

STUDIES OF BIOAVAILABILITY AND FOOD EFFECTS OF MER-101 ZOLEDRONIC ACID TABLETS IN POSTMENOPAUSAL WOMEN

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Background
MER-101 (Orazol) is an alternate administration route for zoledronic acid (ZA) IV infusion (Zometa). The weekly enteric-coated tablet delivers systemic ZA doses equivalent to monthly 4mg infusions. MER-101 uses GIPET to achieve oncological doses with excellent GI tolerability. The objectives of MER-101-01 and MER-101-02 were to examine the bioavailability and food effects on absorption of different strengths and regimens of MER-101 versus ZA 1mg IV infusion.

Methods
MER-101-01, a single weekly dose, open label, 3-way crossover study in 13 osteoporotic women examined 10mg and 20mg MER-101 tablets versus a 1mg IV infusion. Absorption was determined via an LCMS urine assay of aliquots for 48 hours post-dose. Dosing was after an overnight fast, which continued 4-hours post-dose.
MER-101-02, a single-dose, open label, 5-way crossover study in 30 postmenopausal women examined MER-101 15mg and 20mg tablets versus the IV infusion. Absorption was determined using LCMS assay of serum collected pre-dose, and 0.25, 0.5, 1, 1.5, 2, 3, 5, 7, 10, 14, 24, and 36 hours post-dose.

Treatment arms:
(A) MER-101 15mg, overnight fast, breakfast 30 minutes later.
(B) MER-101 20mg, overnight fast, breakfast 30 minutes later.
(C) MER-101 20mg, FDA standardized breakfast.
(D) MER-101 20mg, bedtime, following a 4-hour fast.
(E) ZA 1mg IV infusion.

Safety assessments included AE monitoring, PE, hematology, urinalysis, and blood chemistry panels.

Results
Bioavailability of MER-101 20mg tablet was equal to a 1mg ZA infusion; the 10mg tablet was approximately half the 1mg ZA infusion. Administration of the 20mg tablet with food resulted in a large reduction in bioavailability.
MER-101 absorption improved with the nighttime dosing regimen and with the morning dose/4-hour fasting regimen. Serum profiles indicate retention of enteric tablets in the stomach longer than 30 minutes. The resultant food interaction from the shorter fasting time likely resulted in reduced bioavailability.

Conclusions
The MER-101 20mg tablet dosed weekly for 4 weeks provides a systemic dose equivalent to a 4mg ZA IV infusion.
MER-101 potentially offers a substantial improvement over IV infusion in bisphosphonate therapy for women with breast cancer.

BACKGROUND

Zoledronic acid is a bisphosphonate used in the treatment of bone metastases. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone, decreasing bone resorption by reducing osteoclastic activity. Studies have demonstrated that zoledronic acid reduces the incidence of skeletal-related events (SREs) in metastatic bone cancer. A reduction in levels of markers of bone metabolism, particularly urinary NTX, has been shown to be prognostic of a reduction in SREs [1]. MER-101 has been shown to reduce urinary NTX and serum CTX levels to an extent greater than or equal to the reduction achieved with Zometa IV infusion 4mg administered every 4 weeks.

Zoledronic acid has a molecular weight of 290.1 with an empirical formula $C_8H_{10}N_2O_7P_2 \cdot H_2O$. The structural formula is:



All bisphosphonates, including zoledronic acid, have poor oral bioavailability. This has limited their use in oncological therapies to intravenous infusion to achieve the doses required for efficacy. The local gastric irritation that occurs with existing oral bisphosphonates is also an important consideration in oncological indications, as it can result in esophageal erosions and ulceration.

MER-101 (Orazol)

- Enhances bioavailability substantially to enable an effective oral oncological dose
- Tablet weekly instead of a regimen of IV infusions every 3 or 4 weeks
- Provides an improvement in administration profile:
 - Lower systemic dose taken more frequently
 - Less potential for renal damage due to the lower C_{max}
 - Ability to titrate frequency and dose
 - More frequent exposure of metastatic cells to plasma levels of drug
 - Enteric coating eliminates potential for stomach and esophageal complications associated with other bisphosphonates
 - Enhanced absorption decreases overall GI drug load
- Gastrointestinal Permeation Enhancement Technology (GIPET)
 - Oral platform technology for poorly absorbed compounds based on salts of medium chain fatty acids
 - Physical mixture of enhancer system and drug in a tablet form
 - Facilitates safe absorption - very little effect on the GIT, primary mechanism of mixed micelles to improve transcellular absorption
- Classified as food substance:
 - Reviewed by EU Scientific Committee for Food and determined 'safe in use', and the FAO/WHO Joint Expert Committee of Food Additives, with no limit on intake
 - Listed in the US CFR as a direct food additive with no limit on intake
- Successfully applied to poorly absorbed compounds across several physical/chemical categories

HOW DOES GIPET® WORK?

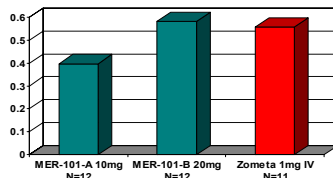


Robert E. Coleman et al. Predictive Value of Bone Resorption and Formation Markers in Cancer Patients with Bone Metastases Receiving the Bisphosphonate Zoledronic Acid. J Clin Oncol 23:4025-4038 © 2005 ASCO

CLINICAL MER-101-01

- MER-101-01 Study**
- Phase 1, single dose, randomized, open label, 3-way crossover study
 - The study population was 13 postmenopausal women with osteoporosis
- Objective**
- To compare absorption of 2 investigational oral dosage forms of zoledronic acid to the market product IV infusion
- Method**
- Three treatment arms:
 - MER-101 Tablet 10mg
 - MER-101 Tablet 20mg
 - Zometa IV infusion 1mg
 - Fasting 10.5 hours prior to dosing until 4 hours post-dose
 - 7 Day interval between dosing
 - Bioavailability was determined from urinary excretion data collected over 48 hours and assayed using LC/MS/MS in urine
- Results**
- Mean urinary excretion of zoledronic acid over 48 hours for the MER-101 Tablet 20mg is comparable to a 1mg infusion of Zometa IV
 - The 10mg tablet was approximately half the 1mg ZA infusion

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



Test Item	Dose	Cumulative Urinary Excretion 0-48 Hours (mg)	Least-Squares Means (95% CI)	Ln Transformed Means	Ratio for Cumulative Excretion Values	Least-Squares Means Ratio 95% CI	Ln Transformed Ratio 95% CI
MER-101A	10mg	17.99 (16.1)	0.358		MER-101A / Zometa	0.723	0.661
MER-101B	20mg	34.93 (33.0)	0.514		MER-101B / Zometa	1.060	0.949
Zometa	1mg	35.67 (21.7)	0.541			0.780 - 1.360	0.687 - 1.310

CLINICAL MER-101-02

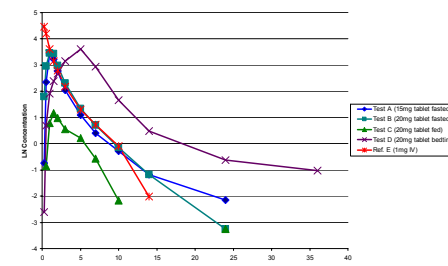
- MER-101-02 Study**
- Single dose, randomized, 5-way crossover study, fasted and fed conditions
 - The study enrolled 30 postmenopausal women
 - 28 subjects had evaluable data
 - 23 subjects completed all treatment arms
- Objective**
- To determine the effect of food on absorption of zoledronic acid
 - To evaluate a nighttime dosing regimen
- Method**
- Five treatment arms:
- MER-101 Tablets 15mg orally after an overnight fast, FDA standardized breakfast 30 minutes post-dosing
 - MER-101 Tablets 20mg orally after an overnight fast, FDA standardized breakfast 30 minutes post-dosing
 - MER-101 Tablets 20mg orally immediately following FDA standardized breakfast
 - MER-101 Tablets 20mg orally at bedtime after a 4-hour fast following supper. Breakfast 10.5 hours post-dosing
 - Zometa IV infused intravenously (1mg in 100mL sterile 0.9% Sodium Chloride, USP) over 15 minutes after an overnight fast, FDA standardized breakfast 30 minutes post-dosing
- 7 Day washout interval between treatment arms
 - Bioavailability was assessed by the appearance of unchanged drug in serum collected at intervals over a 36-hour period after administration of drug
- Results**
- The study demonstrated a substantial food effect that precludes co-administration with food
 - Post-dose fasting time impacts bioavailability. A half-hour fast is not sufficient in all patients
 - The study data from subjects who did not exhibit a food effect with the morning fasted dose confirmed that the zoledronic acid serum AUC from the MER-101 (Orazol) Tablet 20mg is the same as the AUC from the 1mg zoledronic acid infusion
 - The oral tablet is very well tolerated (4 treatment arms were oral)

OVERALL CONCLUSIONS

- Bioavailability of the MER-101 20mg tablet is equal to a 1mg zoledronic acid infusion
- Administration of the 20mg tablet with food results in a large reduction in bioavailability
- MER-101 absorption improves with the nighttime dosing regimen
- Serum profiles indicate retention of enteric tablets in the stomach longer than 30 minutes in some subjects in MER-101-02. The resultant food interaction from the shorter fasting time results in reduced bioavailability
- The MER-101 20mg tablet dosed weekly for 4 weeks provides a systemic dose equivalent to a 4mg ZA IV infusion
- MER-101 potentially offers a substantial improvement over IV infusion in bisphosphonate therapy for oncology patients with bone metastases

CLINICAL MER-101-02 Contd.

MER-101-02 Zoledronic Acid Ln Least-Squares Means of Serum Levels (n=28)



MER-101-02 Untransformed Data: Comparison of AUC of Oral Treatment Groups with IV Infusion

Treatment	Mean AUC _{0-∞} (hCV)	Ratio of Test/Reference 95% CI	Mean AUC _{0-∞} (hCV)	Ratio of Test/Reference 95% CI
15mg Tablet Fasted	0.93	0.507	23.7	0.976
20mg Tablet Fasted	85.6	0.733	120.9	0.831
20mg Tablet Fed	192.2	0.375 - 1.09	67.0	0.358 - 1.30
20mg Tablet Bedtime	10.6	0.108	39.9	0.154
1mg IV Infusion Reference	145.4	0.00 - 0.669	43.8	0.00 - 0.624
20mg Tablet Bedtime	210.8	1.85	278.8	2.30
1mg IV Infusion Reference	116.2	1.50 - 2.21	171.4	1.85 - 2.75
1mg IV Infusion Reference	n/a	n/a	121.8	n/a
1mg IV Infusion Reference	n/a	n/a	15.4	n/a

*AUC_{0-∞} excludes all subjects with substantial food effects, as k_{tr} could not be estimated for these subjects.

MER-101-02 Geometric Means Transformed Data: Comparison of AUC of Oral Treatment Groups with IV Infusion

Treatment	Ln Means AUC _{0-∞}	Ratio of Test/Reference 95% CI	Ln Means AUC _{0-∞}	Ratio of Test/Reference 95% CI
15mg Tablet Fasted	0.427	0.240 - 0.789	97.7	0.593 - 1.11
20mg Tablet Fasted	52.1	0.183 - 0.559	86.3	0.528 - 0.972
20mg Tablet Fed	5.1	0.027 - 0.0796	27.5	0.138 - 0.375
20mg Tablet Bedtime	1.34	0.285 - 2.27	210.4	1.30 - 2.34
1mg IV Infusion Reference	122.2	n/a	120.6	n/a

*AUC_{0-∞} excludes all subjects with substantial food effects, as k_{tr} could not be estimated for these subjects.

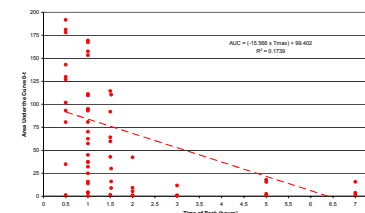
- The statistical analysis for the Least Squares Means dataset indicates that the 20mg tablet has a greater bioavailability than the 15mg tablet. The Ln transformed analysis indicates the opposite
- This is facilitated in part by the food effect given by the meal 30 minutes post dosing, and is demonstrated in the following table:

Protocol / Treatment	Food Effect: # of Subjects with No Absorption		# of Subjects	# with no absorption / # with poor absorption*
	Pre-Dose Fast	Post-Dose Fast		
MER-101-01				
10mg Fasted	10.5h / 4h	12	0 / 0	
20mg Fasted	10.5h / 4h	12	0 / 0	
MER-101-02				
15mg Fasted	10.5h / 0.5h	28	7 / 11	
20mg Fasted	10.5h / 0.5h	27	3 / 7	
20mg Fed	0h / 4h	28	7 / 21	

*Absorption was very poor, and insufficient data are available to calculate the k_{tr} .

- With an enteric coated tablet, time of absorption is dictated by the pH environment of the tablet, therefore, there is some diversity in the time of the peak serum level based on GI transit
- A plot of AUC versus T_{max} indicates that a decrease in bioavailability is seen proportional to the T_{max} when food is consumed with or shortly after the dose. Therefore, with longer tablet GI transit times, more food contact occurs during absorption, and the bioavailability is lower

MER-101-02: 15mg and 20mg Tablets Morning Dosing (Feds A, B, C) AUC 0-∞ vs. T_{max} Subjects with AUC = 8 Excluded



Subjects with T_{max} < 2h Transformed Data: Comparison of AUC of Oral Treatment Groups with IV Infusion

Treatment	AUC-MFE - *	Ratio 95% CI
15mg Tablet Fasted	92.6	0.169
20mg Tablet Fasted	105.2	0.506 - 1.07
20mg Fed	105.2	0.595 - 1.21

*MFE - Minimal Food Effect: subjects with T_{max} less than 2 hours.