CLINICAL STUDY PROTOCOL

Open-Label, Prospective, Multicenter Study to Assess effiCacy and safEty of Lactacol/Lactazak ®, a food supplement in *intestinal colic and bloating*

Open-label, multicenter, prospective, non-comparative, non-interventional study

Protocol code: CBSPH_CBS12122022

Version 1.0/Date: November 27th, 2023

SHORT name: PACE Study

CONFIDENTIALITY STATEMENT

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1 CLINICAL STUDY PROTOCOL

Study Short Name	Open-Label, Prospective, Multicenter Study to Assess efficacy and safety of Lactacol/Lactazak ®, a food supplement, in intestinal colic and bloating
Tested products	Lactacol/Lactazak ® • The food supplement "Lactacol Fiale"(Lactacol), whose notification dated 20 November 2023 is annexed hereto, has the same formula as the food supplement "Lactazak" (PRG 570/2023). (Annex 1) • Lactacol Fiale and Lactazak are the same food supplement with different trade names
Study purpose	To assess efficacy and safety of Lactacol/Lactazak ®
Market Status of the Tested Products	Notified to Health Ministry - General Directorate of Hygiene, Food safety and nutrition protection - 20 November 2023
Study Design:	Open-label, multicenter, prospective, non-comparative, non-interventional study
Protocol number	CBSPH_CBS27112023
Protocol version	1.0
Protocol date	Novemver 27th, 2023
Sponsor	**Pharmunion LLC,** 3524 Silverside Road Suite 358 Wilmington, Delaware, 19810
Manufacturer	**SALIX S.R.L.** **Del Lavoro 14** **36030 Monte Di Malo (Vi) Italia**
CRO	**CEBIS International SRL** 47 Theodor Pallady, Helios Business Centre

Open-Label, Prospective, Multicenter Study to Assess effiCacy and safEty of Lactacol/Lactazak ®, a food supplement in *intestinal colic and bloating*

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CONFIDENTIALITY STATEMENT

1. Study Synopsis

1	Protocol identification:	*CBSPH_CBS27222023* *Version 1.0/Date: November 27th, 2023*
2	Protocol title:	Open-Label, Prospective, Multicenter Study to Assess efficacy and safety of Lactacol/Lactazak ®, a food supplement, in intestinal colic and bloating
3	Products involved:	Lactacol/Lactazak ®
4	Study Design:	*Open-label, multicenter, prospective, non-comparative, non-interventional study*
5	Dosage & administration:	. **Product: LACTAZAK** Route of administration: Oral route **Single dose:** 0.5 ml (700 FCC ALU). **Maximum daily dose:** 6 ml (8400 FCC ALU). **Method of administration:** Prior to use, twist the cap and shake well, use a pipette to collect 0.5 ml of solution and give the baby before each breastfeeding or add to the milk formula for 14 consecutive days. Lactacol/Lactazak ® is degraded, being exposure to high temperatures, so this enzyme should not be added to hot food or liquid. Store at room temperature (up to 25°C), away from heat sources and protected from light. Keep in the original packing. Keep out of the reach of children.

6	Number of subjects:	30
7	Country	Bulgaria
8	Investigators	GP, Pediatrics, Family Doctors
9	No of centers to be involved	1-2
10	Study objective	**Primary Objectives** To assess the product efficiency by: • reducing the baby crying due to colic during study period; • reducing bloating **Secondary Objective** To assess effectiveness of the product administration by the responses at below questions during study period: 1. "How many hours in total does your child sleep per 24-h period?" 2. "How many hours in total do you (as caregiver) sleep per 24-h period?" 3. "How often does your child usually wake during the night?" To assess safety of the product administration in terms of: 1. AE occurrence; 2. Withdrawals due to lack of tolerability
11	Study Endpoints	Primary endpoint Efficacy will be evaluated by: • reducing the number of babies crying episodes per day due to colic's during study period • bloating reduction assessed though 3-point Likert scale Secondary endpoint

		Effectiveness will be evaluated through the collected responses during study period: 1. Change in mean number of hours of child sleep during 24 h, evaluated in a daily manner during study period through a journal 2. Change in mean number of hours of caregiver sleep during 24 h, evaluated in a daily manner during study period through a journal 3. Change in mean number of awakenings during night evaluated in a daily manner during study period through a journal Safety will be assessed though: 1. Number of Adverse events; 2. Number of participants withdrawn due to lack of tolerability
12	Sample size	30
13	Statistical Methods	Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic. Confidence intervals will be presented to one more decimal place than the raw data. Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using N (number per treatment group or overall) as the denominator.
14	Eligibility	**Inclusion Criteria:** • pediatric population 0-4 months;

		• Established diagnosis: FGIDs (intestinal colic and bloating). • Signed Informed Consent for data collecting; **Exclusion Criteria:** • Unwillingness to provide signed Informed Consent for data collecting; • Patients participating in other trials • Allergy to any of the product ingredients
15	Visits:	**3 visits:** • Visit 1 - Screening and enrollment visit; • Visit 2 – Day 14 from Therapy initiation; • Visit 3 - Phone Follow-up
16	Study procedure	This non-interventional study will be conducted in Bulgaria in routine clinical practice by GP, pediatricians, family doctors. Data will be collected prospectively. Lactacol/Lactazak® will be administered in accordance with approved leaflet. Patient demographic data would be collected during screening visit where available (e.g., age, gender, geographic location, Apgar score, type of birth method) All the assessments for primary and secondary objectives will be performed at baseline and periodically according to the national standards, routine clinical practice, and this study protocol.
17	Concomitant medications	All concomitant medications taken or administered in the 6 weeks before screening and during the study will be documented in the CRF.
18	Adverse events:	Adverse events will be monitored and reported accordingly.

2 LIST OF ABBREVIATIONS

AE	:	Adverse Event
BMI	:	Body Mass Index
CRF	:	Case Report Form
GCP	:	Good Clinical Practice
GI	:	Gastro intestinal
ICF	:	Informed Consent Form
ICH	:	International Conference on Harmonization
IMP	:	Investigational Medicinal Product
No	:	Number

3 SIGNATURE OF THE SITE INVESTIGATORS

The signatories agree to the content of the clinical study protocol as presented.

Name: _____ Role: Site Investigator

Date: _____ Signature: _____

Signed copies of this signature page are stored in the sponsor's study files and in the respective center's investigator site file.

4 SIGNATURE OF SPONSOR'S RESPONSIBLE PERSON

The signatory agrees to the content of the clinical study protocol as presented.

Sponsor Signature:

Name: Richard Zakhia

Signature: 

Date: November-27-2023

Signed copies of this signature page are stored in the sponsor's study files and in the respective center's investigator site file.

5 PROJECT TITLE

Open-Label, Prospective, Multicenter Study to Assess efficacy and safety of Lactacol/Lactazak ®, a food supplement, in intestinal colic and bloating

6 PROTOCOL CODE AND VERSION:

Protocol code:	*CBSPH_CBS27112023*
Version & Date	*Version 1.0/Date: November 27th, 2023*

7 OBJECTIVES

Primary objective:

To assess the product efficiency by:

- reducing the baby crying due to colic during study period;
- reducing bloating

Secondary objective:

To assess effectiveness of the product administration by the responses at below questions during study period:

- "How many hours in total does your child sleep per 24-h period?"
- "How many hours in total do you (as caregiver) sleep per 24-h period?"
- "How often does your child usually wake during the night?"

To assess safety of the product administration in terms of:

- AE occurrence;
- Withdrawals due to lack of tolerability

8 BACKGROUND

The most prominent feature of Infant Colics is prolonged crying. Additional characteristics, including clenching of the fists and flexion of the hips, have led to the suggestion that these behaviors are related to abdominal discomfort; thus, the term “colic, “derived from kolikos, the Greek term for colon. Infant colic is challenging for new parents and is a reason for 10% to 20% of paediatrician visits during the early weeks of an infant's life. Colic is estimated at affecting 5% to 40% of infants worldwide. The condition typically presents in the second or third week of life, peaks around 6 weeks, and resolves by the age of 12 weeks in 60% of infants and by 16 weeks of age in 90%. Inconsolable crying, irritability, and screaming without an obvious cause characterize colic; during these episodes of fussiness, which occur more frequently in the evenings, the affected infant classically appears red-faced, draws up the legs and tenses up the abdomen. The traditional methods of soothing the infant often fail to relieve the infant's distress. First described in 1954, the original "Wessel's Rule of 3s" diagnostic criteria (symptoms lasting for 3 hours per day, 3 or more days per week, for 3 or more weeks, starting around 3 weeks of age), has undergone a transition in recent years. The Rome IV criteria describe colic in infants from birth to 5 months of age to make the definition of infantile colic more consistent for research purposes. The criteria are as follows:

- An infant who is <5 months of age when the symptoms start and stop
- Recurrent and prolonged periods of infant crying, fussing, or irritability reported by caregivers that occur without obvious cause and cannot be presented or resolved by caregivers
- No evidence of infant failure to thrive, fever, or illness

While benign and self-limiting, the condition is frustrating for parents and has been linked to maternal postpartum depression and shaken baby syndrome. Since treatments for colic are controversial and inconsistent, the role of the physician as a counsellor and educator to parents is critical. The several factors involved in the etiopathogenesis (food intolerance or allergy to cow's

milk protein, intolerance to lactose, intestinal hyperperistalsis, neuro-hormonal immaturity, maternal anxiety and familial stress), make the management of infants with colics difficult.

Studies have shown up to 40% of babies medically diagnosed with colic actually suffer from transient lactase intolerance, hence the common term “colic associated with lactose intolerance”.

Many of these babies can be helped by pre-treating baby’s feeds with lactase enzymes.

LACTOSE INTOLERANCE is typically a temporary condition for babies and small children.

- Often - young babies don’t produce enough of the enzyme (lactase) because of functional "immaturity of" intestinal enzyme systems
- Lactose overload - breastfeed babies consuming large amounts of breastmilk (usually when their mothers have an oversupply)
- Gut damages: gastroenteritis, food intolerance or allergy, parasitic infection, coeliac disease, bowel surgery
- Rare - genetic condition: primary (or true) lactose intolerance

Infant colic is a characteristic group of behaviors seen in young infants.

A commonly used set of diagnostic criteria was proposed by Morris Wessel and colleagues,1 based on observations of 98 infants in the newborn nursery at Yale, 25 of whom had inconsolable crying. These criteria are summarized by the frequently quoted “rule of 3s”: crying by an otherwise healthy infant that lasts more than 3 hours per day on more than 3 days a week for more than 3 weeks

Pediatricians often use the “Rule of Three” to diagnose colic. Child who cried:

- for more than 3 hours a day
- for more than 3 days a week
- for over 3 weeks

When using the enzyme lactase before each feeding (breast milk and/or a mixture) baby crying because of colic was reduced by half during clinical study.

The study Sponsor introduce Lactacol/Lactazak®, which can be used as dietary supplement to a healthy diet and as a source of lactase enzyme. Lactacol/Lactazak ® characteristics are:

- Contains highly active lactase enzyme of plant origin.
- Resistant to acidic gastric medium.
- Maintains its activity in the conditions of high pH variations.

Lactacol/Lactazak promotes lactose hydrolysis **and it** should be used during each feeding during the first 3-4 months of life. After this period, lactase enzyme is usually produced by the body in sufficient quantities. Lactacol/Lactazak should be gradually withdrawn from feedings.

9 STUDY DESIGN

Open-Label, Prospective, Multicenter Study

10 STUDY TYPE

Observational study

11 FACILITIES

Selected sites in Bulgaria

12 STUDY INVESTIGATORS

GP, pediatricians, family doctors at individual cabinets will recruit the subjects. Adequate number of subjects will be selected and will undergo a standardized screening.

13 STUDY POPULATION

The investigators will enroll in this study 30 subjects accordingly to the inclusion and exclusion criteria.

14 STUDY TREATMENT

Paediatric patients will be enrolled after diagnosis with intestinal colic and bloating. They will be treated with Lactacol/Lactazak ® as presented below:

Product: LACTAZAK, Route of administration: Oral route**, Single dose:** 0.5 ml (700 FCC ALU). **Maximum daily dose:** 6 ml (8400 FCC ALU).

Method of administration: Prior to use, twist the cap and shake well, use a pipette to collect 0.5 ml of solution and give the baby before each breastfeeding or add to the milk formula for 14 consecutive days.

LACTAZAK is degraded, being exposure to high temperatures, so this enzyme should not be added to hot food or liquid. Store at room temperature (up to 25°C), away from heat sources and protected from light. Keep in the original packing. Keep out of the reach of children.

15 STUDY PROCEDURES

This non-interventional study will be conducted by family doctors/Peditrcians in Bulgaria in routine clinical practice. Data will be collected prospectively. Lactacol/Lactazak® will be administered in accordance with approved leaflet. Patient demographic data would be collected during screening visit where available (e.g., age, gender, geographic location, Apgar score, type of birth method)

All the assessments for primary and secondary objectives will be performed at baseline and periodically according to the national standards, routine clinical practice and this study protocol. Medical histories and demographic data (including subject's initials, date of birth) and medication used will be recorded into patient file.

Subjects will attend 3 visits during the study:

Visit 1 (Baseline):

- Concomitant medication
- Patient evaluation of eligibility criteria
- Patient informed consent
- Evaluation of baby crying episodes
- Bloating evaluation
- Child sleep evaluation
- Caregiver sleep evaluation
- Patient Medical History
- Physical examination (weight, height, abdominal girth blood pressure, pulse, temperature, respiration, BMI)
- Treatment Allocation

Visit 2 – Day 14

- Adverse events
- Concomitant medication
- Evaluation of baby crying episodes
- Bloating evaluation
- Child sleep evaluation
- Caregiver sleep evaluation
- Physical examination (weight, height, abdominal girth blood pressure, pulse, temperature, respiration, BMI)
- Recurrence evaluation*
- Treatment adherence **

Visit 3 – Day 28 (Phone Follow-up)

- Adverse events
- Concomitant medication
- Evaluation of baby crying episodes
- Bloating evaluation
- Child sleep evaluation
- Caregiver sleep evaluation

Study Flowchart

Study Flowchart	Visit 1 (Baseline)	Visit 2	Visit 3 Phone Follow-up
	Day 0	Day 15 +/- 2 days	Day 28 +/- 5 days
Patient informed consent	**X**		
Physical examination	**X**	**X**	
Patient evaluation of eligibility criteria	**X**		
Patient Medical History	**X**		
Concomitant medication	**X**	**X**	**X**
Evaluation of baby crying episodes	**X**	**X**	**X**
Bloating evaluation	**X**	**X**	
Child sleep evaluation	**X**	**X**	**X**
Caregiver sleep evaluation	**X**	**X**	**X**
Product Allocation	**X**		
Product adherence		**X**	
Product administration	**X**	**X**	
End of product administration		**X**	
Adverse events		**X**	**X**
Investigator Final evaluation on patient status			**X**

16 OUTCOMES

Primary endpoint

Efficacy will be evaluated by:

- reducing the number of babies crying episodes per day due to colic's during study period
- bloating reduction assessed though 3-point Likert scale

Secondary endpoint

Effectiveness will be evaluated through the collected responses during study period:

4. Change in mean number of hours of child sleep during 24 h, evaluated in a daily manner during study period through a journal
5. Change in mean number of hours of caregiver sleep during 24 h, evaluated in a daily manner during study period through a journal
6. Change in mean number of awakenings during night evaluated in a daily manner during study period through a journal

Safety will be assessed though:

3. Number of Adverse events;
4. Number of participants withdrawn due to lack of tolerability

17 INVESTIGATED MEDICAL PRODUCT

17.1 Lactacol/Lactazak

Lactacol/Lactazak® promotes lactose hydrolysis. It helps lactose digestion by reducing fermentation and gas production. Lactacol/Lactazak® should be used during each feeding during the first 3-4 months of life. After this period, lactase enzyme is usually produced by the body in sufficient quantities, and Lactacol/Lactazak® should be gradually withdrawn from feedings.

17.2 Composition of Lactacol/Lactazak

Use as a dietary supplement to a healthy diet and as an additional source of lactase enzyme.
INGREDIENTS: Sunflower oil; Lactase (Beta-galactosidase); Maltodextrin; Anti-caking agent: mono-and diglycerides of fatty acids (or E 471); Antioxidant: alpha-tocopherol (or E 307).

Route of administration: Oral route

Single dose: 0.5 ml (700 FCC ALU).

Maximum daily dose: 6 ml (8400 FCC ALU).

Lactacol/Lactazak® Characteristics

• Lactase is an enzyme derived from the fermentation of corn maltodextrin by Aspergillus oryzae
• Resistant to acidic gastric medium.
• Maintains its activity in the conditions of high pH variations.

17.2.1 Lactacol/Lactazak® Handling, Storage and Accountability Procedures:

The product will be provided by the Sponsor. Each patient will receive the necessary amount of Lactacol/Lactazak®. The product must be stored at room temperature (25°), away from heat sources, dry places and protected from light. The investigator will keep the Lactacol/Lactazak® accountability during the entire duration of the study.

17.3 Criteria for discontinuation or removal of subjects from the study:

The Investigator may withdraw a subject from the study for any of the following reasons:

i. The subject suffers from significant inter-current illness or undergoes surgery during the course of the study.

ii. The subject experiences an adverse event, and withdrawal would be in the best interest of the subject.

Details of reasons for withdrawal of subjects will be recorded and reported.

The Investigator based on the subject's medical history and health status at the moment of withdrawal/drop-out, in order to ensure the welfare of the subject, will decide the extent of the follow-up safety procedures.

18 STUDY DOCUMENTATION AND CASE REPORT FORM

For each subject enrolled, a CRF will be completed, reviewed, and signed by the Investigator.

19 STUDY MONITORING

CEBIS International will do study monitoring. CEBIS will generate appropriate Monitoring Reports, retained in the Trial Master File, for each visit performed.

20 QUALITY ASSURANCE AUDITS

The raw data generated during the study and the clinical study reports will be liable for inspection and quality audit for conformance to this protocol and all the governing SOPs by an auditor from the Quality Assurance Department of the Sponsor and Investigator.

21 CONFIDENTIALITY OF DATA

The data identifying each study subject by name will be kept confidential and will be accessible to the study personnel, Quality Assurance Auditor during audits and if necessary, to the Institutional Ethics Committee and various regulatory agencies.

22 ARCHIVES

A representative sample of the drug supplies used in the study will be retained at the Clinical Unit. All data generated in connection with this study, together with the original copy of this protocol and the clinical study report will be archived as per current versions of the applicable Standard Operating Procedures.

23 PUBLICATION POLICY

Results obtained from this study are property of the Sponsor. In case of publication, the Investigators will be informed and will be free to cooperate as Authors.

24 DEVIATIONS

All protocol deviations will be appropriately reviewed and documented in the raw data and those, which will affect the integrity of the study, will be reported in the clinical study report. For other deviations their impact on the study will be described.

25 TERMINATION OF THE STUDY

The Sponsor reserves the right to discontinue the trial at any time. Reasons for this termination will be provided to the subjects. The Investigators reserve the right to discontinue the study for safety reasons at any time.

In case the study ends early, the Sponsor must immediately notify the Competent Authorities and Ethics Committee about closing the study, within 15 days after it was stopped, with the clear explanation of the causes and presenting any existent follow-up safety measurements taken.

26 ADVERSE EVENTS

Subjects will be informed to bring to the notice of the medical personnel any adverse events that may occur during their participation in the clinical study.

A physician, either at the site of investigation or at a specialized medical unit, will do treatment of any adverse events.

All adverse events and treatment administered will be recorded in the clinical study report. Adverse events experienced by subjects will be reported as per the applicable standard operating

procedures and followed until the events have subsided. The study may be suspended or terminated depending on the seriousness of the adverse effects.

26.1 Classification method for adverse events and serious adverse events

An **adverse event/experience** (AE) is any unwarranted medical occurrence in a patient. For the purposes of this document, this is intended to include any adverse event whether device related or not.

Adverse Event: Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons whether or not related to the investigational medic al device.

NOTE 1: This includes events related to the investigational device or the comparator.
NOTE 2: This includes events related to the procedures involved (any procedure in the clinical investigation plan).
NOTE 3: For users or other persons this is restricted to events related to the investigational medical device.

Serious adverse event: adverse event that:

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in:

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function, or

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP (Clinical Investigation Plan), without serious deterioration in health, is not considered a serious adverse event.

26.2 Adverse Events Reporting

All adverse events will be recorded on the case report forms provided; a description of the event, intensity, duration, any action (e.g., treatment and follow-up tests) and the outcome should be provided along with the investigator's assessment of the relationship to the trial treatment.

Discrete episodes of chronic conditions occurring during a study period will be reported as adverse events to assess changes in frequency or severity. Adverse events will be documented in terms of a medical diagnosis (es). When this is not possible, the adverse event will be documented in terms of signs and symptoms observed by the investigator or reported by the subject at each study visit. Pre-existing conditions or signs and/or symptoms (including any which are not recognized at study entry but are recognized during the study period) present in a subject prior to the start of the study will be recorded on the Medical History form within the subject's CRF.

26.3 Notification of Serious Adverse Events

Any adverse reaction or abnormal value in the laboratory exams that is defined as Serious Adverse Events (SAEs), and which occurs during this study, will be immediately communicated by the Investigator to Pharmaunion as sponsor of the clinical study using the e-mail address: rz@p-h-u.com & mariana.dumitru@cebis-int.com to take the necessary steps in reporting to the relevant authorities

27 ETHICAL CONSIDERATIONS

27.1 Basic Principles

The study will be conducted according to the current amended version of the Declaration of Helsinki (as per 64th WMA General Assembly, Fortaleza, Brazil, October 2013), and other applicable regulatory requirements and guidelines in EU.

The investigator agrees when signing the protocol to adhere to the instructions and procedures described in it and thereby to adhere to the principles of ICH-Good Clinical Practice of the European Community.

27.2 Informed Consent

The Investigator will inform the subjects about the study through an oral presentation regarding the purpose, procedures that will be carried out, potential hazards and the rights of the subjects. All subjects will be required to understand and sign a consent form summarizing the discussion before study initiation and screening examination. The original copy of the informed consent form will be retained in the Investigator's Trial Master File.

28 ACCEPTANCE CRITERIA OF PROTOCOL DEVIATION

All protocol deviations will be appropriately reviewed and documented in the raw data and those, which will affect the integrity of the study, will be reported in the clinical study report. In addition, deviations from original pharmacokinetic and statistical evaluation plan will be justified in the clinical study report.

29 STATISTICAL METHODS

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic. Confidence intervals will be presented to one more decimal place than the raw data.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using N (number per treatment group or overall) as the denominator.

30 DEMOGRAPHICS

Demographics and baseline disease characteristics will be summarized by descriptive statistics.

Demographic data will include: gender, age, weight, height, blood pressure, pulse, temperature, respiration, BMI. Baseline disease characteristics will include: medical history and concomitant medication.

31 SAFETY ANALYSIS SET

The secondary objective of the study is to assess the safety of the Lactacol/Lactazak® used in patients with FGIDs (intestinal colic and bloating). The Safety Analysis Set (SAF) includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment they received. The Safety Analysis Set will be used for all safety analyses. For each study treatment, numbers of AEs and incidence rates will be tabulated. An event that occurred one or more times on the date of, or after, randomization will contribute one observation to the numerator of the incidence rate. The denominator of the rate will comprise all randomized subjects exposed to the study treatment. If the intensity or seriousness of the AE changes, then the overall intensity or seriousness will be the maximum intensity or seriousness of the multiple occurrences.

Serious adverse events, AEs leading to death and AEs leading to withdrawal of subjects will be tabulated for each treatment group.

32 EFFICACY ANALYSIS SET

- The primary endpoint of the study is to assess the clinical efficacy of the Lactacol/Lactazak® in alleviating the clinical symptomatology by reducing the baby crying due to colic during study period and reducing bloating
- Secondary endpoint of the study is evaluating effectiveness and safety by:

  - ✓ Change in mean number of hours of child sleep during 24 h, evaluated in a daily manner during study period through a journal
  - ✓ Change in mean number of hours of caregiver sleep during 24 h, evaluated in a daily manner during study period through a journal
  - ✓ Change in mean number of awakenings during night evaluated in a daily manner during study period through a journal
  - ✓ Number of Adverse events;
  - ✓ Number of participants withdrawn due to lack of tolerability

P values <0.05 will be considered statistically significant. Statistical analyses will be performed using IBM SPSS Statistics 20 for Windows.

33 REFERENCES

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2. https://pubmed.ncbi.nlm.nih.gov/26447441/

3. https://pubmed.ncbi.nlm.nih.gov/8965762/
4. https://www.sciencedirect.com/science/article/abs/pii/S0889855318300645?via%3Dihub
5. Lactacol/Lactazak presentation – LACTACOL/LACTAZAK drops _NEW
6. https://www.lacteeze.com.au/about-lactose-intolerance/colic-associated-with-lactose-intolerance/