

MER-101: A Bioavailability Study of Various GIPET™ Formulations in Beagle Dogs with Intraduodenal Cannulae.

Purpose

To determine the bioavailability of zoledronic acid from solutions of zoledronic acid in a GIPET™ I (Gastrointestinal Permeation Enhancement Technology systems) matrix administered directly to the duodena of beagle dogs.

Methods

Six beagle dogs which previously had indwelling intraduodenal catheters inserted were administered zoledronic acid formulations once a week over four weeks. During week one, each dog received 1.5mg of zoledronic acid by IV infusion (Zometa®). During week two, 10mg of drug was administered ID with a high dose GIPET™ I in 10mL of water. During week three, 10mg of drug was administered ID with a low dose GIPET™ I in 10mL of water. During week four, 10mg of drug was given in solution with no enhancer.

Urine was collected from the animals over four intervals, 0-4 hours, 4-8 hours, 8-12 hours, and 12-24 hours after dosing. Cage tray rinse samples were also collected. Samples were assayed for zoledronic acid using a LC/MS/MS method.

Results

The absolute bioavailability of drug absorbed from each test formulation based on the reference injection for each dog was calculated by (Test mg excreted/Test Dose/IV Dose/IV mg Excreted).

Approximately half of the administered IV dose was excreted in the urine over the 24-hour period. The data indicate that the absolute bioavailability of a GIPET™ I-enhanced formulation administered via solution to the duodenum of dogs is approximately 7 – 10%.

The %CV for the higher GIPET™ I dose 59.2%, was approximately half of that with the lower dose 117.6%. The lower dose of GIPET™ I had less variability than the unenhanced formulation 149.8%.

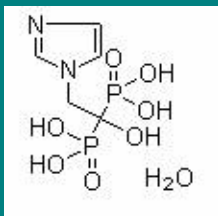
Conclusion

GIPET™ I formulations increased the bioavailability of zoledronic acid in the feasibility dog model described. Variability between animals is decreased by co-administration with GIPET™ I. The results enable selection of lead formulations for development of oral dosage forms of zoledronic acid.

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 C₂H₁₀N₂O₇P₂·H₂O. The structural formula is:



All bisphosphonates, including zoledronic acid, have poor oral bioavailability.

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 Merri^{on} 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.
- ❖ Enteric coating eliminates esophageal reflux issues.

OBJECTIVE

To determine the bioavailability of zoledronic acid from solutions of zoledronic acid in a GIPET™ I (Gastrointestinal Permeation Enhancement Technology systems) matrix administered directly to the duodena of beagle dogs.

MER-101: A Bioavailability Study of Various GIPET™ Formulations in Beagle Dogs with Intraduodenal Cannulae

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METHODOLOGY

❖ Six beagle dogs which previously had indwelling intraduodenal catheters inserted were administered zoledronic acid formulations once a week over four weeks.

❖ The same treatment was administered to all the dogs during each week's dosing.

Treatments – See Table 1:

- ❖ Week 1, IV infusion of 1.5mg of zoledronic acid (Zometa®).
- ❖ Week 2, 10mg administered ID with a high dose GIPET™ I in 10mL of water.
- ❖ Week 3, 10mg administered ID with a low dose GIPET™ I in 10mL of water.
- ❖ Week 4, 10mg in solution with no enhancer.

❖ There was a washout period of one week between different formulations dosed.

❖ Urine was collected from the animals over four intervals, 0-4 hours, 4-8 hours, 8-12 hours, and 12-24 hours after dosing. Cage tray rinse samples were also collected.

❖ Samples were assayed for zoledronic acid using a validated HPLC / Tandem Mass Spec Method. Method range 5 - 5000ng/mL.

❖ The absolute bioavailability of drug absorbed from each test formulation based on the reference injection for each dog was calculated by:

$$\% \text{Bioavailability} = \frac{\text{Test Item mg excreted}}{\text{Test Dose}} \times \frac{\text{IV Dose}}{\text{IV mg Excreted}} \times 100$$

Table 1. Details of the dose of zoledronic acid, formulation and frequency of dosing administered intraduodenally to beagle dogs.

Test item	Dose of zoledronic acid	Route of administration	Formulation details	Frequency of dosing
1	1.5mg	IV	Zometa®	Single dose
2	10mg	ID	GIPET™ I (high dose form. I)	Single dose
3	10mg	ID	GIPET™ I (low dose form. II)	Single dose
4	10mg	ID	Unenhanced	Single dose

RESULTS

- ❖ Approximately half (0.78mg) of the administered IV dose was excreted in the urine over the 24-hour period with a CV of 19.72%. Refer to **Table 2** and **Figure 1**.
- ❖ The data indicate that the absolute bioavailability of a GIPET™ I enhanced formulation administered via solution to the duodenum of the dog is approximately 7 – 10%. Refer to **Table 2**.
- ❖ The CV for the higher GIPET™ I dose (59.2%) was approximately half of that with the lower dose (117.6%).
- ❖ The lower dose of GIPET™ I had less variability than the unenhanced formulation, which was 149.8%.
- ❖ No clinical adverse events were observed as a result of the dosing.

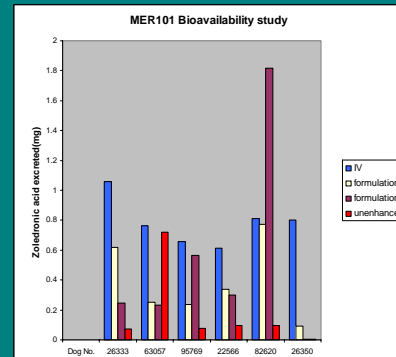


Figure 1.

Table 2. Zoledronic acid GIPET™ I (Mean % Bio+/- SD, CV%)

	Test Item 1 Ref. (IV)	Test Item 2 High Dose GIPET™ I		Test Item 3 Low Dose GIPET™ I		Test Item 4 Unenhanced	
	mg	mg	% Bio	mg	% Bio	mg	% Bio
Average	0.78	0.39	7.3	0.53	10.3	0.18	3.5
Std Dev.	0.15	0.26	4.3	0.66	12.16	0.27	5.28
CV	19.72%	66.8	59.2	124.2	117.6	151.0	149.8

Bioavailability of MER101 in dogs after intraduodenal administration

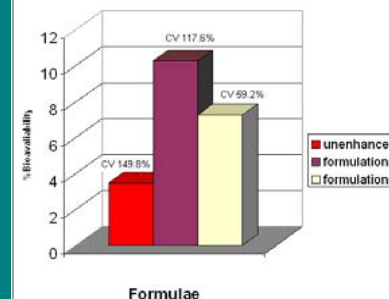


Figure 2.

CONCLUSION

- GIPET™ I formulations increased the bioavailability of zoledronic acid in the feasibility dog model described.
- Variability between animals is decreased by co-administration with GIPET™ I.
- The results enable selection of lead formulations for development of oral dosage forms of zoledronic acid.