Clinical trial results:
A Phase 2, Open-label Study to Evaluate the Efficacy and Safety of Single-Agent MLN0128 and the Combination of MLN0128+MLN1117 Compared With Everolimus in the Treatment of Adult Patients With Advanced or Metastatic Clear-Cell Renal Cell Carcinoma That Has Progressed on Vascular Endothelial Growth Factor-Targeted Therapy

Summary

EudraCT number	2015-002133-22
Trial protocol	ES FR PL GB IT
Global end of trial date	13 October 2020

Results information

Result version number	v1 (current)
This version publication date	29 October 2021
First version publication date	29 October 2021

Trial information

Trial identification

Sponsor protocol code	C31005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02724020
WHO universal trial number (UTN)	U1111-1172-1808

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, MA, United States, 02421
Public contact	Study Director , Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director , Takeda, TrialDisclosures@takeda.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	13 October 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to evaluate the efficacy and safety of single-agent MLN0128 and the combination of MLN0128 + MLN1117 compared with everolimus in the treatment of participants with metastatic clear-cell renal cell carcinoma (mccRCC) that have progressed on vascular endothelial growth factor (VEGF)-targeted therapy.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 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	Poland: 5
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	96
EEA total number of subjects	60

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)	49
From 65 to 84 years	47
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at approximately 60-70 investigative sites in Czech Republic, France, Italy, Poland, Spain, United Kingdom, Canada and United States from 30 June 2016 to 13 October 2020.

Pre-assignment

Screening details:

Participants with a diagnosis of metastatic clear-cell renal cell carcinoma were randomised at a ratio of 1 :1 :1 to open label treatment period with single-agent MLN0128 and the combination of MLN0128 and MLN1117 compared with single-agent everolimus.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Single-agent Everolimus 10 mg QD

Arm description:

Everolimus 10 mg capsules, orally, once daily in a 28-day treatment cycle until disease progression, consent withdrawal, death, or transfer to the Post-trial Access (PTA) program (Median duration of treatment was 15.43 weeks up to end of study).

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

Dosage and administration details:

Everolimus capsules.

Arm title	Arm B: Single-agent MLN0128 30 mg QW

Arm description:

MLN0128 30 mg capsules, orally, once weekly on Days 1, 8, 15, and 22 of a 28-day treatment cycle until disease progression, unacceptable toxicity, consent withdrawal, death, or transfer to the PTA program (Median duration of treatment was 9.64 weeks up to end of study).

Arm type	Experimental
Investigational medicinal product name	MLN0128
Investigational medicinal product code	
Other name	TAK-228, INK0128
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

MLN0128 capsules.

Arm title	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD

Arm description:

MLN0128 4 mg and MLN1117 200 mg capsules, orally, both once daily for 3 days per week (QD X 3) on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day treatment cycle until disease progression, unacceptable toxicity, consent withdrawal, death, or transfer to the PTA program (Median duration of treatment was 9.43 weeks up to end of study).

Arm type	Experimental

Investigational medicinal product name	MLN0128
Investigational medicinal product code	
Other name	TAK-228, INK0128
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
MLN0128 capsules.

Investigational medicinal product name	MLN1117
Investigational medicinal product code	
Other name	TAK-117, INK1117
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
MLN1117 capsules.

Number of subjects in period 1	Arm A: Single-agent Everolimus 10 mg QD	Arm B: Single-agent MLN0128 30 mg QW	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD
Started	32	32	32
Treated (Safety Analysis Set)	32	32	31
Completed	0	0	0
Not completed	32	32	32
Death	16	18	19
Withdrawal by Subject	1	3	5
Site Terminated by Sponsor	15	8	8
Lost to follow-up	-	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Single-agent Everolimus 10 mg QD
Reporting group description:	
Everolimus 10 mg capsules, orally, once daily in a 28-day treatment cycle until disease progression, consent withdrawal, death, or transfer to the Post-trial Access (PTA) program (Median duration of treatment was 15.43 weeks up to end of study).	
Reporting group title	Arm B: Single-agent MLN0128 30 mg QW
Reporting group description:	
MLN0128 30 mg capsules, orally, once weekly on Days 1, 8, 15, and 22 of a 28-day treatment cycle until disease progression, unacceptable toxicity, consent withdrawal, death, or transfer to the PTA program (Median duration of treatment was 9.64 weeks up to end of study).	
Reporting group title	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD
Reporting group description:	
MLN0128 4 mg and MLN1117 200 mg capsules, orally, both once daily for 3 days per week (QD X 3) on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day treatment cycle until disease progression, unacceptable toxicity, consent withdrawal, death, or transfer to the PTA program (Median duration of treatment was 9.43 weeks up to end of study).	

Reporting group values	Arm A: Single-agent Everolimus 10 mg QD	Arm B: Single-agent MLN0128 30 mg QW	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD
Number of subjects	32	32	32
Age categorical Units: Subjects			
Adults (18-64 years)	15	20	14
From 65-84 years	17	12	18
Age continuous Units: years			
arithmetic mean	64.7	61.6	63.3
standard deviation	± 11.41	± 8.90	± 9.06
Gender categorical Units: Subjects			
Female	6	10	7
Male	26	22	25
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	2
Not Hispanic or Latino	28	30	27
Unknown or Not Reported	4	2	3
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	1
White	27	29	27
More than one race	0	0	0
Unknown or Not Reported	4	3	4

Region of Enrollment Units: Subjects			
Czech Republic	1	1	2
France	4	2	2
Italy	11	9	4
Poland	2	2	1
Spain	6	6	7
United Kingdom	4	4	9
Canada	2	1	2
United States	2	7	5
Height			
Number analyzed is the number of participants with data available for height at Baseline. n= 31, 32, 31.			
Units: cm			
arithmetic mean	170.23	171.16	172.01
standard deviation	± 8.489	± 10.626	± 8.349
Weight			
Number analyzed is the number of participants with data available for weight at Baseline. n= 31, 32, 32.			
Units: kg			
arithmetic mean	75.69	78.12	80.40
standard deviation	± 12.449	± 15.473	± 17.896

Reporting group values	Total		
Number of subjects	96		
Age categorical Units: Subjects			
Adults (18-64 years)	49		
From 65-84 years	47		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	23		
Male	73		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	85		
Unknown or Not Reported	9		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	83		
More than one race	0		
Unknown or Not Reported	11		
Region of Enrollment Units: Subjects			

Czech Republic	4		
France	8		
Italy	24		
Poland	5		
Spain	19		
United Kingdom	17		
Canada	5		
United States	14		
Height			
Number analyzed is the number of participants with data available for height at Baseline. n= 31, 32, 31.			
Units: cm			
arithmetic mean			
standard deviation	-		
Weight			
Number analyzed is the number of participants with data available for weight at Baseline. n= 31, 32, 32.			
Units: kg			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Arm A: Single-agent Everolimus 10 mg QD
Reporting group description:	
Everolimus 10 mg capsules, orally, once daily in a 28-day treatment cycle until disease progression, consent withdrawal, death, or transfer to the Post-trial Access (PTA) program (Median duration of treatment was 15.43 weeks up to end of study).	
Reporting group title	Arm B: Single-agent MLN0128 30 mg QW
Reporting group description:	
MLN0128 30 mg capsules, orally, once weekly on Days 1, 8, 15, and 22 of a 28-day treatment cycle until disease progression, unacceptable toxicity, consent withdrawal, death, or transfer to the PTA program (Median duration of treatment was 9.64 weeks up to end of study).	
Reporting group title	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD
Reporting group description:	
MLN0128 4 mg and MLN1117 200 mg capsules, orally, both once daily for 3 days per week (QD X 3) on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day treatment cycle until disease progression, unacceptable toxicity, consent withdrawal, death, or transfer to the PTA program (Median duration of treatment was 9.43 weeks up to end of study).	

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
End point description:	
PFS was defined as the time from the date of randomization to the date of first documentation of progressive disease (PD) or death due to any cause, whichever occurs first. Per Response Evaluation Criteria in Solid Tumors (RECIST) v1 .1 criteria. PD was defined as at least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Full Analysis Set included all randomised participants.	
End point type	Primary
End point timeframe:	
From first dose of study drug up to disease progression or death (up to 51 months)	

End point values	Arm A: Single-agent Everolimus 10 mg QD	Arm B: Single-agent MLN0128 30 mg QW	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	32	
Units: months				
median (confidence interval 95%)	3.8 (2.0 to 5.4)	3.6 (1.9 to 5.7)	3.1 (1.9 to 5.4)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for PFS

Statistical analysis description:

HR obtained by stratified Cox proportion hazard model adjusted for prior lines of therapy and the International Metastatic Renal Cell Carcinoma Database Consortium risk category. A hazard ratio < 1 indicates an advantage compared to Everolimus.

Comparison groups	Arm A: Single-agent Everolimus 10 mg QD v Arm B: Single-agent MLN0128 30 mg QW
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.388
Method	Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	2.36

Statistical analysis title	Statistical Analysis 2 for PFS

Statistical analysis description:

HR obtained by stratified Cox proportion hazard model adjusted for prior lines of therapy and the International Metastatic Renal Cell Carcinoma Database Consortium risk category. A hazard ratio < 1 indicates an advantage compared to Everolimus.

Comparison groups	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD v Arm A: Single-agent Everolimus 10 mg QD
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.667
Method	Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	2.52

Secondary: Number of Participants with Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants with Treatment-Emergent Adverse Events (TEAEs)

End point description:

An AE was defined as any untoward medical occurrence in participants administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. TEAE was defined as the event that occur after administration of the first dose of study drug and through 30 days after the last

dose of study drug. Safety Analysis Set included participants who receive at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From first dose of study drug through 30 days after the last dose of study drug (approximately up to 31 months)

End point values	Arm A: Single-agent Everolimus 10 mg QD	Arm B: Single-agent MLN0128 30 mg QW	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	31	
Units: participants	32	30	31	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival in months was defined as the time from the date of randomisation to the date of death. Full Analysis Set included all randomised participants. 99999 indicates upper limit of 95% CI was not estimable due to fewer number of participants with events.

End point type	Secondary

End point timeframe:

From first dose of study drug through 30 days after the last dose of study drug (up to 51 months)

End point values	Arm A: Single-agent Everolimus 10 mg QD	Arm B: Single-agent MLN0128 30 mg QW	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	32	
Units: months				
median (confidence interval 95%)	22.4 (8.2 to 99999)	16.2 (9.0 to 19.9)	18.1 (6.2 to 23.4)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for OS

Statistical analysis description:

HR obtained by stratified Cox proportion hazard model adjusted for prior lines of therapy and the

International Metastatic Renal Cell Carcinoma Database Consortium risk category. A hazard ratio < 1 indicates an advantage compared to Everolimus.

Comparison groups	Arm A: Single-agent Everolimus 10 mg QD v Arm B: Single-agent MLN0128 30 mg QW
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.212
Method	Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	3.49

Statistical analysis title	Statistical Analysis 2 for OS

Statistical analysis description:

HR obtained by stratified Cox proportion hazard model adjusted for prior lines of therapy and the International Metastatic Renal Cell Carcinoma Database Consortium risk category. A hazard ratio < 1 indicates an advantage compared to Everolimus.

Comparison groups	Arm A: Single-agent Everolimus 10 mg QD v Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.546
Method	Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	2.98

Secondary: Time-to-progression (TTP)

End point title	Time-to-progression (TTP)

End point description:

TTP in months is defined as the time from the date of randomisation to the date of first documentation of progression. Per RECIST v1 .1, PD was defined as at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Full Analysis Set included all randomised participants.

End point type	Secondary

End point timeframe:

From first dose of study drug up to disease progression or death (up to 51 months)

End point values	Arm A: Single-agent Everolimus 10 mg QD	Arm B: Single-agent MLN0128 30 mg QW	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	32	
Units: months				
median (confidence interval 95%)	3.8 (2.0 to 15.6)	3.5 (1.9 to 7.4)	3.7 (1.9 to 10.5)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for TTP

Statistical analysis description:

HR obtained by stratified Cox proportion hazard model adjusted for prior lines of therapy and the International Metastatic Renal Cell Carcinoma Database Consortium risk category. A hazard ratio < 1 indicates an advantage compared to Everolimus.

Comparison groups	Arm A: Single-agent Everolimus 10 mg QD v Arm B: Single-agent MLN0128 30 mg QW
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.156
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	3.05

Statistical analysis title	Statistical Analysis 2 for TTP

Statistical analysis description:

HR obtained by stratified Cox proportion hazard model adjusted for prior lines of therapy and the International Metastatic Renal Cell Carcinoma Database Consortium risk category. A hazard ratio < 1 indicates an advantage compared to Everolimus.

Comparison groups	Arm A: Single-agent Everolimus 10 mg QD v Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.667
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	2.79

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR was defined as the percentage of participants among response evaluable analysis set who achieve a best overall response of complete response (CR) or partial response (PR) based on investigators assessment of response following RECIST 1 .1. CR was defined as disappearance of all target lesions, non-target lesions, no new lesions, and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, no progression in non-target lesion, and no new lesions. Response Evaluable Analysis Set included participants who receive at least 1 dose of study drug, have measurable disease at Baseline and have 1 postbaseline disease assessment.

End point type	Secondary

End point timeframe:

From first dose of study drug to disease progression or death (up to 51 months)

End point values	Arm A: Single-agent Everolimus 10 mg QD	Arm B: Single-agent MLN0128 30 mg QW	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	31	
Units: percentage of participants				
number (not applicable)	15.6	0	6.5	

Statistical analyses

Statistical analysis title	Statistical Analysis for ORR

Statistical analysis description:

Odds ratio and 95% CI was obtained using a stratified Cochran–Mantel–Haenszel (CMH) model with prior lines of therapy and the international metastatic renal cell carcinoma database consortium risk category. As prespecified in protocol, the statistical analysis was performed between arms - Arm A: Single-agent Everolimus 10 mg QD and Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD only.

Comparison groups	Arm A: Single-agent Everolimus 10 mg QD v Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD

Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	2.22

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

CBR is defined as the percentage of participants who achieve a best response of CR, PR or stable disease (SD) of any duration. CR was defined as disappearance of all target lesions, non-target lesions, no new lesions, and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, no progression in non-target lesion, and no new lesions. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Response Evaluable Analysis Set included participants who receive at least 1 dose of study drug, have measurable disease at Baseline and have 1 postbaseline disease assessment.

End point type	Secondary

End point timeframe:

From first dose of study drug up to disease progression or death (up to 51 months)

End point values	Arm A: Single-agent Everolimus 10 mg QD	Arm B: Single-agent MLN0128 30 mg QW	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	31	
Units: percentage of participants				
number (not applicable)	62.5	50.0	54.8	

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for CBR

Statistical analysis description:

Odds ratio and 95% CI was obtained using a stratified CMH model with prior lines of therapy and the international metastatic renal cell carcinoma database consortium risk category.

Comparison groups	Arm A: Single-agent Everolimus 10 mg QD v Arm B: Single-agent MLN0128 30 mg QW

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	1.69

Statistical analysis title	Statistical Analysis 2 for CBR
Statistical analysis description:	
Odds ratio and 95% CI was obtained using a stratified CMH model with prior lines of therapy and the international metastatic renal cell carcinoma database consortium risk category.	
Comparison groups	Arm A: Single-agent Everolimus 10 mg QD v Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	2.21

Secondary: CBR with SD Duration of at least 16 Weeks

End point title	CBR with SD Duration of at least 16 Weeks
End point description:	
CBR with SD duration of at least 4 months (CBR-16) was defined as the percentage of participants who achieve CR or PR of any duration or have SD with duration of at least 16 weeks. CR was defined as disappearance of all target lesions, non-target lesions, no new lesions, and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, no progression in non-target lesion, and no new lesions. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Response Evaluable Analysis Set included participants who receive at least 1 dose of study drug, have measurable disease at Baseline and have 1 postbaseline disease assessment.	
End point type	Secondary
End point timeframe:	
Up to Week 16	

End point values	Arm A: Single-agent Everolimus 10 mg QD	Arm B: Single-agent MLN0128 30 mg QW	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	31	
Units: percentage of participants				
number (not applicable)	40.6	25.0	29.0	

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for CBR (16 weeks)
Statistical analysis description:	
Odds ratio and 95% CI was obtained using a stratified CMH model with prior lines of therapy and the international metastatic renal cell carcinoma database consortium risk category.	
Comparison groups	Arm A: Single-agent Everolimus 10 mg QD v Arm B: Single-agent MLN0128 30 mg QW
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	1.38

Statistical analysis title	Statistical Analysis 2 for CBR (16 weeks)
Statistical analysis description:	
Odds ratio and 95% CI was obtained using a stratified CMH model with prior lines of therapy and the international metastatic renal cell carcinoma database consortium risk category.	
Comparison groups	Arm A: Single-agent Everolimus 10 mg QD v Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.8

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Deaths: From first dose of study drug through end of the study (up to 51 months); Serious and other (non-serious) AEs: From first dose of study drug through 30 days after the last dose of study drug (up to 31 months)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of AEs and abnormal laboratory findings to report irrespective of relation to study treatment. Deaths: Data is reported for FAS: all randomised participants. Adverse Events: Data for is reported for Safety Analysis Set: participants who received >=1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Arm A: Single-agent Everolimus 10 mg QD

Reporting group description:

Everolimus 10 mg capsules, orally, once daily in a 28-day treatment cycle until disease progression, consent withdrawal, death, or transfer to the Post-trial Access (PTA) program (Median duration of treatment was 15.43 weeks up to end of study).

Reporting group title	Arm B: Single-agent MLN0128 30 mg QW

Reporting group description:

MLN0128 30 mg capsules, orally, once weekly on Days 1, 8, 15, and 22 of a 28-day treatment cycle until disease progression, unacceptable toxicity, consent withdrawal, death, or transfer to the PTA program (Median duration of treatment was 9.64 weeks up to end of study).

Reporting group title	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD

Reporting group description:

MLN0128 4 mg and MLN1117 200 mg capsules, orally, both once daily for 3 days per week (QD X 3) on Days 1-3, 8-10, 15-17, and 22-24 of a 28-day treatment cycle until disease progression, unacceptable toxicity, consent withdrawal, death, or transfer to the PTA program (Median duration of treatment was 9.43 weeks up to end of study).

Serious adverse events	Arm A: Single-agent Everolimus 10 mg QD	Arm B: Single-agent MLN0128 30 mg QW	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 32 (59.38%)	13 / 32 (40.63%)	15 / 31 (48.39%)
number of deaths (all causes)	16	18	19
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic renal cell carcinoma			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0

Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
T-cell lymphoma			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	0 / 31 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infarction			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pyrexia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	0 / 31 (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

Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 31 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 32 (3.13%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea at rest			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	0 / 31 (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
Hiccups			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 31 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 31 (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
Transaminases increased			

subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	0 / 31 (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
Femur fracture			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	0 / 31 (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
Pelvic fracture			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 31 (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
Road traffic accident			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 31 (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
Cardiac failure			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 31 (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
Nervous system disorders			
Cerebellar haemorrhage			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 31 (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			
Anaemia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 31 (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
Stomatitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 31 (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
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 31 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			

subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 31 (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
Haematuria			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	0 / 31 (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
Urinary retention			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 31 (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
Muscular weakness			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	0 / 31 (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
Pathological fracture			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 32 (9.38%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Sepsis			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	2 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Abscess jaw			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 31 (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
Pulmonary sepsis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	0 / 31 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 32 (3.13%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Arm A: Single-agent Everolimus 10 mg QD	Arm B: Single-agent MLN0128 30 mg QW	Arm C: Combination of MLN0128 4 mg QD + MLN1117 200 mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 32 (100.00%)	29 / 32 (90.63%)	31 / 31 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 32 (18.75%)	3 / 32 (9.38%)	4 / 31 (12.90%)
occurrences (all)	8	4	4
Hypotension			
subjects affected / exposed	4 / 32 (12.50%)	1 / 32 (3.13%)	1 / 31 (3.23%)
occurrences (all)	5	1	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 32 (59.38%)	12 / 32 (37.50%)	9 / 31 (29.03%)
occurrences (all)	27	19	11
Fatigue			
subjects affected / exposed	10 / 32 (31.25%)	6 / 32 (18.75%)	12 / 31 (38.71%)
occurrences (all)	12	9	16
Pyrexia			
subjects affected / exposed	10 / 32 (31.25%)	3 / 32 (9.38%)	5 / 31 (16.13%)
occurrences (all)	24	4	8
Chest pain			
subjects affected / exposed	2 / 32 (6.25%)	3 / 32 (9.38%)	1 / 31 (3.23%)
occurrences (all)	2	3	1
Influenza like illness			
subjects affected / exposed	4 / 32 (12.50%)	1 / 32 (3.13%)	1 / 31 (3.23%)
occurrences (all)	4	1	1
Chills			
subjects affected / exposed	2 / 32 (6.25%)	2 / 32 (6.25%)	1 / 31 (3.23%)
occurrences (all)	2	2	1
Oedema peripheral			
subjects affected / exposed	4 / 32 (12.50%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	6	0	0
Pain			
subjects affected / exposed	1 / 32 (3.13%)	1 / 32 (3.13%)	2 / 31 (6.45%)
occurrences (all)	1	1	2

Peripheral swelling			
subjects affected / exposed	3 / 32 (9.38%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	4	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	10 / 32 (31.25%)	10 / 32 (31.25%)	5 / 31 (16.13%)
occurrences (all)	12	14	5
Cough			
subjects affected / exposed	11 / 32 (34.38%)	10 / 32 (31.25%)	3 / 31 (9.68%)
occurrences (all)	24	12	5
Dyspnoea exertional			
subjects affected / exposed	2 / 32 (6.25%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	2	2	0
Epistaxis			
subjects affected / exposed	4 / 32 (12.50%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	4	0	0
Nasal dryness			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 32 (9.38%)	2 / 32 (6.25%)	2 / 31 (6.45%)
occurrences (all)	4	2	2
Insomnia			
subjects affected / exposed	3 / 32 (9.38%)	2 / 32 (6.25%)	2 / 31 (6.45%)
occurrences (all)	3	2	2
Investigations			
Weight decreased			
subjects affected / exposed	4 / 32 (12.50%)	9 / 32 (28.13%)	5 / 31 (16.13%)
occurrences (all)	4	9	5
Blood creatinine increased			
subjects affected / exposed	2 / 32 (6.25%)	3 / 32 (9.38%)	2 / 31 (6.45%)
occurrences (all)	2	4	2
Alanine aminotransferase increased			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	4 / 31 (12.90%)
occurrences (all)	0	1	6

Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	4 / 31 (12.90%)
occurrences (all)	0	2	5
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	1	2	0
Amylase increased			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	5
Haemoglobin decreased			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	5	0	0
Lipase increased			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 32 (18.75%)	4 / 32 (12.50%)	4 / 31 (12.90%)
occurrences (all)	8	5	5
Dizziness			
subjects affected / exposed	3 / 32 (9.38%)	4 / 32 (12.50%)	0 / 31 (0.00%)
occurrences (all)	5	4	0
Dysgeusia			
subjects affected / exposed	3 / 32 (9.38%)	0 / 32 (0.00%)	3 / 31 (9.68%)
occurrences (all)	3	0	3
Presyncope			
subjects affected / exposed	3 / 32 (9.38%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	3	0	0
Tremor			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	2 / 31 (6.45%)
occurrences (all)	1	0	2
Memory impairment			

subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Somnolence			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 32 (12.50%)	6 / 32 (18.75%)	4 / 31 (12.90%)
occurrences (all)	4	7	5
Leukocytosis			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 32 (21.88%)	22 / 32 (68.75%)	17 / 31 (54.84%)
occurrences (all)	12	43	28
Vomiting			
subjects affected / exposed	7 / 32 (21.88%)	14 / 32 (43.75%)	13 / 31 (41.94%)
occurrences (all)	9	32	23
Diarrhoea			
subjects affected / exposed	13 / 32 (40.63%)	8 / 32 (25.00%)	11 / 31 (35.48%)
occurrences (all)	20	15	17
Constipation			
subjects affected / exposed	9 / 32 (28.13%)	12 / 32 (37.50%)	5 / 31 (16.13%)
occurrences (all)	11	19	6
Stomatitis			
subjects affected / exposed	12 / 32 (37.50%)	6 / 32 (18.75%)	3 / 31 (9.68%)
occurrences (all)	16	7	3
Abdominal pain			
subjects affected / exposed	5 / 32 (15.63%)	5 / 32 (15.63%)	6 / 31 (19.35%)
occurrences (all)	5	5	7
Dyspepsia			
subjects affected / exposed	4 / 32 (12.50%)	4 / 32 (12.50%)	3 / 31 (9.68%)
occurrences (all)	5	5	4
Dry mouth			

subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	5 / 31 (16.13%)
occurrences (all)	1	3	5
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 32 (9.38%)	1 / 32 (3.13%)	3 / 31 (9.68%)
occurrences (all)	3	1	3
Abdominal pain upper			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	2 / 31 (6.45%)
occurrences (all)	2	2	2
Mouth ulceration			
subjects affected / exposed	3 / 32 (9.38%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences (all)	6	0	1
Dysphagia			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	1	2	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 32 (9.38%)	12 / 32 (37.50%)	6 / 31 (19.35%)
occurrences (all)	3	21	6
Rash			
subjects affected / exposed	3 / 32 (9.38%)	3 / 32 (9.38%)	5 / 31 (16.13%)
occurrences (all)	3	6	5
Dermatitis acneiform			
subjects affected / exposed	6 / 32 (18.75%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	7	2	0
Dry skin			
subjects affected / exposed	4 / 32 (12.50%)	0 / 32 (0.00%)	3 / 31 (9.68%)
occurrences (all)	5	0	3
Rash maculo-papular			
subjects affected / exposed	1 / 32 (3.13%)	1 / 32 (3.13%)	3 / 31 (9.68%)
occurrences (all)	2	1	3
Erythema			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	1 / 31 (3.23%)
occurrences (all)	2	1	1
Dysuria			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 32 (15.63%)	7 / 32 (21.88%)	2 / 31 (6.45%)
occurrences (all)	6	7	2
Pain in extremity			
subjects affected / exposed	6 / 32 (18.75%)	2 / 32 (6.25%)	2 / 31 (6.45%)
occurrences (all)	13	2	2
Arthralgia			
subjects affected / exposed	4 / 32 (12.50%)	1 / 32 (3.13%)	3 / 31 (9.68%)
occurrences (all)	5	1	4
Musculoskeletal pain			
subjects affected / exposed	2 / 32 (6.25%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	3	3	0
Bone pain			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences (all)	4	1	0
Groin pain			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 32 (6.25%)	2 / 32 (6.25%)	2 / 31 (6.45%)
occurrences (all)	5	2	2
Influenza			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	2 / 31 (6.45%)
occurrences (all)	2	0	2
Lower respiratory tract infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
Pneumonia			

subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences (all)	3	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	1	2	0
Nasopharyngitis			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 32 (46.88%)	10 / 32 (31.25%)	11 / 31 (35.48%)
occurrences (all)	19	15	14
Hyperglycaemia			
subjects affected / exposed	4 / 32 (12.50%)	4 / 32 (12.50%)	8 / 31 (25.81%)
occurrences (all)	5	6	13
Hypertriglyceridaemia			
subjects affected / exposed	5 / 32 (15.63%)	2 / 32 (6.25%)	1 / 31 (3.23%)
occurrences (all)	6	2	1
Hyperkalaemia			
subjects affected / exposed	0 / 32 (0.00%)	5 / 32 (15.63%)	2 / 31 (6.45%)
occurrences (all)	0	7	3
Dehydration			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	1 / 31 (3.23%)
occurrences (all)	1	2	1
Hypercalcaemia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	2 / 31 (6.45%)
occurrences (all)	0	3	2
Hypophosphataemia			
subjects affected / exposed	1 / 32 (3.13%)	1 / 32 (3.13%)	2 / 31 (6.45%)
occurrences (all)	1	2	3
Hyperuricaemia			
subjects affected / exposed	0 / 32 (0.00%)	3 / 32 (9.38%)	0 / 31 (0.00%)
occurrences (all)	0	3	0
Hypernatraemia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	0	2	0

Iron deficiency			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Metabolic acidosis			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	0	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2017	The primary purpose of Amendment 4 was to make following changes. Change the dosing conditions for participants receiving weekly MLN0128 in Arm B, such that participants take their doses with a light meal.Add a PK sample collection at 3 to 6 hours post-dose on Cycle 1 Day 1 for participants receiving weekly MLN0128 in Arm B.Clarify that disease assessment images will be collected and reviewed by a sponsor-specified central imaging vendor.Update the description of investigator responsibilities.Clarify the procedures for fasting serum glucose monitoring.Clarify that study drugs should be taken with approximately 240 mL of water.Clarify the instructions for dose modification due to adverse events of alanine aminotransferase or aspartate aminotransferase elevation.
03 October 2017	The primary purpose of Amendment 6 was to make following changes.Remove the exclusion criterion relating to treatment with strong cytochrome P450 (CYP) inhibitors or inducers.Update the list of concomitant medications prohibited during the study.Update the description of potential drug-drug interactions.Update the list of relevant CYP inhibitors and inducers.Remove dietary restrictions related to CYP inhibitors and inducers.Clarify language surrounding the use of contrast with magnetic resonance imaging (MRI).
03 December 2018	The primary purpose of Amendment 9 was to make following changes. Removed long-term follow-up, the option for cross-over treatment from Arm A to Arm B or Arm C and added the option for participants to transfer to a Post-Trial Access (PTA) program.Study closure was defined as when the last participant discontinues treatment.A new section was added detailing the PTA program.Modified the exclusion criterion relating to proton-pump inhibitors (PPIs).Revised the restrictions on concomitant use of proton-pump inhibitors (PPIs).Physical examinations after Screening were changed to symptom-directed physical examinations. The requirement for a confirmatory scan 4 weeks from the previous scan for participants with a complete response (CR) or partial response (PR) was removed. A recommendation was added for radiographic assessment every 6 months after 12 cycles of treatment.The requirement for weight to be measured at Day 15 of Cycles 1 and 2 was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported