Clinical trial results:
Double-blind, randomised, placebo-controlled study evaluating the efficacy and safety of Tavipec capsules in acute Bronchitis
A prospective, multi-centre, parallel group, interventional clinical phase IV study

Summary

EudraCT number	2013-004836-31
Trial protocol	AT
Global end of trial date	04 January 2016

Results information

Result version number	v1 (current)
This version publication date	31 July 2022
First version publication date	31 July 2022
Summary attachment (see zip file)	Double-blind, randomized, placebo-controlled study evaluating the Efficacy and Safety of Tavipec® capsules in acute Bronchitis (Synopsis Tav01-13_2013-004836-31.pdf)

Trial information

Trial identification

Sponsor protocol code	TAV01/13

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pharmazeutische Fabrik Montavit Ges.m.b.H.
Sponsor organisation address	Salzbergstraße 96, Absam, Austria, 6067
Public contact	Mag. Gabriele Zacke, Clinical Trial Department, 0043 0522357926234, gabriele.zacke@montavit.com
Scientific contact	Mag. Gabriele Zacke, Clinical Trial Department, 0043 0522357926234, gabriele.zacke@montavit.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 January 2016
Global end of trial reached?	Yes
Global end of trial date	04 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was the mean difference of a defined total bronchitis severity score (BSS) of 25 % between the verum group and the placebo group after 7 days of full medication dose.

Protection of trial subjects:

Acute bronchitis generally is a self-limiting disease and care for acute bronchitis is primarily supportive and aims on alleviation of symptoms.
Therefore, no problems of ethics, acceptability, and feasibility are assumed to arise from the use of a placebo-concurrent control group.

Moreover, whith the selected inclusion criteria a safety net was broadly spanned to ensure that severe cases of bronchitis requiring antibiotic treatment would be excluded.

Nevertheless, a close monitoring of patients was done. After baseline next evaluation was performed following seven days of treatment, so the detection of a possible worsening of the clinical condition has been guaranteed. In case of treatment failure at this time point, treatment would have been discontinued. Patients were advised about re-consulting at any time during the study if there was a significant worsening of symptoms or occurrence of complications, including a rise in temperature above 39 °C.

For safety reasons, these subjects would have been deemed clinical failures and promptly scheduled for a treatment failure visit.

Background therapy:

Apart from saline inhalation no other concomitant medications were allowed for relief of bronchitis symptoms.

Evidence for comparator:

Tavipec is a herbal medicinal product containing spicae aetheroleum, an essential oil gained from the sun-dried flowers of Lavendula spica L., as the active ingredient. Its main constituents are linalool, 1,8-cineole (synonym: eucalyptol) and camphor.
Tavipec acts secretolytic and promotes expectoration. It positively influences mucociliary clearance and increases phagozytosis capacity, resulting in an increase of unspecific immunity.
Tavipec is authorised in twelve countries world-wide (i.e., Austria, Albania, Bulgaria, Georgia, Iran, Kazakhstan, Kyrgyztan, Modlova, Romania, Thailand, Ukraine and Uzbekistan). The first marketing autorisation was obtained in Austria on February 25, 1959. The experience gained from September 25, 2009 - September 25, 2010, the period which was covered by the Periodic Safety Update Report (PSUR), confirms the established safety profile of Tavipec capsules during this observation period.
According to the summary of product characteristics (SmPC) and package insert (PI), Tavipec is a herbal drug to support specific measures in rhinosinusitis or cough associated with a cold.
The present placebo-controlled clinical study was done to extend information on efficacy and safety of Tavipec capsules in patients suffering from acute bronchitis.

Actual start date of recruitment	03 February 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	Austria: 23
Country: Number of subjects enrolled	Poland: 235
Worldwide total number of subjects	258
EEA total number of subjects	258

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	243
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between May 2014 and January 2016 in 3 study centers in Austria and 5 study centers in Poland by general practitioner, specialist of pneumology or by hospital doctors from pneumology clinics.

Pre-assignment

Screening details:

There was no screening period as it was an acute treatment.
Only patients suffering from uncomplicated acute bronchitis with onset of first symptoms within two days before start of treatment were recruited.
In summary, 269 patients were assessed for eligibility of which 8 patient were excluded after inclusion (n=258).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Each patient received a medication bottle with capsules. In the placebo group the bottles contain Placebo, identical in appearance &taste to verum, being indistinguishable from their respective active investigational drug. Randomisation list was compiled by Sponsor. Packaging and labelling was performed by Sponsor in accordance to Sponsor's SOP. PI received a sealed emergeny envelope for each subject. Each envelope contains the identity of a subject's treatment. Opening was documented in CRF.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

The objective of the study was to evaluate the efficacy and safety of Tavipec® as compared to placebo in patients suffering from acute Bronchitis.
Acute bronchitis generally is a self-limiting disease and care for acute bronchitis is primarily supportive and aims on alleviation of symptoms.
Therefore, no problems of ethics, acceptability, and feasibility are assumed to arise from the use of a placebo-concurrent control group.
Oral intake of two Placebo capsules three times daily for ten days of treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo in form of capsules with gastroresistant coating filled with Medium-Chain Triglycerides (Manufacturer: Pharmazeutische Fabrik Montavit Ges.m.b.H).
The route for all study medications was oral application. Placebo capsules was ingested three times daily (Morning: 2 capsules; Lunchtime: 2 capsules; Evening: 2 capsules)

Patients were instructed to swallow capsules as a whole with some liquid, 30 minutes before a meal.

Arm title	Tavipec

Arm description:

The objective of the study was to evaluate the efficacy and safety of Tavipec® as compared to placebo

in patients suffering from acute Bronchitis.
Oral intake of two Tavipec capsules three times daily for ten days of treatment.

Arm type	Active comparator
Investigational medicinal product name	Tavipec®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tavipec® are capsules with gastroresistant coating containing 10 mg spicae aetheroleum.
The route for all study medications was oral application.
The study medication was provided for the investigators by Pharmazeutische Fabrik Montavit Ges.m.b.H., Austria.

Tavipec was ingested three times daily (Morining: 2 capsules; Lunchtime: 2 capsules; Evening: 2 capsules).

Patients were instructed to swallow capsules as a whole with some liquid, 30 minutes before a meal.

Number of subjects in period 1	Placebo	Tavipec
Started	127	131
Follow-Up	120	125
ITT Analysis day 7	120	125
ITT Analysis (QoL) day 10	112	119
PP Analysis day 7 & 10	110	119
Completed	110	119
Not completed	17	12
Consent withdrawn by subject	3	1
Hospitalization (SAE)	1	-
Treatmet failure	8	-
Treatment failure	-	10
Adverse event, non-fatal	-	1
Non compliance	5	-

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	258	258	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 40.36 ± 14.06	 -	
Gender categorical Units: Subjects			
Female	127	127	
Male	131	131	

Subject analysis sets

Subject analysis set title	Placebo group
Subject analysis set type	Full analysis
Subject analysis set description: Analysis of Placebo group	
Subject analysis set title	Tavipec group
Subject analysis set type	Full analysis
Subject analysis set description: Analysis of Tavipec group	

Reporting group values	Placebo group	Tavipec group	
Number of subjects	127	131	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 40.36 ± 15.04	 40.36 ± 13.11	
Gender categorical Units: Subjects			
Female	68	59	
Male	59	72	

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

The objective of the study was to evaluate the efficacy and safety of Tavipec® as compared to placebo in patients suffering from acute Bronchitis.
Acute bronchitis generally is a self-limiting disease and care for acute bronchitis is primarily supportive and aims on alleviation of symptoms.
Therefore, no problems of ethics, acceptability, and feasibility are assumed to arise from the use of a placebo-concurrent control group.
Oral intake of two Placebo capsules three times daily for ten days of treatment.

Reporting group title	Tavipec

Reporting group description:

The objective of the study was to evaluate the efficacy and safety of Tavipec® as compared to placebo in patients suffering from acute Bronchitis.
Oral intake of two Tavipec capsules three times daily for ten days of treatment.

Subject analysis set title	Placebo group
Subject analysis set type	Full analysis

Subject analysis set description:

Analysis of Placebo group

Subject analysis set title	Tavipec group
Subject analysis set type	Full analysis

Subject analysis set description:

Analysis of Tavipec group

Primary: PRIMARY EFFICACY EVALUATION BSS: Mean change (improvement from baseline) at day 7, ITT/PP

End point title	PRIMARY EFFICACY EVALUATION BSS: Mean change (improvement from baseline) at day 7, ITT/PP

End point description:

As the only primary efficacy parameter the mean difference of a defined total BSS of 25 % between the verum group and the placebo group after 7 days of full medication dose was chosen.
A sum score from signs and symptoms was formed for evaluation purposes, comparing changes from baseline in both treatment groups.
The BSS in the presented study is the sum of the indivual scores of: Cough, Sputum, Rales/rhonchi, Chest pain during coughing and Dyspnea (0= absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe)

End point type	Primary

End point timeframe:

Primary end point was assessed between May 2014 and January 2016

End point values	Placebo group	Tavipec group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	120[1]	125[2]		
Units: score points				
number (confidence interval 95%)	4.53 (4.12 to 4.95)	2.92 (2.44 to 3.394)		

Notes:

[1] - ITT Placebo group used for analysis

[2] - ITT Tavipec group used for analysis

Attachments (see zip file)	Tav01-13_Results_primary endpoint/Tav01-13_Primary

Statistical analyses

Statistical analysis title	Primary endpoint: BSS difference day 0 and 7 (ITT)

Statistical analysis description:

The main efficacy variable is quantitative, however, not necessarily normally distributed;
Therefore a two sided (α = 5 %) Mann-Whitney test (rank-sum test) was applied to test the following hypothesis (null hypothesis):
H0: μ BSS (day 7) placebo = μ BSS (day 7) verum
H1: μ BSS (day 7) placebo ≠ μ BSS (day 7) verum

Comparison groups	Placebo group v Tavipec group
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Confidence interval	
sides	2-sided
Variability estimate	Standard deviation

Secondary: SECONDARY EFFICACY EVALUATION BSS: Mean change (improvement from baseline) at day 10, PP

End point title	SECONDARY EFFICACY EVALUATION BSS: Mean change (improvement from baseline) at day 10, PP

End point description:

As an second efficacy parameter the mean difference of a defined total BSS of 25 % between the verum group and the placebo group after 10 days of full medication dose was chosen.
A sum score from signs and symptoms was formed for evaluation purposes, comparing changes from baseline in both treatment groups.
The BSS in the presented study is the sum of the indivual scores of: Cough, Sputum, Rales/rhonchi, Chest pain during coughing and Dyspnea (0= absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe)

End point type	Secondary

End point timeframe:

May 2014 - January 2016

End point values	Placebo group	Tavipec group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	110[3]	119[4]		
Units: score points				
number (confidence interval 95%)	4.32 (3.77 to 4.886)	6.47 (6.09 to 6.873)		

Notes:

[3] - PP Placebo group used for analysis

[4] - PP Tavipec group used for analysis

Attachments (see zip file)	Tav01-13_Secondary endpoints_results/Tav01-13_Secondary

Statistical analyses

Statistical analysis title	Secondary endpoint: BSS difference day 0 & 10 (PP)

Statistical analysis description:

The main efficacy variable is quantitative, however, not necessarily normally distributed;
Therefore a two sided (α = 5 %) Mann-Whitney test (rank-sum test) was applied to test the following hypothesis (null hypothesis):
H0: μ BSS (day 7) placebo = μ BSS (day 7) verum
H1: μ BSS (day 7) placebo ≠ μ BSS (day 7) verum

Comparison groups	Placebo group v Tavipec group
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: SECONDARY EFFICACY QoL score: Mean change (improvement from baseline) at day 7 and day 10, ITT

End point title	SECONDARY EFFICACY QoL score: Mean change (improvement from baseline) at day 7 and day 10, ITT

End point description:

The impact of the disease on quality of life was evaluated globally by the question "How troublesome are your symptoms of bronchitis". At any visit, patients had to assess their condition on a 10-point scoring system ranging from "Not troublesome" (= 0) to "Worst thinkable troublesome" (= 10).

Results below show mean change at day 10 for ITT (QoL) Placebo and Tavipec group (n = 112 / n = 119).
Summary of all QoL results (baseline, day 7 and day 10) shown in the attachment.

Number of patients of ITT Placebo group (day 7) = 120
Number of patients of ITT Tavipec group (day 7) = 125

End point type	Secondary

End point timeframe:

May 2014 - January 2016

End point values	Placebo group	Tavipec group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112[5]	119[6]		
Units: Number of patients				
number (not applicable)	4.46	6.52		

Notes:

[5] - ITT (QoL) Placebo group for d 10

[6] - ITT (QoL) Tavipec group for d 10

Attachments (see zip file)	Tav01-13_Secondary endpoints_results/Tav01-13_Secondary

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Non-serious AEs assessed by the investigator have to be reported to Montavit by e-mail within 30 days from receipt.
All SAEs have to be reported at latest within 24 hours of the first awareness of the event.

Adverse event reporting additional description:

At each visit, all AEs either reported by the patient or observed by the investigator were evaluated and recorded into the CRF. Each AE was described by its duration, frequency, severity, its relationship to the trial medication, its influence on administration or study medication and a possible requirement of therapy.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Tavipec® capsules

Reporting group description:

Tavipec® capsules with gastroresistant coating; 2 capsules containing 150 mg spicae aetheroleum each, thrice daily

Reporting group title	Placebo

Reporting group description:

Placebo capsules with gastroresistant coating; 2 capsules containing Medium-Chain Triglycerides each, thrice daily

Serious adverse events	Tavipec® capsules	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 131 (0.00%)	1 / 127 (0.79%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Hospitalisation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 131 (0.00%)	1 / 127 (0.79%)	
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: 0 %

Non-serious adverse events	Tavipec® capsules	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 131 (9.92%)	9 / 127 (7.09%)	
Injury, poisoning and procedural complications			
Trauma of left feet	Additional description: HLT Limb injuries NEC (incl. traumatic amputation)		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 131 (0.76%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Hypoacusis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 131 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 131 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 131 (2.29%)	1 / 127 (0.79%)	
occurrences (all)	3	1	
Abdominal discomfort			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 131 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 131 (5.34%)	5 / 127 (3.94%)	
occurrences (all)	7	5	
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 131 (0.76%)	0 / 127 (0.00%)	
occurrences (all)	1	0	

Skin and subcutaneous tissue disorders Rash alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	 2 / 131 (1.53%) 2	 0 / 127 (0.00%) 0	
Musculoskeletal and connective tissue disorders Back pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Back thoracic pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	 0 / 131 (0.00%) 0 0 / 131 (0.00%) 0	 1 / 127 (0.79%) 1 1 / 127 (0.79%) 1	
Infections and infestations Oral herpes alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	 1 / 131 (0.76%) 1	 0 / 127 (0.00%) 0	

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.

n.a

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29209859