Clinical trial results:
A randomized, double blind, placebo-controlled, dose response, phase II, multicentre trial to evaluate the efficacy, safety and pharmacokinetics of oral CR6086 administered at the doses of 30, 90 or 180 mg bid for 12 weeks in combination with methotrexate, in DMARD-naïve patients with early rheumatoid arthritis

Summary

EudraCT number	2016-004834-11
Trial protocol	DK BG PL CZ GB
Global end of trial date	08 January 2019

Results information

Result version number	v1 (current)
This version publication date	25 June 2020
First version publication date	25 June 2020
Summary attachment (see zip file)	CR6086-2-02 Summary of Results (2016-004834-11 CR6086-2-02 Summary of Results.pdf)

Trial information

Trial identification

Sponsor protocol code	CR6086-2-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03163966
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rottapharm Biotech S.r.l.
Sponsor organisation address	Via Valosa di Sopra 9, Monza, Italy, 20900
Public contact	Lucio Rovati, Rottapharm Biotech S.r.l., Via Valosa di Sopra 9, Monza, 20900, Italy, +39 039 9066104, lucio.rovati@rottapharmbiotech.com
Scientific contact	Lucio Rovati, Rottapharm Biotech S.r.l., Via Valosa di Sopra 9, Monza, 20900, Italy, +39 039 9066104, lucio.rovati@rottapharmbiotech.com

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	09 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of oral CR6086 in combination with oral MTX over a 12-week treatment period in DMARD-naïve patients with early RA, in comparison with oral MTX alone.

Protection of trial subjects:

Trial subjects have been strictly monitored, at a frequency higher that usual and with more intensive assessments.
Patients were allowed to take oral corticosteroids (at doses <= 10mg/day) if this was required for a better control of symptoms and pain

Background therapy:

Methotrexate 10-20 mg/week for 13 weeks

Evidence for comparator: -

Actual start date of recruitment	05 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	Poland: 38
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Bulgaria: 105
Country: Number of subjects enrolled	Czech Republic: 37
Country: Number of subjects enrolled	Moldova, Republic of: 49
Country: Number of subjects enrolled	Romania: 5
Worldwide total number of subjects	248
EEA total number of subjects	199

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	195
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period: October 2017 - September 2018
Recruitment countries: CZ, BG, DK, MD, PL, RO, UK

Pre-assignment

Screening details:

478 patients were screened, 15 in DK, 64 in CZ, 66 in PL, 11 in RO, 114 in MD, 200 in BG, 8 in UK. 230 were screening failures. Most common reasons for failure: hsCRP <3mg/L (49%) and NO RF or ACPA (47%)

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

CR6086 30 mg, CR6086 90 mg, CR6086 180 mg and Placebo treatments were identical in appearance. Treatment packs were assigned by an e-system, according to the randomization list.

Arms

Are arms mutually exclusive?	Yes
Arm title	CR6086 30 + MTX

Arm description:

CR6086 30 mg bid in addition to MTX

Arm type	Experimental
Investigational medicinal product name	CR6086
Investigational medicinal product code	CR6086
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

CR6086 30 mg administered bid for 12 weeks

Arm title	CR6086 90 + MTX

Arm description:

CR6086 90 mg administered bid for 12 weeks

Arm type	Experimental
Investigational medicinal product name	CR6086
Investigational medicinal product code	CR6086
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

CR6086 90 mg administered bid for 12 weeks

Arm title	CR6086 180 + MTX

Arm description:

CR6086 180 mg bid in addition to MTX

Arm type	Experimental

Investigational medicinal product name	CR6086
Investigational medicinal product code	CR6086
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
CR6086 180 mg administered bid for 12 weeks

Arm title	Placebo + MTX

Arm description:
Placebo bid + in addition to MTX

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Placebo administered bid for 12 weeks

Number of subjects in period 1	CR6086 30 + MTX	CR6086 90 + MTX	CR6086 180 + MTX
Started	60	61	64
Completed	53	56	51
Not completed	7	5	13
Consent withdrawn by subject	4	3	3
Physician decision	-	-	-
Protocol Deviation	1	1	-
Adverse event, non-fatal	-	1	8
MTX first dose not tolerated	2	-	2

Number of subjects in period 1	Placebo + MTX
Started	63
Completed	56
Not completed	7
Consent withdrawn by subject	2
Physician decision	1
Protocol Deviation	2
Adverse event, non-fatal	1
MTX first dose not tolerated	1

Baseline characteristics

Reporting groups	
Reporting group title	CR6086 30 + MTX
Reporting group description:	
CR6086 30 mg bid in addition to MTX	
Reporting group title	CR6086 90 + MTX
Reporting group description:	
CR6086 90 mg administered bid for 12 weeks	
Reporting group title	CR6086 180 + MTX
Reporting group description:	
CR6086 180 mg bid in addition to MTX	
Reporting group title	Placebo + MTX
Reporting group description:	
Placebo bid + in addition to MTX	

Reporting group values	CR6086 30 + MTX	CR6086 90 + MTX	CR6086 180 + MTX
Number of subjects	60	61	64
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)	45	50	47
From 65-84 years	15	11	17
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	53.3	53.1	54.7
standard deviation	± 13.1	± 11.5	± 12.8
Gender categorical Units: Subjects			
Female	39	42	48
Male	21	19	16
Disease duration			
Patients with disease duration < 12 months were selected. Disease duration < 6 months from symptom onset is the ACR definition of early RA			
Units: Subjects			
< 6 months	23	22	28
>= 6 months	37	39	36
ACR Total score			
The ACR score is based on: -Joint involvement -Serology -Acute phase reactants -Duration of symptoms			

Units: Subjects			
score 7	2	2	3
score 8	2	5	6
score 9	10	2	6
score 10	46	52	49

Reporting group values	Placebo + MTX	Total	
Number of subjects	63	248	
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)	53	195	
From 65-84 years	10	53	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	52.6		
standard deviation	± 10.7	-	
Gender categorical Units: Subjects			
Female	51	180	
Male	12	68	
Disease duration			
Patients with disease duration < 12 months were selected. Disease duration < 6 months from symptom onset is the ACR definition of early RA			
Units: Subjects			
< 6 months	26	99	
>= 6 months	37	149	
ACR Total score			
The ACR score is based on: -Joint involvement -Serology -Acute phase reactants -Duration of symptoms			
Units: Subjects			
score 7	3	10	
score 8	10	23	
score 9	5	23	
score 10	45	192	

End points

End points reporting groups	
Reporting group title	CR6086 30 + MTX
Reporting group description: CR6086 30 mg bid in addition to MTX	
Reporting group title	CR6086 90 + MTX
Reporting group description: CR6086 90 mg administered bid for 12 weeks	
Reporting group title	CR6086 180 + MTX
Reporting group description: CR6086 180 mg bid in addition to MTX	
Reporting group title	Placebo + MTX
Reporting group description: Placebo bid + in addition to MTX	

Primary: ACR20	
End point title	ACR20
End point description: ACR20 is defined as: 20% improvement in tender joint count and 20% improvement in swollen joint count and 20% improvement in at least 3/5 other scores (Patient's assessment of arthritis pain, PtGA of arthritis, PhGA of arthritis, Patient's assessment of physical function (HAQ-DI), Acute-phase reactant value (CRP)	
End point type	Primary
End point timeframe: 12 weeks	

End point values	CR6086 30 + MTX	CR6086 90 + MTX	CR6086 180 + MTX	Placebo + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	59	60	63	62
Units: n of responders	33	42	38	37

Statistical analyses

Statistical analysis title	Superiority of each CR6086 dose over MTX
Statistical analysis description: Pairwise comparisons	
Comparison groups	CR6086 30 + MTX v CR6086 90 + MTX v CR6086 180 + MTX v Placebo + MTX

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.2296 [2]
Method	normal approximation for the difference

Notes:

[1] - Pairwise comparisons using the normal approximation for the difference in binomial proportions

[2] - p value = 0.6765 for CR6086 30 mg + MTX
p value = 0.2296 for CR6086 90 mg + MTX
p value = 0.9418 for CR6086 180 mg + MTX

Post-hoc: ACR20 in patients with 6-12 months disease duration

End point title	ACR20 in patients with 6-12 months disease duration

End point description:

ACR20 is defined as:
20% improvement in tender joint count
and
20% improvement in swollen joint count
and
20% improvement in at least 3/5 other scores
(Patient's assessment of arthritis pain, PtGA of arthritis, PhGA of arthritis, Patient's assessment of physical function (HAQ-DI), Acute-phase reactant value (CRP)

End point type	Post-hoc

End point timeframe:

12 weeks

End point values	CR6086 30 + MTX	CR6086 90 + MTX	CR6086 180 + MTX	Placebo + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	38	35	37
Units: n of responders	18	26	19	18

Statistical analyses

Statistical analysis title	Superiority of each CR6086 dose over MTX

Statistical analysis description:

Pairwise comparisons

Comparison groups	CR6086 30 + MTX v CR6086 90 + MTX v CR6086 180 + MTX v Placebo + MTX
Number of subjects included in analysis	146
Analysis specification	Post-hoc
Analysis type	superiority[3]
P-value	= 0.07 [4]
Method	normal approximation for the difference

Notes:

[3] - Pairwise comparisons using the normal approximation for the difference in binomial proportions

[4] - P value=0.91 for CR6086 30 mg + MTX
P value=0.07 for CR6086 90 mg + MTX
P value=0.63 for CR6086 180 mg + MTX

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the first dose of CR6086 (second week of treatment) to the end of study	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1
Reporting groups	
Reporting group title	CR6086 30 + MTX
Reporting group description: CR6086 30 mg bid in addition to MTX	
Reporting group title	CR6086 90 + MTX
Reporting group description: CR6086 90 mg administered bid for 12 weeks	
Reporting group title	CR6086 180 + MTX
Reporting group description: CR6086 180 mg bid in addition to MTX	
Reporting group title	Placebo + MTX
Reporting group description: Placebo bid + in addition to MTX	

Serious adverse events	CR6086 30 + MTX	CR6086 90 + MTX	CR6086 180 + MTX
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 59 (0.00%)	1 / 60 (1.67%)	1 / 63 (1.59%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Constipation	Additional description: 1 constipation and diverticulitis in the 180 mg CR6086/MTX group considered serious as per the hospitalization criterion and treatment related, in a 60-years-old male patient enrolled in Denmark		
subjects affected / exposed	0 / 59 (0.00%)	0 / 60 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Antisynthetase syndrome	Additional description: 1 antisynthetase syndrome in the 90 mg CR6086/MTX group, considered serious as per the hospitalization and important medical event criteria and treatment not-related, in a 63-years-old female patient enrolled in Czech Republic		
subjects affected / exposed	0 / 59 (0.00%)	1 / 60 (1.67%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Pneumonia	Additional description: 1 bronchopneumonia in the placebo/MTX group considered serious as per the hospitalization criterion and treatment not-related, in a 57-years-old female patient enrolled in Czech Republic		
subjects affected / exposed	0 / 59 (0.00%)	0 / 60 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis	Additional description: 1 constipation and diverticulitis in the 180 mg CR6086/MTX group considered serious as per the hospitalization criterion and treatment related, in a 60-years-old male patient enrolled in Denmark		
subjects affected / exposed	0 / 59 (0.00%)	0 / 60 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo + MTX		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 62 (1.61%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Constipation	Additional description: 1 constipation and diverticulitis in the 180 mg CR6086/MTX group considered serious as per the hospitalization criterion and treatment related, in a 60-years-old male patient enrolled in Denmark		
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Antisynthetase syndrome	Additional description: 1 antisynthetase syndrome in the 90 mg CR6086/MTX group, considered serious as per the hospitalization and important medical event criteria and treatment not-related, in a 63-years-old female patient enrolled in Czech Republic		
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia	Additional description: 1 bronchopneumonia in the placebo/MTX group considered serious as per the hospitalization criterion and treatment not-related, in a 57-years-old female patient enrolled in Czech Republic		
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis	Additional description: 1 constipation and diverticulitis in the 180 mg CR6086/MTX group considered serious as per the hospitalization criterion and treatment related, in a 60-years-old male patient enrolled in Denmark		

subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	CR6086 30 + MTX	CR6086 90 + MTX	CR6086 180 + MTX
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 59 (42.37%)	24 / 60 (40.00%)	32 / 63 (50.79%)
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 59 (0.00%)	3 / 60 (5.00%)	7 / 63 (11.11%)
occurrences (all)	0	3	7
Hepatic enzyme increased			
subjects affected / exposed	1 / 59 (1.69%)	1 / 60 (1.67%)	4 / 63 (6.35%)
occurrences (all)	1	1	4
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 59 (5.08%)	0 / 60 (0.00%)	0 / 63 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 59 (8.47%)	3 / 60 (5.00%)	3 / 63 (4.76%)
occurrences (all)	5	3	3
Abdominal pain upper			
subjects affected / exposed	1 / 59 (1.69%)	4 / 60 (6.67%)	4 / 63 (6.35%)
occurrences (all)	1	4	5
Dyspepsia			
subjects affected / exposed	1 / 59 (1.69%)	0 / 60 (0.00%)	4 / 63 (6.35%)
occurrences (all)	2	0	5

Non-serious adverse events	Placebo + MTX		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 62 (35.48%)		
Investigations			
Blood alkaline phosphatase increased			

subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Hepatic enzyme increased			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2017	The exclusion criterion: 11. Allergy/sensitivity to lactose was changed in 11. Allergy/hypersensitivity/intolerance to any components in CR6086 and MTX, including excipients such as lactose (patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should be excluded), starch, magnesium stearate, cellulose.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported