1. Synopsis

Name of Sponsor/Company: Pharmazeutische Fabrik Montavit Ges.m.b.H. Salzbergstraße 96, 6067 Absam/ Austria	**EudraCT number:** 2013-002977-23
Name of finished product: Tavipec® capsules enteric coated	
Name of active ingredient: Spicae aetheroleum	

Title of Study:	Double-blind, randomised, placebo-controlled study evaluating the Efficacy and Safety of Tavipec® capsules in acute Rhinosinusitis
Study centres:	*4 Study centres in Austria:* 101 Univ. Prof. Dr. med. Herbert Riechelmann, Medical University of Innsbruck, ENT-Department, Anichstraße 35, 6020 Innsbruck 102 Prof. Dr. med. Peter Kufner, Amraserstraße 25, 6020 Innsbruck 110 Ao. Prof. Dr. Christian Müller, General Hospital of Vienna, ENT-Department, Währinger Gürtel 18-20, 1090 Vienna 111 Prim. Ass. Prof. Priv. Doz. Dr. Florian Kral, Kardinal Schwarzenberg´sches Hospital, ENT-Department, Kardinal-Schwarzenberg-Straße 2-6, 5620 Schwarzach im Pongau *6 Study centres in Poland:* 201 Tadeusz Derezinski MD Ph.D., 88-140 Gniewkowo, Dworcowa 8 202 Joanna Bocian-Sobkowska MD Ph.D., 60-185 Skorzewo, Poznanska 74 204 Dorota Wiśniewska MD Ph.D., 87-100 Toruń, Szczytna 20 205 Piotr Kubalski MD Ph.D., 86-300 Grudziadz, Poniatowskiego 15 (address of the administration) Dabrowki 2 and Ikara 4 (places of clinics attending the trial) 206 Witold Szymański MD, 96-232 Regnów, Regnów 86 207 Jerzy Orłowski MD, 26-300 Opoczno, Partyzantow 1A
Phase of development:	IV
Study period (years): **Date of first enrolment:** **Date of last completed:**	3 years 28.01.2014 11.10.2016
Objectives:	*In terms of efficacy:* • Prospective evaluation of effects on relevant symptoms, including rhinorrhoea, postnasal drip, nasal congestion/stuffiness, sinus headache, facial pain, reduction/loss of smell (hyposmia), sublingual temperature <38,3°C, no dental involvement and impairment of general conditions *In terms of impact of disease on quality of life (QOL) from patients´ view:* • Prospective evaluation of change of QOL by global assessment (verbal rating) scale • Prospective evaluation of change of QOL by Sino-Nasal Outcome Test (SNOT-22, questionnaire) *In terms of safety and tolerance:* • Prospective evaluation of side effects (incidence and severity)

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Methodology:	Prospective, multi-centre, parallel group, interventional clinical phase IV study
Number of patients:	Planed: 280 Enrolled: 288 Evaluable for safety analysis: 288 (safety population) ITT-population: 268 Evaluable for efficacy analysis day 5: 253 (per protocol (PP) population day 5) Evaluable for efficacy analysis day 8: 238 (per protocol (PP) population day 8)
Diagnosis and main criteria for inclusion:	Patients of both genders aged between ≥18 and 75 years suffering from uncomplicated acute viral rhinosinusitis without requiring antibiotic treatment were included
Test product: **Dose:** **Mode of administration:** **Batch number**	Tavipec® capsules with gastroresistant coating 2 capsules containing 150mg Spicae aetheroleum each, thrice daily Oral 13253504 **Expiry Date:** 21.03.2016 3611 **Expiry Date:** 09.2019
Reference therapy: **Dose:** **Mode of administration:** **Batch number**	Placebo capsules with gastroresistant coating 2 capsules containing medium chain triglycerides, thrice daily Oral 11536401 **Expiry Date:** 28.02.2015 (Prolongation: 31.12.2016)
Duration of treatment:	7 days

CRITERIA FOR EVALUATION:

Efficacy:

Primary:

- Mean difference of an investigator-evaluated Major Symptom Score (MSS) of 20% between the verum group and the placebo group after 4 days of full medication dose

Secondary:

- Mean difference of an investigator-evaluated MSS of 20% between the verum group and the placebo group after 7 days of full medication dose
- Mean difference of the adapted investigator-evaluated MSS of 20% between the verum group and the placebo group after 4 days of full medication dose
- Mean difference of the adapted investigator-evaluated MSS of 20% between the verum group and the placebo group after 7 days of full medication dose
- Global impact of disease on QOL as assessed by patient
- % of patients with improvement of health-related QOL score as revealed by Sino-Nasal Outcome Test (SNOT-22) by at least ten score points

Safety:

Adverse event rate

Statistical methods:	Primary endpoint: Mann-Whitney test of the null hypothesis Secondary endpoint: Mann-Whitney test, descriptive statistical methods Safety analysis: Descriptive statistical methods

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SUMMARY CONCLUSION:

Efficacy results:

Primary Efficacy Evaluation

- Mean difference of an investigator-evaluated MSS of 20% between the verum group and the placebo group after 4 days of full medication dose (PP day 5)

		Tavipec	Placebo
MSS day 0		8,7344	8,6640
MSS day 5		5,0078	5,5840
Number of patients		128	125
Mann-Whitney test	Significance	p=0,067	
	Significance of Diff. >20%	p=0,638	

Secondary Efficacy Evaluation

- Mean difference of an investigator-evaluated MSS of 20% between the verum group and the placebo group after 7 days of full medication dose (PP day 8)

		Tavipec	Placebo
MSS day 0		8,7295	8,5948
MSS day 8		2,5410	3,5259
Number of patients		122	116
Mann-Whitney test	Significance	p=0,049	
	Significance of Diff. >20%	p=0,893	

- Mean difference of the adapted investigator-evaluated MSS of 20% between the verum group and the placebo group after 7 of full medication dose (PP day 8)

		Tavipec	Placebo
adapted MSS day 0		10,4590	10,2500
adapted MSS day 8		3,0000	4,2759
Number of patients		122	116
Mann-Whitney test	Significance	p=0,040	
	Significance of Diff. >20%	p=0,770	

- Mean difference of the adapted investigator-evaluated MSS of 20% between the verum group and the placebo group after 4 days of full medication dose (PP day 5)

		Tavipec	Placebo
adapted MSS day 0		10,4375	10,3280
adapted MSS day 5		5,9531	6,7040
Number of patients		128	125
Mann-Whitney test	Significance	p=0,065	
	Significance of Diff. >20%	p=0,456	

- Global impact of disease on QOL as assessed by patient: mean difference from baseline to the end of 4 and 7 days of full medication dose (PP day 5, PP day 8)

	Day 5 (PP day 5)		**Day 8** (PP day 8)	
	Tavipec	Placebo	Tavipec	Placebo
Difference to day 0	3,24	2,32	5,23	3,85
Number of patients	128	125	122	116
Mann-Whitney test Significance (p-values)	0,0000027678		0,0000000051	

- % of patients with improvement of health-related QOL score as revealed by SNOT-22 by at least ten score points (PP day 5, PP day 8)

			Change in SNOT-22 day 0-5 ≥10 score points (PP day 5)		**Change in SNOT-22 day 0-8 ≥10 score points** (PP day 8)	
			Frequency	Percent	Frequency	Percent
VERUM	valid	no	24	18,8	5	4,1
		yes	104	81,3	115	94,3
		total	128	100,0	120	98,4
	Missing	system	-	-	2	1,6
	Total		-	-	122	100,0
PLACEBO		no	51	41,1	18	15,7
		yes	73	58,9	97	84,3
		total	124	100,0	115	100,0
Chi-Square test			0,0001025 (Fisher´s exact test 2-sided: 0,0001109)		0,003 (Fisher´s exact test 2-sided: 0,004)	

ADDITIONAL ANALYSES

Adjustment for covariates

To analyse the influence of the initial MSS and single signs and symptoms values at baseline visit on the primary efficacy endpoint those two factors have been chosen as covariates. MSS baseline value as covariate resulted in a significance level for the primary endpoint of p=0,029.

The values of the single symptoms as covariate resulted in a significance level of p<0,05 for nasal obstruction, rhinorrhoea and hyposmia.

Covariates – Tests of Between-Subjects Effects; MSS baseline value as covariate

Dependent variable: MSS (day 5)

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	195,152 [a]	2	97,576	19,250	0,000
Intercept	0,622	1	0,622	0,123	0,726
MSS day 0	174,157	1	174,157	34,358	0,000
Verum Placebo	24,432	1	24,432	4,820	0,029
Error	1267,204	250	5,069		
Total	8549,000	253			
Corrected Total	1462,356	252			

[a] R squared = 0,133 (Adjusted R squared = 0,127)

Covariates – Tests of Between-Subjects Effects; baseline value of MSS single signs and symptoms as covariate

Dependent variable: MSS (day 5)

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	309,631 [a]	7	44,233	9,401	0,000
Intercept	8,539	1	8,539	1,815	0,179
Nasal obstruction	100,268	1	100,268	21,311	0,000
Rhinorrhoea	44,721	1	44,721	9,505	0,002
Postnasal drip	16,863	1	16,863	3,584	0,060
Sinus headache	1,902	1	1,902	0,404	0,526
Facial pain	10,821	1	10,821	2,300	0,131
Hyposmia	28,384	1	28,384	6,033	0,015
Verum Placebo	22,803	1	22,803	4,846	0,029
Error	1152,724	245	4,705		
Total	8549,000	253			
Corrected Total	1462,356	252			

[a] R squared = 0,212 (Adjusted R squared = 0,189)

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Safety Results:

A total of 34 patients (26/147 group Tavipec, 8/141 group placebo) out of 288 reported at least one adverse event (AE). The total number of adverse events was 39 (30 in group Tavipec, 9 in group placebo). 2 out of 39 adverse events (both group Tavipec) have been assessed with a probable relationship to the study medication. Further 23 (20 group Tavipec, 3 group placebo) have been reported with a possible, 6 (3 Tavipec group, 3 placebo group) with an unlikely and 8 (5 Tavipec group, 3 placebo group) with an unrelated relationship to the study medication.
In 3,55% of the patients treated with placebo (5 out of 141) and 14,29% treated with Tavipec (21 out of 147) adverse events occurred that might be related to the study medication.
25 of the 31 potentially related adverse events are diseases of the digestive system mainly abdominal pain (14 group Tavipec, 2 group placebo) and nausea (4 group Tavipec, 1 group placebo), beside diarrhoea, breath odour, dysgeusia (1 group Tavipec respectively) and feeling of fullness in the abdomen (1 group placebo). Furthermore headache, vertigo, sleep disturbance, epistaxis and increased blood pressure have been observed. No adverse event was defined as definitely related and only one AE (abdominal pain, Tavipec group) was classified with severe.

CONCLUSION

Assessment of Major Symptom Score:
During a 4-day treatment course the MSS improved by a mean of 3,7266 and 3,0800 score points in the Tavipec and placebo group, respectively in the PP day 5 population. Resulting in a difference between both groups of 0,6466 score points. The difference between both groups in terms of improvement was in favour of Tavipec, however reached no statistical significance.

After 7 days of full medication dose the mean change of MSS from baseline was 6,1885 score points in the Tavipec group and 5,0689 score points in the placebo group. The Mann-Whitney test shows a significance level of p=0,049. Thus it can be concluded that the MSS at day 8 for the verum group is significantly lower than for the placebo group. Taking the aimed 20% difference into account the significance level decreases to p=0,893.

During a 4-day treatment course the adapted MSS dropped from 10,4375 and 10,3280 score points in the Tavipec and placebo group, respectively at baseline to 5,9531 and 6,7040 score points at day 5, corresponding to an improvement of 4,4844 and 3,6240 score points in those patients. The difference between both groups in terms of improvement was in favour of Tavipec, however reached no statistical significance.

After 7 days of full medication dose the mean difference of the adapted MSS between day 0 and day 8 was 7,4590 and 5,9741 in group Tavipec and placebo. The Mann-Whitney test shows a significance level of p=0,040. Thus it can be concluded that the adapted MSS at day 8 for the verum group is significantly lower than for the placebo group. Taking the aimed 20% difference into account the significance level decreases to p=0,770.

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Assessment of quality of life:

A significant improvement of quality of life (QOL) has been shown on day 5 and day 8 for patients treated with Tavipec (day 5: p=0,0000027678; day 8: p=0,0000000051). After 4 days of full medication dose the QOL score improved by 3,24 and 2,32 score points in the Tavipec and placebo group, respectively. Resulting in a difference between both groups of 0,92 score points. After 7-day treatment, the improvement of QOL score between Tavipec and placebo differed even by 1,37 score points (Tavipec: 5,24; placebo: 3,87).

The analysis of the SNOT-22 results came to the same conclusion. 81,3% of patients treated with Tavipec and 58,9% treated with placebo showed a change in SNOT-22 greater or equal 10 score points from day 0 to day 5. Resulting in a significant higher change in SNOT-22 for the verum group than for the placebo group as confirmed with the Chi-Square test (p=0,0001025).
Also after 7-treatment days the proportion of subjects with change in SNOT-22 for the verum group was significantly higher than for the placebo group as confirmed by the Chi-Square test (p=0,003).

The presented study provides no new information with respect of any safety related concerns. Adverse events such as gastrointestinal tract reactions are known adverse drug reactions of Tavipec and listed in the SmPC.

Date of report: 15.05.2018