Clinical trial results:
The Influence of Polyvalent Mechanical Bacterial Lysate (ISMIGEN®) on Clinical Course of Asthma and Related Immunological parameters in Asthmatic Children (EOLIA Study): Randomized, Double Blind, Placebo-Controlled, Multicentre, Parallel-Group Study

Summary

EudraCT number	2013-000737-12
Trial protocol	PL
Global end of trial date	08 June 2015

Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021
Summary attachment (see zip file)	EOLIA-Clinical trial report synopsis-final version-09-Jun-2016 (EOLIA Report Synopsis - Final Version.pdf)

Trial information

Trial identification

Sponsor protocol code	LPI-1201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02541331
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lallemand Pharma AG
Sponsor organisation address	Via Selva, 2, MASSAGNO, Switzerland, 6900
Public contact	Dr Frédéric DURMONT, Lallemand Pharma AG, 41 919 804 613, officelp@lallemand.com
Scientific contact	Dr Bernard GOUT, BG ClinicalS, 33 682 578 160, b.gout@bgclinicals.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate in IgE-dependent allergic asthmatic children the efficacy of Ismigen® versus Placebo to improve the asthma control level measured by the ACT/P-ACT (Asthma Control Test/ Paediatric Asthma Control Test) score after a 3-month treatment as add-on to routine asthma therapy.

Protection of trial subjects:

Study performed in compliance with GCP
Patients were followed according to routine practices for paediatric asthma.
To minimize pain induced by blood drawing procedures, an anaesthetic patch was systematically proposed to the patients participating in the biological assessments.
Moreover, the volume of blood draws was strickly in compliance with the European Paediatric Regulation.

Background therapy:

All patients were treated with Inhaled Cortico Steroid (ICS)+ Long Acting Beta-2 Agonist (LABA) or ICS + Short Acting Beta-2 Agonist (SABA) prn for asthma attacks.

Evidence for comparator:

No comparator. The design of this randomised trial was placebo controlled.

Actual start date of recruitment	14 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 152
Worldwide total number of subjects	152
EEA total number of subjects	152

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	110
Adolescents (12-17 years)	42
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients were recruted in Poland between 14/07/2014 and 26/09/2014. Four investigation sites were involved: one site at the University Children Hospital of Lublin and three in private clinical practices (site 2- Lublin, Site 3- Chelm, Site 4- Zawadzkie). All patients were screened from the general paediatric allergic asthma population.

Pre-assignment

Screening details:

The screening of the patients was performed during routine medical follow up for asthmatic children.

Period 1

Period 1 title	Screening/inclusion
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Blinding implementation details:

Allocation of product to the patients was performed according to a randomisation list.
Placebo and active were indistinguishable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ismigen

Arm description:

Active

Arm type	Experimental
Investigational medicinal product name	Polyvalent Mechanical Bacterial Lysate (PMBL)
Investigational medicinal product code	J07AX
Other name	Ismigen
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

The study treatment was administered sublingually for a period of three months.
The first ten days of each month, one tablet per day was given at home, in the morning between 6.00 and 9.00 am before any feeding. The patients were instructed to keep the preparation under the tongue for at least 5-7 minutes to ensure prolonged contact with the sublingual mucosae.

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	N/A
Other name	
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

The study treatment (Placebo) was administered sublingually for a period of three months.
The first ten days of each month, one tablet per day was given at home, in the morning between 6.00 and 9.00 am before any feeding. The patients were instructed to keep the preparation under the tongue for at least 5-7 minutes to ensure prolonged contact with the sublingual mucosae.

Number of subjects in period 1	Ismigen	Placebo
Started	75	77
Completed	75	77

Period 2	
Period 2 title	Biology visit (V2)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Blinding implementation details:

same as in previous period. Note that only a subset of voluntary patients was involved in the biology subset (21 Ismigen and 28 Placebo). Due to impossibility to create a period with this lowest patients number as compared to period 3, period 2 has been entered as concerning the whole cohorte. The data are reported in the end point section with the number of patients who performed the visit.

Arms	
Are arms mutually exclusive?	Yes
Arm title	Ismigen

Arm description:

Active

Arm type	Experimental
Investigational medicinal product name	Polyvalent Mechanical Bacterial Lysate (PMBL)
Investigational medicinal product code	J07AX
Other name	Ismigen
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

The study treatment was administered sublingually for a period of three months.
The first ten days of each month, one tablet per day was given at home, in the morning between 6.00 and 9.00 am before any feeding. The patients were instructed to keep the preparation under the tongue for at least 5-7 minutes to ensure prolonged contact with the sublingual mucosae.

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	N/A
Other name	
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

The study treatment (Placebo) was administered sublingually for a period of three months.
The first ten days of each month, one tablet per day was given at home, in the morning between 6.00 and 9.00 am before any feeding. The patients were instructed to keep the preparation under the tongue for at least 5-7 minutes to ensure prolonged contact with the sublingual mucosae.

Number of subjects in period 2	Ismigen	Placebo
Started	75	77
Completed	75	76
Not completed	0	1
Consent withdrawn by subject	-	1

Period 3

Period 3 title	End of Treatment V3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Same as previous period

Arms

Are arms mutually exclusive?	Yes
Arm title	Ismigen

Arm description:

Active

Arm type	Experimental
Investigational medicinal product name	Polyvalent Mechanical Bacterial Lysate (PMBL)
Investigational medicinal product code	J07AX
Other name	Ismigen
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

The study treatment was administered sublingually for a period of three months.
The first ten days of each month, one tablet per day was given at home, in the morning between 6.00 and 9.00 am before any feeding. The patients were instructed to keep the preparation under the tongue for at least 5-7 minutes to ensure prolonged contact with the sublingual mucosae.

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	N/A
Other name	
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

The study treatment (Placebo) was administered sublingually for a period of three months.
The first ten days of each month, one tablet per day was given at home, in the morning between 6.00 and 9.00 am before any feeding. The patients were instructed to keep the preparation under the tongue for at least 5-7 minutes to ensure prolonged contact with the sublingual mucosae.

Number of subjects in period 3	Ismigen	Placebo
Started	75	76
Completed	72	76
Not completed	3	0
Consent withdrawn by subject	1	-
Adverse event, non-fatal	2	-

Period 4

Period 4 title	Follow up 3 months V4
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Same as previous period

Arms

Are arms mutually exclusive?	Yes
Arm title	Ismigen

Arm description:

Active

Arm type	Experimental
Investigational medicinal product name	Polyvalent Mechanical Bacterial Lysate (PMBL)
Investigational medicinal product code	J07AX
Other name	Ismigen
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

The study treatment was administered sublingually for a period of three months.
The first ten days of each month, one tablet per day was given at home, in the morning between 6.00 and 9.00 am before any feeding. The patients were instructed to keep the preparation under the tongue for at least 5-7 minutes to ensure prolonged contact with the sublingual mucosae.

Arm title	Placebo

Arm description:	
Placebo	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	N/A
Other name	
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

The study treatment (Placebo) was administered sublingually for a period of three months.
The first ten days of each month, one tablet per day was given at home, in the morning between 6.00 and 9.00 am before any feeding. The patients were instructed to keep the preparation under the tongue for at least 5-7 minutes to ensure prolonged contact with the sublingual mucosae.

Number of subjects in period 4	Ismigen	Placebo
Started	72	76
Completed	71	75
Not completed	1	1
Prohibited concomitant medication	1	-
Protocol deviation	-	1

Period 5

Period 5 title	Follow up 6 months V5
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Blinding implementation details:

Same as previous period

Arms

Are arms mutually exclusive?	Yes
Arm title	Ismigen

Arm description:

Active

Arm type	Experimental
Investigational medicinal product name	Polyvalent Mechanical Bacterial Lysate (PMBL)
Investigational medicinal product code	J07AX
Other name	Ismigen
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

The study treatment was administered sublingually for a period of three months.
The first ten days of each month, one tablet per day was given at home, in the morning between 6.00 and 9.00 am before any feeding. The patients were instructed to keep the preparation under the tongue

for at least 5-7 minutes to ensure prolonged contact with the sublingual mucosae.

Arm title	Placebo
Arm description: Placebo	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	N/A
Other name	
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

The study treatment (Placebo) was administered sublingually for a period of three months.
The first ten days of each month, one tablet per day was given at home, in the morning between 6.00 and 9.00 am before any feeding. The patients were instructed to keep the preparation under the tongue for at least 5-7 minutes to ensure prolonged contact with the sublingual mucosae.

Number of subjects in period 5	Ismigen	Placebo
Started	71	75
Completed	70	75
Not completed	1	0
Prohibited concomitat medication	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ismigen
Reporting group description: Active	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	Ismigen	Placebo	Total
Number of subjects	75	77	152
Age categorical			
The study was performed in a population of allergic asthmatic children of both genders aged 6 to 16 years with uncontrolled or partly controlled asthma (ACT/P-ACT score ≤ 19).			
Units: Subjects			
Children 6-11 years	56	54	110
Adolescents 12-16 years	19	23	42
Age continuous			
Age (years) at baseline			
Units: years			
arithmetic mean	9.4	9.8	
standard deviation	± 2.7	± 2.6	-
Gender categorical			
Gender at baseline (M/F)			
Units: Subjects			
Female	26	20	46
Male	49	57	106
ACT/P-ACT			
asthma control test and paediatric asthma control test			
Units: arbitrary			
arithmetic mean			
standard deviation	±	±	-
Respiratory infections			
The mean number of respiratory infection per patient during the past 12 months was calculated and referred to baseline characteristic.			
Units: arbitrary			
arithmetic mean			
standard deviation	±	±	-
PAQLQ score			
2 questionnaires available: PAQLQ self-administered version and PAQLQ interviewer-administered version . These tests measure asthma-related quality of life with the 23-item Polish validated version of the PAQLQ for children.			
Units: arbitrary units			
arithmetic mean			
standard deviation	±	±	-
PACQLQ score			
PACQLQ measures how caregivers are limited in their own quality of life by their child’s asthma.The maximal score is 7, which indicates optimal quality of life.			
Units: arbitrary units			

arithmetic mean standard deviation	±	±	-
Red blood cells			
Red blood cells count measured at baseline			
Units: T/L arithmetic mean standard deviation	±	±	-
White blood cells count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	-
neutrophils count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	-
Basophils count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	-
Eosiniophils count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	-
Lymphocytes count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	-
Monocytes count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	-
Platelet count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	-
serum IgE level			
Serum IgE was measured for patients biology subset			
Units: IU/ml arithmetic mean standard deviation	±	±	-
Serum IgA level			
Measured at baseline for patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	-

Serum IgM level			
It was measured at baseline for the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	-
Serum IgG level			
it was measured at baseline for patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	-
Serum IgG1 level			
it was measured at baseline for patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	-
Serum IgG2 level			
It was measured at baseline for the patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	-
Serum IgG3 level			
It was measured at baseline for the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	-
Serum IgG4 level			
It was measured at baseline for the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	-
Serum specific IgG			
Specific IgG against Ismigen antigens were measured for patients of the biology subset			
Units: arbitrary units arithmetic mean standard deviation	±	±	-
Serum specific IgG 500			
The same as previous but with a 1:500 dilutions of antigens			
Units: arbitrary units arithmetic mean standard deviation	±	±	-
Serum specific IgA			
The serum specific IgA against Ismigen antigens was measured as baseline for patients of the biology subset.			
Units: arbitrary units arithmetic mean standard deviation	±	±	-
Serum specific IgA 500 level			
The same as previous but with 1:500 dilutions of Ismigen antigens			
Units: arbitrary units arithmetic mean standard deviation	±	±	-
Serum specific IgM			

Specific IgM against Ismigen antigens were measured at baseline for patients of the biology subset.			
Units: arbitrary units arithmetic mean standard deviation	±	±	-
Serum specific IgM 500			
The same as previous but with 1:500 dilutions of Ismigen antigens			
Units: arbitrary units arithmetic mean standard deviation	±	±	-
T reg expressing CD4+, FoxP3 and high level of CD25			
Phenotype of T lymphocytes: flow cytometric analysis for patients of the biology subset.			
Units: cells/mm3 arithmetic mean standard deviation	±	±	-
Cytotoxic lymphocytes count			
Flow cytometric analysis: phenotype of circulating cytotoxic T lymphocytes			
Units: cells/mm3 arithmetic mean standard deviation	±	±	-
NK cells count			
Phenotype analysis as previously described			
Units: Cells/mm3 arithmetic mean standard deviation	±	±	-
Late activated T Lymphocytes % CD3+			
Phenotype analysis as previously described			
Units: percent of CD3+ cells arithmetic mean standard deviation	±	±	-
Early activated T lymphocytes % CD45+			
Phenotype analysis: CD3+CD69+%CD45+			
Units: % of CD45+ arithmetic mean standard deviation	±	±	-
Early activated T lymphocytes % CD3+			
Phenotype analysis: CD3+CD69+%CD3+			
Units: % of CD3+ cells arithmetic mean standard deviation	±	±	-
Early activated T helper lymphocytes% CD45+			
CD4+CD69+%CD45: Assessment at baseline: phenotype analysis as previously described for other lymphocytes types			
Units: % of CD45+ cells arithmetic mean standard deviation	±	±	-

Subject analysis sets

Subject analysis set title	FAS Ismigen baseline
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS population includes all patients of the Safety set having at least one evaluation of the primary criterion post administration.

Subject analysis set title	FAS Placebo baseline
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS population includes all patients of the Safety set having at least one evaluation of the primary criterion post administration.

Subject analysis set title	FAS Ismigen V2
Subject analysis set type	Full analysis

Subject analysis set description:

idem baseline

Subject analysis set title	FAS Placebo V2
Subject analysis set type	Full analysis

Subject analysis set description:

idem baseline

Subject analysis set title	FAS Ismigen V3
Subject analysis set type	Full analysis

Subject analysis set description:

idem baseline

Subject analysis set title	FAS Placebo V3
Subject analysis set type	Full analysis

Subject analysis set description:

idem baseline

Subject analysis set title	FAS Ismigen V4
Subject analysis set type	Full analysis

Subject analysis set description:

idem baseline

Subject analysis set title	FAS Placebo V4
Subject analysis set type	Full analysis

Subject analysis set description:

idem baseline

Subject analysis set title	FAS Ismigen V5
Subject analysis set type	Full analysis

Subject analysis set description:

idem baseline

Subject analysis set title	FAS Placebo V5
Subject analysis set type	Full analysis

Subject analysis set description:

idem baseline

Reporting group values	FAS Ismigen baseline	FAS Placebo baseline	FAS Ismigen V2
Number of subjects	74	76	21
Age categorical			
The study was performed in a population of allergic asthmatic children of both genders aged 6 to 16 years with uncontrolled or partly controlled asthma (ACT/P-ACT score ≤ 19).			
Units: Subjects			
Children 6-11 years	56	54	
Adolescents 12-16 years	18	22	
Age continuous			
Age (years) at baseline			
Units: years			

arithmetic mean	9.3	9.8	
standard deviation	± 2.7	± 2.6	±

Gender categorical			
Gender at baseline (M/F)			
Units: Subjects			
Female	25	19	
Male	49	57	
ACT/P-ACT			
asthma control test and paediatric asthma control test			
Units: arbitrary			
arithmetic mean	16.8	16.8	
standard deviation	± 2.4	± 2.4	±
Respiratory infections			
The mean number of respiratory infection per patient during the past 12 months was calculated and referred to baseline characteristic.			
Units: arbitrary			
arithmetic mean	3.9	4	
standard deviation	± 1.3	± 1.3	±
PAQLQ score			
2 questionnaires available: PAQLQ self-administered version and PAQLQ interviewer-administered version . These tests measure asthma-related quality of life with the 23-item Polish validated version of the PAQLQ for children.			
Units: arbitrary units			
arithmetic mean	5.8	5.7	
standard deviation	± 0.9	± 1.1	±
PACQLQ score			
PACQLQ measures how caregivers are limited in their own quality of life by their child’s asthma.The maximal score is 7, which indicates optimal quality of life.			
Units: arbitrary units			
arithmetic mean	4.6	4.5	
standard deviation	± 1.2	± 1.2	±
Red blood cells			
Red blood cells count measured at baseline			
Units: T/L			
arithmetic mean	4.80	4.76	
standard deviation	± 0.40	± 0.38	±
White blood cells count			
Assessment at baseline			
Units: G/L			
arithmetic mean	6.64	6.89	
standard deviation	± 1.70	± 3.48	±
neutrophils count			
Assessment at baseline			
Units: G/L			
arithmetic mean	2.87	3.09	
standard deviation	± 1.19	± 2.8	±
Basophils count			
Assessment at baseline			
Units: G/L			
arithmetic mean	0.04	0.03	
standard deviation	± 0.02	± 0.02	±

Eosiniophils count			
Assessment at baseline			
Units: G/L			
arithmetic mean	0.65	0.41	
standard deviation	± 0.39	± 0.26	±
Lymphocytes count			
Assessment at baseline			
Units: G/L			
arithmetic mean	2.4	2.72	
standard deviation	± 0.62	± 1.05	±
Monocytes count			
Assessment at baseline			
Units: G/L			
arithmetic mean	0.67	0.64	
standard deviation	± 0.19	± 0.54	±
Platelet count			
Assessment at baseline			
Units: G/L			
arithmetic mean	283.6	286.5	
standard deviation	± 38.9	± 60.4	±
serum IgE level			
Serum IgE was measured for patients biology subset			
Units: IU/ml			
arithmetic mean	1624.0	502.8	
standard deviation	± 3921.2	± 580.4	±
Serum IgA level			
Measured at baseline for patients of the biology subset			
Units: g/l			
arithmetic mean	1.56	1.47	
standard deviation	± 0.57	± 0.49	±
Serum IgM level			
It was measured at baseline for the biology subset			
Units: g/l			
arithmetic mean	0.99	1.07	
standard deviation	± 0.38	± 0.60	±
Serum IgG level			
it was measured at baseline for patients of the biology subset			
Units: g/l			
arithmetic mean	11.5	9.8	
standard deviation	± 2.2	± 1.8	±
Serum IgG1 level			
it was measured at baseline for patients of the biology subset			
Units: g/l			
arithmetic mean	7.6	6.9	
standard deviation	± 1.7	± 1.5	±
Serum IgG2 level			
It was measured at baseline for the patients of the biology subset			
Units: g/l			
arithmetic mean	3.1	2.2	
standard deviation	± 1.2	± 0.8	±
Serum IgG3 level			
It was measured at baseline for the biology subset			

Units: g/l			
arithmetic mean	0.39	0.43	
standard deviation	± 0.15	± 0.15	±
Serum IgG4 level			
It was measured at baseline for the biology subset			
Units: g/l			
arithmetic mean	1.34	0.71	
standard deviation	± 1.06	± 0.63	±
Serum specific IgG			
Specific IgG against Ismigen antigens were measured for patients of the biology subset			
Units: arbitrary units			
arithmetic mean	8.1	8.6	
standard deviation	± 4.3	± 5.6	±
Serum specific IgG 500			
The same as previous but with a 1:500 dilutions of antigens			
Units: arbitrary units			
arithmetic mean	6.0	5.4	
standard deviation	± 3.7	± 3.1	±
Serum specific IgA			
The serum specific IgA against Ismigen antigens was measured as baseline for patients of the biology subset.			
Units: arbitrary units			
arithmetic mean	4.6	4.8	
standard deviation	± 2.0	± 2.0	±
Serum specific IgA 500 level			
The same as previous but with 1:500 dilutions of Ismigen antigens			
Units: arbitrary units			
arithmetic mean	2.8	3.0	
standard deviation	± 1.1	± 1.3	±
Serum specific IgM			
Specific IgM against Ismigen antigens were measured at baseline for patients of the biology subset.			
Units: arbitrary units			
arithmetic mean	8.9	9.7	
standard deviation	± 3.7	± 3.4	±
Serum specific IgM 500			
The same as previous but with 1:500 dilutions of Ismigen antigens			
Units: arbitrary units			
arithmetic mean	3.9	4.3	
standard deviation	± 1.1	± 2.1	±
T reg expressing CD4+, FoxP3 and high level of CD25			
Phenotype of T lymphocytes: flow cytometric analysis for patients of the biology subset.			
Units: cells/mm3			
arithmetic mean	55.5	71.8	
standard deviation	± 22.7	± 28.9	±
Cytotoxic lymphocytes count			
Flow cytometric analysis: phenotype of circulating cytotoxic T lymphocytes			
Units: cells/mm3			
arithmetic mean	615.6	744.2	
standard deviation	± 264.1	± 372.4	±
NK cells count			
Phenotype analysis as previously described			

Units: Cells/mm3			
arithmetic mean	239.9	286.0	
standard deviation	± 161.5	± 244.1	±
Late activated T Lymphocytes % CD3+			
Phenotype analysis as previously described			
Units: percent of CD3+ cells			
arithmetic mean	18.9	19.2	
standard deviation	± 5.4	± 5.4	±
Early activated T lymphocytes % CD45+			
Phenotype analysis: CD3+CD69+%CD45+			
Units: % of CD45+			
arithmetic mean	7.7	8.1	
standard deviation	± 3.3	± 3.9	±
Early activated T lymphocytes % CD3+			
Phenotype analysis: CD3+CD69+%CD3+			
Units: % of CD3+ cells			
arithmetic mean	11.4	11.5	
standard deviation	± 4.3	± 5.8	±
Early activated T helper lymphocytes% CD45+			
CD4+CD69+%CD45: Assessment at baseline: phenotype analysis as previously described for other lymphocytes types			
Units: % of CD45+ cells			
arithmetic mean	3.8	1.2	
standard deviation	± 7.4	± 0.7	±

Reporting group values	FAS Placebo V2	FAS Ismigen V3	FAS Placebo V3
Number of subjects	28	74	76
Age categorical			
The study was performed in a population of allergic asthmatic children of both genders aged 6 to 16 years with uncontrolled or partly controlled asthma (ACT/P-ACT score ≤ 19).			
Units: Subjects			
Children 6-11 years			
Adolescents 12-16 years			
Age continuous			
Age (years) at baseline			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Gender at baseline (M/F)			
Units: Subjects			
Female			
Male			
ACT/P-ACT			
asthma control test and paediatric asthma control test			
Units: arbitrary			
arithmetic mean			
standard deviation	±	±	±
Respiratory infections			
The mean number of respiratory infection per patient during the past 12 months was calculated and referred to baseline characteristic.			
Units: arbitrary			

arithmetic mean standard deviation	±	±	±
PAQLQ score			
2 questionnaires available: PAQLQ self-administered version and PAQLQ interviewer-administered version . These tests measure asthma-related quality of life with the 23-item Polish validated version of the PAQLQ for children.			
Units: arbitrary units arithmetic mean standard deviation	±	±	±
PACQLQ score			
PACQLQ measures how caregivers are limited in their own quality of life by their child’s asthma.The maximal score is 7, which indicates optimal quality of life.			
Units: arbitrary units arithmetic mean standard deviation	±	±	±
Red blood cells			
Red blood cells count measured at baseline			
Units: T/L arithmetic mean standard deviation	±	±	±
White blood cells count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	±
neutrophils count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	±
Basophils count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	±
Eosiniophils count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	±
Lymphocytes count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	±
Monocytes count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	±
Platelet count			
Assessment at baseline			

Units: G/L arithmetic mean standard deviation	±	±	±
serum IgE level			
Serum IgE was measured for patients biology subset			
Units: IU/ml arithmetic mean standard deviation	±	±	±
Serum IgA level			
Measured at baseline for patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	±
Serum IgM level			
It was measured at baseline for the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	±
Serum IgG level			
it was measured at baseline for patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	±
Serum IgG1 level			
it was measured at baseline for patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	±
Serum IgG2 level			
It was measured at baseline for the patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	±
Serum IgG3 level			
It was measured at baseline for the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	±
Serum IgG4 level			
It was measured at baseline for the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	±
Serum specific IgG			
Specific IgG against Ismigen antigens were measured for patients of the biology subset			
Units: arbitrary units arithmetic mean standard deviation	±	±	±
Serum specific IgG 500			
The same as previous but with a 1:500 dilutions of antigens			
Units: arbitrary units arithmetic mean			

standard deviation	±	±	±
Serum specific IgA			
The serum specific IgA against Ismigen antigens was measured as baseline for patients of the biology subset.			
Units: arbitrary units arithmetic mean standard deviation	±	±	±
Serum specific IgA 500 level			
The same as previous but with 1:500 dilutions of Ismigen antigens			
Units: arbitrary units arithmetic mean standard deviation	±	±	±
Serum specific IgM			
Specific IgM against Ismigen antigens were measured at baseline for patients of the biology subset.			
Units: arbitrary units arithmetic mean standard deviation	±	±	±
Serum specific IgM 500			
The same as previous but with 1:500 dilutions of Ismigen antigens			
Units: arbitrary units arithmetic mean standard deviation	±	±	±
T reg expressing CD4+, FoxP3 and high level of CD25			
Phenotype of T lymphocytes: flow cytometric analysis for patients of the biology subset.			
Units: cells/mm3 arithmetic mean standard deviation	±	±	±
Cytotoxic lymphocytes count			
Flow cytometric analysis: phenotype of circulating cytotoxic T lymphocytes			
Units: cells/mm3 arithmetic mean standard deviation	±	±	±
NK cells count			
Phenotype analysis as previously described			
Units: Cells/mm3 arithmetic mean standard deviation	±	±	±
Late activated T Lymphocytes % CD3+			
Phenotype analysis as previously described			
Units: percent of CD3+ cells arithmetic mean standard deviation	±	±	±
Early activated T lymphocytes % CD45+			
Phenotype analysis: CD3+CD69+%CD45+			
Units: % of CD45+ arithmetic mean standard deviation	±	±	±
Early activated T lymphocytes % CD3+			
Phenotype analysis: CD3+CD69+%CD3+			
Units: % of CD3+ cells arithmetic mean			

standard deviation	±	±	±
Early activated T helper lymphocytes% CD45+			
CD4+CD69+%CD45: Assessment at baseline: phenotype analysis as previously described for other lymphocytes types			
Units: % of CD45+ cells arithmetic mean standard deviation	±	±	±

Reporting group values	FAS Ismigen V4	FAS Placebo V4	FAS Ismigen V5
Number of subjects	74	76	74
Age categorical			
The study was performed in a population of allergic asthmatic children of both genders aged 6 to 16 years with uncontrolled or partly controlled asthma (ACT/P-ACT score ≤ 19).			
Units: Subjects			
Children 6-11 years Adolescents 12-16 years			
Age continuous			
Age (years) at baseline			
Units: years arithmetic mean standard deviation	±	±	±
Gender categorical			
Gender at baseline (M/F)			
Units: Subjects			
Female Male			
ACT/P-ACT			
asthma control test and paediatric asthma control test			
Units: arbitrary arithmetic mean standard deviation	±	±	±
Respiratory infections			
The mean number of respiratory infection per patient during the past 12 months was calculated and referred to baseline characteristic.			
Units: arbitrary arithmetic mean standard deviation	±	±	±
PAQLQ score			
2 questionnaires available: PAQLQ self-administered version and PAQLQ interviewer-administered version . These tests measure asthma-related quality of life with the 23-item Polish validated version of the PAQLQ for children.			
Units: arbitrary units arithmetic mean standard deviation	±	±	±
PACQLQ score			
PACQLQ measures how caregivers are limited in their own quality of life by their child’s asthma.The maximal score is 7, which indicates optimal quality of life.			
Units: arbitrary units arithmetic mean standard deviation	±	±	±
Red blood cells			
Red blood cells count measured at baseline			

Units: T/L arithmetic mean standard deviation	±	±	±
White blood cells count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	±
neutrophils count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	±
Basophils count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	±
Eosiniophils count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	±
Lymphocytes count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	±
Monocytes count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	±
Platelet count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±	±	±
serum IgE level			
Serum IgE was measured for patients biology subset			
Units: IU/ml arithmetic mean standard deviation	±	±	±
Serum IgA level			
Measured at baseline for patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	±
Serum IgM level			
It was measured at baseline for the biology subset			
Units: g/l arithmetic mean			

standard deviation	±	±	±
Serum IgG level			
it was measured at baseline for patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	±
Serum IgG1 level			
it was measured at baseline for patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	±
Serum IgG2 level			
It was measured at baseline for the patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	±
Serum IgG3 level			
It was measured at baseline for the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	±
Serum IgG4 level			
It was measured at baseline for the biology subset			
Units: g/l arithmetic mean standard deviation	±	±	±
Serum specific IgG			
Specific IgG against Ismigen antigens were measured for patients of the biology subset			
Units: arbitrary units arithmetic mean standard deviation	±	±	±
Serum specific IgG 500			
The same as previous but with a 1:500 dilutions of antigens			
Units: arbitrary units arithmetic mean standard deviation	±	±	±
Serum specific IgA			
The serum specific IgA against Ismigen antigens was measured as baseline for patients of the biology subset.			
Units: arbitrary units arithmetic mean standard deviation	±	±	±
Serum specific IgA 500 level			
The same as previous but with 1:500 dilutions of Ismigen antigens			
Units: arbitrary units arithmetic mean standard deviation	±	±	±
Serum specific IgM			
Specific IgM against Ismigen antigens were measured at baseline for patients of the biology subset.			
Units: arbitrary units arithmetic mean standard deviation	±	±	±

Serum specific IgM 500			
The same as previous but with 1:500 dilutions of Ismigen antigens			
Units: arbitrary units arithmetic mean standard deviation	±	±	±
T reg expressing CD4+, FoxP3 and high level of CD25			
Phenotype of T lymphocytes: flow cytometric analysis for patients of the biology subset.			
Units: cells/mm3 arithmetic mean standard deviation	±	±	±
Cytotoxic lymphocytes count			
Flow cytometric analysis: phenotype of circulating cytotoxic T lymphocytes			
Units: cells/mm3 arithmetic mean standard deviation	±	±	±
NK cells count			
Phenotype analysis as previously described			
Units: Cells/mm3 arithmetic mean standard deviation	±	±	±
Late activated T Lymphocytes % CD3+			
Phenotype analysis as previously described			
Units: percent of CD3+ cells arithmetic mean standard deviation	±	±	±
Early activated T lymphocytes % CD45+			
Phenotype analysis: CD3+CD69+%CD45+			
Units: % of CD45+ arithmetic mean standard deviation	±	±	±
Early activated T lymphocytes % CD3+			
Phenotype analysis: CD3+CD69+%CD3+			
Units: % of CD3+ cells arithmetic mean standard deviation	±	±	±
Early activated T helper lymphocytes% CD45+			
CD4+CD69+%CD45: Assessment at baseline: phenotype analysis as previously described for other lymphocytes types			
Units: % of CD45+ cells arithmetic mean standard deviation	±	±	±

Reporting group values	FAS Placebo V5		
Number of subjects	76		
Age categorical			
The study was performed in a population of allergic asthmatic children of both genders aged 6 to 16 years with uncontrolled or partly controlled asthma (ACT/P-ACT score ≤ 19).			
Units: Subjects			
Children 6-11 years Adolescents 12-16 years			

Age continuous			
Age (years) at baseline			
Units: years arithmetic mean standard deviation	±		
Gender categorical			
Gender at baseline (M/F)			
Units: Subjects			
Female Male			
ACT/P-ACT			
asthma control test and paediatric asthma control test			
Units: arbitrary arithmetic mean standard deviation	±		
Respiratory infections			
The mean number of respiratory infection per patient during the past 12 months was calculated and referred to baseline characteristic.			
Units: arbitrary arithmetic mean standard deviation	±		
PAQLQ score			
2 questionnaires available: PAQLQ self-administered version and PAQLQ interviewer-administered version . These tests measure asthma-related quality of life with the 23-item Polish validated version of the PAQLQ for children.			
Units: arbitrary units arithmetic mean standard deviation	±		
PACQLQ score			
PACQLQ measures how caregivers are limited in their own quality of life by their child’s asthma.The maximal score is 7, which indicates optimal quality of life.			
Units: arbitrary units arithmetic mean standard deviation	±		
Red blood cells			
Red blood cells count measured at baseline			
Units: T/L arithmetic mean standard deviation	±		
White blood cells count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±		
neutrophils count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±		
Basophils count			
Assessment at baseline			
Units: G/L			

arithmetic mean standard deviation	±		
Eosiniophils count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±		
Lymphocytes count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±		
Monocytes count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±		
Platelet count			
Assessment at baseline			
Units: G/L arithmetic mean standard deviation	±		
serum IgE level			
Serum IgE was measured for patients biology subset			
Units: IU/ml arithmetic mean standard deviation	±		
Serum IgA level			
Measured at baseline for patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±		
Serum IgM level			
It was measured at baseline for the biology subset			
Units: g/l arithmetic mean standard deviation	±		
Serum IgG level			
it was measured at baseline for patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±		
Serum IgG1 level			
it was measured at baseline for patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±		
Serum IgG2 level			
It was measured at baseline for the patients of the biology subset			
Units: g/l arithmetic mean standard deviation	±		

Serum IgG3 level			
It was measured at baseline for the biology subset			
Units: g/l arithmetic mean standard deviation	±		
Serum IgG4 level			
It was measured at baseline for the biology subset			
Units: g/l arithmetic mean standard deviation	±		
Serum specific IgG			
Specific IgG against Ismigen antigens were measured for patients of the biology subset			
Units: arbitrary units arithmetic mean standard deviation	±		
Serum specific IgG 500			
The same as previous but with a 1:500 dilutions of antigens			
Units: arbitrary units arithmetic mean standard deviation	±		
Serum specific IgA			
The serum specific IgA against Ismigen antigens was measured as baseline for patients of the biology subset.			
Units: arbitrary units arithmetic mean standard deviation	±		
Serum specific IgA 500 level			
The same as previous but with 1:500 dilutions of Ismigen antigens			
Units: arbitrary units arithmetic mean standard deviation	±		
Serum specific IgM			
Specific IgM against Ismigen antigens were measured at baseline for patients of the biology subset.			
Units: arbitrary units arithmetic mean standard deviation	±		
Serum specific IgM 500			
The same as previous but with 1:500 dilutions of Ismigen antigens			
Units: arbitrary units arithmetic mean standard deviation	±		
T reg expressing CD4+, FoxP3 and high level of CD25			
Phenotype of T lymphocytes: flow cytometric analysis for patients of the biology subset.			
Units: cells/mm3 arithmetic mean standard deviation	±		
Cytotoxic lymphocytes count			
Flow cytometric analysis: phenotype of circulating cytotoxic T lymphocytes			
Units: cells/mm3 arithmetic mean standard deviation	±		

NK cells count			
Phenotype analysis as previously described			
Units: Cells/mm3 arithmetic mean standard deviation	±		
Late activated T Lymphocytes % CD3+			
Phenotype analysis as previously described			
Units: percent of CD3+ cells arithmetic mean standard deviation	±		
Early activated T lymphocytes % CD45+			
Phenotype analysis: CD3+CD69+%CD45+			
Units: % of CD45+ arithmetic mean standard deviation	±		
Early activated T lymphocytes % CD3+			
Phenotype analysis: CD3+CD69+%CD3+			
Units: % of CD3+ cells arithmetic mean standard deviation	±		
Early activated T helper lymphocytes% CD45+			
CD4+CD69+%CD45: Assessment at baseline: phenotype analysis as previously described for other lymphocytes types			
Units: % of CD45+ cells arithmetic mean standard deviation	±		

End points

End points reporting groups

Reporting group title	Ismigen

Reporting group description:

Active

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Ismigen

Reporting group description:

Active

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Ismigen

Reporting group description:

Active

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Ismigen

Reporting group description:

Active

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Ismigen

Reporting group description:

Active

Reporting group title	Placebo

Reporting group description:

Placebo

Subject analysis set title	FAS Ismigen baseline
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS population includes all patients of the Safety set having at least one evaluation of the primary criterion post administration.

Subject analysis set title	FAS Placebo baseline
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS population includes all patients of the Safety set having at least one evaluation of the primary criterion post administration.

Subject analysis set title	FAS Ismigen V2
Subject analysis set type	Full analysis

Subject analysis set description:

idem baseline

Subject analysis set title	FAS Placebo V2
Subject analysis set type	Full analysis

Subject analysis set description:

idem baseline

Subject analysis set title	FAS Ismigen V3
Subject analysis set type	Full analysis
Subject analysis set description: idem baseline	
Subject analysis set title	FAS Placebo V3
Subject analysis set type	Full analysis
Subject analysis set description: idem baseline	
Subject analysis set title	FAS Ismigen V4
Subject analysis set type	Full analysis
Subject analysis set description: idem baseline	
Subject analysis set title	FAS Placebo V4
Subject analysis set type	Full analysis
Subject analysis set description: idem baseline	
Subject analysis set title	FAS Ismigen V5
Subject analysis set type	Full analysis
Subject analysis set description: idem baseline	
Subject analysis set title	FAS Placebo V5
Subject analysis set type	Full analysis
Subject analysis set description: idem baseline	

Primary: ACT/P-ACT change from baseline

End point title	ACT/P-ACT change from baseline

End point description:

The main analysis is the target improvement in asthma control level as measured by the mean ACT or P-ACT score at 12 weeks. The ACT or P-ACT will be described at baseline and at 12 weeks as well as the mean change. If the value at 12 weeks is not available, the value at premature withdrawal visit will be used.

The mean change will be compared between the treatment groups using an ANCOVA with the baseline as covariate.

The same analysis will be performed at 24 weeks (3 months follow up) and 36 weeks (6 months follow up)

End point type	Primary

End point timeframe:

End of Treatment V3, Follow up 3 months V4, Follow up 6 months V5

End point values	FAS Ismigen baseline	FAS Placebo baseline	FAS Ismigen V3	FAS Placebo V3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	74	76	74	76
Units: arbitrary				
arithmetic mean (standard deviation)	16.8 (± 2.4)	16.8 (± 2.4)	21.0 (± 3.5)	21.1 (± 3.0)

End point values	FAS Ismigen V4	FAS Placebo V4	FAS Ismigen V5	FAS Placebo V5
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	74	76	74	76
Units: arbitrary				
arithmetic mean (standard deviation)	22.3 (± 3.5)	22.3 (± 3.1)	23.0 (± 2.7)	22.3 (± 3.3)

Statistical analyses

Statistical analysis title	ACT/P-ACT Evolution at end of treatment
Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	150
Analysis specification	Post-hoc
Analysis type	superiority[1]
P-value	= 0.9432 [2]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	12
Variability estimate	Standard deviation

Notes:

[1] - Mean changes compared between groups using an ANCOVA with baseline as covariate. If non normal distributions (Shapiro-Wilk's test), non-parametric covariance analysis (based on ranks): i)to compute the ranks of the response variable (change from baseline) and covariate (baseline value) in the combined treatment group ii) to calculate residuals from linear regression of response ranks on the covariate ranks. Mantel-Haenzel mean score statistic compares the mean values of residuals.

[2] - The absolute changes in P-ACT/ACT scores between baseline and 12 w were similar in both groups (FAS) after the 3 months treatment period. The asthma status for most of the patients could be categorized as "controlled" according to the mean ACT/P-ACT

Statistical analysis title	ACT/P-ACT evolution at V4

Statistical analysis description:

The change from baseline at 24 weeks, will be described and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) will be used.

Comparison groups	FAS Ismigen V4 v FAS Placebo V4
Number of subjects included in analysis	150
Analysis specification	Post-hoc
Analysis type	superiority[3]
P-value	= 0.6472 [4]
Method	ANCOVA
Parameter estimate	Mean difference (net)

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	13
Variability estimate	Standard deviation

Notes:

[3] - Same as previous

[4] - The absolute changes in P-ACT/ACT scores between baseline and 24 w were similar in both groups (FAS after 3 months follow up). The asthma status for most of the patients could be categorized as "controlled" according to the mean ACT/P-ACT.

Statistical analysis title	ACT/P-ACT evolution at V5

Statistical analysis description:

Same as previous at 36 weeks (6 months follow up)

Comparison groups	FAS Ismigen V5 v FAS Placebo V5
Number of subjects included in analysis	150
Analysis specification	Post-hoc
Analysis type	superiority[5]
P-value	= 0.2112 [6]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[5] - Same as previous (cf 24 weeks)

[6] - The absolute changes in P-ACT/ACT scores between baseline and 36 w were similar in both groups (FAS) after the 6 months follow up p. The asthma status for most of the patients could be categorized as "controlled" according to the mean ACT/P-ACT.

Secondary: Number of respiratory tract infections

End point title	Number of respiratory tract infections

End point description:

End point type	Secondary

End point timeframe:

The number of respiratory tract infections is recorded at each study times (Post treatment, 6 months and 9 months follow up) and the mean number per patient is calculated.

End point values	FAS Ismigen V3	FAS Placebo V3	FAS Ismigen V4	FAS Placebo V4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	72	76	71	75
Units: arbitrary				
arithmetic mean (standard deviation)	07 (± 0.8)	0.7 (± 0.9)	0.5 (± 0.7)	0.6 (± 0.8)

End point values	FAS Ismigen V5	FAS Placebo V5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	75		
Units: arbitrary				
arithmetic mean (standard deviation)	0.8 (± 0.9)	0.7 (± 0.8)		

Statistical analyses

Statistical analysis title	Mean number of respiratory infections at V3

Statistical analysis description:

The mean number of respiratory infections per patient will be described at each time (12 weeks, 24 weeks, 36 weeks and all the study) and
comparison between treatment groups using a Student's t test or Wilcoxon’s test in case of non-normality)

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	148
Analysis specification	Post-hoc
Analysis type	superiority[7]
P-value	= 0.712 [8]
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - The mean number of respiratory infections per patient after the treatment period will be compared between treatment groups using a Student's t test or Wilcoxon’s test in case of non-normality)
[8] - No effect of Ismigen treatment on the mean number of respiratory infections after the treatment period

Statistical analysis title	Mean number of respiratory infections at V4

Statistical analysis description:

Same as previous

Comparison groups	FAS Placebo V4 v FAS Ismigen V4
Number of subjects included in analysis	146
Analysis specification	Post-hoc
Analysis type	superiority[9]
P-value	= 0.368 [10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - Same as previous

[10] - No effect of Ismigen treatment on the mean number of respiratory tract infections at 24 weeks

Statistical analysis title	Mean number of respiratory infections at V5

Statistical analysis description:

Same as previous

Comparison groups	FAS Ismigen V5 v FAS Placebo V5
Number of subjects included in analysis	145
Analysis specification	Post-hoc
Analysis type	superiority[11]
P-value	= 0.948 [12]
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - Same as previous

[12] - No effect of Ismigen treatment on mean number of respiratory infections at V5

Secondary: Number of asthma exacerbations

End point title	Number of asthma exacerbations

End point description:

Asthma exacerbations were defined as follows:
-a Mild/Moderate exacerbation requires:
• transient increase in ICS/B2-agonists/Anticholinergics use for ≥ 2 days
or
• Emergency room visits: but no systemic corticosteroids
-a severe exacerbation requires:
• Hospitalization or Emergency room visit, requiring systemic corticosteroids
• Systemic corticosteroids (tablets or injection), ≥ 3 days (but < 7 days).

End point type	Secondary

End point timeframe:

The mean number of asthma exacerbation was recorded at the End of Treatment, at 3 months follow up and at 6 months follow up.

End point values	FAS Ismigen V3	FAS Placebo V3	FAS Ismigen V4	FAS Placebo V4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	72	76	71	75
Units: arbitary units				
arithmetic mean (standard deviation)	0.3 (± 0.6)	0.8 (± 1.1)	0.4 (± 0.7)	0.6 (± 0.9)

End point values	FAS Ismigen V5	FAS Placebo V5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	75		
Units: arbitary units				
arithmetic mean (standard deviation)	0.4 (± 0.7)	0.6 (± 1.1)		

Statistical analyses

Statistical analysis title	Mean nb of asthma exacerbation at V3

Statistical analysis description:

The mean number of asthma exacerbations per patient were compared between treatment groups using a Student's t test or Wilcoxon’s test in case of non-normality) at the End of Treatment

Comparison groups	FAS Placebo V3 v FAS Ismigen V3

Number of subjects included in analysis	148
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.009 [13]
Method	Wilcoxon (Mann-Whitney)

Notes:

[13] - The mean number of asthma exacerbation was significantly lower in the Ismigen group as compared to Placebo group at V3

Statistical analysis title	Mean nb of asthma exacerbation at V4

Statistical analysis description:

Same as previous at the 3 months follow up period

Comparison groups	FAS Ismigen V4 v FAS Placebo V4
Number of subjects included in analysis	146
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.168 [14]
Method	Wilcoxon (Mann-Whitney)

Notes:

[14] - The mean number of asthma exacerbation was not significantly different in the Ismigen group as compared to the Placebo group at the 3 months follow up visit.

Statistical analysis title	Mean nb of asthma exacerbation at V5

Statistical analysis description:

Same as previous for the 6 months follow up period.

Comparison groups	FAS Ismigen V5 v FAS Placebo V5
Number of subjects included in analysis	145
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.444 [15]
Method	Wilcoxon (Mann-Whitney)

Notes:

[15] - The mean number of asthma exacerbation was not significantly different in the Ismigne group as compared to the Placebo group

Secondary: Number of asthma exacerbation related to infection

End point title	Number of asthma exacerbation related to infection

End point description:

Exacerbations related and unrelated to infections
"As per study procedures, and in the absence of laboratory investigations for infections, exacerbations were reported as "related to infection" when occurring during the course of an infection and as "unrelated to infection" in the absence of clinical symptoms of infection."

End point type	Secondary

End point timeframe:

End of Treatment, 3 months follow up, 6 months follow up

End point values	FAS Ismigen V3	FAS Placebo V3	FAS Ismigen V4	FAS Placebo V4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	72	76	71	75
Units: arbitrary unit				
arithmetic mean (standard deviation)	0.2 (± 0.5)	0.4 (± 0.8)	0.1 (± 0.4)	0.2 (± 0.6)

End point values	FAS Ismigen V5	FAS Placebo V5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	75		
Units: arbitrary unit				
arithmetic mean (standard deviation)	0.2 (± 0.5)	0.3 (± 0.7)		

Statistical analyses

Statistical analysis title	Comparison of mean nb of AEX related to inf at V3

Statistical analysis description:

The mean number of asthma exacerbations (AEX) related to infection (Inf) per patient was compared between treatment groups using a Student's t test or Wilcoxon’s test in case of non-normality at the End of Treatment

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	148
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.034 [16]
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - The mean number of asthma exacerbations related to infection was significantly lower in the Ismigen group at the End of Treatment.

Statistical analysis title	Comparison of mean nb of AEX related to inf at V4

Statistical analysis description:

Same as previous

Comparison groups	FAS Ismigen V4 v FAS Placebo V4
Number of subjects included in analysis	146
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.126 [17]
Method	Wilcoxon (Mann-Whitney)

Notes:

[17] - No difference between groups

Statistical analysis title	Comparison of mean nb of AEX related to inf at V5

Statistical analysis description:

Same as previous

Comparison groups	FAS Ismigen V5 v FAS Placebo V5

Number of subjects included in analysis	145
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.274 [18]
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - No difference between groups

Secondary: Asthma exacerbations unrelated to infection

End point title	Asthma exacerbations unrelated to infection

End point description:

Exacerbations related and unrelated to infections
"As per study procedures, and in the absence of laboratory investigations for infections, exacerbations were reported as "related to infection" when occurring during the course of an infection and as "unrelated to infection" in the absence of clinical symptoms of infection."

End point type	Secondary

End point timeframe:

The mean number of asthma exacerbation unrelated to infections was calculated at the End of Treament, at 3 months and 6 months follow up and for the all duration of the study

End point values	FAS Ismigen V3	FAS Placebo V3	FAS Ismigen V4	FAS Placebo V4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	72	76	71	75
Units: arbitrary unit				
arithmetic mean (standard deviation)	0.1 (± 0.3)	0.3 (± 0.7)	0.1 (± 0.4)	0.2 (± 0.6)

End point values	FAS Ismigen V5	FAS Placebo V5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	75		
Units: arbitrary unit				
arithmetic mean (standard deviation)	0.2 (± 0.5)	0.3 (± 0.7)		

Statistical analyses

Statistical analysis title	Comparison of mean nb of AEX unrelated at V3

Statistical analysis description:

The mean number of asthma exacerbations unrelated to infections per patient were compared between treatment groups using a Student's t test or Wilcoxon's test in case of non-normality

Comparison groups	FAS Ismigen V3 v FAS Placebo V3

Number of subjects included in analysis	148
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.057 [19]
Method	Wilcoxon (Mann-Whitney)

Notes:

[19] - Results non significantly different between groups but a trend in favor of ismigen group.

Statistical analysis title	Comparison of mean nb of AEX unrelated at V4

Statistical analysis description:

Same as previous for this period

Comparison groups	FAS Ismigen V4 v FAS Placebo V4
Number of subjects included in analysis	146
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.442 [20]
Method	Wilcoxon (Mann-Whitney)

Notes:

[20] - No significant difference between groups

Statistical analysis title	Comparison of mean nb of AEX unrelated at V5

Statistical analysis description:

Same as previous for this study period

Comparison groups	FAS Ismigen V5 v FAS Placebo V5
Number of subjects included in analysis	145
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.924 [21]
Method	Wilcoxon (Mann-Whitney)

Notes:

[21] - No significant difference between groups

Secondary: Number of day per patient with asthma exacerbations

End point title	Number of day per patient with asthma exacerbations

End point description:

Mean of the total duration of asthma exacerbations per patient

End point type	Secondary

End point timeframe:

The number of days with asthma exacerbation was measured at all study times: End of Treatment, Follow up 3months, Follow up 6 months

End point values	FAS Ismigen V3	FAS Placebo V3	FAS Ismigen V4	FAS Placebo V4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	18	32	22	30
Units: day				
arithmetic mean (standard deviation)	10.6 (± 10.7)	12 (± 8.5)	8.4 (± 5.4)	10.4 (± 6.2)

End point values	FAS Ismigen V5	FAS Placebo V5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	24		
Units: day				
arithmetic mean (standard deviation)	9.7 (± 5.3)	11.5 (± 9.7)		

Statistical analyses

Statistical analysis title	Comparison of mean number of days with AEX at V3

Statistical analysis description:

The number of days with exacerbation per patient wil be compared between treatment groups using a Student's t test or Wilcoxon’s test in case of non-normality

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	50
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.292 [22]
Method	Wilcoxon (Mann-Whitney)

Notes:

[22] - The mean number of days with asthma exacerbations per patient was not significantly different between groups at the End of treatment. To be noticed however that the number of patients with asthma exacerbation was lower in the ismigen group

Statistical analysis title	Comparison of mean nb of days with AEX at V4

Statistical analysis description:

-The number of days with exacerbation per patient at V4 will be compared between treatment groups using a Student's t test or Wilcoxon’s test in case of non-normality

Comparison groups	FAS Ismigen V4 v FAS Placebo V4
Number of subjects included in analysis	52
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.209 [23]
Method	Wilcoxon (Mann-Whitney)

Notes:

[23] - No difference between groups

Statistical analysis title	Comparison of mean nb of days with AEX at V5

Statistical analysis description:

Same as previous

Comparison groups	FAS Placebo V5 v FAS Ismigen V5

Number of subjects included in analysis	43
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.787 [24]
Method	Wilcoxon (Mann-Whitney)

Notes:

[24] - No difference between groups

Secondary: Mean duration of asthma exacerbation per event

End point title	Mean duration of asthma exacerbation per event

End point description:

A mean duration of AEX duration (days) per event was calculated.

End point type	Secondary

End point timeframe:

This endpoint was measured at the End of Treatment, Follow up 3 months and 6 months

End point values	FAS Ismigen V3	FAS Placebo V3	FAS Ismigen V4	FAS Placebo V4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	18	32	22	30
Units: day				
arithmetic mean (standard deviation)	8.7 (± 6.3)	6.7 (± 3.8)	6.4 (± 3.1)	6.7 (± 4.5)

End point values	FAS Ismigen V5	FAS Placebo V5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	24		
Units: day				
arithmetic mean (standard deviation)	6.6 (± 3.3)	6.4 (± 4.1)		

Statistical analyses

Statistical analysis title	Comparison of mean duration of AEX at V3

Statistical analysis description:

The mean duration per event (days) was compared between treatment groups using a Student's t test or Wilcoxon’s test in case of non-normality at V3

Comparison groups	FAS Placebo V3 v FAS Ismigen V3
Number of subjects included in analysis	50
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.149 [25]
Method	Wilcoxon (Mann-Whitney)

Notes:
[25] - No difference between groups

Statistical analysis title	Comparison of mean duration of AEX at V4
Statistical analysis description: Same as previous	
Comparison groups	FAS Ismigen V4 v FAS Placebo V4
Number of subjects included in analysis	52
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.705 [26]
Method	Wilcoxon (Mann-Whitney)

Notes:
[26] - No difference beetween groups

Statistical analysis title	Comparison of mean duration of AEX at V5
Statistical analysis description: Same as previous	
Comparison groups	FAS Ismigen V5 v FAS Placebo V5
Number of subjects included in analysis	43
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.531 [27]
Method	Wilcoxon (Mann-Whitney)

Notes:
[27] - No difference between groups

Secondary: Number of school days lost because of asthma exacerbation

End point title	Number of school days lost because of asthma exacerbation
End point description:	
End point type	Secondary
End point timeframe: The number of school days lost or days without normal activities because of asthma exacerbation was determined at V3, V4, V5	

End point values	FAS Ismigen V3	FAS Placebo V3	FAS Ismigen V4	FAS Placebo V4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	18	32	22	30
Units: days				
arithmetic mean (standard deviation)	3.0 (± 3.7)	4.1 (± 5.1)	2.1 (± 2.5)	3.6 (± 4.9)

End point values	FAS Ismigen V5	FAS Placebo V5		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	24		
Units: days				
arithmetic mean (standard deviation)	5.1 (± 4.7)	4.5 (± 5.4)		

Statistical analyses

Statistical analysis title	Comparison of school days lost at V3

Statistical analysis description:

Comparison between groups of the number of school days lost or without normal activities because of asthma exacerbation at the End of treatment

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	50
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.523 [28]
Method	Wilcoxon (Mann-Whitney)

Notes:

[28] - No significant difference between groups

Statistical analysis title	Comparison of school days lost at V4

Statistical analysis description:

same as previous

Comparison groups	FAS Ismigen V4 v FAS Placebo V4
Number of subjects included in analysis	52
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.455 [29]
Method	Wilcoxon (Mann-Whitney)

Notes:

[29] - No significant difference between groups

Statistical analysis title	Comparison of school days lost at V5

Statistical analysis description:

same as previous

Comparison groups	FAS Ismigen V5 v FAS Placebo V5
Number of subjects included in analysis	43
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.456 [30]
Method	Wilcoxon (Mann-Whitney)

Notes:

[30] - No significant difference

Secondary: Number of days of SABA use for exacerbation relief

End point title	Number of days of SABA use for exacerbation relief

End point description:

End point type	Secondary

End point timeframe:

The mean nb of days of SABA use for AEX relief per patient was calculated for the all duration of the study
Were considered as SABA: pure ß2 agonist or combined inhaled/nebulized SABA+ inhaled/nebulized anticholinergics or Symbicort for exacerbations.

End point values	FAS Ismigen V5	FAS Placebo V5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	47		
Units: days				
arithmetic mean (standard deviation)	11.5 (± 11.2)	15.6 (± 10.2)		

Statistical analyses

Statistical analysis title	Comparison of the number of days of SABA use

Statistical analysis description:

The number of days of SABA used for asthma exacerbation was compared between groups.

Comparison groups	FAS Ismigen V5 v FAS Placebo V5
Number of subjects included in analysis	84
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.016 [31]
Method	Wilcoxon (Mann-Whitney)

Notes:

[31] - The mean number of days of SABA use for exacerbation relief from V1 to V5 was statistically lower in the Ismigen group as compared to the Placebo group.

Secondary: Time to first asthma exacerbation

End point title	Time to first asthma exacerbation

End point description:

End point type	Secondary

End point timeframe:

This endpoint was measured for the all duration of the study, from baseline to V5

End point values	FAS Ismigen V5	FAS Placebo V5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	49		
Units: weeks				
arithmetic mean (standard deviation)	25 (± 1.4)	19.7 (± 1.7)		

Statistical analyses

Statistical analysis title	comparison of time to first asthma exacerbation

Statistical analysis description:

The time to first mild/moderate or severe asthma exacerbation is defined by the time between the start date of treatment and the date of the first mild/moderate or severe asthma exacerbation. For patients with no mild/moderate or severe asthma exacerbation, they are censored at the last assessment date. The global survival (period without exacerbation) is estimated using a survival analysis (Kaplan-Meier).

Comparison groups	FAS Ismigen V5 v FAS Placebo V5
Number of subjects included in analysis	91
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0905 [32]
Method	Logrank

Notes:

[32] - No difference between groups

Secondary: Time to second asthma exacerbation

End point title	Time to second asthma exacerbation

End point description:

End point type	Secondary

End point timeframe:

The time to second asthma exacerbation is measured between baseline and V5

End point values	FAS Ismigen V5	FAS Placebo V5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	49		
Units: weeks				
arithmetic mean (standard deviation)	32.7 (± 0.9)	25.9 (± 1.4)		

Statistical analyses

Statistical analysis title	Comparaison of time to second asthma exacerbation

Statistical analysis description:

The time to second mild/moderate or severe asthma exacerbation is defined by the time between the start date of treatment and the date of the second mild/moderate or severe asthma exacerbation. For patients with no mild/moderate or severe asthma exacerbation, they will be censored at the last assessment date. The global survival (period without exacerbation) is estimated using a survival analysis (Kaplan-Meier) .

Comparison groups	FAS Ismigen V5 v FAS Placebo V5

Number of subjects included in analysis	91
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0024 [33]
Method	Logrank

Notes:

[33] - The time to onset of second asthma exacerbation is significantly longer for the Ismigen® group

Secondary: Time to third asthma exacerbation

End point title	Time to third asthma exacerbation

End point description:

End point type	Secondary

End point timeframe:

The time to third asthma exacerbation is measured between baseline and V5.

End point values	FAS Ismigen V5	FAS Placebo V5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	49		
Units: weeks				
arithmetic mean (standard deviation)	35.3 (± 0.6)	31.5 (± 1.2)		

Statistical analyses

Statistical analysis title	Comparison of time to third asthma exacerbation

Statistical analysis description:

The time to third mild/moderate or severe asthma exacerbation is defined by the time between the start date of treatment and the date of the third mild/moderate or severe asthma exacerbation . For patients with no mild/moderate or severe asthma exacerbation, they are censored at the last assessment date. The global survival (period without exacerbation) is estimated using a survival analysis (Kaplan-Meier).

Comparison groups	FAS Ismigen V5 v FAS Placebo V5
Number of subjects included in analysis	91
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0004 [34]
Method	Logrank

Notes:

[34] - The time to onset of third asthma exacerbation is significantly longer for the Ismigen® group

Secondary: Evolution of PAQLQ score between baseline and 36w

End point title	Evolution of PAQLQ score between baseline and 36w

End point description:

End point type	Secondary

End point timeframe:

The evolution of PAQLQ score was evaluated between baseline and 36 weeks

End point values	FAS Ismigen V5	FAS Placebo V5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	75		
Units: arbitrary unit				
arithmetic mean (standard deviation)	0.6 (± 0.8)	0.7 (± 0.1)		

Statistical analyses

Statistical analysis title	Comparison of evolution of PAQLQ scores

Statistical analysis description:

Changes from baseline (absolute)is calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) is used.

Comparison groups	FAS Ismigen V5 v FAS Placebo V5
Number of subjects included in analysis	145
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.5673 [35]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[35] - No significant difference between groups

Secondary: Evolution of PACQLQ between baseline and 36 w

End point title	Evolution of PACQLQ between baseline and 36 w

End point description:

End point type	Secondary

End point timeframe:

Scores will be calculated and described at each time (inclusion and 36 weeks). For patients prematurely withdrawn, the questionnaire performed at premature withdrawal visit will be used for the 36 weeks visit.
Changes from baseline will be calculated .

End point values	FAS Ismigen V5	FAS Placebo V5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	75		
Units: Arbitrary unit				
arithmetic mean (standard deviation)	1.3 (± 1.2)	1.2 (± 1.1)		

Statistical analyses

Statistical analysis title	Comparison of evolution of PACQLQ score

Statistical analysis description:

Changes from baseline are calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) is used.

Comparison groups	FAS Ismigen V5 v FAS Placebo V5
Number of subjects included in analysis	145
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2172 [36]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[36] - No significant difference between groups

Secondary: Evolution of red blood cells count

End point title	Evolution of red blood cells count

End point description:

End point type	Secondary

End point timeframe:

The evolution of blood cells count between baseline and 12 weeks has been calculated.

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	28		
Units: T/L				
arithmetic mean (standard deviation)	-0.02 (± 0.27)	0.06 (± 0.29)		

Statistical analyses

Statistical analysis title	Comparison of the evolution of red BLC

Statistical analysis description:

Changes from baseline was calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4178 [37]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[37] - no significant difference

Secondary: Evolution of white blood cells count

End point title	Evolution of white blood cells count

End point description:

End point type	Secondary

End point timeframe:

The evolution was measured between baseline and 12 weeks

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	28		
Units: G/L				
arithmetic mean (standard deviation)	0.4 (± 1.51)	0.13 (± 3.53)		

Statistical analyses

Statistical analysis title	Comparison of the evolution of white BCC

Statistical analysis description:

As previously explained for red blood cells

Comparison groups	FAS Ismigen V3 v FAS Placebo V3

Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.9046 [38]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:
[38] - No significant difference between groups

Secondary: Evolution of neutrophils count

End point title	Evolution of neutrophils count

End point description:

End point type	Secondary

End point timeframe:
Evolution between baseline and 12 weeks

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	28		
Units: G/L				
arithmetic mean (standard deviation)	0.27 (± 1.28)	0.33 (± 2.53)		

Statistical analyses

Statistical analysis title	Comparison of evolution of neutrophils

Statistical analysis description:
Same as described for other blood cells

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4697 [39]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:
[39] - No difference between groups

Secondary: Evolution of basophils count

End point title	Evolution of basophils count

End point description:

End point type	Secondary

End point timeframe:
The evolution was measured between baseline and 12 weeks

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	28		
Units: G/L				
arithmetic mean (standard deviation)	0 (± 0.02)	0 (± 0.01)		

Statistical analyses

Statistical analysis title	Comparison of evolution of basophils count
Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.9838 [40]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:
[40] - no significant difference

Secondary: Evolution of lymphocytes count

End point title	Evolution of lymphocytes count

End point description:

End point type	Secondary

End point timeframe:
The evolution was measured between baseline and 12 weeks

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	28		
Units: G/L				
arithmetic mean (standard deviation)	0.12 (± 0.49)	-0.3 (± 0.86)		

Statistical analyses

Statistical analysis title	Comparison of the evolution of lymphocytes count
Statistical analysis description:	
Same as previously described for other blood cells count.	
Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0141 [41]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[41] - The evolution of the lymphocytes count was significantly different between groups. The lymphocytes number increased in the Ismigen group whereas it decreased in the Placebo group.

Secondary: Evolution of the eosinophils count

End point title	Evolution of the eosinophils count
End point description:	
End point type	Secondary
End point timeframe:	
The evolution was measured between baseline and 12 weeks	

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	28		
Units: G/L				
arithmetic mean (standard deviation)	0.01 (± 0.21)	0.06 (± 0.27)		

Statistical analyses

Statistical analysis title	Comparison of the evolution of eosinophils count
Statistical analysis description: Same as previously described for other blood cells counts.	
Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.8243 [42]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:
[42] - no significant difference between groups

Secondary: Evolution of monocytes count	
End point title	Evolution of monocytes count
End point description:	
End point type	Secondary
End point timeframe: The evolution was measured between baseline and 12 weeks	

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	28		
Units: G/L				
arithmetic mean (standard deviation)	0.01 (± 0.21)	0.04 (± 0.57)		

Statistical analyses

Statistical analysis title	Comparison of the evolution of monocytes count
Statistical analysis description: Same as previously described for other blood cells count	
Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.5564 [43]
Method	ANCOVA
Parameter estimate	Mean difference (net)

Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[43] - No significant difference between groups.

Secondary: Evolution of platelet count

End point title	Evolution of platelet count

End point description:

End point type	Secondary

End point timeframe:

The evolution was measured between baseline and 12 weeks

End point values	FAS Placebo V3	FAS Ismigen V4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	28		
Units: G/L				
arithmetic mean (standard deviation)	0.7 (± 38.2)	-13.2 (± 45.3)		

Statistical analyses

Statistical analysis title	Comaprison of the evolution of platelet counts

Statistical analysis description:

Same as previously described for other blood cells count

Comparison groups	FAS Placebo V3 v FAS Ismigen V4
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2621 [44]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[44] - No significant difference

Secondary: Evolution of IgE level

End point title	Evolution of IgE level

End point description:

End point type	Secondary

End point timeframe:

The evolution of serum IgE level was measured between baseline and 12 weeks

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	28		
Units: IU/ml				
arithmetic mean (standard deviation)	216.5 (± 574.3)	-16.7 (± 257.1)		

Statistical analyses

Statistical analysis title	Comparison of evolution of IgE level

Statistical analysis description:

Changes from baseline was calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2995 [45]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[45] - No significant difference between groups

Secondary: Evolution of IgA level

End point title	Evolution of IgA level

End point description:

End point type	Secondary

End point timeframe:

The evolution between baseline and 12 weeks was calculated for each arm

End point values	FAS Placebo V3	FAS Ismigen V4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	28		
Units: g/l				
arithmetic mean (standard deviation)	0.08 (± 0.2)	0.08 (± 0.33)		

Statistical analyses

Statistical analysis title	Comparison of the evolution of IgA level

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Placebo V3 v FAS Ismigen V4
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.5828 [46]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[46] - no difference between groups

Secondary: Evolution of IgM level

End point title	Evolution of IgM level

End point description:

End point type	Secondary

End point timeframe:

Same as for other non specific serum immunoglobulines

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	28		
Units: g/l				
arithmetic mean (standard deviation)	0.05 (± 0.14)	0.03 (± 0.28)		

Statistical analyses

Statistical analysis title	Comparison of evolution of IgM level

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.6998 [47]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[47] - No significant differences between groups

Secondary: Evolution of IgG level

End point title	Evolution of IgG level

End point description:

End point type	Secondary

End point timeframe:

the evolution was measured between baseline and 12 weeks

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	28		
Units: g/l				
arithmetic mean (standard deviation)	0.1 (± 1.1)	0.3 (± 0.9)		

Statistical analyses

Statistical analysis title	Compairison of the evolution of IgG level at V3

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3

Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.6649 [48]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[48] - No difference between groups

Secondary: Evolution of IgG1 level

End point title	Evolution of IgG1 level

End point description:

End point type	Secondary

End point timeframe:

The evolution was measured between baseline and 12 weeks

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	28		
Units: g/l				
arithmetic mean (standard deviation)	0 (± 0.8)	0.2 (± 0.8)		

Statistical analyses

Statistical analysis title	Comparison of the evolution of IgG1 level

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk’s test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.5966 [49]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:
[49] - non significant difference between groups

Secondary: Evolution of IgG2 level

End point title	Evolution of IgG2 level

End point description:

End point type	Secondary

End point timeframe:
The evolution was measured between baseline and 12 weeks

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	28		
Units: g/l				
arithmetic mean (standard deviation)	0.1 (± 0.2)	0.1 (± 0.2)		

Statistical analyses

Statistical analysis title	Comparison of the evolution of IgG2 level

Statistical analysis description:
Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.7402 [50]
Method	ANCOVA
Parameter estimate	Median difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:
[50] - No significant difference between groups

Secondary: Evolution of IgG3 level

End point title	Evolution of IgG3 level

End point description:

End point type	Secondary

End point timeframe:
The evolution was calculated between baseline and 12 weeks

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	28		
Units: g/l				
arithmetic mean (standard deviation)	0.03 (± 0.09)	0.03 (± 0.08)		

Statistical analyses

Statistical analysis title	Comparison of the evolution of IgG3 level

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2762 [51]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[51] - No significant difference between groups

Secondary: Evolution of IgG4 level

End point title	Evolution of IgG4 level

End point description:

End point type	Secondary

End point timeframe:

The evolution was calculated between baseline and 12 weeks

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	28		
Units: g/l				
arithmetic mean (standard deviation)	-0.02 (± 0.2)	0.08 (± 0.28)		

Statistical analyses

Statistical analysis title	Comparison of evolution of IgG4 level

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.3571 [52]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[52] - No significant difference between groups

Secondary: Evolution of specific IgG level

End point title	Evolution of specific IgG level

End point description:

End point type	Secondary

End point timeframe:

The change from baseline of this laboratory parameter was described at 3 weeks and 12 weeks.

End point values	FAS Ismigen V2	FAS Placebo V2	FAS Ismigen V3	FAS Placebo V3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	26	19	27
Units: arbitrary units				
arithmetic mean (standard deviation)	1.2 (± 3.1)	0.6 (± 2.9)	0.2 (± 2.9)	0.5 (± 2.7)

Statistical analyses

Statistical analysis title	Comparison of evolution of specific IgG at V2

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Placebo V2 v FAS Ismigen V2
Number of subjects included in analysis	43
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4923 [53]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[53] - No significant difference between groups

Statistical analysis title	Comparison of evolution of specific IgG at V3

Statistical analysis description:

Same as previous

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	46
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.7593 [54]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[54] - No significant difference between groups

Secondary: Evolution of specific IgG 500 level

End point title	Evolution of specific IgG 500 level

End point description:

End point type	Secondary

End point timeframe:

The evolution was measured between baseline and 3 weeks then 12 weeks.

End point values	FAS Ismigen V2	FAS Placebo V2	FAS Ismigen V3	FAS Placebo V3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	26	19	27
Units: arbitrary units				
arithmetic mean (standard deviation)	0 (± 1.7)	0.3 (± 1.4)	0.4 (± 2.6)	0.4 (± 1)

Statistical analyses

Statistical analysis title	Comparison of evolution of specific IgG500 at V2

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V2 v FAS Placebo V2
Number of subjects included in analysis	43
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.731 [55]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[55] - No significant difference between groups.

Statistical analysis title	Comparison of evolution of IgG500 at V3

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	46
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.3189 [56]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[56] - No significant difference between groups.

Secondary: Evolution of specific IgA level

End point title	Evolution of specific IgA level

End point description:

End point type	Secondary

End point timeframe:

The evolution of specific IgA level was between baseline and 3 weeks and between baseline and 12 weeks.

End point values	FAS Ismigen V2	FAS Placebo V2	FAS Ismigen V3	FAS Placebo V3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	26	19	27
Units: arbitrary units				
arithmetic mean (standard deviation)	0.5 (± 2.6)	0.1 (± 1.6)	0.3 (± 1.9)	0 (± 1.5)

Statistical analyses

Statistical analysis title	Comparison of the evolution of specific IgA at V2

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V2 v FAS Placebo V2
Number of subjects included in analysis	43
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.8525 [57]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[57] - No significant difference between groups

Statistical analysis title	Comparison of the evolution of specific IgA at V3

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3

Number of subjects included in analysis	46
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.6794 [58]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[58] - No significant difference between groups

Secondary: Evolution of specific IgA 500 level

End point title	Evolution of specific IgA 500 level

End point description:

End point type	Secondary

End point timeframe:

The evolution of specific IgA500 was calculated between baseline and V2 and between baseline and V3

End point values	FAS Ismigen V2	FAS Placebo V2	FAS Ismigen V3	FAS Placebo V3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	26	17	27
Units: arbitrary units				
arithmetic mean (standard deviation)	0.8 (± 2.5)	0 (± 1.5)	0.1 (± 1.6)	-0.1 (± 1.1)

Statistical analyses

Statistical analysis title	Comparison of the evolution of IgA500 at V2

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V2 v FAS Placebo V2
Number of subjects included in analysis	43
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.6538 [59]
Method	ANCOVA
Parameter estimate	Mean difference (net)

Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[59] - No significant difference between groups

Statistical analysis title	Comparison of evolution of specific IgG500 at V3

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.9069 [60]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[60] - No signifiant difference between groups

Secondary: Evolution of specific IgM level

End point title	Evolution of specific IgM level

End point description:

End point type	Secondary

End point timeframe:

The evolution of the specific IgM level was calculated between baseline and V2 and between baseline and V3

End point values	FAS Ismigen V2	FAS Placebo V2	FAS Ismigen V3	FAS Placebo V3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	26	19	27
Units: arbitrary units				
arithmetic mean (standard deviation)	-0.7 (± 0.2)	-0.5 (± 2.1)	0.4 (± 3)	0.3 (± 1.5)

Statistical analyses

Statistical analysis title	Comparison of the evolution of specific IgM at V2
Comparison groups	FAS Ismigen V2 v FAS Placebo V2
Number of subjects included in analysis	43
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.6892 [61]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[61] - No significant difference

Statistical analysis title	Comparison of the evolution of specific IgM at V3

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	46
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4485 [62]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[62] - No significant difference between groups

Secondary: Evolution of specific IgM 500 level

End point title	Evolution of specific IgM 500 level

End point description:

End point type	Secondary

End point timeframe:

The evolution of specific IgM500 level was calculated between baseline and V2 and between baseline and V3

End point values	FAS Ismigen V2	FAS Placebo V2	FAS Ismigen V3	FAS Placebo V3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	26	19	27
Units: arbitrary units				
arithmetic mean (standard deviation)	0.1 (± 1.1)	-0.3 (± 1.7)	0.3 (± 1.4)	0.3 (± 1.6)

Statistical analyses

Statistical analysis title	Comparison of evolution of specific IgM500 at V2

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V2 v FAS Placebo V2
Number of subjects included in analysis	43
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.6547 [63]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[63] - No significant difference

Statistical analysis title	Comparison of evolution of specific IgM500 at V3

Statistical analysis description:

Changes from baseline were calculated and compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) was used.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	46
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.8737 [64]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[64] - No significant difference between groups

Secondary: Evolution of Treg counts at V3

End point title	Evolution of Treg counts at V3

End point description:

End point type	Secondary

End point timeframe:

The evolution of Treg level was measured between baseline and V3

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	28		
Units: cells/mm3				
arithmetic mean (standard deviation)	6.5 (± 37.3)	-0.8 (± 24.8)		

Statistical analyses

Statistical analysis title	Comparison of the evolution of Treg counts

Statistical analysis description:

The change from baseline at each time 12 weeks is compared between the treatment groups using an ANCOVA with the baseline as covariate. In case of non normal distributions (evaluated by Shapiro-Wilk's test), a non-parametric analysis of covariance (based on ranks) is used.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0395 [65]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[65] - The evolution of the level of T regulatory cells (Treg) expressing CD4, FoxP3 and high level of CD25 was significantly different between groups (p=0.0395). An increase was observed in treated patients while a reduction was detected in Placebo.

Secondary: Evolution of cytotoxic T lymphocytes counts at V3

End point title	Evolution of cytotoxic T lymphocytes counts at V3

End point description:

End point type	Secondary

End point timeframe:

Evolution between baseline and V3

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	28		
Units: cells/mm3				
arithmetic mean (standard deviation)	136.6 (± 324.3)	-92.7 (± 282.8)		

Statistical analyses

Statistical analysis title	Comparison of the evolution of Cytotoxic T lymp
Statistical analysis description: As previously described for treg	
Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0181 [66]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[66] - The evolution of CD3+CD8+ lymphocyte count was significantly different between groups (p=0. 0181). An increase was observed in treated patients while a reduction was detected in Placebo.

Secondary: Evolution of NK cells count at V3

End point title	Evolution of NK cells count at V3
End point description:	
End point type	Secondary
End point timeframe: Evolution between baseline and V3	

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	28		
Units: cells/mm3				
arithmetic mean (standard deviation)	19.1 (± 114.8)	-35 (± 164)		

Statistical analyses

Statistical analysis title	Comparison of evolution of NK cells count
Statistical analysis description:	
As previously described for other white blood cells phenotypes	
Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0463 [67]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[67] - The evolution of NK cells CD3-CD16+CD56+ (count) was significantly different between groups (p=0.0463). An increase was observed in Ismigen® treated patients while a reduction was detected in Placebo.

Secondary: Evolution of late activated T lymphocytes % CD3+ at V3

End point title	Evolution of late activated T lymphocytes % CD3+ at V3
End point description:	
End point type	Secondary
End point timeframe:	
Evolution between baseline and V3 of late activated lymphocytes % CD3+ (CD3+CD25+%CD3+)	

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	28		
Units: percent of CD3+ cells				
arithmetic mean (standard deviation)	-0.6 (± 5.3)	0.7 (± 4.1)		

Statistical analyses

Statistical analysis title	Comparison of (CD3+CD25+)%CD3+ at V3
Statistical analysis description:	
As previously described for other white blood cells phenotypes	

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0243 [68]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[68] - The evolution of T cells CD3+CD25+ (% of T cells CD3+) was significantly different between groups (p=0.0243). A reduction was observed in the treated group while in the Placebo group an increase was detected.

Secondary: Evolution of early activated T lymphocytes%CD45+ at V3

End point title	Evolution of early activated T lymphocytes%CD45+ at V3

End point description:

End point type	Secondary

End point timeframe:

Evolution was measured between baseline and V3

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	28		
Units: % of CD45+ cells				
arithmetic mean (standard deviation)	-1.1 (± 3.8)	2.3 (± 11.5)		

Statistical analyses

Statistical analysis title	Comparison of evolution of (CD3+CD69+)%CD45+

Statistical analysis description:

As previously described for other phenotypes

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0129 [69]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[69] - The evolution of T cells CD3+CD69+ (% of lymphocytes CD45+) was significantly different between groups (p=0.0129). A reduction was observed in the treated group while in the Placebo group an increase was detected.

Secondary: Evolution of early activated T lymphocytes% CD3+ at V3

End point title	Evolution of early activated T lymphocytes% CD3+ at V3

End point description:

End point type	Secondary

End point timeframe:

The evolution was measured between baseline and V3

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	28		
Units: % of CD3+ cells				
arithmetic mean (standard deviation)	-2.2 (± 5.2)	2.5 (± 15.3)		

Statistical analyses

Statistical analysis title	Comparison of evolution of (CD3+CD69+)%CD+3

Statistical analysis description:

Same as previously described for other phenotypes.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.014 [70]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[70] - The evolution of T cells CD3+CD69+ (% of T cells CD3+) was significantly different between groups (p=0.0140). A reduction was observed in the treated group while in the Placebo group an increase was detected.

Secondary: Evolution of early activated T helper lymphocytes%CD45+ at V3

End point title	Evolution of early activated T helper lymphocytes%CD45+ at V3

End point description:

End point type	Secondary

End point timeframe:

The evolution was measured between baseline and V3

End point values	FAS Ismigen V3	FAS Placebo V3		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	28		
Units: % of CD45+ cells				
arithmetic mean (standard deviation)	-1.1 (± 2)	-0.1 (± 2.6)		

Statistical analyses

Statistical analysis title	Comparison of the evolution of CD4+CD69+%CD45+

Statistical analysis description:

Same as previously described for other phenotypes.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.019 [71]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[71] - The evolution of T cells CD4+CD69+ lymphocytes expressed as % of CD45+ cells was significantly different between groups: this percentage decreased in Ismigen® group whereas only a slight decrease was observed in the Placebo group .

Secondary: Total duration of infections (per patient)

End point title	Total duration of infections (per patient)

End point description:

End point type	Secondary

End point timeframe:

The total duration of infections was measured at V3, V4, V5

End point values	FAS Ismigen V3	FAS Placebo V3	FAS Ismigen V4	FAS Placebo V4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	35	32	28	36
Units: days				
arithmetic mean (standard deviation)	10.2 (± 5.3)	10.9 (± 6.8)	8.5 (± 4.9)	10.0 (± 6.3)

End point values	FAS Ismigen V5	FAS Placebo V5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	39		
Units: days				
arithmetic mean (standard deviation)	10.0 (± 5.5)	12.2 (± 12)		

Statistical analyses

Statistical analysis title	Comparison of total duration of RI at V3

Statistical analysis description:

The total duration of infections per patient (days) was compared between treatment groups using a Student's t test or Wilcoxon's test in case of non-normality.

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	67
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.89 [72]
Method	Wilcoxon (Mann-Whitney)

Notes:

[72] - No significant difference between groups.

Statistical analysis title	Comparison of total duration of RI at V4

Statistical analysis description:

Same as previously described.

Comparison groups	FAS Ismigen V4 v FAS Placebo V4
Number of subjects included in analysis	64
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.471 [73]
Method	Wilcoxon (Mann-Whitney)

Notes:

[73] - No significant difference between groups

Statistical analysis title	Comparison of total duration of RI at V5

Statistical analysis description:

Same as previously described.

Comparison groups	FAS Ismigen V5 v FAS Placebo V5
Number of subjects included in analysis	74
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.884 [74]
Method	Wilcoxon (Mann-Whitney)

Notes:
[74] - No significant difference between groups

Secondary: Number of school days lost because of respiratory infections

End point title	Number of school days lost because of respiratory infections

End point description:
School days lost or without normal activities.

End point type	Secondary

End point timeframe:
This parameter was calculated at V3, V4, V5

End point values	FAS Ismigen V3	FAS Placebo V3	FAS Ismigen V4	FAS Placebo V4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	35	32	28	36
Units: days				
arithmetic mean (standard deviation)	3.6 (± 4.2)	4.8 (± 4.8)	2.6 (± 3.0)	5.8 (± 5.1)

End point values	FAS Ismigen V5	FAS Placebo V5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	39		
Units: days				
arithmetic mean (standard deviation)	5.7 (± 4.7)	5.9 (± 6.2)		

Statistical analyses

Statistical analysis title	Comparison of school days lost because RI at V3

Statistical analysis description:
The number of school days lost (or days without normal activity) was compared between treatment groups using a Student's t test or Wilcoxon’s test in case of non-normality)

Comparison groups	FAS Ismigen V3 v FAS Placebo V3
Number of subjects included in analysis	67
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.375 [75]
Method	Wilcoxon (Mann-Whitney)

Notes:
[75] - No significant difference between groups

Statistical analysis title	Comparison of school days lost because of RI at V4

Statistical analysis description:
Same as previously described

Comparison groups	FAS Ismigen V4 v FAS Placebo V4

Number of subjects included in analysis	64
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.008 [76]
Method	Wilcoxon (Mann-Whitney)

Notes:

[76] - The number of school days lost was significantly lower in Ismigen® group as compared to Placebo group. However, the relevance of this isolated result should be questioned.

Statistical analysis title	Comparison of school days lost because RI at V5

Statistical analysis description:

Same as previously described

Comparison groups	FAS Ismigen V5 v FAS Placebo V5
Number of subjects included in analysis	74
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.646 [77]
Method	Wilcoxon (Mann-Whitney)

Notes:

[77] - No significant difference between groups

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported at all study times: V2, V3, V4, V5

Adverse event reporting additional description:

All the AE, SAE reported in the diary or reported during the visit by the patients, discovered during the visit or notified by a hospital department were recorded in the CRF after validation by the investigator. In case of SAE (no SUSAR occurred during the study), SAE forms were filled until resolution or stabilization of the SAE.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Ismigen

Reporting group description:

Treatment emergent adverse events were reported all over the study for all the patients of the Ismigen group who have taken at least 1 Ismigen tablet (safety population): 75 patients in the Ismigen group and 76 patients in the Placebo group.

Reporting group title	Placebo

Reporting group description:

Treatment emergent adverse events were reported all over the study for all the patients of the Placebo group who have taken at least 1 Ismigen tablet (safety population).

Serious adverse events	Ismigen	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 75 (1.33%)	3 / 76 (3.95%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
VIIth nerve paralysis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Status asthmaticus			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Ismigen	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 75 (94.67%)	67 / 76 (88.16%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 75 (8.00%)	3 / 76 (3.95%)	
occurrences (all)	6	3	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	42 / 75 (56.00%)	49 / 76 (64.47%)	
occurrences (all)	79	146	
Rhinitis allergic			
subjects affected / exposed	10 / 75 (13.33%)	14 / 76 (18.42%)	
occurrences (all)	15	22	
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	38 / 75 (50.67%)	35 / 76 (46.05%)	
occurrences (all)	56	63	
Pharyngitis			
subjects affected / exposed	22 / 75 (29.33%)	25 / 76 (32.89%)	
occurrences (all)	36	32	
Bronchitis			
subjects affected / exposed	13 / 75 (17.33%)	19 / 76 (25.00%)	
occurrences (all)	13	28	
Laryngitis			
subjects affected / exposed	8 / 75 (10.67%)	4 / 76 (5.26%)	
occurrences (all)	11	5	
Sinusitis			
subjects affected / exposed	7 / 75 (9.33%)	8 / 76 (10.53%)	
occurrences (all)	7	11	
Acute sinusitis			
subjects affected / exposed	4 / 75 (5.33%)	1 / 76 (1.32%)	
occurrences (all)	4	1	
Influenza			
subjects affected / exposed	0 / 75 (0.00%)	5 / 76 (6.58%)	
occurrences (all)	0	5	
Tonsillitis			
subjects affected / exposed	6 / 75 (8.00%)	2 / 76 (2.63%)	
occurrences (all)	8	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the limited blood sample volume available in accordance with paediatric regulation , samples were insufficient for most patients to perform cytokines measurements planned in the protocol. Available results are included in the full report.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/20920766

http://www.ncbi.nlm.nih.gov/pubmed/16936237

http://www.ncbi.nlm.nih.gov/pubmed/17353040

http://www.ncbi.nlm.nih.gov/pubmed/8901365

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