Clinical trial results:
A national prospective study of patients with hepatitis induced by immune checkpoint inhibitors; Characterization of liver injury, outcome of therapy and randomization to either prednisolone or mycophenolate mofetil treatment in case of relapse

Summary

EudraCT number	2020-004483-26
Trial protocol	DK
Global end of trial date	06 September 2024

Results information

Result version number	v1 (current)
This version publication date	16 November 2025
First version publication date	16 November 2025

Trial information

Trial identification

Sponsor protocol code	AA2032

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04810156
WHO universal trial number (UTN)	-
Other trial identifiers	The Danish Medical Agencies: 2020092719, Ethical Committee of the Capital Region of Denmark: H-20062916, the Capital Region's Data Unit: P-2020-959

Notes:

Sponsors

Sponsor organisation name	National Center for Cancer Immune Therapy (CCIT-DK), Department of Oncology
Sponsor organisation address	Borgmester Ib Juuls Vej 9, 4th floor, Herlev, Denmark, 2730
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 September 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2024
Global end of trial reached?	Yes
Global end of trial date	06 September 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study is performed to evaluate the crucially important question of which patients with immune-related hepatitis will respond to standard treatment with steroids and who needs treatment with a second line immunosuppressive agent in this case steroids plus mycophenolate mofetil. Treatment efficacy is evaluated as the percentage reduction in liver transaminases or bilirubin, assessed by the number of days to achieve a ≥20% reduction in either ALT, AST, or bilirubin.

Protection of trial subjects:

The clinical trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. The study protocol, informed consent forms, and all patient materials were reviewed and approved by the Ethics Committee and the Danish Medical Agency prior to trial initiation. Patient confidentiality was maintained by the use of coded identifiers, and all personal data were handled in compliance with the data protection legislation through the use of the RedCap database.

Written informed consent was obtained from all patients before any study-related procedures. In addition to the general study consent, participants provided specific written consent for liver biopsy and for the collection and analysis of blood samples for investigational purposes. Patients were fully informed of the nature, purpose, and potential risks of these procedures, as well as their right to withdraw consent at any time without consequences for their future medical care. Patients receiving anticoagulant therapy had treatment temporarily paused according to local clinical guidelines before undergoing liver biopsy to minimize the risk of bleeding. All patients were offered prophylactic therapy (proton pump inhibitors, calcium and vitamin D supplements) to reduce risk of gastroduodenal ulcers and osteoporosis.

The protection and safety of trial patients were monitored by the GCP unit through regular monitoring visits, including safety reporting, and adherence to approved procedures. All adverse events were recorded and evaluated for seriousness and causality.

Background therapy:

Immune-related hepatitis is among the most common immune-related adverse events (irAEs) associated with immune checkpoint inhibitor (ICI) therapy in patients with cancer. It accounts for approximately 20% of fatal irAE cases and often necessitates discontinuation of ICIs. The condition is characterized by elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or alkaline phosphatase (ALP) levels, with or without increased bilirubin, following ICI exposure and after exclusion of other causes of liver injury.

Ir-hepatitis is observed in up to 15–23% of patients treated with a combination of anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) and anti-programmed cell death protein-1 (anti-PD-1) with grade 3-4 occurring in 6–12% of patients, whereas only 4–9% of patients treated with monotherapy develop ir-hepatitis (grade 3–4: 1–4%). The underlying mechanisms remain incompletely understood but are thought to reflect immune activation pathways responsible for the antitumor effects of ICIs.

According to international guidelines, grade 3–4 ir-hepatitis requires permanent discontinuation of ICIs, hospitalization, and treatment with intravenous methylprednisolone (1–2 mg/kg/day). However, 23–35% of patients are steroid-resistant or steroid-dependent and require additional immunosuppressive therapy. Mycophenolate mofetil (MMF) is the recommended second-line treatment, whereas the more T-cell–targeted immunosuppressant tacrolimus is considered third line. To date, no

directly compared the efficacy of MMF and tacrolimus in patients with steroid-resistant ir-hepatitis.

This prospective study aimed to characterize immune-related hepatitis and its clinical phenotypes and to evaluate treatment outcomes in patients with ICI-induced grade 3–4 ir-hepatitis.

Evidence for comparator:

The study was initially designed to randomize patients with steroid-resistant or steroid-dependent immune-related hepatitis to receive additional treatment with either mycophenolate mofetil (MMF) or tacrolimus, respectively. However, due to a slower-than-expected recruitment rate, this randomization was cancelled. Instead, these patients received MMF as standard-of-care as proposed by international guidelines.

In a subsequent protocol amendment, the study design was modified to include randomization of patients with relapsing immune-related hepatitis (also referred to as steroid-dependent cases) to receive either an increased dose of corticosteroids or MMF (Cohort B). Nevertheless, this part of the study was never initiated due to limited available resources.

Actual start date of recruitment	26 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 34
Worldwide total number of subjects	34
EEA total number of subjects	34

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	12
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from Apr 2021 to Jan 2024 at the Departments of Oncology and Gastroenterology at Herlev Hospital, Rigshospitalet, and Aarhus University Hospital, Denmark. 47 patients were screened; 37 patients met criteria and started therapy; 3 patients were later excluded (inaccessible liver biopsy, n=2, and non-adherence to therapy, n=1)

Pre-assignment

Screening details:

Patients with solid cancers who developed ICI-induced ≥grade 3 hepatitis within 6 months and were willing to undergo liver biopsy were screened by physical exam, detailed history, CT/US scan and comprehensive blood tests.

Pre-assignment period milestones

Number of subjects started	37[1]
Number of subjects completed	34

Pre-assignment subject non-completion reasons

Reason: Number of subjects	non-compliance: 1
Reason: Number of subjects	Physician decision: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Three patients were later excluded due to inaccessible liver biopsy and non-adherence to treatment and therefore not included in the trial data.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

NA

Arms

Arm title	Immune-related hepatitis

Arm description:

All patients received intravenous methylprednisolone at a dose of 2 mg/kg/day for a minimum of 72 hours (three boluses). Treatment response was evaluated after 72 hours of steroid initiation. In patients with mixed or cholestatic drug-induced liver injury phenotypes, additional weight-based oral ursodeoxycholic acid (UDCA) was administered, and treatment response was re-evaluated on Day 7.

Patients demonstrating adequate response transitioned to a tapering regimen of oral prednisolone. In cases of insufficient response, defined as <20% decline in ALT, AST, or bilirubin, mycophenolate mofetil (MMF) was initiated as second-line therapy.

Arm type	Experimental
Investigational medicinal product name	prednisolone
Investigational medicinal product code	
Other name	methylprednisolone, solu-medrol, steroids
Pharmaceutical forms	Capsule, Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

All patients discontinued ICI therapy and received IV methylprednisolone (Solu-Medrol) as a loading dose of 2 mg/kg/day for a minimum of 72 hours (three boluses) before treatment evaluation. For patients with a mixed or cholestatic drug-induced liver injury phenotype, additional weight-based

peroral doses of ursodeoxycholic acid (UDCA) were administered. These UDCA-patients were evaluated twice (after 72 hours and day 7) due to the known longer time to response in these phenotypes. Once a response was achieved (defined as a reduction of more than 20% in ALT, AST, or bilirubin levels), patients transitioned to a tapering regimen of oral prednisolone for 4–6 weeks (the dosage of prednisolone may vary according to the levels of liver enzymes, other irAEs, and patient condition).

Investigational medicinal product name	mycophenolate mofetil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Treatment was initiated at 500 mg twice daily on Day 1, increased to 1000 mg twice daily on Day 2. This dosage was continued until 8 weeks after discontinuation of prednisolone. Dose reductions were permitted in the event of adverse reactions or tolerability issues.

Number of subjects in period 1	Immune-related hepatitis
Started	34
Completed	34

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	34	34	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	12	12	
From 65-84 years	22	22	
85 years and over	0	0	
overall trial	0	0	
Age continuous Units: years			
median	70		
full range (min-max)	37 to 80	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	20	20	
Liver metastasis Units: Subjects			
Yes	10	10	
No	24	24	
Alcohol consumption, units/week Units: Subjects			
0-2	26	26	
3-6	3	3	
≥7	5	5	

Subject analysis sets	
Subject analysis set title	Steroid-responders
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients demonstrating a ≥20% reduction of either ALT, AST, or bilirubin within 72 hours were defined as "steroid-responders". Notably, patients with mixed or cholestatic phenotypes (see definition below), who had a potentially slower treatment response, were included as steroid-responders if they achieved ≥20% reduction of either ALT, AST, or bilirubin within 7 days.

Subject analysis set title	Steroid-unresponsive

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who did not have a ≥20% reduction of ALT, AST, or bilirubin levels at the 72-hour evaluation or day 7 (mixed and cholestatic DILI) were classified as "steroid-unresponsive".

Subject analysis set title	Steroid-dependent
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients experiencing a recurrence of CTCAE grade ≥2 ir-hepatitis during tapering of prednisolone or within four weeks of discontinuing prednisolone were characterized as "steroid-dependent".

Reporting group values	Steroid-responders	Steroid-unresponsive	Steroid-dependent
Number of subjects	20	6	8
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	4	1
From 65-84 years	13	2	7
85 years and over	0	0	0
overall trial	0	0	0
Age continuous Units: years			
median	65	61	71
full range (min-max)	37 to 75	41 to 80	53 to 80
Gender categorical Units: Subjects			
Female	11	3	0
Male	9	3	8
Liver metastasis Units: Subjects			
Yes	4	4	2
No	16	2	6
Alcohol consumption, units/week Units: Subjects			
0-2	18	5	3
3-6	0	1	2
≥7	2	0	3

End points

End points reporting groups

Reporting group title	Immune-related hepatitis

Reporting group description:

All patients received intravenous methylprednisolone at a dose of 2 mg/kg/day for a minimum of 72 hours (three boluses). Treatment response was evaluated after 72 hours of steroid initiation. In patients with mixed or cholestatic drug-induced liver injury phenotypes, additional weight-based oral ursodeoxycholic acid (UDCA) was administered, and treatment response was re-evaluated on Day 7.

Patients demonstrating adequate response transitioned to a tapering regimen of oral prednisolone. In cases of insufficient response, defined as <20% decline in ALT, AST, or bilirubin, mycophenolate mofetil (MMF) was initiated as second-line therapy.

Subject analysis set title	Steroid-responders
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients demonstrating a ≥20% reduction of either ALT, AST, or bilirubin within 72 hours were defined as "steroid-responders". Notably, patients with mixed or cholestatic phenotypes (see definition below), who had a potentially slower treatment response, were included as steroid-responders if they achieved ≥20% reduction of either ALT, AST, or bilirubin within 7 days.

Subject analysis set title	Steroid-unresponsive
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who did not have a ≥20% reduction of ALT, AST, or bilirubin levels at the 72-hour evaluation or day 7 (mixed and cholestatic DILI) were classified as "steroid-unresponsive".

Subject analysis set title	Steroid-dependent
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients experiencing a recurrence of CTCAE grade ≥2 ir-hepatitis during tapering of prednisolone or within four weeks of discontinuing prednisolone were characterized as "steroid-dependent".

Primary: Response rate to steroids

End point title	Response rate to steroids[1]

End point description:

Response to steroid therapy, defined as the time (in days) from treatment initiation to the first occurrence of a ≥20% reduction in at least one of the following laboratory parameters: ALT, AST, or bilirubin. A response was considered achieved if this reduction occurred within three days of starting treatment.

End point type	Primary

End point timeframe:

Apr 2021 to Sep 2024

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: descriptive statistic - no statistical analysis for these points

End point values	Immune-related hepatitis			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: subjects	34			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to transition to oral prednisolone and discharge

End point title	Time to transition to oral prednisolone and discharge

End point description:

End point type	Secondary

End point timeframe:

apr 2021 - sept 2024

End point values	Immune-related hepatitis			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: days	34			

Statistical analyses

No statistical analyses for this end point

Secondary: Recurrence rate of ir-hepatitis

End point title	Recurrence rate of ir-hepatitis

End point description:

The number of patients experiencing relapse of ir-hepatitis CTCAE grade ≥2, excluding other aetiologies for liver injury.

End point type	Secondary

End point timeframe:

apr 2021 - sept 2024

End point values	Immune-related hepatitis			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: subjects	34			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: cumulative steroid equivalents and mycophenolate mofetil doses

End point title	cumulative steroid equivalents and mycophenolate mofetil doses

End point description:

cumulative steroid equivalents and MMF doses

End point type	Other pre-specified

End point timeframe:

apr 2021 - sept 2024

End point values	Immune-related hepatitis			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: mg	34			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected and reported over a 3-month follow-up period from initiation of steroids for all patients. For patients who received mycophenolate mofetil (MMF), safety data were collected and reported up to 6 months following MMF initiation

Adverse event reporting additional description:

AEs of Grade ≥ 3 and considered MMF-related were recorded in the eCRF and patient electronic journal at each consultation and followed until improvement to Grade ≤ 2 for over 10 weeks. Non-serious AEs not meeting the protocol-defined reporting threshold (Grade ≥3 and drug-related) were recorded in the CTCAE log. All drug-related AEs are reported:

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups

Reporting group title	all patients

Reporting group description:

Patients with cancer and suspected Grade ≥3 immune-related hepatitis induced by immune checkpoint inhibitor therapy. All patients were treated with high-dose steroids (methylprednisolone 2 mg/kg, minimum of three doses) followed by a prednisolone tapering regimen. Patients who were steroid-resistant, steroid-unresponsive, or steroid-dependent received subsequent treatment with mycophenolate mofetil (MMF) at a total daily dose of 1000–2000 mg.

34 patients were included for study analyses. Three patients were excluded due to either inaccessibility for liver biopsy (n=2) or non-adherence to study treatment (n=1) - these patients are not included in the safety analysis.

Serious adverse events	all patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 34 (5.88%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	0		
Vascular disorders			
Transient ischaemic attack	Additional description: Unrelated to treatment. Known risk factors for TIA. The patient recovered without sequelae following standard medical management. No other serious adverse events were reported.		
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diverticulitis intestinal perforated	Additional description: The patient had intestinal diverticulitis with perforation on Day 2 after steroid initiation. Managed conservatively, fully recovered. Unrelated to treatment. Later excluded from efficacy analysis due to liver biopsy contraindication.		

subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	all patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 34 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Arthralgia			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	0		
Cardiac disorders			
Hypertension			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Tremor			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Insomnia			

subjects affected / exposed	28 / 34 (82.35%)		
occurrences (all)	28		
Anxiety			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Mood altered			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		
Thrombocytopenia			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Eye disorders			
Vision blurred			
subjects affected / exposed	6 / 34 (17.65%)		
occurrences (all)	6		
Dry eye			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	15 / 34 (44.12%)		
occurrences (all)	15		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 34 (23.53%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Epigastric discomfort			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Oral candidiasis			

subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		
Fat redistribution			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	4		
Infections and infestations			
Neutropenia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 June 2022	The planned randomization was cancelled due to low recruitment. The trial was resumed as a non-randomized, single-arm study in which all participants received corticosteroids as standard of care. Patients with steroid-unresponsive or steroid-dependent disease received mycophenolate mofetil as second-line immunosuppression, according to international guidelines. No patients received tacrolimus as second-line immunosuppresive.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A relatively small number of patients, especially in subgroups of steroid-unresponsive patients, hinders definitive conclusions

Notes: