CONFIDENTIAL

„Clinical Trial to Evaluate the Efficacy and Safety of Oral TRANSIDOSE in Patients Suffering from Constipation"

TRANSIDOSE-Study

Statistical Report

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Contents

Study synopsis

Titel of study:	Clinical Trial to Evaluate the Efficacy and Safety of Oral TRANSIDOSE in Patients Suffering from Constipation
Short title:	TRANSIDOSE-Study
Indication:	Constipation with associated symptoms
Objectives:	Evaluation of efficacy and safety of TRANSIDOSE
Study design:	open-label study with one active group, single center
Study population; inclusion- /exclusion criteria:	Inclusion criteria: - Age of the patients: ≥ 18 years - Male and female patients (if female – adequate contraception in case of child bearing potential) - Stool frequency less than 3 per week - Compliance with Rome III criteria - Colonoscopy Exclusion criteria: - Age of the patients: < 18 years - Positive result of colonoscopy - Alarm symptoms - Hypersensitivity to the active substances or any excipients - Organic inflammatory bowel disease - Toxic megacolon - Gastrointestinal obstruction or subocclusive syndromes - Painful abdominal syndromes of undetermined origin - Pregnancy - Presumed non-cooperativeness - Legal incapacity - Any clinical condition which does not justify study participation in the investigator's opinion - Participation in a clinical trial < 4 weeks - Parallel participation in a clinical trial - Repeated participation in this clinical trial
Number of subjects:	30 patients
Trial treatment:	Active treatment period of 2 weeks; usage of 1 active medicine: TRANSIDOSE; oral intake of 1 up to 2 sachets (to each 10 g) in the evening but not shortly before bedtime

Primary endpoint:	Number of complete sponaneous defecations per week after a treatment of two weeks compared with the baseline situation
Secondary endpoints:	Constipation symptoms (bloating, pain, discomfort, bowel movements, excessive exertion, unsatisfactory defecation); Bristol Stool Form Scale; patient judgement of efficacy; safety parameters (adverse events; vital signs, laboratory results; patient judgement of tolerability; clinical global impression (CGI))
Biostatistics:	Descriptive analysis; analysis of primary endpoint by Wilcoxon matched-pairs signed rank-test; examination of the influence of the daily dose of lactulose by analysis of variance for repeated measurements; comparison of secondary endpoints by Wilcoxon, sign or symmetry tests
Duration of the trial:	Overall duration of the trial: 3 weeks (1 week wash-out period follwoed by 2 weeks active treatment

1. General study information

Medical Background and Relevance

Constipation is a frequent disorder which affects male and female patients; the portion of prevalence in female patients is higher. Affected patients have a considerable psychological stress. Patients suffering from constipation report a reduced stool frequency as well as abnormal stool consistency (lumpy, hard stools). Careful medical examination and accurate histories are essential in order to find the most appropriate treatment for these patients. Associated conditions like the irritable bowel syndrome (IBS), Morbus Parkinson, or opioid use for example should be taken into consideration.

The medical product TRANSIDOSE is a sweetened and flavoured pharmaceutical preparation containing a specific pure crystallized lactulose without galactose dispersed in oral Vaseline to obtain the desired consistency and overall protection with a specific patented hydrophobic coating, maintaining 100% of the osmotic pressure.
TRANSIDOSE is a glossy paste, yellow to orange-yellow, opaque and compact, finely granular, packaged in 10 g sachets.
Besides the active ingredient lactulose TRANSIDOSE contains as further components: oral vaseline (hydrophobic coating), aspartame (sweetener), cholesterol (emulsifier), lactic acid (flavour enhancing agent), bixin oil (colouring agent) as well as mandarin oil, lemon oil and sweet orange oil (flavouring agents).

Lactulose in general is a well-known laxative which acts through its osmotic power in the intestine. It is usually used either in the form of a 50% solution or in a pure powdered form. In these presentations, the active oral doses of lactulose range from 10 to 30 grams per day. These high doses can result in undesirable side effects such as flatulence or bloating.

In the TRANSIDOSE product, the lactulose is mixed with a hydrophobic substance (oral Vaseline) having a melting point near 37°C, in order to preserve 100% of the osmotic pressure. Anhydrous lactulose is thus available in the intestinal tract. Using these conditions, it was possible to lower the clinical working daily doses to 1.75 to 5.25 grams of lactulose per day for an adult, with an average daily dosage of 3.5 g (= 1 stick of 10 g of TRANSIDOSE).

The objectives of this clinical trial are the evaluation of the efficacy and safety of TRANSIDOSE.

Design / Course of the Study

Candidates for the participation in this monocentric clinical trial are male and female patients as of 18 years of age, suffering from constipation with associated symptoms. Indication for inclusion in the study are rare bowel movements (stool frequency less than three times a week) and the fulfillment of the Rome III criteria. Moreover, a colonoscopy should be done.

The overall duration of the study will be three weeks. The study is introduced by a wash-out period of one week. During this period, patients should not use laxatives. Afterwards the two-week active treatment period follows. The daily dosage during treatment will range between 10 g and 20 g TRANSIDOSE (1 to 2 sachets corresponding to 3.5 to 7 g lactulose), taken orally as single dose in the evening but not shortly before bedtime.
If diarrhea occurs, the dosage has to be reduce. If diarrhea persists the treatment with TRANSIDOSE has to be discontinued.

All patients are examined according to the following schedule in one-week intervals..

Table 1: Flow Chart

	T_{-7} (Start wash-out)	T_0 (Start treatment)	T_7 (Visit after 1 week)	T_{14} (Final visit)
Physical Examination	X	X		X
Constipation symptoms	X	X	X	X
Stool frequency	X	X	X	X
B(ristol) S(tool) F(orm) S(cale)	X	X	X	X
Laboratory Tests *	X			X
Rome III Criteria	X			
Colonoscopy	X			
Alarm Symptoms	X			
Adverse Events		X	X	X
Dosing			X	X
Vital Signs	X	X	X	X
Global Efficacy				X
Global Tolerability				X
C(linical) G(lobal) I(mpression)				X

* Following parameters will be measured: complete blood count, sodium, potassium, calcium, glucose, ALAT, creatinin, TSH

Follow-up visits may be appropriate in case of persisting adverse events.

2. Methods

The independent statistical analysis for this study was carried out by the Institute for Biometry and Medical Informatics at the University of Magdeburg based on the analysis plan (study protocol version 1.4 from December 11rd, 2013, section 9). The analyses were done with the software IBM SPSS Statistics, Version 21.
The basis of the analyses are the questionnaires that were filled out to the individual examinations by the physician. The items of these questionnaires were registered by a medical information specialist in an appropriately prepared SPSS data file. To ensure the accuracy of the data a second acquisition by another documentalist was carried out, followed by cross-check of the two data files.

Two study populations are analyzed: The per-protocol (PP) population includes the cases that have no protocol deviations. The intention-to-treat (ITT) population is based on all cases that have received at least one dose of the test substance. Missing values are replaced here by the LOCF principle.

The primary endpoint was the number of spontaneaous evacuation per week after a treatment of two weeks compared with the baseline situation. Secondary endpoints were further statements about the efficacy of the therapy as well as to their safety. Regarding the efficacy of the study medication constipation symptoms (bloating, pain, discomfort, bowel movements, excessive exertion, unsatisfactory defecation), the Bristol Stool Form Scale and the global efficacy evaluation by the patient were examined. In connection with the tolerability and safety, adverse events, vital signs, laboratory results, the global assessment of tolerability by the patient as well as the overall clinical impression (Clinical Global Impression Scale, CGI) were evaluated.

First, descriptive analyses over all study time points were executed. The results were reported as frequencies or as location- and scattering parameters (including the 95% confidence intervals).
Only the primary endpoint (rate of defecations per week) was tested confirmatory. The analysis was performed using Wilcoxon matched-pairs signed rank-test. Furthermore, the possible influence of the daily dose of lactulose on the rate of defecations was considered using analysis of variance (ANOVA) for repeated measurements.
The secondary endpoints were compared depending on the scale level by Wilcoxon, sign or symmetry tests.
All analyzes were performed with two-sided tests. Significance was taken at $p < 0.05$.

3. Patient Flow

The period from inclusion of the first patient to the inclusion of the last patient was more than 15 months. Within this period, a total of 10 patients were included. Originally 30 patients were planned. Of the 10 patients included 8 patients have officially completed the study after two weeks treatment. 2 patients finished the study at own request prematurely – the one patient after one week treatment, the other before beginning of treatment.

4. Basic Data

All 10 study patients are women aged from 39 to 70 years. The diagnosis was first made at an age of 6 to 54 years. Table 1 gives an overview on the patient population at study entry.

Table 1: Patient characteristics

Sex	male female		0 (0%) 10 (100%)
Ethnic group	caucasian latino		9 (90%) 1 (10%)
Social status	single married		4 (40%) 6 (60%)
Age	Mean ± SD Median ; (Min ; Max)		55.9±11.1 61 ; (39 ; 70)
Height (cm)	Mean ± SD Median ; (Min ; Max)		163.5±5.9 164 ; (154 ; 172)
Weight (kg)	Mean ± SD Median ; (Min ; Max)		66.1±18.4 65.5 ; (46 ; 104)
BMI	Mean ± SD Median ; (Min ; Max)		24.5±5.7 24.6 ; (18. ; 35.2)
Age at diagnosis	Mean ± SD Median ; (Min ; Max)		32.5±14.2 36.5 ; (6 ; 54)
Pre-treatment	yes no		5 (50%) 5 (50%)
Result of pre-treatment	Efficacy	very good good moderate poor	0 1 2 1
	Tolerability	very good good moderate poor	1 0 3 0
Concomitant diseases	yes no		8 (80%) 2 (20%)
Concomitant medication	yes no		9 (90%) 1 (10%)

No patient showed physical or psychiatric abnormalities in relation to the medical history.

In Tables 2 to 5 the results of the screening examination are summarized. The results include information on vital signs and constipation diagnostic.

Table 2: Vital signs

Systolic blood pressure	Mean ± SD Median ; (Min ; Max)	124.5±12.7 125.5 ; (98 ; 140)
Diastolic blood pressure	Mean ± SD Median ; (Min ; Max)	77.4±9.5 80 ; (61 ; 92)

Heart rate	Mean ± SD Median ; (Min ; Max)	67.7±6.4 67.5 ; (61 ; 83)

Table 3: Stool frequency, Bristol Stool Form Scale

Stool frequency (per week)	Mean ± SD 95% CI (Min ; Max)	1.6±0.52 [1.23 ; 1,97] (1 ; 2)
Bristol Stool Forms	- Type 1 - Type 2 - Type 3 - Type 4 - Type 5 - 7	8 (80%) 1 (10%) 0 (0%) 1 (10%) 0 (0%)

Table 4: Constipation symptoms

	not present	mild	moderate	severe	severe to extreme	extreme
Bloating	0	2	6	2	0	0
Pain	0	4	6	0	0	0
Discomfort	1	5	3	0	0	1
Bowel Movements	0	5	3	2	0	0
Excessive Straining	0	1	2	6	0	1
Unsatisfactory Defecations	0	1	2	5	1	1

Table 5: ROME III criteria

	yes
Presence for at least 3 months during a period of 6 months	10 (100%)
Insufficient criteria for irritable bowel syndrome	10 (100%)
No, or rarely loose stools present w/o use of laxatives	10 (100%)
Straining	9 (90%)
Lumpy or hard stools	9 (90%)
Sensation of incomplete defecations	5 (50%)
Sensation of anorectal obstruction / blockage	1 (10%)
Manual manoeuvres to facilitate defecation	0 (0%)
Fewer than 3 defecations per week	9 (90%)

None of the patients showed any alarm symptoms or situations.

5. Analyses of Efficacy

Intention-to-treat population

Two patients discontinued the study early – one of them even before beginning of treatment. The ITT-Analysis thus includes 9 cases. The missing values were replaced by the LOCF principle.

Concerning the primary outcome criterion, the difference of number of spontaneaous evacuation per week after a treatment of two weeks compared with the baseline situation were calculated and tested using Wilcoxon matched-pairs signed rank-test.
Here, a significant increase was observed (p = 0.004). The Hodges-Lehmann estimator for the median increase as the related effect estimator was 3.5 with 95% confidence interval (CI) of [2.0; 4.5]. The mean increase amounted at 3.3 evacuations (95% CI [2.1; 4.6]).
The mean daily dose of TRANSIDOSE was 12.5 ± 3.9 g (corresponding to 1.25 ± 0.39 sacchets per day), which confirmed a lower daily dosage of lactulose of 4.38 ± 1.36 g. The analysis of variance for repeated measurements revealed no significant effect of dose on the increase of defecations (p = 0.685).
Regarding individual constipation symptoms (bloating, pain, discomfort, bowel movements, excessive straining, unsatisfactory defecation) partially improvements were observed, which, however, were not significant.
With respect to the Bristol Stool Form Scale, a significant improvement (p = 0.016) could be shown.
The corresponding results are summarized in Tables 6 to 8 and in Figure 1.

Table 6: Results - defecations

		Baseline	After 2 weeks	p-value Wilcoxon test
	n	9	9	
Stool frequency	Mean ± SD 95% CI Median	1.67±0.50 (1.28 ; 2.05) 2.0	5.00±1.94 (3.51 ; 6.49) 5.0	0.004

Figure 1: Error bars for defecations

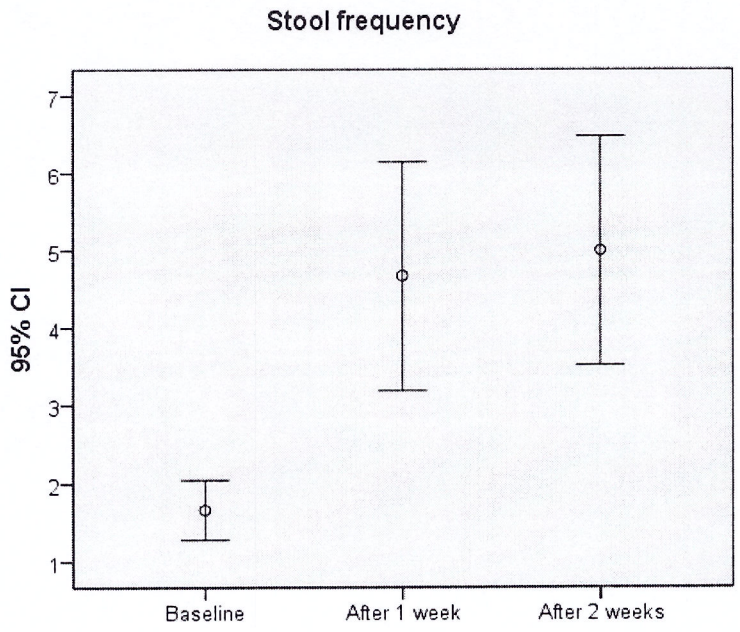

Table 7: Results - constipation symptoms

		not present	mild	moderate	severe	severe to extreme	extreme
Bloating	Baseline	0	2	5	2	0	0
	After 2 weeks	1	0	6	2	0	0
	p-value Sign test: 1.000						
Pain	Baseline	0	4	5	0	0	0
	After 2 weeks	2	2	5	0	0	0
	p-value Sign test: 1.000						
Discomfort	Baseline	1	5	2	0	0	1
	After 2 weeks	4	1	4	0	0	0
	p-value Sign test: 0.375						
Bowel Movements	Baseline	0	5	3	1	0	0
	After 2 weeks	2	6	1	0	0	0
	p-value Sign test: 0.125						
Excessive Straining	Baseline	0	1	2	5	0	1
	After 2 weeks	4	1	2	1	0	1
	p-value Sign test: 0.125						
Unsatisfactory Defecations	Baseline	0	1	2	4	1	1
	After 2 weeks	1	3	2	2	0	1
	p-value Sign test: 0.219						

Table 8: Results - Bristol Stool Forms Scale

		Typ 1	Typ 2	Typ 3	Typ 4	Typ 5	Typ 6
BSFS	Baseline	7	1	0	1	0	0
	After 2 weeks	1	2	2	2	1	1
	p-value Sign test: 0.016			p-value Wilcoxon test: 0.016			

The patient's judgement of efficacy at the end of the study showed a median value of 2 ("good"). Two patients evaluated the efficacy with very good, four patients with good, two with moderate and one with poor (see Tab. 9).

Table 9: Results _ patient's judgement of efficacy

Efficacy	very good	2 (22.2%)
	good	4 (44.4%)
	moderate	2 (22.2%)
	poor	1 (11.1%)

Per-protocol population

A total of 8 patients completed the study properly. These cases were included in the per protocol analysis.
With respect to the primary criterion here also a significant increase of defecations was observed (p = 0.008). The Hodges-Lehmann estimator for the median increase was 3.75 with 95% CI of [2.5; 5.0]. The mean increase arose at 3.6 evacuations (95% CI [2.4; 4.9]).
The mean daily dose of lactulose was 13.1 ± 3.5 g (corresponding to 1.31 ± 0.35 sacchets per day), which confirmed a lower daily dosage of lactulose of 4.58 ± 1.22 g. There was also no significant effect of dose on the increase of defecations (p = 0.123).
Concerning individual constipation symptoms (bloating, pain, discomfort, bowel movements, excessive straining, unsatisfactory defecation) again partially improvements were observed.
Regarding the Bristol Stool Form Scale, there was a significant improvement (p = 0.016).
The described results are summarized in Tab. 10 to 12 and in Fig. 2.

Table 10: Results defecations

		Baseline	After 2 weeks	p-value Wilcoxon test
	n	8	8	
Stool frequency	Mean ± SD 95% CI Median	1.62±0.52 (1.19 ; 2.06) 2.0	5.25±1.91 (3.65 ; 6.85) 5.5	0.008

Figure 2: Error bars defecations

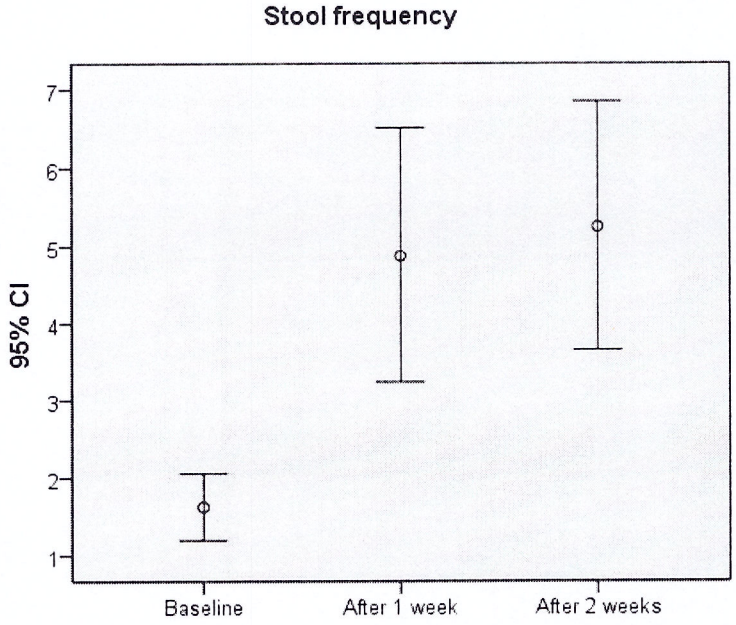

Table 11: Results constipation symptoms

		not present	mild	moderate	severe	severe to extreme	extreme
Bloating	Baseline	0	2	5	1	0	0
	After 2 weeks	1	0	6	1	0	0
	p-value Sign test: 1.000						
Pain	Baseline	0	3	5	0	0	0
	After 2 weeks	2	2	4	0	0	0
	p-value Sign test: 0.625						
Discomfort	Baseline	1	4	2	0	0	1
	After 2 weeks	4	1	3	0	0	0
	p-value Sign test: 0.125						
Bowel Movements	Baseline	0	4	3	1	0	0
	After 2 weeks	2	5	1	0	0	0
	p-value Sign test: 0.125						
Excessive Straining	Baseline	0	1	1	5	0	1
	After 2 weeks	3	1	2	1	0	1
	p-value Sign test: 0.219						
Unsatisfactory Defecations	Baseline	0	0	2	4	1	1
	After 2 weeks	1	3	2	2	0	0
	p-value Sign test: 0.063						

Table 12: Results Bristol Stool Forms Scale

		Typ 1	Typ 2	Typ 3	Typ 4	Typ 5	Typ 6
BSFS	Baseline	7	1	0	0	0	0
	After 2 weeks	1	2	2	1	1	1
	p-value Sign test: 0.016			p-value Wilcoxon test: 0.016			

The patient judgement of efficacy at the end of the study showed a median value of 2 (“good”).

Table 13: Results Patient judgement of efficacy

Efficacy	very good	2 (25.0%)
	good	4 (50.0%)
	moderate	2 (25.0%)

6. Analyses of Safety

Adverse Events

With regard to adverse events, the occurrence of bloating, pain, discomfort, bowel movements, excessive exertion, unsatisfactory defecation at the individual days of treatment was documented.
So in 9 patients a total of 195 adverse events were reported. Bloating and unsatisfactory defecation occurred in 8 patients, pain and excessive straining in 7 patients, discomfort in 6 patients, bowel movements and other events in 1 patient.
Table 14 provides an overview of the kind, severity, course and causality of adverse events.

Table 14: Adverse Events with details

			N
	Number AEs		195
		Duration (days)	
Kind AE	Bloating	1 to 11	42 (21.5%)
	Pain	1 to 6	41 (21.0%)
	Discomfort	1 to 7	31 (15.9%)
	Bowel Movements	1 to 2	4 (2.1%)
	Excessive Straining	1 to 6	36 (18.5%)
	Unsatisfactory Defecations	1 to 9	38 (19.5%)
	Other	1	3 (1.5%)
Severity	mild		48 (24.6%)
	moderate		71 (36.4%)
	severe		56 (28.7%)
	extreme		20 (10.3%)
Serious AE	no		195 (100.0%)
	yes		0 (0.0%)
Unexpected AE	no		195 (100.0%)
	yes		0 (0.0%)
Course (outcome)	persisting		175 (89.7%)
	disappeared after withdrawal		20 (10.3%)
Relation to other drug / disease	no		194 (99.5%)
	yes		0
Relation to study drug	no		3 (1.5%)
	possible		185 (94.9%)

Vital signs

In relation to the mean arterial pressure and the heart rate, comparison of mean values after two weeks versus baseline values showed a slight non-significant increase.

Table 15: Vital signs

		Baseline	After 2 weeks
	n	8	8
Mean arterial pressure (mmHG)	Mean ± SD Median (Min ; Max)	91.1±10.2 92.7 (73 ; 104)	93.6±6.8 93.5 (81 ; 105)
Heart rate (beats/min)	Mean ± SD Median (Min ; Max)	68.9±6.7 68 (61 ; 83)	71.8±11.5 67 (61 ; 92)

The examination of body systems (skin, lung, cardiac, abdomen, liver, neurologic, psychiatric, other) revealed at no time any abnormalities.

Laboratory results

Regarding hematology, there were consistently decreasing values in all variables (Tab. 16). But only in the erythrocytes, the difference was significant (p=0.047).

Table 16: Hematology

		Baseline	After 2 weeks
	n	8	8
Leucocytes (Gpt/L)	Mean ± SD Median (Min ; Max)	7.2±1.8 6.4 (5.2 ; 10.0)	6.3±1.8 5.95 (4.9 ; 10.4)
Erythrocytes (Tpt/L)	Mean ± SD Median (Min ; Max)	4.7±0.3 4.6 (4.2 ; 5.1)	4.6±0.3 4.6 (4.2 ; 4.9)
Hemoglobin (mmol/L)	Mean ± SD Median (Min ; Max)	8.8±0.4 8.8 (8.1 ; 9.4)	8.6±0.4 8.6 (8.2 ; 9.2)
Hematocrit (L/L)	Mean ± SD Median (Min ; Max)	0.42±0.03 0.43 (0.38 ; 0.45)	0.41±0.02 0.41 (0.39 ; 0.44)
Platelets (Gpt/L)	Mean ± SD Median (Min ; Max)	275.5±60.1 266.5 (217.0 ; 408.0)	245.0±34.8 245 (205.0 ; 310.0)

Concerning clinical chemistry, sodium and creatinine showed a slight increase of values, all other parameters a slight decrease. All changes were not significant.

Table 17: Clinical chemistry

		Baseline	After 2 weeks
	n	8	8
Sodium (mmol/L)	Mean ± SD Median (Min ; Max)	141.1±1.6 141 (139 ; 143)	141.9±3.0 142.5 (137 ; 146)
Potassium (mmol/L)	Mean ± SD Median (Min ; Max)	4.39±0.27 4.37 (3.98 ; 4.73)	4.32±0.27 4.36 (3.88 ; 4.66)
Calcium (mval/l)	Mean ± SD Median (Min ; Max)	2.38±0.06 2.37 (2.30 ; 2.50)	2.36±0.08 2.34 (2.28 ; 2.50)
Glucose (mmol/L)	Mean ± SD Median (Min ; Max)	6.1±1.2 5.8 (4.8 ; 8.8)	5.7±1.6 5.3 (4.0 ; 9.2)
ALAT (µmol/s.L.)	Mean ± SD Median (Min ; Max)	0.56±0.45 0.36 (0.21 ; 1.51)	0.54±0.48 0.38 (0.20 ; 1.67)
Creatinine (µmol/s.L.)	Mean ± SD Median (Min ; Max)	65.5±11.7 63.5 (49.0 ; 90.0)	66.5±11.4 65.5 (51.0 ; 89.0)

Finally, the TSH-value showed a slight increase which was not significant as well.

Table 18: Thyreoid Stimulating Hormon

		Baseline	After 2 weeks
	n	8	8
TSH (mU/L)	Mean ± SD Median (Min ; Max)	0.74±0.75 0.55 (0.01 ; 2.32)	1.00±1.06 0.74 (0.01 ; 2.96)

Patient judgement of tolerability and clinical global impression

The global assessment of tolerability by the patient at the end of the study showed a median value of 3 (“moderate”). And the clinical global impression CGI, rated by an independent rater (benefit / risk evaluation) revealed a median value of 2 (“good”) regarding efficacy and a median value of 3 (“moderate”) regarding tolerability. The corresponding frequencies are summarized in the Table 13.

Table 13: Results Patient judgement of tolerability; CGI

Patient judgement	Tolerability		
		very good	1 (11.1%)
		good	3 (33.3%)
		moderate	4 (44.4%)
		poor	1 (11.1%)

Clinical global impression	Efficacy	very good	2 (22.2%)
		good	3 (33.3%)
		moderate	3 (33.3%)
		poor	1 (11.1%)
	Tolerability	very good	1 (11.1%)
		good	3 (33.3%)
		moderate	4 (44.4%)
		poor	1 (11.1%)

7. Summary

The results of the present single-armed study showed positive effects in terms of the effectiveness of TRANSIDOSE at treating constipation. Particularly, a significant change in the pre-post-comparison regarding the primary endpoint could be demonstrated - in both the intention-to-treat population and the per-protocol-population.

The daily dose of TRANSIDOSE was 12.5 ±3.9 grams (or 13.1 ±3.5 grams) which confirmed a lower daily dose of lactulose of 4.38 ± 1.36 (4.58 ± 1.22 grams) compared with a daily dose of 10 to 30grams of current marketed lactulose solutions.

The number of enrolled patients reached a total of 10, thus only one third of the expected 30 patients. Insofar it is not surprising that some of the changes in secondary endpoints are not significant, though at least certain tendencies could be observed. Regarding individual constipation symptoms, there were no significant improvements after treatment. But concerning the Bristol Stool Form Scale, a significant improvement could be shown.

No serious adverse events have been observed in these 10 patients.

Magdeburg, September 7th 2016

Anke Lux

Prof. Dr. Siegfried Kropf