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MEDICAL REVIEW(S)

CLINICAL REVIEW

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(Proposed) Trade Name	Binosto
Therapeutic Class	Bisphosphonate
Applicant	EffRx Pharmaceuticals SA
Formulation	Oral effervescent tablet
Dosing Regimen	70 mg PO weekly
Indication	Osteoporosis
Intended Population	Men and Postmenopausal women

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on evidence of clinical safety of Binosto which appears to be equivalent to that of the approved comparator product, Fosamax, and the determination of pharmacokinetic bioequivalence of these products by the Division of Clinical Pharmacology, this reviewer recommends approval of Binosto for the following two indications:

- Treatment of osteoporosis in postmenopausal women; and
- Treatment to increase bone mass in men with osteoporosis.

1.2 Risk Benefit Assessment

Osteoporosis affects over 10 million Americans and is a major cause of morbidity and mortality in older adults. Among Caucasian women over 50 years of age, ~50% will experience an osteoporotic fracture in their lifetime, and ~17% will suffer a hip fracture. About 30% of women > 50 years old have a fractured vertebra, the most common fracture site. Osteoporotic fractures often result in chronic pain, deformity, disability and/or death, as well as great economic cost. Mortality risk is increased following either a hip or vertebral fracture (Hasserijs 2005; Ioannidis 2009). Approximately 20% of women die within a year of hip fracture (Johnell 2004); most who survive do not recover their pre-fracture ambulatory and functional status, and 20% require long-term nursing home care. Although men are affected less frequently than women, they incur almost a third of all hip fractures, from which their mortality risk is even higher than that of women.

Bisphosphonates (BPs), including Fosamax (alendronate sodium), are the first-line treatment of choice for most osteoporosis patients, having demonstrated robust efficacy in reducing fracture risk and maintained a favorable safety profile over many years. Clinical trials of Fosamax have demonstrated significant increases, over placebo and baseline, in bone mass of lumbar spine, femoral neck, and hip trochanter in female and male patients with osteoporosis, as well as reduced loss of height. In women with postmenopausal osteoporosis (PMO), trials have shown significant reductions in fractures; in women with previous vertebral fractures, new fractures of vertebrae, hip and wrist were reduced by about half. Relative to other treatment options, BPs have the advantage that their actions are highly specific to bone tissue.

Despite availability of effective therapy, osteoporosis is widely under-diagnosed and under-treated. Approved drugs, including orally administered BPs, are associated with

low rates of patient adherence and compliance. Literature reports that over half of women who start oral BPs discontinue within one year, and that this group has poorer outcomes. Upper GI adverse effects (see below) are the most frequently cited reason; dosing instructions to help prevent such reactions are frequently not adhered to by patients. (Rabenda 2009)

The most important BP safety issue is the potential for over-suppression of bone turnover, especially with long term use, resulting in osteonecrosis of the jaw (ONJ) or atypical femur fractures. However, no causal association with BP use has been clearly established, in osteoporosis patients, for these conditions. Moreover, ONJ and atypical femur fractures are both very uncommon, occurring in probably <0.1% of BP-treated osteoporosis patients (Lo 2010, Shane 2010). Recent relative risk calculations based upon data from the 3-year FIT trial of alendronate in postmenopausal women with mean age 71 years, BMD T-score of -1.6 and baseline vertebral fractures, revealed that the number of nonvertebral or clinical (i.e. symptomatic) vertebral fractures that could be averted by BP treatment would be at least 10 and 23 times greater, respectively, than the number of atypical femur fractures (some of which are unrelated to BP treatment). In a population similar but without baseline vertebral fractures (4-year FIT trial), therefore with only moderate fracture risk, these rates of “typical fractures” averted by BP treatment would still be 7 and 10 times greater (nonvertebral and vertebral respectively) than the “atypical” fractures. The task force conclusion was that “the risk-benefit ratio clearly favors BP treatment in women at high risk of fracture.” (Shane 2010)

Because of the potential for over-suppression of bone metabolism, FDA has recently conducted a comprehensive evaluation of the available data regarding long term BP use in osteoporosis. As BPs are incorporated into bone mineral and remain there for very prolonged periods, their benefit in terms of improved BMD and reduced fracture risk tended to persist when the drug was discontinued after 3-5 years of use. No subset of patients clearly showed added benefit from continued treatment beyond this point in time. Considering the diminishing benefits and possibly increasing risks of continuing long-term treatment, class labeling for BPs now includes a statement about the need to re-evaluate patients during prolonged use. This issue was discussed at a joint meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee on September 9, 2011; committee members recommended strengthening the labeling language regarding long term BP use. Changes to labeling may help to preserve the favorable benefit:risk ratio of these drugs in treating osteoporosis.

Upper gastrointestinal tract (especially esophageal) mucosal irritation may occur with oral BPs, including rare instances of severe esophagitis with ulceration or bleeding. However, clinical trials have generally shown minimal difference in GI effects between alendronate and placebo when labeled dosing instructions are followed, i.e. administration with a full glass of water, then maintenance of an upright position for at least 30 minutes and until after eating. One recent study suggests that oral BPs may be

associated with a small increase in risk of esophageal carcinoma. However, evidence is conflicting, with another study showing a reduced risk, and still others showing no difference. Even if there is an association, the absolute risk would be low relative to the number of fractures prevented, including life-threatening hip fractures. According to SEER data, the background incidence of esophageal carcinoma in U.S. adults age ≥ 65 years is 23.3 per 100,000 patient-years; the worst-case estimate from the only positive study is that oral BP exposure may double this rate. For comparison, in osteoporosis patients, ~700-1000 nonvertebral fractures and ~1000-2300 clinical (symptomatic) vertebral fractures, per 100,000 patient-years, would be avoided by use of oral BPs. (Liberman 1995; Black 1996)

Binosto is an effervescent tablet of alendronate 70 mg intended to treat women with postmenopausal osteoporosis (PMO) and to increase bone mass in men with osteoporosis, with once-weekly administration. It closely resembles the reference listed drug, Fosamax 70 mg oral tablet, except for the type of formulation; therefore differences in safety or efficacy are unlikely except in the domains of either bioavailability or upper GI safety/tolerability. It is possible that if the Binosto effervescent tablet did not dissolve completely prior to administration, such that alendronate particles were in prolonged contact with esophageal mucosa, this product could in theory cause greater risk for esophagitis than Fosamax tablets (assuming the latter are taken correctly). However, dissolution data show that this is very unlikely to occur if the product is prepared as intended, i.e. allowing adequate time and stirring for dissolution of the effervescent tablet prior to ingestion (b) (4)



The evidence provided from studies AE-1212-001-EM and SCO5361 involving 248 subjects suggests that adverse effects (GI and others) of Binosto are essentially equivalent to Fosamax. There were somewhat more instances of dyspepsia/heartburn and nausea with Binosto relative to Fosamax, however clinical significance was evidently minimal, and interpretation must take into account the open-label design of the studies. There were no cases of oral BP-related severe esophagitis; the usual markers of this toxicity, i.e. dysphagia and odynophagia, were not seen except in one subject who had transient dysphagia following a dose of the comparator, Fosamax. Thus, there is no evidence to indicate that risk of important GI adverse events would be increased (or decreased) with Binosto in comparison to Fosamax. Subjects at higher risk for upper GI adverse effects were excluded from studies of Binosto, consistent with prior Fosamax trials and approved Fosamax labeling, which would also apply to this product.

There are no clinical efficacy data presented in this application, as it is based upon demonstration of bioequivalence of Binosto 70 mg effervescent tablet to Fosamax 70 mg tablet. The standard for bioequivalence has been met by study AE-1212-001-EM, and given that the safety data are also comparable, this reviewer's conclusion is that for

the intended osteoporosis populations, and similarly to the reference drug Fosamax, the benefits of treatment exceed the risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

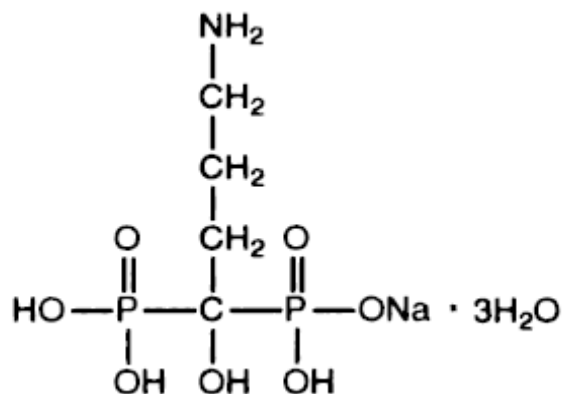
An FDA safety communication in October 2010 addressed the emerging potential BP safety issue of atypical femur fractures. Subsequently, class labeling related to atypical fractures, and a Medication Guide-only Risk Evaluation and Mitigation Strategy (REMS), were implemented for all BPs for the purpose of informing patients about this and other potential BP risks. Therefore, this NDA for Binosto included a proposed REMS, including Medication Guide and a timetable for submission of REMS Assessments. Subsequently, the review division has determined that a REMS is no longer needed to ensure that the benefits of bisphosphonates outweigh their risks. Therefore a REMS will no longer be required for Fosamax, the reference listed drug for this application, nor will it be required for Binosto. The Medication Guide will continue to be part of the approved labeling of this and other BPs in accordance with 21 CFR 208.1. The Applicant's Medication Guide proposal will be reviewed by the Patient Labeling Team.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarketing required studies are recommended.

2 Introduction and Regulatory Background

2.1 Product Information



Alendronate sodium trihydrate

The active ingredient in Binosto is alendronate sodium trihydrate, a nitrogenated bisphosphonate (BP). BPs are analogues of pyrophosphate which become incorporated

into calcium hydroxyapatite mineral within bone tissue. There they inhibit the bone-resorptive activity of osteoclasts, which generally results in increased bone mineral density and strength, and reduced risk for bone fracture. Several BPs are used clinically to treat osteoporosis and other bone disorders characterized by excessive bone resorption, such as glucocorticoid-induced osteoporosis, Paget's disease and bone metastases.

Alendronate, like other orally administered BPs, is poorly absorbed (< 1%), especially in the presence of food, therefore must be taken in a fasting state. It has the potential for mucosal irritant effects in the upper GI tract, particularly the esophagus (see Section 2.4) therefore should be taken in an upright position with adequate water.

This NDA is a 505(b)(2) application whose central purpose is to establish bioequivalence of Binosto to the prototypic alendronate, Fosamax. Binosto is an effervescent tablet containing alendronate 70 mg (free acid equivalent), with a citrate buffer system to maintain gastric pH at ~5. It contains 653 mg sodium per tablet. It is intended for the patient to dissolve in 120 mL water which is consumed after an overnight fast, once weekly for women with PMO or for men with osteoporosis. Consistent with Fosamax labeling, Binosto is intended to be taken at least 30 minutes before the first food, beverage, or medication of the day, followed by maintenance of an upright position for at least 30 minutes and until after eating. The indication, target population, dose regimen and dosing instructions of Binosto closely match those of the Fosamax 70 mg tablet (the RLD) and Fosamax 70 mg oral solution.

The Applicant's rationale in developing Binosto was based upon evidence that BP-related esophagitis may be caused by undissolved or particulate BP from tablets, and may be potentiated by reflux of gastric acid (see Section 2.4). (b) (4)



Reviewer comment: *It is unknown whether effervescent tablets of alendronate may be preferred over regular tablets by some patients for reasons of taste, convenience, perception of improved tolerability, etc. Thus it is possible that this type of formulation may improve compliance with treatment, but no evidence exists to support this, and the Applicant makes no claims in this regard.*

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 lists all drug products approved for treatment of postmenopausal osteoporosis; those also approved to increase bone mass in men with osteoporosis are marked with an asterisk (*). All of these products act through inhibition of bone resorption by

osteoclasts, with the exception of PTH (Forteo), which by stimulating osteoblasts has an anabolic effect on bone tissue. All except for calcitonin have demonstrated efficacy in reducing osteoporotic fractures in postmenopausal women. All are recommended to be taken in conjunction with supplemental calcium and vitamin D if dietary intake is inadequate.

Table 1 Approved Products for Osteoporosis Treatment

Class	Drug	Route	Dose
Bisphosphonates	Fosamax* (alendronate)	Oral	10 mg daily*†
		Oral	70 mg weekly* (tablet† and oral solution)
	Fosamax Plus D* (alendronate/ cholecalciferol)	Oral	70 mg/2800 IU weekly*
		Oral	70 mg/5600 IU weekly*
	Actonel* (risedronate)	Oral	5 mg daily†
		Oral	35 mg weekly*‡
		Oral	150 mg monthly
	Atelvia (risedronate)	Oral	35 mg weekly
Estrogen agonist/ antagonist	Boniva (ibandronate)	Oral	150 mg monthly
		IV	3 mg every 3 months
	Reclast* (zoledronic acid)	IV	5 mg yearly*
Estrogen agonist/ antagonist	Evista (raloxifene)	Oral	60 mg daily
Calcitonin†	Miacalcin	SQ	100 IU every other day
	Miacalcin	Nasal	200 IU daily†
	Fortical	Nasal	200 IU daily
Approval limited to osteoporosis patients at high risk for fracture**			
PTH analog	Forteo* (teriparatide)	SQ	20 mcg daily*
RANKL antibody	Prolia (denosumab)	SQ	60 mg every 6 months
* Approved for men as well as postmenopausal women † Approval based on BMD, not fracture efficacy ‡ Generics also approved ** Defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy			

2.3 Availability of Proposed Active Ingredient in the United States

Fosamax® (alendronate sodium/Merck), together with generic alendronate, is the most widely prescribed osteoporosis drug in the world. It was first approved in the US in

September 1995 for the treatment of postmenopausal osteoporosis (NDA 020560), based upon clinical trials in women with PMO demonstrating increases in bone mineral density (BMD) and reductions in vertebral fractures.. Subsequently, significant reductions in other fractures including the hip were demonstrated in women with PMO. In 2000, Fosamax was approved as well for men with osteoporosis (hypogonadal or idiopathic), based upon BMD effects that were similar to those in women. As has been the case with other BPs and with teriparatide, studies in men were not designed to evaluate fractures; therefore this labeled indication is for “treatment to increase bone mass in men with osteoporosis”, rather than “treatment of osteoporosis”.

The initially approved Fosamax dose for osteoporosis was a once daily 10 mg tablet to be taken when fasting. Because the daily dosing regimen is inconvenient for many patients, the Fosamax 10 mg daily tablet has been largely replaced in clinical practice by a 70 mg once-weekly Fosamax tablet which was approved in October 2000, based upon BMD effects which are comparable to 10 mg daily. A once-weekly Fosamax oral solution (NDA 021575) of 70 mg in 75 mL (to be followed by ≥ 2 oz. water) was also approved in September 2003 as an alternative for patients preferring a solution or unable to swallow the tablet. Approval of the solution was based upon equal bioavailability (though not strict bioequivalence, because urine sampling intervals were not short enough to calculate E_{max}) to the 70 mg tablet, and additional nonclinical and clinical safety data. Although other doses of Fosamax are approved for Paget’s disease (1995), treatment of glucocorticoid-induced osteoporosis (1999), and/or prevention of postmenopausal osteoporosis (1997), the 70 mg tablet and 70 mg solution are approved for only 2 indications:

- Treatment of osteoporosis in postmenopausal women (PMO); and
- Treatment to increase bone mass in men with osteoporosis.

Unfortunately, poor compliance has been a major limitation of oral BP treatment of osteoporosis, despite development of weekly- and even monthly-administration regimens. There are several possible explanations for this, including the perceived potential for upper GI adverse effects (see below, section 2.4).

Fosamax and other BPs are used off-label in children with various metabolic bone diseases, however efficacy and safety have not been shown in pediatric populations.

2.4 Important Safety Issues With Consideration to Related Drugs

Alendronate and other BPs selectively localize to sites of active bone remodeling, where they suppress osteoclast activity and bone resorption. BPs also have the potential to block normal mineralization of bone matrix, but this effect is clinically insignificant for the nitrogenated BPs such as alendronate. BPs become incorporated into bone matrix and remain there for years, therefore normal bone resorption and turnover may remain suppressed long after administration is stopped.

Recently, there has been concern about the potential for adverse effects of BPs related to prolonged over-suppression of bone metabolism, especially osteonecrosis of the jaw (ONJ) and atypical femoral fractures (subtrochanteric and diaphyseal). Class labeling for all bisphosphonates used to treat osteoporosis now includes Warnings and Precautions pertaining to these conditions, as well as language indicating the uncertainty about long-term (> 3-5 years) BP use.

Other BP safety issues addressed by Warnings and/or Precautions are the upper GI effects of oral BPs (see below), hypocalcemia (related to suppressed bone resorption; generally mild and asymptomatic), and musculoskeletal pain (mechanism unknown). An increased risk of atrial fibrillation with BP use has been suggested by some studies, however more definitive recent data showed no association. Another, primarily theoretical risk is that of potential fetal skeletal toxicity from previous maternal BP use, because of the very long persistence of these substances in bone tissue.

Alendronate: Upper GI toxicity

The major issue involved in this application, other than bioequivalence of the new product to Fosamax, is its potential for the upper GI mucosal-irritant effects attributed to oral BPs including alendronate, risedronate and ibandronate. .

This potential was recognized prior to Fosamax approval in 1995 and was confirmed by **postmarketing case reports**, during the first 3 years following approval. Typical symptoms reported in such cases were dysphagia, odynophagia, chest or epigastric pain, or hematemesis. In many cases, patients admitted not drinking adequate water with the tablet, and/or lying down after taking it. Endoscopic features included esophagitis, which was in some cases severe with ulceration and occasionally stricture. Such cases were attributed to tablets becoming stuck in the esophagus, akin to other reported examples of “pill esophagitis”; in some, birefringent crystalline material appearing identical to the matrix material of the alendronate tablet was found within inflammatory esophageal exudates. Some patients experienced reflux-like symptoms after lying down. These factors led to more specific instructions for dosing (see below) in 1996; since then, serious GI events appear to have declined.

Clinical trials, in which patients are systematically instructed to take BPs with a full glass of water and remain upright for at least 30 or 60 minutes, have generally not shown major differences from placebo in GI tolerability, though it should be noted that these trials excluded some higher-risk patients. The **phase 3 alendronate trials** for PMO excluded women with upper GI disease or symptoms and/or acid-reducing medication use, but not NSAID use. These 3-year trials (total n=994) reported that incidence of upper GI AEs with alendronate 10 mg daily was similar overall to placebo: 42.3% vs. 39.0% for overall GI AEs; 0.5% vs. 0.8% for serious GI AEs; and 1.0% vs. 2.0% for GI AEs resulting in withdrawal. Esophageal events of any type were reported by 4.6% of alendronate patients vs. 2.0% of placebo patients, but none were serious or led to discontinuation. Of all individual upper GI AEs, only abdominal pain (20.4% vs. 13.9%)

and dysphagia (2.0% vs. 0.3%) were significantly more common with alendronate 10 mg. GI effects in alendronate 5 mg and 20 mg arms were similar to 10 mg. (Watts 1999) Extension of the phase 3 trials to 7 years showed no increase in upper GI AEs over time. (Tonino 2000)

The large 3-4.5 year **Fracture Intervention Trials (FIT)** of alendronate in postmenopausal women with low BMD (mean age 69 y/o, 97% white) also excluded some women with major upper GI tract disease (e.g. recent ulcer, upper GI bleeding or daily medication for dyspepsia). However, only 1.4% of screened women were excluded for these reasons; those with less severe conditions (e.g. hiatal hernia, GERD, esophagitis, heartburn) or regular NSAID use were not excluded. Similar to the phase 3 findings, retrospective meta-analysis of pooled GI-safety data showed minimal differences between alendronate (5 mg daily x 2 yrs, then 10 mg daily) and placebo in overall upper GI AEs. (**Table 2**) The alendronate group showed greater proportions with serious esophageal events (0.3% vs. 0.2%), discontinuation due to an esophageal event (0.8% vs. 0.3%), or esophagitis not reported as reflux (0.7% vs. 0.4%); none of these differences were statistically significant. As expected from other studies, age ≥ 75 y/o, previous upper GI disease and NSAID use were each associated with increased upper GI events, but alendronate did not significantly increase risk further within these groups. (Bauer 2000)

Table 2 Fosamax FIT trials: Subject incidence of upper GI tract AEs

	Alendronate	Placebo
# of subjects enrolled	3236	3223
# who completed study	3038 (94%)	3042 (94%)
Any upper GI AE	47.5%	46.2%
Hospitalization due to upper GI AE	2.0%	1.8%
Discontinuation due to upper GI AE	3.2%	2.7%
Gastroduodenal perforation/ ulcer/ bleeding	1.6%	1.9%
Abdominal pain	13.7%	13.1%
Dyspepsia	18.2%	19.1%
Nausea	10.9%	11.8%
Vomiting	3.4%	3.1%
Anorexia	0.7%	0.9%
Any esophageal AE	10.0%	9.4%
Serious esophageal AE	0.3%	0.2%
Discontinuation due to esophageal AE	0.8%	0.3%
Acid regurgitation/reflux esophagitis	8.6%	8.3%
Esophagitis/ erosive esophagitis	0.8%	0.4%
Esophageal ulcer	0.2%	0.2%
Esophageal stricture	0.3%	0.2%
Esophageal perforation/ bleeding	0%	0%
Dysphagia/ odynophagia/ esophagalgia	1.0%	0.8%

Gastritis	2.5%	2.3%
Gastric ulcer	0.8%	0.8%
Duodenitis	0.2%	0.1%
Duodenal ulcer	0.1%	0.3%
Source: Bauer (2000)		

Other large osteoporosis RCTs (Pols 1999, Hosking 1998) have also shown no consistent differences between alendronate and placebo in GI safety and tolerability. The same applies to studies in men, patients on glucocorticoids, and patients with Paget's disease; the latter involved a higher alendronate dose (40 mg daily).

The high placebo rate of upper GI symptoms in these trials is consistent with high prevalence of these symptoms in older women, particularly in those with (untreated) osteoporosis, which may be due in part to a high prevalence of concomitant NSAID use. In addition, there is an apparent tendency for oral BP therapy to increase reporting: one study found that upper GI AEs were reported by ~17% of subjects assigned to either alendronate or matching oral placebo, but by <1% of an open-label nasal calcitonin comparison group. (Downs 2000) Similarly, two studies of patients who reported previous upper GI intolerance to alendronate showed no difference in tolerability upon rechallenge with oral BP (with alendronate in one study, and risedronate in the other), compared to placebo.

Many studies have used **endoscopy** to evaluate BP-related effects on upper GI mucosa. Like the phase 3 and FIT trials, these have generally not shown major differences between oral BP and placebo. This is particularly true for esophageal effects; no study has shown an increase in endoscopic esophageal lesions with BP treatment. Information about mucosal effects in the stomach is more conflicting. Some studies, mostly uncontrolled, have shown gastric erosions or ulcers in patients taking daily alendronate, and two studies suggested a higher frequency of these with alendronate compared to risedronate (neither study had a placebo group). However, endoscopic mucosal lesions did not correlate with symptoms in any of the investigations, and such lesions may be found in up to 20% of healthy, asymptomatic patients and are thus of unknown significance. Higher quality endoscopic studies with a placebo group and at least 4 week duration have failed to prove significant alendronate-related mucosal damage in esophagus, stomach or duodenum. (Cryer 2002)

Because **NSAIDs** are used by approximately half of osteoporosis patients and may cause gastritis, gastric ulcers and upper GI bleeding, there is concern over a possible additive or synergistic effect with oral BPs. There is limited nonclinical (see below) and clinical evidence to support this. An endoscopic study in 26 healthy volunteers found a significantly higher incidence of gastric erosions following 10 days of treatment with both alendronate 10 mg/d and naproxen 500 mg BID, compared with either drug alone. (Graham and Malaty 2001) An observational study found significant drops in hemoglobin levels in patients receiving alendronate plus an NSAID, which were not

seen in groups receiving either alendronate alone, or calcitonin plus an NSAID. (Rothschild 2000) However, the clinical significance of these findings is unclear, and large epidemiologic studies have shown that whereas osteoporosis itself (like NSAID use) appears to be associated with higher risk for gastric or duodenal perforations, ulcers, and bleeding (“PUBs”), alendronate therapy did not further add to this risk. (Donahue 2002)

Most of the available alendronate safety data involve the 10 mg daily dose, but GI tolerability of 70 mg weekly alendronate appears to be at least as good. A 1-year RCT with a total of 1258 PMO patients compared 3 dose regimens: 10 mg daily, 35 mg twice a week, and 70 mg weekly. Upper GI AEs were reported by 22.4%, 23.8% and 23.5% respectively; serious upper GI AEs were reported in 1.4%, 0% and 0% respectively. There was a trend toward lower incidence of AEs suggestive of esophageal, gastric or duodenal irritation for the twice-weekly and weekly groups, relative to daily dosing. Within the 70 mg weekly dose group, there was no temporal relationship between dosing and time of onset of GI AEs. (Schnitzer 2000) Another study of alendronate 70 mg weekly vs. placebo found no difference in endoscopic gastric erosions. These clinical findings are consistent with canine studies which suggest that larger weekly doses of BP may be less irritating to mucosa than smaller daily doses (see below).

Fosamax oral buffered solution is, like Binosto after it is dissolved, a citrate-buffered solution containing 70 mg alendronate for weekly administration. The NDA (021575, approved 2003) for this solution included safety data from 157 subjects in 3 clinical pharmacology studies. Two open label studies found similar patterns of GI AEs between the solution (35 or 70 mg, in 75 mL) and 70 mg Fosamax tablets. Higher doses (140 mg/75 mL, 280 mg/75 mL, 375 mg/100 mL) had, surprisingly, somewhat fewer GI AEs than 70 mg/75 mL. Only one study had a small number of placebo-solution subjects, who had somewhat fewer GI AEs than Fosamax solution. Reviewers concluded that safety of Fosamax tablet and solution appeared to be equivalent, therefore these products share the same labeling. To date, there is no evidence from postmarketing reports that GI safety of the oral solution differs from the tablet.

Fosamax GI-related labeling

In response to the early Fosamax postmarketing reports of severe GI events, labeled dosing instructions for alendronate were implemented in 1996 specifying that patients should swallow the tablet with a “full glass of water (6-8 oz.)” and then remain upright “for at least 30 minutes and until after their first food of the day.” Other oral BPs approved subsequently for osteoporosis (risedronate, ibandronate) are believed to have a similar potential for upper GI irritation, therefore GI-related class labeling for all oral BPs has been implemented as follows:

CONTRAINDICATIONS

- *Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia*

- *Inability to stand or sit upright for at least 30 minutes*

WARNINGS

FOSAMAX, like other bisphosphonates administered orally, may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis, or ulcers).

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates including FOSAMAX. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue FOSAMAX and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking oral bisphosphonates including FOSAMAX and/or who fail to swallow oral bisphosphonates including FOSAMAX with the recommended full glass (6-8 oz) of water, and/or who continue to take oral bisphosphonates including FOSAMAX after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION). In patients who cannot comply with dosing instructions due to mental disability, therapy with FOSAMAX should be used under appropriate supervision.

There have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications, although no increased risk was observed in controlled clinical trials.

In addition, Fosamax labeling includes the following Contraindication:

- *Do not administer FOSAMAX oral solution to patients at increased risk of aspiration.*

Mechanism of Alendronate GI Toxicity: Nonclinical Studies

The mechanism by which nitrogenated BPs cause upper GI injury has been extensively investigated. In the esophagus, a local irritant effect is mediated by factors including prolonged mucosal contact of the tablet or tablet fragments and/or high local alendronate concentrations; low pH environment related to gastroesophageal reflux (fasting gastric pH is typically ~1-2); and preexisting mucosal inflammation.

Peter et al (1998) used an *in vivo* dog model, in which various alendronate solutions were infused by gavage tube over 30 minutes into the esophagus under anesthesia, daily for 5 days. It was found that esophageal irritation/ulceration occurred when alendronate 0.2 mg/mL was given in simulated gastric juice with pepsin at pH 2.0; such damage did not occur with the same acidic solution without alendronate, or in

alendronate solutions at higher pH's of 3.5 or 5.0. It was concluded that the free acid form of alendronate, which predominates at pH=2, is more irritating than the sodium salt form found at pH>3, and that reflux of acidic alendronate from stomach to esophagus was the mechanism of injury. The investigators also found that alendronate at higher pH (5.0) was capable of causing esophageal ulcers in dogs who had preexisting esophageal acid-induced inflammation, consistent with potential to exacerbate pre-existing reflux esophagitis. Esophageal damage in these studies was predominantly distal, consistent with a reflux-mediated process.

Because of the apparent key role of esophageal pH, Merck used a citrate buffer system (b) (4) in development of its Fosamax oral solution, which has an alendronate concentration of 0.93 mg/mL. The NDA (021575) included reports from 4 esophageal irritation studies in dogs using the same *in vivo* dog model used in the above-mentioned study. Gavage infusions of pH-buffered alendronate in concentrations of 0.93, 3.73, or 7.47 mg/mL were administered either once or weekly x4 weeks. Only the highest concentration (7.47 mg/mL, 8x the concentration of Fosamax oral solution, or 17x the human dose by mg/m²) produced erosions or ulcerations, and only after 4 weekly doses, not after a single dose. Thus, alendronate concentrations that were much higher than the 0.2 mg/mL from the previous study were nevertheless better tolerated, either because of the less-frequent administration (weekly vs. daily), or the higher pH (or both). Another canine study showed no esophageal irritation with 0.8 mg/mL of alendronate at pH=2 once a week for 4 weeks, in contrast to daily doses of 0.2 mg/mL, also suggesting that a weekly interval between doses may be beneficial in mitigating damage.

In regard to the stomach, it has been proposed that oral BPs may attenuate the hydrophobic protective mucosal barrier to luminal acid, particularly in the presence of NSAID's. Animal studies have shown that very high intragastric concentrations of BPs, together with SC indomethacin, induced gastric lesions in rats and rabbits. However, it was concluded that gastric mucosa appears to be much less sensitive to BPs than esophageal mucosa, as effects were seen only with doses > 100x those given to humans.

Oral Bisphosphonates and Esophageal Cancer

Although bisphosphonates may have antineoplastic effects in some circumstances, an association between oral BPs and esophageal carcinoma was recently proposed. The mucosal irritant effects of these drugs, and specifically a proposed analogy between BP esophagitis and reflux esophagitis, could provide plausibility for this link.

Esophageal squamous carcinoma, related to smoking and alcohol, has declined in incidence over the past 30-40 years. Esophageal adenocarcinoma, by contrast, has increased more than 6-fold in the U.S., in parallel to the rising prevalence of gastroesophageal reflux, which is believed to be due to factors such as obesity and the declining prevalence of *H. pylori*. Chronic acid reflux, in some patients, results in

epithelial changes: columnar metaplasia of squamous epithelium, followed by intestinal metaplasia (i.e. “Barrett’s esophagus”), followed by increasing dysplasia and adenocarcinoma. This sequence is believed to apply to almost all esophageal adenocarcinomas; no other mechanism of carcinogenesis is known. Gastric adenocarcinoma, by contrast, is etiologically linked in most cases to *H. pylori* infection (a lesser number of cases is related to autoimmune gastritis) and has been declining in incidence. Difficulty in classifying these malignancies may occur, as a large proportion of adenocarcinomas are located in the esophagogastric junction (EGJ) or “cardia” region, and local invasion present at the time of diagnosis makes their origin (i.e. esophageal vs. gastric) often unclear. In the absence of a clear defining criteria, the ICD system has historically classified all adenocarcinomas near the EGJ as gastric. However, many authors now believe that this assignation is incorrect, and that these malignancies are mostly if not all of esophageal origin. (Wijetunge 2010) This view is supported by epidemiologic data showing that EGJ adenocarcinomas are increasing in incidence over the past 30 years, similar to esophageal adenocarcinoma and the reverse of gastric adenocarcinoma; that they are associated with symptomatic reflux disease; and that they predominantly affect males. This evidence was recognized in 2009 by the American Joint Commission of Cancer (AJCC), which in its most recent Cancer Staging Manual classifies EGJ tumors as esophageal. (Edge 2009)

The issue of a bisphosphonate link to esophageal carcinoma was initiated with a correspondence to NEJM based upon AERS reports (Wysowski 2009). There were 23 U.S. cases that followed BP exposure (all involving alendronate), and 31 cases from Europe and Japan that followed BP exposure (21 with alendronate, 10 with others). Most of the reports (74%) involved women, which is at odds with the strong preponderance of males with esophageal cancer, but not unexpected as ~90% of BP users are female. There was little information on known risk factors, except that 4 of the patients were noted to have Barrett’s esophagus; this resulted in adding this condition to the Warnings and Precautions in oral BP labeling. The median time from initial BP exposure to cancer diagnosis was 2.1 years in the U.S. cases and 1.3 years in the others.

In follow-up to this initial report, Merck conducted a review of its data on alendronate relative to this issue (NDA 020560, SD-508, submitted 4/9/09). It was noted that 2 year rodent carcinogenicity studies showed no increase in esophageal or other GI tract malignancies, and that 3 year exposure in dogs did not result in hyperplastic or neoplastic changes in the esophagus. In alendronate clinical trials, a total of 2 patients had developed esophageal cancer:

- A 52 year old man entered a study of alendronate for Paget’s disease. Ten days after beginning the drug, he developed pain, difficulty swallowing and vomiting; shortly thereafter an EGD revealed adenocarcinoma of the esophagus with metastases.

- A 57 year old man with CAD and history of prostate cancer, who had taken alendronate for 4 years, entered a trial of lipid lowering drugs; 3 months into the trial he was diagnosed with esophageal cancer.

In regard to postmarketing reports, Merck identified from its worldwide safety database a total of 62 cases of esophageal cancer, over a period of 13 years, in patients who had received oral alendronate, which they believe includes the alendronate cases reported by Wysowski. The median age was 70 y/o (range 30-88) and 73% were women. In the 42 cases in which there was enough information to estimate time from initial alendronate exposure to onset/diagnosis of cancer, the median latency was 20 months (range 5 days to 10 years). Latency exceeded 3 years in only 6 cases. Regarding predisposing factors, many of the 62 cases had a history of GERD or use of acid-reducing medications, and 4 had Barrett's esophagus. Cases in which cell type was reported included 12 with adenocarcinoma, 10 with squamous cell carcinoma, and 1 with undifferentiated carcinoma; in several cases, the narrative suggests the lesion was likely not an esophageal primary. Endoscopic findings in several cases note stricture or ulceration, which may indicate that obstruction to passage of alendronate tablet caused irritation which could have expedited detection of the cancer. There has been no secular trend in the number of these reports, either in absolute numbers or relative to estimated worldwide exposure. (**Table 3**) The latency period of this malignancy is unknown.

Table3 Postmarketing reports of esophageal cancer associated with alendronate[‡]

Year	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
# of cases reported	2	4	11	7	5	5	4	4	7	4	2	3	4*	6**
[‡] as reported to Merck * covers only months of Jan-Feb 2009 (initial report to NEJM was 1/1/09) Source: submission to NDA 020560, SD-508, 4/9/09 except for: **6 cases for reporting period Sept 2009-Sept 2010 reported in Nov 2010 PADER to NDA 20-560														

Based on these reported cases, the cumulative worldwide reporting rate of esophageal cancer over this 13-year period was 0.13 per 100,000 patient-years of alendronate exposure. According to SEER data, the background incidence in U.S. adults age ≥ 65 years is 23.3 per 100,000 patient-years (37.5 per 100,000 among men and 11.2 per 100,000 among women. (Ries, 2001)

Reviewer comment: Alendronate postmarketing reports of esophageal cancer thus represent only ~1% of the background rate, and show no sign of an upward trend. The likelihood that clinicians or patients (or attorneys) would report cases of oral BP/esophageal cancer to AERS is unknown, but would likely be greater than with other drug/cancer combinations, because of universal awareness of the BP/esophagitis relationship.

Prompted by the letter to NEJM, at least 6 research groups have investigated the possible association of esophageal cancer with BPs: 3 using data from the U.K. primary care General Practice Research Database (GPRD), 1 using the Danish national cohort, 1 using U.S. Medicare data, and 1 using the U.S. national VA database.

Green et al (2010), using GPRD data, compared previous oral BP use in 2954 esophageal cancer patients, 2018 gastric cancer patients, and 10641 colorectal cancer patients, with 5 controls per case. The cases were matched for age, gender, general practice and observation time; analysis adjusted for smoking, alcohol and BMI. The odds ratio for BP exposure was increased for esophageal cancer patients (1.30, 95%CI = 1.02 to 1.66, $p=0.02$), and was not increased for either gastric cancer patients (0.87, 95%CI = 0.64 to 1.19) or colorectal cancer patients (0.87, 95%CI = 0.77 to 1.00). The esophageal cancer risk appeared even greater with a larger number of prescriptions or longer duration of use. Mean observation time between BP use and cancer diagnosis was 7.7 years.

Several weaknesses of this study, some of which have been observed by other authors (Pazianas, 2011), deserve mention. About half of the BP exposure in the esophageal cancer patients involved etidronate, a non-nitrogenated BP that has not been associated with esophagitis and therefore lacks the proposed biologic mechanism of carcinogenesis. The adjusted risk ratios for alendronate and risedronate individually were not statistically significant in the Green study, and there was no analysis done for these 2 drugs pooled together (i.e. excluding etidronate). Another factor is that case definition was by ICD-10 codes; as noted above, these may misclassify many EGJ tumors of esophageal origin as being gastric tumors. As noted by Pazianas, accelerated discovery of an esophageal tumor prompted by BP use resulting in an earlier EGD might assign more EGJ tumors correctly to the esophagus, relative to cancers in non-BP treated patients. This would help account for the higher esophageal but lower gastric cancer risk seen in BP users in the Green study. Another factor is that the case control design of this study resulted in an esophageal cancer study population that was 64% male, because of the male predominance of this disease; findings therefore may be of limited relevance to the overwhelmingly female population of BP users. A case control design also does not adequately address the issue of competing risks, which may be very significant in frail osteoporosis patients.

Cardwell et al (2010) also used GPRD data in a retrospective cohort study. A total of 41,826 BP exposed patients and 41,826 controls were matched for age, gender and general practice. Unlike the Green study, 81% were female. After a mean follow-up time of 4.5 years, there were no differences between BP users and controls in risk of esophageal and gastric cancer combined (adjusted HR 0.96, 95%CI = 0.74 to 1.25), or in risk of esophageal cancer alone (adjusted HR 1.07, 95%CI = 0.77 to 1.49). Risk was also unaffected by type of BP (nitrogenated or non-nitrogenated alone, alendronate alone) or duration of use. Patients who took alendronate for more than 2 years had a HR for esophageal cancer of 0.85 (95%CI = 0.45-1.61). Neither this study nor the Green

study validated diagnoses by review of primary patient records, or determined cell type (squamous cell vs. adenocarcinoma), which would be of great importance as these malignancies appear to be pathogenetically distinct.

Merck, independently from the above groups, is sponsoring another study, limited to women, also in the GPRD database, conducted by Dr. Alec Walker of WHISCON LLC. Data were analyzed in both a case control and retrospective cohort manner. (b) (4)

A validation study in a sub-sample, comparing electronic GPRD records to information in the primary patient charts, showed that in many cases, there was a delay of several months between the onset of symptoms or date of cancer diagnosis, and the entry of the diagnostic code into the GPRD. The investigator felt that this may cause inclusion of many cases in which the actual "latency period" was implausibly short. In addition, findings could be biased if patterns in recording diagnoses between different practices correlate with patterns of prescribing BPs. Therefore this investigation is continuing with chart abstraction in all cancer cases or possible cases, focusing particularly on date of clinical onset; chart review will also enable identification of the cancer cell type in most cases. This added information is not available in the other epidemiologic studies, which did not perform intensive chart review. Another report incorporating this additional data is tentatively set for submission in December, 2011.

Abrahamsen et al (2009) evaluated a cohort of patients with fractures from the Danish national registers: 13,678 oral BP users and 27,356 non-BP users were matched for age, gender and fracture type. Over a median follow-up time of 2.2 years, BP users had significantly reduced risk for esophageal cancer (HR 0.35, 95%CI = 0.14 to 0.85, $p=0.02$) compared to controls. Risks for gastric cancer (HR 1.23; 95%CI = 0.68 to 2.22) and esophageal or gastric cancer combined (HR 0.78, 95%CI = 0.49 to 1.26) were not significantly different.

In a recent article (Abrahamsen 2011) this group extended their analysis of Danish registry data in a larger cohort of 30,606 alendronate users (all women ≥ 50 y/o) and 122,424 matched controls. They found that endoscopy had been done in 4.1% of alendronate users in the year before treatment, compared to only 1.7% of controls ($p<0.001$); the higher endoscopy frequency in alendronate users persisted in the year after starting treatment (4.5% vs. 2.1% control, $p<0.001$). Out of 318 subjects with esophageal or gastric cancer, 10% had codes for both esophageal and gastric cancer at different contacts; this anatomically ambiguous group was included in the combined outcome only. After a median follow-up time of 3.5 years on treatment, the HR for esophageal cancer was 0.71 (95%CI = 0.43 to 1.19) and for gastric cancer was 0.61 (95%CI = 0.39 to 0.97), adjusted for comorbidity (Charlson) and baseline endoscopy. Risk for the combined (esophageal + gastric) outcome was significantly decreased

(adjusted OR 0.63, 95%CI = 0.45 to 0.87). Risk reductions were greater in alendronate users with ≥ 10 prescriptions: esophageal Ca adjusted OR 0.51 (95%CI = 0.25 to 1.02); gastric Ca adjusted OR 0.42 (95%CI = 0.22 to 0.81); and combined outcome adjusted OR 0.44 (95%CI = 0.27 to 0.69). A comparison of alendronate and etidronate users showed no significant differences.

Unlike the other studies, mortality was also examined: at 3 years, risk was significantly reduced for esophageal cancer death (HR 0.45, 95%CI = 0.22 to 0.92) and gastric cancer death (HR 0.51, 95%CI = 0.27 to 0.96). In a smaller subgroup with long term data (N=25,820), the 9 year risk of esophageal cancer death was adjusted OR 1.01 (95%CI = 0.52 to 1.95); for gastric cancer death was adjusted OR 0.44 (95%CI = 0.19 to 1.03); and for combined cancer death was adjusted OR 0.70 (95%CI = 0.42 to 1.17).

Solomon et al (2009) searched U.S. Medicare claims data of patients who were beginning osteoporosis treatments. Esophageal cancer incidence rates (per 100,000 patient-years) were 26.7 for patients receiving oral BPs and 48.4 for patients receiving other osteoporosis medications (e.g. raloxifene or calcitonin). The rate in oral BP users was not significantly different from SEER registry data for the ≥ 65 year age group (23.7 per 100,000 patient years).

Nguyen et al (2010) limited their study to patients with pre-existing Barrett's esophagus, a population with esophageal adenocarcinoma risk that is ~30-125 -fold greater than the general population. In a cohort of 11,823 Barrett's patients identified in the Department of Veterans Affairs database, 116 patients who developed esophageal adenocarcinoma at least 6 months following diagnosis of Barrett's were matched with 696 controls who had Barrett's but did not develop cancer. Previous oral BP use (alendronate) was identified in 1.7% vs. 1.9% of cases vs. controls, with an incidence density ratio of 0.92 (95%CI, 0.21 to 4.15). The authors concluded that among patients with Barrett's esophagus, oral BPs did not increase the cancer risk. Weaknesses of this study are that 97% of cases were men, and that BP use was so uncommon: only 2 oral BP users developed cancer.

Reviewer comment: *Of these 6 epidemiologic studies of BPs and esophageal cancer , 1 appears to show an increased risk, 1 a decreased risk, and 3 show no difference in risk; the remaining study is ongoing. Postmarketing and epidemiologic data related to this putative risk are difficult to evaluate because of the large number of confounding factors. For example, oral BPs may be preferentially prescribed for patients without GERD, which would tend to mask a tendency to increase esophageal cancer risk. On the other hand, it is likely that use of oral BPs leads to endoscopy with earlier detection of esophageal cancers in at least some patients. During 3-year alendronate clinical trials, 40-50% of subjects reported upper GI adverse events. In clinical practice, patients who are prescribed an oral BP are universally warned about GI problems. For patients who report such symptoms, the current standard of care in any patient > 45-50 y/o presenting with new upper GI symptoms (regardless of BP use), as recommended by*

numerous consensus panels, is to perform endoscopy; this procedure would be very unlikely to miss an existing neoplasm. A patient with a previously undetected esophageal tumor may be even more likely to experience symptoms due to the tumor causing obstruction to passage of a BP tablet, resulting in esophagitis and prompting an endoscopy. .

In summary, there is little evidence to suggest an association of alendronate or other oral BPs with esophageal cancer, given that:

- the number of spontaneous postmarketing reports represents only ~1% of the expected background rate of esophageal cancer, and is not increasing after 15 years of extensive marketing;*
- latency period between BP exposure and cancer onset is very short in many reported cases, and not well documented in others;*
- a short latency period would imply a mechanism involving not carcinogenesis but tumor promotion in high risk (i.e. Barrett's) patients, however studies have failed to show that the latter are at increased risk from oral BP exposure;*
- case definition (squamous cell vs. adenocarcinoma, and esophageal vs. gastric) is frequently not well documented; and*
- epidemiologic studies give conflicting results, probably because of many confounding factors, particularly the greater tendency of oral BP users to undergo endoscopy.*

It is clear that there is not a marked increase in esophageal cancer risk with oral BPs. Whether there is a slight increase in risk, no effect, or a reduced risk, may be difficult to resolve.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A Pre-NDA package with questions was submitted on October 3, 2008. The Applicant stated their intent to pursue a 505(b)(2) application for effervescent alendronate based upon bioequivalence (BE) to Fosamax tablet, and the Division agreed that, if BE criteria were met and there were no new safety issues, no other clinical data would be needed, nor nonclinical studies in the absence of new excipients or impurities requiring qualification. The Applicant had conducted a gastric imaging and pH telemetry study (BC-118-07) (b) (4)



IND 103130 for effervescent alendronate was opened on June 23, 2009. The submission included reports of two clinical studies which had been conducted in Europe:

- SCO5361, a bioequivalence and food effect study comparing the 70 mg effervescent tablet to the 70 mg Fosamax tablet
- BC-118-07, a gastric imaging and pH telemetry study

Study SCO5361 had failed to prove bioequivalence of the effervescent tablet to the Fosamax tablet, with 90%-confidence lower limit for AUC slightly below the acceptable range. [REDACTED] (b) (4)

[REDACTED] in a second bioequivalence study, AE-1212-001-EM. Although this study was also not intended to be conducted under the IND, the protocol was included in the original IND submission, and several Division comments were sent to the Applicant on 10/2/09 and incorporated into the protocol.

Study AE-1212-001-EM was conducted in Germany in 2009-2010, and the Applicant believes that the results demonstrate bioequivalence to Fosamax 70 mg tablet sufficient for approval. A Pre-NDA meeting was held on September 1, 2010. The Applicant confirmed that their formulation had not changed between the two BE studies (SCO5361 and AE-1212-001-EM) except for [REDACTED] (b) (4)

[REDACTED] In response to Division request, they agreed to submit the individual study reports and CRFs, and to pool safety data from the two BE studies in an Integrated Summary of Safety in the NDA. They were asked to “provide a discussion of all adverse events of interest (those noted in the current Fosamax labeling) and any differences in safety signals between the two studies that might be attributable to the alendronate particle size.” The Division stated that a comprehensive literature review was not needed for this 505(b)(2) application, but that an in-depth discussion should be included regarding the GI tolerability of the product, particularly the issue of alendronate particulate matter thereupon.

This NDA was submitted on December 21, 2010 and was received the following day. A small business waiver of the PDUFA fee was also requested, and the Applicant was made aware that this would delay initiation of the review. The fee waiver was granted on February 15, 2011, and the Applicant was informed that the review process would begin, effective on that date.

2.6 Other Relevant Background Information

Not applicable

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This application is mostly based upon data from a pivotal BE study (AE-1212-001-EM) conducted at a single clinical site in Germany, CRS Clinical Research Services Mannheim GmbH, under supervision of Nycomed GmbH of Konstanz, Germany, which is the Applicant's European partner. (b) (4)

(b) (4) The Office of Scientific Investigation (OSI) conducted a GCP inspection of the clinical site in Mannheim and did not issue a Form 483 for this site (compliance classification = NAI).

OSI also conducted a GLP inspection of the (b) (4) bioanalytic facility in (b) (4), and issued a Form 483 expressing concern regarding the validity of some of the alendronate PK data from study AE-1212-001-EM. At issue was the identification by OSI inspectors of chromatographic interferences in 11 of the PK batches. OSI recommended either re-assay of these 11 batches, or exclusion of their data from the bioequivalence analyses. These options were discussed at a teleconference on 10/12/11 between DRUP and the Applicant; the plan agreed upon was that the Applicant would repeat the statistical analyses without the data from the 11 batches in question. Subsequently on 10/27/11, the Applicant submitted (#0019) the requested re-analyses with their conclusion that the bioequivalence criteria (Ae_{0-48} and E_{max}) were still met. Because additional time was needed for OCP3 to review the re-analysis prior to approval, this was considered a major amendment and the PDUFA Goal Date for this NDA was extended from 12/15/11 to 3/15/12. Subsequently, upon review, it has been determined that the re-analyzed data are acceptable.

3.2 Compliance with Good Clinical Practices

All 3 clinical studies include statements that they were conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki. All studies appear to have been conducted in compliance with their protocols and with IEC and informed consent requirements.

3.3 Financial Disclosures

A Financial Disclosure form (3454) states that there was no arrangement by which compensation of the investigators or sub-investigators of studies AE-1212-001-EM or SCO5361 could be affected by the outcomes of these studies, and that no investigators had any financial arrangements or interests to disclose as defined in 21 CFR 54.4.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

A brief summary is provided here; for details please see reviews by Dr. Hitesh Shroff (CMC) and Dr. Tien-Mien Chen (Biopharmaceutics).

The alendronate sodium drug substance for this product is manufactured, (b) (4) and tested for release and stability in accordance with GMP at (b) (4) under DMF (b) (4). The effervescent tablet drug product is manufactured by (b) (4). The tablets are packaged in aluminum foil composite blister strips; each container will contain blisters with either 4 tablets or (b) (4).

The initial, unsuccessful bioequivalence study SCO5361 and the pharmacodynamic study BC-118-07 both used drug product manufactured with (b) (4). The second, successful BE study AE-1212-001-EM used drug product that was identical except (b) (4) as would the marketed drug product.

The drug product is a round, 2.5-cm diameter effervescent tablet with total mass of 4.05 g and containing:

- Sodium alendronate trihydrate, (b) (4), 91.37 mg, equivalent to alendronate 70 mg (free acid)
- Monosodium citrate anhydrous, (b) (4)
- Citric acid anhydrous, (b) (4)
- Sodium hydrogen carbonate, (b) (4)
- Sodium carbonate anhydrous, (b) (4)
- Strawberry flavor, sweeteners

There is approx. 653 mg (28 mEq) of sodium per tablet. For comparison, an Alka Seltzer tablet has 445 mg of sodium. According to 21 CFR 331.11(k)(1) governing OTC sodium bicarbonate-containing antacid products, these quantities are within the 100 mEq maximum allowable daily dosage limit for sodium (for patients > 60 y/o). According to 21 CFR 201.64, labeling for OTC drug products intended for oral ingestion must contain the following statement under the heading "Warning" if the amount of sodium present in the labeled maximum daily dose of the product is >140 mg: "Ask a doctor before use if you have....a sodium-restricted diet." There are apparently no similar regulations governing sodium content or labeling for Rx drugs.

Reviewer comment: *Because this product's osteoporosis target population has a high prevalence of hypertension and level of cardiovascular risk, its labeling should include a warning regarding sodium content that is at least as substantive as the warning on OTC products.*

The solution prepared by dissolving the tablet in 120 mL of water has a pH of ~5 and provides an acid neutralizing capacity of ~13-14 mEq, which is more than adequate to neutralize basal (fasting) gastric acid output (ULN is ~ 10 mEq/hr in men, 5 mEq/hr in women).

The solubility of sodium alendronate in water is ~10 mg/mL; this tablet yields a 0.58 mg/mL solution when prepared as prescribed. Mean tablet "disintegration" time was reported to be 18-21 seconds (b) (4)

Table 4 Assay Data after 1-5 minutes in solution for effervescent tablet batches manufactured with (b) (4) (Source: M3.2.P.2, Table 1)

Batch 2046-8007 (b) (4)		Batch 2046-8008 (b) (4)	
Condition	Assay as Alendronic Acid (%) (b) (4)	Condition	Assay as Alendronic Acid (%) (b) (4)
Content assay	(b) (4)	Content assay	(b) (4)
1 minute Ws	(b) (4)	1 minute Ws	(b) (4)
2 minutes Ws	(b) (4)	2 minutes Ws	(b) (4)
3 minutes Ws	(b) (4)	3 minutes Ws	(b) (4)
5 minutes Ws	(b) (4)	5 minutes Ws	(b) (4)
1 minute S	(b) (4)	1 minute S	(b) (4)
2 minutes S	(b) (4)	2 minutes S	(b) (4)
3 minutes S	(b) (4)	3 minutes S	(b) (4)
5 minutes S	(b) (4)	5 minutes S	(b) (4)

S = Stirred; Ws = Without stirring.

Table 5 Assay Data after 3-5 minutes in solution for an effervescent tablet batch manufactured with (b) (4) (Source: M3.2.P.2, Table 2)

Batch	Assay as Alendronic Acid (%)		
	After 1 Minute Effervescent Reaction and Further 2 Minutes Standing	After 3 Minutes Standing and 1 Minute Stirring	After 3 Minutes Standing and 2 Minutes Stirring
2046-8004 (b) (4)	(b) (4)		

In response to an Information Request from the Division for further information regarding the possibility of significant particulate matter in the drug product solution prior to ingestion, the Applicant submitted (on 09-Aug-2011, #0011) results of 3 new *in vitro* studies:

- Placebo and Binosto effervescent tablets were placed in 200 mL water at 15-25°C; after 3-5 minutes the visual appearances of the solutions were the same, i.e. a small amount of residue was present in each. The investigator concluded that the residue most likely represented undissolved particles of an excipient(s) rather than alendronate.
- Placebo and Binosto effervescent tablets was placed in 120 mL of water; after 5 minutes, the solutions were run through paper filters. The filters was then sprayed with Ninhydrin (which produces a color reaction with the amino group in alendronate). Filters from both placebo and Binosto tablets produced “trace” to “very slight” violet coloration. As a positive control, 1% of the Binosto dose (i.e. 0.7 mg alendronate) was placed on a paper filter and with Ninhydrin produced a much more distinct violet coloration. The conclusion was that the quantity of undissolved sodium alendronate in the Binosto solution, if any, was (b) (4) of the administered dose.
- Within a stability study, Binosto tablets were placed in solution for 5 minutes, and assay of the solutions showed alendronate content (b) (4) below that of the tablets.

In the initial clinical BE study, SCO5361, (b) (4), the report states that the solution was prepared with 120 mL water at room temperature between 10-20 minutes before administration and stirred “until the tablet had fully dissolved.” However, investigators recorded observations that particles or crystals remained on the sides of the glass after subjects drank the solution. In the second BE study, AE-1212-001-EM, (b) (4), the solution was prepared between 5-15 minutes before administration with 120 mL water at room temperature, and then stirred with a spoon for 10 seconds immediately before intake.

Reviewer comment: *It is important for product safety that the alendronate be fully dissolved prior to ingestion. Product labeling should direct the patient to follow the dosing instructions used in study AE-1212-001-EM, including allowing at least 5 minutes for dissolution, with adequate stirring. Shorter times based on time to observed tablet “disintegration” and/or cessation of effervescence would not be appropriate.*

The clinical studies, and apparently also the in vitro dissolution studies, used only room temperature water in which to dissolve the effervescent tablets. There are no data available on the effect of temperature on alendronate dissolution with this product, therefore it is unclear whether safety/tolerability may be adversely affected if patients were to use water from the refrigerator to prepare their dose of this product. Though such use would be unlikely to present a significant safety issue, product labeling should clearly state that only room temperature water should be used, as in the clinical studies.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

This 505(b)(2) NDA refers to NDA 020560 for pharmacology studies and general toxicity, genotoxicity, reproductive toxicity, carcinogenicity and special toxicity (esophageal irritation) studies, and to NDA 021575 for additional esophageal irritation studies in dogs. The Applicant was previously informed that additional pharmacology/toxicology studies would not be required in the absence of either new excipients, or impurities in amounts sufficient to require qualification. The application claims there are none, therefore no new nonclinical studies have been performed.

4.4 Clinical Pharmacology

A very brief summary is provided here; please refer to comprehensive review of this product by Dr. Hyunjin Kim of the Division of Clinical Pharmacology, and to approved labeling of Fosamax.

4.4.1 Mechanism of Action

Alendronate, like other BPs, localizes to sites of bone resorption, where it becomes incorporated into bone matrix and inhibits the bone-resorptive activity of osteoclasts. This generally results in reduction in bone turnover, increase in bone mass and mineral density, and reduced tendency to fracture. Histology and histomorphometry have demonstrated that bone quality appears to be preserved.

4.4.2 Pharmacodynamics

No studies were done with this new product relative to its pharmacodynamic properties in bone tissue, which are assumed to be identical to Fosamax. One GI pharmacodynamic study, BC-118-07, was conducted in order to compare the effect of Binosto on gastric pH and motility with that of Fosamax. It was found that, as expected due to the citrate buffer of Binosto, gastric pH remained above 3 for at least the 30 minutes immediately after dosing, unlike with Fosamax where the pH was >3 for only a

few minutes after dosing. (b) (4)

Please see Appendix 9.4.3 for additional details of this study.

4.4.3 Pharmacokinetics

Alendronate, like other oral BPs, has poor absorption (~0.7% relative to IV), which is even further diminished if there is food in the stomach. Labeling notes that antacids block absorption; this is because most antacids contain divalent cations which complex BPs. Binosto contains antacids however these use a univalent cation (sodium). Oral BP absorption may be improved under conditions of higher gastric pH: in 10 postmenopausal women, high doses of IV ranitidine producing intragastric pH > 6 led to a near-doubling of alendronate bioavailability. (Gertz 1995) The reason is unclear but may reflect improved solubility of alendronate sodium at higher pH. Proton pump inhibitors, which are commonly co-prescribed with BPs, may increase osteoporotic fracture risk and may attenuate the antifracture efficacy of alendronate (an effect not seen with H2 antagonists), but their effect on alendronate absorption is unknown. (Abrahamsen 2011)

Fosamax labeling indicates that, in order to allow absorption, patients should fast overnight, and continue to refrain from eating until at least 30 minutes after administration. The two BE studies in this application, however, continued this fast until 4 hours after administration. The Applicant states that this is consistent with FDA guidance documents, and with previous alendronate PK studies. The first BE study, SCO5361, also included an arm in which patients ate a meal only 15 minutes after Binosto; absorption was markedly reduced, consistent with other alendronate studies.

Alendronate is not metabolized. Because of the low absorption followed by rapid redistribution to bone (~60%) or excretion in the urine (~40%), plasma concentrations are generally too low for analytical detection. Therefore urine levels have been the standard for alendronate PK analysis, and were used in the two BE studies in this application. The main PK endpoints in these studies were Ae_{0-48} (cumulative urinary excretion, 0-48 hrs post-dose) and E_{max} (maximal urinary excretion rate). Because of its incorporation into bone matrix, the $t_{1/2}$ of alendronate is estimated to exceed 10 years.

Pharmacokinetics of alendronate do not appear to vary significantly with age or gender. The drug is not recommended for patients with more severe renal insufficiency ($CrCl < 35$ mL/min) because of inadequate clinical data in this population.

5 Sources of Clinical Data

The Applicant was informed in Pre-IND communication (11/6/08), and at the Pre-NDA meeting (9/1/10), that if strict bioequivalence with Fosamax 70 mg tablet is established for this product, no additional clinical efficacy data would be needed for registration.

They have conducted two PK bioequivalence studies, SCO5361 and AE-1212-001-EM, and one GI pharmacodynamic study, BC-118-07. The first PK study, SCO5361, failed to establish bioequivalence to Fosamax 70 mg tablet, causing the Applicant to re-formulate their product (b) (4). Subsequently, study AE-1212-001-EM was conducted using the new formulation, and the Applicant concludes that bioequivalence was demonstrated. They also contend that safety data from the 3 studies do not show any safety signals. Study reports and datasets from all 3 studies are included in the submission. In addition, clinical efficacy and safety data from NDA 020560 as reflected in current Fosamax labeling are incorporated by reference.

The first two clinical studies were sponsored by EffRx and the pivotal BE trial, AE-1212-001-EM, was sponsored by the European partner, Nycomed Group. Although all 3 studies were conducted outside of IND 103130, the draft and final protocols for AE-1212-001-EM were submitted for FDA comment, and several changes were made accordingly.

The 2 BE studies were conducted in Germany, and the small GI pharmacodynamics study in Scotland. All of the patients in the 2 BE studies were white. The 74-day letter asked the Applicant to provide a rationale for the applicability of the data to the U.S. population. Their response (5/24/11) was as follows:

- Per Fosamax PI, BMD response to alendronate does not vary by age, race, baseline rate of bone turnover, or baseline BMD
- Also per Fosamax PI, pharmacokinetics do not vary by age or gender
- Although effects of race/ethnicity on alendronate PK have not been studied, lack of metabolism of BPs indicates a low likelihood of sensitivity to ethnic factors (per ICH *Guidance for Industry E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data*, Sept 2006)
- The practice of medicine is similar in the U.S. and Europe
- There is extensive global clinical experience, using the same dose regimens in all regions, that has shown no sign of differences in safety or efficacy across racial/ethnic groups

5.1 Tables of Studies/Clinical Trials

Table 6 List of Clinical Studies

Type of Study	Study Design	Test Products	Primary endpoints	Subjects
Study AE-1212-001-EM				
Bioequivalence (b) (4)	Open-label, 4-period, crossover, single-dose, replicate design	EffRx effervescent tablet 70 mg; Fosamax tablet 70 mg; fasting conditions	Pharmacokinetics: Ae_{0-48} , E_{max}	70 healthy women, 45 healthy men

Study SCO5361				
Bioequivalence (b) (4)	Open-label. 3-period, crossover, single- dose	EffRx effervescent tablet 70 mg (fasting, fed); Fosamax tablet 70 mg (fasting)	Pharmaco- kinetics: Ae ₀₋₄₈	134* healthy women
Study BC-118-07				
Gastrointestinal pharmacodynamics (b) (4)	Open-label. 3-period, crossover, single- dose	EffRx effervescent tablet 70 mg; reference effervescent powder 70mg; Fosamax tablet 70 mg; fasting conditions	Gastric emptying times for alendronate; gastric pH	12 healthy women
* One of the 134 women randomized in SCO5361 did not receive study drug				

5.2 Review Strategy

This clinical review focuses on safety findings, in particular upper GI adverse effects of Binosto compared to Fosamax tablet, primarily from the two PK studies, SCO5361 and AE-1212-001-EM. Bioavailability and bioequivalence data from these studies were reviewed by Dr. Hyunjin Kim of the Division of Clinical Pharmacology. The GI pharmacodynamic study, BC-118-07, is also reviewed briefly here, although it was not considered essential for approval and will not be used in labeling.

5.3 Discussion of Individual Studies/Clinical Trials

Please see Appendix 9.4 for detailed discussion of the 3 individual studies included in this application.

6 Review of Efficacy

Efficacy Summary

No clinical efficacy studies have been conducted with this new product. This 505(b)(2) application relies on the FDA's findings of efficacy of the reference listed product, Fosamax (alendronate) 70 mg tablet (NDA 020560), administered once weekly for:

- Treatment of osteoporosis in postmenopausal women (PMO); and
- Treatment to increase bone mass in men with osteoporosis.

Fosamax, as outlined in its labeling, has demonstrated significant increases over placebo in bone mass of lumbar spine, femoral neck, hip trochanter and total body in both of these populations. In addition, in women with PMO, there were significant reductions demonstrated in fractures of vertebrae, hip and wrist as well as overall clinical fractures.

This application is based upon pharmacokinetic bioequivalence of Binosto to Fosamax; these data are reviewed by Dr. Hyunjin Kim of the Division of Clinical Pharmacology.

7 Review of Safety

Safety Summary

Assuming pharmacokinetic bioequivalence of Binosto and Fosamax, safety is expected to be equivalent for these two products, with the possible exception of a difference in upper GI safety/tolerability related to the type of formulation. Fosamax tablets have the potential to cause esophagitis, which may include ulceration and/or stricture formation in severe or unrecognized cases. However, when Fosamax is prescribed appropriately and taken correctly (with adequate water, upright position), controlled trials have shown that such events are very infrequent, and similar to placebo (see section 2.4).

Factors that may promote esophagitis from alendronate and other oral bisphosphonates include impaction of the tablet (or fragments thereof) causing prolonged mucosal contact in the esophagus; reflux of gastric acid; and pre-existing mucosal inflammation, e.g. from reflux esophagitis. Solubilization data on Binosto appear to show that the alendronate is dissolved completely within 5 minutes with stirring, and the product's pH buffering system, which was demonstrated clinically in study BC-118-07, may tend to mitigate any reflux effects. In order to help prevent esophagitis related to mucosal contact with undissolved alendronate from this new product, the labeling should specify that preparation of each dose would reproduce the procedure used in study AE-1212-001-EM, i.e. allowing at least 5 minutes for dissolution of the effervescent tablet in 4 oz. of room temperature plain water, and stirring for 10 seconds prior to ingestion.

Data from studies AE-1212-001-EM and SCO5361 in 248 healthy male and female subjects, age 45-75, are consistent with equivalent safety of Binosto and Fosamax. The adverse events and minor changes in serum calcium and phosphorus seen were consistent with the well-established safety profile of Fosamax. There were no deaths, and no imbalances between the two drugs in serious events or events leading to study withdrawal. In the data from the 4-hr post-dose fasting periods, GI events were reported by 11.6% of subjects following Binosto and 12.0% of subjects following Fosamax. No GI AEs were considered serious, or required any intervention. GI AEs were more common in women than in men with both drugs. There were very few non-Caucasian or elderly subjects in the studies, but no evidence indicates that relative safety of these two drugs would be likely to differ within these populations.

In the 4-hr-fasted treatment periods of the two BE studies, a preferred term relevant to potential esophagitis, dyspepsia (including verbatim term heartburn), occurred more frequently following Binosto (6 events, vs. 1 with Fosamax, or 2.5% of subjects vs. 0.4%). In the study (AE-1212-001-EM) (b) (4), the form intended for marketing, there were 2 events of dyspepsia (following 221 Binosto doses in 115 subjects). Episodes of dyspepsia occurred mostly within a few hours of administration of Binosto. All were apparently minor, and none resulted in study dropout. Among the 8 subjects in both studies who experienced dyspepsia following Binosto (either fasted or fed), all received two doses of Binosto, yet reported dyspepsia after only one of the doses. The symptoms that have been most typical of serious oral BP-related esophagitis, i.e. dysphagia and odynophagia, were not seen, except for one subject with dysphagia at 1.5 hrs following Fosamax. Younger subjects (≤ 57 y/o) accounted for the excess of dyspepsia with Binosto relative to Fosamax.

Nausea was also more common with Binosto relative to Fosamax (14 events vs. 8, or 5.4% of subjects vs. 3.3%), but incidence of vomiting was about equal. Half of the nausea episodes were within 1 hr of dose. It is possible that characteristics of the formulation, such as the taste or effervescence/CO₂ generation, may have contributed to some of these symptoms in this open-label study. As with dyspepsia, younger subjects (≤ 57 y/o) accounted for the moderate excess of nausea with Binosto relative to Fosamax.

Diarrhea, in contrast, was somewhat more common with Fosamax compared to Binosto. There were no serious GI AEs, and only one subject discontinued due to a GI AE (nausea/vomiting after Fosamax).

Issues of BP safety related to long-term suppression of bone turnover could not be addressed in these short-term studies, and should not differ between Binosto and Fosamax, given systemic bioequivalence.

Because of its acid buffering and effervescent properties, Binosto contains 653 mg (28.4 mEq) of sodium per tablet, equivalent to ~1600 mg dietary NaCl. There was no evidence of a significant effect on blood pressure in the healthy subjects in the submitted studies. However, Fosamax is used predominantly by elderly women, a population with very high prevalence of hypertension and risk for congestive heart failure (CHF) and stroke; there is some published evidence that lapses in dietary sodium restriction may contribute to hospital admissions for CHF. Although this is unlikely to be a significant safety issue for this product, information about the sodium content of Binosto should be included in physician and patient labeling. At minimum this should be consistent with current regulations governing OTC drugs, which require a labeled warning to the patient if the amount of sodium present in the maximum daily dose of the product is >140 mg (see section 4.1)

In summary, there is no evidence indicating that safety of Binosto 70 mg effervescent tablet is expected to differ significantly from that of Fosamax 70 mg tablet.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In addition to reliance on clinical safety information for the RLD, Fosamax (NDA 020560), this application includes safety data from 248 subjects in two BE studies (AE-1212-001-EM and SCO5361), and 12 subjects in a GI pharmacodynamic study, BC-118-07. All 3 studies used a crossover design, so that subjects received the effervescent tablet as well as Fosamax for comparison.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the submitted application was coded in MedDRA version 12.0. Investigators classified all AEs as to severity (mild, moderate, severe) and causality (not related, possible, probable). The Applicant adhered to the definition and reporting requirements for serious adverse events, as defined by the ICH guidelines.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As requested by the Division at the pre-NDA meeting of 9/1/10, most of the safety data from the two BE studies were pooled for the Integrated Summary of Safety (ISS). This included demographics, exposure, AEs, concomitant medications, reasons for premature termination, serum calcium and phosphorus, and vital signs.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The ISS pooled safety population consists of 248 healthy subjects (203 women, 45 men, mean age 57, all Caucasian) in the two bioequivalence studies who received at least 1 dose of Binosto. These studies used a crossover design, and ~95% of subjects received two doses of the effervescent formulation, as well as 1 or 2 doses of the RLD Fosamax tablet for comparison. A total of 479 doses of Binosto was administered in these 2 studies; 349 (73%) of these doses were followed by 4 hr additional fast and 130 (27%) were followed by a meal 15 minutes later. About half (258) of these doses were

the initial formulation (b) (4). In the third, smaller, scintigraphic study, BC-118-07, 11 subjects received single doses of Binosto and Fosamax (fasting). These numbers compare favorably with the safety population (157 subjects; 75 men and 82 women) reviewed for NDA 021575 for Fosamax oral solution, a similar product.

Bioequivalence of Binosto and Fosamax signifies that differences in safety between these 2 treatments are unlikely, with the possible exception of upper GI adverse effects, especially esophagitis, related to the differing formulations. Because these GI effects typically occur acutely, i.e. within hours to a few days of oral BP administration, the short time frame for comparison in the studies, involving single rather than repeated doses, is adequate.

The subjects in the 2 BE studies were 82% female, consistent with the Fosamax target population. (Table 7) They were somewhat younger (mean 57 y/o, range 45-75) and healthier than this population, and all were Caucasian and European. However, the safety profile of Fosamax is well known, and there is no evidence that its safety (or efficacy) differs across age, gender, racial or ethnic groups. (Older age and presence of osteoporosis are associated with greater risk for upper GI disorders including ulceration and bleeding, but there is no good evidence that oral BPs add further to this risk.)

Table 7 Demographics and other baseline characteristics: ISS Pooled Safety Populations

Parameter	Study AE-1212-001-EM (N=115) n (%)	Study SCO5361 (N=133) n (%)	Both studies (N=248) n (%)
Age (years)			
Mean ± SD	56.6 ± 7.9	58.1 ± 8.6	57.4 ± 8.3
Median	54	59	57
Range	45 - 73	45 - 75	45 - 75
< 65 y/o	92 (80.0%)	95 (71.4%)	187 (75.4%)
≥ 65 y/o	23 (20.0%)	38 (28.6%)	61 (24.6%)
≥ 75 y/o	0	1 (0.8%)	1 (0.4%)
Gender			
Male	45 (39.1%)	-	45 (18.1%)
Female	70 (60.9%)	133 (100%)	203 (81.9%)
BMI (kg/m²)			
Mean ± SD	24.8 ± 2.3	24 ± 3	24.3 ± 2.7
Median	25	23.6	24.35
Range	19 - 28	19 - 29.8	19 - 29.8
"Normal" (18.5-25)	51 (44.3%)	83 (62.4%)	134 (54.0%)
"Overweight" (25-30)	64 (55.7%)	50 (37.6%)	114 (46.0%)

Source: Summary of Clinical Safety, M 2.7.4

The 12 subjects in the scintigraphic study (BD-118-07) were women age 20-31 (mean 24.5); 8 were Caucasian, 3 were Asian, and 1 was “other” race. Subjects in study AE-1212-001-EM included 30% who had never smoked, 36% who were past smokers, and 34% who were current smokers (≤ 10 cigarettes/day). Subjects with a history of major upper GI disease were excluded.

The demographics of the study populations and the overall drug exposure in the submitted studies appear to be adequate for safety evaluation.

7.2.2 Explorations for Dose Response

Only one dose of the effervescent tablet was investigated (70 mg), because of the intent to demonstrate bioequivalence with 70 mg Fosamax tablet.

7.2.3 Special Animal and/or In Vitro Testing

Because of the reliance on Fosamax data, Binosto has not been tested in animals. It is possible that its esophageal toxicity could differ from Fosamax, however canine studies conducted prior to approval of Fosamax oral solution demonstrated absence of esophagitis with weekly (x4wks) administration of either a pH-buffered solution of $> 6x$ the alendronate concentration of Binosto, or an acidic solution (pH=2) with $\sim 1.5x$ the alendronate concentration of Binosto.

7.2.4 Routine Clinical Testing

In both BE trials of the new product, subjects were asked about adverse events at 4, 12, 24, 28, 36, and 48 hrs after each dose and at end of study (within 9 days of the last dose). Investigators used open-ended, neutral questioning, and recorded all AEs including start and stop dates/times, intensity, treatment and outcome, as well as seriousness and causality.

In both BE studies, vital signs were recorded at 4, 12, 24 and 48 hrs after each dose. In study AE-1212-001-EM, these were also recorded at 28 and 36 hrs post dose, and in study SCO5361, also at 2 and 8 hrs post dose. In both studies, serum Ca/Phos were measured predose and 24 and 48 hrs after each dose. Clinical chemistry and hematology and ECGs were conducted at screening and at end of study.

These assessments were adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Bisphosphonates are not metabolized and do not interact with other drugs systemically. As discussed in section 2.4, it is possible that oral BPs may add to the upper GI irritant

potential of aspirin or NSAIDs, though this has not been proven. Binosto is not expected to differ from Fosamax in this regard.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Establishing (at least) equivalent upper GI safety and tolerability of Binosto relative to Fosamax is essential to this application. A total of 256 subjects among the 3 studies received at least one dose of the effervescent formulation, and most of these received two separate doses, as well as 1-2 doses of the comparator, Fosamax. Subjects with upper GI conditions indicative of higher risk for bisphosphonate-related GI AEs e.g. dysphagia, esophageal disease, gastritis/duodenitis, UGI bleeding or previous surgery were appropriately excluded, consistent with previous Fosamax clinical trials and Fosamax labeling.

GI safety/tolerability was assessed by means of AE recording in the two BE studies. There are two potential weaknesses of this approach. One is that the studies were open-label; this is probably unavoidable because of the formulation and dosing instructions. Also because of the PK evaluations sought, the timing of food intake differed from labeling instructions for Fosamax, which permit patients to eat >30 minutes after administration. Most of the data with the new product were generated with subjects continuing their overnight fast until 4 hours after alendronate dosing, which would probably increase the potential for upper GI adverse effects. However, it is not likely that this effect would differ significantly between the two alendronate products; therefore this approach is acceptable.

The gastric emptying and pH studies performed in study BC-118-07 provide some supportive evidence in favor of the GI safety of this product. However, the physiological data gathered in this study of young women may not be applicable to the target osteoporosis population, and in any event the clinical relevance of such findings has not been shown. Other means of assessing GI tolerance, such as endoscopy, would have been essential if there had been serious or severe upper GI events, however there were none.

If Binosto and Fosamax 70 mg tablet are bioequivalent, there should be no difference in other (i.e. non-upper GI-related) aspects of bisphosphonate safety, such as potential over-suppression of bone metabolism. Such effects would not be expected in the short-term studies conducted, in any event.

7.3 Major Safety Results

An overview of AEs in the ISS pooled studies is given in **Table 8**. The safety comparisons most relevant to this application, particularly regarding GI safety, are between the “Binosto/fasted” and Fosamax treatment periods, which in both major ISS

studies involved a 4 hr fast following study drug administration. The table also includes results for the third treatment, “Binosto/fed” (15-min postdose fast), and for Binosto/all subjects (both 15 min and 4 hr fast periods), with the caveat that the “Binosto/fed” treatment was given only once per subject (it was not used in the replicate-treatment study), therefore exposure per subject was less for this method. Conversely, the Binosto/all subjects findings reflect a higher number of exposures per subject compared to Fosamax.

Table 8 Overview of Adverse Events: ISS Pooled Safety Population

	Binosto 70 mg			Fosamax 70 mg
	All subjects (N = 245) n (%)	Fed (N = 130) n (%)	Fasted (N = 241) n (%)	Fasted (N = 241) n (%)
Number of doses	479	130	349	351
# subjects with at least 1:				
Adverse Event	148 (60.4)	69 (53.1)	119 (49.4)	118 (49.0)
Adverse Event leading to premature withdrawal	3 (1.2)	3 (2.3)	0	2 (0.8)
Serious Adverse Event	0	0	0	2 (0.8)
GI Adverse Event	43 (17.6)	18 (13.8)	30 (12.4)	31 (12.9)
Adverse Events by severity ^a :				
Mild	75 (30.6)	40 (30.8)	63 (26.1)	69 (28.6)
Moderate	70 (28.6)	27 (20.8)	55 (22.8)	48 (19.9)
Severe	3 (1.2)	2 (1.5)	1 (0.4)	1 (0.4)
Adverse Events by causality ^b :				
Not related	22 (9.0)	14 (10.8)	19 (7.9)	21 (8.7)
Possible	14 (5.7)	0	14 (5.8)	8 (3.3)
Probable	112 (45.7)	55 (42.3)	86 (35.7)	89 (36.9)
n (%) = number (percent) of exposed subjects with adverse events				
^a each subject counted only once, by worst severity for that subject				
^b each subject counted only once, by most related category for that subject				
Source: Summary of Clinical Safety, Table 6				

7.3.1 Deaths

There were no deaths in any of the studies.

7.3.2 Nonfatal Serious Adverse Events

Among the 3 studies, there were 2 SAEs, both during study AE-1212-001-EM, and both associated with Fosamax, the comparator:

- Subject 031, a 70 y/o female with a prior history of hypertension, was noted to have elevated BP after receiving Fosamax tablet (period 3): 191/98 mm Hg at 12 hrs post-dose

and 191/99 mm Hg at 24 hrs. She was sent to her family doctor who treated her with multiple medications, and was withdrawn from the study. The blood pressure came down.

- Subject 107, a 54 y/o male, developed left lower leg thrombosis 4 days after Fosamax tablet in period 4, after end-of-study data had been collected. He was hospitalized and treated with anticoagulants.

Neither of these events were considered study drug-related by investigators.

7.3.3 Dropouts and/or Discontinuations

Of the 248 subjects in the ISS pooled safety population, 231 completed the studies; 6 of those who terminated prematurely did so because of adverse effects. Only one of these appears to be, and was considered by investigators as, study drug-related (subject 014 in study SCO5361 with nausea/vomiting). The AE-related discontinuations were as follows:

Study AE-1212-001-EM:

- Subject 031, a 70 y/o female, discontinued due to **high blood pressure** occurring following **Fosamax**; this was considered an SAE (the only discontinuation due to an SAE; see section 7.3.2)

Study SCO5361:

- Subject 010, a 59 y/o female, discontinued due to mild **nasopharyngitis** which began 25 days after her period 2 dose which was **Binosto/fed** (she had also experienced vomiting previously in period 1, following (Binosto/fasted))
- Subject 014, a 57 y/o female, was administered **Fosamax** tablet in period 1, experienced **nausea** ~3 hrs later and **vomiting** ~7 hrs later
- Subject 034, a 75 y/o female, discontinued due to **hypertension**. She had a baseline BP in her 1st period of 191/91, received **Binosto/fed** and continued to have high readings over 48 hrs in the range of 170-204/ 79-96. She remained asymptomatic and was discontinued from the study because of the blood pressure and referred to PMD. She had no prior history of hypertension
- Subject 061, a 55 y/o female, received **Binosto/fed** (period 1), and developed severe **back pain** 14 hrs later, which resolved after 17 days
- Subject 108, a 45 y/o female, received **Binosto/fed** (period 1), and developed moderate **bronchitis** 2 days later, which resolved after 26 days

In addition, one subject in the scintigraphic study BD-118-07 discontinued due to an AE:

- Subject 008, a 27 y/o woman developed an “**earache, sore throat and sore face**” the evening after the first dose period (b) (4), which the investigator attributed to placement of the NG tube used in the study

7.3.4 Significant Adverse Events

7.3.4.1 GI Adverse Events

Comparing the two 4-hr-fasted groups in the ISS, GI events were reported by 11.6% of subjects following Binosto and 12.0% of subjects following Fosamax. (**Table 9**) In the earlier study SCO5361 (b) (4), overall GI AEs were somewhat more common following Binosto/fasted compared to Fosamax (14.1% vs. 10.2% of subjects). In study AE-1212-001-EM (b) (4), this pattern reversed (8.7% of subjects with Binosto/fasted vs. 13.9% with Fosamax). It is unclear whether this difference could be related to the change in formulation. GI AEs of all types occurred more frequently in women than men following either drug; the 45 male subjects experienced only 6 GI AEs overall.

Dyspepsia/heartburn was more frequent following Binosto/fasted compared to Fosamax, with 6 cases (in 6 subjects) vs. 1. Moreover, the one event with Fosamax was reported at 13 days post-treatment and was therefore considered not treatment related; the 6 events with Binosto/fasted occurred at 0.5, 1, 2, 3, 5, and 36 hrs post dose. (**Table 11**) In the study (AE-1212-001-EM) (b) (4), the 2 dyspepsia events that occurred were in each subject's first of two Binosto treatment periods, and symptoms did not recur in the second such period or in either Fosamax period. (Similarly in the other study SCO5361, dyspepsia did not occur after more than 1 of the 3 drug treatments for any subject.) In addition, all of the dyspepsia events in both studies were "mild"; none resulted in either discontinuation or use of concomitant medications (e.g. acid-reducing or antacids), and all resolved (median 8.5 hr duration, maximum 19 hr). Notably, younger subjects (less than the median age of 57 y/o) appeared more susceptible to dyspepsia with Binosto (fed or fasted: 6 subjects, vs. none after Fosamax); among subjects over 57 y/o, 2 had dyspepsia with Binosto (fasted or fed) vs. 1 with Fosamax. There were no AEs of dysphagia or odynophagia, except for one subject with dysphagia at 1.5 hrs following Fosamax, thus there is no evidence that Binosto caused potentially serious esophagitis.

In both studies, nausea was also experienced by more subjects following Binosto/fasted (5.4%, vs. 3.3% with Fosamax). However, "moderate" nausea (as opposed to "mild") and vomiting were about equal between these two groups. (**Table 10**) Of the 14 episodes of nausea following Binosto/fasted, 7 occurred within 1 hr of dose; the others were at 3, 5, 14, 14, 30 and 34 hrs and at 13 days. The 6 cases of vomiting following Binosto/fasted occurred at 7, 8, 10, 13, 30 and 32 hrs postdose. (The time course of these symptoms following Fosamax was generally similar.) There was only one dropout resulting from these (or any other GI) symptoms: one patient with nausea and vomiting at 3 and 7 hrs (respectively) following a dose of Fosamax. As with dyspepsia, younger subjects (less than the median, 57 y/o) accounted for the greater frequency of nausea with Binosto compared to Fosamax.

A total of 12 subjects experienced more than one upper GI AE (dyspepsia, nausea, vomiting, or abdominal pain upper). In 7 of these subjects, events occurred following both Binosto (either fasted or fed) and Fosamax, consistent with a common mechanism and/or increased susceptibility of some individuals. Most of these recurrences involved nausea and/or vomiting; as noted above, dyspepsia tended not to recur within subjects.

Diarrhea occurred in more subjects following Fosamax (6.2%, vs. 2.1% with Binosto/fasted), though this did not apply to the Binosto/fed treatment period, in which 6.9% had diarrhea. In study AE-1212-001-EM, 8 of the 16 diarrhea events occurred in the first of 4 crossover treatment periods for that subject; however in study SCO5361, diarrhea events were evenly distributed among the subjects' 3 treatment periods. The sequence of treatments was random in both studies so should not have created a bias toward one treatment; the lack of blinding could have had such an effect but this seems unlikely. There was one episode of "moderate" diarrhea (Fosamax related); the rest were "mild". (Table 10)

Table 9 GI Adverse Events[†] by Treatment: ISS Pooled Safety Population**

System Organ Class Preferred Term	Binosto 70 mg						Fosamax 70 mg	
	All subjects (N = 245)		Fed (N = 130)		Fasted (N = 241)		Fasted (N = 241)	
	E	n (%)	E	n (%)	E	n (%)	E	n (%)
Gastrointestinal disorders‡	57	43 (17.6)	21	18 (13.8)	36	28 (11.6)	34	29 (12.0)
Diarrhea	14	13 (5.3)	9	9 (6.9)	5	5 (2.1)	16	15 (6.2)
Nausea	17	14 (5.7)	3	3 (2.3)	14	13 (5.4)	8	8 (3.3)
Vomiting	9	9 (3.7)	3	3 (2.3)	6	6 (2.5)	5	5 (2.1)
Dyspepsia	9	8 (3.3)	3	2 (1.5)	6	6 (2.5)	1	1 (0.4)
Flatulence	5	4 (1.6)	2	2 (1.5)	3	3 (1.2)	1	1 (0.4)
Constipation	2	2 (0.8)	1	1 (0.8)	1	1 (0.4)	1	1 (0.4)
Abdominal pain upper	1	1 (0.4)	-	-	1	1 (0.4)	1	1 (0.4)
Dysphagia	-	-	-	-	-	-	1	1 (0.4)

** Note that compared to the "Binosto/fasted" and "Fosamax/fasted" groups, the "Binosto/all subjects" and "Binosto/fed" groups represent higher and lower alendronate exposure per subject, respectively
E = number of adverse events
n (%) = number (percent) of exposed subjects with adverse events
‡ excludes 4 events in GI SOC of chapped lips, oral dysesthesia, paresthesia oral, dry mouth
Source: Summary of Clinical Safety, M 2.7.4 and study reports/ ADAE datasets of respective studies

Table 10 Severity of GI Adverse Events in Fasted Treatment Groups: ISS Pooled Safety Population

Preferred Term	Binosto 70 mg N = 241			Fosamax 70 mg N = 241		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Diarrhea	5	0	0	14	1	0
Nausea	10	3	0	4	4	0
Vomiting	4	2	0	1	4	0
Dyspepsia	6	0	0	1	0	0
Flatulence	3	0	0	1	0	0

Constipation	1	0	0	1	0	0
Abdominal pain upper	0	1	0	1	0	0
Dysphagia	0	0	0	1	0	0
Source ISS Attachment 2, Table 7, M 2.7.4						

Table 11 GI Adverse Events by time to onset after study drug administration: ISS Pooled Safety Population

Preferred Term Study Drug	Number of events by time to onset				
	≤ 30 min	30 min - 4 hr	4 hr - 12 hr	12 hr - 24 hr	> 24 hr
Total GI events	3	21	24	16	26
Dyspepsia					
Binosto/fed	-	1	-	2	-
Binosto/fasted	1	3	1	-	1
Fosamax/fasted	-	-	-	-	1
Nausea					
Binosto/fed	-	1	2	-	-
Binosto/fasted	2	6	1	2	3
Fosamax/fasted	-	3	2	1	2
Vomiting					
Binosto/fed	-	-	2	-	1
Binosto/fasted	-	-	3	1	2
Fosamax/fasted	-	-	4	-	1
Dysphagia					
Binosto/fed	-	-	-	-	-
Binosto/fasted	-	-	-	-	-
Fosamax/fasted	-	1	-	-	-
Abdominal pain upper					
Binosto/fed	-	-	-	-	-
Binosto/fasted	-	-	-	-	1
Fosamax/fasted	-	1	-	-	-
Flatulence					
Binosto/fed	-	1	1	-	-
Binosto/fasted	-	-	2	-	1
Fosamax/fasted	-	-	-	-	1
Diarrhea					
Binosto/fed	-	2	2	4	1
Binosto/fasted	-	1	1	1	2
Fosamax/fasted	-	1	2	5	8
Constipation					
Binosto/fed	-	-	-	-	1
Binosto/fasted	-	1	-	-	-
Fosamax/fasted	-	-	1	-	-
Source: ISS Summary of Clinical Safety, Table 13					

7.3.4.2 Other Significant Adverse Events

Despite moderately high sodium content of Binosto, there were no discernible differences in vital signs compared to Fosamax (see Section 7.4.3).

One subject on Binosto/fed had glaucoma. Other eye disorders were balanced: following Binosto/fasted, one subject had eye swelling and another had vision blurred; following Fosamax, one subject had eye swelling and ocular hyperemia.

Fatigue was more frequent following Binosto/fed (14.6% of subjects) than either Binosto/fasted (6.6%) or Fosamax (7.5%).

There were no apparent differences between treatments in incidence of infections, musculoskeletal complaints, headaches, dizziness, syncope, sore throat, respiratory symptoms or other categories of AEs.

7.3.5 Submission Specific Primary Safety Concerns

There were no new or unexpected safety issues raised in this submission.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common AEs associated with both drugs, consistent with the known safety profile of alendronate, were headache, fatigue, diarrhea, nausea, back pain, pain in extremity, and nasopharyngitis. (**Table 12**) In the primary comparison of Binosto/fasted and Fosamax, the potential imbalances seen were in events of diarrhea, dyspepsia and nausea; please see section 7.3.4.1 for further discussion.

Table 12 Common Adverse Events (> 3% in any treatment group): subject incidence in ISS Pooled Safety Population**

System Organ Class Preferred Term	Binosto 70 mg			Fosamax 70 mg
	All subjects (N = 245) n (%)	Fed (N = 130) n (%)	Fasted (N = 241) n (%)	Fasted (N = 241) n (%)
Gastrointestinal disorders	43 (17.6)	18 (13.8)	30 (12.4)	31 (12.9)
Diarrhea	13 (5.3)	9 (6.9)	5 (2.1)	15 (6.2)
Dyspepsia	8 (3.3)	2 (1.5)	6 (2.5)	1 (0.4)
Nausea	14 (5.7)	3 (2.3)	13 (5.4)	8 (3.3)
Vomiting	9 (3.7)	3 (2.3)	6 (2.5)	5 (2.1)
General Disorders and administration site conditions	33 (1.5)	20 (15.4)	16 (6.6)	18 (7.5)
Fatigue	32 (13.1)	19 (14.6)	16 (6.6)	18 (7.5)

Infections and infestations	16 (6.5)	6 (4.6)	10 (4.1)	6 (2.5)
Nasopharyngitis	11 (4.5)	3 (2.3)	8 (3.3)	4 (1.7)
Musculoskeletal and connective tissue disorders	30 (12.2)	15 (11.5)	19 (7.9)	27 (11.2)
Back pain	11 (4.5)	5 (3.8)	7 (2.9)	11 (4.6)
Pain in extremity	11 (4.5)	4 (3.1)	8 (3.3)	8 (3.3)
Nervous system disorders	97 (39.6)	31 (23.8)	81 (33.6)	74 (30.7)
Headache	93 (38.0)	31 (23.8)	77 (32.0)	72 (29.9)
** Note that compared to the fasting groups in the 2 right columns, the "Binosto/all subjects" and "Binosto/fed" groups represent higher and lower alendronate exposure per subject, respectively n (%) = number (percent) of exposed subjects with adverse events Source: Summary of Clinical Safety, Table 7, M 2.7.4				

7.4.2 Laboratory Findings

Alendronate and other BPs are well known to cause minor, asymptomatic decreases in serum calcium and phosphorus levels, primarily related to inhibition of bone resorption. These data were pooled for ISS analysis including shift tables, and modest declines in the levels were seen at 24 and 48 hrs following administration of both Binosto and Fosamax in both of the BE trials. As would be expected, there was no appreciable difference between the two drugs. Other laboratory parameters (hematology, chemistry profile, urinalysis) were measured at screening and final visit; these were not pooled for the ISS, but showed no patterns of change from baseline or between drug treatments.

7.4.3 Vital Signs

Although alendronate and other bisphosphonates appear to have no significant cardiovascular effects, blood pressure is relevant for this product because it contains a significant quantity of sodium (~653 mg/tablet) related to the acid buffering and effervescent properties. This amount is equivalent to ~1600 mg dietary NaCl and is more than 3x the quantity of sodium in Fosamax oral solution. (Fosamax tablet has a negligible sodium content.) Recent USDA guidelines recommend limiting sodium to 1500 mg/day for those over 50 y/o, even without cardiovascular disease. Fosamax is used predominantly in elderly women, a population with very high rates of hypertension, congestive heart failure and stroke. In patients with heart failure, nonadherence to sodium-restricted diet has been estimated by some authors to contribute to as many as half of hospital admissions for exacerbations.

Vital signs were recorded in the 2 BE studies at frequent intervals from predose to 48 hrs postdose, and the ISS includes descriptive statistics for the data from 4-hr fasted periods. (**Table 13**) Mean blood pressure declined modestly from baseline to around 24 hrs, with no apparent difference between the two drug treatments.

Table 13 Blood Pressure by treatment (4-hr fasted treatment groups), ISS Pooled Safety Population

	Binosto 70 mg				Fosamax 70 mg			
	N	Mean	SD	Max	N	Mean	SD	Max
Systolic (mm Hg)								
Baseline	241	123.8	16.2	184	241	124.7	16.0	186
2 hr	128	120.1	17.4	171	127	121.8	18.9	186
4 hr	241	124.6	16.2	184	241	125.1	16.0	181
8 hr	128	116.7	16.1	190	127	118.0	17.2	169
12 hr	241	123.7	15.5	182	241	123.2	15.3	199
24 hr	241	119.3	14.9	170	241	119.0	15.3	175
28 hr	113	119.9	13.9	162	114	118.1	12.5	161
36 hr	113	124.9	13.6	166	114	124.1	13.6	177
48 hr	241	123.9	14.7	171	240	122.0	15.6	189
Diastolic BP (mm Hg)								
Baseline	241	80.3	9.6	111	241	80.5	10.3	110
2 hr	128	80.1	9.4	109	127	82.1	11.5	142
4 hr	241	79.6	9.3	106	241	80.2	9.5	112
8 hr	128	77.3	9.1	99	127	78.0	10.1	111
12 hr	241	78.7	9.6	105	241	78.2	9.6	109
24 hr	241	78.3	9.2	108	241	78.0	8.6	110
28 hr	113	75.4	9.2	98	114	74.8	8.9	100
36 hr	113	76.8	8.9	102	114	76.9	9.2	100
48 hr	241	80.4	8.7	104	240	80.3	9.8	112

Source: Table 32, ISS Summary of Safety

The ISS also analyzed the number of subjects who had “potentially clinically important” changes in vital signs, including systolic BP ≥ 180 mmHg with increase of ≥ 20 mm Hg and diastolic BP ≥ 105 mmHg with increase of ≥ 15 mm Hg. The number of subjects meeting these criteria was no more than 2 for each of the drug treatments (4-hr-fasted) at each timepoint. The few subjects who had more than one elevated blood pressure reading tended to have high-normal or elevated readings throughout the study, including at screening and baseline, and following each of their study drug treatments. The quantity and level of the highest pressure readings following Binosto did not appear to exceed that following Fosamax.

AEs of hypertension, diastolic hypertension or systolic hypertension were reported in 5 subjects associated with Binosto/fasted, 4 subjects associated with Fosamax, and none associated with Binosto/fed. One of these (a subject with high blood pressure following Fosamax) dropped out because of this AE.

7.4.4 Electrocardiograms (ECGs)

Bisphosphonates have not been associated with cardiac effects except for a possible increased incidence of atrial fibrillation in older patients. ECGs were recorded at screening and end of study in the 2 BE studies. No ECG abnormalities were considered clinically significant.

7.4.5 Special Safety Studies/Clinical Trials

Because this NDA is based upon bioequivalence, no special safety assessments (e.g. bone biopsies) were required or performed.

7.4.6 Immunogenicity

BPs are not immunogenic; no studies were performed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Only one dose of this effervescent tablet, 70 mg weekly based on bioequivalence, has been investigated.

7.5.2 Time Dependency for Adverse Events

This was not assessed in the single-dose, short-term studies conducted. Potential adverse effects of long-term BP treatment (oversuppression of bone) should not differ from Fosamax (see Section 2.4).

7.5.3 Drug-Demographic Interactions

GI adverse events of most types, and some non-GI AEs (e.g. fatigue, back pain, pain in the extremity, headache) occurred more frequently in female compared to male subjects, but this applied to Fosamax as well as Binosto (see Section 7.3.4.1). GI adverse effects of oral BPs are not known to correlate with age, though elderly subjects have a higher baseline risk of many GI events. However, the somewhat greater frequency of dyspepsia and nausea with Binosto/fasted compared to Fosamax in these studies was accounted for by the younger subjects (≤ 57 y/o), for reasons unclear. There were very few elderly subjects in the studies, so tolerability specifically in this group is uncertain. Virtually all subjects were Caucasian, however extensive experience with Fosamax has shown no evidence that safety varies with race/ethnicity. Analysis of AEs by subjects' BMI (< 25 and ≥ 25) showed no differences.

7.5.4 Drug-Disease Interactions

Studies enrolled only healthy volunteers.

7.5.5 Drug-Drug Interactions

Bisphosphonates are not metabolized and do not affect P450 enzymes, therefore are not generally implicated in drug interactions. No DDI studies were included in this submission.

7.6 Additional Safety Evaluations

Not applicable.

7.6.1 Human Carcinogenicity

Please see Section 2.4 for discussion of possible relationship of alendronate with esophageal cancer. No data in this application are relevant to this issue.

7.6.2 Human Reproduction and Pregnancy Data

As noted in labeling of Fosamax, which is Pregnancy Category C, there are no good data in humans relative to the theoretical risk of fetal skeletal harm. Binosto would not be expected to differ from Fosamax in this regard.

7.6.3 Pediatrics and Assessment of Effects on Growth

The proposed indication is limited to treating postmenopausal women and men with osteoporosis. Fosamax is used off-label in some children with metabolic bone diseases, however a controlled trial (in response to a Written Request) failed to establish efficacy or safety in this age group. Current Fosamax labeling indicates that it is not indicated for use in children, and Binosto will have the same labeling. The Pediatric Review Committee has agreed to a full waiver for pediatric studies of Binosto, and none are currently planned.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

BPs have not been associated with abuse potential or dependency/withdrawal.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Binosto has not been marketed in any country. There is extensive postmarketing experience with alendronate since 1995; please see Section 2.4.

9 Appendices

9.1 Literature Review/References

According to agreement at the pre-NDA meeting, no comprehensive literature review was performed by the Applicant. The following is a list of pertinent literature cited in this review.

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9.2 Labeling Recommendations

This 505(b)(2) application relies on FDA findings regarding the safety and efficacy of Fosamax. The new product is expected to have comparable safety and efficacy, therefore labeling should be essentially the same as for Fosamax, except for differences in the formulation and dosing instructions, and omission of sections of the Fosamax label that pertain only to other doses/indications (prevention of PMO, glucocorticoid-induced osteoporosis, Paget's disease). See separate document for final approved label.

9.3 Advisory Committee Meeting

No Advisory Committee meeting was held for this NDA as the active ingredient is not a new molecular entity, and no major safety or efficacy concerns were discovered during the review.

9.4 Review of Individual Studies

9.4.1 Bioequivalence Study AE-1212-001-EM

Single-site, open label, four period cross-over replicate trial after single dose administration of a new alendronate 70 mg formulation, a buffered effervescent soluble tablet, under fasting conditions, to assess the bioequivalence versus a marketed oral tablet formulation (Fosamax® once-weekly 70 mg) in healthy volunteers.

This Phase 1 bioequivalence trial was conducted at a single site, CRS Clinical Research Services, in Mannheim, Germany under supervision of Nycomed GmbH of Konstanz, Germany. The original design included only women; this was amended to include men, as advised by the Division because of the Applicant's goal of an indication for both men and women in the U.S. (In the E.U., alendronate 70 mg weekly is only approved for women.) The protocol (v.2) was submitted with the original IND on 6/23/09; there were no subsequent amendments.

Primary Objective: to establish bioequivalence to Fosamax, which (for FDA) requires the 90% CI of the test:reference ratio for each of the following parameters to fall within the acceptance range of 80-125%:

- **Ae₀₋₄₈ (cumulative alendronate urinary excretion to 48 hrs post-dose, in µg)**
- **E_{max} (maximal rate of alendronate urinary excretion, in µg/hr)**

Secondary Objectives:

- Ae (alendronate excretion during each collection interval)
- E_t (alendronate excretion rate during each collection interval)
- t (E_{max}) (time of the maximum urinary excretion)
- t_{1/2} (terminal elimination half-life)
- Safety variables: AEs, vital signs, ECG, physical exam, clinical labs esp. Ca, Phos

Subjects: The study population was planned to consist of 70 healthy Caucasian females (pre- or post-menopause) and 45 healthy males, age 45-75. This number of subjects was chosen based on calculations that 100 subjects (after dropouts/missing values) would be needed for 86% power to show bioequivalence by both Ae₀₋₄₈ and E_{max}. Relevant entry criteria were as follows:

Inclusion criteria:

- Healthy based on H&P, blood pressure, pulse rate, ECG, clinical labs

- Nonsmoker, ex-smoker or light smoker (≤ 10 cigarettes/day)
- BMI = 18-28 kg/m²

Exclusion criteria:

- Significant hepatic, renal, GI, cardiovascular, pulmonary, hematological or other condition that might affect either safety or pharmacokinetics
- Upper GI disease e.g. dysphagia, esophageal disease, gastritis/duodenitis, UGI bleeding or previous surgery
- Esophageal abnormalities or conditions which may delay esophageal emptying
- Inability to stand/sit upright for 30 min
- Chronic use of acid-reducing medications (antacids, H2RAs, PPIs) within 3 mos
- Hypocalcemia (< 2.0 mMol/L)
- Use of bisphosphonates within 3 mos
- Regular or recent use of any medication, except hormonal contraceptives or hormone replacement (including thyroid)
- Pregnancy or lack of contraception
- Alcohol/drug abuse

Study AE-1212-001-EM Design:

Each subject received 4 single-dose open-label alendronate treatments: 2 each of Fosamax 70 mg tablet and Binosto effervescent tablet 70 mg, with a washout period of 14-28 days between periods. Subjects were randomized to receive the 4 treatments either in the sequence *Fosamax/Binosto/Fosamax/Binosto* or the sequence *Binosto/Fosamax/Binosto/Fosamax*.

Each treatment was given after an overnight fast. The effervescent solution was prepared ≥ 5 minutes and ≤ 15 minutes before administration with the tablet dissolved in 120 mL water (room temperature) and stirred for 10 seconds immediately before intake. Fosamax tablet was swallowed with 240 mL water (room temperature), as per its labeling. After treatments, subjects remained upright and NPO (except for water) for 4 hrs.

Reviewer comment: *The 4-hr post-dose period of continued fasting differs from the “at least one-half hour” period specified in Fosamax labeling. The application states that this was done in order to comply with FDA’s Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (2003), and to avoid any confounding effect of food on the PK evaluation of the 2 formulations. The prolonged fast probably increased the potential for upper GI adverse effects, though this would apply equally to both treatments.*

In order to assure urine output adequate for PK measurements, subjects were asked to maintain very high water intake, beginning with at least 100 mL every 30 minutes beginning 2 hrs pre-dose until 30 min post-dose, followed by 240 mL at 2 hrs and also at 4 hrs post-dose. At 6 hrs post-dose, subjects who had received Binosto were offered an extra 120 mL, to equalize the overall water intake for the 2 treatments. The goal for total water intake was 1.4-1.9 L in the first 12 hr and 2.3-2.8 L in the first 24 hr. Volvic®

bottled water was used exclusively, because its mineral content is very low (comparable to New York City tap water, per data submitted), and its use precluded that of other bottled waters.

Reviewer comment: *The large amounts of water drank by subjects differ somewhat from Fosamax labeling, which has no specific instructions regarding water intake except for the 6-8 oz. taken with the tablet. In response to FDA questions about this in the 74-day letter, the Applicant made the following comments:*

- *Previous alendronate PK studies have generally placed no restrictions on water intake, and some have prescribed a high intake similar to the regimen in this study*
- *Based on published estimates of gastric emptying times of plain water in an otherwise empty stomach (mean $T_{1/2} < 15$ minutes), it is calculated that even if all of the recommended 400 mL of water is consumed by subjects over the 2 hrs prior to administration per the protocol, only 33 mL of residual water would remain in the stomach at the time of dosing, which then adds an additional 120 mL or 240 mL. Thus, the additional water volume would result in minimal difference from Fosamax labeled instructions, or from proposed Binosto dosing instructions.*
- *Prior studies of Fosamax 70 mg oral solution showed that it was equally bioavailable relative to Fosamax 70 mg tablet, despite differences in the accompanying volume of liquid (135 mL vs. 250 mL respectively).*

It is unlikely that the large amounts of water, much of which were consumed before dosing of the study drug, would significantly alter safety assessments, particularly as the total water amount was the same for the 2 alendronate products.

Demographics

There were 70 female and 45 male subjects, all Caucasian, and all healthy. (**Table 14**) There were 30% who had never smoked, 36% who were past smokers, and 34% who were current smokers (≤ 10 cigarettes/day). None gave a history of heavy alcohol use. None gave a history of any GI disorders.

Table 14 Study AE-1212-001-EM: Demographic and baseline characteristics

Age (years)	Males	Females	M/F Combined
n	45	70	115
Mean $\pm$ SD	54.5 $\pm$ 7.3	58.0 $\pm$ 8.0	56.6 $\pm$ 7.9
Min - Max	45 - 73	45 - 73	45 - 73
Body height (cm)			
n	45	70	115
Mean $\pm$ SD	177 $\pm$ 6.4	162 $\pm$ 6.0	168 $\pm$ 9.4
Min - Max	163 - 191	150 - 178	150 - 191
Body weight (kg)			
n	45	70	115
Mean $\pm$ SD	79.2 $\pm$ 9.6	64.3 $\pm$ 8.2	70.1 $\pm$ 11.4
Min - Max	60 - 99	45 - 87	45 - 99

Body mass index (kg/m ²)			
n	45	70	115
Mean ± SD	25.3 ± 2.1	24.5 ± 2.5	24.8 ± 2.3
Min - Max	21 - 28	19 - 28	19 - 28
Source: Table 14.1.1, CSR			

Disposition

Out of 115 subjects randomized and treated with at least one of the study drugs, 107 completed all 4 periods. Dropouts by period were 3, 2, 2 and 1. One withdrawal was caused by an adverse event (Subject 031, for hypertension), 2 by protocol deviations (009-F, 109-M, apparently due to lost urine samples), and 5 for non-medical reasons (subject request) (039-F, 043-M, 102-M, 129-M, 145-M). There were 10 subjects who had a protocol deviation during the study: 6 with drinking schedule deviations, 4 with urine sample deviations, and 3 with lack of an end-of-study exam.

Prior/concomitant medications

There were 18 subjects, all female, who reported prior (and ongoing) medication use that was allowed: 10 with estrogens and/or progestogens; 5 with thyroid replacement; 2 with IUD's; and 1 with acetaminophen for headache. The only concomitant medications recorded were: anticoagulants in one subject who experienced DVT, and antihypertensives in another subject who experienced worsening of hypertension (see SAEs below); SMX/TMP for cystitis in one subject; eye drops (steroid/antibiotic) in one subject; and acetaminophen in numerous others. There were no reports of use of aspirin, NSAIDs, or acid-reducing medications. In the event of dyspepsia or nausea symptoms, the protocol allowed concomitant treatment with antacids, metoclopramide and/or dimenhydrinate; however none of these were used.

Study AE-1212-001-EM: Results

Pharmacokinetics

Please refer to review by Dr. Hyunjin Kim of the Division of Clinical Pharmacology.

Following each administration of one of the study drugs, urine was collected for 48 hours for PK determinations, in the following intervals (in hours): -2-0; 0-0.5; 0.5-1; 1-2; 2-4; 4-6; 6-8; 8-12; 12-18; 18-24; 24-30; 30-36; 36-42; and 42-48. No subject vomited or took antacids within 4 hrs of dose, which would have invalidated that subject's PK data.

In brief, according to the Study Report, point estimates for the primary PK parameters, for the overall study population of men and women (n=112), were:

- **Ae₀₋₄₈ ratio** (Binosto/Fosamax) = **88%** (90%CI = **83%, 94%**)
- **E_{max} ratios** (Binosto/Fosamax) = **90%** (90%CI = **85%, 97%**)

Thus, the 90% confidence intervals for both parameters were within the FDA's acceptance range of 80-125% Variability in these parameters (%CV) within each subject was slightly less for the effervescent tablet compared to Fosamax, and variability between subjects was similar for the two treatments. Absorption/excretion of

alendronate was very rapid, with $t(E_{\max})$ of 0.75 hr for Binosto and 0.74 hr for Fosamax; $t_{1/2}$ was also very similar at ~20 hrs for both products.

During the review cycle, an OSI inspection concluded that the PK data from 11 batches were unreliable, and recommended removal of these batches from the analysis (see Section 3.1). Re-analysis without these batches (n=103) by the Applicant and Dr. Kim showed that the above primary PK parameter ratios and confidence intervals did not change, therefore the criteria for bioequivalence were still met.

Study AE-1212-001-EM: Safety Findings

Adverse Effects

Out of 115 subjects, 108 completed all 4 dose-periods. Subjects were asked about adverse events predose and at 4, 12, 24, 28, 36, and 48 hrs after each dose and at end of study (4-9 days after last dose).

There were no deaths. During the study, there were 2 SAEs, both after Fosamax, neither of which was considered study drug related:

- Subject 031, a 70 y/o female with a prior history of mild hypertension (not on treatment), was noted to have elevated BP after receiving Fosamax tablet (period 3): after predose BP of 170/98, BP was 191/98 mm Hg at 12 hrs post-dose and 191/99 mm Hg at 24 hrs. She was sent to her family doctor who treated her with multiple medications, and was withdrawn from the study. The blood pressure came down. This was the only subject in the study who was withdrawn because of an AE.
- Subject 107, a 54 y/o male, developed left lower leg thrombosis 4 days after Fosamax tablet in period 4, after end-of-study data had been collected. He was hospitalized and treated with anticoagulants. This was the only AE in the study which was still ongoing at the end of the study.

About half the subjects experienced at least 1 AE with each of the 2 study drugs. (**Table 15**) With Binosto, there were 105 AEs in 57 subjects; with Fosamax, there were 100 AEs in 61 subjects. The most frequently reported AEs overall, consistent with the known safety profile of Fosamax, were headache (51.3% of subjects), diarrhea (12.2%), fatigue (7.8%), pain in the extremities (7.8%), back pain (7.8%), nasopharyngitis (7.0%) and nausea (6.1%). The intensity of AEs was about the same overall for Binosto AEs vs. Fosamax AEs: 54% were rated mild, 44% moderate, and 2% severe in each treatment group. Causality was “likely related” according to investigator for 61.4% of Binosto reactions and 73.8% of Fosamax reactions.

Table 15 Study AE-1212-001-EM: Subject Incidence of Treatment-emergent Adverse Effects by treatment (all subjects, all TEAEs)

System Organ Class Preferred Term	Binosto 70 mg (N=113) n (%)	Fosamax 70 mg (N=114) n (%)	Overall (N=115) n (%)
Overall (≥ 1 AE)	57 (50.4)	61 (53.5)	81 (70.4)
Nervous system disorders	44 (38.9)	42 (36.8)	61 (53.0)
Headache	41 (36.3)	42 (36.8)	59 (51.3)
Dizziness	2 (1.8)	1 (0.9)	3 (2.6)
Hemicephalgia	1 (0.9)	-	1 (0.9)
Paresthesia	1 (0.9)	-	1 (0.9)
Gastrointestinal disorders	11 (9.7)	18 (15.8)	24 (20.9)
Diarrhea	4 (3.5)	11 (9.6)	14 (12.2)
Nausea	5 (4.4)	3 (2.6)	7 (6.1)
Dyspepsia	2 (1.8)	-	2 (1.7)
Vomiting	1 (0.9)	1 (0.9)	2 (1.7)
Abdominal pain upper	-	1 (0.9)	1 (0.9)
Dry mouth	-	1 (0.9)	1 (0.9)
Oral dysesthesia	-	1 (0.9)	1 (0.9)
Paresthesia oral	1 (0.9)	-	1 (0.9)
Musculoskeletal and connective tissue disorders	7 (6.2)	12 (10.5)	15 (13.0)
Back pain	4 (3.5)	5 (4.4)	9 (7.8)
Pain in extremity	2 (1.8)	4 (3.5)	4 (3.5)
Muscle tightness	-	2 (1.8)	2 (1.7)
Myalgia	1 (0.9)	1 (0.9)	1 (0.9)
Neck pain	-	1 (0.9)	1 (0.9)
Infections and infestations	7 (6.2)	3 (2.6)	10 (8.7)
Nasopharyngitis	6 (5.3)	2 (1.8)	8 (7.0)
Rhinitis	1 (0.9)	1 (0.9)	2 (1.7)
Cystitis	1 (0.9)	-	1 (0.9)
General disorders and administration site conditions	6 (5.3)	4 (3.5)	9 (7.8)
Fatigue	6 (5.3)	4 (3.5)	9 (7.8)
Vascular disorders	4 (3.5)	2 (1.8)	6 (5.2)
Systolic hypertension	3 (2.7)	1 (0.9)	4 (3.5)
Diastolic hypertension	1 (0.9)	-	1 (0.9)
Thrombosis	-	1 (0.9)	1 (0.9)
Eye disorders	1 (0.9)	1 (0.9)	2 (1.7)
Eye swelling	1 (0.9)	1 (0.9)	2 (1.7)
Ocular hyperemia	-	1 (0.9)	1 (0.9)
Investigations	-	1 (0.9)	1 (0.9)
Heart rate increased	-	1 (0.9)	1 (0.9)

Respiratory, thoracic and mediastinal disorders	-	1 (0.9)	1 (0.9)
Oropharyngeal pain	-	1 (0.9)	1 (0.9)
Skin and subcutaneous tissue disorders	1 (0.9)	-	1 (0.9)
Rash	1 (0.9)	-	1 (0.9)
n (%) = number (percent) of exposed subjects with adverse events Source: Table 18, CSR, ADAE dataset			

GI Adverse Events

GI adverse events were experienced by 20.9% of study participants; their average age of 57 y/o was the same as that of the overall study population. Events were reported by higher proportions of female subjects (25.7%) compared to males (13.3%). According to narratives, none of these subjects had any prior GI or other relevant medical history.

Overall, GI AEs were somewhat more common with Fosamax (19 episodes in 18 subjects) compared to Binosto (14 episodes in 11 subjects). (**Table 16**) A greater frequency of diarrhea with Fosamax accounts for this imbalance. No GI AEs were serious or resulted in discontinuation; almost all were mild and required no treatment, and none were “severe” in intensity. Most were considered by the investigators to be “likely related” to treatment; a few were “unlikely” with no imbalance between the treatments in this regard.

There were 2 episodes of “**dyspepsia/heartburn**” (PT/verbatim) following Binosto administration and none following Fosamax. Both episodes were considered “mild” and required no treatment; both occurred on the subject’s first exposure to Binosto and then did not recur at their second exposure. One of these events occurred at 2 hrs post-dose and resolved after 15 hrs. The other occurred at 36 hrs post-dose (after the evening meal of the day after dosing), and resolved in 4.5 hrs. There were no reports of dysphagia or odynophagia.

There were 6 episodes of **nausea** following Binosto (at 0.5, 1, 1, 3, 14 and 34 hrs post-dose) and 3 episodes of nausea following Fosamax (at 1, 34 and 34 hrs post-dose). All nausea events were “mild” except one episode following Fosamax which was “moderate”. There was one episode of **vomiting** associated with each treatment: one at 10 hrs following Binosto and one at 7 hrs following Fosamax.

One episode of **abdominal pain upper**, “mild”, occurred 2 hrs following a Fosamax dose.

Diarrhea was more common with Fosamax (12 episodes) than Binosto (4 episodes). Half (8/16) of these episodes occurred following the first of the 4 treatment periods for that subject, but only 2 of the 14 subjects involved had a recurrence of diarrhea following a subsequent treatment. All episodes of diarrhea were “mild” except for one

“moderate” episode following Fosamax, and most occurred between 24-48 hrs post-dose for both treatments.

Although subjects each received 4 doses of the 2 study drugs, they did not experience a given GI AE more than once, with the exception of the 2 subjects who each had 2 episodes of diarrhea at 29-48 hrs after a dose, and one subject with nausea after each of 3 treatments (2 with Binosto including one with vomiting, and 1 with Fosamax).

Table 16 Study AE-1212-001-EM: Frequency of treatment emergent GI adverse events by treatment and gender

System Organ Class Preferred Term	Binosto 70 mg		Fosamax 70 mg		Overall	
	E	n (%)	E	n (%)	E	n (%)
Male subjects (N=45)						
Gastrointestinal disorders (all)	2	2 (4.4%)	4	4 (8.9%)	6	6 (13.3%)
Diarrhea	1	1 (2.2%)	2	2 (4.4%)	3	3 (6.7%)
Nausea	1	1 (2.2%)	-	-	1	1 (2.2%)
Vomiting	-	-	1	1 (2.2%)	1	1 (2.2%)
Abdominal pain upper	-	-	1	1 (2.2%)	1	1 (2.2%)
Female subjects (N=70)						
Gastrointestinal disorders (all)	12	9 (13.2%)	15	14 (20.0%)	27	18 (25.7%)
Diarrhea	3	3 (4.4%)	10	9 (12.9%)	13	11 (15.7%)
Nausea	5	4 (5.9%)	3	3 (4.3%)	8	6 (8.6%)
Dyspepsia	2	2 (2.9%)	-	-	2	2 (2.9%)
Vomiting	1	1 (1.5%)	-	-	1	1 (1.4%)
Dry mouth	-	-	1	1 (1.4%)	1	1 (1.4%)
Oral dysesthesia	-	-	1	1 (1.4%)	1	1 (1.4%)
Paresthesia oral	1	1 (1.5%)	-	-	1	1 (1.4%)
All subjects (N=115)						
Gastrointestinal disorders (all)	14	11 (9.7%)	19	18 (15.8%)	33	24 (20.9%)
Diarrhea	4	4 (3.5%)	12	11 (9.6%)	16	14 (12.2%)
Nausea	6	5 (4.4%)	3	3 (2.6%)	9	7 (6.1%)
Dyspepsia	2	2 (1.8%)	-	-	2	2 (1.7%)
Vomiting	1	1 (0.9%)	1	1 (0.9%)	2	2 (1.7%)
Abdominal pain upper	-	-	1	1 (0.9%)	1	1 (0.9%)
Dry mouth	-	-	1	1 (0.9%)	1	1 (0.9%)
Oral dysesthesia	-	-	1	1 (0.9%)	1	1 (0.9%)
Paresthesia oral	1	1 (0.9%)	-	-	1	1 (0.9%)
E = number of adverse events						
n (%) = number (percent) of exposed subjects with adverse events						
Source: Tables 14.3.1.2-1 and 14.3.1.2-2, CSR, ADAE dataset						

Vital Signs, ECGs, physical exam

Vital signs were measured before each dose of study drug and at 4, 12, 24, 28, 36 and 48 hrs after each dose. Mean blood pressure showed no clinically relevant changes from baseline or between treatments. (Table 17)

Table 17 Study AE-1212-001-EM: Blood Pressure Changes from Baseline, by treatment

	Binosto 70 mg				Fosamax 70 mg			
	N	Mean	SD	Max	N	Mean	SD	Max
Systolic (mm Hg)								
Baseline	221	123.3	13.9	162	224	123.7	14.0	170
4 hr	221	1.4	9.1	23	224	2.1	9.1	45
12 hr	221	1.3	11.4	40	224	0.3	9.5	25
24 hr	221	-1.6	9.2	21	224	-2.4	9.7	23
28 hr	221	-3.7	10.0	21	224	-5.5	9.4	19
36 hr	220	1.4	11.6	31	224	0.4	11.0	29
48 hr	220	0.2	9.5	27	224	0.0	10.3	32
Diastolic (mm Hg)								
Baseline	221	77.6	10.0	105	224	77.7	9.9	104
4 hr	221	-0.3	6.5	18	224	0.2	6.3	23
12 hr	221	-1.6	8.0	21	224	-2.0	7.5	36
24 hr	221	-1.2	6.2	24	224	-0.8	6.7	29
28 hr	221	-2.3	6.5	1	224	-3.0	7.0	39
36 hr	220	-0.8	7.9	25	224	-0.8	7.6	37
48 hr	220	0.1	7.4	24	224	-0.3	7.8	36

Source: Table 14.3.5.5-, CSR

AEs related to hypertension (defined as systolic >170, or >40 above baseline, or diastolic >105) were reported in 5 subjects, all of whom had elevated ($\geq 140/90$) blood pressure predose during the period when the hypertensive AE occurred. One of these events (subject 031, see above, SAEs) occurred 12 hrs after a Fosamax tablet (max BP 191/99) and resulted in study discontinuation. The other 4 (subjects 032, 103, 108, 140) occurred following the effervescent tablet, with max BPs of 175/89, 173/105, 171/97 (all at 4 hrs post-dose) and 152/117 (at 24 hrs post-dose). There was a previous history of hypertension in 2 of these 5 subjects (who were both female); the other 3 (who were all male) had no history of HTN and exhibited BP elevations following Binosto.

ECGs and physical exams were at screening and EOS. No ECG abnormalities were considered clinically significant. Four subjects had changes in physical exam during but not at end of study: 3 related to URI symptoms and one with a red swollen eyelid.

Laboratory

Serum calcium was measured predose and at 24 and 48 hrs after each dose, and showed the moderate declines expected with BP treatment. There was no difference between Binosto and Fosamax: mean values at 24 and 48 hrs were 0.16 mg/dL and 0.21 mg/dL, respectively, below baseline for both treatments. Between screening and end of study (EOS, i.e. after all 4 treatments), calcium levels shifted from normal to low in 1/45 males and 2/70 females, and from normal to high in 1 female (EOS values in these 4 cases were 8.32, 8.56, 7.64 and 10.52 mg/dL respectively). There were no clinically apparent signs or symptoms of hypocalcemia.

Serum phosphorus likewise declined modestly after each dose, as expected. Mean values at 24 and 48 hrs were 0.06 and 0.14 mmol/L below baseline, respectively, for either drug. Between screening and EOS, phosphorus level shifted from normal to low in 12, low to normal in 6, and high to normal in 1.

Clinical labs were done at screening and EOS (4-9 days after last dose). Shift tables show few shifts in LFTs, amylase, Na/K, glucose or urate, and no values markedly outside normal range. Creatinine level shifted from high to normal in 11 subjects, and normal to high (0.94 mg/dL) in 1.

Hematologic and coagulation parameters showed no notable trends between screening and end of study.

There were no lab abnormalities that were considered clinically significant by the investigator, except for one subject with urine sediment related to an episode of cystitis.

Summary of safety, study AE-112-01-EM

Among the 115 subjects randomized and treated, 107 completed all 4 periods of the study. There were no deaths. The two serious AEs, and the one study dropout caused by an AE, were both associated with the comparator, Fosamax, and both clearly unrelated to this treatment. Adverse events overall were fairly evenly distributed between the two drugs and were consistent with the known safety profile of alendronate. The most frequently reported AEs overall, consistent with the known safety profile of Fosamax, were headache, diarrhea, fatigue, pain in the extremities, back pain, nasopharyngitis and nausea. GI AEs were somewhat more common with Fosamax compared to Binosto, except for dyspepsia/heartburn and nausea, which were slightly more common with Binosto, and diarrhea, which was more common with Fosamax. There were no complaints of dysphagia or other indicators of possible esophagitis. More women than men experienced GI AEs with either drug. Serum calcium and phosphorus levels declined slightly as expected, with no difference between treatments. There were no notable safety findings, or differences between treatments, in regard to other laboratory parameters, vital signs or ECGs.

9.4.2 Bioequivalence Study SCO5361

An open, randomized, single-dose, three-period, cross-over study to assess the bioequivalence of an alendronate 70 mg effervescent tablet vs. a standard oral formulation followed by a standard breakfast and under fasting conditions in healthy women aged 45 to 75 years.

This Phase 1 study differs from AE-1212-001-EM primarily in that it involved only women, and was designed to measure food effects as well as fasting bioequivalence. SCO5361 was conducted at a single site, Scope International AG, in Hamburg, Germany under sponsorship of EffRx. It was completed prior to opening of IND 103,130. Because the study missed its primary endpoint for bioequivalence, which resulted in subsequent re-formulation of the drug product, the PK data are not being relied upon for this application. However, the safety data are considered relevant, with the caveat that because an earlier formulation (b) (4) was used, upper GI tolerability may differ from that of the new (b) (4) formulation which was used in the subsequent BE trial, AE-1212-001-EM, and planned to be used in marketing.

Objectives:

Primary Objective: Ae_{0-48} (cumulative alendronate urinary excretion to 48 hrs post-dose, in μg)

Secondary Objectives:

- E_{max} (maximal rate of alendronate urinary excretion, in $\mu\text{g/hr}$)
- $t(E_{\text{max}})$ (time of the maximum urinary excretion)
- $t_{1/2}$ (terminal elimination half-life)
- Safety variables: AEs, vital signs, ECG, physical exam, clinical labs esp. Ca, Phos

Subjects:

Inclusion criteria:

- Healthy female Caucasian, age 45-75
- Healthy based on H&P, blood pressure, pulse rate, ECG, clinical labs
- Nonsmoker, ex-smoker or light smoker (≤ 10 cigarettes/day)
- BMI = 19-30 kg/m^2

Exclusion criteria:

- Significant hepatic, renal, GI, cardiovascular, pulmonary, hematological or other condition that might affect either safety or pharmacokinetics
- Upper GI disease i.e. esophageal disease, gastritis/duodenitis, ulcers, UGI bleeding
- Hypocalcemia ($< 2.0 \text{ mMol/L}$)
- Use of bisphosphonates within 3 mos
- Regular or recent use of any medication, except hormonal contraceptives
- Pregnancy or lack of contraception
- Alcohol/drug abuse

Study SCO5361 Design: At least 130 subjects were planned to be recruited. Each subject received in succession 3 single-dose open-label alendronate treatments:

- **Fosamax 70 mg** tablet with 240 mL water followed by **4 hrs** additional fast
- **Binosto 70 mg** tablet dissolved in 120 mL water followed by **4 hrs** additional fast ("Binosto/fasted")

- **Binosto 70 mg** tablet dissolved in 120 mL water followed by standard breakfast **15 min** later (“Binosto/fed”)

The sequence of treatments was random for each subject, with a washout period of 14-28 days between treatments.

Each treatment was given after an overnight fast. The effervescent solution was prepared ≥ 10 minutes and ≤ 20 minutes before administration with the tablet added to 120 mL of Volvic® water, stirred “until the tablet had fully dissolved”, and then drank. Fosamax tablet was swallowed with 240 mL water. Subjects were asked to drink large amounts of Volvic® water before and after dosing, using the same regimen described above for study AE-1212-001-EM. After each treatment, subjects remained upright for 4 hrs. The meals given at either 15 minutes or 4 hrs after dosing were standardized and low in calcium.

Reviewer note: As noted above in discussion of study AE-1212-001-EM, the protocol differs from Fosamax dosing instructions in timing of food intake and amount of water intake. Delaying food until 4 hrs post dose probably would increase GI side effects; it is unclear what the effect would be of moving it up to only 15 minutes post dose.

Demographics

All subjects in study SCO5361 were healthy Caucasian women. (**Table 18**) No data were provided on smoking status.

Table 18 Study SCO5361: Demographic and baseline characteristics (female gender, n = 133)

Age (years)	
Mean $\pm$ SD	58.1 $\pm$ 8.6
Min - Max	45 - 75
Body height (cm)	
Mean $\pm$ SD	165.7 $\pm$ 5.3
Min - Max	154 - 180
Body weight (kg)	
Mean $\pm$ SD	65.9 $\pm$ 9.3
Min - Max	46 - 96
Body mass index (kg/m ²)	
Mean $\pm$ SD	23.97 $\pm$ 2.96
Min - Max	19.0 - 29.8
Source: Table 2, CSR	

Disposition: One subject was randomized but did not receive study drug. Of the remaining 133, 132 completed at least 1 period and 124 completed all 3 periods. Nine subjects withdrew from the study: 5 because of AEs (see below) and 4 for non-medical reasons. There were 6 dropouts after the first period and 2 after the second.

Prior/concomitant medications

The original protocol allowed no concomitant medications except for acetaminophen, which was used by 47 subjects, and hormonal contraceptives, which were used by 2 subjects.

During the trial, several subjects suffered from moderate nausea and/or vomiting; after agreement with the Applicant, metoclopramide (1 subject) or dimenhydrinate (5 subjects) were allowed to treat these symptoms (though not within 8 hrs of dosing).

One subject (084) self-administered a single dose of ranitidine for upper abdominal pain 2 days after her last dose (Binosto/fasted). Two subjects used diclofenac (for groin pain and back pain) though not in close proximity to the study drug. Other concomitant medications reported were naratriptane and roxithromycin for headache and rhinitis by one subject; oral antibiotics and ibuprofen for bronchitis and psoriasis dermatitis by another; and latanoprost eye drops for glaucoma by another.

Study SCO5361: Results

Pharmacokinetics

Urine samples for alendronate PK determination were collected at the same intervals, to 48 hrs post dose, as in study AE-1212-001-EM.

In the comparison between the two treatments followed by 4 hrs additional fast, the bioavailability of Binosto relative to Fosamax was measured as a mean Ae_{0-48} ratio of 85.75%. Because the 90% CI of 79.54-92.44% for this parameter extended just below the predefined acceptance range of 80-125%, criteria for bioequivalence were not met. The comparison of maximal excretion rates (a secondary endpoint) did meet these criteria: E_{max} ratio mean was 90.65%, with 90% CI = 83.89-97.96%. Variability in Ae_{0-48} was somewhat lower with Binosto compared to Fosamax (%CV 51.1% vs. 64.9%). Rapidity of absorption/excretion was similar between Binosto and Fosamax: mean $t(E_{max})$ was 1.46 hr and 1.28 hr, respectively and mean $t_{1/2}$ was 4.90 hr and 4.76 hr, respectively.

Reviewer note: It is interesting that $t(E_{max})$ of Binosto(fasted) was longer than in study AE-1212-001-EM (1.46 hr vs. 0.75 hr), (b) (4)

However, $t(E_{max})$ of Fosamax tablet was also longer (1.28 hr vs. 0.74 hr) in this study.

[In the third arm, in which administration of Binosto was followed by a meal 15 min later, bioavailability was reduced by half relative to Fosamax: Ae_{0-48} ratio = 49.77%, 90%CI = 46.19-53.62%. This is consistent with previous alendronate PK studies of food effects, and the Applicant is not continuing to investigate this method.]

The Applicant offered two possible explanations for the lack of bioequivalence (in the 4-hr fasting arms) (b) (4)

(Because of this observation, the product was subsequently re-formulated in order to promote more rapid and complete dissolution.)

Safety Findings

Adverse Effects

Out of 134 subjects enrolled, 133 received at least one of the 3 planned treatments and were analyzed for safety. Of these, 131 received at least one dose of Binosto (with either 15 min or 4 hr post dose fast), and 125 received all 3 treatments. Subjects were asked about adverse events at 4, 12, 24, 28, 36, and 48 hrs after each dose and at end of study (4-9 days after last dose).

There were no deaths or serious AEs. With each of the 3 treatments, about half of the 133 subjects dosed experienced at least 1 AE. (**Table 19**) With Binosto/fasted, there were 100 AEs in 62 subjects (48% of total). With Binosto/fed, there were 107 AEs in 69 subjects (53% of total). With Fosamax, there were 96 AEs in 57 subjects (45% of total). The most frequently reported AEs overall, consistent with the known safety profile of Fosamax, were headache (47% of subjects), fatigue (27%), nausea (9%), diarrhea (9%), pain in the extremities (8%), back pain (8%), vomiting (8%), dyspepsia (5%), nasopharyngitis (5%) and flatulence (3%).

Table 19 Study SCO5361: Subject Incidence of Treatment-emergent Adverse Effects by treatment period (all subjects, all AEs)

System Organ Class Preferred Term	Binosto/ fasted 70 mg (N=128) n (%)	Binosto/ fed 70 mg (N=130) n (%)	Fosamax 70 mg (N=127) n (%)	Overall (N=133) n (%)
Overall (≥ 1 AE)	62 (48)	69 (53)	57 (45)	103 (77)
Nervous system disorders	37 (29)	31 (24)	32 (25)	64 (48)
Headache	36 (28)	31 (24)	30 (24)	62 (47)
Dizziness	1 (1)	-	3 (2)	3 (2)
Paresthesia	-	1 (1)	-	1 (1)
Gastrointestinal disorders	19 (15)	18 (14)	13 (10)	38 (29)
Diarrhea	1 (1)	9 (7)	4 (3)	12 (9)
Nausea	8 (6)	3 (2)	5 (4)	12 (9)
Vomiting	5 (4)	3 (2)	4 (3)	11 (8)
Dyspepsia	4 (3)	2 (2)	1 (1)	7 (5)
Flatulence	3 (2)	2 (2)	1 (1)	4 (3)
Constipation	1 (1)	1 (1)	1 (1)	3 (2)
Abdominal pain upper	1 (1)	-	-	1 (1)
Chapped lips	1 (1)	-	-	1 (1)
Dysphagia	-	-	1 (1)	1 (1)
General disorders and administration site conditions	10 (8)	20 (15)	14 (11)	36 (27)

Fatigue	10 (8)	19 (15)	14 (11)	36 (27)
Hyperhidrosis	1 (1)	-	-	1 (1)
Pyrexia	-	1 (1)	-	1 (1)
Musculoskeletal and connective tissue disorders	12 (9)	15 (12)	15 (12)	31 (23)
Back pain	3 (2)	5 (4)	6 (5)	11 (8)
Pain in extremity	6 (5)	4 (3)	4 (3)	11 (8)
Musculoskeletal pain	-	1 (1)	2 (2)	3 (2)
Musculoskeletal stiffness	-	2 (2)	1 (1)	3 (2)
Myalgia	1 (1)	1 (1)	1 (1)	3 (2)
Sciatica	1 (1)	1 (1)	1 (1)	3 (2)
Musculoskeletal chest pain	1 (1)	1 (1)	-	2 (2)
Arthralgia	1 (1)	1 (1)	-	1 (1)
Bone pain	-	-	1 (1)	1 (1)
Groin pain	1 (1)	-	-	1 (1)
Infections and infestations	3 (2)	6 (5)	3 (2)	11 (8)
Nasopharyngitis	2 (2)	3 (2)	2 (2)	7 (5)
Rhinitis	1 (1)	2 (2)	1 (1)	4 (3)
Bronchitis	-	1 (1)	-	1 (1)
Respiratory, thoracic and mediastinal disorders	1 (1)	3 (2)	3 (2)	7 (5)
Cough	-	2 (2)	2 (2)	4 (3)
Pharyngolaryngeal pain	1 (1)	1 (1)	-	2 (2)
Nasal dryness	-	-	1 (1)	1 (1)
Vascular disorders	2 (2)	1 (1)	3 (2)	6 (5)
Hypertension	1 (1)	-	3 (2)	4 (3)
Syncope vasovagal	1 (1)	1 (1)	-	2 (2)
Reproductive system and breast disorders	1 (1)	1 (1)	2 (2)	4 (3)
Metrorrhagia	1 (1)	-	2 (2)	3 (2)
Pelvic discomfort	-	1 (1)	-	1 (1)
Skin and subcutaneous tissue disorders	1 (1)	2 (2)	1 (1)	4 (3)
Dermatitis psoriasiform	-	1 (1)	-	1 (1)
Erythema	1 (1)	-	-	1 (1)
Nail disorder	-	-	1 (1)	1 (1)
Pruritis	-	1 (1)	-	1 (1)
Eye disorders	1 (1)	2 (2)	-	3 (2)
Dry eye	-	1 (1)	-	1 (1)
Glaucoma	-	1 (1)	-	1 (1)
Vision blurred	1 (1)	-	-	1 (1)
Ear and labyrinth disorders	-	1 (1)	1 (1)	2 (2)
Ear pain	-	1 (1)	1 (1)	2 (2)
Injury, poisoning and procedural complications	-	-	1 (1)	1 (1)
Joint sprain	-	-	1 (1)	1 (1)

Metabolism and nutrition disorders	-	1 (1)	-	1 (1)
Edema peripheral	-	1 (1)	-	1 (1)
Psychiatric disorders	1 (1)	-	-	1 (1)
Sleep disorder	1 (1)	-	-	1 (1)
Renal and urinary disorders	1 (1)	-	-	1 (1)
Dysuria	1 (1)	-	-	1 (1)
n (%) = number (percent) of exposed subjects with adverse events Source: Table 15, CSR, ADAE dataset				

With each treatment, ~2/3 of AEs were “mild” and ~1/3 were “moderate”. Only 2 AEs were considered “severe”, both following Binosto/fed: an episode of back pain (subject 061), and an episode of nausea (subject 019). Causality was “likely related” according to investigator for 70%, 66% and 68% of reactions to Binosto fasted/fed and Fosamax, respectively.

There were 5 dropouts due to AEs:

- Subject 010, a 59 y/o female, discontinued due to mild **nasopharyngitis** which began 25 days after her period 2 dose which was **Binosto/fed** (she had also experienced vomiting previously in period 1, following (Binosto/fasted))
- Subject 014, a 57 y/o female, was administered **Fosamax** tablet in period 1, experienced **nausea** ~3 hrs later and **vomiting** ~7 hrs later; she was treated with metoclopramide
- Subject 034, a 75 y/o female, discontinued due to **hypertension**. She had a baseline BP in her 1st period of 191/91, received **Binosto/fed** and continued to have high readings over 48 hrs in the range of 170-204/ 79-96. She remained asymptomatic and was discontinued from the study because of the blood pressure and referred to PMD. She had no prior history of hypertension
- Subject 061, a 55 y/o female, received **Binosto/fed** (period 1), and developed severe **back pain** 14 hrs later, which resolved after 17 days
- Subject 108, a 45 y/o female, received **Binosto/fed** (period 1), and developed moderate **bronchitis** 3 days later, which resolved after 26 days

One subject (039), a 70 y/o woman, apparently had glaucoma newly diagnosed during the trial. This diagnosis was recorded 2 weeks after the first treatment, (Binosto)/fed, and she was treated with latanoprost eye drops; no other details are provided. Other than this AE, at the end of the trial, all AEs had resolved except for 2 events “improved” (rhinitis, psoriasisiform dermatitis).

GI Adverse Events

Among the 28% of subjects who experienced GI AEs (**Table 20**), the mean age (57 y/o) was the same as the overall study population. None of the GI AEs met SAE criteria.

Most were considered “likely related” to study drug and were “mild” in severity. One resulted in study discontinuation: subject 014 received her first treatment (Fosamax tablet), then had nausea 3 hrs post-dose and vomiting 7 hrs post-dose.

Unlike study AE-1212-001-EM, (b) (4) overall GI AEs were somewhat more common with Binosto (either fasted or fed) than with Fosamax. There were no major imbalances between treatment periods in individual PTs, though as in the other BE study, AEs of dyspepsia/heartburn and nausea (but not vomiting) were somewhat more common following Binosto than Fosamax.

All of the **dyspepsia/heartburn** events (after any of the 3 treatments) were “mild”, and no concomitant medications (e.g. acid-reducing) were used to treat these symptoms in any subject. The 4 such events (in subjects 009, 055, 019 and 234) that occurred following Binosto/fasted were at 0.5, 1, 3, and 5 hrs post-dose; the durations of symptoms were 3.5, 7, 19 and 8.5 hrs respectively. The 3 dyspepsia/heartburn events that occurred following Binosto/fed (in subjects 051 and 093) were at 14, 1.5 and 18 hrs post-dose; the durations of symptoms were at 3.5, 9 and 9 hrs respectively. The only dyspepsia/heartburn event following Fosamax occurred at 13 days post-treatment, and was the only dyspepsia event considered not probably treatment related. Of the 7 subjects who had dyspepsia symptoms after one of the 3 treatments in this study, none had these symptoms after either of the other treatments. Of the 6 subjects who had dyspepsia symptoms after one of the 2 Binosto treatments (fed and fasted) in this study, 3 had this symptom after the first treatment and 3 had this symptom after the second treatment. Only one episode of dysphagia occurred, 1.5 hrs following a Fosamax dose; it resolved in 7.5 hrs.

As in study AE-1212-001-EM, half (4/8) of the events of **nausea** following Binosto/fasted occurred within 1 hr post-dose, and the others at 5 hr, 14 hr, 30 hr and 13 days. The **vomiting** AEs following this treatment were at 7, 8, 13, 30 and 32 hrs post-dose. Nausea events following Fosamax were at 2, 3, 6, 9 and 16 hrs post dose and vomiting events were at 6, 7, 10 and 51 hrs post dose. Of the 28 nausea or vomiting AEs in the study overall, 6 were treated with either metoclopramide or dimenhydrinate; no other type of GI AE required any treatment.

Similar to one subject in study AE-1212-001-EM, 5 subjects in this study experienced nausea, vomiting and/or dyspepsia with both Fosamax and at least one of the two Binosto treatments, consistent with a common mechanism and/or increased susceptibility of individuals.

As upper GI disorders were an exclusion criterion, only 3 of the 37 subjects with GI AEs gave any previous GI history: subjects 002 and 023 both gave a history of ileus, and developed during the study diarrhea and flatulence respectively; and subject 009 reported a history of intestinal surgery, and developed dyspepsia.

Table 20 Study SCO5361: Frequency of treatment emergent GI adverse events by treatment period

System Organ Class Preferred Term	Binosto/ fasted 70 mg (N=128)		Binosto/ fed 70 mg (N=130)		Fosamax 70 mg (N=127)		Overall (N=133)	
	E	n (%)	E	n (%)	E	n (%)	E	n (%)
Gastrointestinal disorders (all*)	23	18 (14.1%)	21	18 (13.8%)	17	13 (10.2%)	61	37 (27.8%)
Nausea	8	8 (6.3%)	3	3 (2.3%)	5	5 (3.9%)	16	12 (9.0%)
Diarrhea	1	1 (0.8%)	9	9 (6.9%)	4	4 (3.1%)	14	12 (9.0%)
Vomiting	5	5 (3.9%)	3	3 (2.3%)	4	4 (3.1%)	12	11 (8.3%)
Dyspepsia (includes verbatim term heartburn)	4	4 (3.1%)	3	2 (1.5%)	1	1 (0.8%)	8	7 (5.3%)
Flatulence	3	3 (2.3%)	2	2 (1.5%)	1	1 (0.8%)	6	4 (3.0%)
Constipation	1	1 (0.8%)	1	1 (0.8%)	1	1 (0.8%)	3	3 (2.3%)
Abdominal pain upper	1	1 (0.8%)	-	-	-	-	1	1 (0.8%)
Dysphagia	-	-	-	-	1	1 (0.8%)	1	1 (0.8%)

E = number of adverse events
n (%) = number (percent) of exposed subjects with adverse events
* one event of "chapped lips" not included
Source: Table 16, CSR, ADAE dataset

Vital Signs, ECGs, physical exam

Vital signs were measured before each dose of study drug and at 2, 4, 8, 12, 24, and 48 hrs after each dose. There were no clinically relevant changes from baseline or between treatments in blood pressure. (Table 21)

Table 21 Study SCO5361: Blood Pressure by treatment (4-hr fasted treatment groups)

	Binosto/fasted 70 mg				Fosamax 70 mg			
	N	Mean	SD	Max	N	Mean	SD	Max
Systolic (mm Hg)								
Baseline	128	124.0	18.4	184	127	125.5	18.3	186
2 hr	128	120.1	17.4	171	127	121.7	18.9	186
4 hr	128	124.3	18.3	184	127	124.4	18.4	181
8 hr	128	116.7	16.1	190	127	118.0	17.2	169
12 hr	128	122.8	17.6	182	127	122.4	17.0	199
24 hr	128	117.0	16.1	170	127	117.1	16.9	175
48 hr	128	124.1	16.1	171	126	122.3	17.6	189
Diastolic (mm Hg)								
Baseline	128	82.7	9.4	111	127	82.9	10.7	110
2 hr	128	80.1	9.4	109	127	82.0	11.6	142
4 hr	128	81.7	9.4	106	127	81.9	10.2	112
8 hr	128	77.3	9.1	99	127	78.0	10.1	111
12 hr	128	81.1	9.9	105	127	80.1	9.7	109
24 hr	128	79.7	8.9	103	127	78.8	8.9	110
48 hr	128	82.8	8.3	104	126	82.8	10.3	112

Source: Tables 198-203, Appendix 2, CSR

There were 11 subjects who had elevated blood pressure at baseline. During the study, there were 3 “hypertension” AEs following Fosamax tablet vs. 1 after Binosto.. One of these resulted in a discontinuation: subject 034, who had no history of HTN, had a baseline BP in her 1st period of 191/91, received Binosto/fed and continued to have high readings over 48 hrs in the range of 170-204/ 79-96. She remained asymptomatic and was discontinued from the study because of the blood pressure.

ECG parameters and physical exam findings did not show any clinically relevant changes from screening to post-study visit.

Laboratory

Serum calcium and phosphorus were measured predose, and at 24 and 48 hrs after each dose. Following Binosto/fasted, mean serum calcium declined from baseline by 0.13 mg/dL at 24 hrs and 0.11 mg/dL at 48 hrs. Following Fosamax, mean serum calcium declined by 0.15 mg/dL at 24 hrs, but recovered to 0.01 mg/dL above baseline at 48 hrs. At 24 and 48 hrs within each treatment period, there were a few calcium values below 8.0 mg/dL; the lowest was 7.6 mg/dL following Fosamax.

Mean serum phosphorus declined by the same amount (0.13 and 0.17 mmol/L at 24 and 48 hrs respectively) from baseline following either of these treatments.

Measured at screening and post study (~7 days after last dose), there were no clinically relevant changes in hematology or serum chemistry profiles.

Summary of safety, study SCO5361

Among the 133 female subjects randomized and treated with at least one dose, 124 received all 3 treatments and completed the study. There were no deaths or serious AEs. Five subjects dropped out due to an adverse effect; only one of these (nausea and vomiting following a dose of Fosamax) appears to have been study drug-related. AEs were distributed fairly evenly among the 3 treatments. The most frequently reported AEs overall, consistent with the known safety profile of Fosamax, were headache, fatigue, nausea, diarrhea, pain in the extremities, back pain, vomiting, dyspepsia, nasopharyngitis and flatulence. Gastrointestinal AEs were somewhat more common with Binosto relative to Fosamax; none were serious. More subjects reported dyspepsia/heartburn symptoms following Binosto compared to Fosamax, though episodes were mild and did not require treatment or lead to study withdrawal, and the only event of dysphagia came after a Fosamax dose. Nausea was also somewhat more common following Binosto/fasted, though not following Binosto/fed. Serum calcium and phosphorus levels declined slightly as expected, with no difference between treatments. There were no notable safety findings, or differences between treatments, in regard to other laboratory parameters, vital signs or ECGs.

9.4.3 GI Pharmacodynamic Study BC-118-07

A scintigraphic study to investigate the differences in gastric emptying and gastric pH of a conventional tablet versus two effervescent formulations of alendronate.

This study, conducted by Bio-Images Research Ltd. at a single site in Glasgow, UK, was designed to investigate the potential for improved GI tolerability of Binosto over Fosamax tablets through measurements of gastric emptying and gastric pH.

Subjects: 12 healthy females age 20-31, BMI 18-30, nonsmokers, without alcohol or drug abuse, without GI disorders and not using any medications

Study Design: this was an open-label, 3-way crossover study. After overnight fast, subjects received 3 treatment periods in random order, separated by at least 7 days:

- Treatment A – Fosamax tablet 70 mg in 240 mL water
- Treatment B – Binosto effervescent tablet (b) (4) 70 mg in 100 mL water, then 20 mL water rinse of dosing glass
- Treatment C – comparator effervescent powder formulation (b) (4) in 100 mL water, then 20 mL rinse of dosing glass. This formulation was apparently similar in composition to Treatment B including sodium bicarbonate buffer (b) (4)

All 3 formulations were labeled with ^{99m}Tc-DTPA to allow gastric emptying to be measured using gamma scintigraphy. After the dose, images were taken every 5 minutes until gastric emptying of isotope was complete (no p.o. intake was allowed until this point). Images were correlated with gastric pH measurements taken by a nasogastric pH telemetry sensor inserted 3 hrs prior to dose. Subjects taking medications that affect stomach acid were excluded.

Study BC-118-07: Results

Ten subjects completed the study; one withdrew because of an AE, and one withdrew consent.

Imaging showed that the radiolabeled Fosamax tablet promptly entered the stomach in each case, as did all of the radiolabel contained in the 100 mL water used to dissolve the effervescent tablets. (The alendronate molecule itself however was not radiolabeled.) Fosamax tablets disintegrated within a mean of 5.9 ± 4.4 minutes. In most subjects it appeared that disintegration was not complete until the tablet core reached the duodenum. Contrary to investigator expectations, gastric emptying of radiolabel was slightly slower with Binosto, and slightly faster with the (b) (4), compared with Fosamax tablet, though with great variability for all 3 (Table 22)

Table 22 Study BC-118-07: Gastric emptying times

Parameter	Binosto	(b) (4)	Fosamax tablet
Gastric emptying onset (Mean ± SD)	6.6 ± 7.0 min	2.3 ± 2.1 min	9.9 ± 6.3 min
T ₅₀ (Mean ± SD)	34.4 ± 23.3 min*	23.2 ± 20.0 min	28.0 ± 25.6 min
T ₉₀ (Mean ± SD)	71.6 ± 48.3 min	56.9 ± 33.9 min	63.2 ± 35.4 min
T ₅₀ = time to 50% gastric emptying of radiolabel T ₉₀ = time to 90% gastric emptying of radiolabel * = significantly longer than (b) (4) (p=0.05); no other differences significant			

Gastric pH rose above 3 immediately after the dose of the 2 effervescent formulations (due to citrate buffer) and remained elevated for much longer than with Fosamax, where the pH rose much less (due to dilution only) and remained above 3 for a mean of only 3.9 minutes. The Applicant combines pH and gastric emptying time (T₅₀, T₉₀) data based on the hypothesis that potential for esophageal damage exists as long as alendronate remains in an acidic (pH<3) stomach from which it could reflux. (Table 23)

Table 23 Study BC-118-07: Gastric pH parameters relative to gastric emptying

Parameter	Binosto	Merck blend	Fosamax tablet
pH at T ₅₀	3.5 ± 1.3*	4.6 ± 2.3	1.9 ± 0.5
pH at T ₉₀	1.8 ± 0.8	1.4 ± 0.3	1.3 ± 0.3
Time to cross pH3 threshold	56 ± 56 min†	23.8 ± 15.7 min†	3.9 ± 3.0 min
T ₅₀ -pH3 threshold crossing time	-21.6 ± 42.4 min†	-0.6 ± 17.2 min†	26.9 ± 27.8 min
T ₉₀ -pH3 threshold crossing time	15.7 ± 42.2 min†	33.1 ± 32.4 min†	61.7 ± 36.1 min
T ₅₀ = time to 50% gastric emptying of radiolabel T ₉₀ = time to 90% gastric emptying of radiolabel * = significantly higher than Fosamax (p=0.008) † = p<0.05 compared to Fosamax			

Because of acid buffering, mean pH at T₅₀ was significantly higher in subjects treated with Binosto than in Fosamax subjects (p=0.008). In most subjects with the 2 effervescent (buffered) formulations, more than 50% (but less than 90%) of alendronate had left the stomach before pH dropped below 3, in contrast to Fosamax which yielded considerable quantities of acidic alendronate for a prolonged period. In every subject following Binosto administration, gastric pH remained > 3 for at least 30 minutes; in practice, this is the point at which many patients would eat a meal, which would then maintain the higher pH for probably an additional 1-2 hrs.

Reviewer comment: There was a great deal of variability in these measurements, and their clinical significance is not entirely clear. However, this study does show that the effervescent tablet significantly buffers gastric acid during the 30-60 minutes after administration, compared to Fosamax tablet. Given the nonclinical evidence that pH plays an important role in BP-related esophagitis, this study provides some useful supportive safety information.

Study BC-118-07: Safety

Twelve AEs were reported in 9 of the 12 subjects in this study; none were serious.

One subject, a 27 y/o woman, withdrew from the study due to an AE of earache, sore throat and sore face the evening after the first dose period [REDACTED] (b) (4). The investigator's assessment was that this was caused by placement of the NG tube.

Other than this subject, the other AEs in this study were (1 of each):

- Binosto: cold, feeling hot, NG tube irritation
- Fosamax: menstrual pain, nausea (slight)
- [REDACTED] (b) (4) sore back, sore throat

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/s/

STEPHEN R VOSS

02/07/2012

THERESA E KEHOE

02/07/2012

I concur with Dr. Voss's review and recommendations

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202344

**Applicant: EffRx
Pharmaceuticals SA**

Stamp Date: February 15, 2011

Drug Name: Steovess™ 70-mg Effervescent Tablets

**NDA/BLA Type: NDA
Standard**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	Efficacy is based on bioequivalence
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			See Comments for Sponsor
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(2), reference drug = Fosamax 70 mg tablet
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			X	Efficacy is based upon bioequivalence to the RLD

File name: 5 Clinical Filing Checklist for NDA BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		See Comments for Sponsor
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	Safety based on RLD
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	Safety based on RLD
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Rationale for waiver is given
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		See Comments for Sponsor
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			List of investigators not attached to Form 3454
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes__

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comments for Sponsor:

1. Your risk/benefit discussion (M 2.5) regarding the potential for upper GI irritation of your product includes the issue of buffering of gastric acid, but does not address the role of alendronate particulate matter. Please submit and discuss the evidence that your (b) (4) product does not result in significant particulate matter which may be retained within the esophagus.

2. Provide a rationale for the applicability of your data to the U.S. population/practice of medicine, as discussed in *Guidance for Industry E5 - Ethnic Factors in the Acceptability of Foreign Clinical Data* (September 2006), accessible at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073120.pdf>.

Stephen Voss M.D.	March 30, 2011
Reviewing Medical Officer	Date
Theresa Kehoe M.D.	March 30, 2011
Clinical Team Leader	Date

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

/s/

STEPHEN R VOSS
03/30/2011

THERESA E KEHOE
03/30/2011