ELIMINATING THE BISPHOSPHONATE DOSING RITUAL WITH AN IMPROVED DOSAGE FORM OF ALENDRONATE, MER-103

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OBJECTIVE
To evaluate alternative dosing regimens and patient tolerance for alendronate tablets utilizing GIPET™ (Gastrointestinal Permeation Enhancement Technology), Merrion's proprietary technology, to enhance absorption via oral enteric coated tablets. Each MER-103 GIPET™ tablet contains 6mg alendronate and was evaluated relative to a 35mg Fosamax® tablet dosed conventionally.

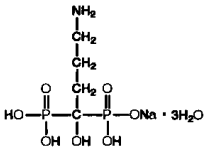
DESIGN
A single dose, four-way crossover study in 16 postmenopausal females. The control, Fosamax® 35mg tablet (Trt A), was dosed per the PI (after an overnight fast, patient remained upright and fasted for 4 hours post-dose). The 6mg GIPET™ tablet was dosed the same as the reference (Trt B), at bedtime 4 hours after an evening meal (Trt C) and in the morning with standard FDA high fat breakfast (Trt D). MER-103 tablets can be dosed at bedtime because the enteric coating releases in the intestine, obviating the bisphosphonate-induced gastric reflux and esophageal erosions. There was at least a 7-day washout between treatment periods. Absorption was assessed based on HPLC quantification of urinary excretion of alendronate.

RESULTS
Absorption from 6mg GIPET™ tablets was excellent when dosed in the morning or at bedtime, and indicated equivalence to Fosamax® 70mg tablets. Alendronate was absorbed even in the presence of food, though absorption was reduced. The dose-corrected bioavailability of GIPET™ treatments relative to Fosamax® were: 1180%536 (Trt B), 1536%1554 (Trt C), and 283%559 (Trt D). All GIPET™ treatments were well tolerated.

CONCLUSION
These data indicate that GIPET™ alendronate 6mg tablets dosed either morning or evening are bioequivalent to 70mg Fosamax® tablets. Because the MER-103 formulation is absorbed in the small intestine, side effects in the stomach and esophagus are avoided. GIPET™ alendronate 6mg tablets eliminate the morning dosing ritual associated with conventional bisphosphonate administration.

BACKGROUND

Alendronate sodium is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. With its amino terminal group, it belongs to a second generation of bisphosphonates and is sometimes referred to as an amino bisphosphonate. The empirical formula of alendronate sodium is $C_4H_{12}NNaO7P_2{\cdot}_3H_2O$ with a molecular weight of 325.12. The structural formula is:



Sold under the tradename Fosamax® in the US, it is indicated for the prevention and treatment of primary and secondary osteoporosis, and for Paget's disease.

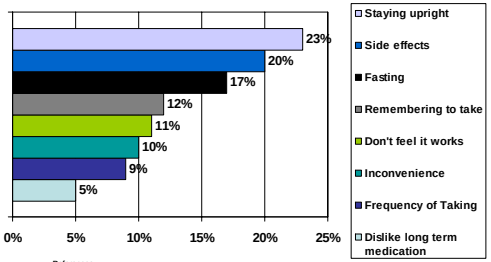
The systemic bioavailability of alendronate from Fosamax® tablets is extremely low:

- Approximately 0.6% is absorbed when administered after an overnight fast and two hours before a standardized breakfast.
- Administration with coffee reduces bioavailability by 60%.
- The bioavailability is essentially negligible when taken with or up to 2 hours after meals.
- The absorbed drug rapidly partitions in vivo, with approximately 50% binding to the exposed bone surface and the remainder being excreted unchanged in urine within 48 hours of dosing.

All bisphosphonates, including alendronate, can cause esophagitis unless the very specific dosing instructions provided in the label are carried out. These instructions, which also include precautions relative to the bioavailability issues, dictate that dosing must occur:

- After arising.
- After an overnight fast.
- With no food intake for at least 30 minutes after dosing.
- With at least 6 oz. of water.
- Patients may not lie down for at least 30 minutes and until food is consumed.

Consumer research has demonstrated that this morning dosing ritual is a major compliance issue with osteoporosis therapy. Up to 60% of weekly bisphosphonate patients stop taking treatment during the first year of therapy. The chart in **Figure 1** below illustrates the primary issues of patients discontinuing therapy.



References
1. Fosamax Package Insert, Physicians Desk Reference 2007, 61st Edition. Thompson PDR, Montvale, NJ, pp 1969-1977.
2. www.iofbonehealth.org/download/osteofound/filemanager/publications/pdf/ International Osteoporosis Foundation. The Adherence Gap Report – why osteoporosis patients don't continue with treatment.

GIPET™ is Merrion's proprietary system for oral absorption enhancement.

GIPET™
- Is a simple, inexpensive oral technology for poorly absorbed compounds.
- Enables oral administration of peptides, oligonucleotides, polysaccharides, small molecules.
- Is based on GRAS-listed compounds as formulation aids.
- Is enteric coated tablets or capsules.
- Invokes no chemical modification to drug molecules.
- Improves bioavailability 5 to 14-fold.
- Facilitates safe absorption enhancement.

Background (contd.)

GIPET™ offers another substantial advantage in therapy for bisphosphonates, since all current products are given as immediate release products. MER-103 enteric coated tablets provide the possibility to develop alternative dosing regimens and thereby alleviate the morning dosing ritual.

STUDY OBJECTIVE

To evaluate alternative dosing regimens for a MER-103, GIPET™ enhanced formulation of alendronate relative to Fosamax®, administered after an overnight fast.

STUDY DESIGN

- Single dose four-way crossover bioavailability study.
- 7-day washout.
- 17 non-smoking, postmenopausal women.
- 15 women completed all legs.
- Mean age 56.5 years, range 44 to 76 years.
- Mean height 64.2 inches, mean weight 187.2 pounds.

Four treatment groups:
- **Treatment A**: Fosamax® 35mg tablet, dosed after overnight fast. Subjects remained fasted and upright for 4-hours post-dose.
- **Treatment B**: MER-103 6mg tablet dosed same as Fosamax® tablet.
- **Treatment C**: MER-103 6mg tablet dosed at bedtime (10.30pm) following 6:00pm supper. Subjects supine for at least 2 hours post-dose.
- **Treatment D**: MER-103 6mg tablet dosed with standard FDA high fat breakfast after overnight fast.

Urinalysis
- Urine collections pre-dose and 0-12, 12-24, 24-36, 36-48 hours post-dose.
- All urine output from each patient was collected and measured.
- Urine assay HPLC with fluorescence detection (LOQ of alendronate urinary assay 2ng/mL; assay range 2 - 500ng/mL).

RESULTS

Analyses of the data were carried out in WinNonlin Version 4.0.1 (Pharsight Corporation, USA). Relative bioavailability for the treatments in the study were carried out twice, with the Fosamax® 35mg tablet used as a reference, and with the MER-103 6mg fasted treatment leg used as a reference.

Results of each analysis are in **Table 1.** Results are adjusted by the doses administered, and indicate that approximately 12 times more alendronate is absorbed from a MER-103 tablet versus Fosamax®. This indicates that a 3 mg tablet can be used as the prevention dose, and a 6 mg tablet as the treatment dose.

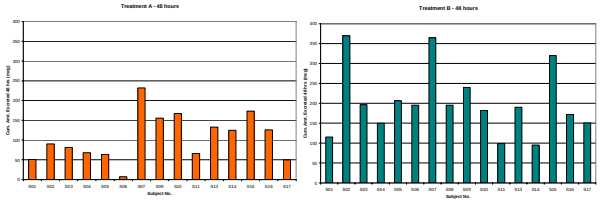
Results of each analysis are in **Table 1.** The amounts excreted by each subject for the two reference treatments are shown in **Figure 2.**

Table 1. Summary of relative bioavailability calculated with Fosamax® 35mg (Trt A) or MER-103 6mg tablet (Trt B) used as a reference.

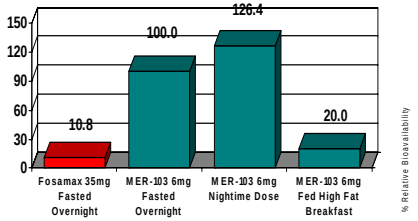
PK Parameters (Mean ± SD)	Fosamax® 35mg Fasted (Trt A)	MER-103 6mg Fasted (Trt B)	MER-103 6mg Night time (Trt C)	MER-103 6mg Fed high fat (Trt D)
Relative Bioavailability % (Ref Fosamax® 35mg) CV%		1180.3 ± 535.7 45.4	1536.4 ± 1554.4 101.2	282.9 ± 558.5 197.4
Relative Bioavailability % (Ref MER-103 6mg Fasted) CV%	10.2 ± 4.8 46.6		126.6 ± 104.2 82.3	20.0 ± 35.0 174.9

RESULTS (contd.)

Figure 2 provides a visual representation of the reduced intersubject variability, with MER-103 compared to Fosamax® seen in the CV% in **Table 1**.



The bioavailability relative to MER-103 6mg Tablets (Fasted Overnight) Treatment B, is shown in **Figure 3** below:



DISCUSSION

MER-103 6mg tablets:

- Deliver approximately twice as much alendronate systemically as Fosamax® 35mg tablets.
- Are expected to be bioequivalent to Fosamax® 70mg.
- Are enteric-coated tablets to deliver 6mg directly to absorption site in intestine.
- Eliminate possibility of gastric reflux and esophageal erosion.
- 12-fold dose reduction significantly decreases exposure of GIT to drug.
- Further decrease possibilities of adverse effects.
- Reduce variability in absorption between patients.
- Night time dosing yields absorption equivalent to fasted dosing, with variability similar to Fosamax®.
- Had no serious adverse events reported during study.

Although substantial amounts of alendronate are absorbed when MER-103 is co-administered with food, the increase in intersubject variability does not suggest that this approach should be pursued. This aspect, in conjunction with the enteric coating and reduced drug exposure to the GI tract, indicates that MER-103 is a viable night-time dosing treatment alternative to the current bisphosphonate treatment's morning ritual.

CONCLUSION

- **MER-103 6mg tablets are approximately 12 times more bioavailable than Fosamax® 35mg.**
- **One MER-103 6mg tablet appears to be approximately bioequivalent to one Fosamax® 70mg tablet.**
- **With an enteric coating and the reduced dose, the GIT exposure to MER-103 tablets is a fraction of that with Fosamax®.**

MER-103 6mg tablets are an improved alternative to bisphosphonate products currently marketed. The key advantages over Fosamax® as well as other bisphosphonates include an altered site of absorption to proximal small intestine via enteric coating, to substantially reduce gastrointestinal side effects, improve tolerability, patient compliance, and eliminate the early morning dosing regimen and requirement to remain upright or standing with fasting after dosing.