Guy's and St Thomas' NHS
NHS Foundation Trust

A randomised, double blind, crossover study to determine the mechanism of action of Gaviscon Advance in Gastro-Oesophageal Reflux Disease (GORD)

END OF STUDY REPORT TO MHRA

1. Details of Chief Investigator

Name:	Mr. T. Wong MD, MA FRCP
Address:	Oesophageal Laboratory, Department of Gastroenterology, St. Thomas' Hospital, Lambeth Palace Road, London, SE1 7EH, UK
Telephone:	020 7188 2491
E-mail:	Terry.Wong@gstt.nhs.uk

2. Details of study

Full title of study:	A randomised, double blind, crossover study to determine the mechanism of action of Gaviscon Advance in Gastro-Oesophageal Reflux Disease (GORD)
REC reference number:	10/H0802/85
Sponsor:	Guy's and St. Thomas' NHS Foundation Trust
EudraCT Number:	2010-019072-68
Number of Centres	1
Number of Patients	20

3. Commencement and completion dates in the UK

First Patient First Visit	03-Jun-2011
Last Patient Last Visit	28-Sep-2011

4. Study Design

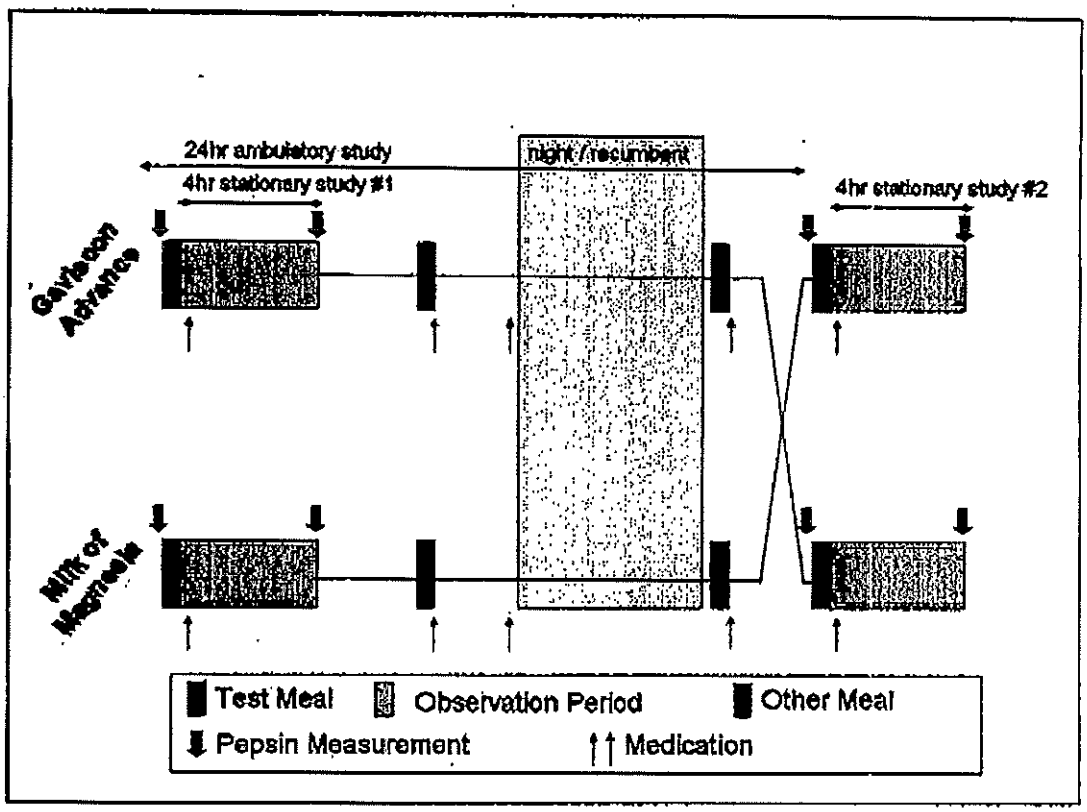
A randomized controlled, double blind cross-over study will be performed over a 28hr period monitored by continuous pH-impedance monitoring. The study design provides detailed data of the frequency and severity of reflux following ingestion of 10ml Gaviscon Advance (GA) or Milk of Magnesia (MM) Antacid for 4 hours after a refluxogenic test meal and over a 24hr ambulatory period. In addition important technical data concerning the use of Gaviscon Advance during pH-impedance monitoring will be acquired.

The test period will include two identical test meals (lunch) with patients randomised to take 10ml Gaviscon Advance or Milk of Magnesia (non-raft forming antacid) after the test meal . The 28hr period will comprise of two 4hr close monitoring periods and an intervening 20hr ambulatory monitoring period (see flow diagram).
Patients receiving 10ml Gaviscon Advance or Milk of Magnesia antacid after the first test meal will, during the ambulatory period, take the same medication after the evening meal, before bed and after a standardized breakfast on the following day (i.e. on four occasions) before returning to the oesophageal laboratory. The alternate medication will be taken after the second test meal and the patient will be observed for the second 4 hour monitoring period.

Gaviscon Advance and Milk of Magnesia (study comparator) are safe, over-the-counter anti-acids which are commonly used; the dose of both drugs to be administered will be of 10 ml on 5 occasions (Four times Gaviscon Advance or Milk of Magnesia during the 24 hours ambulatory study and once the alternate treatment after the second test meal) in strict accordance with manufacturer's guidelines. Side effects from both are extremely rare: Gaviscon Advance (=1/10,000) patients may develop allergic manifestations such as urticaria or bronchospasm, anaphylactic or anaphylactoid reactions.

Milk of Magnesia can result in diarrhoea if taken in very large quantities. Adverse events can occur in case of kidney failure but all chronic co-morbid conditions will have been excluded prior to recruitment into the study.

Clinical assessment flow chart



In the clinical assessment described below (n=20) a test meal is provided on two occasions separated by 24hrs. In addition to the mechanistic procedures, at the end of the study following the second test meal and 4 hr observation period, one further dose of 10ml Gaviscon Advance or Milk of Magnesia will be provided. The patient will then be asked to repeatedly swallow 10ml aliquots of standard orange juice (pH2) until the pH and impedance sensors provide an accurate measurement. For the pH sensor this is defined as the number of swallows until a measurement pH<2 is recorded (applications required to pH<4 will also be noted). For the impedance sensor the number of swallows until a rapid, sequential drop and recovery in impedance from above 3000 to below 1000 Ohms in all sensors will be recorded (i.e. typical measurements recorded as a fluid bolus passes through the empty oesophagus into the stomach).

5. Study Objectives

The mechanistic effectiveness of Gaviscon Advance after meals for suppressing acid and non-acid reflux will be examined in patients with typical reflux symptoms. Reference

standard pH-impedance monitoring will document the clinical effectiveness of the alginate on suppressing acid and non-acid reflux events. A novel pepsin assay will provide a direct assessment of pharyngeal exposure to gastric refluxate.[26]
'Gaviscon Advance' will be compared to an antacid (Milk of Magnesia) that does not exhibit raft forming properties.

The study hypothesis is that Gaviscon Advance:

1. Will not impair the sensitivity of pH-impedance monitoring.
2. Suppresses both non-acid and acid reflux (distal and proximal reflux events) assessed by pH-impedance over a 4 hour period after a standardized test meal and over 24hr ambulatory monitoring
3. Reduces the presence of pepsin in expectorated saliva 4 hours after a test meal

Reflux symptoms will be documented; however these mechanistic studies are powered to assess the effects of Gaviscon Advance reflux events and not clinical response.

The primary endpoint is the number of reflux episodes (acid and non-acid) during the 4 hr postprandial period following ingestion of Gaviscon Advance or Milk of Magnesia. Secondary endpoints include % time for oesophageal acid exposure and the number of reflux episodes during the 24hr ambulatory pH-impedance monitoring. The pepsin concentration in saliva after the 4hr postprandial period will also be assessed.

6. Study Results

Study population:

Mean Age 40 (range 25-63); 9 male: 11 female

Endoscopic findings:

Technical assessment (Table 1): After intake of 20ml Gaviscon Advance or Milk of Magnesia the pH and impedance signal fully recovered after median 6 (2-12) and 4 (2-10) swallows of orange juice.
Modest increase in number of swallows to recovery of signal for Gaviscon Advance
Clearance depended more on oesophageal function than either Gaviscon Advance or Milk of Magnesia

N=20	Baseline pH	# swallows volume (7<1000 Ohms) clearance	#swallows chemical (pH<4) clearance
MM	4 (3-10)	2 (1-4)	2 (2-3)
	P<0.001	p=0.012	P=0.006

Table 1. Technical assessment of Gaviscon Advance vs. Milk of Magnesia vs. Water

Clinical assessment: During the 4 hour postprandial observation acid exposure time (mean 2.3% (SD 3.3%) vs. 3.4% (4.2%), p=0.296) and number of distal reflux events (20.5 (13.6) vs. 22.5 (9.4), p=0.500) was similar after ingestion of Gaviscon Advance and Milk of Magnesia. There was a trend to less proximal reflux events with the alginate compared to the antacid (10.5 (8.9) vs. 13.9 (8.3), p=0.070). No difference in the number of symptoms (5.0 (6.0) vs. 4.2 (8.3), p=0.701) and reflux related symptoms (2.5 (4.0) vs. 2.8 (5.6), p=0.988) was reported.

Although there was no difference in the number of reflux symptoms, the mean Symptom Index for heartburn was pathological in the MM (61%) and negative in the GA (38%) group.

	Reflux events *Acid events* # (SD)	Proximal reflux events # (SD)	Esophageal Acid Exposure %time pH<4	Total Reflux Symptoms #	Reflux related symptoms #
Milk of Magnesia	Total 22.5 (9.4) Acid 9.0 (0.0)	13.9 (8.3)	3.4% (4.2%)	4.2 (8.3)	2.8 (5.6)

Table 2. Clinical study which compares primary and secondary measurements of oesophageal acid/non-acid exposure in the Gaviscon Advance and Milk of Magnesia groups during a four hour observation period that followed a standardised meal.

7. Discussion

Standard pH-impedance monitoring is suitable for clinical studies of reflux suppression in patients with GORD if concomitant antacids and alginates are included. This clinical study confirmed similar suppression of distal reflux[7] although there was a trend towards an improved suppression of proximal reflux and reduced reflux-symptoms association in the Alginate-containing antacid group.

Inconsistency between direct and indirect measurement may be due to "false positive" events on the catheter-based testing due
to shortening of oesophagus during swallows.

8. Safety Evaluation

No safety issues have been raised in relation to this study.

No SUSARs, SAEs or SARs were reported.

9. Conclusions

Standard pH-impedance monitoring is suitable for clinical studies of reflux suppression in GORD patients. The clinical study documented similar suppression of distal reflux but a trend to increased suppression of proximal reflux by Gaviscon Advance compared to Milk of Magnesia. This feasibility data indicates that clinical trials of reflux suppression will require a minimum of 70 GORD patients (power 90%, $p<0.05$) to demonstrate significant effects on reflux suppression clinical trials by alginates compared to antacids.

10. Declaration

Signature of Chief Investigator:	
Print name:	Mr. T. Wong
Date of submission:	17/12/2012