ISRCTN71510134 https://doi.org/10.1186/ISRCTN71510134

# RESOLVE: A research study investigating the effectiveness of a medicine called Dropizol for treating severe diarrhoea caused by cancer treatments

| | | |
|---|---|---|
| **Submission date**<br>24/12/2024 | **Recruitment status**<br>Stopped | [X] Prospectively registered<br>[ ] Protocol<br>[ ] Statistical analysis plan<br>[ ] Results<br>[ ] Individual participant data<br>[ ] Record updated in last year |
| **Registration date**<br>04/03/2025 | **Overall study status**<br>Stopped | |
| **Last Edited**<br>08/05/2025 | **Condition category**<br>Digestive System | |

## Plain English summary of protocol

Background and study aims

Many people with cancer develop severe diarrhoea during chemotherapy or radiotherapy treatment - affecting up to 80% of patients. This can be dangerous, causing dehydration and malnutrition, and may force doctors to pause vital cancer treatments. Often, loperamide is used as a treatment, but this doesn't always work well enough for many patients with severe diarrhoea. This study will test if a medicine called Dropizol (made from opium) works better than loperamide for treating severe cancer treatment-related diarrhoea. The research will compare three approaches: Dropizol alone, loperamide alone, or both medicines together.

Who can participate?

The study will involve 279 adults with cancer who develop severe diarrhoea during their cancer treatment. To take part, participants must be 18 or over, receiving chemotherapy and/or radiotherapy, and experiencing severe diarrhoea that hasn't responded well enough to initial loperamide treatment.

What does the study involve?

For each participant, the study will last approximately 4 weeks. Everyone will first receive standard loperamide treatment for 12-36 hours. If this doesn't help enough to treat their diarrhoea, they will be randomly assigned to one of the three treatment groups for up to 5 days. Participants will complete regular questionnaires about their symptoms and quality of life and will be monitored regularly by their healthcare team, either as inpatients or outpatients, depending on the severity of their symptoms.

What are the possible benefits and risks of participating?

Possible benefits of taking part: It is unknown if taking Dropizol will have additional benefits. Dropizol may, or may not, help an individual participant personally, but will help people in the

future receive the best evidence-based care. The results of the trial could help improve the treatment of this common and distressing side effect, potentially helping more patients complete their planned cancer therapy without interruption.

Possible risks of taking part: With any medicine, there is a risk of side effects. Common side effects of loperamide include headache, constipation, nausea, stomach wind. Common side effects of Dropizol include drowsiness, constipation, dry mouth, difficulty urinating, dizziness, headache. More serious but rare side effects of both medications include bowel complications such as paralytic ileus (a condition where your bowels stop moving properly) and toxic megacolon (inflamed or infected colon).

Where is the study run from?
The study is led by the Chief Investigator, Dr Pablo Nenclares at Barts Cancer Centre in London, and is coordinated by Lindus Health, a CRO (clinical research organisation) based in London. The research will take place at NHS hospitals with specialist cancer (oncology) services across the UK

When is the study starting and how long is it expected to run for?
December 2024 to July 2026

Who is funding the study?
The study is funded by Pharmanovia (the company that owns Dropizol)

Who is the main contact?
The RESOLVE trial team can be contacted on resolve@lindushealth.com

# Contact information

### Type(s)
Public, Scientific

### Contact name
Miss Alexandra Robbins

### Contact details
2nd Floor, 90 Union Street
London
United Kingdom
SE10NW
+44 800 058 4113
alex@lindushealth.com

### Type(s)
Principal Investigator

### Contact name
Dr Pablo Nenclares

### Contact details
St Bartholomew's Hospital, W Smithfield
London
United Kingdom

EC1A 7BE
+44 20 3465 5131
pablo.nenclares1@nhs.net

# Additional identifiers

### EudraCT/CTIS number
Nil known

### IRAS number
1011453

### ClinicalTrials.gov number
Nil known

### Secondary identifying numbers
PNV-DRO-401, CPMS 66100

# Study information

### Scientific Title
RESOLVE: An open label, parallel arm, randomised controlled trial to assess the efficacy of Dropizol as a treatment for radiotherapy- and/or chemotherapy- induced severe diarrhoea in people with cancer

### Acronym
RESOLVE

### Study objectives
Primary objective:
The aim of the trial is to assess the effectiveness of Dropizol as treatment for severe diarrhoea in people receiving radiotherapy, chemotherapy or combined radiotherapy and chemotherapy for their cancer.

Secondary objectives:
To assess:
Time to resolution of diarrhoea
Improvement in quality of life
Improvement of gastrointestinal symptoms
Healthcare resource utilisation, such as length of hospital admission and requirement for intensive care admission, and number and type of healthcare service interactions
Diarrhoea recurrence rate prior to next chemotherapy and/or radiotherapy cycle
Safety and tolerability of Dropizol alone and in combination with loperamide

### Ethics approval required
Ethics approval required

### Ethics approval(s)

Approved 28/02/2025, East Midlands - Nottingham 2 Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 1048 154; nottingham2.rec@hra.nhs.uk), ref: 25/EM/0013

## Study design
Interventional randomized parallel-group placebo-controlled trial

## Primary study design
Interventional

## Secondary study design
Randomised parallel trial

## Study setting(s)
Hospital

## Study type(s)
Safety, Efficacy

## Participant information sheet

## Health condition(s) or problem(s) studied
Severe diarrhoea

## Interventions
Run-In Period:
Intervention: Loperamide.
Dose: 4 mg (2 tablets) starting dose, followed by 2 mg (1 tablet) after each loose stool.
Route: Oral capsules.
Duration: 12-36 hours.

Control Arm:
Intervention:
Loperamide. 2 mg (1 tablet) after each loose stool.
Route: Oral capsules.
Duration: up to 3 days.

Arm 1:
Intervention: Dropizol.
Dose: 5 mg (10 drops) three times daily (30 drops in total). The dose may be increased by the participant's trial doctor depending on how they respond (total single dose should not exceed 10 mg (20 drops) and total daily dose should not be more than 60 mg (120 drops).
Route: Oral drops.
Duration: up to 5 days.

Arm 2:
Intervention: Loperamide and Dropizol.
Dose: 2 mg (1 tablet) after each loose stool. Dropizol: 5 mg (10 drops) three times daily (30 drops in total). The dose may be increased by the participant's trial doctor depending on how they respond (the total single dose should not exceed 10 mg (20 drops) and total daily dose should

not exceed 60 mg (120 drops).
Route: Loperamide: Oral capsules. Dropizol: Oral drops.
Duration: up to 5 days.

Follow-up activity: Daily follow-up whilst on treatment and at the end of treatment, followed by 3 follow-up visits on days 7, 14 and 21 after randomisation (phone calls or hospital visits depending on inpatient/outpatient status).

Randomisation process: web-based randomisation system.

### Intervention Type
Drug

### Pharmaceutical study type(s)
Pharmacoeconomic

### Phase
Phase IV

### Drug/device/biological/vaccine name(s)
Loperamide, dropizol

### Primary outcome measure
The proportion of participants achieving a 50% reduction in stool frequency recorded above their normal baseline is measured using clinical assessment of diarrhoea at baseline until the end of treatment

### Secondary outcome measures
1. Time to resolution is measured using clinical assessment at baseline and day 21 post-randomisation
2. Improvement of quality of life score is measured using EQ-5D-5L at baseline, 48 hours, and day 7 post-randomisation
3. Improvement of gastrointestinal symptoms is measured using PROMIS-GI at baseline and day 7 post-randomisation
4. Healthcare resource utilisation is measured using medical records and an HCRU questionnaire at baseline, end of treatment, and days 7, 14, and 21 post-randomisation
5. Recurrence rate prior to the next chemotherapy and/or radiotherapy cycle is measured using clinical assessment of diarrhoea at baseline, days 1-5 on treatment, and days 7, 14, and 21 post-randomisation
6. Safety and tolerability are measured using adverse event reporting from the start of the run-in period until day 21 post-randomisation

### Overall study start date
20/12/2024

### Completion date
01/07/2026

### Reason abandoned (if study stopped)
The trial, which had not yet opened to recruitment, was terminated early for commercial reasons

# Eligibility

### Key inclusion criteria

Current participant inclusion criteria as of 07/03/2025:
1. Aged 18 years or above.
2. Chemotherapy- and/or radiotherapy-induced severe diarrhoea, defined by adapted Common Terminology Criteria for Adverse Events (CTCAE) v5.07 grading, as below:
2.1. Grade 2 with at least 1 of the following additional risk factors leading to the investigator classifying the diarrhoea as severe:
2.1.1. Older age, defined as 65 or over
2.1.2. Female
2.1.3. Eastern Cooperative Oncology Group (ECOG) >2
2.1.4. Associated bowel pathology such as lactose intolerance
2.1.5. Presence of tumour in bowel
2.1.6. Treatment with agents such as irinotecan or capecitabine
2.1.7. Weekly chemotherapy schedule
2.1.8. Infusional chemotherapy
2.1.9. Prior history of cancer treatment induced diarrhoea
2.1.10. Concomitant abdominal-pelvic radiation and chemotherapy
or
2.2. Grade 3
or
2.3. Grade 4
3. At the point of randomisation to be currently experiencing an episode of severe diarrhoea where the use of loperamide has not given sufficient effect.
4. Able and willing to give consent to the trial prior to participation.
5. Have access to a smartphone, tablet or laptop with internet access.
6. Female participants of child bearing potential(1) must be willing to ensure that they or their partner use effective contraception(2) or be willing to abstain(3) from sex during the trial.
7. Male participants must use a condom whilst receiving trial treatment and for 3 months after receiving the last IMP dose when having sexual intercourse with a woman of childbearing potential or a pregnant or breastfeeding partner. In addition, female partners of male participants should be advised to also use highly effective contraception if they are of childbearing potential.
8. In the Investigator’s opinion, is able and willing to comply with all trial requirements.
9. Willing to allow his or her General Practitioner, if appropriate, to be notified of participation in the trial.

(1) Females/women of child bearing potential are defined as: Fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, menopausal status will be confirmed in line with NICE guidance.

(2) Highly effective methods have typical-use failure rates of less than 1% and include sterilisation, long-acting reversible contraceptive (LARC) methods (intrauterine devices) and combined or progesterone-only hormonal contraception associated with inhibition of ovulation.

(3) Sexual abstinence is defined as: Refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

Previous participant inclusion criteria:
1. Aged 18 years or above
2. Chemotherapy- and/or radiotherapy-induced severe diarrhoea, defined by adapted Common Terminology Criteria for Adverse Events (CTCAE) v5.07 grading, as below:
2.1. Grade 2 with at least 1 of the following additional risk factors leading to the investigator classifying the diarrhoea as severe:
2.1.1. Older age, defined as 65 or over
2.1.2. Female
2.1.3. Eastern Cooperative Oncology Group (ECOG) >2
2.1.4. Associated bowel pathology such as lactose intolerance
2.1.5. Presence of tumour in bowel
2.1.6. Treatment with agents such as irinotecan or capecitabine
2.1.7. Weekly chemotherapy schedule
2.1.8. Infusional chemotherapy
2.1.9. Prior history of cancer treatment-induced diarrhoea
2.1.10. Concomitant abdominal-pelvic radiation and chemotherapy
2.2. Grade 3
2.3. Grade 4
3. At the point of randomisation to be currently experiencing an episode of severe diarrhoea where the use of loperamide has not given sufficient effect
4. Able and willing to give consent to the trial prior to participation
5. Have access to a smartphone or tablet
6. Female participants of childbearing potential and male participants whose partner is of child-bearing potential must be willing to ensure that they or their partner use effective contraception or be willing to abstain from sex during the trial (1)
7. In the Investigator’s opinion, is able and willing to comply with all trial requirements
8. Willing to allow his or her General Practitioner, if appropriate, to be notified of participation in the trial

(1) Highly effective methods have typical-use failure rates of less than 1% and include sterilisation, long-acting reversible contraceptive (LARC) methods (intrauterine devices) and combined or progesterone-only hormonal contraception associated with inhibition of ovulation

## Participant type(s)
Patient

## Age group
Adult

## Lower age limit
18 Years

## Sex
Both

## Target number of participants
279

## Key exclusion criteria
1. Current treatment with immunotherapy or targeted therapies
2. Severe renal or hepatic impairment, defined as eGFR less than 40 ml/min/1.73 m² and LFTs above 2 x the ULN (1)
3. Confirmed or suspected pancreatitis
4. At risk of paralytic ileus
5. Known history of:
5.1. Opiate dependency
5.2. Alcohol use disorder
5.3. Glaucoma
5.4. Delirium tremens
5.5. Severe head trauma
5.6. Chronic obstructive pulmonary disease
5.7. Acute asthma
5.8. Severe respiratory depression with hypoxia and/or hypercapnia
5.9. Heart failure secondary to lung disease
6. Participants who have a stoma
7. Participants at high risk of falls
8. Participants with Clostridium difficile (C. diff) infection (2)
9. Participants who are intolerant to loperamide (3)
10. Any other significant disease or disorder which, in the opinion of the Investigator, may put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial
11. Female participants of child bearing potential who are pregnant, lactating or planning pregnancy during the course of the trial. Female participants of child bearing potential who have not already had a negative pregnancy test prior to commencing chemotherapy or radiotherapy should complete a pregnancy test to confirm they are not pregnant
12. Surgical operation within the past 7 days or scheduled within a week after randomisation
13. Co-enrolment in another clinical trial of investigational medicinal products (CTIMP)
14. Hypersensitivity to the active substances or to the excipients
15. Ongoing use of the following medications: disulfiram, metronidazole, morphine agonists /antagonists (buprenorphine, nalbuphine, nalmefene, naltrexone, pentazocine) and opioids (e.g. alfentanil, butorphanol, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, oxycodone, oxymorphone, remifentanil, sufentanil, tapentadol, tramadol). Participants who are expected to require any of these medications during the trial are also excluded (4)

(1) LFTs include ALT and AST. Kidney and liver function results from blood tests conducted as SoC within the previous 48 hours are permitted
(2) C. diff results from stool sample tests conducted as SoC within the previous 48 hours are permitted
(3) Unable to tolerate the adverse effects of loperamide
(4) Investigators should refer to the SmPCs for a full list of warnings and precautions, and should exclude participants at their discretion if concerned about cautionary interactions of the IMPs and concomitant medications

## Date of first enrolment
01/05/2025

**Date of final enrolment**
01/06/2026

# Locations

**Countries of recruitment**
England

United Kingdom

**Study participating centre**
-
United Kingdom
-

# Sponsor information

**Organisation**
Pharmanovia (Atnahs Pharma UK Ltd)

**Sponsor details**
Dr Mushtaque Mastim - Head of Clinical Development
Smartworks Times Square Building
Tower C – 9th Floor
Andheri Kurla Road, Chimatpada,
Marol, Andheri
Mumbai
India
400056
+91 99796 57577
mushtaque.mastim@pharmanovia.com

**Sponsor type**
Industry

**Website**
https://pharmanovia.com/contact/

# Funder(s)

**Funder type**
Industry

**Funder Name**
Pharmanovia

# Results and Publications

### Publication and dissemination plan
1. Peer reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on website
5. Submission to regulatory authorities

### Intention to publish date
01/07/2027

### Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date / Data sharing statement to be made available at a later date. Requests that are made will be evaluated on a case-by-case basis and only where adequate consent and safeguards are in place in line with GDPR and data processing agreements.

### IPD sharing plan summary
Data sharing statement to be made available at a later date