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

Protocol code: CBSPH_CBS12122022/ Version 1.0/Date: November 27th, 2023

SHORT name: PACE Study

CLINICAL STUDY REPORT

Version 1.0/ July 1st, 2024

1. Signature pages for clinical study report

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Signed:

Date: 10.07.2024

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2. BACKGROUND

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
Study title	Open-Label, Prospective, Multicenter Study to Assess efficacy and safety of Lactacol/Lactazak ®, a food supplement, in intestinal colic and bloating
Protocol number	CBSPH_CBS27112023
Study Objective	**<u>Primary Objectives</u>** To assess the product efficiency by: • reducing the baby crying due to colic during study period; • reducing bloating **<u>Secondary Objective</u>** 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
Study Endpoints	Primary endpoint Efficacy was 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 was evaluated through the collected responses during study period: • 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during study period through a journal Safety was assessed though: • Number of Adverse events; • Number of participants withdrawn due to lack of tolerability
Study Setting	Private medical clinic in Bulgaria
Study Dates	First Subject In: January 23rd, 2024 Last Subject In: May 16th, 2024
Study product	Lactacol/Lactazak ®
Study Procedure	This non-interventional study will be conducted in Bulgaria in routine clinical practice by GP, paediatricians, 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.
Study Population and inclusion & exclusion criteria	**Inclusion Criteria:** • paediatric population 1-4 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
Study duration per patient	28 Days
Dosage & administration:	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.
Visits	**3 visits:** • Visit 1 - Screening and enrollment visit; • Visit 2 – Day 14 from Therapy initiation; • Visit 3 - Phone Follow-up (Day 28)
Sample size	30
Statistical methods	Continuous data were summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. The minimum and maximum was reported to the same number of decimal places as the raw data recorded in the database. The mean and median was reported to one more decimal place than the raw data recorded in the database. The SD was 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.
Concomitant Medication	All concomitant medications taken or administered in the 6 weeks before screening and during the study will be documented in the CRF.
Adverse events	Adverse events will be monitored and reported accordingly.
Regulatory Statement:	The Study has been performed according to the revised Declaration of Helsinki for biomedical research involving human subject; the rules of Good Clinical Practice (GCP) of the European Community CPMP (CPMP/ICH/135/195; ICH Topic E6);
Safety Statement	All definitions for adverse events, serious adverse event, incident, serious incident and device deficiencies are in accordance with the REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC and MDCG 2020-10/1 Safety reporting in clinical Studys of medical devices under the Regulation (EU) 2017/745.

3. LIST OF ABBREVIATIONS & DEFINITION OF TERMS

AE	:	Adverse Event
CRF	:	Case Report Form
GCP	:	Good Clinical Practice
ICF	:	Informed Consent Form
CRF	:	Case Report Form
GCP	:	Good Clinical Practice
ICH	:	International Conference on Harmonization
No	:	Number

4. ETHICAL CONDUCT OF THE STUDY

The Study was performed in Bulgaria, according to the revised Declaration of Helsinki for biomedical research involving human subject, the rules of Good Clinical Practice (GCP) of the European Community, CPMP (CPMP/ICH/135/195; ICH Topic E6. A copy after the Ethical Committee favorable opinion can be found in **Appendix 1**

4.1 SUBJECT INFORMATION AND CONSENT

All subjects provided written informed consent to participate in the Study prior to being screened. The subject information sheet detailed the procedures involved in the study (aims, methodology. potential risks, anticipated benefits) and the investigator explained these to each subject. The subject signed the consent form to indicate that the information was explained and understood. The subject was allowed time to consider the information presented before signing and dating the informed consent form to indicate that they fully understood the information, and willingly volunteered to participate in the Study. The subject was given a copy of the informed consent form for their information. One original copy of the informed consent was kept in a confidential file in the Investigators center records. A sample of the subject information sheet and consent form can be found at ***Appendix 2.***

5. INTRODUCTION

4. *The Study was conducted in Ambulatory clinic by Family Doctor (with the date when they were initiated and the date of first subject in) as presented below:*

Table 1. Study location

No	Site	Country	Investigator Name	EC Response Date	SIV (date)	FPI (date)
1	Site 001 - 8 Akademic Stefan Mladenov, Street, 1700 Sofia	Bulgaria	Dr. Zlatka Etropolska	NA	January 19th, 2024	January 23rd, 2024

5.1. STUDY METHODOLOGY

This non-interventional study was conducted by family doctors/Paediatricians in Bulgaria in routine clinical practice. Data were collected prospectively. Lactacol/Lactazak® was administered in accordance with approved leaflet. Patient demographic data were 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 were 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 were recorded into patient file.

Subjects attended 3 visits during the study according to below table:

Table 2. 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**

6. 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.

7. Statistical Analysis

7.1. SUBJECTS DISPOSITION

Table 3. Subjects Disposition by Site and Investigators

No	Site	Country	Investigator Name	FPI (date)	Patients Enrolled	LPLV
1	Site 001- 8 Akademic Stefan Mladenov, Street, 1700 Sofia	Bulgaria	Dr. Zlatka Etropolska	January 23rd, 2024	30	June 13th, 2024

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Table 4. Demographic Data

		Lactacol/Lactazak ® N=30
Age (months)	Mean ± SD	1.8 (±1.01)
	Median (Min-Max)	2.0 (1-4)
Gender (n,%)	Female	15 (50%)
	Male	15 (50%)
APGAR score	Mean ± SD	7.9 (±0.78)
	Median (Min-Max)	8.0 (5-9)
Type of birth method (n,%)	Partus normalis	13 (43%)
	Sectio Caesarea	17 (57%)
Environment (n,%)	Rural	25 (83%)
	Urban	5 (17%)

5. *Table 4. Physical Examination*

Lactacol/Lactazak ®

N=30

		D0	D14	p-value
Weight (Kg)	Mean	4.91	5.46	<0.001
	SD	1.30	1.29	
	Median	4.57	5.30	
	Min	2.93	3.47	
	Max	7.15	7.8	
Height (cm)	Mean	54.72	55.45	0.0001
	SD	4.17	3.95	
	Median	54.00	54.50	
	Min	48	49	
	Max	64	64	
Body Mass Index	Mean	16.19	17.52	<0.001
	SD	2.30	2.09	
	Median	15.85	17.40	
	Min	12.2	13.9	
	Max	21.3	22.5	
Temperature (°C)	Mean	36.67	36.64	0.680
	SD	0.26	0.27	
	Median	36.75	36.65	
	Min	36.2	36.2	
	Max	37.1	37.1	
Heart rate (beats/min)	Mean	97.53	94.40	0.221
	SD	4.80	14.59	
	Median	97.50	95.50	
	Min	90	30	
	Max	108	134	
Breathing rate (resp/min)	Mean	38.50	38.27	0.922
	SD	4.88	11.51	
	Median	39.00	36.00	
	Min	30	30	
	Max	48	94	
Systolic blood pressure (mmHg)	Mean	65.73	66.47	0.666
	SD	7.23	5.91	
	Median	65.00	65.00	
	Min	50	55	
	Max	80	75	
Diastolic blood pressure (mmHg)	Mean	42.67	40.00	0.036
	SD	5.53	5.41	
	Median	45.00	40.00	
	Min	35	30	
	Max	55	55	
Abdominal girth	Mean	38.78	37.83	0.0005
	SD	3.28	2.84	
	Median	38.00	37.75	
	Min	34	34	
	Max	46	44	

6. Treatment adherence

	Lactacol/Lactazak ® N=30
Subjects that took at least 80% of the investigational product	30 (100%)

7. EFFICACY RESULTS

1. Reducing the number of babies crying episodes per day due to colic's during study period

Table 7. Number of babies crying episodes per day due to colic

Time	N	Mean	Median	Std. Deviation	Minimum	Maximum
D0	30	5.50	5.50	2.19	2	11
D01	30	5.40	5.00	1.75	2	10
D02	30	4.33	4.00	1.32	2	8
D03	30	3.57	4.00	1.04	2	6
D04	30	3.23	3.00	.86	2	5
D05	30	3.00	3.00	.87	1	4
D06	30	2.47	2.00	.97	0	4
D07	30	2.07	2.00	.78	1	4
D08	30	2.17	2.00	.91	0	4
D09	30	1.83	2.00	1.09	0	5
D10	30	1.47	1.00	1.25	0	5
D11	29	.97	1.00	1.02	0	4
D12	29	.93	1.00	1.07	0	4
D13	29	.52	.00	.87	0	3
D14	29	.41	.00	.78	0	3
D28	30	.60	1.00	.67	0	3

Table 8. Multiple Comparisons

(I) Time	(J) Time	Mean Difference (I-J)	p-value
D01	D0	-.100	1.000
D02	D0	-1.167*	.001
D03	D0	-1.933*	<.001
D04	D0	-2.267*	<.001
D05	D0	-2.500*	<.001
D06	D0	-3.033*	<.001
D07	D0	-3.433*	<.001
D08	D0	-3.333*	<.001
D09	D0	-3.667*	<.001
D10	D0	-4.033*	<.001
D11	D0	-4.534*	<.001
D12	D0	-4.569*	<.001
D13	D0	-4.983*	<.001
D14	D0	-5.086*	<.001
D28	D0	-4.900*	<.001

*. The mean difference is significant at the 0.05 level.

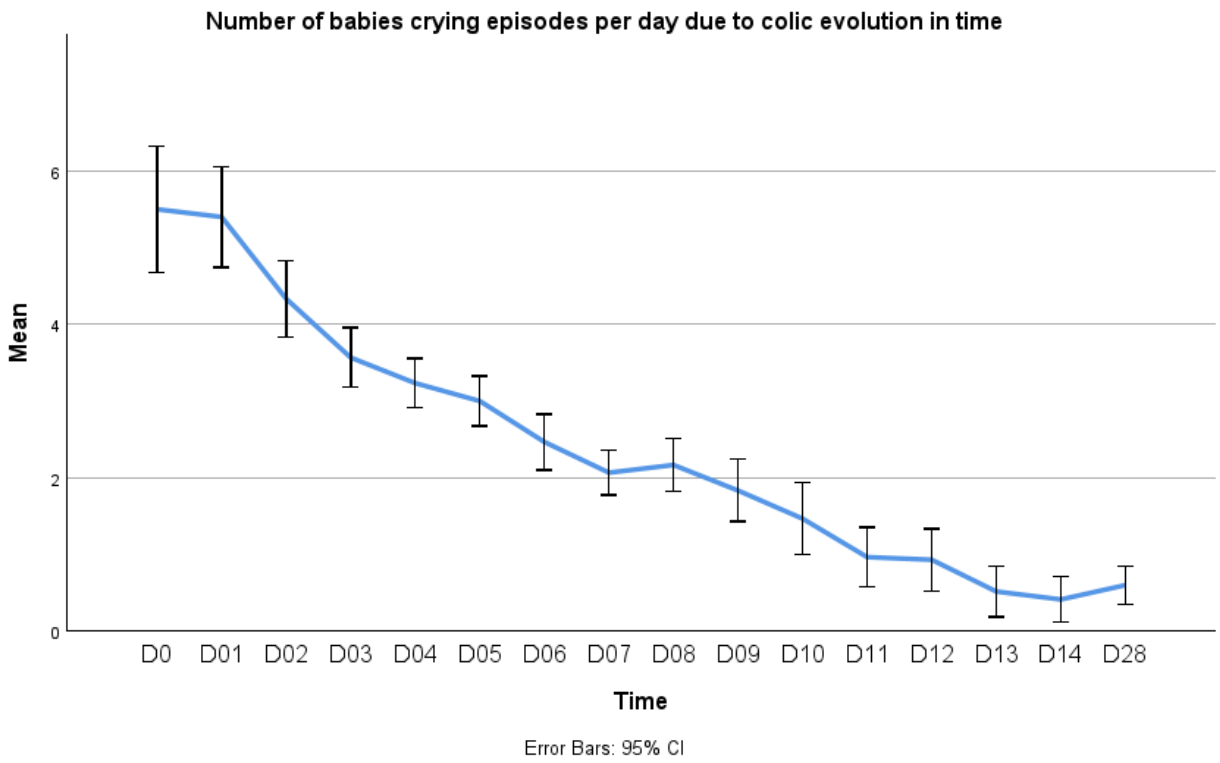


Figure 1. Number of babies crying episodes per day due to colic (Mean Value)

1.2. Bloating reduction assessed though 3-point Likert scale

Table 9. Bloating evaluation

Time	N	Mean	Median	Std. Deviation	Minimum	Maximum
D0	30	2.50	3.00	.57	1	3
D01	30	2.33	2.00	.55	1	3
D02	30	2.07	2.00	.45	1	3
D03	30	1.80	2.00	.41	1	2
D04	30	1.77	2.00	.43	1	2
D05	30	1.50	1.50	.51	1	2
D06	30	1.33	1.00	.48	1	2
D07	30	1.23	1.00	.43	1	2
D08	30	1.13	1.00	.35	1	2
D09	30	1.23	1.00	.50	1	3
D10	30	1.23	1.00	.50	1	3
D11	29	1.03	1.00	.19	1	2
D12	29	1.10	1.00	.31	1	2
D13	29	1.07	1.00	.26	1	2
D14	29	1.07	1.00	.26	1	2
D28	30	1.20	1.00	.41	1	2

Table 10. Multiple Comparisons

(I) Time	(J) Time	Mean Difference (I-J)	p-value
D01	D0	-.167	.699
D02	D0	-.433*	.001
D03	D0	-.700*	<.001
D04	D0	-.733*	<.001
D05	D0	-1.000*	<.001
D06	D0	-1.167*	<.001
D07	D0	-1.267*	<.001
D08	D0	-1.367*	<.001
D09	D0	-1.267*	<.001
D10	D0	-1.267*	<.001
D11	D0	-1.466*	<.001
D12	D0	-1.397*	<.001
D13	D0	-1.431*	<.001
D14	D0	-1.431*	<.001
D28	D0	-1.300*	<.001

*. The mean difference is significant at the 0.05 level.

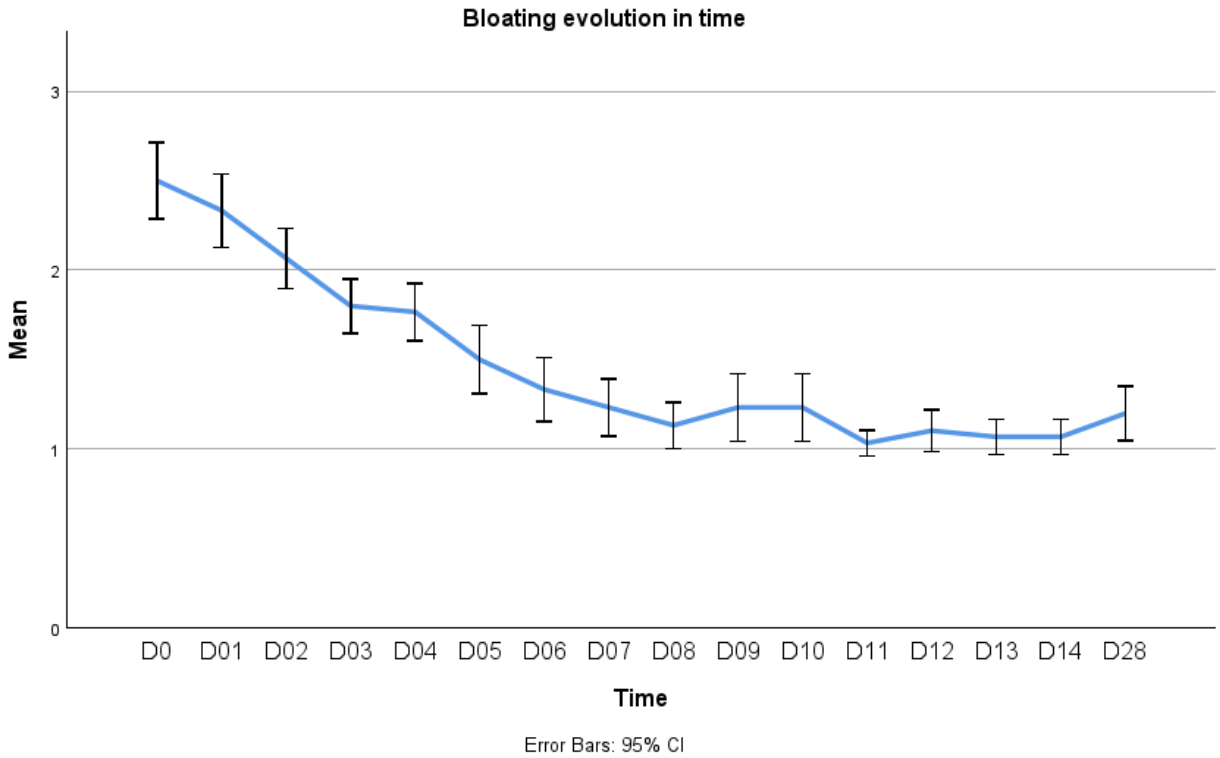


Fig.2. Bloating Evolution

Change in mean number of hours of child sleep during 24 h, evaluated in a daily manner during study period through a journal

Table 11. Number of hours of child sleep during 24 h

Time	N	Mean	Median	Std. Deviation	Minimum	Maximum
D0	30	10.00	10.00	2.27	3	14
D01	30	10.57	10.00	2.27	4	15
D02	30	11.30	11.00	1.90	7	15
D03	30	12.23	12.00	1.76	8	15
D04	30	12.93	13.00	1.53	10	15
D05	30	13.17	13.00	1.74	10	16
D06	30	13.90	14.50	1.83	10	16
D07	30	14.20	14.00	1.54	10	16
D08	30	14.27	14.00	1.28	11	17
D09	30	14.50	15.00	1.57	10	18
D10	30	14.70	15.00	1.82	8	18
D11	29	14.97	15.00	1.40	12	17
D12	29	14.86	15.00	1.30	12	17
D13	29	15.00	15.00	1.56	10	18
D14	29	15.38	15.00	1.08	14	18
D28	30	15.10	15.00	1.32	12	18

Table 12. Multiple Comparisons

(I) Time	(J) Time	Mean Difference (I-J)	p-value
D01	D0	.567	.840
D02	D0	1.300*	.031
D03	D0	2.233*	<.001
D04	D0	2.933*	<.001
D05	D0	3.167*	<.001
D06	D0	3.900*	<.001
D07	D0	4.200*	<.001
D08	D0	4.267*	<.001
D09	D0	4.500*	<.001
D10	D0	4.700*	<.001
D11	D0	4.966*	<.001
D12	D0	4.862*	<.001
D13	D0	5.000*	<.001
D14	D0	5.379*	<.001
D28	D0	5.100*	<.001

*. The mean difference is significant at the 0.05 level.

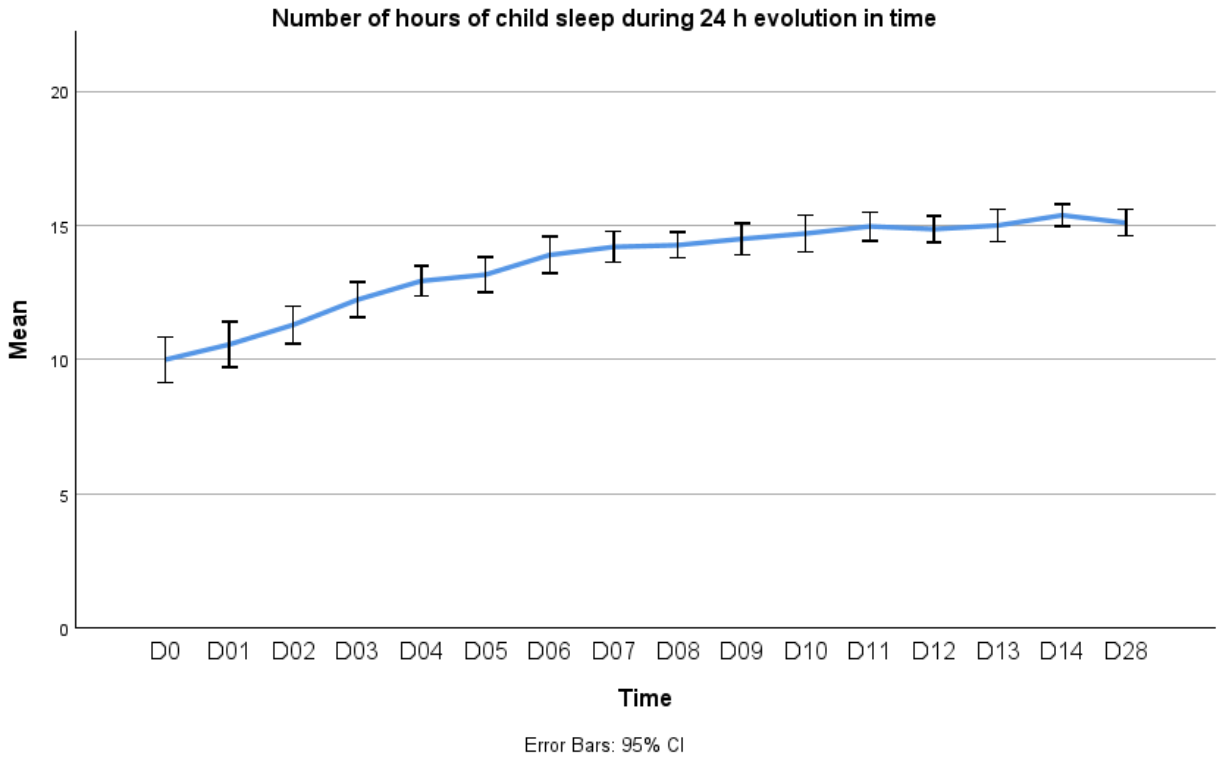


Fig.3. Number of Hours of child sleep during 24h

Change in mean number of hours of caregiver sleep during 24 h, evaluated in a daily manner during study period through a journal

Table 13. Number of hours of caregiver sleep during 24 h

Time	N	Mean	Median	Std. Deviation	Minimum	Maximum
D0	30	4.53	4.50	1.33	2	7
D01	30	4.57	4.50	.90	3	6
D02	30	4.93	5.00	.94	4	7
D03	30	5.37	5.00	.81	4	7
D04	30	5.33	5.50	.84	4	7
D05	30	5.63	6.00	1.03	4	8
D06	30	5.87	6.00	.94	4	7
D07	30	6.03	6.00	.93	4	7
D08	30	6.03	6.00	1.03	4	8
D09	30	6.23	6.00	.82	5	8
D10	30	6.07	6.00	.98	3	8
D11	29	6.55	7.00	.78	5	8
D12	29	6.34	6.00	.97	5	8
D13	29	6.59	7.00	.87	5	8
D14	29	6.66	7.00	.90	5	8
D28	30	6.60	7.00	1.22	2	8

Table 14. Multiple Comparisons

(I) Time	(J) Time	Mean Difference (I-J)	p-value
D01	D0	.033	1.000
D02	D0	.400	.627
D03	D0	.833*	.011
D04	D0	.800*	.017
D05	D0	1.100*	<.001
D06	D0	1.333*	<.001
D07	D0	1.500*	<.001
D08	D0	1.500*	<.001
D09	D0	1.700*	<.001
D10	D0	1.533*	<.001
D11	D0	2.018*	<.001
D12	D0	1.811*	<.001
D13	D0	2.053*	<.001
D14	D0	2.122*	<.001
D28	D0	2.067*	<.001

*. The mean difference is significant at the 0.05 level.

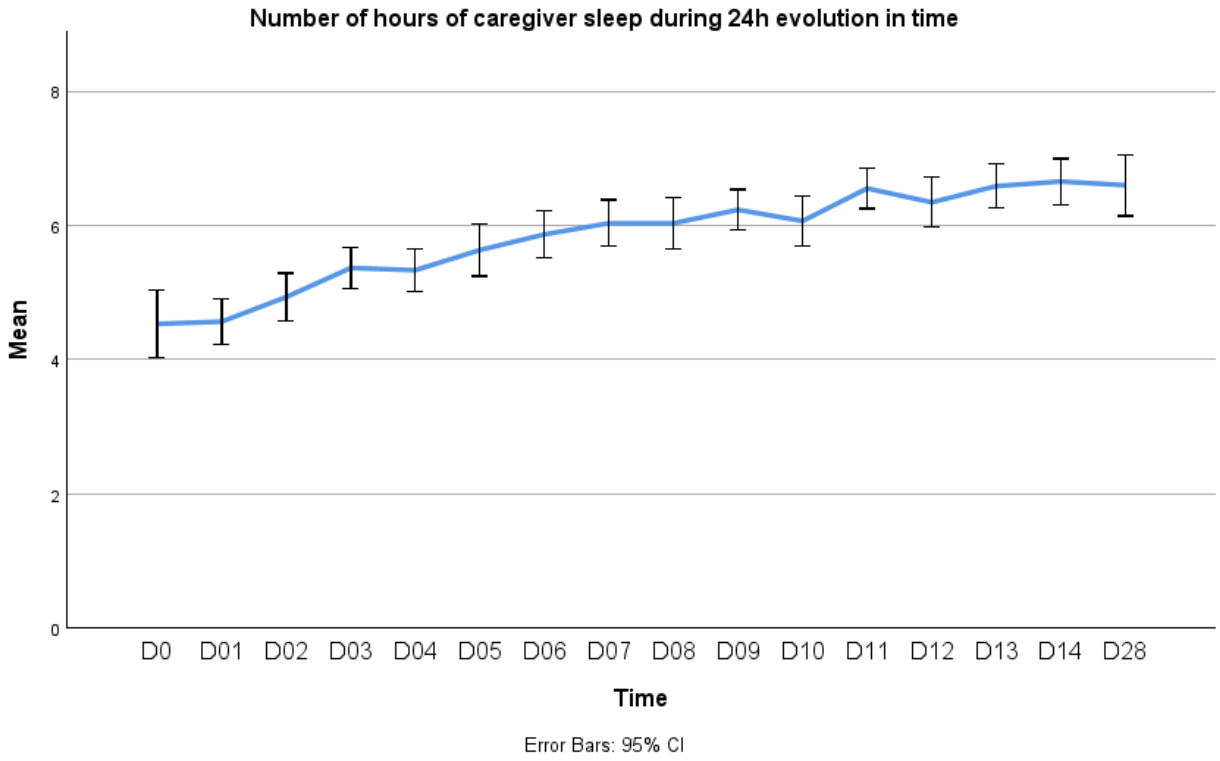


Fig.3. Number of Hours of caregiver sleep during 24h

Change in mean number of awakenings during night evaluated in a daily manner during

Table 15. Number of awakenings during night

Time	N	Mean	Median	Std. Deviation	Minimum	Maximum
D0	30	3.93	4.00	1.17	2	7
D01	30	3.87	4.00	1.11	2	6
D02	30	3.50	3.00	.90	2	6
D03	30	3.33	3.00	.88	2	5
D04	30	2.93	3.00	.78	2	4
D05	30	2.73	3.00	.78	2	4
D06	30	2.63	2.00	.85	2	4
D07	30	2.47	2.00	.86	1	4
D08	30	2.40	2.00	.86	1	4
D09	30	2.27	2.00	.64	1	4
D10	30	2.37	2.00	.96	1	5
D11	29	2.07	2.00	.84	1	4
D12	29	2.10	2.00	.72	1	4
D13	29	1.90	2.00	.67	1	4
D14	29	1.59	1.00	.73	1	4
D28	30	1.83	2.00	1.09	1	6

Table 16. Multiple Comparisons

(I) Time	(J) Time	Mean Difference (I-J)	p-value
D01	D0	-.067	1.000
D02	D0	-.433	.399
D03	D0	-.600	.085
D04	D0	-1.000*	<.001
D05	D0	-1.200*	<.001
D06	D0	-1.300*	<.001
D07	D0	-1.467*	<.001
D08	D0	-1.533*	<.001
D09	D0	-1.667*	<.001
D10	D0	-1.567*	<.001
D11	D0	-1.864*	<.001
D12	D0	-1.830*	<.001
D13	D0	-2.037*	<.001
D14	D0	-2.347*	<.001
D28	D0	-2.100*	<.001

*. The mean difference is significant at the 0.05 level.

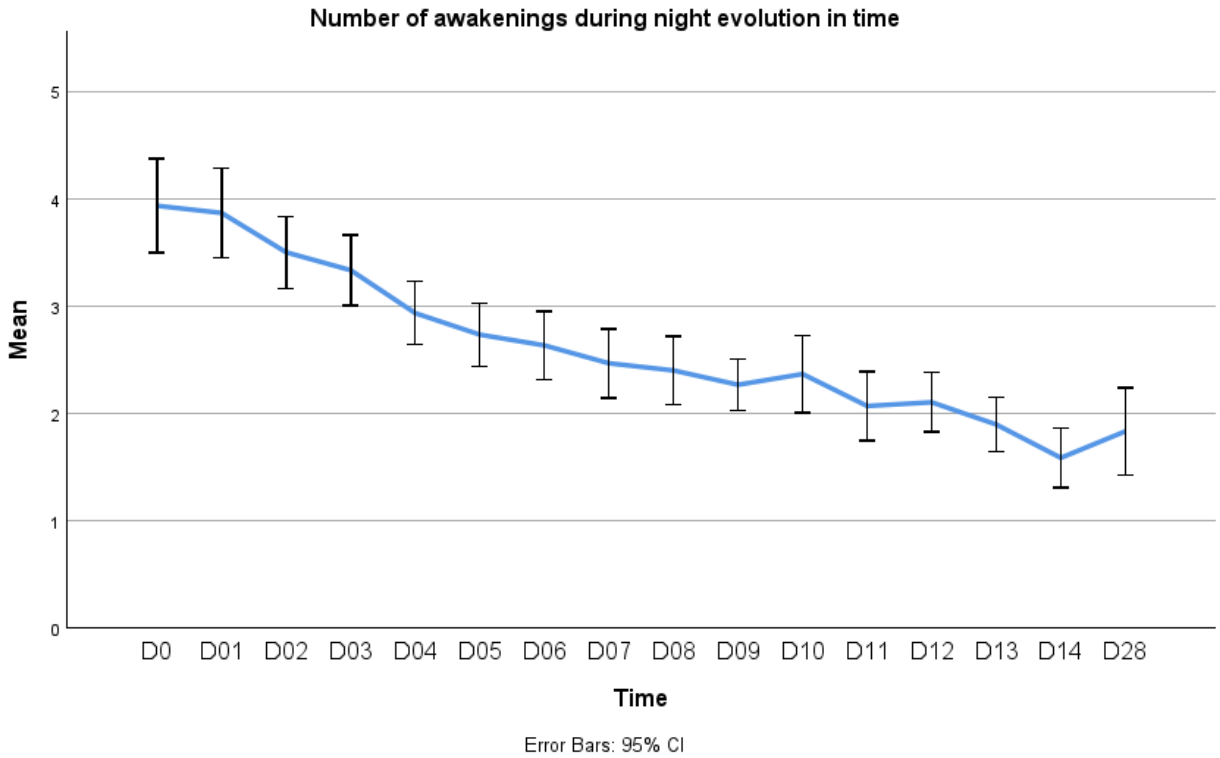


Fig.4. Number of awakenings during night

8. RESULTS

Data of 30 subjects selected according to study protocol inclusion criteria and exclusion criteria. Data belonging to the subjects includes information about their journey under the post marketing clinical follow-up from Visit 1(Day 0) to Visit 3 (Day 28), collecting the data necessary for efficacy and safety evaluation.

In Table 4, below are presented the demographics and baseline characteristics of the subjects. there were included according to inclusion & exclusion criteria 15 female participants, and 15 % of male subjects with a mean age of 1.5 (±1.01) months, the youngest participant was 1 month, while the eldest was 4 months.

Table 4. Demographic Data

		Lactacol/Lactazak ® N=30
Age (months)	Mean ± SD	1.8 (±1.01)
	Median (Min-Max)	2.0 (1-4)
Gender (n,%)	Female	15 (50%)
	Male	15 (50%)
APGAR score	Mean ± SD	7.9 (±0.78)
	Median (Min-Max)	8.0 (5-9)
Type of birth method (n,%)	Partus normalis	13 (43%)
	Sectio Caesarea	17 (57%)
Environment (n,%)	Rural	25 (83%)
	Urban	5 (17%)

8.1. Efficacy Results

8.1. 1. Reducing the number of babies crying episodes per day due to colic's during study period

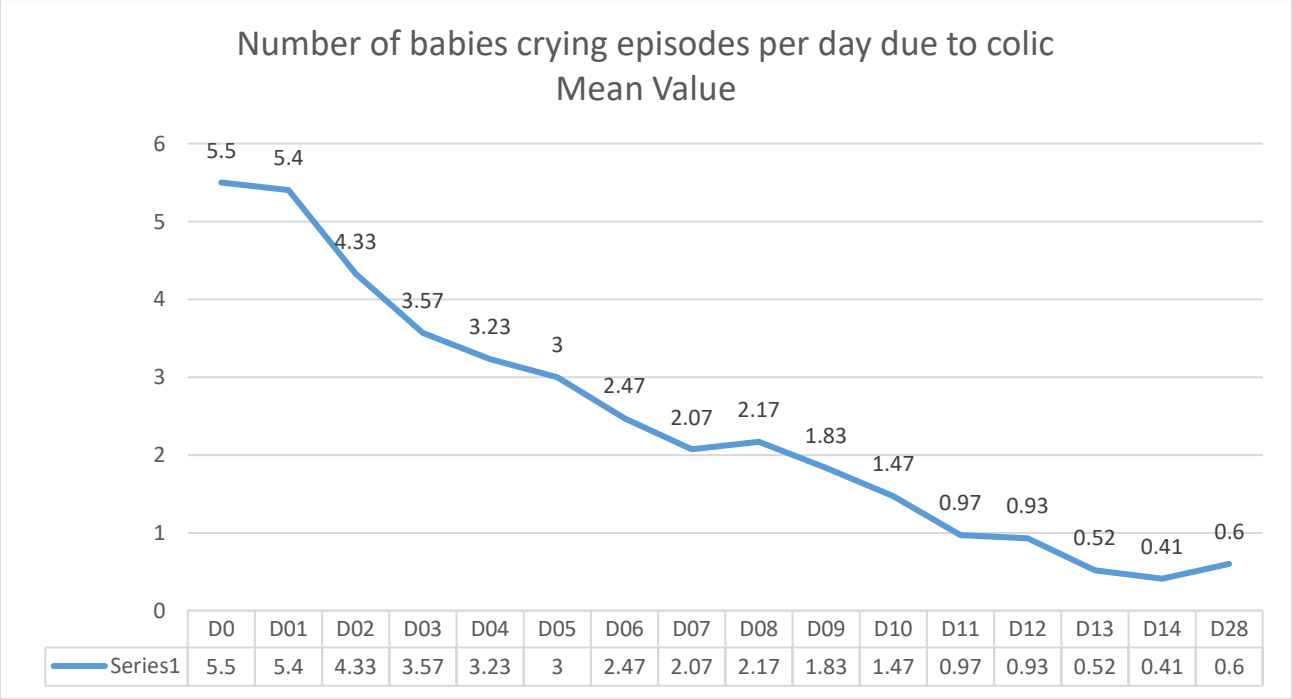
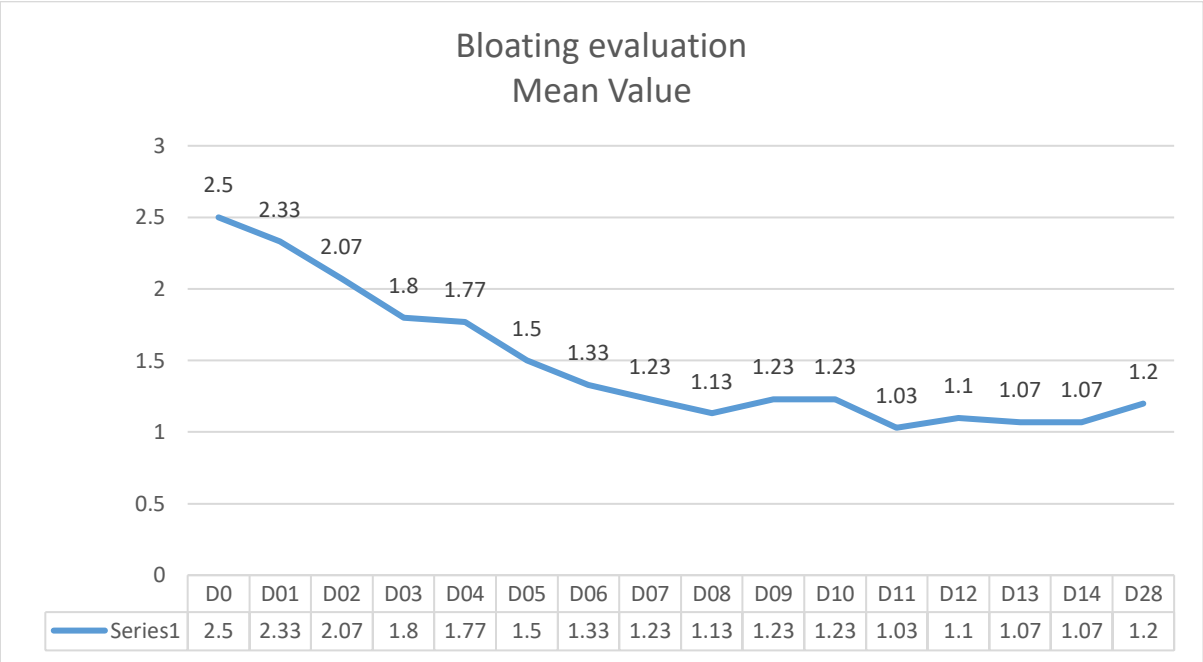


Fig. 5. Number of babies crying episodes per day due to colic Mean Value

- The Mean number of babies crying episodes per day due to colic's at Day 0 was 5.5
- At the end of treatment period, at Day 14, the mean number of babies crying episodes per day due to colic's was 0.41
- Starting with Day 3 of study treatment, a statistically significant (p=0.001) improvement in terms of number of babies crying episodes per day, was registered throughout Day 28, as presented in Table 8 above.

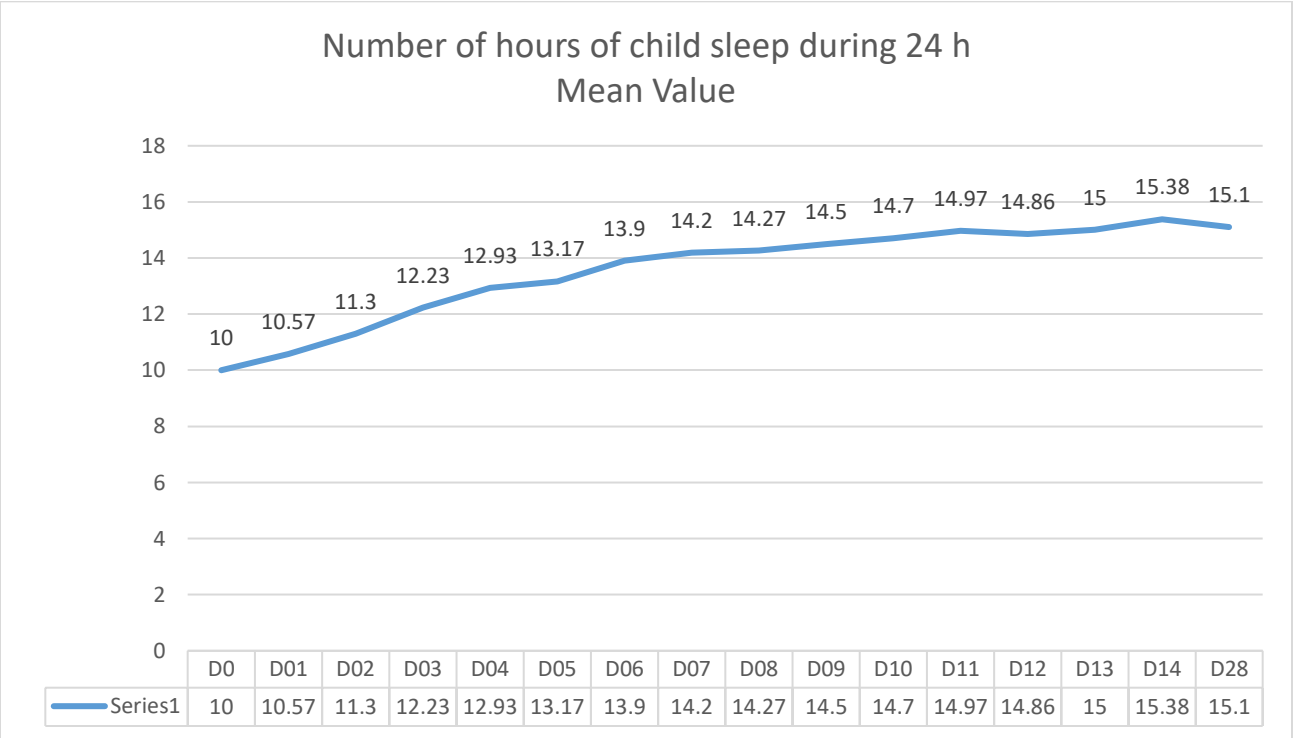
1.3. Bloating reduction assessed though 3-point Likert scale



	D0	D01	D02	D03	D04	D05	D06	D07	D08	D09	D10	D11	D12	D13	D14	D28
Series1	2.5	2.33	2.07	1.8	1.77	1.5	1.33	1.23	1.13	1.23	1.23	1.03	1.1	1.07	1.07	1.2

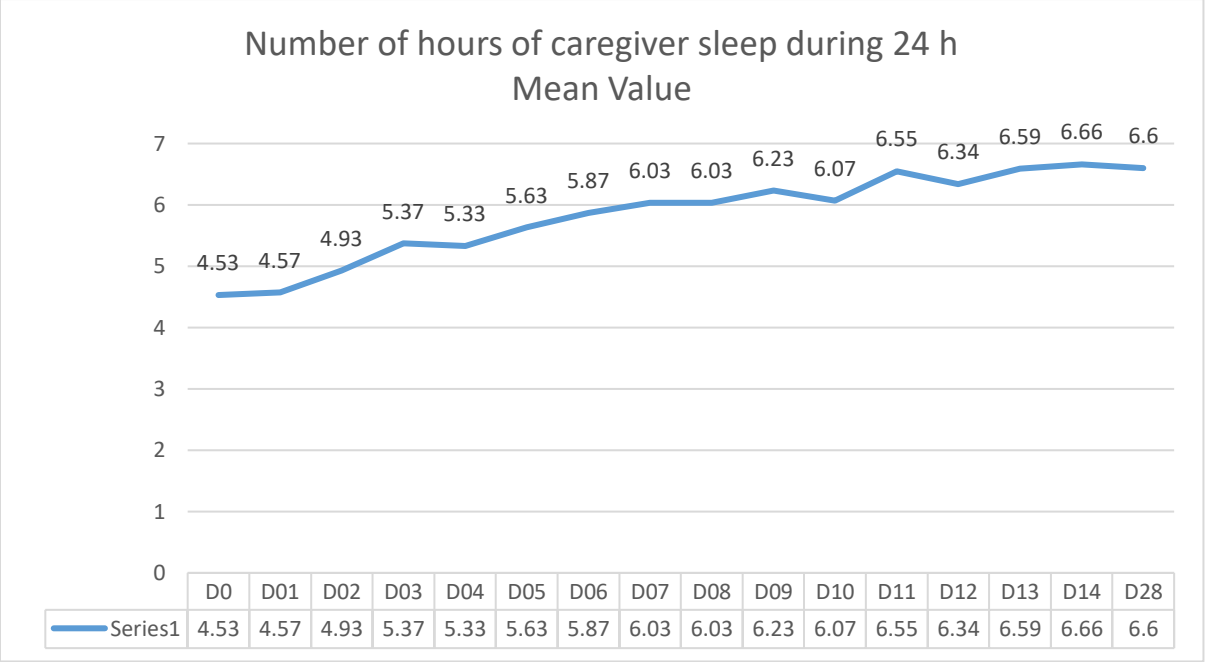
- Bloating evaluation was done using a **3-point Likert scale, where 1 was None, 2 = Moderately, 3 - Intense**
- The Mean Value evaluation of bloating symptom at Day 0 was 2.5
- At the end of treatment period, at Day 14, the mean value evaluation of bloating symptom was 1.07
- Starting with Day 2 of study treatment, a statistically significant (p=0.001) improvement in terms of number of babies crying episodes per day, was registered throughout Day 28, as presented in Table 10 above.

Change in mean number of hours of child sleep during 24 h, evaluated in a daily manner during study period through a journal



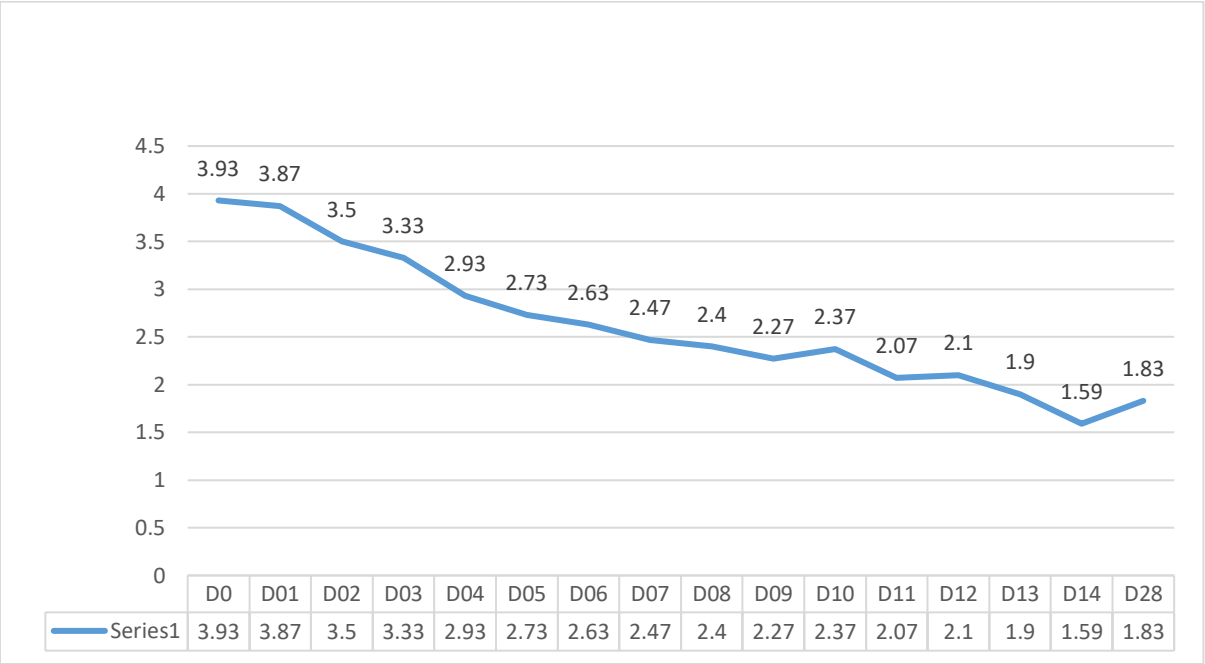
- The mean number of hours of child sleep during 24 h, due to colic's at Day 0 was 10 h
- At the end of treatment period, at Day 14, the mean number of hours of child sleep during 24 h was 15.38
- Starting with Day 2 of study treatment, a statistically significant (p=0.031) improvement in terms of number of hours of child sleep during 24 h, was registered throughout Day 28, as presented in Table 12 above.

Change in mean number of hours of caregiver sleep during 24 h, evaluated in a daily manner during study period through a journal



- The mean number of hours of caregiver sleep during 24 h, due to infant colic's at Day 0 was 4.53 h
- At the end of treatment period, at Day 14, the mean number of hours of caregiver sleep during 24 h was 6.66 hours
- Starting with Day 3 of study treatment, a statistically significant (p=0.011) improvement in terms of number of hours of child sleep during 24 h, was registered throughout Day 28, as presented in Table 14 above.

Change in mean number of awakenings during night evaluated in a daily manner during



- The mean number of **awakenings during night**, due to infant colic's at Day 0 was 3.93
- At the end of treatment period, at Day 14, the mean number of **awakenings during night** was 1.59
- Starting with Day 4 of study treatment, a statistically significant (p=0.001) improvement in terms of number of hours of child sleep during 24 h, was registered throughout Day 28, as presented in Table 16 above.

9. SAFETY RESULTS

1.1 Adverse events

One adverse event and one serious adverse event occurred during the study but they were not related to the investigational treatment.

Adverse Event	Onsed Date	End Date	Severity	Causality Assessment	Outcome	Please specify which sequelae the patient did experience	Remedial actions	Is Event Serious?
Hopsitalization due to bronchiolitis	19.02.2024	24.02.2024	Moderate	Not related	Recovered without sequelae	No	Permanent stop	Yes
Rhinopharingitis	26.04.2024	03.05.2024	Mild	Not related	Recovered without sequelae	No	None	No

6.66% (2) of the participants presented adverse events, but not related to study product
93.34% (28) participants presented no adverse events

There was no product deficiency reported during study period.

1.1 **Participants withdrawn due to lack of tolerability**

No participants withdrawn due to lack of tolerability.

10. CONCLUSIONS

For this report it has been analyzed data of 30 subjects selected according to study protocol inclusion criteria and exclusion criteria. Data belonging to the subjects includes information about their journey under the post marketing clinical follow-up from Visit 1(Day 0) to Visit 3 (Day 28), collecting the data necessary for efficacy and safety evaluation.

Demographic Data

In Table 4 are presented the demographics and baseline characteristics of the subjects. there were included according to inclusion & exclusion criteria 15 female participants, and 15 % of male subjects with a mean age of 1.5 (±1.01) months, the youngest participant was 1 month, while the eldest was 4 months .

EFFICACY RESULTS:

Lactacol/Lactazak ® showed efficacy by:

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

Also, Lactacol/Lactazak showed effectiveness by:

1. Increasing the number of hours of child sleep during 24 h, evaluated in a daily manner during study period through a journal
2. Increasing number of hours of caregiver sleep during 24 h, evaluated in a daily manner during study period through a journal
3. Reducing the number of awakenings during night evaluated in a daily manner during study period through a journal

SAFETY RESULTS:

Lactacol/Lactazak ® has a good safety profile and no adverse events were registered during the study related to product administration.

During study period, no quality complaints related to device deficiency were reported. No subjects discontinued treatment due to adverse events related to product administration.

LIST OF APPENDIXES:

Appendix 1 – EC Favorable opinion

Appendix 2 - Subject information sheet and consent form template

REFERENCES

- Product leaflet;