Trials

STUDY PROTOCOL

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Normal saline versus lactated Ringer's solution for acute pancreatitis resuscitation, an open-label multicenter randomized controlled trial: the WATERLAND trial study protocol

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Abstract

Background Some evidence suggests that fluid resuscitation with lactated Ringer's solution (LR) may have an anti-inflammatory effect on acute pancreatitis (AP) when compared to normal saline (NS) and may be associated with a decrease in severity, but existing single-center randomized controlled trials showed conflicting results. The WATERLAND trial aims to investigate the efficacy and safety of fluid resuscitation using LR compared to NS in patients with AP.

Methods The WATERLAND trial is an international multicenter, open-label, parallel-group, randomized, controlled, superiority trial. Patients will be randomly assigned in a 1:1 ratio to receive LR versus NS-based fluid resuscitation for at least 48 h. The primary outcome will be moderately severe or severe AP, according to the revision of the Atlanta classification. The secondary objectives of the WATERLAND trial are to determine the effect of LR versus NS fluid resuscitation on several efficacy and safety outcomes in patients with AP.

A total sample of 720 patients, 360 in the LR group and 360 in the NS group, will achieve 90% power to detect a difference between the group proportions of 10%, assuming that the frequency of moderately severe or severe AP in the LR group will be 17%. A loss to follow-up of 10% of patients is expected, so the total sample size will be 396 patients in each treatment arm (792 patients overall). The test statistic used is the two-sided Z test with pooled variance set at a 0.05 significance level.

Discussion The WATERLAND study aims to improve the early management of AP. Fluid resuscitation is an inexpensive treatment available in any hospital center worldwide. If a better evolution of pancreatitis is demonstrated in one of the treatment arms, it would have important repercussions in the management of this frequent disease.

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Trial registration ClinicalTrials.gov, NCT05781243. Registration date on January 4, 2023. EudraCT number 2023–000010-18, first posted March 23, 2023.

Keywords Acute pancreatitis, Fluid resuscitation, Lactated Ringer solution, Normal saline, Randomized controlled trial

Administrative information

Title {1}	Normal saline versus lactated Ringer's solution for acute pancreatitis resuscitation, an open-label multicenter randomized controlled trial: the WATERLAND trial
Trial registration {2a and 2b}	EudraCT number 2023–000010-18, date of registration January 4, 2023. ClinicalTrials.gov Identifier: NCT05781243, first posted March 23, 2023
Protocol version {3}	Version 4, September 18, 2023. Version 1 was approved by the central ethics committee (Comité Ético de Investigación con Medicamentos, Hospital General Universitario Dr. Balmis, Alicante, Spain, project code 2023–031) on March 9, 2023. Version 4 was approved on September 29, 2023.
Funding {4}	*Proyectos de I + D + I en Salud 2022, Acción Estratégica en Salud 2021–2023*, grant number: PI22/00980, Instituto de Salud Carlos III, Ministry of Science and Innovation, Government of Spain, Madrid, Spain. Beca Gonzalo Miño, Spanish Association of Gastroenterology (Asociación Española de Gastroenterología, AEG), grant number: Gonzalo Miño Grant 2024, Madrid, Spain. Beca Intramural, Alicante Institute of Health and Biomedical Research (ISABIAL), grant number: ayudas intramurales de ISABIAL modalidad C 2023, Alicante, Spain. UEG Research Prize, United European Gastroenterology (UEG), grant number: UEG Research Prize 2024, Vienna, Austria.
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Role of sponsor {5c}	This is a researcher-driven study. The sponsor participated in the study design and will participate in the collection, management, analysis, and interpretation of data, writing of the report, and the decision to submit the report for publication. The sponsor declares no conflicts of interest. Funders are not directly involved in the study. Private companies with economic interest in fluid resuscitation will not be involved in this study.

{}: SPIRIT checklist item numbers [1]

Introduction

Background and rationale (SPIRIT checklist item number {6a}) [1]

Acute pancreatitis (AP) is the third leading cause of hospital admission and readmission for digestive diseases

(nearly 300,000 diagnoses in the USA in 2018) [2]. Furthermore, its incidence is increasing, and the median total cost per hospitalization in 2018 amounted to $22,817 [2]. AP is an acute inflammatory disease with variable severity. According to the revision of the Atlanta classification (RAC), severe AP is defined by the development of persistent organ failure (lasting more than 48 h), moderately severe by the presence of local complications, exacerbation of comorbidity, or transient organ failure (lasting ≤ 48 h), and mild AP by the absence of organ failure, exacerbation of comorbidity and local complications. [3] Mild cases have minimal local and systemic inflammation with an uncomplicated clinical course and often a prompt recovery. Local complications, e.g., acute peripancreatic fluid collections, pancreatic, or peripancreatic fat necrosis [3], occur in one-third of patients and are associated with a longer hospital stay, greater morbidity, and increased hospital costs. [4, 5] Of greatest concern are patients who develop uncontrolled systemic inflammatory response syndrome (SIRS) that can lead to organ failure, which is associated with significant mortality [4].

The control of inflammation in the initial phase of AP may alter the clinical course of the disease by reducing the development of local and systemic complications and thus decreasing patient suffering, mortality, and costs. Unfortunately, no treatment has consistently been shown to decrease the incidence of moderately severe or severe AP [6–8]. The current early management of AP consists of supportive treatment in which fluid resuscitation has played a central role in the last two decades [9]. Research in fluid resuscitation has focused on the volume of fluids (aggressive or moderate) [10–13] and the type of fluid. The recently published WATERFALL study demonstrated that early aggressive fluid resuscitation was associated with three times more episodes of fluid overload than moderate hydration and does not appear to reduce the severity of AP compared to moderate hydration [14].

Regarding the type of fluid which is best for AP, published results are conflicting. The two major types of fluids used in medicine are crystalloids and colloids. Crystalloids have an osmotic pressure equivalent to plasma and contain water-soluble electrolytes such as sodium [15]. Colloids, which have a higher oncotic pressure, were designed to allow the supplied water to remain more effectively and durably in the intravascular compartment than crystalloids. However, published trials do not suggest that they improve clinical results in intensive care patients [15–17] which has dampened enthusiasm for their widespread use. The two crystalloids most frequently used in clinical practice include normal saline (NS) and lactated Ringer's solution (LR). NS contains water and 0.9% sodium chloride (154 mEq/L of sodium and chlorine). With a chlorine content higher than plasma, large-volume infusions of NS may result in hyperchloremic acidosis [15]. LR contains less sodium and chloride (130 and 109 mEq/L, respectively) and contains 28 mEq/L of lactate, in addition to calcium and potassium. LR is a balanced crystalloid due to its more neutral effect on acid–base physiology [15]. In vitro studies suggest that the lactate present in the LR may have an anti-inflammatory effect [18].

In 2011, Wu et al. published an open-label clinical trial that included 40 patients with double randomization to (A) LR or NS and (B) to a goal-directed volume protocol (titration to blood urea nitrogen levels) or standard management. No differences were detected in goal-directed versus standard management, but patients treated with LR had a lower incidence of SIRS and lower C-reactive protein (CRP) blood levels 24 h after recruitment [19]. In 2018, our group published a triple-blind randomized clinical trial with 40 patients from a single center. We described that LR was associated with lower CRP levels at 48 and 72 h [18]. In a 2018 open-label randomized clinical trial by Choosakul et al., 47 patients received LR or NS, demonstrating a lower proportion of patients with SIRS at 24 h but not thereafter [20]. We conducted a larger double-blind randomized clinical trial with 121 patients with predicted mild AP. In this study, LR was associated with a similar degree of inflammation as NS but with a shorter hospital stay and lower intensive care unit (ICU) admission [21]. A recent single-center randomized clinical trial with 51 patients (Karki et al.) also described less inflammation with LR [22]. There have been several meta-analyses of these studies, including our review, which incorporated unpublished data by contacting trial authors (248 patients from 4 trials were included) [23]. In these studies, patients who received LR were less likely to suffer moderately severe or severe pancreatitis (odds ratio (OR) 0.49, 95% confidence interval (CI) 0.25–0.97), there were no differences in inflammation (SIRS) or organ failure, but they were less likely to be admitted to the ICU (OR 0.33, 95% CI 0.13–0.81) or to develop local complications (OR 0.42, 95% CI 0.20–0.88). It has been described in other different clinical scenarios than AP that NS is associated with renal failure [24]. Clinical trials in other diseases have shown conflicting results. In a double-blind clinical trial at four hospital centers of critically ill patients, no benefit was shown for balanced fluids (Plasma-Lyte 148, which does not contain lactate) compared to NS [25]. In another single-center open-label clinical trial of critically ill patients comparing Plasma-Lyte A or LR versus NS, it was shown that NS was associated with a greater probability of renal failure [24]. Very recently, a double-blind study was published of critically ill patients from 53 ICUs that did not observe advantages of Plasma-Lyte 148 compared to NS [26].

Reporting guidelines

This protocol follows the recommendations of SPIRIT 2013 Statement: Definition of Standard Protocol Elements for Clinical Trials [1]. Numbers in curly brackets, e.g., {5a} are SPIRIT element identifiers.

Objectives {7}

The null hypothesis is that there is no difference in the incidence of moderately severe or severe disease in patients with AP receiving fluid resuscitation based on LR compared to NS. The alternative hypothesis is that fluid resuscitation based on LR is associated with a lower incidence of moderately severe or severe AP.

The primary objective of the WATERLAND trial is to investigate the effect of fluid resuscitation based on LR versus NS on the severity of AP (frequency of moderately severe or severe disease).

The secondary objectives of the WATERLAND trial are to determine the effect of LR versus NS fluid resuscitation on several efficacy and safety outcomes in patients with AP.

Trial design {8}

The WATERLAND trial is an international multicenter, open-label, parallel-group, randomized, controlled, superiority trial promoted by the ERICA (int*ER*national league aga*I*nst biliary-pancreati*C* dise*A*ses) consortium. Patients will be randomly assigned in a 1:1 ratio to receive LR versus NS-based fluid resuscitation. WATERLAND trial is a low-risk interventional pharmacological clinical trial.

Methods

Participants, interventions, and outcomes

Study setting {9}

The WATERLAND study is open to international academic or non-academic level 2 and level 3 hospitals. Current participating centers can be found on the following link: https://clinicaltrials.gov/ct2/show/NCT05781243

Eligibility criteria {10}

Center eligibility: hospitals that care for patients admitted for AP that can offer continuous care, with the availability of blood tests, abdominal ultrasound, abdominal computed tomography (CT), magnetic resonance imaging, endoscopic retrograde cholangiopancreatography (ERCP), interventional radiology, and ICU.

Patient eligibility: inclusion and exclusion criteria are provided in Table 1.

Informed consent {26a}

The local study collaborators will obtain informed consent from potential trial participants or authorized surrogates. Informed consent is provided in the protocol in Additional file 1.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Biological samples will not be obtained.

Interventions

Explanation for the choice of comparators {6b}

As discussed in the background, some randomized clinical trials suggest that LR may be associated with less inflammation and better outcomes than NS. WATERLAND will compare LR—and NS-based fluid resuscitation in patients with AP.

Intervention description {11a}

The volume of fluids is based on the moderate treatment arm of the WATERFALL trial (1.5 mL/kg/h preceded by bolus 10 mL/kg if the patient has hypovolemia). [14] The "participant timeline" shows more details; see below.

Criteria for discontinuing or modifying allocated interventions {11b}

LR and NS are fluids routinely used to treat AP and other diseases. The incidence of adverse effects in both is very low. In case of hyperkalemia or hypercalcemia, the treating physician may discontinue the infusion of LR, which has a small amount of potassium and calcium, and the adverse effect will be recorded. NS can be associated with hyperchloremic acidosis if administered in massive amounts, so the treating physician may decide to suspend this fluid in case of this complication, as mentioned above. Patients may leave the study at any time after signing the informed consent.

Strategies to improve adherence to interventions {11c}

Adherence is assessed based on the percentage of subjects receiving $\geq 80\%$ of the planned amount of fluids according to the study protocol in the first 48 h. No measures are required to improve adherence to the interventions since it is an acute disease, and the study fluid is administered during the first days of hospitalization.

Relevant concomitant care permitted or prohibited during the trial {11d}

Potassium administration should be 40 mEq per day in both arms of treatment during fasting unless a higher or lower dose is clinically indicated. LR contains potassium at a concentration of 4 mEq/l and NS contains no potassium, which will be considered in the calculation of daily potassium administration. The attending physician will decide on feeding, treatment with analgesics, antibiotics, indications for ERCP, drainage, and all other treatment measures and administer as clinically appropriate.

Table 1 Patient inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Patient is 18 years or older 2. Diagnosis of acute pancreatitis according to the revision of the Atlanta classification (Banks et al., Gut 2013), which requires at least two of the following three criteria: (A) typical abdominal pain, (B) increase in serum amylase or lipase levels higher than three times the upper limit of normality, and (C) signs of acute pancreatitis in imaging 3. Signature of informed consent	1. New York Heart Association class II heart failure (slight limitation of physical activity; fatigue, palpitations, or dyspnea with ordinal physical activity) or worse, or ejection fraction < 50% in the last echocardiography 2. Decompensated cirrhosis (Child's class B or C) 3. Hyper or hyponatremia (< 135 or > 145 mEq/L) 4. Hyperkalemia (> 5 mEq/L) 5. Hypercalcemia (albumin or protein-corrected calcium > 10.5 mg/dL or 2.62 mmol/L) 6. Criteria for moderately severe or severe acute pancreatitis (revision of the Atlanta classification, Banks et al., Gut 2013) at recruitment: any of the following: (A) presence of creatinine ≥ 1.9 mg/dL or ≥ 170 mmol/l, (B) PaO2/FiO2 ≤ 300, (C) systolic blood pressure < 90 mmHg despite initial fluid resuscitation, (D) presence of local complications (acute peripancreatic fluid collections, acute necrotic collection, pseudocyst, walled-off necrosis, gastric outlet dysfunction, splenic or portal vein thrombosis, or colonic necrosis), and (E) exacerbation of previous comorbidity such as coronary artery disease or chronic lung disease, precipitated by the acute pancreatitis 7. Signs of volume overload or heart failure at recruitment (peripheral edema, pulmonary rales, or increased jugular ingurgitation at 45°) 8. Time from pain onset to arrival to emergency room > 24 h 9. Time from confirmation of pancreatitis to randomization > 8 h 10. Chronic pancreatitis defined by a Wirsung duct ≥ 4 mm and/or pancreatic calcifications 11. More than one previous episode of acute pancreatitis (only to episodes of acute pancreatitis are allowed, one of them the present episode)

Provisions for post-trial care {30}

Patients will be managed after the trial by the attending physician at his or her discretion.

Outcomes {12}

Most outcomes will be assessed between randomization and 30 days after randomization unless assessment at 24, 48, or 72 h is specified; see Tables 2 and 4.

Efficacy outcomes

The primary outcome will be moderately severe or severe AP, defined according to the RAC [3]. Moderately severe AP is defined in the first 4 weeks after disease onset as the presence of local complications (acute peripancreatic fluid collections, acute necrotic collection, gastric outlet dysfunction, splenic or portal vein thrombosis, and colonic necrosis) or systemic complications (exacerbation of a preexisting coexisting condition, such as coronary artery disease or chronic lung disease, precipitated by AP) or transient organ failure (organ failure that resolves within 48 h). Severe AP is defined as persistent (lasting more than 48 h) organ failure. Organ failure is defined according to the modified Marshall score by the presence of any of the following criteria: (A) kidney failure as a creatinine ≥ 1.9 mg/dL or > 170 μmol/L, (B) cardiovascular failure as a systolic blood pressure < 90 mmHg despite fluid resuscitation, and (C) respiratory failure as a PaO2/FIO2 ≤ 300 [3]. Patients with moderately severe or severe AP have increased morbidity (more time to oral refeeding, greater need for invasive treatment, more frequency of ICU admission, higher hospital stay, and increased mortality risk) [4]. Moderately severe or severe AP was the primary efficacy outcome used in the WATERFALL trial, which compared aggressive versus moderate fluid resuscitation in acute pancreatitis [14]. RAC definitions for local complications diagnosed within the first 4 weeks after disease onset [3] are as follows:

> Acute peripancreatic fluid collections: peripancreatic fluid associated with interstitial edematous pancreatitis with no associated peripancreatic necrosis. This term applies only to areas of peripancreatic fluid seen within the first four weeks after the onset of interstitial edematous pancreatitis and without the features of a pseudocyst.
>
> Acute necrotic collection: a collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis; the necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues. Heterogeneous and non-liquid density of varying degrees in different locations (some appear homogeneous early in their course). No definable wall encapsulating the collection. Location: intrapancreatic and/or extrapancreatic.
>
> Gastric outlet dysfunction: gastric outlet dysfunction typically presents with early satiety, weight loss, nausea, vomiting, and abdominal pain [27]. RAC

Table 2 Primary and secondary efficacy outcomes

Outcome	Analysis metric	Method of aggregation	Timing of outcome assessment	Definition
Moderately severe or severe AP[a]	Final value	Proportion	30d	RAC: presence of local complications, exacerbation of previous comorbidity or organ failure
Local complications (specific local complications will be also recorded)	Final value	Proportion	30d	RAC: presence of acute peripancreatic fluid collections, acute necrotic collection, gastric outlet dysfunction, splenic mesenteric, or portal vein thrombosis, and colonic necrosis (see main text for definitions)
Necrotizing pancreatitis	Final value	Proportion	30d	RAC: presence of acute necrotic collections (see main text for definition)
Infection of pancreatic collections or necrosis	Final value	Proportion	30d	Extraluminal gas in the pancreatic and/or peripancreatic tissues on CT scan or when a sample from the collection/necrosis contains pus or is positive for bacteria and/or fungi on Gram stain or culture
SIRS at 24 and 48 h	Final value	Proportion, stratified by baseline presence or absence of SIRS criteria	At randomization, 24 h, and 48 h after randomization	At least two criteria: (A) pulse > 90 beats/min, (B) respirations > 20/min or arterial blood $PaCO_2$ < 32 mm Hg, (C) temperature < 36 °C or > 38 °C, (D) white blood cell count < 4000 cells/mm3 or > 12,000 cells/mm3 or > 10% bands
Number of SIRS criteria at 24 and 48 h	Final value	Median, stratified by baseline presence or absence of SIRS criteria	At randomization, 24 h, and 48 h after randomization	SIRS criteria: (A) pulse > 90 beats/min, (B) respirations > 20/min or < arterial blood $PaCO_2$ < 32 mm Hg, (C) temperature < 36 °C or > 38 °C, (D) white blood cell count < 4000 cells/mm3 or > 12,000 cells/mm3 or > 10% bands
PAN-PROMISE symptom scale at 24 and 48 h	Change from baseline and final value	Mean or median	At randomization, 24 h, and 48 h after randomization	PAN-PROMISE scale: a seven-symptom patient-reported outcome measurement scale (range, 0 to 10 for each symptom; overall range, 0 to 70, with higher scores indicating higher symptom intensity)
Time to oral refeeding	Final value	Mean or median	30d	Days from baseline to oral refeeding
Invasive treatment	Final value	Proportion	30d	Any of the following: thoracocentesis due to pancreatitis-induced pleural effusion, percutaneous and/or endoscopic drainage of pancreatic or peripancreatic fluid collections or necrosis, endoscopic or surgical necrosectomy, endoscopic retrograde cholangiopancreatography due to (A) ruptured common bile duct, (B) jaundice caused by compression of the common bile duct, and (C) main pancreatic duct leakage
Nutritional support	Final value	Proportion	30d	Use of enteral (nasogastric or nasojejunal) or parenteral feeding
Intensive care unit admission	Final value	Proportion	30d	Admission in the intensive care unit

Table 2 (continued)

Outcome	Analysis metric	Method of aggregation	Timing of outcome assessment	Definition
Exacerbation of coexisting condition	Final value	Proportion	30d	RAC: exacerbation of pre-existing co-morbidity, such as coronary artery disease or chronic lung disease, precipitated by the acute pancreatitis
Any organ failure	Final value	Proportion	30d	RAC: see main text for definitions
Persistent organ failure	Final value	Proportion	30d	RAC: see main text for definitions
Shock	Final value	Proportion	30d	RAC: see main text for definitions
Respiratory failure	Final value	Proportion	30d	RAC: see main text for definitions
Kidney failure	Final value	Proportion	30d	RAC: see main text for definitions
Death	Final value	Proportion	30d	Death from randomization to 30 days after randomization
Hospital stay	Final value	Proportion	30d	Days from presentation in the emergency room to 30 days after randomization. Includes readmissions due to symptoms or complications related to the index episode
C-reactive protein at 48 h	Final value	Mean or median	48 h after randomization	Blood levels of c-reactive protein
Hypovolemia	Final value	Proportion	At randomization, 24 h, and 48 h after randomization	See Table 3

Mean or median: for quantitative variables, the method of aggregation will depend on the normal or non-parametric distribution of the data

AP Acute pancreatitis, *PAN-PROMISE study* definitions provided in de-Madaria et al., Gut 2021 [5], *Hr* hours, *30d* from the date of randomization to 30 days after randomization, *RAC* definition according to the revision of the Atlanta classification [3]. *SIRS* Systemic inflammatory response syndrome

[a] Primary outcome

provides no definition. In WATERLAND, it will be defined as a delay in gastric emptying that requires medical treatment (fasting, nasogastric or nasojejunal tube, prokinetics, etc.) or invasive treatment. Paralytic ileus should be ruled out.
Splenic or portal vein thrombosis: RAC provides no definition. In WATERLAND, it will be defined as partial or complete thrombosis in the splenic or portal vein in imaging. Mesenteric vein thrombosis will also be recorded.
Colonic necrosis: RAC provides no definition. In WATERLAND, it will be defined as colonic necrosis in imaging, endoscopy, or evidenced in surgical intervention.
Infection of pancreatic collections or necrosis: extraluminal gas in the pancreatic and/or peripancreatic tissues on CT scan or when a sample from the collection/necrosis contains pus or it is positive for bacteria and/or fungi on Gram stain or culture (adapted from RAC).
Mild AP without imaging tests: if a patient has mild AP, with rapid resolution of pain, absence of SIRS 48 h after admission, and discharge within the first 5 days of admission, it is assumed that the patient has no local complications even without imaging evidence.

Table 2 lists secondary outcome variables and their definitions. The PAN-PROMISE scale will be used to measure patient wellness. PAN-PROMISE is a patient-reported outcome measurement (PROM) that measures seven symptoms (range 0 to 10 for each symptom; overall range 0 to 70, with higher scores indicating higher symptom intensity) [5].

Safety outcomes

The safety outcomes will be a (A) a composite variable involving any of the following: fluid overload, acute kidney injury, hyperkalemia, hypercalcemia, hyperchloremia, or acidosis and (B) the individual components of the composite variable. The attending physician will manage these complications as clinically appropriate. Fluid overload is defined in Table 3 [14]. Safety outcomes are defined in Table 4.

Severity of fluid overload is defined (14) as:

A Mild: patients respond to medical treatment or decrease in volume infusion rate, and the PaO2/FIO2 never decreases < 300.
B Moderate: patients respond to medical treatment or decrease in volume/infusion rate and have at least one measurement with PaO2/FIO2 < 300.
C Severe: patients require invasive or non-invasive mechanical ventilation, and/or hemofiltration, or expire due to overload.

NS has been associated with an increased risk of renal failure [24]. Acute kidney injury will be defined according to the KDIGO classification: increase in serum creatinine of ≥ 0.3 mg/dL within 48 h or ≥ 50% within 7 days or urine output of < 0.5 mL/kg/h for > 6 h [28]. LR contains small quantities of potassium and calcium, so hyperkalemia and hypercalcemia are safety outcomes. As mentioned, the recommended daily potassium administration will be 40 mEq/day in both treatment arms during fasting unless a higher or lower dose is clinically indicated. NS has high chloride content, and this fluid has been associated with hyperchloremic acidosis [29], so levels of chloride and pH will be measured.

Other variables

The volume of fluids administered in the first 48 h after recruitment will be provided. This trial promotes the participation of patients from diverse backgrounds. Race will be recorded following the "Collection of Race and Ethnicity Data in Clinical Trials" 2016 recommendations of the FDA [30]. Sex will be recorded as sex assigned at birth (male/female).

Participant timeline {13}

The participant timeline is summarized in Fig. 1.

Step 1. At recruitment: check for baseline hypovolemia criteria (Table 3) and SIRS (Table 2). Patients without hypovolemia will receive a continuous LR or NS intravenous infusion of 1.5 mL/kg/h. Patients who meet hypovolemia criteria will first receive an LR or NS 10 mL/kg intravenous bolus (over 2 h) of the study fluid, followed by an LR or NS infusion of 1.5 mL/kg/h. Oral food is allowed if the patient is willing to start oral feeding. The baseline PAN-PROMISE scale will be assessed [5].
Step 2. Follow-up until the 24-h checkpoint: in case of systolic blood pressure < 90 mmHg or urine output < 0.5 mL/kg/h, a 10 mL/kg intravenous bolus over 30 to 120 min will be administered, depending on the physician's assessment of the patient's condition. The bolus can be repeated if needed, as many times as necessary. In case of suspicion of fluid overload (Table 3), the attending physician can decrease or stop fluid resuscitation and administer treatment for fluid overload if needed. Tests to rule out other medical conditions (ischemic heart disease, lung

Table 3 Criteria for hypovolemia and fluid overload

Hypovolemia **≥ 1 criteria**	**Fluid overload** **≥ 1 criteria: suspicion of fluid overload** **≥ 2 criteria: confirmed fluid overload** **ARDS must be ruled out**
Criterion 1. New onset (in the absence of baseline chronic kidney failure) creatinine > 1.1 mg/dL or BUN > 20 mg/dL, equivalent to urea > 43 mg/dL Criterion 2. Hematocrit > 44% Criterion 3. Increase in creatinine and/or BUN and/or urea from the previous value Criterion 4. Urine output < 0.75 mL/kg/hour Criterion 5. Systolic blood pressure < 90 mmHg without other explanation than hypovolemia Criterion 6. Signs and/or symptoms of dehydration (intense thirst, dehydrated oral mucosa, decreased skin turgor–skin pinch)	Criterion 1. Hemodynamic-imaging evidence (at least one): A. Non-invasive diagnostic evidence of heart failure (i.e., echocardiographic) B. Radiographic evidence of pulmonary congestion C. Invasive cardiac catheterization suggesting evidence of heart failure [i.e., pulmonary capillary wedge pressure (or left ventricular end-diastolic pressure) > 18 mmHg, right arterial pressure (or central venous pressure) > 12 mmHg, or cardiac index < 2.2 L/min per m2] Criterion 2. Heart failure symptoms: Dyspnea Criterion 3. Heart failure signs (at least one): A. Peripheral edema B. Pulmonary rales C. Increased jugular venous pressure, hepatojugular reflux, or both ARDS must be ruled out: ARDS is defined by all the following four criteria: A. Onset within 1 week of the pancreatitis onset or later due to severe sepsis B. Bilateral opacities not fully explained by effusions, lobar collapse, or nodules C. Respiratory failure not fully explained by cardiac failure or fluid overload needs objective assessment (i.e., echocardiography) to exclude hydrostatic edema if no risk factor is present D. PaO2/FIO2 ≤ 300

Based on the WATERFALL trial, de-Madaria et al., New England Journal of Medicine 2022. ARDS definition is based on the modified Berlin definition, Ranieri et al., JAMA 2012

ARDS acute respiratory distress syndrome, *BUN* blood urea nitrogen

Table 4 Safety outcomes

Outcome	Analysis metric	Method of aggregation	Time point	Definition
Fluid overload	Final value	Proportion	From randomization to 72 h thereafter	See Table 3. The 72-h period was chosen because of the analysis of fluid overload in the WATERFALL study: the median (interquartile range) of occurrence of fluid overload was 46 h (30–64)
Acute kidney injury	Final value	Proportion	At 24 h and 48 h after randomization	KDIGO: see main text for definitions
Hyperkalemia	Final value	Mean or median	At 24 h and 48 h after randomization	Venous potassium > 5 mEq/L
Hypercalcemia	Final value	Mean or median	At 24 h, and 48 h after randomization	Venous calcium corrected by proteins > 10.5 mg/dL or 2.62 mmol/L
Hyperchloremia	Final value	Mean or median	At 24 h, and 48 h after randomization	Venous chloride > 106 mEq/L
Acidosis	Final value	Mean or median	At 24 h, and 48 h after randomization	Venous blood pH < 7.35
Hyperchloremic acidosis	Final value	Proportion	At 24 h, and 48 h after randomization	Venous chloride > 106 mEq/L + venous blood pH < 7.35
Safety compound variable	Final value	Proportion	From randomization to 48 h thereafter (72 h for fluid overload)	Requires at least one of the previous safety variables

Hr hours, *KDIGO* kidney disease improving global outcomes

embolism, etc.) will be performed according to the attending physician's assessment of the patient.

Step 3. 24-h checkpoint. Anamnesis, blood test, and physical examination will be performed. Oral feeding will be considered in patients under null per mouth. All patients will maintain an infusion of 1.5 mL/kg/h except those suspected of fluid overload (in that case, the physician will proceed as in step 2). PAN-PROMISE, hypovolemia, fluid overload, SIRS, and outcomes based on blood determinations (except for CRP) will be assessed.

		Study period			
	Enrolment	Allocation	Post-allocation		Close-out
Timepoint	Within 8 hours from AP diagnosis	0 hour	24 hours	48 hours	72 hours	From allocation to 30 days after allocation
Enrolment:						
Eligibility screen	X					
Informed consent	X					
Allocation	X					
Interventions*:						
RL arm		< ---------- >				
NS arm		< ---------- >				
Assessments:						
SIRS	X		X	X		
Hypovolemia	X		X	X		
PAN-PROMISE		X	X	X		
K, Ca, Cl, pH, AKI			X	X		
CRP				X		
Fluid overload			X	X	X	
All other outcomes						X

Fig. 1 Schedule of enrolment, interventions, and assessments. Asterisk indicates the mandatory period for receiving the study fluid is 48 h, but if patients need fluids for more time, the study fluid will be used as long as necessary. AKI acute kidney injury, K, Ca, Cl, pH, CRP potassium, calcium, chloride, pH, and c-reactive protein, respectively. NS normal saline. PAN-PROMISE PAN-PROMISE acute pancreatitis symptom scale. RL lactated Ringer solution. SIRS systemic inflammatory response syndrome

Step 4. Follow-up until the 48-h checkpoint: the patient will be managed as in step 2.

STEP 5. 48-h checkpoint. Anamnesis, blood test, and physical examination will be performed. Fluid resuscitation will be stopped in those patients tolerating oral feeding for more than 8 h, with normal or hypervolemia. In case of hypovolemia or patients without tolerance to oral food, proceed as in step 2 until normal volemia and oral tolerance are reached. PAN-PROMISE, SIRS, hypovolemia, fluid overload, and outcomes based on blood determinations will be assessed.

Step 6. Follow-up until discharge. The patient can be discharged at the 48-h checkpoint in case of mild pancreatitis and tolerance to oral diet or later, according to the patient status determined by the attending physician. Fluid overload will be assessed also at 72 h. CT scan for the diagnosis of local complications should be performed on day 3 or later in case of SIRS at 48 h, increased CRP at 48 h (more than 15 mg/dL or more than 150 mg/L) or when clinically indicated according to the attending physician.

Step 7. Follow-up up to 30 days after randomization. Many outcome variables are assessed 30 days after randomization (Table 2). When this period has elapsed, an assessment will be performed to determine whether the patient has been readmitted; this can be done by phone call.

Sample size {14}

The WATERFALL trial had a frequency of moderately severe or severe AP in the moderate fluid resuscitation arm of treatment (based on LR) of 17% [14]. In a recent systematic review, patients who received LR-based fluid resuscitation were less likely to develop moderately severe or severe pancreatitis than patients receiving NS, with an OR of 0.49, 95% CI 0.25–0.97 [23]. The differences in the incidence of moderately severe or severe pancreatitis in the four included randomized controlled trials between LR and NS ranged from 10 to 14%, favoring LR [23]. For this reason, we expect an incidence of moderately severe or severe AP in the NS arm of 27%. Patients will be assigned in a 1:1 ratio. A total sample of 720 patients, 360 in the LR group and 360 in the NS group, will achieve 90% power to detect a difference between the group proportions of 10% (the smaller difference observed in the four RTCs [23]), assuming that the frequency of moderately severe or severe AP in LR group will be 17%. The frequency in the NS group is assumed to be 17% under the null hypothesis and 27% under the alternative hypothesis. A loss to follow-up of 10% of patients is expected, so the sample size will be 396 patients in each treatment arm (792 patients in total). The test statistic used is the two-sided Z test with pooled variance set at a 0.05 significance level.

Recruitment {15}

WATERLAND is an international multicenter study. Current participating centers can be found on the following link: https://clinicaltrials.gov/ct2/show/NCT05781243

The study has been shared through these communication channels:

1. Previous ERICA consortium collaborators [4, 5, 13, 14]
2. National and international gastroenterology, surgery, and pancreatology associations (see "Acknowledgements")
3. ERICA consortium website (ericaresearch.com)
4. ERICA consortium and the researchers' personal social networks
5. Meetings and symposiums

Assignment of interventions: allocation

Sequence generation {16a}

Sequence assignment will be performed using computer-generated random numbers. Random assignments will be stratified by center, presence or absence of baseline SIRS, and presence or absence of baseline hypovolemia. The randomization process will be performed using the block.random function of the "psych" library of R. Only the study coordinator (AVR) and the Dr. Balmis General University Hospital's Department of Clinical Pharmacology will have access to the sequence.

Concealment mechanism {16b}

Randomization will be integrated into the web-based electronic case report form (REDCap) [31].

Implementation {16c}

The allocation sequence will be generated by the Department of Clinical Pharmacology of the Dr. Balmis General University Hospital and entered in REDCap by the study coordinator. REDCap will randomize every new patient the study collaborators enter in their centers.

Assignment of interventions: blinding

Who will be blinded {17a}

Only data analysts will be blinded. For this purpose, they will be administered a database in which the arm of treatment (NS or LR) will be replaced by randomly assigned labels A and B.

Procedure for unblinding if needed {17b}

The design is open label so unblinding will not occur.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Before recruitment begins, collaborators will receive training on the study through a teleconference with the study coordinator. Video tutorials on the study will be available in the electronic case report form (REDCap). The electronic case report form, the randomization process, the importance of avoiding missing data, and the importance of accurate data entry will be explained and highlighted. The web-based electronic case report is based on the REDCap platform [31, 32], provided by the Spanish Association of Gastroenterology (AEG). The promotors have extensive experience in this platform.

Plans to promote participant retention and complete follow-up {18b}

The WATERLAND trial only covers from randomization to 30 days thereafter, so complete follow-up will be easily achievable. Centers that do not adequately follow patients may be dropped from the study. The study coordinator, AVR, will oversee patient and center monitoring.

Data management {19}

The forms have been designed to explain every variable to promote data quality. Quantitative variables will include alarms for extreme values. To minimize errors and ensure timely monitoring, filling out the web form directly online will be required. Logical alarms will be set when two or more variables are contradictory, e.g., classifying AP as severe in a patient without persistent organ failure. Local collaborators caring for patients with AP will enter the study data into the electronic case report form.

Confidentiality {27}

The data will be stored in the REDCap node of the AEG, a secure database. Each center has a "Data Access Group" that ensures that only patient records from their center can be accessed. Patient data are entered after the informed consent of the patient or their legal guardian has been obtained, which will have been previously approved by the ethics committees of the participating centers after checking compliance with current legislation (in terms of data protection in Europe: Organic Law 3/2018 of December 5, Regulation 2016/679 of the European Parliament and of the Council of April 27,

2016), which includes information to the patient on the processing of their data, with the right to access, rectification, cancelation, and opposition.

The data are anonymized. Participants will be allocated using an individual trial identification number; information that can identify the patient is not included in the database. The Steering Committee, coordination committee, and data analysts will have access to the final dataset. The ownership of the data belongs to the ERICA consortium; collaborating centers are offered the possibility of access to the global database if they wish to carry out an ancillary study (post hoc studies with different objectives to the original) to WATERLAND trial based on its database, after submitting a report containing an introduction, hypothesis, objectives, methodology, and expected impact. The decision will be made unanimously by the trial Steering Committee. After the central Institutional Review Board approval, the database exported to a statistical package (SPSS or Stata) will be shared in a password-protected zip file that will be sent to the collaborator by another means of communication from which he/she receives the file. The provision of specific anonymized data to other researchers for meta-analysis will be encouraged. To this end, data will be provided (see {31a}) without providing granular details that could compromise patient privacy.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}.

Biological samples will not be collected.

Statistical methods

The Statistical Analysis Plan version 1, June 30, 2024, available in the protocol in Additional file 1, specifies detailed statistical methods.

Statistical methods for primary and secondary outcomes {20a}

Normality will be assessed using the Lilliefors-corrected Kolmogorov–Smirnov test. The number and percentage of primary and secondary categorical outcomes will be reported for each treatment group. Continuous data will be reported by mean and standard deviation if data are normal and median and interquartile range if data are skewed. To calculate the *p*-value for the primary outcome and secondary safety outcomes, the Cochran–Mantel–Haenszel method will be utilized, with adjustments made for randomization stratification factors including center, baseline SIRS presence, and baseline hypovolemia presence. In addition, this procedure will yield adjusted relative risks and their corresponding 95% confidence intervals for all outcomes, also accounting for any variables that display imbalances among randomized groups. For continuous variables, adjusted relative risks will be calculated using multiple regression models adjusted for randomization stratification factors and any variable that display imbalances among randomized groups to analyze the effect of the continuous variable itself. Additionally, the Cochran–Mantel–Haenszel method will be applied to compare high values (above the median) to low values (at or below the median), providing a comprehensive analysis of the data. Briefly (see more details in the Statistical Analysis Plan version 1, June 30, 2024, available in the protocol in Additional file 1), the intention-to-treat population will include all randomized patients, following the intention-to-treat principle. The safety (per-protocol) population will include all randomized patients, according to the fluid that was actually received. Patients receiving no fluid will not be included in the safety population. Efficacy outcomes will be tested in the intention-to-treat population, and safety outcomes will be tested in the safety population.

The analysis will be conducted using SPSS version 29 or higher (IBM), SAS software version 9.4 or higher (SAS Institute), and R software version 4.4.1 or higher. Statistical analysis will be performed by PM, PZ, and EMNM.

Interim analyses {21b}

Given the low expected incidence of adverse events in both arms of treatment, no interim analysis has been predefined. There will be two a priori stopping rules: clear evidence of harm in one trial group over the other (safety) as adjudicated by the Data and Safety Monitoring Committee and a slow recruitment rate determined by the Steering Committee.

Methods for additional analyses {20b}

The following pre-specified subgroup analyses will be performed on the primary and secondary outcomes:

- Baseline presence and absence of SIRS
- Baseline presence and absence of hypovolemia
- Sex

There is no provision for correction for multiplicity for subgroup analysis, so results will be reported as point estimates with two-sided 95% CI.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Adherence is assessed based on the percentage of subjects receiving $\geq 80\%$ of the planned volume of fluids

according to the study protocol in the first 48 h after randomization. The attending physician will assess it. Details about intention-to-treat and per-protocol populations are available in the paragraph "Statistical methods for primary and secondary outcomes" above. More details are specified in the Statistical Analysis Plan version 1, June 30, 2024, available in the protocol in Additional file 1.

Our goal is to reduce or eliminate missing data during recruitment through concerted efforts. If, despite these efforts, missing data occur, we will assess the amount and pattern of missing data. The purpose of this assessment is to analyze the amount of missing data on the primary variables and other variables and determine the nature of the missingness (missing completely random, missing at random, or missing at non-random). We will use the Multivariate Imputation by Chained Equations (MICE) using creating multiple datasets for ten times and results will be combined using Rubin's rules [33]. MICE is useful when the pattern of missing data is random (MAR) or when the proportion of missing data exceeds 5% and does not follow a missing not at random (MNAR) pattern. [34] In cases where missing data follow a missing not at random (MNAR) pattern, we will employ sensitivity analyses to examine the impact of different assumptions about the missing data mechanism on our results. Additionally, we will consider Bayesian imputation methods to address the potential bias introduced by MNAR data.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

Members of the ERICA consortium that recruited patients in the WATERLAND trial may claim access to the final dataset to perform ancillary studies; as discussed above, the Steering Committee will study these proposals. The datasets analyzed during the current study will be published in an open-access repository. Statistical codes are available from the corresponding author on reasonable request, as is the full protocol.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The study will be coordinated by the Gastroenterology and the Clinical Pharmacology Departments of the Dr. Balmis General University Hospital, Alicante, Spain. The Coordination Committee will include the principal investigator and promotor (EdM, gastroenterologist), the study coordinator (AVR), and a clinical pharmacologist (PZ). This committee will provide daily support to the study collaborators. The Coordination Committee will meet every month or in situations requiring important decisions.

The trial Steering Committee comprises a group of international pancreatologists (LG, AGGP, AC, YHB, GC, JLB), an acute pancreatitis patient advocate (CLV), and an expert in statistics (PM). They will meet (via teleconference) every 3 months or in situations requiring important decisions. The Steering Committee had the following tasks: (A) to supervise the overall progress of the trial, (B) to review and consider the Data and Safety Monitoring Committee (DSMC) reports and recommendations, (C) to discuss and decide post hoc analyses after the study is complete, and (D) to participate in writing the final publication.

Composition of the Data and Safety Monitoring Committee, its role, and reporting structure {21a}

The DSMC will comprise a nephrologist, an intensivist, and a clinical pharmacologist. It will evaluate all reported adverse events. Safety reports will be issued as reported and analyzed by the steering committee.

Adverse event reporting and harms {22}

The WATERLAND trial investigates two fluids used routinely for over 100 years; adverse events and harms are expected to be very low. The DSMC oversees the detection of possible adverse events and harms and proposes to the Steering Committee how to proceed. The local collaborators can report safety problems to the study coordinator who would contact the DSMC.

Frequency and plans for auditing trial conduct {23}

AVR, the study coordinator, will oversee the study audits. Participant enrolment, eligibility, allocation to study groups, adherence to trial interventions, reporting of harms, and completeness, accuracy, and timeliness of data collection will be monitored. Given the international nature of the study, the audits will be carried out through the analysis of the electronic case report form (REDCap) and telematic contact with the collaborating researchers. An initial audit of the participating centers (completeness, accuracy, and timeliness of data collection) will be performed after the complete data entry of the first three patients then every ten patients. Also, the funding institutions (particularly Instituto de Salud Carlos III, the main funding source) can decide to perform external audits.

Plans for communicating important protocol amendments to relevant parties {25}

The Steering Committee can decide to make protocol amendments. In that case, the study coordinator will inform the Institutional Review Boards, change the study registries, and inform the study collaborators. All

amendments will be registered, and the changes and their dates will be explained in the final publication supplementary material. All changes from this protocol will be identified as post hoc analyses in the final publication.

Dissemination plans {31a}

The results of the WATERLAND trial will be presented at international meetings and published in a peer-reviewed scientific journal. The article will be published with an open-access license if the scientific journal has that possibility. The results will be shared through the social networks of the ERICA consortium (Twitter: @ERICA-consortium) and its website (www.ericaresearch.com). The authors will write a lay summary to share with all participants. With the help of the patient advocate, informative material will be produced for the general public, and a press release will be issued. The data will be available in a public open data repository. The register records will be updated for EudraCT and ClincalTrials.gov.

Authorship criteria:

1 to 15 patients: two investigators from the center will be acknowledged as collaborators in the supplementary appendix of the final publication.
16 to 30 patients: one investigator will be included as a co-author of the study, and two other investigators from the center will be acknowledged as collaborators in the supplementary appendix of the final publication.
31 to 50 patients: two investigators will be included as co-authors of the study, and 1 investigator from the center will be acknowledged as a collaborator in the supplementary appendix of the final publication.
51 or more: three investigators will be included as co-authors of the study.

Discussion

The WATERLAND trial is an international multicenter, open-label, parallel-group, randomized, controlled, superiority trial aiming to compare the efficacy and safety of moderate fluid resuscitation based on LR versus NS in AP. The study has been designed to recruit both patients with predicted mild and predicted severe AP, thus, with different ranges of severity of disease, but patients that have baseline criteria for moderately severe or severe disease will be excluded, as this is the main efficacy outcome, and the hypothesis of the study is that fluid therapy may improve the course of the disease, preventing the development of complications. The study will be open-label, as the logistics for an international double-blinded randomized controlled trial on fluid resuscitation are challenging. The efficacy outcome is moderately severe or severe disease, a compound variable that includes local complications, organ failure, and exacerbation of previous comorbidity [3]. Patients with those complications have more morbidity and risk of mortality [4]. Both arms of treatment are safe, but concerns about hyperchloremic acidosis have been raised in patients receiving high doses of NS [29]. LR and NS administration will be based on the results of the WATERFALL trial, which demonstrated that 1.5 mL/kg/h (preceded by a bolus of 10 mL/kg only in patients with hypovolemia) is safer that a more aggressive strategy (20 mL/kg bolus in all patients, followed by 3 mL/kg/h) [14]. LR and NS are fluids used in AP daily for more than 100 years, so this is a low interventional pharmacological randomized controlled trial. Low interventional clinical trials, according to the European Union Clinical Trials Regulation No 536/2014 should fulfill the following requirements: (A) the investigational medicinal products, excluding placebos, are authorized; (B) according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the marketing authorization or the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned, and (C) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned. Most countries do not require insurance for patients included in low interventional trials, which helps the WATERLAND trial to be performed in an international scenario; if a center or country requires insurance, an attempt will be made to cover it through the grants that support this project.

Finally, the ERICA consortium has experience in international multicenter studies [4–6] and studies on fluid resuscitation [13, 14, 18].

Trial status

Protocol version 4, September 18, 2023. Recruitment started in June 2023. Recruitment is expected to be completed in December 2024.

Abbreviations

AEG	Spanish association of gastroenterology
AP	Acute pancreatitis
CI	Confidence intervals
CRP	C-reactive protein
CT	Computed tomography
DSMC	Data safety and monitoring committee
ERCP	Endoscopic retrograde cholangiopancreatography
ERICA	International League Against Biliary-Pancreatic Diseases
ICU	Intensive care unit
ISCIII	Instituto de Salud Carlos III
LR	Lactated Ringer's solution
NS	Normal saline
OR	Odds ratio
RAC	Revision of the Atlanta classification
SIRS	Systemic inflammatory response syndrome

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08539-2.

Additional file 1. Appendix with SAPR1.

Acknowledgements
The researchers acknowledge the Spanish Association of Gastroenterology (AEG) for providing the REDCap electronic case report form, and AEG, the European Pancreatic Club (EPC), and the Spanish Association of Pancreatology (AESPANC) for their endorsement and support in sharing the trial through their communication channels to help recruiting centers. The researchers would like to thank the Scientific Committee of the United European Gastroenterology (UEG) for the UEG Research Prize 2024 to Enrique de-Madaria and the research grant that it entails, and the scientific committee of AEG for the Gonzalo Miño grant. Finally, thanks to the Instituto de Salud Carlos III (ISCIII) for making this study possible through a public competitive grant; the ISCIII has supported all our randomized controlled trials with these grants.

Authors' contributions {31b}
EdM is the principal investigator; he conceived the study, applied for grants, and led the proposal and protocol development. PM, PZ, and EMNM were the lead trial methodologists. The other authors contributed to the study design and the proposal's development. All authors read and approved the final manuscript for this protocol.

Funding {4}
The WATERLAND trial is funded by a grant (grant number PI22/00980) from ISCIII, Madrid, Spain, the national and international reference in biomedical research and public health in Spain. It is the Public Research Organization of the Government of Spain, responsible for funding and executing national biomedical research. It depends on the Ministry of Science, Innovation, and Universities.
Other grants:
• UEG Research Prize, United European Gastroenterology, grant number: UEG Research Prize 2024, Vienna, Austria.
• Beca Gonzalo Miño, Spanish Association of Gastroenterology (Asociación Española de Gastroenterología, AEG), grant number: Gonzalo Miño Grant 2024, Madrid, Spain.
• Beca Intramural, Alicante Institute of Health and Biomedical Research (ISABIAL), grant number: ayudas intramurales de ISABIAL modalidad C 2023, Alicante, Spain.
• None of the funders were or will be involved in the study design, collection, analysis, data interpretation, or manuscript writing.

Data availability {29}
The Steering Committee, coordination committee, and statistical advisors will have access to the final dataset. Members of the ERICA consortium that recruited patients in the WATERLAND trial may claim access to the final dataset to perform ancillary studies; the Steering Committee will study these proposals. Any data required to support the protocol can be supplied on request.

Declarations

Ethics approval and consent to participate {24}
Dr. Balmis General University Hospital"s research ethics committee (Comité de Investigación con Medicamentos, CEiM) will be considered as the central institutional review board. All participating centers must have permission from their local institutional review boards to participate in WATERLAND.

Consent for publication {32}
Not applicable—no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form available from the corresponding author on request.

Competing interests {28}
This is a researcher-driven study. There is little if any, commercial interest in the results of the WATERLAND trial. No industry involvement will be allowed in this study, and the study committee members and collaborators will not be able to participate in this trial in case of conflicts of interest. A declaration of conflicts of interest will be mandatory to be part of the WATERLAND trial.

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Received: 26 July 2024 Accepted: 8 October 2024
Published online: 21 October 2024

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