



## Clinical trial results:

### **Capecitabine in combination with Bendamustine in women with pretreated locally advanced or metastatic Her2-negative breast cancer, a Phase II Trial**

#### **Summary**

EudraCT number	2012-005593-64
Trial protocol	AT
Global end of trial date	15 March 2018

#### **Results information**

Result version number	v1 (current)
This version publication date	23 March 2019
First version publication date	23 March 2019

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	AGMT_MBC-6
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01891277
WHO universal trial number (UTN)	-

Notes:

##### **Sponsors**

Sponsor organisation name	AGMT
Sponsor organisation address	Gentzgasse 60/20, Vienna, Austria, 1180
Public contact	Daniela Wolkersdorfer, AGMT, 0043 (0)66264044411, d.wolkersdorfer@agmt.at
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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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	16 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2018
Global end of trial reached?	Yes
Global end of trial date	15 March 2018
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The efficacy of a capecitabine plus bendamustine combination regimen in the treatment of Her2-negative advanced metastatic breast cancer, in terms of overall response rates (complete or partial Response)

Protection of trial subjects:

Safety assessments were scheduled 3-weekly during treatment until 28 days after end of study treatment. Recommendations for dose modifications in case of toxicity were done in protocol. Only patients with adequate haematology, liver and renal function could have been included. Patients with known hypersensitivity to the study drugs capecitabine and bendamustine or their excipients were excluded from study participation.

Background therapy:

Capecitabine was dosed at 1000mg/m<sup>2</sup> twice daily for 14 days, followed by a 7-day rest period for a total cycle time of 21 days (until disease progression or unacceptable toxic effects).

Evidence for comparator:

None.

Actual start date of recruitment	09 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Austria: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

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**Subjects enrolled per age group**

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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)	26
From 65 to 84 years	14
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

In stage 1 of AGMT MBC-6, 20 patients were recruited from September 2013 to July 2014 in Austria. Fulfilling the efficacy criterion, the study was continued enrolling another 20 patients from October 2014 to May 2015 (Stage 2). A total of 40 patients were recruited in eight Austrian centers.

### Pre-assignment

Screening details:

Female patients, age  $\geq 18$  years were screened. The patients had to have advanced or metastatic Her2-negative breast cancer, histologically confirmed and had to be progredient after anthracycline and/or taxane treatment (palliative or neoadjuvant or adjuvant).

### Period 1

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

### Arms

Arm title	Bendamustin/Capecitabine
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Arm description:

Bendamustin in addition to backbone capecitabine, followed by capecitabine monotherapy.

Arm type	Experimental
Investigational medicinal product name	Bendamustin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bendamustine 80mg/m<sup>2</sup> were administered on day 1 and 8 of a three week cycle (for a maximum of eight cycles).

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine was dosed at 1000mg/m<sup>2</sup> twice daily for 14 days, followed by a 7-day rest period for a total cycle time of 21 days (until disease progression or unacceptable toxic effects).

<b>Number of subjects in period 1</b>	Bendamustin/Capecitabine
Started	40
Completed	27
Not completed	13
Adverse event, serious fatal	1
Physician decision	3
Consent withdrawn by subject	5

Therapy paused for more than 2 cycles	1
Adverse event, non-fatal	3

## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	40	40	
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	60		
full range (min-max)	29 to 77	-	
Gender categorical			
Units: Subjects			
Female	40	40	
Male	0	0	

## End points

### End points reporting groups

Reporting group title	Bendamustin/Capecitabine
Reporting group description: Bendamustin in addition to backbone capecitabine, followed by capecitabine monotherapy.	

### Primary: Overall Response Rate

End point title	Overall Response Rate <sup>[1]</sup>
End point description: Overall tumor response rates (complete response (CR) or partial response (PR), determined by radiologic evaluation according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1))	
End point type	Primary

End point timeframe:

Best response evaluated from start of study therapy until end of study participation (progression or withdrawal).

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: No statistical analysis is provided as this is a one armed, open label, non-comparative study.

According to the pre-specified design, the regimen was concluded to be efficacious since 18 responses were observed in the study exceeding the efficacy criterion of 13 or more responses out of 40 at the end of trial.

End point values	Bendamustin/Capecitabine			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Patients				
CR	1			
PR	17			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All patients having received at least one dose of the study medication were followed for (serious) adverse events for 28 days after discontinuing study treatment or completion of study treatment.

Adverse event reporting additional description:

Progression of disease (including death due to the underlying malignant disease) was not to be regarded as SAE.

Due to the seriousness of the disease, certain conditions defined as SAEs were excluded from expedited reporting i.e.: elective hospitalization and surgery for treatment of disease or to simplify treatment or study procedures.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	21

### Reporting groups

Reporting group title	Safety population
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Reporting group description:

All patients having received at least one dose of the study medication were followed for (serious) adverse events for 28 days after discontinuing study treatment or completion of study treatment.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 40 (65.00%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	1		
Vascular disorders			
Embolism			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		



Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiomyopathy			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			
Peripheral motor neuropathy			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia macrocytic			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Faecaloma			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toothache			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Device related infection			

subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile infection				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth infection				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				

subjects affected / exposed	1 / 40 (2.50%)		
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>	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 40 (92.50%)		
Vascular disorders			
Lymphoedema			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Thrombosis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Hot flush			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	29 / 40 (72.50%)		
occurrences (all)	58		
Oedema peripheral			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	8		
Pain			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Influenza like illness			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Chills			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Non-cardiac chest pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Feeling cold</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>General physical health deterioration</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 40 (5.00%)</p> <p>3</p> <p>2 / 40 (5.00%)</p> <p>2</p> <p>2 / 40 (5.00%)</p> <p>2</p> <p>2 / 40 (5.00%)</p> <p>2</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>9 / 40 (22.50%)</p> <p>10</p> <p>7 / 40 (17.50%)</p> <p>12</p>		
<p>Psychiatric disorders</p> <p>Depression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 40 (5.00%)</p> <p>2</p>		
<p>Investigations</p> <p>Weight decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Platelet count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>White blood cell count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neutrophil count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lymphocyte count decreased</p>	<p>4 / 40 (10.00%)</p> <p>4</p> <p>4 / 40 (10.00%)</p> <p>5</p> <p>4 / 40 (10.00%)</p> <p>7</p> <p>2 / 40 (5.00%)</p> <p>2</p>		

subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Nervous system disorders Peripheral sensory neuropathy subjects affected / exposed occurrences (all)  Dysgeusia subjects affected / exposed occurrences (all)  Polyneuropathy subjects affected / exposed occurrences (all)  Headache subjects affected / exposed occurrences (all)  Dizziness subjects affected / exposed occurrences (all)  Presyncope subjects affected / exposed occurrences (all)  Paraesthesia subjects affected / exposed occurrences (all)  Neuropathy peripheral subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 9  7 / 40 (17.50%) 7  6 / 40 (15.00%) 6  6 / 40 (15.00%) 9  5 / 40 (12.50%) 9  2 / 40 (5.00%) 2  2 / 40 (5.00%) 2  2 / 40 (5.00%) 3		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)  Leukopenia	15 / 40 (37.50%) 36		

subjects affected / exposed	13 / 40 (32.50%)		
occurrences (all)	35		
Anaemia			
subjects affected / exposed	9 / 40 (22.50%)		
occurrences (all)	13		
Thrombocytopenia			
subjects affected / exposed	8 / 40 (20.00%)		
occurrences (all)	11		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	7		
Eye disorders			
Eyelid oedema			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	19 / 40 (47.50%)		
occurrences (all)	34		
Diarrhoea			
subjects affected / exposed	14 / 40 (35.00%)		
occurrences (all)	31		
Stomatitis			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	11		
Vomiting			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	11		
Toothache			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
Abdominal pain upper			



subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	7		
Dry mouth			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Haematochezia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Abdominal distension			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	22 / 40 (55.00%)		
occurrences (all)	54		
Night sweats			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Alopecia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Rash			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	4		
Erythema			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pruritus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dry skin</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Skin fissures</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 40 (5.00%)</p> <p>2</p> <p>2 / 40 (5.00%)</p> <p>2</p> <p>2 / 40 (5.00%)</p> <p>2</p> <p>2 / 40 (5.00%)</p> <p>5</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Musculoskeletal chest pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Bone pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Musculoskeletal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 40 (12.50%)</p> <p>5</p> <p>4 / 40 (10.00%)</p> <p>4</p> <p>3 / 40 (7.50%)</p> <p>3</p> <p>3 / 40 (7.50%)</p> <p>3</p> <p>2 / 40 (5.00%)</p> <p>2</p> <p>2 / 40 (5.00%)</p> <p>3</p>		
<p>Infections and infestations</p> <p>Oral herpes</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasopharyngitis</p>	<p>10 / 40 (25.00%)</p> <p>16</p>		

subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	7		
Bronchitis			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Rhinitis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 40 (20.00%)		
occurrences (all)	10		
Hypokalaemia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported