International Journal of Pharmaceutics 432 (2012) 57–62

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Modulation of gastric pH by a buffered soluble effervescent formulation: A possible means of improving gastric tolerability of alendronate

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ARTICLE INFO

Article history:
Received 23 April 2012
Received in revised form 25 April 2012
Accepted 26 April 2012
Available online 4 May 2012

Keywords:
Alendronate
Gastric transit
pH
Gamma scintigraphy
Gastric tolerability
Buffering
Binosto™
Steovess™

ABSTRACT

Gastrointestinal side-effects of alendronate (ALN) are believed to be associated with oesophageal lodging of tablets and perhaps reflux of gastric contents with alendronate under strongly acidic pH conditions. This leads to unfavourable posture restrictions when dosing.

This clinical study evaluated gastric emptying and gastric pH after administration of Fosamax® tablets and a novel effervescent ALN formulation with a high buffering capacity. This novel formulation, EX101, was developed to potentially improve gastric tolerance.

Gastric pH was monitored by nasogastric probes. Gastric emptying was determined simultaneously by scintigraphic imaging of ^{99m}Tc-DTPA labelled formulations.

Both formulations tested rapidly cleared the oesophagus and there were no statistically significant or physiologically relevant differences in gastric emptying times. Mean pH at time to 50% gastric emptying of the radiolabel was significantly higher in EX101-treated subjects compared to those treated with Fosamax®. At time to 90% gastric emptying of the radiolabel, mean pH values were comparable.

Mucosal exposure to ALN at pH less than 3 is irritating to gastro-oesophageal tissue. Ingestion of Fosamax® resulted in ALN being present in the stomach at a pH below 3 within minutes. EX101 minimised the possibility of exposing the oesophagus (in case of reflux) to acidified ALN.

1. Introduction

The true cost to society of osteoporosis has been shown to be very high and is steadily rising. According to data from the International Osteoporosis Foundation, a "majority of the total costs (combined costs in France, Germany, Italy, Spain, UK and Sweden) was for the acute management of fracture whilst pharmacological prevention and treatment only represented 4.7% of total costs; in 2025, the projected number of fractures will increase by 29% reaching 3.2 million fractures, with health care costs increasing to €38.5 billion" (Ström et al., 2011).

A key factor in rising costs is poor compliance and adherence to therapy, which may be exacerbated by the use of generic oral solid tablet versions of the drug (Ringe and Moller, 2009). Poorer effectiveness may result from faster disintegration times of many generics that increase the likelihood of adherence of particulate matter to the oesophageal mucosa (Kanis et al., 2012). These authors also asserted that a relevant number of generic tablets have displayed cleavage rupture, leading to large pieces of tablets being strongly adherent to the oesophageal mucosa.

Oral bisphosphonates used in the treatment of osteoporosis, such as alendronate (ALN), are recognised as oesophageal irritants despite good upper gastrointestinal (GI) tolerability in Phase III trials (Abid et al., 2005; Liberman et al., 1995; Black et al., 1996; Castell, 1996). In a normal clinical setting, where patients are not often offered frequent follow-up visits and regular reminders on how to take the medication, oesophageal and gastric side effects are among the most common reasons for giving up bisphosphonate therapy (Tosteson et al., 2003).

GI adverse events reported during ALN tablet therapy include dyspepsia, dysphagia, and oesophageal ulcers (Fosamax® package insert; Thomson et al., 2002; Adachi et al., 2001). Chemical oesophagitis has been described, with erosions, ulcerations, and exudative inflammation, and case reports suggest that these adverse events are associated with failure to follow dosing instructions (de Groen et al., 1996).

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http://dx.doi.org/10.1016/j.ijpharm.2012.04.073

Based on the incidence of these adverse events, the dosing instructions for Fosamax® were modified to stress the importance of taking the medication with a full (6–8 oz/180–240 mL glass of plain water, and maintaining the fast and remaining in an upright position for 30 min after dosing).

Dissolution of tablets in situ will provide a mechanism by which oesophageal irritation ("pill oesophagitis" as per Abraham et al., 1999) is likely to develop, especially on repeated insult. The cellular processes that lead to mucosal ulceration have been described (Abraham et al., 1999; Argenzio and Eisemann, 1996) and crystalline drug substance has been shown to be present in biopsies from ALN-induced oesophagitis (Abraham et al., 1999).

It is likely that lodging of an ALN tablet, caused by inadequate water flow or inappropriate posture on dosing, is a main cause of oesophagitis. It is postulated that if ALN is administered as a liquid, this could be prevented. Furthermore, preclinical evidence also suggests that acid control can support better gastric tolerance, as investigations have shown that GI lesions are most severe when oesophageal mucosal tissue is exposed to bisphosphonates in the presence of stomach acid (Dobrucali et al., 2002).

Exposure of beagle dogs to ALN solutions demonstrated that oesophageal irritancy potential is correlated with acidity, with solutions of pH below 2 having significant irritancy potential. In contrast, exposure of ALN above pH 3.5 was totally benign (Peter et al., 1998). Merck NDA 21-575 Pharmacology Review concluded that "... multiple factors contribute to the development of clinical oesophagitis including prolonged contact of the tablet with the mucosa, reflux of acidic gastric contents containing ALN ...Under acid conditions (pH <3), ALN exists in the free acid form (>67%) which is more irritating than the sodium salt form".

The EX101 formulation was designed to fully solubilise ALN in a palatable solution of relatively high pH (approximately pH 5) with high acid neutralising capacity, to achieve two characteristics: to minimise solid (particulate) ALN from contacting the mucosa and to prevent strong stomach acid being present with ALN in the stomach, diminishing damage potential in cases of oesophageal reflux. Both of these factors are expected to reduce the GI liabilities of ALN administration, and are consistent with observations with this and other classes of pharmaceutical products.

EX101 has, to date, received marketing authorisations in the EU and the USA, and will be sold as Binosto™ or Steovess™ in various territories.

A clinical scintigraphic study was designed to evaluate the gastric environment differences between standard tablet formulations and soluble effervescent formulations of ALN. The investigation focused on gastric pH and gastric transit parameters.

The specific study objectives were:

- To evaluate potential dosing advantages of a soluble effervescent ALN formulations when compared to a conventional ALN tablet.
- To assess the gastric pH after dosing of effervescent and conventional ALN tablet formulations.
- To determine differences between the upper GI transit of effervescent vs. tablet ALN formulations during post-dose fasting by determining gastric emptying times of the formulations.

The study was designed to assess the gastric emptying and gastric pH parameters post-dose. Primary Evaluation Variables (endpoints) fell into two categories: gastric transit and gastric pH.

To assess gastric transit, the primary variables were gastric emptying $t_{50\%}$ (time after dosing to 50% emptying of radiolabel from stomach) and gastric emptying $t_{90\%}$ (time after dosing to 90% emptying of radiolabel from stomach).

To assess gastric pH, the primary variables were pH at $t_{50\%}$ and pH at $t_{90\%}$. Secondary variables were time for gastric contents' pH to go below pH 3 after dosing and pH at 30 min after dosing, because a 30 min post-dosing fast is recommended to improve bioavailability.

2. Materials and methods

2.1. Clinical study design

This was a single centre, open label, randomised, two-way crossover study in 12 healthy female volunteers. The sample size for this study was selected on the basis of previous pilot studies using this imaging technique to provide descriptive data and not to support rigorous statistical analyses.

Subjects underwent a pre-study screening medical examination within the 28 days prior to dosing. Female volunteers aged 18–60 years inclusive, in good general health with a body mass index in the range 18.0–29.9 kg/m^2 were eligible for inclusion in the study. Eligible subjects attended three dosing days which were separated by at least 7 days to allow for washout of drug and radiolabel.

The treatments received were as follows:

- Treatment A – Fosamax® tablets
- Treatment B – Test effervescent formulation of EX101, a highly buffered effervescent soluble preparation of alendronate

The effervescent formulation was manufactured by SwissCo Development AG, Switzerland; Fosamax® was obtained from Merck Sharpe and Dohme Ltd., Germany. Technetium-99m diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) was supplied by the West of Scotland Radionuclide Dispensary, Glasgow, UK. All Investigational Medicinal Products (IMPs) were radiolabelled by Bio-Images Research Ltd. under Good Manufacturing Practice (GMP) conditions.

Subjects were admitted to the study centre 3 h prior to dosing on study days. On arrival, subjects were questioned on adherence to study restrictions that included pre-dose fasting for at least 10 h which included fasting from fluids 2 h pre-dose, no consumption of alcohol or caffeine for 24 h pre-dose and no smoking 24 h pre-dose. Subjects were also required to abstain from prescribed and over-the-counter medications for 14 days and 48 h pre-dose, respectively, unless the medication was approved by a study physician. No soluble effervescent or effervescent component-containing products were to be taken.

Prior to dosing, the subjects were also pregnancy tested and fitted with naso-gastric tubes for monitoring gastric pH levels. External radioactive markers (approximately 0.01 MBq ^{99m}Tc) were taped to the chest and back to enable accurate alignment of sequential images.

Subjects were dosed after an overnight fast, in accordance with dosing instructions for oral bisphosphonates. EX101 contained 70 mg free alendronate per dose, and were dissolved in 100 mL Volvic water, a commercial mineral water, radiolabelled with 4 MBq ^{99m}Tc-DTPA at time of dosing. An additional 20 mL Volvic water was added to the empty dosing glass, swirled and then swallowed.

Fosamax® tablets containing 70 mg alendronate were radiolabelled by drilling a 1.19 mm diameter hole in the non-contact edge of sufficient depth to incorporate ^{99m}Tc-DTPA-labelled lactose for a dose of 4 MBq at time of dosing. Fosamax® tablets were administered with 240 mL Volvic water.

Volvic water was selected as a standard low mineral content (divalent cation) still water, because instruction leaflets advise patients to dose bisphoshonates with this type of water. Volvic has a mineral content equivalent to many municipal water supplies ("tap water") (Azoulay et al., 2001).

Scintigraphy was performed with the subject in a standing position using a Siemens e-Cam gamma camera fitted with a low energy, high resolution collimator. Images were acquired immediately after dosing and then every 5 min until complete gastric emptying was observed. pH monitoring was conducted from 2 h prior to dosing until 4 h post-dose.

Subjects returned for a post-study medical evaluation within 14 days of the final dosing day.

The clinical study protocol and all amendments, participant information sheet, consent form and other study documents were approved by Tayside Committee on Medical Research Ethics B prior to study commencement. The Medicines and Healthcare Products Regulatory Agency (MHRA) reviewed and approved the study. The radiation dosimetry in the clinical study protocol was approved prior to study commencement by the Administration of Radioactive Substance Advisory Committee (ARSAC). This study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

2.2. Analytical methods

2.2.1. Statistical evaluation

Regarding statistical and analytical plans, this study was investigative in nature and was sized to provide clear directional outcomes regarding gastric pH and gastric transit. Statistical analyses were then conducted according to pre-agreed standard methods.

To descriptively evaluate the differences between treatments, gastric emptying and pH parameters derived from analysis were compared using the Wilcoxon signed rank test.

No changes in the conduct of the study or planned analyses were made, no amendments to the protocol were made after study initiation, but three additional parameters were calculated based on observations. These were (1) time to crossing pH 3 threshold after dosing, (2) gastric exposure time to free acid form of ALN and (3) the stomach pH at 30 min in subjects that did not achieve $t_{50\%}$ within 30 min.

2.2.2. Scintigraphic and gastric pH monitoring analyses

The scintigraphic data was analysed using the WebLink® image analysis program (Link Medical, Hampshire, UK). The exact times of all scintigraphic images were recorded and used in data processing according to standard protocol procedures.

The times of onset and completion of gastric emptying were determined by qualitative assessment of the scintigraphic images by two blinded, independent trained personnel. The times and sites of onset and completion of radiolabel release from Fosamax® tablet (if applicable) were also determined in this manner. Precise times for gastric emptying and release of radiolabel could not be determined due to the intervals between acquisitions of images. The times presented represent the midpoint of the 5 min interval between the image at which the event was observed and the previous image.

The numerical descriptors of gastric emptying, i.e. time to 50% and 90% gastric emptying of the radiolabel ($t_{50\%}$ and $t_{90\%}$, respectively) were calculated using a validated Excel spreadsheet. Briefly, the analysis process consisted of grouping the scintigraphic images according to Subject and Assessment Visit, then aligning them using either the radioactive marker or the stomach outline. A universal region of interest (ROI) was drawn around the stomach area of the aligned images and the counts transferred to the Excel spreadsheet. Similarly, a smaller ROI was drawn in the area away from the stomach to obtain background counts. The spreadsheet then calculated the $t_{50\%}$ and $t_{90\%}$ with consideration to background and radioactive decay correction factors.

There were five instances where $t_{90\%}$ was not achieved during the imaging time. Preliminary ROI analysis on the study day had indicated $t_{90\%}$ had been reached. However upon complete analysis incorporating background and decay correction factors, the percentage of maximum radioactive counts remaining in the stomach was only approaching 10%, and did not go below 10%. For all five instances where this occurred, the final value was less than 20%. In these cases, $t_{90\%}$ was taken as the mid-point between the final image time and 5 min post-final image time.

At the end of each study day, the pH monitoring data was uploaded to the GastroTrac™ program (Version 4.3, Alpine Biomed Corp., CA) for graph plotting and further analysis. The values for pH at $t_{50\%}$ and $t_{90\%}$ were determined by obtaining the mean of the five or six pH values recorded within that minute. These values returned were cross-checked with the pH trace to ensure it was not a false reading due to a peak or trough artefact of the measurement. On occasions where this occurred, the approximate values were agreed upon by two analysts.

The measurement of gastric pH was highly relevant for this study as it has been shown that pH can impact significantly on the tolerability parameters of ALN (Peter et al., 1998). The time taken for the gastric pH to fall below pH 3 after dosing was determined for each dosing occasion. This time was then subtracted from the corresponding $t_{50\%}$ and $t_{90\%}$ to obtain the parameters, Exposure Time_{50} and Exposure Time_{90}, respectively. The higher the positive integer of the value, the greater the length of exposure time of the gastric mucosa to the free acid form of ALN. A negative value indicates that the gastric pH remained above pH 3 at $t_{50\%}$ and $t_{90\%}$.

3. Results and discussion

Of the 12 subjects that were entered into the study, 10 subjects completed both study treatment visits. Two subjects withdrew consent to participate.

The age of the subjects ranged from 20 to 31 years, with a mean of 24.5 ± 4.1 years. Their mean height and weight at screening were 1.64 ± 0.07 m and 66.75 ± 9.33 kg, respectively. All subjects were in good general health with no significant medical history. Concomitant medications used during the study period were contraceptives, over-the-counter pain medication, vitamins and supplements and thrush medication. All medications were approved by the study physician.

There were 12 adverse events reported. All were single in episode; eight were of mild intensity and four of moderate intensity. Six were assessed as having no relationship to the study and four as a non-dosing procedure (insertion of naso-gastric tube). One subject reported feeling hot after administration of EX101; this was assessed as unlikely to be related to the study drug. Another subject felt slightly nauseous after treatment with Fosamax®; this was believed to be possibly related to the study drug.

The scintigraphic images clearly showed that all subjects treated with Fosamax® were able to swallow the tablet, which was then immediately observed in the stomach. EX101 was completely rinsed into the stomach after administration.

3.1. Effect of treatment type on gastric emptying

Two specific timepoints on the gastric emptying curve were determined in order to numerically compare the effects of the treatments on gastric emptying. These are $t_{50\%}$ and $t_{90\%}$, defined in Section 2.2.2.

The mean (±S.D.) values for $t_{50\%}$ were 28.0 ± 25.6 min and 34.4 ± 23.3 min for Fosamax® tablets and EX101, respectively. Mean values for $t_{90\%}$ were 63.2 ± 35.4 min and 71.6 ± 48.3 min for Fosamax® tablets and EX101, respectively.

The $t_{50\%}$ and $t_{90\%}$ values for Fosamax® were comparable to that of other conventional tablets (Kelly et al., 2003). The $t_{90\%}$ values for

Table 1
Mean values for gastric pH parameters.

	Fosamax® (mean ± SD)	EX101 (mean ± SD)	*p*-Value[a]
pH at $t_{50\%}$	1.9 ± 0.5	3.5 ± 1.2	0.008[c]
pH at $t_{90\%}$	1.3 ± 0.3	1.8 ± 0.8	0.155
Time to cross pH 3 threshold (min post-dose)	3.9 ± 3.0	56.0 ± 56.0	0.014[c]
Exposure Time$_{50}$ (min)	26.9 ± 27.8	−21.6 ± 42.4[b]	0.014[c]
Exposure Time$_{90}$ (min)	61.7 ± 36.1	15.7 ± 42.2	0.014[c]

[a] Wilcoxon signed rank test, Fosamax® vs. EX101.
[b] A negative value indicates no exposure to acidified ALN.
[c] Statistically significant difference.

Table 2
Stomach pH at 30 min post-dose in subjects where $t_{50\%}$ > 30 min.

Subject	Fosamax®		EX101	
	$t_{50\%}$ (min)	pH	$t_{50\%}$ (min)	pH
003	87.6	2.07	75.0	4.16
004	NA[a]	NA[a]	51.0	5.22
005	NA[a]	NA[a]	47.4	4.80
006	30.6	ND[b]	72.6	3.49
009	64.8	1.2	NA[a]	NA[a]

[a] Not applicable as $t_{50\%}$ was <30 min.
[b] Not determined due to malfunction of pH telemetry equipment.

EX101 were higher than expected as buffers of pH 3 and 7 have been shown to have mean gastric residence times of 46.7 and 14.4 min, respectively (Chaw et al., 2001). These authors also suggest that ingestion volume, pH and ionic strength may have effects on gastric emptying, but the full range and extent of these effects and the nature of their interaction are yet unresolved.

The $t_{50\%}$ and $t_{90\%}$ differences between Fosamax® tablets and EX101 were not significantly different, as judged by Wilcoxon signed rank test.

There was considerable variability in gastric emptying after ingestion of both formulations, and no clear trend was observed across the treatments. Surprisingly, the effervescent formulation did not trigger a consistent and rapid emptying event compared to the Fosamax® tablets. Furthermore, the differences (or lack of difference) between formulations were not considered to be physiologically relevant.

Assuming most patients adhere to the post-dose fasting label instructions of 30 min but fast no longer than 30 min, any time to emptying beyond 30 min is most likely irrelevant to the tolerability of the dosage form, as ingestion of food or drink will decrease stomach acidity and bisphosphonates might bind to food or drink components.

3.2. *Effect of treatment on gastric pH and impact on risk of ALN adverse events*

Table 1 shows the mean values for the five pH-related parameters derived from monitoring of gastric pH. At $t_{50\%}$, the mean pH values were significantly higher after dosing with the effervescent formulations as compared to the Fosamax® tablet. The pH at $t_{50\%}$ for each subject was generally higher after dosing with EX101 than with Fosamax®.

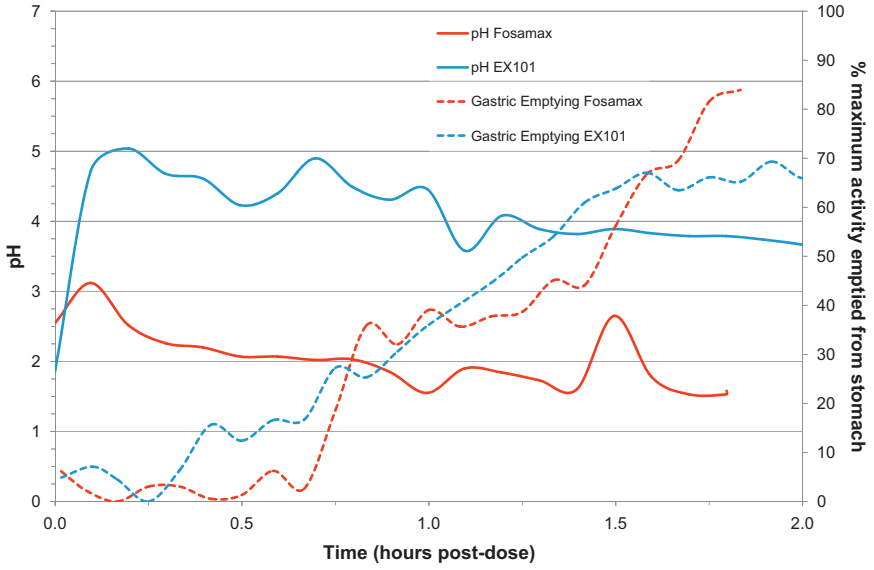

Fig. 1. Collated gastric emptying and gastric pH curves following administration of Fosamax® and EX101 for Subject 003.

Gastric emptying was associated with a decrease in stomach pH in both effervescent formulations. However, if ALN solution transits the stomach, the risk of oesophageal injury may be diminished as stomach content volume is reduced (and less likely to reflux). Hence the critical phase for risk assessment is deemed to be the time period to half emptying ($t_{50\%}$) or to 30 min post-dose. To assess this risk, the stomach pH at 30 min in subjects that did not achieve $t_{50\%}$ within 30 min was determined and is shown in Table 2.

The results for these Fosamax® subjects ($n = 2$) with $t_{50\%}$ greater than 30 min for which there are pH data available indicate that acidic ALN is present in their stomachs at 30 min. Conversely, all EX101 subjects in this subgroup maintained an elevated pH at 30 min. This difference was consistent with the different buffering capacities of the formulations.

The mean Exposure Time$_{50}$ values were −21.6 min (i.e. no strongly acidic ALN exposure) for EX101 and 26.9 min for Fosamax®. Results from statistical tests detailed showed that these results were statistically significant ($p = 0.014$).

Graphically, the difference in the gastric environment after dosing is illustrated in Fig. 1, taking Subject 003 as an example. The stomach pH after Fosamax® treatment rapidly returned to an acidic condition, whereas the EX101 environment remained well above pH 3 after treatment and before complete radiolabel emptying. Fosamax® and EX101 transited the stomach in a comparable time frame. The gastric environment after EX101 treatment remained elevated past 30 min (and past $t_{50\%}$), maintaining a non-strongly acidic environment where other studies have demonstrated that ALN exposure under these conditions is not associated with mucosal damage.

It must be noted that the pH at $t_{50\%}$ can be confounded by the rate of gastric emptying; as stomach contents empty, the pH also decreases. This is illustrated in the gastric emptying/pH overlay of Fig. 1.

All dosage forms administered were well tolerated and completely reached the stomach without oesophageal adhesion on all dosing occasions. There were no statistically significant or physiologically relevant differences in gastric emptying times between Fosamax® and the effervescent solutions.

ALN administered as Fosamax® tablets, according to dosing instructions, did not lodge in the oesophagus, but once present in the stomach and dissolved, resulted in solubilised ALN in a very acidic environment, with potential for mucosal irritancy. ALN administered as a solubilised form as EX101 showed no potential for oesophageal exposure to solid ALN, and the gastric environment was generally established and maintained above pH 3 until gastric emptying or food ingestion.

4. Conclusions

With alendronate, as with other potentially injurious agents, the most effective strategy is to prevent the problem. The soluble and highly buffered effervescent formulation of ALN (EX101) delivered ALN to the stomach completely, with no retention of dosage form in the oesophagus. This mitigated the potential for "pill oesophagitis" that can result from contact of solid ALN with the oesophageal mucosa.

The results of this clinical study imply that because the pH of EX101 solution and that of the stomach after dosing is immediately buffered to levels above pH 3, the risk of exposing the stomach and oesophageal lining to acidified ALN is negligible. Furthermore, in the potential case of a reflux event, the oesophagus would not be exposed to strongly acidified ALN solution because the gastric contents are buffered until food would normally be introduced into the stomach (30 min after dosing).

Fosamax®, conversely, is ingested as a solid and if taken as directed with a large glass of water in the vertical position, enters the stomach directly as observed in the results of this clinical study. However, improper administration can result in tablets lodging in the oesophagus. Furthermore, the stomach pH after Fosamax® ingestion was found to be strongly acidic, a recognised risk factor for oesophageal irritancy of ALN.

This study did not investigate the post-dosing behaviour of generic versions of alendronate, hence the question posed by Kanis et al. (2012) and Ringe and Moller (2009) regarding compliance to therapy with generic forms of alendronate remains unresolved.

ALN in EX101 is not present in the stomach in a strongly acidic environment, and hence has gastric sparing potential, even if gastric contents are refluxed. We conclude that EX101 offers the potential for enhanced gastric tolerability of orally administered bisphosphonates such as ALN.

Acknowledgement

The authors would like to thank Sister Shona Thomson of the Department of Gastroenterology, Glasgow Royal Infirmary for her kind assistance in facilitating the pH telemetry component of this clinical study.

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