Original Article

Efficacy and safety of APT036 versus simethicone in the treatment of functional bloating: a multicentre, randomised, double-blind, parallel group, clinical study

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Background: Bloating is a common symptom reported by around 16% to 31% of the general population. Functional bloating is diagnosed in patients with recurrent symptoms of bloating who do not meet the diagnostic criteria of irritable bowel syndrome or other functional gastrointestinal disorders.

Methods: This double-blind, multicentre, randomised study compared the safety and efficacy of APT036 (xyloglucan plus tyndallized *Lactobacillus reuteri* and *Bifidobacterium brevis*; Aprotecol®) and simethicone in treating functional bloating in adults. APT036 or simethicone were administered orally (3 times/day) for 20 consecutive days, with evaluations at baseline, and on Days 2, 10, 20 (end of treatment) and 30 (follow-up visit). The main outcome measure was safety. Efficacy was assessed at each visit by patient-reported symptom severity (Likert scale) and abdominal girth measurement. A hydrogen breath test was performed at baseline and Day 20.

Results: Both APT036 (n=54) and simethicone (n=54) were well tolerated by study subjects; no adverse effects were reported with either treatment. Compared with simethicone, APT036 significantly reduced abdominal distension (P=0.008) and flatulence (P=0.010) from baseline to Day 30. The baseline hydrogen breath test confirmed the presence of small intestinal bacterial overgrowth (SIBO) in all subjects. At Day 20, mean hydrogen gas elevation was below the threshold for a diagnosis of SIBO (<12 ppm above basal on glucose administration) in both study arms.

Conclusions: Both APT036 and simethicone had good safety profiles but APT036 was superior to simethicone in relieving symptoms of functional bloating.

Keywords: APT036; simethicone; functional bloating; hydrogen breath test

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Introduction

Bloating is a common symptom reported by around 16% to 31% of the general population (1-4). In the absence of a consensus definition, bloating is generally considered to be the subjective sensation of increased abdominal pressure. The related term, abdominal distension, is the objective

increase in abdominal girth which may accompany bloating (5-7).

Bloating is a heterogeneous condition and is a common complaint in individuals with functional gastrointestinal disorders (FGIDs) comprising irritable bowel syndrome (IBS), functional dyspepsia, and functional constipation (6). Under Rome III criteria, a diagnosis of functional bloating is made in patients with recurrent symptoms of bloating who do not meet the diagnostic criteria of IBS or other FGIDs (5,6).

Although the pathophysiology of bloating is not completely understood, multiple factors are known to be involved and their relative contribution varies between individuals. Potential mechanisms include increased luminal gas production, impaired gas handling and clearance, small intestinal distension due to excessive luminal fluid, small intestinal bacterial overgrowth (SIBO) or other changes in the gut microbiota, altered gut motility, visceral hypersensitivity, hard stool or constipation, food intolerance and carbohydrate malabsorption, abnormal abdominal-diaphragmatic muscle function, and altered pelvic floor function (5-7).

Functional bloating can arise without any predisposing factors and is unlikely to be completely resolved with medication and/or lifestyle modification such as a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) in IBS. Medicinal treatment options include: stimulants of intestinal fluid secretion and motility—lubiprostone and linaclotide; antidepressants—citalopram and fluoxetine; the antibiotic rifaximin; probiotics such as *Bifidobacterium bifidum* MIMBb75, *Lactobacillus plantarum* 299v or combinations of multiple bacterial species, although their efficacy is inconclusive; prokinetics—prucalopride and formerly tegaserod which was withdrawn from the world market in 2007 due to the risk of serious cardiovascular adverse effects; antispasmodics—mebeverine and otilonium bromide; and gas-reducing agents e.g. simethicone (5-7).

Simethicone is an inert substance with antifoaming activity that reduces bloating, abdominal discomfort, and abdominal pain by dispersing and preventing the formation of mucus-surrounded gas pockets along the gastrointestinal tract (8). It was first approved for use by the US Food and Drug Administration in 1952 (9). Simethicone may act as a topical mucosal barrier providing protection against irritants such as gastric acid, biliary salts and acetylsalicylic acid (9,10). In the treatment of IBS, a meta-analysis showed that global symptoms and bloating were improved by the addition of simethicone to antispasmodic agents (11).

APT036 (Aprotecol®) contains xyloglucan which is extracted from the seeds of the tamarind tree *Tamarindus indica*. Xyloglucan has been approved in Europe (MED class III) for restoring the physiological functions of the intestinal walls. Available in capsule form for adults, and powder for paediatric use, xyloglucan has been specifically formulated to control and reduce gastrointestinal symptoms of varying aetiologies, such as abdominal tension and frequent faecal emissions. Xyloglucan's 'mucin-like' molecular structure forms a bio-protective film on intestinal mucosa which thereby improves mucosal resistance to intestinal pathogens and helps to restore normal intestinal function (12). The Aprotecol formulation also includes the tyndallized lactic-bacterial strains *Lactobacillus reuteri* and *Bifidobacterium brevis*, which prevent and reduce symptoms in subjects with altered gut flora (13).

The current study aimed to evaluate the safety and efficacy of APT036 in adult patients with functional bloating, using simethicone as a comparator.

Methods

This multicentre, double-blind, randomised, parallel-group study was conducted at gastroenterology outpatient medical centres in Romania. Patients were enrolled by gastroenterology or internal medicine specialist physicians. The study was registered with EudraCT Number 2014-00556572.

Inclusion criteria were male or female patients between 18 and 65 years of age, of Caucasian race, with a diagnosis of functional bloating. Subjects were required to provide written informed consent to participate in the study prior to screening.

Subjects who met any of the following criteria were not eligible for study admission: pregnant or breastfeeding women; allergy to one of the product ingredients; impossibility to attend study visits; health status not allowing study participation; diabetic patients; patients treated with antibiotics or those using purgatives within two weeks prior to the hydrogen breath test.

Using a computer-generated randomisation scheme, subjects were assigned in a 1:1 ratio to receive APT036 or simethicone for 20 consecutive days. Treatments were administered orally each day according to the approved product label: 1 capsule 3 times/day. Patients and investigators were blinded to treatment. Treatment adherence was monitored by pill counts.

The evaluation period was 30 days and subjects attended five clinic visits: at baseline (Visit 1); after 2 days of treatment (Visit 2); after 10 days of treatment (Visit 3); after 20 days of treatment (Visit 4; end of treatment); at 10 days after the end of treatment (Visit 5; follow-up).

Patients' demographic data and medical history were recorded at baseline. At baseline and end of treatment, subjects underwent a hydrogen breath test. At baseline and at each study visit including follow-up, the following assessments were performed: abdominal girth measurement; general medical investigation; clinical symptoms evaluation based on patient journals; concomitant medication evaluation; and safety assessment.

Patient data were collected using purpose-designed case report forms (CRF, see Supplementary Material).

Subjects were free to withdraw from the study at any time without providing a reason. Investigators could withdraw subjects if deemed appropriate for safety or ethical reasons or if the study was deemed detrimental to the well-being of the patient.

Study objectives

The primary objective of the study was to evaluate the safety of APT036 in adult patients with functional bloating.

The secondary objective of the study was to assess the clinical efficacy of APT036 versus simethicone in alleviating symptoms of functional bloating.

Study outcome measures

Safety was assessed by the occurrence of adverse events during the study (frequency, intensity, and relationship with study treatments) as reported by the patient or observed by the physician, and by the results of clinical parameters monitored and vital signs examined at each study visit.

Clinical efficacy was evaluated according to patient-reported symptom severity using the Likert scale and recorded in daily journals; by measuring patients' abdominal girth at each study visit; and by the change between baseline and end of treatment in the hydrogen breath test.

The hydrogen breath test was performed before and after glucose administration. A total of five measurements were taken: one before ingesting glucose and four at 30-minute intervals for a 2-hour period after glucose ingestion. A positive hydrogen breath test was defined as a hydrogen gas elevation of 12 parts per million (ppm) at two time points (ideally for two consecutive measurements) within the 2 hours following the glucose-loading dose. Clinically, an increase of ≥12 ppm above basal on the glucose positive hydrogen breath test supports a diagnosis of SIBO.

Ethical considerations

The study was performed in accordance with Good Clinical Practice in conducting human clinical trials and the World Medical Association (WMA) Declaration of Helsinki regarding Ethical Principles for Medical Research Involving Human Subjects adopted during the 64th WMA General Assembly at Fortaleza in Brazil on October 2013. The study gained full approval from the România Academia de Stiinţe Medicale, Comisia Naţională de Bioetică a Medicamentului şi a Dispozitivelor Medicale on 3 February 2016 under approval number 7DM/03.02.2016.

The study was performed in compliance with the requirements of the National Agency of Medicine and Medical Devices of Romania and National Ethical Committee for Biomedical Research. The study gained full regulatory approval from the National Agency of Medicine and Medical Devices of Romania on 11 February 2016.

Statistical methods

Based on previous data showing an expected mean difference of at least 0.26 and a standard deviation of 0.41768 between any two groups for 'duration of bloating and distension in adult patients', it was calculated that at least 54 randomly selected subjects per group (108 subjects in total) were required to ensure a power of 0.90 at a 5% significance level for comparisons of safety and efficacy between APT036 and simethicone.

All subjects who received at least one dose of APT036 or simethicone were included in the safety analysis. All subjects who received at least one dose of APT036 or simethicone were included in the intention-to-treat efficacy analysis.

Results were summarized using descriptive statistics: mean ± standard deviation (SD) for continuous variables and absolute (n) and relative (%) frequency counts for categorical variables.

To determine whether APT036 and simethicone were effective in alleviating the symptoms of functional bloating, an initial paired t-test was conducted to measure whether a statistical difference existed between baseline and different time points (e.g., study visits) in the entire patient population, without differentiating between study arms. Exploratory statistical tests were then performed to test

Table 1 Demographic and baseline characteristics of enrolled patients

Characteristics	APT036 (n=54)	Simethicone (n=54)
Gender M:F, n (%)	12 (22.2):42 (77.8)	16 (29.6):38 (70.4)
Age, years (mean ± SD)	41.4±11.21	44.4±12.2
Body mass index, kg/m^2 (mean ± SD)	26.5±5.3	26.8±4.8
Blood pressure, mm Hg (systolic/diastolic; mean ± SD)	129±12.1/75±6.6	132±9.1/77±8.2
Heart rate, bpm (mean ± SD)	71±1.4	70±1.7
Comorbidities, n (%)		
Allergies	5 (9.3)	1 (1.9)
Dermatological disease	2 (3.7)	4 (5.6)
Genito-urinary disease	9 (16.7)	4 (7.4)
Immune disease	0	0
Central nervous system disease	0	0
Psychiatric disease	0	0
Obstetric-gynaecological disease	5 (9.3)	2 (3.7)

bpm, beats per minute; SD, standard deviation.

whether APT036 and simethicone differed in their ability to reduce the symptoms of functional bloating. Depending on the type of data, the analyses performed included t-test, Mann–Whitney U, χ^2, and Wilcoxon signed-rank tests.

Differences in group scores between and among clinical variables were calculated using analysis of variance (ANOVA). Clinical symptoms and signs of functional abdominal bloating were associated with variables such as age, gender, treatment dose, or other recorded variables. Depending on the type of associated variables, correlation estimates were based on Pearson correlation coefficient, Spearman's rank correlation coefficient, and/or Kendall tau rank correlation coefficient.

Clinical study protocol

The protocol summary is available as supplementary information (*Tables S1*,*S2*).

Results

The study took place between 11 February and 10 September 2017. A total of 108 patients, enrolled at six gastroenterology outpatient medical centres in Romania (Bucharest: 4; Oradea: 1; Timisoara: 1), were randomised to receive APT036 (n=54) or simethicone (n=54). Patients' demographic and baseline characteristics are summarised in *Table 1*. All patients completed the study (*Figure 1*) and their data were analysed for safety and efficacy.

No adverse events, serious adverse events, or serious unexpected adverse reactions were reported with APT036 or simethicone by patients or investigators during the study.

There were no significant differences between APT036 and simethicone in the evolution of clinical parameters and vital signs from baseline to Day 30 (*Table 2*).

Combined assessment of the entire study population, without differentiating between APT036 and simethicone treatment groups, indicated statistically significant reductions between baseline and Day 2 in the clinical symptom of 'distention'; statistically significant reductions between baseline and Days 10 and 20 in all clinical symptoms; and statistically significant reductions between Day 20 and Day 30 in the clinical symptoms of 'distension' and 'flatulence' (*Table 3*).

Comparing baseline with Day 30, there were statistically significance differences in favour of APT036 over simethicone in the number of subjects with symptoms of abdominal distension (P=0.008; *Figure 2A*) and flatulence (P=0.010; *Figure 2B*). Although the evolution from baseline to Day 30 in the number of subjects with abdominal pain also favoured APT036 (46 to 0 patients versus 35 to 5 patients with simethicone; *Figure 2C*), the difference between

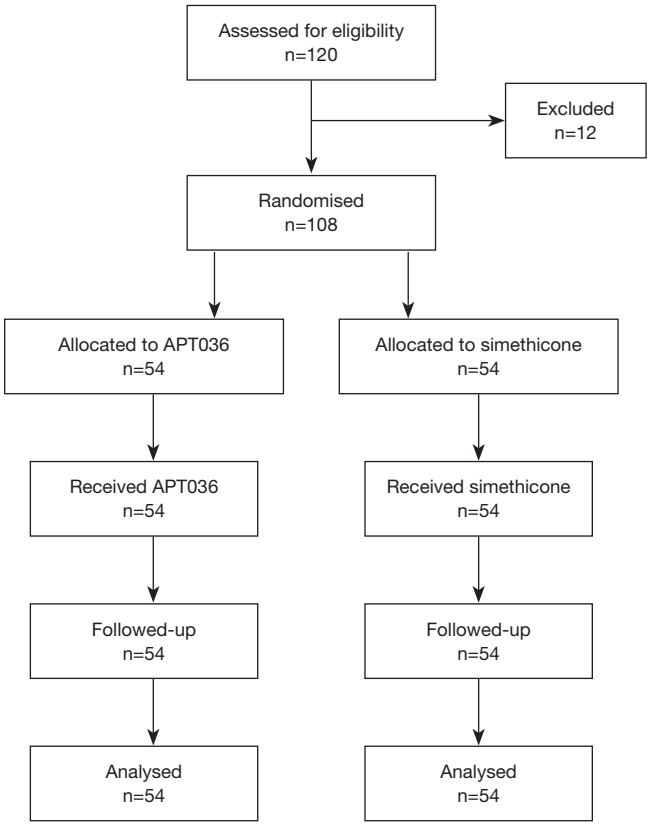

Figure 1 Study flow chart.

treatment groups did not reach statistical significance (P>0.05).

At baseline, the hydrogen breath test indicated the presence of SIBO in all subjects in both study arms (*Table 4*). Hydrogen gas elevation above basal levels after glucose administration was 14.3 ppm in both the APT036 and simethicone treatment groups, fulfilling the criteria for a diagnosis of SIBO. At the end of treatment (Day 20), all subjects in both treatment arms showed reduced hydrogen gas production. Mean peak hydrogen gas elevation was 8.8 ppm above basal with APT036 and simethicone (i.e., below the threshold for a diagnosis of SIBO), with no statistically significant difference between treatment groups.

Discussion

This multicentre, randomised, double-blind, parallel-group study was conducted to compare the safety and efficacy of APT036 and simethicone in patients with functional bloating. Both formulations were well tolerated by study subjects. With regard to the primary outcome measure, no adverse events, serious adverse events or serious unexpected severe adverse reactions were reported by patients or investigators throughout the study. Vital signs examined at baseline and follow-up were within normal ranges at each

Table 2 Evolution in clinical parameters and vital signs between baseline and follow-up

Parameter	APT036 (n=54)		Simethicone (n=54)	
	Baseline	Day 30	Baseline	Day 30
Abdominal girth, cm (mean)	97	85	94	93
Body mass index, kg/m^2 (mean)	26.6	24.3	26.9	26.5
Systolic blood pressure, mmHg (mean)	129	125	124	120
Diastolic blood pressure, mmHg (mean)	65	60	57	62
Heart rate, bpm	65	60	62	64

Table 3 Statistical differences (paired t-test) between baseline and study time points for mean changes in clinical symptoms of functional bloating in the entire patient population (APT036 + simethicone groups)

Symptom	Day 2	Day 10	Day 20 (end of treatment)	Day 30 (end of treatment follow-up)
Distension	0.007*	0.000*	0.000*	0.028*†
Flatulence	0.230	0.000*	0.000*	0.023*†
Abdominal pain	0.099	0.000*	0.000*	0.457†

*, values indicate statistically significant reductions in symptom scores as evaluated by patients using the Likert's scale and recorded in patient diaries. †, statistical difference from Day 20 to Day 30.

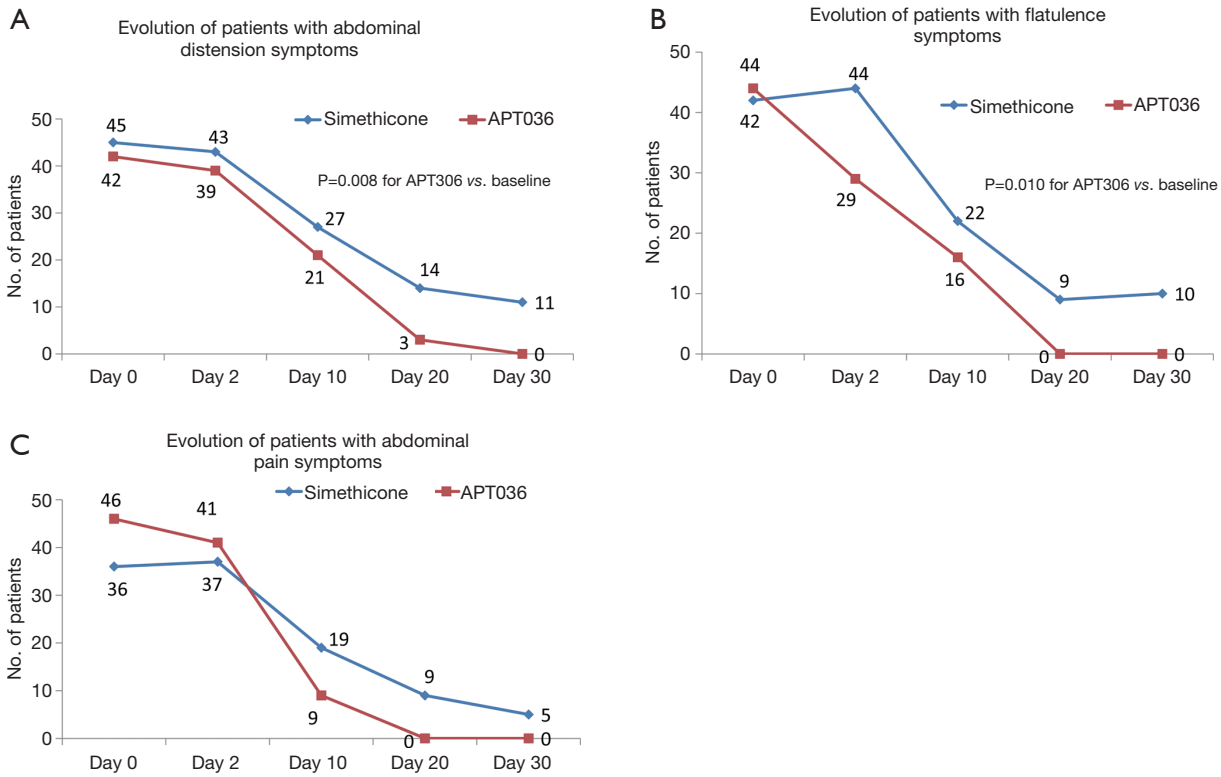

Figure 2 Evolution in the number of patients with symptoms of (A) abdominal distension, (B) flatulence, and (C) abdominal pain from baseline to the final follow-up visit.

Table 4 Hydrogen breath test (HBT) measurements at baseline and end of treatment (Day 20)

Parameter	APT036 (n=54)		Simethicone (n=54)	
	Baseline	Day 20	Baseline	Day 20
HBT basal	9.5	7.1	9.4	7.1
HBT peak	23.8	15.9	23.7	15.9
Change: peak – basal HBT	14.3	8.8	14.3	8.8

Results show mean levels of hydrogen gas production (parts per million) before and after glucose administration.

time point.

Efficacy analysis on clinical symptoms of functional bloating showed a better evolution with APT036 than simethicone for multiple symptoms. Compared with simethicone, APT036 significantly reduced abdominal distension (P=0.008) and flatulence (P=0.010) from baseline to the follow-up visit. APT036 also reduced symptoms of abdominal pain over the 30-day observation period compared with simethicone, although the difference was not statistically significant.

Hydrogen breath testing provides a safe, inexpensive, and non-invasive alternative to jejunal aspiration culture for the diagnosis of SIBO (14). Moreover, it may represent a more inclusive definition of SIBO because it is likely to include cases of distal small-bowel bacterial overgrowth and pathologic bacterial strains not identified by culturing techniques. The hydrogen breath test performed at baseline confirmed SIBO in all subjects (increase of >12 ppm above basal following glucose ingestion). Both APT036 and simethicone reduced patients' production of hydrogen gas. At the end of treatment on Day 20, mean hydrogen breath test results in both study arms were below the threshold

for a SIBO diagnosis (<12 ppm above basal after glucose ingestion), with no significant difference between APT036 and simethicone.

Disruption of intestinal epithelial barrier function is associated with several diseases including inflammatory bowel disease, IBS and celiac disease (15). In addition, the integrity of other mucosal barriers such as the respiratory epithelial barrier is an important defence against inflammatory and infectious diseases, e.g., chronic obstructive pulmonary disease, acute respiratory distress syndrome, and asthma (16,17). Non-pharmacological approaches such as xyloglucan, with demonstrated protective barrier properties, offer an alternative approach for managing a range of diseases characterised by mucosal disruption. In clinical trials, xyloglucan has been shown to reduce symptoms of gastroenteritis in children and adults (18,19), symptoms of rhinosinusitis (20), and dry eye syndrome (21). Treatment of IBS patients with a similar mucosal protector containing film-forming reticulated proteins plus oligo- and polysaccharides relieved abdominal pain and flatulence (22). In placebo-controlled trials, reticulated proteins were also effective in treating urinary tract infections (23,24). In a pilot study, APT198K (xyloglucan plus heat-killed *Lactobacillus reuteri* SGL01 and *Bifidobacterium brevis* SGB01) was superior to a lactase dietary supplement in reducing the mean duration of crying per episode in 46 children with infantile colic (25). The current study of APT036 extends evidence for the safety and efficacy of xyloglucan-containing medical devices, with demonstrated protective barrier properties, to the treatment of functional bloating.

A major limitation of randomized clinical trials is their restriction to interventions that are meant to have a positive treatment effect. Another limitation relates to the difficulty in interpreting or generalizing the results because the studied population is not wholly representative of the population treated in usual practice. Further studies of APT036 in patients with various comorbidities are required. The limitations of clinical trials also include the specificity of the question to be answered. Indeed, the narrow perspective of many trials excludes important information related to the consequences of the intervention on quality of life, treatment satisfaction or costs. A solution consists of developing a disease management approach that involves implementation of real-life studies performed in thousands of patients and with a long duration of follow-up.

In conclusion, APT036 had a good safety profile and was significantly superior to simethicone in relieving symptoms of functional bloating, namely abdominal distension and flatulence.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study gained full approval from the România Academia de Stiinţe Medicale, Comisia Naţională de Bioetică a Medicamentului şi a Dispozitivelor Medicale on 3 February 2016 under approval number 7DM/03.02.2016, and full regulatory approval from the National Agency of Medicine and Medical Devices of Romania on 11 February 2016.

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Supplementary

Table S1 Clinical study protocol

Items	Description
Test products/arms	Aprotecol® (Group 1) *vs.* Degasil® (Simethicone) (Group 2)
Study purpose	A comparative study between two medical devices in treating the Functional Abdominal Bloating in adults
Market status of the tested products	Aprotecol® is an approved CE marked Medical Device; Degasil® (Simethicone) is an approved CE marked Medical Device
Clinical study phase	IV
EudraCT No.	2014-005565-72
Protocol number	CNA1212-14
Protocol date	December 2014

Table S2 Protocol summary

No.	Items	Description
1	Protocol code	CNA1212-14
2	Protocol title	Efficacy and Safety of APT036 (APROTECOL capsules) versus Simethicone in the Treatment of Functional Abdominal Bloating: A Multicenter Randomized, Double- Blind, Parallel Group, Active Controlled Clinical Study (ESCAPE)
3	Products to be evaluated	One group will receive APT036 (APROTECOL capsules) and the other study group will receive DEGASIL (Simethicone capsules): Group 1, APT036 (APROTECOL capsules); Group 2, DEGASIL (Simethicone capsules)
4	Study design	A double blind, parallel, randomized, multicenter study
5	Dose	According to the approved leaflets for both medical devices: Aprotecol and Degasil
6	Number of subjects	108, in 2 equal groups of 54
7	Condition for administration	The investigational medical devices will be administered to the eligible subjects who gave their informed consent to participate at the study. The treatments (Aprotecol or Degasil) will be administrated by oral route according to their leaflets
8	Study objectives	The primary objective of the study is to evaluate the safety of Aprotecol in adult patients with Functional Abdominal Bloating
		The secondary objective of the study is to assess the clinical efficacy of Aprotecol *vs.* Simethicone in alleviating the symptomatology of Functional Abdominal Bloating
9	Efficacy evaluation	Symptom reduction—as assessed by the Likert scale, by using a daily journal kept for the entire period of the study treatment and throughout the 10-day follow-up period and also by measuring the abdominal girth at every visit in the doctor's office
		Assessing the patients with F.A.B, possibly caused by SIBO with the use of the Hydrogen Breath Test
		The primary efficacy endpoints for the study will be the change from Visit 1 to Day 20 (V4) in a 2-hour HBT total hydrogen production test
10	Visits	Visit 1—baseline visit;
		Visit 2—after 2 days of treatment;
		Visit 3—after 10 days of treatment;
		Visit 4—after 20 days of treatment;
		Visit 5—Follow-up visit, at 10 days after Visit 4
11	Study procedure	Each subject will be assigned randomly to the Group 1 or Group 2;
		Patients will be treated with either APT036 (APROTECOL oral capsules) or DEGASIL (Simethicone oral capsules);
		Dosage schedule for the treatments will be according to the approved leaflet for both medical devices for every day for 20 consecutive days;
		The treatments (Aprotecol or Degasil) will be administrated by oral route every day
12	Concomitant medications	All concomitant medications taken or administered in the 4 weeks before screening and during the study will be documented in the CRF
13	Adverse events	Adverse events will be monitored at baseline visit, during the study and at visits 2, 3, 4 as well as at the end of the study and will be reported accordingly

Case Report Form (CRF)

Subject's code:_____ **Subject's initials:_____**

Investigational site:

The investigator/ subinvestigator will complete this CRF after careful consultation of study protocol!
Any modification will be executed in accordance to SOP!

CASE REPORT FORM
(CRF)

(Confidential)

Efficacy and Safety of APT036 versus Simethicone in the Treatment of Functional Abdominal Bloating: A Multicenter, Randomized, Double-Blind, Parallel Group, Active Controlled Clinical Study

Study Acronim: ESCAPE Study

Investigator: .....

Subjects' reference no.: _____	Subject's code: _____
Did the subject complete the study?	Yes ☐ No ☐

Date of beginning of writing the CRF: ____/_____/_____
day month year

Date of completion of the CRF: ____/_____/_____
day month year

EudraCT number:
Protocol code:

Screening examination

Informed consent given in written form: Date: ___/___/____ Time: ___/___
Day month year hour min

Subject's demographics and anthropometrics data:

Date of birth: ___/___/____ Age: ____ years Sex: M ☐ F ☐
Day month year

Screening examination

Assessment date: ___/___/____
day month year

Medical history:

		If "Yes" specify and evaluate*:	NS / CS
1. Allergies	No ☐ Yes ☐		
2. Dermatological disease	No ☐ Yes ☐		
3. Genitourinary disease	No ☐ Yes ☐		
4. Immune & connective tissue disease	No ☐ Yes ☐		
5. Nervous system and sense organs disease	No ☐ Yes ☐		
6. Psychiatric disease	No ☐ Yes ☐		
7. Other disease	No ☐ Yes ☐		

***NS- not significant; CS- clinically significant**

Obstetrics and gynecological history:

17. Gynecological / Obstetrical disease:	No ☐	Yes ☐	Specify & evaluate: _____
18. Pregnancy/birth/lactation/abortion:	No ☐	Yes ☐	Date of last pregnancy/birth/abortion: ___/___/____ day month year

Physical examination

Height (cm): ___/___/____ Weight: ____ Kg BMI: _____ Abdominal girth_____

Concomitant Medication

No.	***Disease***	***Prior Concomitant Medication (****6 month before being included)*	***Concomitant Medication***

Clinical status (related to symptoms of Functional Bloating in the last 24 hours before the visit 1)

System	Method of evaluation	Results			
1. Bloating	Likert scale				
2. Distension	Likert scale				
3. Flatulence	Likert scale				
4. Abdominal pain	Likert scale				
5. Stool emission	Bristol Scale	No. of stools`		Type of stool	
6. HBT result	HBT				

Diagnostic: _____

Pregnancy test

Positive result ☐ ***Negative result*** ☐ ***Date of the test:*** _____

ADVERSE EVENT
Has the patient experienced any AE since informed consent?
Yes ☐ No ☐
*If Yes, please fill in the AE form and concomitant medication form

Comments if any:

_____

_____

_____

INCLUSION CRITERIA			
	Yes	***No***	***NAP***
1. Adults between 18 and 65 years of age,	☐	☐	☐
2. Caucasian race	☐	☐	☐
3. Suffering of functional abdominal bloating	☐	☐	☐

EXCLUSION CRITERIA			
	Yes	***No***	***NAP***
1. Pregnant women or breastfeeding	☐	☐	☐
2. Unwilling to sign the Informed Consent Form;	☐	☐	☐
3. Allergy to one of the product ingredients;	☐	☐	☐
4. Impossibility to come at the study visits	☐	☐	☐
5. Health status not allowing the participation in the study	☐	☐	☐
6. Diabetic patients	☐	☐	☐
7. Patients treated with antibiotics 2 weeks prior the Hydrogen Breath Test schedule	☐	☐	☐
8. Patients that were using purgatives within 2 weeks prior Hydrogen Breath Test.	☐	☐	☐

Patient randomization procedure:
Subjects' reference no.: _____

Enrollment in the present study:
The criteria are set to assure a homogenous subject population without accompanying diseases interfering with the conduct and scientific evaluation of the results. After reviewing of all the results and comparison with the inclusion and exclusion criteria, the subject is:

☐ **Eligible** ☐ **Non-eligible**

In case the subject is eligible, then will be included in the study with the:

Subject code: ____ Group 1 ☐ Group 2 ☐

Has the patient receive a proper training on how to administer the treatment? Yes ☐ No ☐
Remarks:

Date of inclusion: ___/___/____ **day month year**	**Date of treatment start:** ___/___/____ **day month year**	**Date of treatment stop:** ___/___/____ **day month year**

INVESTIGATOR:

Date (day/ month/ year)___/___/____

MONITOR:

Date (day/ month/ year)___/___/____

Visit 2 examination (After 2 days of treatment)

Assessment date: ___/___/____
Day month year

Physical examination

Height (cm): ___/___/____ Weight: ____ Kg BMI: _____ Abdominal girth

System	Method of evaluation	Results			
7. Bloating	Likert scale				
8. Distension	Likert scale				
9. Flatulence	Likert scale				
10. Abdominal pain	Likert scale				
11. Stool emission	Bristol Scale	No. of stools`		Type of stool	
12. HBT result	HBT	NA			

Concomitant Medication

No.	***Disease***	***Prior Concomitant Medication (****6 month before being included)*	***Concomitant Medication***

Comments if any:

ADVERSE EVENT
Has the patient experienced any AE since informed consent?
Yes ☐ No ☐
***If Yes, please fill in the AE form and concomitant medication form**

INVESTIGATOR:

Date (day/ month/ year)___/___/____

MONITOR:

Date (day/ month/ year)___/___/____

Visit 3 examination (After 10 days of treatment)

Assessment date: ___/___/____
Day month year

Physical examination

Height (cm): ___/___/____ Weight: ____ Kg BMI: _____ Abdominal girth

System	Method of evaluation	Results			
13. Bloating	Likert scale				
14. Distension	Likert scale				
15. Flatulence	Likert scale				
16. Abdominal pain	Likert scale				
17. Stool emission	Bristol Scale	No. of stools`		Type of stool	
18. HBT result	HBT	NA			

Concomitant Medication

No.	***Disease***	***Prior Concomitant Medication (****6 month before being included)*	***Concomitant Medication***

Comments if any:

ADVERSE EVENT
Has the patient experienced any AE since informed consent?
Yes ☐ No ☐
***If Yes, please fill in the AE form and concomitant medication form**

INVESTIGATOR:

Date (day/ month/ year)___/___/____

MONITOR:

Date (day/ month/ year)___/___/____

Visit 4 examination (After 20 days of treatment)

Assessment date: ___/___/____
Day month year

Physical examination

Height (cm): ___/___/____ Weight: ____ Kg BMI: _____ Abdominal girth

System	Method of evaluation	Results			
19. Bloating	Likert scale				
20. Distension	Likert scale				
21. Flatulence	Likert scale				
22. Abdominal pain	Likert scale				
23. Stool emission	Bristol Scale	No. of stools`		Type of stool	
24. HBT result	HBT				

Concomitant Medication

No.	***Disease***	***Prior Concomitant Medication (****6 month before being included)*	***Concomitant Medication***

Comments if any:

ADVERSE EVENT
Has the patient experienced any AE since informed consent?
Yes ☐ No ☐
***If Yes, please fill in the AE form and concomitant medication form**

INVESTIGATOR:

Date (day/ month/ year)___/___/____

MONITOR:

Date (day/ month/ year)___/___/____

Visit 5 examination (After 10 days After visit 4)

Assessment date: ___/___/____
Day month year

Physical examination

Height (cm): ___/___/____ Weight: ____ Kg BMI: _____ Abdominal girth

System	Method of evaluation	Results			
25. Bloating	Likert scale				
26. Distension	Likert scale				
27. Flatulence	Likert scale				
28. Abdominal pain	Likert scale				
29. Stool emission	Bristol Scale	No. of stools`		Type of stool	
30. HBT result	HBT	NA			

Concomitant Medication

No.	***Disease***	***Prior Concomitant Medication (****6 month before being included)*	***Concomitant Medication***

Comments if any:

ADVERSE EVENT
Has the patient experienced any AE since informed consent?
Yes ☐ No ☐
***If Yes, please fill in the AE form and concomitant medication form**

INVESTIGATOR:

Date (day/ month/ year)___/___/____

MONITOR:

Date (day/ month/ year)___/___/____

Adverse event record

ONSET TIME: **Date:** **ADVERSE EVENT:**		**PRE DOSE** ☐ **POST DOSE** ☐	**LAST DOSE** TIME: DATE:
		REPORT METHOD	**SEVERITY**
		Spontaneous ☐ **Observed** ☐ **Elicited** ☐	**Not assessed** ☐ **Absent** ☐ **Mild** ☐ **Moderate** ☐ **Severe** ☐
REPORTING TIME:	Date:		
COMMENTS:			
Give details of non-drug and drug therapies, appropriate dosage form, route and frequency of administration and duration including dates			

INVESTIGATOR:

Date (day/ month/ year)___/___/____

MONITOR:

Date (day/ month/ year)___/___/____

RESOLUTION: YES ☐ (If yes) TIME: DATE: NO ☐ (If NO please follow up)

Recorded by: Date ___/___/____

day/ month/ year

The following will be filled in consultation with Clinical Investigator

SERIOUSNESS	**ACTION**	**OUTCOME**
Serious ☐	**None** ☐	**Recovered without sequel** ☐
Not Serious ☐	**Increased Surveillance** ☐	**Recovered with sequel** ☐
LIKELIHOOD	**Treatment*** ☐	**Ongoing** ☐
Expected ☐	**Study drug discontinuation** ☐	**Died** ☐
Unexpected ☐	**Other** ☐	**Not known** ☐

*Please complete the Concomitant Medication record

Recorded by: Date ___/___/____

day/ month/ year

INVESTIGATOR:

Date (day/ month/ year)___/___/____

MONITOR:

Date (day/ month/ year)___/___/____

Follow-Up Adverse Event Record

ADVERSE EVENT:	**REPORTING TIME** **TIME:** **DATE:**
FOLLOW-UP	
COMMENTS:	

SEVERITY	**ACTION**	**RESOLUTION**	Recorded by: Date:
Not assessed ☐	**None** ☐	YES ☐ (If yes)	
Absent ☐	**Increased Surveillance** ☐	TIME:	
Mild ☐	**Treatment*** ☐	DATE:	
Moderate ☐	**Study drug discontinuation** ☐	NO ☐ (If NO please follow up)	
Severe ☐	**Other** ☐		

FOLLOW-UP	REPORTING TIME:	Date:
COMMENTS:		

INVESTIGATOR:

Date (day/ month/ year)___/___/____

MONITOR:

Date (day/ month/ year)___/___/____

SEVERITY	**ACTION**	**RESOLUTION**	Recorded by:
Not assessed ☐	**None** ☐	YES ☐ (If yes)	
Absent ☐	**Increased Surveillance** ☐	TIME:	
Mild ☐	**Treatment*** ☐	DATE:	Date:
Moderate ☐	**Study drug discontinuation** ☐	NO ☐ (If NO please follow up)	
Severe ☐	**Other** ☐		

*Please complete the Concomitant Medication Record

Concomitant medication record

Name of medication/ active substance/ concentration	Dose/Day	Route of administration	Date/period of administration	Drug-IMP Interaction	Suitability for continuing the study*
				Yes □ No □	Yes □ No □
				Yes □ No □	Yes □ No □
				Yes □ No □	Yes □ No □
				Yes □ No □	Yes □ No □
				Yes □ No □	Yes □ No □
				Yes □ No □	Yes □ No □
				Yes □ No □	Yes □ No □
				Yes □ No □	Yes □ No □
				Yes □ No □	Yes □ No □
				Yes □ No □	Yes □ No □
				Yes □ No □	Yes □ No □
				Yes □ No □	Yes □ No □
				Yes □ No □	Yes □ No □

*If the subject is not suitable for continuing the study, please complete the Subject Withdrawal/ Drop-out Sheet

INVESTIGATOR:

Date (day/ month/ year)___/___/____

MONITOR:

Date (day/ month/ year)___/___/____

Investigator's conclusion about the subject

Has the subject performed all study visits according to the protocol?

No □ Yes □

(*If the answer is negative, please complete the Withdrawal / Drop-out sheet*)

Last contact date: ____/____/___
day month year

Investigator's declaration

I undersigned, certify that this subject has been under my responsibility during the study and the delivered information and the content of the file are accurate. This study has been conducted in accordance with study protocol no. ……., version 01 and with the ethical and professional requirements of GCP and Declaration of Helsinki.

Date:

Name:

Signature