Final Study Report

Title	**Prospective observational study on the utilization and treatment results of patients newly treated with Dropizol® (opium tincture) under conditions of everyday practice**
Acronym	CLARIFY DROPZIOL
Stud design:	Non-interventional observational study
Product:	Dropizol® **Comparator:** none
Study phase:	Postmarketing
BfArM ID:	7294
GWT ID:	13608
Study Director:	[redacted]
Statistician:	[redacted]
Report version:	1.0 **Date:** 25 May 2021
Sponsor:	GWT-TUD GmbH, Dresden Germany

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1 Synopsis

Name of Investigational Product	Dropizol 10 mg/ml
ATC Code	A07DA02
Name(s) of Active Ingredient(s)	Opium tincture
Dosage form	solution
Mode of administration	oral drops
Marketing Authorization Holder	Pharmanovia A/S Copenhagen Towers Oerestads Boulevard 108 DK-2300 Copenhagen S Denmark
Study funders	Pharmanovia A/S, Copenhagen, Denmark Innocur GmbH, Frankfurt, Germany
Indication	Symptomatic treatment of severe diarrhoea in adults, when use of other anti-diarrhoea treatments have not given sufficient effect.
ICD-10	K52 - Other noninfective gastroenteritis and colitis
Protocol no. BfArM	Nr. 7294
DRKS	DRKS00017294
Title	Prospective observational study on the utilization and treatment results of patients newly treated with Dropizol (opium tincture) under conditions of everyday practice
Short Title	CLARIFY Dropizol®
Study phase	Postmarketing
STUDY TIMELINES	
Initiation	13. May 2019
Database closure	23. April 2021
Study report	25. May 2021
STUDY AIMS AND OBJECTIVES	
The primary objective of this study was to document the therapy and outcomes of patients with severe diarrhoea and an indication for Dropizol®. In addition, the study aimed to assess patient characteristics, risk factors and quality of life, including current diarrhoea symptoms.	
STUDY DESIGN	
Study Type	Non-interventional
Control Type	None

Study Design	Open, non-randomised, prospective
Blinding/Masking	None
Setting	Multicenter: hospitals and practices in all parts of Germany

Study endpoints

Primary:

• Change in number of stools per day at approximately 10 days compared to baseline (treatment initiation)

• Ileostomy patients: change in excretion quantity (ml) in bag at approximately 10 days compared to baseline (treatment initiation)

• Dropizol® dosage at approximately 10 days compared to baseline

Secondary:

• Change in number of stools per day at 6 months (or end of observation) compared to baseline (treatment initiation)

• In ileostomy patients: change in excretion quantity (ml) in bag at end of observation compared to baseline

  o at reversal of ileostomy

  o at introduction of new line of chemotherapy (adjuvant therapy)

  o in any case not later than 6 months

• Dropizol® dosage at 6 months (or end of observation) compared to baseline (treatment initiation)

• Time to effect (= days of Dropizol® treatment leading to normalized frequency of stools per day)

• Dosing pattern (number of Dropizol® doses per day)

• QoL (by EQ-5D VAS) at 6 months (or end of observation) compared to baseline (treatment initiation)

• in oncology patients only, facultatively: Systemic Treatment-Induced Diarrhea Assessment Tool (STIDAT) total score at 6 months (or end of observation) compared to baseline (treatment initiation).

SUBJECT SELECTION	
Number of patients	62
Number of centers	15
Number of cohorts	1

Eligibility Criteria

- Severe diarrhea, e.g. diarrhea caused by cytostatic drugs, radiation or neuroendocrine tumors, if the use of other antidiarrheal drugs has not had sufficient effect
- Written consent before the first documentation
- Use of Dropizol® within the provisions of the Summary of Product Characteristics (SmPC)

Criteria for non-eligibility

- Contraindications as described in the SmPC
- Lack of cognitive and linguistic ability to participate in the study
- Patient (probably) not available for follow-up period (up to 6 months)
- Pregnancy

Key results

In a prospective non-interventional study in Germany, 51 internal patients (from 14 centers) and 11 surgical patients (from 4 centers) were documented. Patients were on average 61.0 ± 14.8 years old (from 26 to 84 years) and 56.5% were women.

The current diarrhea episode before Dropizol treatment was 21 days in the median in internal patients and 3 days in surgical patients. In 40 patients (64.5%) loperamide was given as pre-therapy. Dropizol was given on day 1 at an average dose of 11.2 ± 5.6 drops per day (range 2 to 30 drops), and after 2 months at a dose of 23.2 ± 17.3 drops. In 19 patients, the dose on day 10 was the same as the starting dose. For internal patients, the number of stools decreased from 7.8 ± 6.9 on day 1 to 5.6 ± 5.2 on day 5 and 6.7 ± 5.2 on day 14. A decrease of at least 50% was reported in 16 patients (44.4%), and of 20 - 49% in 12 patients (33.3%) . The stool frequency was 6.2 ± 4.7 after 2 months, 7.0 ± 4.6 after 4 months, and 6.0 ± 3.5 after 6 months.
In surgical patients (after ileostomy), the amount of excretion in the pouch reached the maximum of 2.1 ± 1.1 liters on the second day of Dropizol application, and decreased to 1.3 ± 0.4 liters by day 14.
The effectiveness of Dropizol on the school grade scale was rated at an average of 2.2 ± 1.1 after 10-14 days, and tolerability at 1.5 ± 1.9. The values remained similar during the course of follow-up.

Adverse drug reactions were reported by 3 patients: one patient had one episode of headache, another of dizziness and fatigue, another of constipation (which led to the termination of therapy). All cases were not serious.

Conclusions

Under Dropizol therapy, rapid and sustained therapy success was observed with very good tolerability. In a substantial proportion of patients Dropizol was not titrated despite the number of stools are excretion volumes were still high.

Keywords
Diarrhoea, therapy, effectiveness, tolerability, ileostomy, oncology, real-word evidence.

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2 List of abbreviations

ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical Classification System
CRF	Case Report/Record Form
CRO	Contract Research Organization
ED-5D	EuroQuol 5 dimensions
MedDRA	Medical Dictionary for Regulatory Activities
SD	Standard deviation
SmPC	Summary of Product Characteristics
STIDAT	Systemic Treatment-Induced Diarrhea Assessment Tool
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
VAS	Visual analogue scale

3 Participating sites

A total of 15 sites contributed one or more patients to the study (Appendix). Not all sites became active.

4 Other responsible parties

Study Director for the sponsor was [redacted], GWT-TUD GmbH, Clinical Research/ Epidemiological center, Freiberger Str. 33, D-01067 Dresden. Clinical operations were supervised by [redacted] and [redacted], GWT-TUD GmbH. The electronic data capture website and database were programmed by [redacted]. Data management and statistical analyses were performed by [redacted] GWT-TUD GmbH. The report was prepared by [redacted].

5 Milestones

Table 1: Study milestones

Milestone	Date	Details
Approval of study materials by Ethikkommission der Landesärztekammer Baden-Württemberg	06-May-2019	F-2019-042
Registration at Deutsches Register Klinischer Studien	15-May-2019	DRKS00017294
Registration of study by BfArM	07-May-2019	No. 7294
Initiation	13-May-2019	
Database lock	23-April-2021	
Final report of study results	25-May-2021	

6 Rationale and background

Opium tincture has been used for many decades to treat severe diarrhea. In the form of Tinctura Opii simplex (synonyms: Tinctura Opii normata, Standardized Opium Tincture ph. Eur) the composition is standardized and has been in use for more than a century.[1] The opium is mixed in alcohol (31-34 vol%) and water. It contains morphine (1%), codeine, thebain, noscapin (= narcotin), papaverine, narcein, etc.[1]

Dropizol® is currently the only ready-to-use opium tincture in Germany and other European countries. It is obtained from raw opium grown according to Good Agriculture Practice (GAP) and produced according to Good Manufacturing Practice (GMP). In August 2018, Dropizol® was approved by the Federal Institute for Medicinal Products and Medical Devices (BfArM). The current indication specifies the treatment of severe diarrhea in adults when no

sufficient effect has been achieved by the use of other antidiarrheals.[2] The preparation is subject to the Narcotics Act and must be prescribed on a narcotics prescription. In the standardized ready-to-use medicine, 20 drops correspond to exactly one milliliter of liquid and contain, among other alkaloids, 10 mg of morphine. The daily dose should not exceed 120 drops (equivalent to 60 mg morphine).[2]

Opium tincture binds in the gastrointestinal tract mainly to μ-opioid receptors. It slows down intestinal peristalsis, reduces secretion, increases absorption in the small intestine and the tone of the sphincter.[3] Studies of the human intestine suggest that δ-opioid receptors have a smaller but potentially clinically significant contribution to opioid-induced inhibition of muscle activity in the gastrointestinal tract.[4] The antidiarrheic effect of the opium tincture is not subject to tolerance development (as opposed to the pain-inhibiting effect and the effect on motility in the upper gastrointestinal tract). This is due to differences in signal transmission and regulation of the μ-opioid receptor.[5] Opium tincture has a slower onset of action than morphine.[6] The mixture of several alkaloids in the opium tincture seems to have a better tolerability than individual alkaloids or other opiates.[7]

Severe diarrhea, which may be treatable by opium tincture, occurs in about 30% of patients on chemotherapy, especially with fluoropyrimidine, irinotecan or EGFR inhibitors for gastrointestinal malignancies.[8,9] 70% of patients who have to undergo radiotherapy of the abdomen or pelvis are also temporarily affected by severe diarrhea.[10,11] In the current guideline of the German Society for Hematology and Medical Oncology (DGHO) is a recommendation that opium drops can be used in loperamide-refractory diarrhea alongside codeine, morphine or atropine.[9,12]

Opium tincture can also be used as an antidiarrheic medication for patients with a temporary ileostomy, e.g. after resection of rectal cancer. These often have very thin and large-volume excretions, which can lead to dehydration and electrolyte loss.[13,14] A high amount of secretion is defined in Great Britain as > 2 liters, in Germany > 1 liter. Patients with short bowel (after conditions such as ulcerative colitis, Crohn's disease, trauma, or vascular events) also often suffer from severe diarrhea, which sometimes requires lifelong treatment.[15]

Opiates (especially morphine) in opium tincture (1% morphine, 0.3% codeine) are dosed much lower in the treatment of diarrhea than morphine doses in pain therapy. [17]

The central effects with oral administration are significantly lower and less frequent than after parenteral (subcutaneous or intramuscular) administration. Side effects are especially the undesirable effects of morphine such as effects on the psyche (usually drowsiness, euphoria, occasionally dysphoria), fatigue, altered taste sensations, dizziness, physical and psychological dependence.[2]

Despite frequent use in severe diarrhea, there are no controlled studies or observational studies for opium tincture. There an unmet need for the collection of such data. The present study was conducted to characterize patients receiving opium tincture as a ready-to-use drug (Dropizol®) in terms of demography, cause of diarrhea, disease history and previous or accompanying medication, and to describe the use of Dropizol® under real-world conditions

(treatment history, previous trials for the treatment of diarrhea, earlier titration, current dosage, duration of the stable dose, efficacy, safety).

7 Research question and objectives

The primary objective of this study was to document the therapy and outcomes of patients with severe diarrhea and an indication for Dropizol®.

In addition, the study aims to assess patient characteristics, risk factors and quality of life, including current diarrhoea symptoms.

8 Amendments and updates to the protocol

None.

It was originally planned to end the study after the start in May 2019 at the end of the first quarter of 2020. However, the duration had to be extended by one year, as recruitment was much slower than planned. The reasons cited by the centres were: logistical effort, other priorities for multimorbid patients, restrictions in everyday practice and surgery plan by Covid-19 pandemic. Of the originally planned 250 patients, 62 could be documented.

9 Research methods

9.1 Study design

Prospective, multi-centre, non-interventional observational study with duration of up to 6 months per patient.

9.2 Setting

Medical doctors in hospitals and private practices (including oncologists, radiologists, surgeons, internists and general practitioners) who regularly treat patients with severe diarrhoea and are capable to document their course over a longer period of time. Centers in other European countries were invited to join the study at a later time point.

9.3 Patients

9.3.1 Eligibility and non-eligibility criteria

Eligibility criteria

Adult patients of both sexes were eligible for documentation in the study if they met the following criteria:

- Severe diarrhoea, e.g. diarrhoea caused by cytostatic drugs, radiation or neuroendocrine tumours, if the use of other antidiarrheal drugs has not had sufficient effect.
- Written consent before the first documentation.
- Use of Dropizol® within the provisions of the Summary of Product Characteristics (SmPC).

Non-eligibility criteria

- Contraindications as described in the SmPC.
- Lack of cognitive and linguistic ability to participate in the study.
- Patient (probably) not available for follow-up period (up to 6 months).
- Pregnancy

At the participating sites, patients meeting all eligibility criteria and no non-eligibility criterion were invited to participate the in the study. No other methods (such as adverting) were used.

9.3.2 Documentation schedule

Data were entered by the documenting person at each site at the prespecified timepoints.

The study was purely observational and the treating physicians determined the diagnosis, therapy and frequency of doctor/patient contacts. The documentation plan applied if the described visits (or telephone contacts) between doctor and patient took place (if data was available):

- Inclusion ("baseline") = start of documentation
- Follow-up visit after approximately 10 to 14 days

to record the titration of Dropizol®.

- 3 follow-up visits approximately every 2 months (at approximately 2 months, approximately 4 months, and approximately 6 months)

  which could be performed as on-site visit or as telephone appointment.

Each patient was to be documented over the entire treatment period with Dropizol®, but not longer than 6 months.

In the oncology setting, Dropizol use was to be documented until the end of the respective therapy line.

If adverse drug reactions (ADRs) occurred in connection with Dropizol® during documentation, these were also recorded and reported between visits.

9.4 Variables

The list of study parameters is presented in Table 1:

Table 1. Study parameters

Visit	#1	#2	#3	#4	#5
Parameters/ Measures	**Baseline = Dropizol initiation**	**approximately at 10 -14 days [a]**	**approxi-mately at 2 months**	**approxi-mately at 4 months**	**approxi-mately at 6 months**
Patient information, declaration of informed consent	x				
Demographic data	x				
Patient history	x				
Basic clinical information	x				
Underlying disease					
Reason for severe diarrhoea	x				
Number of stools (oncological patients) or excretion volume (ileostomy)	x	x	x	x	x
Diarrhoea CTC grade	x	x	x	x	x
Previous/current other therapies for diarrhoea	x	x	x	x	x
Dropizol	x	**Treatment course and dosing at discretion of treating physician**			
Effectiveness and Tolerability of Dropizol		x	x	x	**x**
Adverse drug reaction (ADR) monitoring [b]	x	x	x	x	x
Reason for study/therapy termination/discontinuation		at last available visit			
Patient-related outcomes [c]					
Diarrhoea questionnaire STIDAT	x	x	x	x	x
Quality of life EQ-5D visual analogue scale	x	x	x	x	x
Oncology: QLQ-C30 [d]	x	x	x	x	x

[a] approximately 10 days (= as discharge from hospital) or approximately 14 days (in ambulatory patients) days

[b] ADR were recorded from the time when the subject gave Informed Consent until the end of study.
[c] if the patient was willing to fill out the questionnaires
[d] QLQ-C30 was planned in selected oncology centers, but not used

The data collection form (CRF) is provided in the Appendix 2.

9.5 Data sources and measurement

Data on individual patients were extracted from patient charts (medical records) by the investigator or study nurse. Internal patients received patient questionnaires at each visit.

9.6 Study size

The study size was determined by feasibility aspects. No formal sample size calculation was performed.

9.7 Statistical methods

9.7.1 Main summary measures and statistical methods

The statistical evaluation of all collected data was done on a descriptive basis. Data were analyzed and the results presented in tables and graphs. Continuous numeric variables were expressed in number of evaluable values, mean, standard deviation, median, minimum and maximum. For categorical variables, frequency counts were applied (absolute and relative frequencies).

No specific statistical hypothesis testing was performed.

Results are shown for the total cohort.

9.7.2 Missing values

Missing values were shown by number and percentages in the respective post-text tables. No imputations were made.

9.7.3 Sensitivity analyses

Sensitivity analyses were not performed.

9.8 Quality control

Statistical plausibility checks were performed on outlier values. Data were reviewed by the study director for medical consistency. In case of missing or inconsistent values, queries were

raised to investigators. No on-site monitoring was performed as during much of the study duration, access to sites was restricted due to the Covid-19 situation.

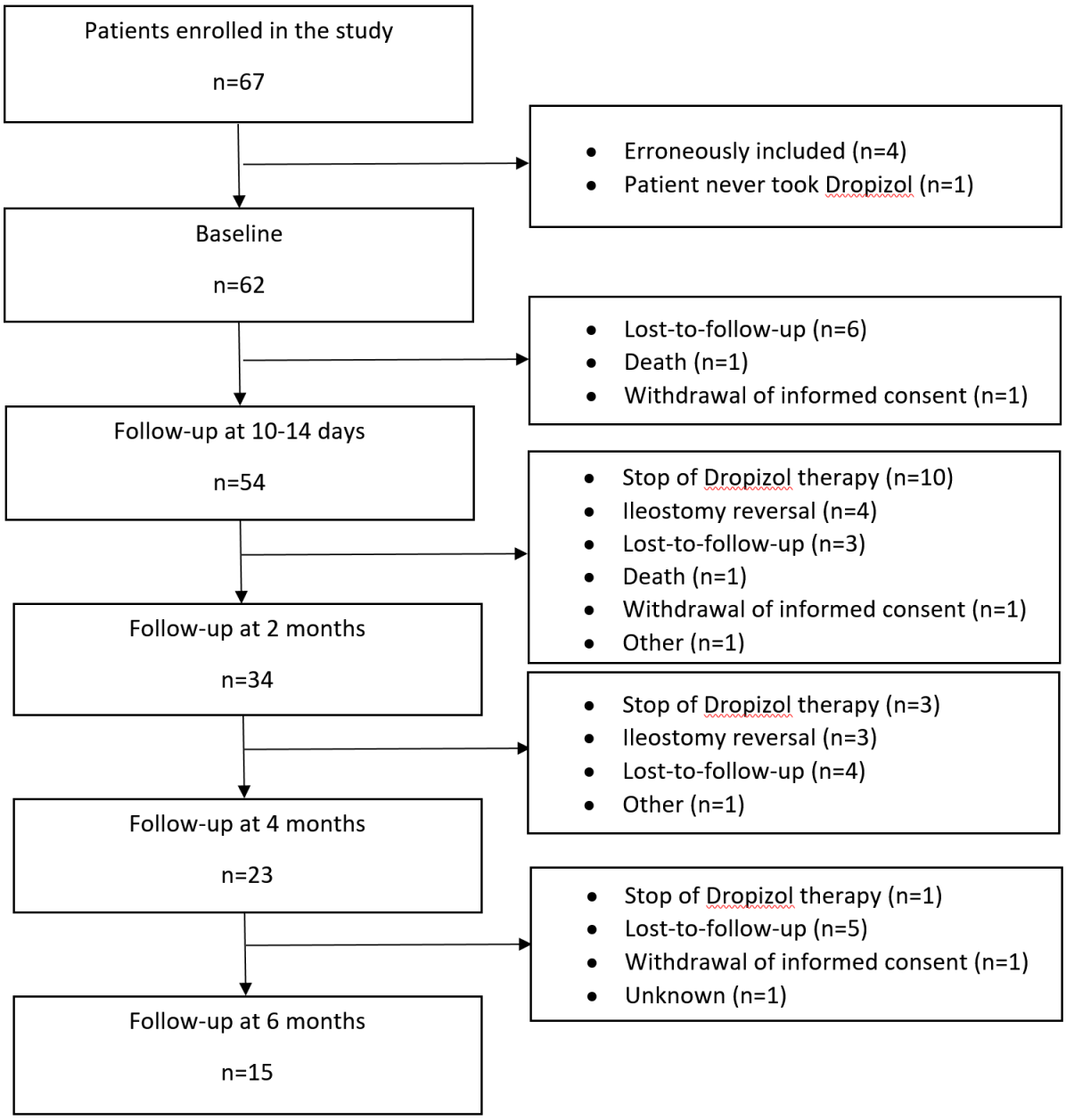
10 Results

10.1 Patient disposition

In 15 centres (14 internal medicine, 4 surgical), a total of 62 patients were documented. All patients fulfilled the eligibility criteria (post-text Table 1.1).

The flow-chart shows the patient disposition over time (Figure 1).

Figure 1. STROBE flow chart

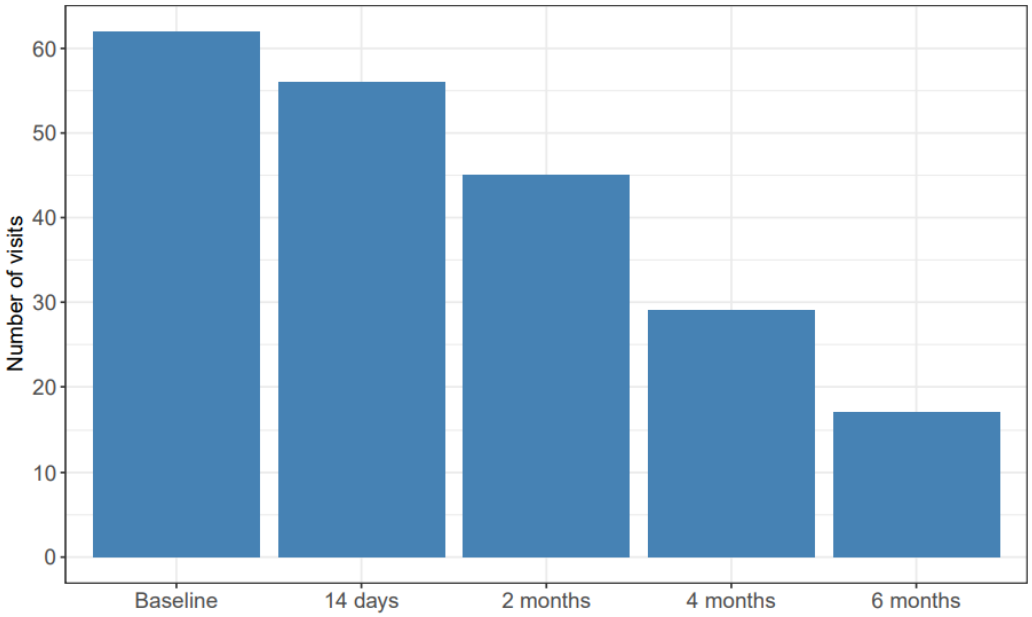


On average, patients had 3 visits (median), with a mean follow-up time of 94 days and a mean time to end of observation of 75 days. Five patients had a baseline visit only. Details are shown in post-text table 0.2.

At the data cut-off on 23 April 2021, 15 patients (24.2%) had completed all visits, 16 (25.8%) were on ongoing therapy. The study was stopped before the maximum follow-up time of 6 months due to earlier stop of Dropizol therapy in 23 patients (37.1%). Other causes were death

(2 patients, 3.2%), lost to follow-up (2 cases, 3.2%), withdrawal of informed consent (3 patients, 3.3%) and an unknown cause in 1 patient (post text Table 0.3). The number of visits is shown in Figure 2.

Figure 2. Number of visits.



Source: Post-text Figure 0.1

10.2 Characteristics of patients

10.2.1 Demographics

Basic demographic data of the patients are shown in post-text Table 1.2.

Of the 62 documented patients, 27 patients (43.5%) were males, and 35 (56.5%) were females. Mean age of patients was 61.0 ±14.8 years, the age range was 26 to 84 years.

All patients were Caucasian/white.

In terms of employment status, 12 patients (19.4%) were employed full time, 4 (6.5%) part time, 35 (56.5%) were retired, and 11 (17.7%) reported “other”.

Severe disability status (“Schwerbehinderung”) was reported by 21 patients (33.1%).

10.2.2 Diarrhea characteristics

Diarrhoea characteristits are presented in detail in post-text Table 1.3.

The duration of the current diarrhoea episode was median of 14 days (internal patients 21 days, surgical patients with high output secretion 5 days). Diarrhea occurred in patients with chemotherapy (n=23), ulcerative colitis (n=9), short bowel syndrome (n=7), Crohn's disease (n=7), malignancy (n=5), radiotherapy (n=3), or adenomatous polyposis (n=1) (multiple nominations possible). “Other” causes were reported in 21 cases (33.3%) and are presented in the footnote of post-text Table 1.3.

In 15 patients (24.6%) diarrhoea was classified as intermittent, at 41 (67.2%) as permanent, at 5 (8.2%) no classification has been made. The surgical patients with (temporary) ileostomy were classified as having intermittent diarrhoea.

10.2.3 Diarrhea pre-treatment

In 40 patients (64.5%) loperamide was reported as pre-therapy, at an average dose of 8.6 (± 7.1) mg per day and a maximum dose of 32 mg per day (in 4 patients > 16 mg per day).

As other pre-treatments, the following were reported: opium tincture (other than Dropizol®) in 5 cases, morphine in 1 case, psyllium (dietary fibers, “Flohsamen”) in 15 cases, other herbals in 3 cases, proton pump inhibitors in 3 cases, budesonide in 2 cases, and other medications in 16 patients. Details are shown in post-text table 1.4.

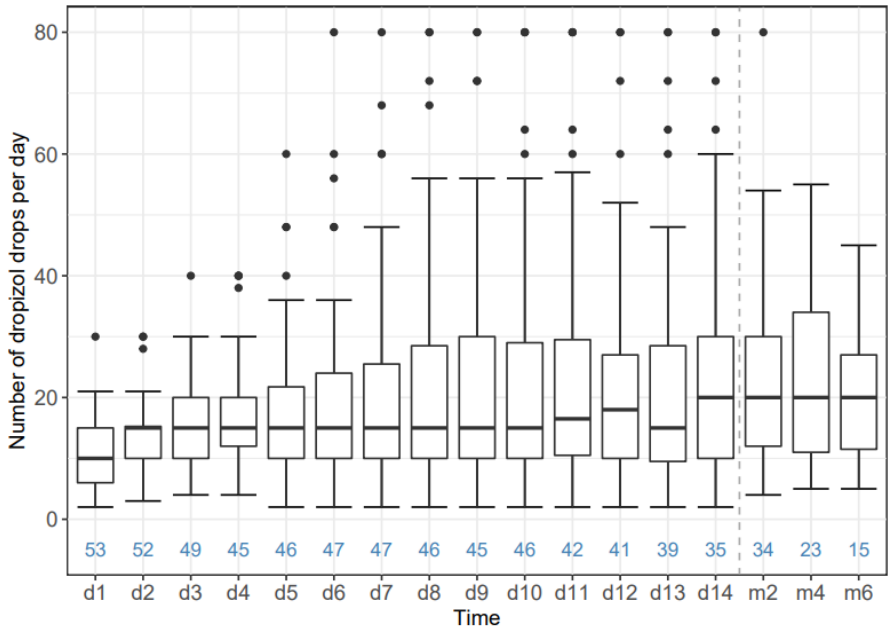
10.3 Course of Dropizol dosing

Dropizol® was planned as long-term therapy in 46 patients (78.0%), and as short-term therapy in 13 patients (22.0%).

Dropizol was given on the first day of use at an average dose of 11.2 ± 5.6 drops per day, with a range of 2 to 30 drops. On the following days, the mean dose was increased (e.g. day 5 18.3 ± 12.8 drops, day 10 22.7 ± 20.5 drops, day 14 25.7 ± 21.7 drops) (Figure 3).

After 2 months (n=34), the dosage was 23.2 ± 17.3 drops, after 4 months (n=23) 23.6 ± 14.5 drops, and after 6 months (n=15) 20.8 ± 12.6 drops.

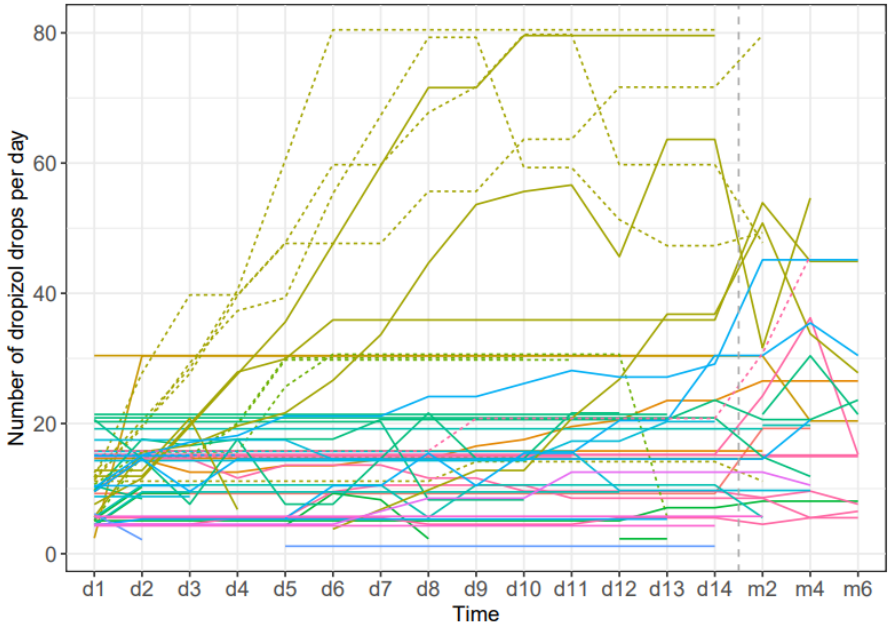
Figure 3. Box-whisker plots on number of Dropizol drops per day from day 1 to 14 and at 2, 4 and 6 months



Legend Figure: Number of observations given in blue. d1, d2 …d14 = day 1 to d14; m2, m4 and m6 = month 2,4 and 6 respectively. Boxes show the first quartile to the third quartile, the horizontal line the median. The whiskers go from each quartile to the minimum or maximum value. The dots show outlier values.

Dropizol usage was highly variable across patients as shown in Figure 4. Upward dose titration between days 1 and 10 was performed in 24 patients (49.0%). Of these, four patients were titrated in several stages to 80 drops a day, and in two of these patients the dose was reduced again). Conversely, 19 patients (38.8%) were not titrated in the first 10 days (unchanged dosage), and in 6 patients (12.2%) it was reduced. The mean dose increase between day 1 and day 10 was 1.0 ± 21.0 drops (range 18.0 drops decrease to 72.0 drops increase).

Figure 4. Number of Dropizol drops per day from day 1 to 14 and at 2, 4 and 6 months, by individual patients.

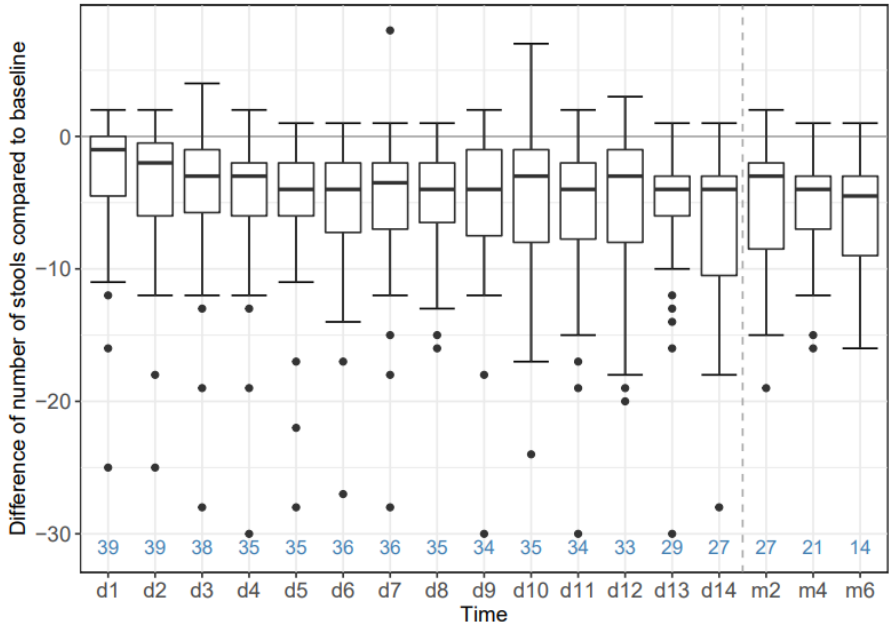


Legend Figure: Lines of patients of the same center have the same colour. Lines of surgical patients are dotted. d1, d2 …d14 = day 1 to d14; m2, m4 and m6 = month 2,4 and 6 respectively.

10.4 Number of stools

In the 36 non-surgical patients, the number of stools decreased from 7.8 ± 6.9 on day 1 to 5.6 ± 5.2 on day 5 and 6.7 ± 5.2 on day 14 (Figure 5). A decrease in stools of at least 50% between day 1 and day 10 was observed in 16 patients, 20-49% in 12 patients, 0-19% in 5 patients, and an increase in three patients . At 2 months, the frequency was 6.2 ± 4.7 stools, at 4 months 7.0 ± 4.6 stools, and at 6 months 6.0 ± 3.5 stools.

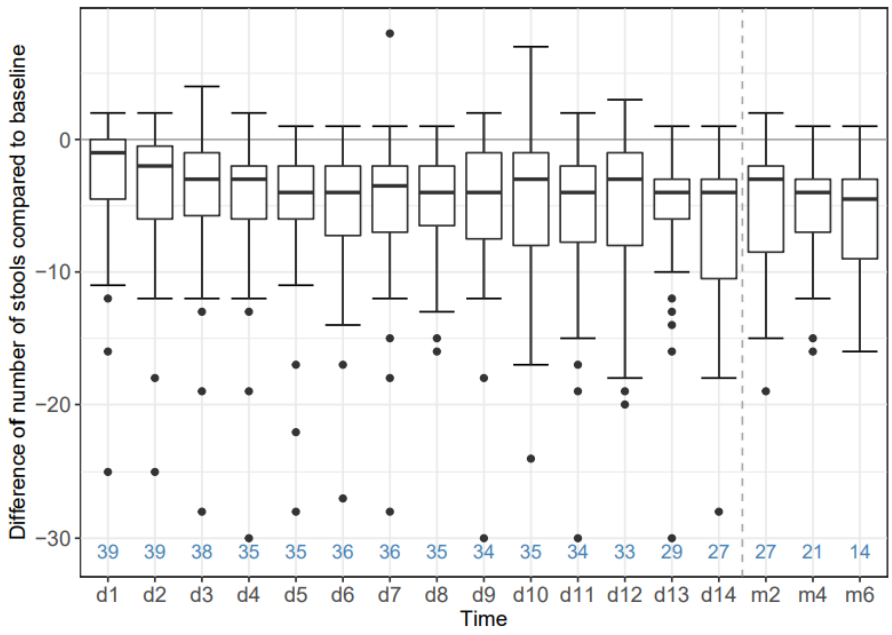
Figure 5. Box-whisker plots on number of stools per day in non-surgical patients from day 1 to 14 and at 2, 4 and 6 months



Legend Figure: Number of observations given in blue. d1, d2 …d14 = day 1 to d14; m2, m4 and m6 = month 2,4 and 6 respectively. Boxes show the first quartile to the third quartile, the horizontal line the median. The whiskers go from each quartile to the minimum or maximum value. The dots show outlier values.

After 10 days of treatment, of the 37 internal patients with available values at this visit, 25 patients (67.6%) had up to 6 stools per day and were thus below the definition limit for severe diarrhoea. Conversely, 32.4% of patients had 7 or more stools and thus by definition were inadequately treated. The rate of patients who were below the severe diarrhoea threshold and those who had severe diarrhoea despite treatment was similar in patients with flat Dropizol dosage and those with dose increase over time.

Figure 6. Difference of number of stools compared to baseline for day 1 (d1) to day 14 (d14) and for 2, 4 and 6 months (m2, m4 and m6, respectively) in non-surgical patients



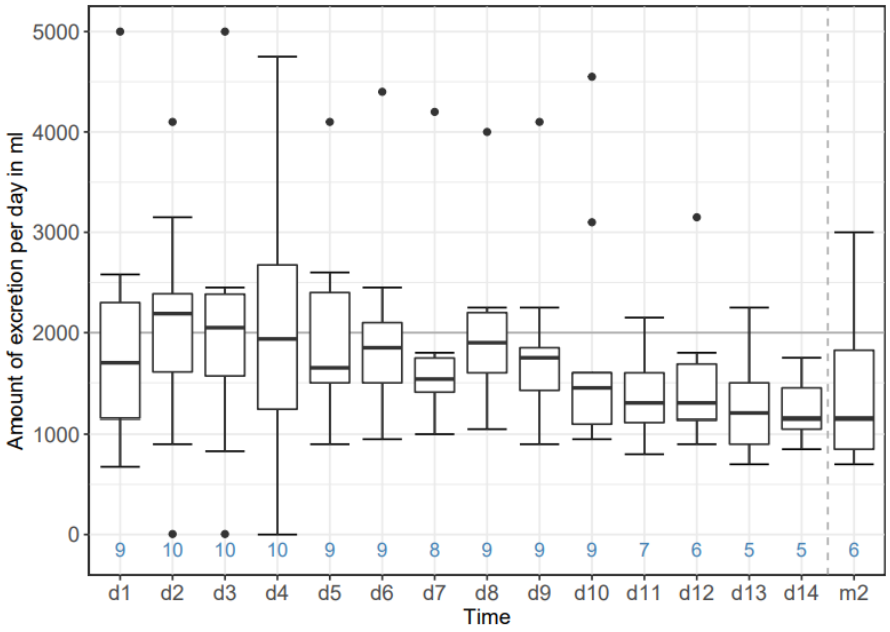
Legend Figure 6. d1, d2 …d14 = day 1 to d14; m2, m4 and m6 = month 2,4 and 6 respectively. Boxes show the first quartile to the third quartile, the horizontal line the median. The whiskers go from each quartile to the minimum or maximum value. The dots show outlier values.

Individual course of stool frequency, by patient, are shown in post-text figure 7.4.

10.5 Excretion in the stoma bag

The mean excretion quantity in the bag reached the maximum of 2.1 ± 1.1 litres on the second day of Dropizol application, and decreased to 1.3 ± 0.4 litres by day 14 (Figure 7). One patient achieved a decrease in excretion by at least 50%, two patients by 20-49%, one patient of 0-19%, and 4 patients had an increase in excretion between day 1 and day 10. Of the 9 patients with historical data, 7 achieved an excretion level less than 2000 ml/day, one of which was less than 1000 ml/day.

Figure 7. Surgical patients only: Amount of excretion in ml per day from day 1 to day 14 and at 2 months (m2).



Legend Figure: Numbers of observations in blue. No data available for 4- and 6-months-visits. d1, d2 …d14 = day 1 to d14; m2 = month 2. Boxes show the first quartile to the third quartile, the horizontal line the median. The whiskers go from each quartile to the minimum or maximum value. The dots show outlier values.

The amount of excretion in ml per day from day 1 to day 14 (d1 to d14) and at 2 months (m2), individually for patients, is shown in post-text figure 7.6.

10.6 Concomitant medication

During FU, the antidiarrheal drugs from baseline were overall maintained (Table 2).

Table 2. Concomitant antidiarrheal medication

	Day 14	**FU 2 months**	**FU 4 months**	**FU 6 months**
N with information	54	34	23	15
Medication				
Loperamide	5	6	6	4
Flea seed shells	12	12	3	5
Other herbs	2	4	2	0

Proton pump inhibitors	3	5	2	2
Budesonide	2	2	1	1

10.7 STIDAT

The STIDAT score was determined in non-surgical patients. Compared to baseline, quality of life by this scale improved markedly from 3.6 to 2.4 points at day 10 to 14. During further follow-up, mean values were between 2.1 and 2.9. Details are shown in Table 3 and post-text tables 1.5, 2.6, 3.4, 4.4 and 5.4.

Table 3. STIDAT over time

	Baseline	FU 10-14 days	FU 2 months	FU 4 months	FU 6 months
N with information	44	29	25	20	14
STIDAT, mean ± SD	3.6 ±1.5	2.4 ±1.5	2.3 ±1.3	2.9 ±1.4	2.2 ± 1.0
median	3.1	2.1	2.3	3.0	2.3

10.8 Quality of life

The EQ-5D visual analogue score, that ranges from 0 (worst health one can imagine) to 100 (best health one can imagine) was determined in non-surgical patients. Compared to baseline, quality of life by this scale improved markedly from 43.1 to 58.5 points at day 10 to 14. During further follow-up, mean values were between 55.42 and 61.0. Details are shown in Table 4 and post-text tables 1.5, 2.6, 3.4, 4.4 and 5.4.

Table 4. QoL by EQ-5D VAS over time

	Baseline	FU 10-14 days	FU 2 months	FU 4 months	FU 6 months
N with information	45	35	27	20	15
EQ-5D, mean ± SD median	43.1 ± 21.2 45.0	58.5 ± 22.6 60.0	55.4 ± 23.7 60.0	61.0 ± 19.7 60.0	59.1 ± 28.5 65.0

10.9 Effectiveness as assessed by physicians

The effectiveness of Dropizol on the school grade scale of 1 (best) to 6 (worst) was evaluated at an average of 2.2 ± 1.1 after 10-14 days. During further follow-up, mean values were between 2.1 and 2.5. Details are shown in Table 5 and post-text tables 2.5, 3.3, 4.3 and 5.3.

Table 5. Effectiveness by physician rating

		FU 10-14 days	FU 2 months	FU 4 months	FU 6 months
N with information		53	36	24	16
Physician assessment by rating scale					
Mean ± SD		2.2 ± 1.1	2.1 ± 0.8	2.5 ± 0.8	2.2 ± 1.0
Median		2.0	2.0	2.0	2.0

10.10 Tolerability as assessed by physicians

The tolerability of Dropizol on the school grade scale of 1 to 6 was evaluated at an average of 1.5 ± 1.0 after 10-14 days. During further follow-up, mean values were between 1.4 and 1.9. Details are shown in Table 6 and post-text tables 2.5, 3.3, 4.3 and 5.3.

Table 6. Tolerability by physician rating

		FU 10-14 days	FU 2 months	FU 4 months	FU 6 months
N with information		53	36	24	16
Physician assessment by rating scale					
Mean ± SD		1.5 ± 1.0	1.6 ± 0.8	1.4 ± 0.5	1.9 ± 2.0
Median		1.0	1.5	1.0	2.0

10.11 Side effects reports

Adverse drug reactions were reported by 3 patients: one patient had one episode of headache, another of dizziness and fatigue, another of constipation (which led to the termination of therapy). All cases were not serious.

11 Discussion

11.1 Key results

Opium tincture 10 mg/ml has been used for over 100 years and has been approved as a ready-to-use drug (Dropizol®) for the treatment of severe diarrhea in 2018.

In the observational CLARIFY study, for the first time, data on Dropizol® were systematically collected within the approved indication "severe diarrhoea". They show that the patients were treated with very different doses over time, generally achieving rapid and good treatment success.

Pre-treatment. Nearly all patients had received pre-treatment, mostly with loperamide, a drug from the opioid class. Loperamide has been approved up to a maximum daily dose of 8 mg per day, and 16 mg per day can be taken on medical prescription. In CLARIFY, higher daily doses were reported in four patients. Principally, such high doses are associated with an increased risk of cardiac side effects: QT prolongations, torsades de-pointes and other ventricular arrhythmias, as well as syncope and cardiac arrest have been reported in large studies.[18] Activated carbon was not used in CLARIFY, flea seed shells in 15 patients.

Dosage patterns. According to the product labelling (SmPC), the usual daily starting dose for Dropizol for adults is 10-30 drops (divided in 2 - 3 daily administrations). In CLAIRFY, the dose was rather at the lower end, on average at 12 drops daily, with a broad range of 2 to 30 drops daily. Thus, in no case higher starting doses than recommended in the SmPC were used. In the course of the observation, it was noticeable that more than a third of the patients maintained the original starting dose for at least 10 days, i.e. did not titrate. This is an indication that some patients have not been made aware of the possibility or necessity of titration or did not implement the recommendation. In other patients, on the other hand, the dose was roughly doubled after 10 days compared to the starting dose and increased somewhat later. The maximum dose of 120 drops per day recommended in the SmPC was not nearly reached (maximum dose in CLARIFY 80 drops per day).[2]

Effectiveness. From a physician point of view, the effectiveness of Dropizol rated after 10-14 days treatment was good, as expressed in the school grade 2.4 (on a range of 1 best to 6 worst). Probably better results could have been achieved in practice, as many (internal) patients had 7 stools per day and thus still had severe diarrhoea by definition.

Tolerability. The tolerability of Dropizol was very good, according to the doctors' general assessment. The reported side effects headache, dizziness and constipation are known effects

of opium tincture; they were mild and temporary. Symptoms of dependence were not observed after discontinuation.

Quality of life. The suffering pressure of patients with diarrhea (in combination with the underlying conditions) is high,[19] as shown in our study by the relatively low quality of life score of about 50 (on the 0-100 EQ-5D scale). During the first 10-14 days, QoL improved substantially, which could be due, among other things, to the antidiarheic treatment. On the STIDAT, compared to baseline, the score improved considerably from the "severe diarrhea" category to the "moderate diarrhea" category after 10-14 days and stayed in that category over time.

In surgical patients, the results were congruent to those of the other patients. The excretion rate into the bag was significantly reduced in many patients (or at least did not increase). Also, in this group of patients, a stronger therapy effect could possibly have been realized with an increase in the dose.

11.2 Limitations

Some methodological considerations need to be taken into account. Among the strengths of the study are the inclusion of investigators with various specialties and the broad patient spectrum. However, participants in the study may represent a (positive) selection in terms of compliant patients and of physicians who have a higher-than-average level of expertise, are interested in the research questions and willing to undergo quality control measures.

Various sources of bias and confounding can distort any true causal association. Physicians assign diarrhea patients to specific medications based on their rating of disease severity, disease duration, presence of comorbidities, or other factors. This may potentially introduce allocation or channeling bias and confound the association between treatment and outcomes. There is potential for missing data and for inaccurate reporting of the frequency or severity of adverse drug reactions.

11.3 Generalizability

The study used relatively broad eligibility criteria. However, as the study was limited to few patients in 15 centers only, results cannot be generalized without caution. Data cannot be extrapolated to the patients with other underlying diseases without caution.

12 Conclusion

In summary, under Dropizol therapy, a rapid and sustained therapy success was observed, with very good tolerability. Dropizol was dosed cautiously, so the effectiveness could probably be improved to a greater extent.

13 References

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14 Appendices: list of stand-alone documents

1. Observational plan
2. Case Report Form
3. Statistical Analysis Plan
4. Post-text Tables, Figures and Listings
5. Approval letter by Ethics Committee at Landesärztekammer Baden-Württemberg
6. Confirmation of registration by BfArM
7. List of sites