ where 75-125 % range was acceptable; for precision (% CV), the pre-specified acceptance criteria was ≤20 % for all QCs, except at LLOQ where a % CV of ≤25 % was acceptable. The results from QCs in the validation batches are shown below; data demonstrate that the pre-specified acceptance criteria were met:

	Accuracy (% Nominal)	Inter-run Precision (% CV)	Intra-run Precision (% CV)
Serum (validation)	95.3 % to 107 %	12 % to 13.6 %	11.3% to 12.8%
Urine (validation)	95.4 % to 108 %	6.99 % to 12.6 %	6.56 % to 11.9 %

Sample analysis: Serum and urine samples from phase 1 PK study 2002020 were analyzed using the validated ELISA techniques. All standards, QCs (6 per run at L, M, H) and unknowns were run in duplicate. Sample analysis was conducted according to the study protocol and in adherence to SOPs in place at the time of analyses.

Serum analysis: Ninety-five (46 %) of the analyzed samples had concentrations below the limit of quantitation (BQL). Data from 43 samples couldn't be reported (NR) due to insufficient sample volume for re-assay, subsequent to failed initial analyses. Sixty-four (31 %) of samples had detectable serum concentrations of risedronate. The reported range of risedronate concentrations in serum was 0.2-3.69 ng/ml and no samples were diluted. Runs were accepted or rejected based on the performance of QC samples included with each batch (i.e. accuracy of QCs within 80-120 % and % CV for duplicate QCs ≤ 20 % in at least 4 out of 6 QCs).

	Specimen Analysis		Method Validation	
Analyte	% Nominal (accuracy)	%CV (precision)	% Nominal (accuracy)	%CV (precision)
NE-58095	92.2% to 104.5%	10.8% to 13.3%	95.3% to 107%	12.0% to 13.6%

Urine analysis: A total of 324 urine samples from study 2002020 were analyzed. 124 samples (38 %) had concentrations below detection [BQL]. The range of urine samples was 0.2-157 ng/ml. Approximately 12 % of urine samples were diluted to fit within the validated range [0.2-9.6 ng/ml]. Runs were accepted or rejected based on QCs run throughout the samples. The ranges of precision and accuracy for sample analysis QCs are shown in comparison to method validation results. The high % CV range for QCs was due to four high QCs that had low recovery compared to the rest and thereby created a high variability. Nevertheless the runs were acceptable as at least 4 out of 6 QCs remained within the acceptable range specified *a priori*.

	Specimen Analysis		Method Validation	
Analyte	% Nominal (accuracy)	%CV (precision)	% Nominal (accuracy)	%CV (precision)
NE-58095	84.1% to 99.7%	14.2% to 32.2%	95.4% to 108%	6.99% to 12.6%

Analytical issues and resolution: While the assays for risedronate in human serum and urine were done in adherence to the assay protocols and SOPs in place at the time, there were some issues with the standard acceptance criteria specified in the analytical protocol. These were identified by DSI during their inspection of (b) (4) in relation to two adult Actonel studies. DSI noted in their review that the assay protocol allowed partial masking of one of the duplicate calibration points when mean of duplicates exceeds 20 % of nominal. A % CV-based criterion was also not required for accepting calibration standards.

Sponsor in their response to the division's queries in this regard (IR letter dated April 8, 2009) maintained that the criteria used for accepting calibration standards was objective and that all assays were done in adherence to these acceptance criteria that were specified a priori in the validation and assay protocols. The main objective of the acceptance criteria for calibration curve per the sponsor was to improve the curve fit by appropriately editing the calibration points that had the highest impact on the inaccuracy of the calibrators, and therefore, minimizing the error at each calibration point. The calibration curve editing (partial and full data point masking) was limited to two (2) full calibration points, one (1) full and two (2) partial points (equivalent of two full points) or a maximum of three (3) partial points if needed.

Sponsor also noted that 28 (19 urine and 9 serum) of the 37 analytical runs conducted in support of study 2002020 met the batch acceptance criteria recommended by the bioanalytical method validation guidance (i.e. 50 % of QCs at each concentration level and at least 67 % (4 of 6) of overall batch QCs must be within specification for accuracy), which supports the performance of the analytical method. In addition, sponsor notes that the inter-batch accuracy of QC samples analyzed as part of sample analysis was excellent for all accepted batches, supporting that the bioanalytical data is reliable.

To further address the issue of data validity, the sponsor submitted reprocessed analytical data from affected runs in study 2002020 using the more conservative criteria proposed by the FDA. There were in total one serum (# 7A) and three urine (# 9B, 10B and 11B) runs in study 2002020 that allowed partial calibration point masking. In their new analyses, sponsor rejected both duplicate calibration points when the mean response was greater than 20 % of the nominal value. Upon reprocessing with the new criteria there was no affect on the acceptability of the QC samples according to the batch acceptance criteria. For all urine runs, the newly calculated unknowns were within 20 % of the originally reported values suggesting that partial calibration point editing had no significant impact on the reported urine sample data.

For serum run 7A, re-processing resulted in deletion of 4 standard points in serum run 7A, three of which were consecutive (0.3, 0.4, 0.8 ng/ml). Although the overall run was deemed successful as at least 4 out of 6 QCs were acceptable within batch acceptance criteria, the duplicate values for the mid QC sample (0.5 ng/ml) which is within the range of the rejected standards (0.3-0.8 ng/ml) demonstrated the highest deviation from the originally reported values (32 % difference); in addition, the recalibrated standard curve resulted in 4 out of 20 unknowns to deviate by > 20 % from the previously reported values (within 20.2 to 30.9 %).

The study samples that demonstrated the most deviation from their previously reported values appeared to fall within the missing standard curve range (0.3-0.8 ng/ml) suggesting that deletion of these consecutive standards had an untoward influence on the overall performance of the standard curve in predicting QC and unknown sample concentrations.

Therefore, due to the questionable nature of this run, PK data resulting from samples included in this run were not included in the final parameter analysis i.e. data from subjects 2004, 2005 and 2006 was excluded.

Independent audit: In February of 2007, FDA recommended all sponsor's with analytical data from two locations of (b) (4) services [2000-2004] to either repeat study, re-analyze samples or conduct a third party audit of the data due to issues with data integrity. Since one of the affected (b) (4) locations include the (b) (4) location used in the analysis of the Risedronate pediatric study samples, and because it was done during the affected time frame, the sponsor has submitted the findings from an independent audit conducted by (b) (4) .

Following a review of all raw data and records at (b) (4) associated with the analytical validation and sample assays of the pediatric PK study, the third party audit report by (b) (4) group concluded that the assay for risedronate in human serum and urine was adequately validated and sufficient for producing accurate and reproducible results. The audit firm in a follow-up communication noted that while the calibrator acceptance criteria could have been more consistent across the standards and unknowns/QCs, overall it should not impact the final study conclusions. In addition, they note that all assays were done in adherence to a priori acceptance criteria stipulated in the protocol and no deviations in this regard were noted during their audit.

Reviewer comments: Based on a review of the analytical reports (validation and assay portions), independent audit conclusions and the sponsor's response to the division's IR letter dated 04/08/2009 (which included supporting information from reprocessed data), reviewer finds that the analytical methodologies employed for risedronate analysis in serum and urine samples are sufficiently validated. The assays were done in adherence to protocols and SOPs in place at the time of the study. The analytical results are valid for use in pharmacokinetic analysis of risedronate in children from PK study 2002020.

3 Detailed Labeling Recommendations

Additions to the label are underlined and deletions are shown as ~~strikethroughs~~.

Highlights of Prescribing Information
USE IN SPECIFIC POPULATIONS

ACTONEL is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) (5.5, 8.6, 12.3).

Full Prescribing Information
8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use
ACTONEL is not indicated for use in pediatric patients.

(b) (4)

(b) (4)

(b) (4)

4 Appendix

4.1 Individual Study Reviews

Study 2002020: This was an open-label, parallel group, randomized, single dose PK and safety/tolerability study in pediatric patients with OI (ages 5-15 years). Patients were group into two body weight strata (10-30 Kg or > 30 Kg) and within each group patients were randomized to one of two doses as shown: 1) 2.5 mg or 5 mg risedronate in 10-30 Kg cohort and 2) 5 mg or 10 mg risedronate dose in > 30 Kg BW cohort.

Following an overnight fasting, patients received a single dose of the drug at least 2 hours before the first food or drink of the day. 2.5 mg or 5 mg tablets were used for administering doses ranging 2.5 mg to 10 mg. While most patients received the tablet dosage form, patients who could not swallow the tablet were allowed to use a dosing spoon (b) (4) , where in tablet(s) was dissolved in 10 ml of water and swallowed. The dosing spoon was rinsed with water and that volume was also consumed. All doses were then immediately followed by intake of at least 120 ml water irrespective of tablet or dosing spoon. 10 patients in this single dose PK study utilized the dosing spoon.

PK sampling: Blood samples were obtained pre-dose and at 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose and urine samples for risedronate analysis were obtained over the following collection intervals: pre-dose and 0-1, 1-4, 4-12, and 12-24 hours post-dose. Patients were discharged from the study centers 24 hours after dosing. Additional timed urine collections (over 4 to 12 hours) were obtained on Days 4 and 6 post-dose and then twice a week for the next 3 weeks with a minimum of 2 days between each collection.

Bioanalytical analysis: Analysis was conducted by (b) (4) facility using validated ELISA techniques for detection of risedronate in serum and urine samples. The lower limit of quantitation was 0.2 ng/ml in both the matrices. Since the bioanalysis was conducted by (b) (4) facility during the affected time-frame (2000-2004), an independent audit was commissioned by the sponsor (b) (4) to assess the validity of the risedronate assay. A review of the validation and assay reports for study 2002020, the third party audit findings and additional

supporting information resulting from sponsor's response to the division's IR letter issued April 8, 2009, have found the assay to be adequate.

Pharmacokinetic analysis: Risedronate serum concentration-time and urinary excretion rate-time data were simultaneously analyzed using WinNonlin Professional (Version 4.1), and the following equations:

$$C = \sum_{i=1}^{n} C_i e^{-\lambda_i (t - t_{lag})} \qquad \text{(equation 1)}$$

$$\frac{dA_e}{dt} = CL_r \sum_{i=1}^{n} C_i e^{-\lambda_i (t_{mid} - t_{lag})} \qquad \text{(equation 2)}$$

where: $C_n = -1 \cdot \left(\sum_{i=1}^{n-1} C_i \right)$ (equation 3)

where C is the serum concentration of risedronate, t is the time after administration of the dose, dAe/dt is the urinary excretion rate occurring at the midpoint of the collection interval, tmid is the midpoint time of the urine collection interval after administration of the dose, tlag is the lag time before onset of drug absorption, n is the number of exponents necessary to characterize serum concentration-time and urinary excretion rate-time profiles, Ci is the ith coefficient, λi is the ith exponent, CLr is the renal clearance of risedronate, and Cn is the coefficient associated with λn.
Initial pharmacokinetic parameter estimates were obtained from a previous study conducted in healthy subjects. Predicted serum concentrations and urinary excretion rates were weighted (1, 1/p or 1/p2) for use in data analysis, where p is the predicted value for that function. Decisions on appropriate weighting and number of exponents required to characterize the serum concentration-time and urinary excretion rate-time profiles were based on randomness of scatter of observed data about the fitted line, sum of weighted squared residuals, and precision of the estimated parameters. Estimated maximum serum concentration (Cmax) and the time of occurrence of Cmax (tmax) were derived from equation 1. Area under the serum concentration-time curve from 0 to infinity (AUC), terminal exponential half-life (t½,Z), oral clearance (CLo), and terminal volume of distribution uncorrected for bioavailability (VZ/F) were obtained from the coefficients and exponents using standard equations. Cumulative urinary excretion (Ae) of risedronate was obtained as the product of AUC and CLr and normalized by dose (A'e).

To assess the impact of baseline covariates such as age, weight, gender, and creatinine clearance on PK parameters, a multiple linear regression analysis was conducted for each PK parameter. In each linear regression model, the PK parameter was used as the dependent variable and treatment, gender, age, weight, and creatinine clearance were treated as covariates. An intercept was also fitted in these models. Each of the covariates was tested for significance at a < 0.05 level.

Pharmacokinetic Results: A total of 28 patients (15 females and 13 males) completed the study. A total of 10 patients used the dosing spoon. PK parameters could not be computed from all dosed individuals due to the following reasons: 1) Five individuals had no reported serum concentrations due to inadequate sample volume for reanalysis following failure of QCs during their first run; 2) Data from three subjects was not included in the final PK

analysis by this reviewer due to concerns with the integrity of their analytical run 7A as explained further:
During sample analysis, (b) (4) allowed partial calibration data point masking to bring the standards into compliance when the mean of the duplicates was > 20 % of nominal. In response to the division's IR letter in this regard, sponsor submitted reprocessed data using revised criteria that require complete standard point elimination instead of partial masking if mean of duplicated was > 20 % nominal. Sponsor submitted the data for reprocessed standards, unknown and QC sample data for 4 affected runs (1 serum and 3 urine). This reviewer has utilized the reprocessed data for PK parameter analysis. While the urine runs remained acceptable after re-processing, four standards in the serum run 7A (3 of which were consecutive standards) had to be rejected based on the new criteria. Therefore, for the purposes of this review, PK data resulting from subjects in serum run 7A (patients #s 2004, 2005, 2006) were deemed questionable and were not included in the final PK analysis of risedronate in pediatric OI patients. A summary of pharmacokinetic parameters obtained by simultaneous pharmacokinetic analysis of serum and urine concentration data from the remaining individuals is shown below.

Mean ± SD (% CV)	**10-30 Kg Cohort**		**> 30 Kg Cohort**	
	2.5 mg	**5 mg**	**5 mg**	**10 mg**
Cmax (ng/ml)	0.85 ± 0.42 (48 %)	1.42 ± 0.38 (26 %)	1.47 ± 0.05 (13 %)	2.10 ± 0.56 (27 %)
Tmax (h); median(range)	0.35 (0.23-0.59)	0.26 (0.13-0.88)	0.45 (0.42-0.49)	0.66 (0.18-1.99)
AUC 0-∞ (ng.h/ml)	6.19 ± 2.45 (40 %)	5.82 ± 1.28 (22 %)	13.6 ± 1.51 (11 %)	14.67 ± 2.86 (19 %)
T1/2 (h)	322 ± 269 (83 %)	397 ± 332 (84 %)	264 ± 232 (88 %)	490 ± 224 (45 %)
Clo (L/h/kg)	25.3 ± 12.5 (49 %)	41 ± 13 (32 %)	9 ± 1 (11 %)	18 ± 3 (16 %)
CLR (L/h/kg)	0.1 ± 0.04 (44 %)	0.10 ± 0.09 (85 %)	0.019 (82 %)	0.085 (35 %)
Vz (L/kg)	8598 ± 4536 (53 %)	22138 ± 17936 (81 %)	3287 ± 2880 (87 %)	13307 ± 6828 (51 %)
Ae' (%)	0.37 ± 0.19 (50 %)	0.24 ± 0.16 (66 %)	0.21 ± 0.11 (50 %)	0.37 ± 0.26 (46 %)

Pharmacokinetic data summarized represent mean (% CV) values from n = 5-7 individuals in the lower body weight cohort (10-30 Kg) and n = 2-3 individuals in the higher body weight cohort (>30 Kg).

- Tmax for risedronate was obtained within 0.3-0.7 hours post-dose.
- Peak risedronate concentrations (Cmax) demonstrated dose related increases (0.85 – 2.1 ng/ml). Mean peak concentrations following a 5 mg dose were comparable in both low and high BW cohorts (~1.4 ng/ml).
- A consistent trend for dose-related increase in AUC values was not demonstrated within each body weight stratum. In general, AUC values following the 2.5 mg and 5 mg doses in the low BW cohort were comparable (6.19 and 5.82 ng.h/ml, respectively), while AUC values in the high BW cohort were also comparable

following 5 mg and 10 mg doses (13.6 vs. 14.67 ng.h/ml, respectively). Due to low sample size, particularly in the higher body weight stratum (n = 2-3) it is difficult to conclusively comment on any PK related trends.

- Terminal elimination T1/2 values were long (264-490 hours) across all doses evaluated.
- Ae', the cumulative amount of risedronate in urine from time 0 to infinity, normalized to dose and expressed as % was comparable at all doses.

PK comparability to that of adult Actonel data (historical data):

- The following table provided by the sponsor summarizes PK data for a 5 mg dose of risedronate in adults.

Table 14
Risedronate Pharmacokinetic Parameters After Oral Administration to Adults

Treatment Group	Statistic	AUC (ng•h/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{½,z}$ (h)	CL_r (L/h/kg)	CL_o (L/h/kg)	A'_e (%)
RMD008894[a] 5 mg group	N	31	31	31	31	31	31	31
	Mean	6.601	1.025	0.734	478.657	0.06644	14.605	0.519
	CV (%)	58.5	47.8	15.9	42.1	22.9	40.9	36.9
	Median	5.13	0.8438	0.74	453.29	0.0674	14.36	0.460
	Minimum	(b) (4)						
	Maximum							
HMR 4003E/1001[b] 5 mg group	N	18	18	18	NA	18	18	18
	Mean	9.342	1.7274	0.6209	NA	0.04398	8.914	0.545
	CV (%)	31.9	52.3	55.4	NA	66	36.7	86.9
	Median	9.055	1.4915	0.672	NA	0.0353	8.185	0.414
	Minimum	(b) (4)						
	Maximum							
RSD005794[c] 5 mg group	N	22	22	22	22	22	22	22
	Mean	3.86	0.94	0.87	202.18	0.2236	22.03	1.259
	CV (%)	41.2	40.1	40.8	35.0	112.2	57.9	142.4
	Median	3.92	0.91	0.90	202.48	0.1592	17.13	0.767
	Minimum	(b) (4)						
	Maximum							

NA = not available
AUC for studies RMD008894 and HMR 4003E/1001 is the area under the dosing interval (24 hours) at steady state; for study RSD005794 it is area under the serum concentration-time profile from time 0 to ∞.
C_{max} and t_{max} for studies RMD008894 and HMR 4003E/1001 refers to Day 1.
[a] RMD008894: A Study to Determine the Linearity of Risedronate Pharmacokinetics Over Time, Upon Multiple Dose Administration of 2.5 or 5 mg to Postmenopausal Women.
[b] HMR 4003E/1001: Comparison of Daily (5 mg/day) versus Weekly (35 and 50 mg/week) Oral Dosing Regimens of Risedronate on Bone Turnover (Biochemical Markers) and Assessment of Pharmacokinetic Profiles in Postmenopausal Women.
[c] RSD005794: A Study to Determine the Dose Linearity and Safety of Risedronate After a Single Oral Dose of 2.5, 5, or 30 mg to Normal Healthy Volunteers.

- There is inadequate data to support claim of similar clearances in adults vs. pediatrics.

- Exploration of covariates in study 2002020: To assess the impact of baseline covariates such as age, weight, gender, and creatinine clearance on PK parameters, a multiple linear regression analysis ($p < 0.05$) was conducted by the sponsor for each PK parameter of the pediatric PK study 2002020.

Table 12
Relationship Between Baseline Factors and PK Parameters
(P-values from Analysis of Variance Model)

Pharmacokinetic Parameter	Dose	Sex	Age	Body Weight	CL_{cr}
A_e	0.0799	0.5134	0.3391	0.0115	0.0278
A_e(0-12h)	0.0493	0.9109	0.6769	0.0520	0.0205
A_e(0-24h)	0.0324	0.9970	0.6585	0.0591	0.0237
A'_e	0.3343	0.2213	0.3141	0.0586	0.0896
$AUC_{(0-\infty)}$	0.0273	0.9343	0.3466	0.0967	0.0618
CL_O	0.0873	0.7045	0.2454	0.0966	0.0569
CL_O; adjusted by body weight	0.2620	0.7318	0.6802	0.8882	0.1232
CL_r	0.3262	0.5538	0.2141	0.1995	0.1242
CL_r; adjusted by body weight	0.9918	0.4235	0.0972	0.9144	0.0622
C_{max}	0.0016	0.9664	0.5148	0.1871	0.5323
$t_{1/2,z}$	0.3147	0.3003	0.2051	0.3597	0.2735
t_{lag}	0.4333	0.7708	0.8850	0.3855	0.7773
t_{max}	0.7553	0.3775	0.7791	0.0430	0.2531
V_z/F	0.0602	0.4575	0.0501	0.0647	0.0280
V_z/F; adjusted by body weight	0.1234	0.5780	0.0814	0.2248	0.0389

A_e is the cumulative amount of drug excreted in urine from time 0 to ∞; A_e(0-12h) is the cumulative amount of drug excreted in urine from time 0 to 12 hours post-dose; A_e(0-24h) is the cumulative amount of drug excreted in urine from time 0 to 24 hours post-dose; A'_e is the cumulative amount of drug excreted in urine from time 0 to ∞, normalized for dose, and expressed as a percentage; $AUC_{0-\infty}$ is the area under the serum concentration-time profile from time 0 to ∞; CL_{cr} is creatinine clearance, estimated using the Traub & Johnson equation; CL_O is the oral clearance; CL_r is the renal clearance; C_{max} is the maximum serum concentration; $t_{1/2,z}$ is the half-life of the terminal exponential phase; t_{lag} is the lag time; t_{max} is the time of occurrence of C_{max}; and V_z/F is the terminal volume of distribution, uncorrected for bioavailability.
The 2 treatment groups of 5 mg were combined into one group for this model
Report generated on 21APR04:09:15 by areas/RISEDRONATE/oipedpk/batch4/pkparam/pvalues_ancova_creatclean_thre.sas
SAS 8.2 running HP-UX B.11.11 U on bdhp4368 for user ah5912, database hardlocked on 04mar04.
Corresponding data can be found in Appendix 2.3.

- Results show that none of the risedronate pharmacokinetic parameters was significantly affected by age or gender, although the relationship of age approached statistical significance with Vz prior to body weight adjustment.
- The relationship between drug dose and exposure parameters (Cmax, AUC) was statistically significant, while PK parameters such as T1/2, CLo, CLr did not show a relationship to dose, with the exception of Vz/F. The latter relationship became insignificant when Vz was adjusted to body weight.
- The relationship of CLo and CLr (adjusted to BW) with that of Clcr approached statistical significance. Clcr had an influence on the cumulative amount of drug excreted in urine, although this association was not statistically significant when the cumulative amount was normalized to dose (Ae').
- The relationship between body weight and dose-normalized cumulative amount of drug excreted in urine (Ae') approached statistical significance, probably due to a baseline discrepancy in Clcr across groups, the mean values for which were higher in high body weight cohorts.

Safety: A total of 27 AEs were reported by 13 of the 28 enrolled patients (46.4%). No one withdrew from the study and only one serious AE (Crohn's Disease in Patient 79552001 in the 10 mg group and assessed as doubtfully drug-related) was reported. All AEs were mild or moderate in severity and 7 (25.9%) of the AEs were thought by the Investigator to be related to study drug.

The most commonly reported AEs were nausea and diarrhea, each was reported by 3 patients (nausea: 1 patient in the 2.5 mg group, 1 patient in the 5 mg, ≤ 30 kg group, and 1 patient in the 10 mg group; diarrhea: 1 patient in the 5 mg, ≤ 30 kg group and 2 patients in the 10 mg group). Two patients (2.5 mg group) reported upper GI AEs (both upper abdominal pain). Both events were mild; 1 was assessed as possibly related and the other as doubtfully related to study drug. Both patients recovered and completed the study. Four AEs (3 fractures and 1 Crohn's disease) were ongoing at study completion. No trend was observed for AEs across treatment groups, although the 10 mg group had the greatest proportion of patients with AEs.

Table 13
Overall Treatment-Emergent Adverse Events Profile
(Intent-to-Treat Population)

	2.5 mg (≤ 30 kg) (N=8) n (%)	5 mg (≤ 30 kg) (N=8) n (%)	5 mg (> 30 kg) (N=6) n (%)	10 mg (> 30 kg) (N=6) n (%)
Number (%) of patients with AEs	3 (37.5)	3 (37.5)	2 (33.3)	5 (83.3)
Number of AEs reported	7	6	2	12
Mean number of AEs per patients with AEs	2.33	2	1	2.4
Number (%) of patients with serious AEs	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Number of serious AEs reported	0	0	0	1
Number (%) of patients with expeditable AEs	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Number of expeditable AEs	0	0	0	1
Number (%) of patients with upper GI AEs reported	2 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of upper GI AEs reported	2	0	0	0
Number (%) of patients with moderate-to-severe upper GI AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of moderate-to-severe upper GI AEs	0	0	0	0
Number (%) of patients with possibly and probably related treatment-emergent AEs	1 (12.5)	1 (12.5)	0 (0.0)	5 (83.3)

Patients who experienced one or more AEs are counted only once.
N = number of patients within specified Randomized treatment.
n(%) = number and percent of patients who reported adverse events within specified randomized treatment, patients reporting the same AE more than once were counted only once
Corresponding data can be found in Appendix 3.6 Table 1
Report generated on 15APR04:17:26 by areas/RISEDRONATE/oipedpk/batch4/programs/aetable/aetable_aesum_hardcode.sas
SAS 8.2 running HP-UX B.11.11 U on bdhp4368 for user ah5912, database hardlocked on 04mar04.

Tablet vs. dosing spoon: PK data are shown across the tablet and dosing spoon (dissolved) formulations:

Tablet

Dose Cohort	BW Cohor	Patient ID	Cmax (ng/	Tmax (h)	AUC (ng.h	T1/2 (h)	Clo (L/h)	CLR (L/h/k	Vz (L)	Ae' (%)
2.5 mg	10-30 Kg	(b) (4)								
		Average	**1.00**	**0.42**	**6.71**	**256**	**400**	**0.09**	**140975**	**0.33**
		Stdev	**0.45**	**0.16**	**2.35**	**158**	**124**	**0.04**	**90815**	**0.08**

Dosing spoon

Patient ID	Cmax (ng/	Tmax (h)	AUC (ng.h	T1/2 (h)	Clo (L/h)	CLR (L/h/k	Vz (L)	Ae' (%)
(b) (4)								
Average	**0.66**	**0.31**	**5.42**	**424**	**528**	**0.10**	**236454**	**0.43**
Stdev	**0.35**	**0.23**	**2.72**	**453**	**265**	**0.06**	**182981**	**0.30**

Dose Cohort	BW Cohor	Patient ID	Cmax (ng/	Tmax (h)	AUC (ng.h	T1/2 (h)	Clo (L/h)	CLR (L/h/k	Vz (L)	Ae' (%)
5 mg	10-30 Kg	(b) (4)								
		Average	**1.26**	**0.48**	**6.39**	**438**	**789**	**0.12**	**483616**	**0.28**
		stdev	**0.41**	**0.30**	**0.73**	**479**	**96**	**0.12**	**500779**	**0.21**

Dosing spoon

Patient ID	Cmax (ng/	Tmax (h)	AUC (ng.h	T1/2 (h)	Clo (L/h)	CLR (L/h/k	Vz (L)	Ae' (%)
(b) (4)								
Average	**1.64**	**0.26**	**5.79**	**355**	**902**	**0.08**	**506319**	**0.18**
Std dev	**0.29**	**0.19**	**1.81**	**200**	**279**	**0.02**	**431117**	**0.03**

Solubility and water hardness technical report: Following the pre-NDA meeting with DRUP, the sponsor had conducted in vitro experiments to verify that following preparation of the active ingredient (risedronate) is fully dissolved and to investigate the potential impact of water hardness on drug solubility.

For assessment of active ingredient solubility, samples were prepared according to the following standardized procedure:

(b) (4)

4.2 OCP Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**20-835/SE8-035**	**Brand Name**	**Actonel**
OCP Division	**DCP3**	**Generic Name**	**Risedronate Sodium**
Medical Division	**DRUP**	**Drug Class**	**Bisphosphonate**
OCP Reviewer	**Sandhya Apparaju, Ph.D.**	**Indication(s)**	**Pediatric Osteogenesis Imperfecta (OI)**
OCP Team Leader	**Myong Jin Kim, Pharm.D.**	**Dosage Form**	**Tablet**
		Dosing Regimen	
Date of Submission	**01/26/2009**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**05/26/2009**	**Sponsor**	**Proctor & Gamble/ Sanofi-Aventis**
PDUFA Due Date	**07/26/2009**	**Priority Classification**	**Priority**
Division Due Date			

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary				
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**2**		**Study assay reports are included; method validation reports will be requested**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**X**	1		**Study 2002020**
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	**X**			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**X**			**This is a pediatric sNDA**
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**X**	1		
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	**X**	1		In vitro tests to assess solubility of tablet dosage form (b) (4)
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	**X**			This is a pediatric sNDA
Literature References				
Total Number of Studies		**8**		Total 6 including the (b) (4) audit report and analytical method validation reports to be submitted.
Filability and QBR comments				

	"X" if yes	Comments
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Fulfillment of pediatric written request** **Conclusions of third party audit**	
Other comments or information not included above	**Sponsor is not seeking a pediatric Indication (osteogenesis imperfecta).**	
Primary reviewer Signature and Date	**Sandhya Apparaju**	
Secondary reviewer Signature and Date		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sandhya Apparaju
6/4/2009 09:34:45 AM
BIOPHARMACEUTICS

Myong-Jin Kim
6/4/2009 01:16:54 PM
BIOPHARMACEUTICS