European Medicines Agency
Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT

FOR

GASTROMOTAL

International non-proprietary name (INN):
1-^{13}C-caprylic acid

Procedure No. EMEA/H/C/724

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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LIST OF ABBREVIATIONS

ASM	Active substance manufactory
CASRN	Chemical Abstract Services Registry Number
CNS	Central nervous system
CV	Cardiovascular
GC	Gas chromatography
GI	Gastrointestinal
IP	Intraperitoneally
IRMS	Isotope-ratio-mass-spectrometry
IV	Intravenous
MAA	Marketing authorisation application
MS	Mass spectrometry
NF	National formular
NMR	Nuclear magnetic resonance
NMT	Not more than
OA	Octanoic acid
PK	Pharmacokinetics
PO	Orally
RH	Relative humidity

I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the Rapporteurs consider that the application for Gastromotal for the *in vivo* diagnosis of solid-phase gastric half emptying time in gastric motility disorders, is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

II. EXECUTIVE SUMMARY

II.1 Problem statement

Gastric emptying is a highly co-ordinated physiological response to the presence of food. It is subjected to inter-individual and intra-individual variations and may be disturbed by a variety of conditions, e.g. diabetes mellitus, dystrophia mytonica, progressive Duchenne's muscular dystrophy, polymyositis and dermatomyositis, progressive systemic sclerosis, chronic gastritis, carcinomas of the stomach, pancreas acute, chronic infections and neoplastic disorders. Accelerated or delayed gastric emptying may be associated with dyspeptic complaints such as feeling of fullness.

When describing gastric emptying, a distinction is made between solids and liquids. The emptying of liquids starts immediately after ingestion. It is best described by an exponential curve as a constant fraction of the liquid content of the stomach is emptied per unit of time. The rate of emptying of liquids is determined by many factors such as caloric content, osmolarity and content of fat. Gastric emptying of solids is characterised by an initial phase in which no emptying is occurring (lag phase). Subsequently, an emptying phase which is approximately linear and influenced by feed back from the duodenum/ileum.

The gold standard for measuring gastric emptying is radioscintigraphy. A test meal with a known amount of radioactive marker (one for the liquid phase and one for the solid phase) is ingested. The amount of marker retained in the stomach is determined by gamma-cameras over the stomach region. Based on the curve of retained marker over time, gastric emptying parameters can be determined.

There are a number of factors affecting the test result. As concerns the test meal, the ideal composition (the volume, the caloric load, the relative amount of carbohydrates, proteins and fat, the presence of non-digestible fibres) in order to detect gastric emptying disorders with greatest sensitivity and specificity, has never been established. However, meal size and composition should be standardised to obtain reproducible results. As concerns the interpretation of the raw data from the retention curves, several parameters have been proposed for interpretation. Gastric emptying data are usually analysed by mathematical fitting curves which permit calculation of parameters, which reflect the physiology of gastric emptying, including the biphasic nature of emptying of solids (i.e. for solids, a lag phase followed by an emptying phase). Frequently used is the power exponential formula by Siegel et al. Whatever technique of curve fitting is used, it remains important to check it with the original data to ensure that there is no operator bias.

Although being considered the gold standard for measuring gastric emptying, the radioscintigraphy method has some limitations. First of all exposure to radiation precludes repeated use. Secondly, the test is expensive and requires advanced equipment and trained staff.

Several other techniques have been suggested for measuring gastric emptying. These include ultrasonography, magnetic resonance imaging and impedance measurements. However all these tests have drawbacks/limitations. The applicant argues that there is a need for a simple, inexpensive and safe test that can reliably measure gastric emptying rates. For that purpose, the applicant investigated the octanoic acid breath test for measurement of gastric emptying of solids. Octanoic acid (marked with either ^{13}C or ^{14}C) breath test has been under extensive investigation by independent researchers for some time. The rationale of a breath test to measure gastric emptying of solids is based on the firm retention of a marker in the solid phase of a test meal during mixing and grinding in the stomach, followed by a rapid disintegration of the labelled solid phase in the duodenum with subsequent absorption of the marker and oxidation to labelled $^{13}CO_2$ once the meal reaches the digestive environment of the duodenum. The results of previously published studies suggests that the ^{13}C-octanoic acid breath test results correlated well with results obtained by the golden standard method

and that the test was useful for detection gastric emptying rates various diseases. However other studies have cast doubt about the validity of both concept and results.

II.2 About the product

The applicant has further developed the ^{13}C-octanoic acid breath test for measuring gastric emptying rates and is presenting an application for a marketing authorisation for Gastromotal. The active ingredient is:

Caprylic acid-1-^{13}C 90 mg = 100 µl in a syringe

No excipients are included.

The claimed indication is for in vivo diagnosis of gastric emptying rate.

The breath test is a single administration of 90 mg Caprylic acid-1-^{13}C together with a standardised test meal (1 fried egg, 2 slices of white bread, 150 ml drink (tap water), and 5 g butter). Breath samples collected in glass or plastic container are analysed by isotope ratio mass spectrometer (IRMS) The development programme/Compliance with CHMP Guidance/Scientific Advice

The non-clinical dossier is based on published data referring to non-labelled OA, except for a single-dose toxicity study in mice that used the labelled drug substance as test material. This approach is justified as the presence of the isotope label does not alter the biological properties of the compound. Moreover, OA is a naturally occurring fatty acid that has regulatory approval as a food additive and is commonly consumed as foods or food components.

The clinical development program for Gastromotal consists of 5 supportive studies (in which Gastromotal was used for evaluation of the pharmacodynamics effects of an other investigational drug) and 2 reference method validation studies investigating the diagnostic properties of the Gastromotal ^{13}C-octanoic acid breath test in comparison with the gold standard, radioscintigraphy using ^{99m}Tc-albumin colloid. The former studies were carried out by an external companyand the latter by INFAI GmbH.

Type of Study	**Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**
Supportive study	S246.1.102.01	evaluation of gastric emptying	open / no control	oral appl. 100 mg single dose	24	healthy male	single appl.
Supportive study	S246.1.107.01	evaluation of gastric emptying	open / no control	oral appl. 100 mg single dose	24	healthy male	single appl.
Supportive study	S246.1.110	evaluation of gastric emptying	open / no control	oral appl. 100 mg single dose	23	healthy male	single appl.
Supportive study	S246.1.109.01	evaluation of gastric emptying	open / no control	oral appl. 100 mg single dose	24	healthy male	single appl.
Supportive study	S246.1.104.01	evaluation of gastric emptying	open / no control	oral appl. 100 mg single dose	12	diabetes m. patients	single appl.
Validation of breath test	OA99/1/001	validation of breath test	open 13C octanoic acid vs. radioscintigraphy 99m TC-albumin	oral appl. 90 mg single dose	126	inclusion criteria	single appl.

Validation of breath test	AA00/01	validation of breath test	open 13C octanoic acid vs. radioscintigraphy 99m TC-albumin	oral appl. 90 mg single dose	100	inclusion criteria	single appl.

In the application form, it is stated that EMEA/CHMP provided scientific advice for this application. However, the applicant has only submitted minutes from a pre-submission meeting with EMEA staff.
A relevant guideline for this specific area exists (CPMP/EWP/1119/98: Points to Consider on the Evaluation of the diagnostic agents). Compliance with this guideline is not commented on by the applicant.

II.3 General comments on compliance with GMP, GLP, GCP

The drug product is manufactured (dispensed) by INFAI, Bochum, Germany. INFAI's equipment for NMR, mass spectrometry, elemental analysis and chemical analysis is situated in their site in Cologne.
INFAI has a valid German license for manufacture of this type of product at the premises.
INFAI has submitted a declaration of GMP compliance for the drug substance manufacturer.

The only toxicity study conducted with the drug substance is GLP-compliant. There is little or no information about the GLP status of those studies whose results have been gleaned from the open literature. Due to the inherent safety of OA, this is not considered a matter of concern.

All supporting studies and controlled efficacy studies have been carried out according to GCP.

II.4 Type of application and other comments on the submitted dossier

The present assessment concerns a complete and independent application (stand-alone application) for Gastromotal, oral liquid 90 mg.
The applicant has submitted a risk management plan

The quality part of the dossier is in general considered acceptable.
There have been no changes in the present formulation compared to the formulation used in clinical trials.

The quality of the non-clinical overview and summary is based on bibliography which is a compilation of published abstracts.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
1-^{13}C-Caprylic acid is an isotopically enriched caprylic acid.

Drug Product
The drug product is an oral liquid. 90 mg 1-^{13}C-Caprylic acid corresponding to 100 µl is filled into a 1ml glass syringe. The drug product contains no excipients. There is no formulation or processing as such so similar concerns apply as for the drug substance.

Stability studies have been performed at ICH conditions. Photo stability should be addressed.

The drug product is supplied as a test kit containing the syringe, sample containers and a bendable straw.

III.2 Non clinical aspects

Pharmacology

Gastromotal is a diagnostic agent containing liquid 1-^{13}C-caprylic acid, i.e. octanoic acid ("OA", CASRN 124-07-2) labelled at the C1 position (the functional carboxylic group) with the non-radioactive isotope ^{13}C. It is administered orally as a single dose of 90 mg (about 2 mg/kg in a 50-kg person). The diagnostic use of 1-^{13}C-caprylic acid depends on its being metabolised to ^{13}C-labelled CO_2. As such, the product is not intended to have any pharmacological effect. The data on primary pharmacodynamics are limited to a review of published papers on the diagnostic use of 1-^{13}C-OA in experimental animals. The data on secondary pharmacodynamics and safety pharmacology are bibliographic and refer to unlabelled OA.

According to the published literature, 1-^{13}C OA has been successfully employed to investigate the gastric emptying rate in mice, rats, cats, ponies and dogs. Since the proposed test has been validated in humans by direct comparison with conventional scintigraphy, these animal studies are not considered relevant.

A number of in-vitro and in-vivo studies indicate that OA may alter the metabolism of fat, proteins and carbohydrates. These findings, however, were either obtained in vitro at OA concentrations ranging from 0.5-5 mM (about 70-700 mg/L), or in vivo at dose levels equal to or higher than 250 mg/kg). Therefore, they are not considered relevant to the proposed administration of a single oral dose of 90 mg per intervention, that is, about 2 mg/kg in a 50-kg person.

Conventional safety pharmacology studies were not conducted. However, findings reported in the literature indicate that OA may cause CNS depression, ventricular fibrillation and a small increase in intestinal permeability in rodents and pigs if administered parenterally at dose levels above 450 mg/kg, or at organ preparations at perfusate concentrations above 700 mg/L. In monkeys given a 30-minute IV infusion of OA, the only effects of a 720 mg/kg dose were transient muscle relaxation and sleepiness. Although extremely high doses of OA may have CNS, CV and GI effects, this is not a cause for concern as the proposed dose level of Gastromotal in humans implies a safety margin of more than 100.

There are no studies of pharmacodynamic interactions. This is considered acceptable as OA is not expected to have pharmacological effects at the proposed human dose.

Pharmacokinetics

There are no formal PK studies with the drug substance. Some data pertaining to the distribution, metabolism and elimination of OA have been obtained from the literature. Since it is well known that medium-chain fatty acids such as OA are absorbed from the small intestine, highly bound to albumin and subject to rapid metabolism, the scarcity of PK data is not considered critical. In most of the studies in the bibliography, OA was quantified by GC. Some studies used radioactive OA. There is no verifiable information on the validity of these methods.

Total clearance (Cl), volume of distribution (Vd) and mean residence time (MRT) have been measured in rats exposed to 75, 150 or 350 mg/kg of OA administered by IV injection. Total clearance and the volume of distribution declined with dose whereas mean residence time increased. This indicates saturable elimination and binding mechanisms and probably reflects the fact that medium-chain fatty acids are eliminated through metabolism and bind to albumin with high affinity.

Distribution data are very limited, but studies conducted using radioactive OA indicate that it is taken up at high rates by, and rapidly cleared from, the liver, with 98% of radioactivity detected in the parenchymal cells. Some studies suggest that OA crosses the blood-brain as well as the placental barrier.

There are no relevant data on metabolism, but it is common knowledge that medium-chain fatty acids such as OA are metabolised through β-oxidation to water, CO_2 and two-carbon fragments, which are incorporated into chemicals required for bodily function, such as long-chain fatty acids.

OA is not excreted in urine because filtration is low due to albumin binding and because it is actively reabsorbed by the tubular organic anion transport system.

Metabolic interactions are unlikely as OA is metabolised exclusively by β-oxidation. A few drugs, e.g. insulin detemir, also bind to the fatty acid binding sites. However, since there are several high-affinity fatty acid binding sites on the albumin molecule and orally administered OA is rapidly removed from the circulation by the liver, a single oral dose of 90 mg (0.624 mmol) is unlikely to result in any detectable displacement of such drugs.

Taken together, the data on PK are scant. It is well known, however, that medium-chain fatty acids such as OA are absorbed from the small intestine, highly bound to albumin and subject to rapid metabolism. Therefore, the scarcity of PK data is not considered critical.

Toxicology
A single-dose GLP toxicity study conducted in mice showed OA to be non-toxic at a limit dose of 5,000 mg/kg PO. Using allometric scaling this corresponds to a no-toxic-effect level of 400 mg/kg. Based on the proposed human dose, this is equivalent to a safety margin of 200.

There are no experimental data on the repeat-dose toxicity of OA.

OA was among 300 chemicals tested for bacterial mutagenesis under the auspices of the US National Toxicology Program (Zeiger et al., 1988). These tests were conducted in S. typhimurium strains TA100, TA1535, TA1537, TA97 and TA98 at OA concentrations from 0-3,333 μg/plate, with and without metabolic activation. Based on consistently negative results, OA was classified as non-mutagenic in this test. Other genotoxocity test results have been reported in the literature (Datta et al., 1983; Sentein & Vannereau, 1973; Zimmermann, 1983),.

There are no experimental data on the carcinogenic potential of OA. Nor are such data required as Gastromotal is not intended for repeated administration.

The bibliography on reproductive and developmental toxicity includes one in-vitro study in rat embryos exposed to 260 μg/mL and one in-vivo study in pregnant rats exposed to 2,700 mg/kg/day of OA. Both papers conclude that OA did not cause significant developmental toxicity, but neither contains sufficient data to permit independent assessment. There are no data on fertility or peri- and postnatal developmental toxicity.

Local tolerance data have not been provided. OA is an organic acid and as such could cause irritation when swallowed. However, as Gastromotal is intended to be mixed with a standardised meal prior to intake, this is considered an unlikely event. Moreover, there are no reports of gastrointestinal disorders among the 333 cases included in the clinical safety database.

An environmental risk assessment has not been provided and is not required as naturally occurring lipids are unlikely to result in significant risk to the environment.

In conclusion, the only useful toxicity studies are a single-dose limit study in one species and a conventional assay for bacterial mutagenesis which showed that the drug substance has low oral toxicity and that OA is non-mutagenic in the Ames test. Such limited test results would not meet the requirements for a new chemical substance even if the latter were to be administered only once in a lifetime. However, OA is not a new chemical entity, but a naturally occurring fatty acid found in many foods as a component of triglycerides. Such foods include dairy products, where OA accounts for about 1% of total fats, and vegetable oils such as coconut oil or palm oil, where it is present in concentrations of 7.5% and 3.3%, respectively. Thus, the proposed dose of 90 mg of OA is equivalent to the contents in one glass of full-fat milk (200 ml), one heaped spoonful of cream (25 ml) or a quantity of butter that would just suffice to butter one sandwich (9 g). Furthermore, OA is approved by the FDA as a generally recognized as safe (GRAS) substance and direct food additive and in the EU as a flavouring agent at a level of 100 ppm. As such, there can be no non-clinical concerns about the proposed use of OA and further non-clinical studies are not considered necessary.

III.3 Clinical aspects

Pharmacokinetics

The applicant has not performed studies of the pharmacokinetics of ^{13}C-octanoic acid. Octanoic acid is a naturally occurring nutrient, a medium chain fatty acid, naturally occurring in butter, coconut oil, palm oil etc. It is well known from animal studies that medium chain fatty acids such as octanoic acid are readily absorbed from the duodenum, transported via the portal vein to the liver where it undergoes β-oxidation to acetyl-CoA, which is further degraded in the citric acid cycle to CO_2. The pharmacokinetics of ^{13}C-octanoic acid is not expected to deviate from that of naturally occurring octanoic acid. Consequently, it is acceptable, that the applicant has not performed any pharmacokinetic studies of ^{13}C-octanoic acid in humans.
Meaningful data regarding absorption, metabolism, distribution, and elimination of 1-^{13}C-caprylic acid and the generated $^{13}CO_2$ respectively, in normal as well as in special human populations, e.g. patients with renal or hepatic impairment, patients with obesity or anorexia, elderly, and children were not presented.

The rationale of the 1-^{13}C-caprylic acid breath test is based on the firm retention of ^{13}C-labelled caprylic acid in the solid phase of a standardised test meal during mixing and grinding in the stomach, followed by rapid absorption from the chyme entering into the duodenum, an immediate and maximal oxidation in the liver to labelled CO_2 and a fast exhalation in the breath.

According to the literature and the statements of the applicant, the gastric emptying of the test meal, and not the postgastric processing of the label, is considered the rate-limiting step in the rate of $^{13}CO_2$ exhalation in breath after ingestion of the labelled test meal.

The potential pharmacokinetic interactions have not been discussed.

Pharmacodynamics

The applicant has not performed any studies of the pharmacodynamics of octanoic acid. Considering the nature of the product (diagnostic agent not aiming at exhibiting any pharmacodynamics effect) as well as the fact that, octanoic acid is a naturally occurring nutrient, occurring in e.g. coconut oil and palm oil, the lack of such studies is acceptable.

Clinical efficacy

For the proof of efficacy, the applicant presents two “pivotal” and five “supportive” studies.
No separate dose finding studies have been performed. As part of one of the two main studies, a 50% reduction of the dose of ^{13}C-octanoic acid(45 mg) l was investigated. However, it is stated that this yielded unsatisfactory results and consequently the lower dose was abandoned. No data are provided. Higher doses were not studied. Because in most studies used 90 mg of ^{13}C-octanoic acid.
The applicant presents five phase I (the phase I relating to another active substance) studies carried out by an external company which investigated the safety, tolerability, and pharmacokinetics a developmental drug , a motilin agonist, in healthy male volunteers and diabetic patients suffering from delayed gastric emptying. The effect of the drug on gastric emptying rate was evaluated by 1-^{13}C-caprylic acid breath test. Analysis of the $^{12}C/^{13}C$ ratio in the exhalation and calculation of the gastric emptying parameters were done by the applicant.

The studies show an acceleration of the gastric emptying caused by the developmental drug in oral as well as in intravenous formulation. The used ^{13}C-breath test was able to assess the effect of the test drugs on gastric emptying parameters and can be regarded to be sensitive to detect change.

However, these studies appear to be of questionable relevance for the application of the breath test in a stricter sense, mainly because they are non-comparative studies for the evaluation of gastric emptying and therefore do not give any information about the reliability of the applied test concerning the diagnosis of disorders of gastric emptying.

These studies can only be considered supportive.

The two studies designed as pivotal studies are of nearly identical design. Both clinical studies were two-centre, open, non-randomised studies with the simultaneous application of the ^{13}C-octanoic breath test and a ^{99}Tc-scintigraphy for measuring of gastric emptying.

Study participants could either be healthy volunteers (17) or subjects with a medical indication (GORD or diabetes) for the determination of gastric emptying rate (209) with an age of at least 18 years, and a signed informed consent.

The primary objective of the studies was the validation of the ^{13}C-octanoic acid breath test for the determination of gastric emptying rate in comparison with the gold standard, ^{99}Tc-albumin colloid based radioscintigraphy.
Secondary objectives were the investigation of the correlation between the gastric emptying coefficient and the half emptying time, the investigation of the validity of the test in subgroups (of different diseases, or with different medication) and the investigation of the influence of demographic data, concomitant diseases, and concomitant medications on the test results.

For both methods lag-time, half-emptying time, and a gastric emptying coefficient were determined. Some details in the description of the methods and calculation of results are still missing and should be provided

A comparison of the two diagnostic methods was to be performed with the calculation of Lin's concordance correlation coefficient K (which was expected to be at least 0.85 for $t_{1/2}$ and t_{lag}), which was the primary endpoint.
The "gold standard" regarding the decision for normal or delayed gastric emptying was a literature based half-emptying time ($t_{1/2}$) of 90 minutes.

In the first study, OA/99/1/001, 150 subjects were enrolled in the two study centres (one in the UK and one in Germany). For efficacy analysis, the data of 126 patients only were included. The first 20 subjects were excluded due to technical difficulties prior to the analysis of results.

Gastric half emptying time and lag time were calculated as 100.3±62.9 minutes, and 43.1±34.1 minutes (arithmetic means), respectively by the experimental (breath test) method and as 94.2± 47.9 and 44.5 ±31.4 minutes with the reference method (scintigraphy). Delayed gastric emptying (according to a cut off value of 90 minutes) was determined for 47.6% for the reference, and 45.2% in the experimental method. Lin's correlation coefficient was determined as r^2=0.721 for t ½ and r^2=0.011 for the lag time.

The following results were achieved after calculation of sensitivity, specificity, positive and negative predictive value (PPV/NPV) for the parameter $t_{1/2}$:

Table 1: Display of accuracy figures:

Parameter	t ½					
	UK centre		German centre		overall	
Sensitivity	36/45	80.0%	10/15	66.7%	46/60	**76.7%**
Specificity	35/42	83.3%	20/24	83.3%	55/66	**83.3%**
PPV	36/43	83.7%	10/14	71.4%	46/57	80.7%
NPV	35/44	79.5%	20/25	80.0%	55/69	79.7%

In the second study, AA/00/01, 160 subjects were enrolled (of which 40 were to receive 45.5 mg, i.e. half the dose only) in the two study centres (one in the UK and one in the Czech Republic). For efficacy analysis, the data of 100 patients only were included. All results of the patients receiving the low dose were excluded from evaluation.
Gastric half emptying time and lag time were calculated as 109.3±59.7 minutes, and 52.8±44.4 minutes (arithmetic means), respectively by the experimental method, and as 93.6±46.4 and 56.2±36.9 minutes with the reference method. Delayed gastric emptying (according to a cut off value of 90

minutes) was determined for 43% for the reference, and 55.0% in the experimental method (a "borderline" statistical difference). Lin's correlation coefficient was determined as r^2=0.504 for t ½ and r^2=0.579 for the lag time.

The following results were achieved after calculation of sensitivity, specificity, positive and negative predictive value (PPV/NPV) for the parameter $t_{1/2}$:

Table 2: Display of accuracy figures:

Parameter	t ½					
	UK centre		Czech centre		overall	
Sensitivity	33/38	86.8	5/5	100	38/43	**88.4**
Specificity	36/48	75.0	4/9	44.4	40/57	**70.2**
PPV	33/45	73.3	5/10	50.0	38/55	69.1
NPV	36/41	87.8	4/4	100	40/45	80.9

The applicant additionally presents a meta-analysis based on the two open, phase III studies (referred to as the pivotal studies). This meta-analysis is attached to the appendices of each of the study reports. No protocol for this meta-analysis is presented.

The analysis presented includes the total of 226 subjects deemed evaluable in the two pivotal studies. The analysis was performed in October 2004.

The correlation (according to the method by Lin) between the two methods for half emptying time was modest with r^2=0.628 (95%CI: 0.547; 0.697).
A low correlation had to be stated for the parameter t_{lag}: r^2=0.339; 95%CI: 0.220; 0.448).
Both tests agreed on a delayed gastric half emptying time in 84/226 (37.2%) subjects. However, the number of patients diagnosed with delayed gastric emptying was 49.6% for the experimental method, and 45.6% for the reference method.

The pooled evaluation of sensitivity and specificity for all subjects is displayed in the following table:

Table 3: Display of accuracy figures:

Parameter	t ½					
	Study OA99/1/001		Study AA00/01		Pooled results	
Sensitivity	46/60	**76.7%**	38/43	**88.4**	84/103	**81.6**
Specificity	55/66	**83.3%**	40/57	**70.2**	95/123	**77.2**
PPV	46/57	80.7%	38/55	69.1	84/112	75.0
NPV	55/69	79.7%	40/45	80.9	95/114	83.3

It is noted that the reproducibility of the breath test has not been studied.

In conclusion, the diagnostic performance of the Gastromotal breath test is moderate. Diagnostic sensitivity and specificity are moderately high (around 80%) In the light of the problems with the diagnostic performance of the test, the impact on diagnostic thinking as well as impact on therapeutic decisions and clinical outcome (as addressed in EMEA/CPMP Points to Consider on the evaluation of diagnostic agents) should be addressed.

Clinical safety

Exposure to the study drug is remarkably low with 333 healthy volunteers and patients altogether. However, this is not considered a real problem because of the excellent safety record of the compound, which is not unexpected considering the nature of the "active" substance being a natural part of nutrition, and supposed to be taken only once without continuous exposure.

There were no reports of adverse events in the literature; however, the literature was not systematically looked through for adverse events.

All studies presented by the applicant do not give a single adverse event reported during the application of the breath test.
However, from the check of the patient data listings it has to be concluded that adverse event reporting was obviously not handled properly, either by the investigators or by the sponsors, as in one study 4 events were described that definitely should have been reported as adverse events.

After a thorough review of the existing records a total of 4 adverse events were recorded. These included nausea, vomiting and headache with a frequency between 0.1 % and 1%.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

As concerns the quality of the product there are still some outstanding issues that need to be resolved before a final evaluation of the quality of the drug can be made. As regards the non-clinical documentation all outstanding issues have been resolved.
In terms of the clinical aspects there are no major safety concerns. However, the benefit of the drug has not been unequivocally demonstrated. As previously detailed the diagnostic performance of the test is not compelling and the impact on diagnostic thinking as well as impact on therapeutic decisions and clinical outcome (as addressed in EMEA/CPMP Points to Consider on the evaluation of diagnostic agents) has not been adequately addressed.