

MER-101 TABLETS: A PILOT BIOAVAILABILITY STUDY OF A NOVEL ORAL FORMULATION OF ZOLEDRONIC ACID

Thomas W. Leonard¹, Catherine McHugh², Bozena Adamczyk², Angela Walsh²

¹ Merrion Pharmaceuticals LLC, Wilmington, North Carolina, United States
² Merrion Pharmaceuticals Ireland Ltd, Dublin, Ireland

Introduction

The purpose of the study was to compare the absorption of two strengths of an investigational oral dosage form of MER-101, a tablet form of zoledronic acid, to the parenteral reference product, commercially-available zoledronic acid intravenous infusion, (Zometa® Injection, Novartis). MER-101 was developed by Merrion Pharmaceuticals using GIPET™ I technology to improve the oral bioavailability of zoledronic acid and thereby enable the development of an oral dosage form. GIPET™ I is based on proprietary penetration enhancers which improve the absorption of such drugs in the small intestine. There is no chemical modification to the active drug. The enhancer system is comprised of food-based material which is on the US GRAS list. These are important factors in reducing regulatory requirements and the time to market. GIPET™ technology is equally applicable to small molecules, macromolecules and biologics, and is broadly applicable over a wide range of marketed and emerging products.

Zoledronic acid is a bisphosphonate used in the treatment of bone metastases. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxylapatite found in bone. The current marketed dosage form of zoledronic acid is a given as an infusion to overcome the limitations of oral dosing of bisphosphonates, including low bioavailability, gastric irritation, and gastric reflux.

Experimental Procedures

The study was a single-dose, three-way crossover bioequivalence study in 13 postmenopausal female subjects with osteoporosis. There was a washout period of at least 7 days between dosing days. Cumulative urinary excretion of zoledronic acid over a 48-hour period was used as the basis for the pharmacokinetic analysis. Eleven subjects successfully completed all treatment periods of the study and were included in the final analysis.

The treatments administered during the clinical trial were: MER-101 10mg and 20mg Enteric Coated Tablets and Zometa® Injection 1mg, administered as a 15-minute infusion in 100mL of normal saline. The treatments were well tolerated in all cases.

Data Summary

The MER-101 20mg tablet had a mean 48-hour urinary excretion of zoledronic acid approximately 44% greater than the MER-101 10mg tablet. The MER-101 20mg tablet had a mean zoledronic acid excretion that was similar to the Zometa® 1mg Injection (0.514mg and 0.541mg respectively).

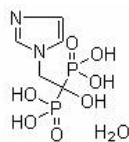
Conclusions

A tablet dosage form of zoledronic acid was successfully developed which will allow once weekly treatment of patients. The dose administered via a 20mg tablet equals that of a 1mg intravenous infusion. MER-101 was well tolerated and there were no serious adverse events associated with its administration.

BACKGROUND

Zoledronic acid is a bisphosphonate which is a potent inhibitor of osteoclastic bone resorption. It is sold in the US as a concentrated solution for intravenous infusion under the tradename Zometa® (Novartis). It is indicated for the treatment of hypercalcemia of malignancy, multiple myeloma, and bone metastases of solid tumors.

Zoledronic acid has a molecular weight of 290.1 with an empirical formula $C_8H_{10}N_2O_7P_2H_2O$. The structural formula is:



All bisphosphonates, including zoledronic acid, have poor oral bioavailability. Studies carried out by Merrion in beagle dogs indicate an oral bioavailability of approximately 3.5%.

The current marketed dosage form of zoledronic acid is given as an intravenous infusion to overcome the issues with oral dosing of bisphosphonates, including:

- Low bioavailability.
- Gastric irritation.
- Gastric reflux.

The gastric reflux induced by bisphosphonates can result in esophageal erosions. This effect is minimized by dosing requirements imposed on all marketed oral bisphosphonates that patients remain upright for 30 to 60 minutes after dosing. This could prove to be a difficult task for the metastatic cancer population for whom Zometa® is indicated.

MER-101 was developed by Merrion Pharmaceuticals using their GIPET™ technology to improve the oral bioavailability of zoledronic acid to enable the development of an oral dosage form. GIPET™ technology has demonstrated improved oral absorption of a number of compounds, and bisphosphonates in particular.

GIPET™

- Is based on GRAS-listed proprietary penetration enhancers.
- No chemical or physical alteration of the drug molecule is involved.
- Preclinical dog studies have demonstrated enhanced absorption of zoledronic acid of approximately 7-10%.
- Enteric coating eliminates esophageal reflux issues.

The MER-101 development program is based on weekly administration of zoledronic acid, which should yield improved therapy due to the ability to better target rapidly growing metastatic tissues. The oral doses were chosen to result in comparable absorption to the standard parenteral dose of 4mg/month. Since the dosing target is a once-a-week, each tablet should deliver 1mg.

STUDY OBJECTIVE

To compare the absorption from two strengths, 10mg and 20mg MER-101 enteric coated tablets to the parenteral reference product, commercially-available zoledronic acid intravenous infusion, (Zometa® Injection, Novartis).

STUDY DESIGN

- Single-dose, three-way crossover bioavailability.
- 7 day washout between each of the three periods.
- 12 postmenopausal women with osteoporosis (13 enrolled).
- Mean age 60.4 years, range 49 to 69.
- Mean height 63.9 inches.
- Mean weight 182.1 pounds.

Treatments were administered:

- After an overnight fast.
- With a full glass of water.
- Patients remained fasted and upright for 4 hours post-dose.

Treatment arms:

- MER-101A enteric coated tablet (10mg zoledronic acid).
- MER-101B enteric coated tablet (20mg zoledronic acid).
- Zometa® Injection 1mg 15 minute infusion in 100mL normal saline.

Pharmacokinetic samples:

- Cumulative urinary excretion of zoledronic acid.
- Urine collections pre-dose and 0-12, 12-24, 24-36, and 36-48 hours post-dose.
- All urine output from each patient was collected and measured.
- Urine assay HPLC with tandem mass spectrometry (LOQ of zoledronic acid urinary assay 4.99ng/mL; assay range 4.99-4989.60ng/mL).

RESULTS

- A total of 12 subjects completed all dosing arms of the study.
- All pharmacokinetic calculations were performed using SAS (PC version 6.12).
- Subject 1 inadvertently did not receive the dose in the IV infusion and was excluded from all statistical evaluations.

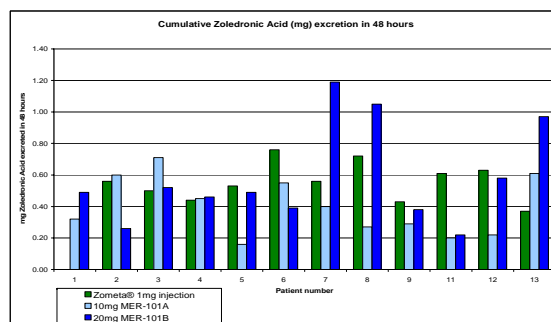
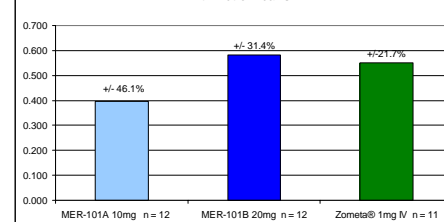


TABLE 1		Cumulative Urinary Excretion 0-48 Hours (mg)	
Test Item	Dose	Least Square Means	Ln Transformed Means
MER-101A	10mg	0.397	0.358
MER-101B	20mg	0.583	0.514
Zometa®	1mg	0.550	0.541

RESULTS (contd.)

TABLE 2	Ratio for Cumulative Excretion Values	
Test Item	Least Square Mean Ratio (90% CI)	Ln Transformed Ratio (90% CI)
MER-101A / Zometa®	0.723 (0.42 - 1.02)	0.661 (0.48 - 0.91)
MER-101B / Zometa®	1.060 (0.76 - 1.36)	0.949 (0.69 - 1.31)
MER-101B / MER-101A	1.466 (1.06 - 1.87)	1.436 (1.05 - 1.96)

MER-101-01 Results Zoledronic Acid in Urine(mg) Arithmetic Means



DISCUSSION

- MER-101 20mg tablets gave 44% greater mean 48-hour urinary excretion of zoledronic acid versus MER-101 10mg tablets, based on the analysis of the Ln transform data.
- Mean zoledronic acid excretion for MER-101 20mg tablets was similar to Zometa® 1mg Injection (0.514mg and 0.541mg respectively).

CONCLUSION

- A tablet dosage form of zoledronic acid has been successfully developed to enable a once weekly treatment regimen.
- The dose administered via a 20mg tablet is equivalent to a 1mg intravenous infusion.
- The MER-101 tablets were well-tolerated and there were no serious adverse events associated with administration.
- MER-101 tablets are an improved alternative to bisphosphonate products currently marketed.
- They enable a weekly administration of zoledronic acid, which should yield improved therapy due to the ability to better target rapidly growing metastatic tissues.
- The key advantages 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 requirement to remain upright or standing with fasting after dosing.
- There is currently an unmet market need for an oral bisphosphonate in oncology.
- The advantages of oral tablets include:
 - ❖ Improved quality of life for the patient.
 - ❖ Flexibility in the dosing regimen.
 - ❖ Improved compliance.