Clinical trial results:
A Phase 1b Dose Exploration Trial with MK-8628, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, in Subjects with Selected Advanced Solid Tumors

Summary

EudraCT number	2015-005488-18
Trial protocol	ES BE FR
Global end of trial date	26 April 2017

Results information

Result version number	v1 (current)
This version publication date	20 April 2018
First version publication date	20 April 2018

Trial information

Trial identification

Sponsor protocol code	8628-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02698176
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-8628-006, IND Number: 123,715

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	26 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 April 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study determined the recommended phase 2 dose (RP2D) of MK-8628 (formerly known as OTX015) for further studies in participants with advanced nuclear protein in testis (NUT) midline carcinoma (NMC), triple negative breast cancer (TNBC), non-small cell lung cancer (NSCLC), or castration-resistant prostate cancer (CRPC). This was a 2 part study: Part A was a dose-escalation study and established the RP2D by evaluating dose limiting toxicity (DLT), safety, discontinuation, and early efficacy. Part B was to enroll participants with NMC only and evaluate safety and efficacy. The sponsor decided to terminate the program after the dose levels tested in Part A due to limited efficacy signals and not due to safety-related concerns. No participants entered or were treated in Part B of the study.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 May 2016
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	Belgium: 2
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	13
EEA total number of subjects	7

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)	2
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase I, multi-center, open-label, dose-escalating study in participants with advanced or metastatic NSCLC, TNBC, CRPC, or NMC for which standard therapy either does not exist, has proven ineffective, intolerable, or unacceptable.

Pre-assignment

Screening details:

Participants with CRPC, NMC, and TNBC were enrolled in the study; no participants with NSCLC were enrolled. All participants had a Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of ≤1 and 76.9% of participants had 2 or more prior lines of therapy. No participants were enrolled in Part B of the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	MK-8628 20 mg CRPC Cohort-Part A

Arm description:

Participants in the CRPC cohort in Part A of the study received MK-8628 20 mg PO, BID, in a fasted state for 21 consecutive days per cycle. Participants received MK-8628 in continuous cycles up to 24 months.

Arm type	Experimental
Investigational medicinal product name	MK-8628
Investigational medicinal product code	
Other name	OTX015
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered PO, BID, in a fasted state, for 21 consecutive days per cycle and administered in consecutive cycles for up to 24 months

Arm title	MK-8628 20 mg NMC Cohort-Part A

Arm description:

Participants in the NMC cohort in Part A of the study received MK-8628 20 mg PO, BID, in a fasted state for 21 consecutive days per cycle. Participants received MK-8628 in continuous cycles up to 24 months.

Arm type	Experimental
Investigational medicinal product name	MK-8628
Investigational medicinal product code	
Other name	OTX015
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered PO, BID, in a fasted state, for 21 consecutive days per cycle and administered in consecutive cycles for up to 24 months

Arm title	MK-8628 20 mg TNBC Cohort-Part A

Arm description:

Participants in the TNBC cohort in Part A of the study received MK-8628 20 mg PO, BID, in a fasted state for 21 consecutive days per cycle. Participants received MK-8628 in continuous cycles up to 24 months.

Arm type	Experimental

Investigational medicinal product name	MK-8628
Investigational medicinal product code	
Other name	OTX015
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered PO, BID, in a fasted state, for 21 consecutive days per cycle and administered in consecutive cycles for up to 24 months

Number of subjects in period 1	MK-8628 20 mg CRPC Cohort-Part A	MK-8628 20 mg NMC Cohort-Part A	MK-8628 20 mg TNBC Cohort-Part A
Started	9	3	1
Completed	0	0	0
Not completed	9	3	1
Clinical progression	3	-	-
Adverse event, non-fatal	2	-	-
Progressive disease	4	3	1

Baseline characteristics

Reporting groups	
Reporting group title	MK-8628 20 mg CRPC Cohort-Part A
Reporting group description:	
Participants in the CRPC cohort in Part A of the study received MK-8628 20 mg PO, BID, in a fasted state for 21 consecutive days per cycle. Participants received MK-8628 in continuous cycles up to 24 months.	
Reporting group title	MK-8628 20 mg NMC Cohort-Part A
Reporting group description:	
Participants in the NMC cohort in Part A of the study received MK-8628 20 mg PO, BID, in a fasted state for 21 consecutive days per cycle. Participants received MK-8628 in continuous cycles up to 24 months.	
Reporting group title	MK-8628 20 mg TNBC Cohort-Part A
Reporting group description:	
Participants in the TNBC cohort in Part A of the study received MK-8628 20 mg PO, BID, in a fasted state for 21 consecutive days per cycle. Participants received MK-8628 in continuous cycles up to 24 months.	

Reporting group values	MK-8628 20 mg CRPC Cohort-Part A	MK-8628 20 mg NMC Cohort-Part A	MK-8628 20 mg TNBC Cohort-Part A
Number of subjects	9	3	1
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)	0	2	0
From 65-84 years	9	1	1
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	71.2	42.7	66.0
full range (min-max)	67 to 81	30 to 67	66 to 66
Gender Categorical Units: Subjects			
Female	0	1	1
Male	9	2	0

Reporting group values	Total		
Number of subjects	13		
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)	2		
From 65-84 years	11		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
full range (min-max)	-		
Gender Categorical Units: Subjects			
Female	2		
Male	11		

End points

End points reporting groups

Reporting group title	MK-8628 20 mg CRPC Cohort-Part A

Reporting group description:

Participants in the CRPC cohort in Part A of the study received MK-8628 20 mg PO, BID, in a fasted state for 21 consecutive days per cycle. Participants received MK-8628 in continuous cycles up to 24 months.

Reporting group title	MK-8628 20 mg NMC Cohort-Part A

Reporting group description:

Participants in the NMC cohort in Part A of the study received MK-8628 20 mg PO, BID, in a fasted state for 21 consecutive days per cycle. Participants received MK-8628 in continuous cycles up to 24 months.

Reporting group title	MK-8628 20 mg TNBC Cohort-Part A

Reporting group description:

Participants in the TNBC cohort in Part A of the study received MK-8628 20 mg PO, BID, in a fasted state for 21 consecutive days per cycle. Participants received MK-8628 in continuous cycles up to 24 months.

Subject analysis set title	MK-8628 20 mg CRPC Cohort-Part A
Subject analysis set type	Full analysis

Subject analysis set description:

Participants in the CRPC cohort in Part A of the study received at least 1 dose of MK-8628 20 mg PO, BID, in a fasted state for 21 consecutive days per cycle. Participants received MK-8628 in continuous cycles up to 24 months. No participants were enrolled in Part B of the study.

Subject analysis set title	MK-8628 20 mg NMC Cohort-Part A
Subject analysis set type	Full analysis

Subject analysis set description:

Participants in the NMC cohort in Part A of the study received at least 1 dose of MK-8628 20 mg PO, BID, in a fasted state for 21 consecutive days per cycle. Participants received MK-8628 in continuous cycles up to 24 months. No participants were enrolled in Part B of the study.

Subject analysis set title	MK-8628 20 mg TNBC Cohort-Part A
Subject analysis set type	Full analysis

Subject analysis set description:

Participants in the TNBC cohort in Part A of the study received at least 1 dose of MK-8628 20 mg PO, BID, in a fasted state for 21 consecutive days per cycle. Participants received MK-8628 in continuous cycles up to 24 months. No participants were enrolled in Part B of the study.

Subject analysis set title	MK-8628 20 mg-PK Cohort
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Total number of participants from all 3 cohorts (CRPC+NMC+TNBC) in Part A of the study that received at least 1 dose of MK-8628 20 mg PO, BID, in a fasted state and had data available for the Pharmacokinetic (PK) parameter being analyzed.

Subject analysis set title	MK-8628 20 mg CRPC Cohort-Part A: DLT Cohort
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in CRPC Cohort in Part A of the study that received at least 85% of the planned MK-8628 20 mg dose (18 days) PO, BID, in a fasted state or experienced a DLT during the first 21-day cycle.

Subject analysis set title	MK-8628 20 mg NMC Cohort-Part A: DLT Cohort
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in NMC Cohort in Part A of the study that received at least 85% of the planned MK-8628 20 mg dose (18 days) PO, BID, in a fasted state or experienced a DLT during the first 21-day cycle.

Subject analysis set title	MK-8628 20 mg TNBC Cohort-Part A: DLT Cohort
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in TNBC Cohort in Part A of the study that received at least 85% of the planned MK-8628 20 mg dose (18 days) PO, BID, in a fasted state or experienced a DLT during the first 21-day cycle.

Subject analysis set title	MK-8628 20 mg CRPC Cohort-Part A: Safety Cohort
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants in CRPC Cohort in Part A of the study that received at least 1 dose of MK-8628 20 mg PO, BID, in a fasted state. No participants were enrolled in Part B of the study.

Subject analysis set title	MK-8628 20 mg NMC Cohort-Part A: Safety Cohort
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants in NMC Cohort in Part A of the study that received at least 1 dose of MK-8628 20 mg PO, BID, in a fasted state. No participants were enrolled in Part B of the study.

Subject analysis set title	MK-8628 20 mg TNBC Cohort-Part A: Safety Cohort
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants in TNBC Cohort in Part A of the study that received at least 1 dose of MK-8628 20 mg PO, BID, in a fasted state. No participants were enrolled in Part B of the study.

Primary: Number of Participants Who Experienced a Dose Limiting Toxicity (DLT) During Cycle 1

End point title	Number of Participants Who Experienced a Dose Limiting Toxicity (DLT) During Cycle 1

End point description:

A DLT was any of the following deemed drug related (DR) by investigator: Grade (G)4 hematologic toxicity lasting ≥7 days except thrombocytopenia; G4 thrombocytopenia; G3 thrombocytopenia with bleeding; G3 or 4 febrile neutropenia. G4 non-hematologic (NH) toxicity (not laboratory); G3 NH toxicity (not laboratory), nausea, vomiting, or diarrhea lasting >3 days despite supportive care; G3 or 4 NH laboratory abnormality requiring medical intervention, hospitalization, or persisting >1 week; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8X Upper Limit of Normal(ULN); ALT or AST >5XULN for >2 weeks; ALT or AST >3XULN and total bilirubin >2XULN or international normalization ratio >1.5; ALT or AST >3XULN with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%); DR adverse event leading to discontinuation or >20% missed planned doses in Cycle 1; DR toxicity causing >2 week delay in starting Cycle 2; or G5 toxicity.

End point type	Primary

End point timeframe:

From time of first dose up to the end of the first cycle (up to 21 days)

End point values	MK-8628 20 mg CRPC Cohort-Part A: DLT Cohort	MK-8628 20 mg NMC Cohort-Part A: DLT Cohort	MK-8628 20 mg TNBC Cohort-Part A: DLT Cohort	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	3	1	
Units: Participants	2	1	0	

Statistical analyses

Statistical analysis title	Estimation of DLT Rate

Statistical analysis description:

A point estimate and a 2-sided 80% Bayesian credible interval for DLT rate was estimated for the total number of participants from all 3 cohorts (CRPC+NMC+TNBC) that were evaluable for DLT analysis based on a non-informative prior distribution of Beta (1,1).

Comparison groups	MK-8628 20 mg CRPC Cohort-Part A: DLT Cohort v MK-8628

	20 mg NMC Cohort-Part A: DLT Cohort v MK-8628 20 mg TNBC Cohort-Part A: DLT Cohort
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	DLT Rate and Bayesian credible interval
Point estimate	0.25
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.121
upper limit	0.418

Secondary: Number of Participants Who Experienced at Least One Adverse Event (AE)

End point title	Number of Participants Who Experienced at Least One Adverse Event (AE)

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product/protocol-specified procedure, whether or not considered related to the medicinal product/protocol-specified procedure. Any worsening of a preexisting condition temporally associated with the use of the product was also an AE. The number of participants who experienced at least one AE is presented.

End point type	Secondary

End point timeframe:

From time of first dose until the end of the 30-day follow-up (up to 25 months)

End point values	MK-8628 20 mg CRPC Cohort-Part A: Safety Cohort	MK-8628 20 mg NMC Cohort-Part A: Safety Cohort	MK-8628 20 mg TNBC Cohort-Part A: Safety Cohort	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	3	1	
Units: Participants	9	3	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Treatment Due to an AE

End point title	Number of Participants Who Discontinued Study Treatment Due to an AE

End point description:

The number of participants who discontinued study treatment due to an AE is presented.

End point type	Secondary

End point timeframe:

From time of first dose until the end of treatment (up to 24 months)

End point values	MK-8628 20 mg CRPC Cohort-Part A: Safety Cohort	MK-8628 20 mg NMC Cohort-Part A: Safety Cohort	MK-8628 20 mg TNBC Cohort-Part A: Safety Cohort	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	3	1	
Units: Participants	2	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR was defined as the number of the participants in the analysis population who had a Complete Response (CR: Disappearance of all target lesions Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions per RECIST 1.1) and lack of progression according to the guidelines for prostate cancer endpoints developed by Prostate Cancer Clinical Trials Working Group (PCWG) 2 as assessed by investigator radiologic review. The number of participants who achieved a CR or PR is presented.

End point type	Secondary

End point timeframe:

Assessed every 6 weeks from time of first dose until disease progression (up to 24 months)

End point values	MK-8628 20 mg CRPC Cohort-Part A	MK-8628 20 mg NMC Cohort-Part A	MK-8628 20 mg TNBC Cohort-Part A	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	3	1	
Units: Participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

For participants who demonstrated CR or PR, DOR was defined as the time from first documented evidence of CR or PR per RECIST 1.1 until disease progression per RECIST 1.1 and PCWG2 or death due

to any cause, whichever occurred first. Per RECIST 1.1, progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions was also considered progression per RECIST 1.1. Per PCWG2, progressive disease was defined as a confirmed increase of at least two new lesions on a bone scan. DOR assessments were assessed by investigator radiologic review. The DOR for all participants who experienced a CR or PR is presented. Since no participants experienced a CR or PR, DOR could not be calculated.

End point type	Secondary

End point timeframe:

Assessed every 6 weeks from time of first dose until disease progression (up to 24 months)

End point values	MK-8628 20 mg CRPC Cohort-Part A	MK-8628 20 mg NMC Cohort-Part A	MK-8628 20 mg TNBC Cohort-Part A	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[1]	0[2]	0[3]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[1] - No participants had a response of CR or PR.

[2] - No participants had a response of CR or PR.

[3] - No participants had a response of CR or PR.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

DCR was defined as the number of subjects with CR, PR, or stable disease (SD) as assessed by investigator radiologic review according to RECIST version 1.1 and PCWG2. CR: defined as disappearance of all target and all non-target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than <10 mm per RECIST 1.1. PR: defined as at least a 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters along with absence of new lesions and disease progression in non-target lesions per RECIST 1.1. SD: defined as, neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study per RECIST 1.1 and lack of a confirmed increase of at least two new lesions on a bone scan per PCWG2. The number of participants who experienced DCR is presented.

End point type	Secondary

End point timeframe:

Assessed every 6 weeks from time of first dose until disease progression (up to 24 months)

End point values	MK-8628 20 mg CRPC Cohort-Part A	MK-8628 20 mg NMC Cohort-Part A	MK-8628 20 mg TNBC Cohort-Part A	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9[4]	3	1	
Units: Participants	6	0	0	

Notes:

[4] - Best Response was Stable Disease

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Maximum Concentration (Cmax) of MK-8628

End point title	Observed Maximum Concentration (Cmax) of MK-8628

End point description:

Blood samples were obtained at specified time points for the pharmacokinetic (PK) analysis of Cmax of MK-8628. MK-8628 concentrations were analyzed using ultra-performance liquid chromatography coupled with a tandem mass spectrometry. The Cmax of MK-8628 after oral administration is presented.

End point type	Secondary

End point timeframe:

Cycle1/Day 1: predose, 20 minutes, 1 hour, 2.25 hours (hrs), 3.25 hrs, 8 hrs, and 12 hrs postdose

End point values	MK-8628 20 mg-PK Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: ng/mL				
arithmetic mean (standard deviation)	355 (± 157)			

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Minimum Concentration (Cmin) of MK-8628

End point title	Observed Minimum Concentration (Cmin) of MK-8628

End point description:

Blood samples were obtained at specified time points for the PK analysis of Cmin of MK-8628. MK-8628 concentrations were analyzed using ultra-performance liquid chromatography coupled with a tandem mass spectrometry. The Cmin of MK-8628 after oral administration is presented.

End point type	Secondary

End point timeframe:

Cycle1/Day 1: predose, 20 minutes, 1 hour, 2.25 hours (hrs), 3.25 hrs, 8 hrs, and 12 hrs postdose

End point values	MK-8628 20 mg-PK Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: ng/mL				
arithmetic mean (standard deviation)	111 (± 45.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Concentration (Tmax) of MK-8628

End point title	Time to Maximum Concentration (Tmax) of MK-8628

End point description:

Blood samples were obtained at specified time points for the PK analysis of Tmax of MK-8628. MK-8628 concentrations were analyzed using ultra-performance liquid chromatography coupled with a tandem mass spectrometry. The Tmax of MK-8628 after oral administration is presented.

End point type	Secondary

End point timeframe:

Cycle1/Day 1: predose, 20 minutes, 1 hour, 2.25 hours (hrs), 3.25 hrs, 8 hrs, and 12 hrs postdose

End point values	MK-8628 20 mg-PK Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: hours				
median (full range (min-max))	2.25 (1.00 to 3.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Terminal Half-Life (t1/2) of MK-8628

End point title	Apparent Terminal Half-Life (t1/2) of MK-8628

End point description:

Blood samples were obtained at specified time points for the PK analysis of t1/2 of MK-8628. MK-8628 concentrations were analyzed using ultra-performance liquid chromatography coupled with a tandem mass spectrometry. The t1/2 of MK-8628 after oral administration is presented. Due to limited PK sampling for t1/2, caution must be exercised when interpreting the results of t1/2, CL/F, and AUC 0-∞ values.

End point type	Secondary

End point timeframe:

Cycle1/Day 1: predose, 20 minutes, 1 hour, 2.25 hours (hrs), 3.25 hrs, 8 hrs, and 12 hrs postdose

End point values	MK-8628 20 mg-PK Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: hours				
arithmetic mean (standard deviation)	6.17 (± 1.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Total Body Clearance (CL/F) of MK-8628

End point title	Apparent Total Body Clearance (CL/F) of MK-8628

End point description:

Blood samples were obtained at specified time points for the PK analysis of CL/F of MK-8628. MK-8628 concentrations were analyzed using ultra-performance liquid chromatography coupled with a tandem mass spectrometry. The CL/F of MK-8628 after oral administration is presented. Due to limited PK sampling for t1/2, caution must be exercised when interpreting the results of t1/2, CL/F, and AUC 0-∞ values.

End point type	Secondary

End point timeframe:

Cycle1/Day 1: predose, 20 minutes, 1 hour, 2.25 hours (hrs), 3.25 hrs, 8 hrs, and 12 hrs postdose

End point values	MK-8628 20 mg-PK Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: Liters/hour				
arithmetic mean (standard deviation)	6.44 (± 2.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution During the Terminal Phase (Vz/F) of MK-8628

End point title	Apparent Volume of Distribution During the Terminal Phase (Vz/F) of MK-8628

End point description:

Blood samples were obtained at specified time points for the PK analysis of Vz/F of MK-8628. MK-8628 concentrations were analyzed using ultra-performance liquid chromatography coupled with a tandem mass spectrometry. The Vz/F of MK-8628 after oral administration is presented.

End point type	Secondary

End point timeframe:

Cycle1/Day 1: predose, 20 minutes, 1 hour, 2.25 hours (hrs), 3.25 hrs, 8 hrs, and 12 hrs postdose

End point values	MK-8628 20 mg-PK Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: Liters				
arithmetic mean (standard deviation)	55.0 (± 15.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve of MK-8628 From Time 0 to Infinity (AUC 0-∞)

End point title	Area Under the Concentration-time Curve of MK-8628 From Time 0 to Infinity (AUC 0-∞)

End point description:

Blood samples were obtained at specified time points for the PK analysis of AUC 0-∞ of MK-8628. MK-8628 concentrations were analyzed using ultra-performance liquid chromatography coupled with a tandem mass spectrometry. The AUC 0-∞ of MK-8628 after oral administration is presented. Due to limited PK sampling for t1/2, caution must be exercised when interpreting the results of t1/2, CL/F, and AUC 0-∞ values.

End point type	Secondary

End point timeframe:

Cycle1/Day 1: predose, 20 minutes, 1 hour, 2.25 hours (hrs), 3.25 hrs, 8 hrs, and 12 hrs postdose

End point values	MK-8628 20 mg-PK Cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: hours•ng/mL				
arithmetic mean (standard deviation)	3520 (± 1410)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From time of first dose until the end of the 30-day follow-up (up to 25 months)	
Adverse event reporting additional description:	
The safety population consisted of all participants who received at least one dose of study treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	MK-8628 20 mg CRPC Cohort-Part A: Safety Cohort
Reporting group description:	
Participants in CRPC Cohort in Part A of the study that received at least 1 dose of MK-8628 20 mg PO, BID, in a fasted state.	
Reporting group title	MK-8628 20 mg NMC Cohort-Part A: Safety Cohort
Reporting group description:	
Participants in NMC Cohort in Part A of the study that received at least 1 dose of MK-8628 20 mg PO, BID, in a fasted state.	
Reporting group title	MK-8628 20 mg TNBC Cohort-Part A: Safety Cohort
Reporting group description:	
Participants in TNBC Cohort in Part A of the study that received at least 1 dose of MK-8628 20 mg PO, BID, in a fasted state.	

Serious adverse events	MK-8628 20 mg CRPC Cohort-Part A: Safety Cohort	MK-8628 20 mg NMC Cohort-Part A: Safety Cohort	MK-8628 20 mg TNBC Cohort-Part A: Safety Cohort
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	2 / 3 (66.67%)	0 / 1 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 3 (33.33%)	0 / 1 (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
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 3 (33.33%)	0 / 1 (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
Cognitive disorder			

subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	MK-8628 20 mg CRPC Cohort-Part A: Safety Cohort	MK-8628 20 mg NMC Cohort-Part A: Safety Cohort	MK-8628 20 mg TNBC Cohort-Part A: Safety Cohort
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	3 / 3 (100.00%)	1 / 1 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 9 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Hypertension			

subjects affected / exposed	0 / 9 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 9 (22.22%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	2	1	0
Fatigue			
subjects affected / exposed	2 / 9 (22.22%)	2 / 3 (66.67%)	0 / 1 (0.00%)
occurrences (all)	4	2	0
Mucosal inflammation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	2 / 9 (22.22%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Reproductive system and breast disorders			
Scrotal oedema			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 9 (11.11%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)	2 / 3 (66.67%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Dyspnoea exertional			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	3	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	3	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
C-reactive protein increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 3 (0.00%)	1 / 1 (100.00%)
occurrences (all)	0	0	1
Platelet count decreased			
subjects affected / exposed	2 / 9 (22.22%)	0 / 3 (0.00%)	1 / 1 (100.00%)
occurrences (all)	2	0	1
Weight decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dysgeusia			

subjects affected / exposed	0 / 9 (0.00%)	2 / 3 (66.67%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Headache			
subjects affected / exposed	0 / 9 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 9 (22.22%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Leukocytosis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Leukopenia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 3 (0.00%)	1 / 1 (100.00%)
occurrences (all)	0	0	1
Thrombocytopenia			
subjects affected / exposed	2 / 9 (22.22%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 9 (33.33%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	4	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			

subjects affected / exposed	3 / 9 (33.33%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	7	1	0
Dyspepsia			
subjects affected / exposed	2 / 9 (22.22%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Dysphagia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	6 / 9 (66.67%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	7	1	0
Odynophagia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	3 / 9 (33.33%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	4	1	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 9 (0.00%)	2 / 3 (66.67%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Erythema			
subjects affected / exposed	0 / 9 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 9 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Bone pain			
subjects affected / exposed	2 / 9 (22.22%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 9 (11.11%)	2 / 3 (66.67%)	0 / 1 (0.00%)
occurrences (all)	1	2	0
Myalgia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Sepsis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 9 (22.22%)	2 / 3 (66.67%)	0 / 1 (0.00%)
occurrences (all)	2	2	0
Dehydration			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			

subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Hypophosphataemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 November 2016	Amendment 01: Primary reason for amendment was to incorporate revisions to the eligibility criteria to update the requirement for contraception.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

This study was terminated 16-Dec-2016 because limited efficacy was detected. The study was not terminated due to safety reasons.

Notes: