



## Clinical trial results: CHECKPOINT INHIBITOR INDUCED COLITIS AND ARTHRITIS – IMMUNOMODULATION WITH IL-6 BLOCKADE AND EXPLORATION OF DISEASE MECHANISMS

### Summary

EudraCT number	2018-002595-41
Trial protocol	DK
Global end of trial date	29 September 2020

### Results information

Result version number	v1 (current)
This version publication date	10 October 2021
First version publication date	10 October 2021

### Trial information

#### Trial identification

Sponsor protocol code	AA1820
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03601611
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Herlev and Gentofte Hospital, Department of Oncology
Sponsor organisation address	Borgmester Ib Juuls Vej 1, Herlev, Denmark, 2730
Public contact	Coordinating Investigator, Herlev and Gentofte Hospital, +45 38682898, inna.chen@regionh.dk
Scientific contact	Coordinating Investigator, Herlev and Gentofte Hospital, +45 38682898, inna.chen@regionh.dk

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	29 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2020
Global end of trial reached?	Yes
Global end of trial date	29 September 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the clinical benefit of IL-6 inhibition by tocilizumab on diarrhea and/or colitis and/or arthritis induced by checkpoint inhibitors in patients with solid tumors within 8 weeks of treatment start.

Protection of trial subjects:

Patients that signed informed consent and fulfilling eligibility criteria were included. Continued monitoring of standard safety parameters during treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 January 2019
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: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	10
From 65 to 84 years	10
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The trial was opened for recruitment in January 2019 and closed for enrollment in January 2020 per protocol. Patients were included at a single site, Herlev Hospital, Denmark.

### Pre-assignment

Screening details:

Eligible patients were 18 years or older with solid tumors who were treated with ICIs and had grade >1 ir-colitis and/or ir-arthritis . Systemic glucocorticoids or other immunosuppressive drugs were not allowed within a 14-day screening period.

### Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	Tocilizumab
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients will receive tocilizumab 8 mg/kg milligram(s)/kilogram, Q4W for at least 2 cycles or until worsening or lack of improvement of symptoms, in case of unacceptable toxicity, withdrawal of consent or clear clinical deterioration

Number of subjects in period 1	Tocilizumab
Started	20
Completed	19
Not completed	1
non confirmation of colitis	1

## Baseline characteristics

### Reporting groups

Reporting group title	Treatment
Reporting group description: -	

Reporting group values	Treatment	Total	
Number of subjects	20	20	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
median	64		
full range (min-max)	30 to 77	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	11	11	
Type of immune related AE			
Units: Subjects			
Colitis and diarrhea	9	9	
Arthritis and arthralgia	9	9	
both Colitis and Arthritis	2	2	

### Subject analysis sets

Subject analysis set title	efficacy
Subject analysis set type	Per protocol

Subject analysis set description:

Patients with confirmed diagnosis of ir-arthritis , ir-colitis or both, that have recieved at least one dose of tocilizumab.

Reporting group values	efficacy		
Number of subjects	19		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			

Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years median full range (min-max)	63 30 to 77		
Gender categorical Units: Subjects			
Female Male	9 10		
Type of immune related AE Units: Subjects			
Colitis and diarrhea Arthritis and arthralgia both Colitis and Arthritis	8 9 2		

## End points

### End points reporting groups

Reporting group title	Tocilizumab
Reporting group description:	-
Subject analysis set title	efficacy
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients with confirmed diagnosis of ir-arthritis , ir-colitis or both, that have recieved at least one dose of tocilizumab.	

### Primary: $\geq 1$ grade improvement at week 8

End point title	$\geq 1$ grade improvement at week 8 <sup>[1]</sup>
End point description:	
End point type	Primary
End point timeframe:	
8 weeks after treatment start.	

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: According to Simon's 2-stage optimal design, a sample size of 20 is required to be able to confirm the alternative hypothesis that symptom improvement in  $\geq 80\%$  of patients with 80% probability given the alternative hypothesis is true and reject the null hypothesis that symptom improvement is  $< 50\%$  with 5% probability given that the null hypothesis is true. The alternative hypothesis will be rejected if at least one grade improvement is observed for  $\leq 13$  patients.

End point values	efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	19 <sup>[2]</sup>			
Units: subjects				
$\geq 1$ grade improvement of irAE symptoms at week 8	15			
Stable irAE symptoms	2			
no response to treatment	2			

Notes:

[2] - For 1 of the 20 patients irColitis was not confirmed and patient was excluded from efficacy analysis

### Statistical analyses

No statistical analyses for this end point

### Secondary: sustained glucocorticoid-free remission at week 24

End point title	sustained glucocorticoid-free remission at week 24
End point description:	
End point type	Secondary
End point timeframe:	
24 weeks after treatment start	

<b>End point values</b>	efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: subjects				
glucocorticoid-free remission at week 24	12			
missing sustained remission	7			

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of treatment until 30 days after last dose

Adverse event reporting additional description:

All serious AE are reported. non serious event with relationship to tocilizumab only

Assessment type	Systematic
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### Dictionary used

Dictionary name	NCI-CTCAE
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Dictionary version	5
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### Reporting groups

Reporting group title	Tocilizumab
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Reporting group description: -

Serious adverse events	Tocilizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 20 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Allergic reaction			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Septic shock			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			



subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Tocilizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 20 (80.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Neutrophil count decreased			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	14		
Platelet count decreased			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	13		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
flu like symptoms			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Eye disorders			
Dry eye			

subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Anorexia subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 3		
Nausea subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Vomiting subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Respiratory, thoracic and mediastinal disorders			
Hoarseness subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Dry skin subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Eczema subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Infections and infestations			
Rhinitis subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2019	<p>amended to enhance clarity and consistency of the protocol. Additionally, study times lines were updated</p> <ul style="list-style-type: none"><li>- clarify specific blood tests, separating rheumatological and gastrointestinal analyses respectively and analyses for all patients.</li><li>- Timepoint clarification of fecal specimens collection</li><li>- Clarification of definition of EOT and EOS visit in case of treatment duration of <math>\geq 6</math> months.</li><li>- Clarification of days and study assessment per protocol which will be performed as soon as possible upon request, however, it should not delay treatment start with tocilizumab. Delay within <math>\leq 72</math> h from the time of reference due to preparing (cleansing) for colonoscopy or other investigations is up to investigator</li><li>- Clarification in the study flowchart that assessments Day 3 and 8 only are required after first administration of tocilizumab as well as the control visit at the Department of Rheumatology or Gastroenterology are to be performed approximately 4 weeks after first administration of tocilizumab</li><li>- Correction regarding immunohistochemically staining to rule out CMV infection which will be performed in the biopsies</li><li>- Based on regional guidelines for rheumatological patients the tocilizumab infusion over 30 minutes is allowed after 5. Cycle in the absence of infusion related events</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported