

**Clinical trial results:****A Phase 1 Study of XL184 (Cabozantinib, IND# 116059) in Children and Adolescents with Recurrent or Refractory Solid Tumors, Including CNS Tumors****Summary**

EudraCT number	2018-004591-35
Trial protocol	Outside EU/EEA
Global end of trial date	31 December 2019

Results information

Result version number	v1 (current)
This version publication date	27 August 2021
First version publication date	27 August 2021

Trial information**Trial identification**

Sponsor protocol code	ADVL1211
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01709435
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	National Cancer Institute Cancer Therapy Evaluation Program (NCI/CTEP)
Sponsor organisation address	9609 Medical Center Drive, Bethesda, United States, MD 20892
Public contact	Medical Director, Ipsen Innovation, clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen Innovation, clinical.trials@ipsen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001143-PIP01-11
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 December 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives were to identify a maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D), to characterise the toxicity profile, and to describe the pharmacokinetics (PK) of XL184 (cabozantinib) in a population of paediatric subjects aged 2 to 18 years (inclusive).

Protection of trial subjects:

The study was conducted in accordance with National Cancer Institute (NCI) standards, policies and procedures of NCI and the Children's Oncology Group (COG) and in accordance with applicable laws. COG is an NCI supported National Clinical Trials Network group. The study was conducted according to the ethical principles of the Declaration of Helsinki. This study was conducted in accordance with all applicable regulatory requirements according to the policies and procedures of NCI and COG.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 November 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	41
EEA total number of subjects	0

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)	18
Adolescents (12-17 years)	19
Adults (18-64 years)	4

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase 1 limited dose-escalation study was conducted in children and adolescent subjects with recurrent or refractory solid tumors including central nervous system tumors at 16 investigational sites in the United States of America that included at least one subject.

Pre-assignment

Screening details:

Part A: Dose-escalation phase to determine the MTD and/or RP2D; Part B: an evaluation of subjects with medullary thyroid cancer (MTC) at the MTD/RP2D or below; and PK Expansion: for further collection of PK, safety, and efficacy information at 40 mg/m². 41 subjects were enrolled into the study, of whom 39 subjects were treated with XL184.

Period 1

Period 1 title	Treatment Assignment to Treatment Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	XL184 30 mg/m ² /day

Arm description:

Subjects were assigned to receive XL184 30 milligrams per meter squared per day (mg/m²/day) administered orally.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	XL184 40 mg/m ² /day

Arm description:

Subjects were assigned to receive XL184 40 mg/m²/day administered orally.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	XL184 55 mg/m ² /day

Arm description:

Subjects were assigned to receive XL184 55 mg/m²/day administered orally.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day
Started	6	23	12
Completed	6	21	12
Not completed	0	2	0
Physician decision	-	1	-
Adverse event, non-fatal	-	1	-

Period 2

Period 2 title	Treatment Period
Is this the baseline period?	Yes ^[1]
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	XL184 30 mg/m ² /day

Arm description:

Subjects received XL184 30 mg/m²/day administered orally.

Arm type	Experimental
Investigational medicinal product name	Cabozantinib
Investigational medicinal product code	XL184
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

XL184 tablets were administered orally at a starting dose of 30 mg/m²/day (Dose Level 1). Additional dose levels are 23 mg/m²/day (Dose Level -1), 30 mg/m²/day (Dose Level 1), 40 mg/m²/day (Dose Level 2), and 55 mg/m²/day (Dose Level 3). The dose was escalated using a rolling six design. Doses were not escalated beyond 55 mg/m²/day.

Arm title	XL184 40 mg/m ² /day
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Arm description:

Subjects received XL184 40 mg/m²/day administered orally.

Arm type	Experimental
Investigational medicinal product name	Cabozantinib
Investigational medicinal product code	XL184
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

XL184 tablets were administered orally at a starting dose of 30 mg/m²/day (Dose Level 1). Additional dose levels are 23 mg/m²/day (Dose Level -1), 30 mg/m²/day (Dose Level 1), 40 mg/m²/day (Dose Level 2), and 55 mg/m²/day (Dose Level 3). The dose was escalated using a rolling six design. Doses were not escalated beyond 55 mg/m²/day.

Arm title	XL184 55 mg/m ² /day
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Arm description:

Subjects received XL184 55 mg/m²/day administered orally.

Arm type	Experimental
Investigational medicinal product name	Cabozantinib
Investigational medicinal product code	XL184
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

XL184 tablets were administered orally at a starting dose of 30 mg/m²/day (Dose Level 1). Additional dose levels are 23 mg/m²/day (Dose Level -1), 30 mg/m²/day (Dose Level 1), 40 mg/m²/day (Dose Level 2), and 55 mg/m²/day (Dose Level 3). The dose was escalated using a rolling six design. Doses were not escalated beyond 55 mg/m²/day.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 presents data for all subjects assigned treatment. Period 2 presents data for all subjects who received the study drug. The baseline characteristics are based on subjects who were assigned treatment and who received the study drug; therefore, Period 2 is the baseline period.

Number of subjects in period 2^[2]	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day
Started	6	21	12
Completed	0	1	0
Not completed	6	20	12
Physician decision	-	3	-
Adverse event, non-fatal	1	-	2
Subject/Guardian Decision	-	2	5
Evidence of Progressive Disease	5	15	5

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Period 1 presents data for all subjects assigned treatment. Period 2 presents data for all subjects who received the study drug. The baseline characteristics are based on subjects who were assigned treatment and who received the study drug; therefore, Period 2 is the baseline period.

Period 3

Period 3 title	Follow-up Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	XL184 30 mg/m ² /day

Arm description:

Subjects received XL184 30 mg/m²/day administered orally during the treatment period.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	XL184 40 mg/m ² /day

Arm description:

Subjects received XL184 40 mg/m²/day administered orally during the treatment period.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	XL184 55 mg/m ² /day

Arm description:

Subjects received XL184 55 mg/m²/day administered orally during the treatment period.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day
Started	6	17	10
Completed	3	7	4
Not completed	3	10	6
Death	3	6	5
Ongoing	-	1	-
Subject/Guardian Decision	-	2	1
Lost to follow-up	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	XL184 30 mg/m ² /day
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Reporting group description:

Subjects received XL184 30 mg/m²/day administered orally.

Reporting group title	XL184 40 mg/m ² /day
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Reporting group description:

Subjects received XL184 40 mg/m²/day administered orally.

Reporting group title	XL184 55 mg/m ² /day
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Reporting group description:

Subjects received XL184 55 mg/m²/day administered orally.

Reporting group values	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day
Number of subjects	6	21	12
Age categorical			
Units: Subjects			
<12 years	1	11	6
≥12 years to ≤18 years	5	10	6
Age continuous			
Units: years			
arithmetic mean	15.2	11.3	12.6
standard deviation	± 2.79	± 4.53	± 3.55
Gender categorical			
Units: Subjects			
Female	2	10	7
Male	4	11	5
Race			
Units: Subjects			
White	3	13	9
Black or African American	2	2	3
Asian	0	3	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Unknown	1	3	0
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	4	21	11
Hispanic or Latino	2	0	1
Unknown	0	0	0
Body Surface Area (BSA)			
Units: Meters ²			
arithmetic mean	1.468	1.303	1.278
standard deviation	± 0.3916	± 0.4673	± 0.3058

Reporting group values	Total		
Number of subjects	39		

Age categorical Units: Subjects			
<12 years	18		
≥12 years to ≤18 years	21		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	19		
Male	20		
Race Units: Subjects			
White	25		
Black or African American	7		
Asian	3		
American Indian or Alaska Native	0		
Native Hawaiian or Other Pacific Islander	0		
Unknown	4		
Ethnicity Units: Subjects			
Not Hispanic or Latino	36		
Hispanic or Latino	3		
Unknown	0		
Body Surface Area (BSA) Units: Meters^2 arithmetic mean standard deviation	-		

Subject analysis sets

Subject analysis set title	Pooled Analysis
Subject analysis set type	Full analysis
Subject analysis set description: The Safety population included all subjects who received at least one dose of study drug.	

Reporting group values	Pooled Analysis		
Number of subjects	39		
Age categorical Units: Subjects			
<12 years	18		
≥12 years to ≤18 years	21		
Age continuous Units: years arithmetic mean standard deviation	12.3 ± 4.17		
Gender categorical Units: Subjects			
Female	19		

Male	20		
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Race			
Units: Subjects			
White	25		
Black or African American	7		
Asian	3		
American Indian or Alaska Native	0		
Native Hawaiian or Other Pacific Islander	0		
Unknown	4		
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	36		
Hispanic or Latino	3		
Unknown	0		
Body Surface Area (BSA)			
Units: Meters^2			
arithmetic mean	1.321		
standard deviation	± 0.4079		

End points

End points reporting groups

Reporting group title	XL184 30 mg/m ² /day
Reporting group description: Subjects were assigned to receive XL184 30 milligrams per meter squared per day (mg/m ² /day) administered orally.	
Reporting group title	XL184 40 mg/m ² /day
Reporting group description: Subjects were assigned to receive XL184 40 mg/m ² /day administered orally.	
Reporting group title	XL184 55 mg/m ² /day
Reporting group description: Subjects were assigned to receive XL184 55 mg/m ² /day administered orally.	
Reporting group title	XL184 30 mg/m ² /day
Reporting group description: Subjects received XL184 30 mg/m ² /day administered orally.	
Reporting group title	XL184 40 mg/m ² /day
Reporting group description: Subjects received XL184 40 mg/m ² /day administered orally.	
Reporting group title	XL184 55 mg/m ² /day
Reporting group description: Subjects received XL184 55 mg/m ² /day administered orally.	
Reporting group title	XL184 30 mg/m ² /day
Reporting group description: Subjects received XL184 30 mg/m ² /day administered orally during the treatment period.	
Reporting group title	XL184 40 mg/m ² /day
Reporting group description: Subjects received XL184 40 mg/m ² /day administered orally during the treatment period.	
Reporting group title	XL184 55 mg/m ² /day
Reporting group description: Subjects received XL184 55 mg/m ² /day administered orally during the treatment period.	
Subject analysis set title	Pooled Analysis
Subject analysis set type	Full analysis
Subject analysis set description: The Safety population included all subjects who received at least one dose of study drug.	

Primary: MTD of XL184

End point title	MTD of XL184 ^[1]
End point description: The MTD was defined as the highest dose at which fewer than one-third of subjects experienced a dose-limiting toxicity (DLT) during Cycle 1 of therapy. '99999' denotes that the MTD was not reached in this study. The Safety population included all subjects who received at least one dose of study drug.	
End point type	Primary
End point timeframe: Up to Cycle 1 Day 28	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No additional statistical analysis was pre-specified for this endpoint.	

End point values	Pooled Analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	39			
Units: mg/m ² /day				
number (not applicable)	99999			

Statistical analyses

No statistical analyses for this end point

Primary: RP2D of XL184

End point title	RP2D of XL184 ^[2]
End point description: A RP2D was established based on tolerability, pharmacokinetic parameters and response, if applicable. The Safety population included all subjects who received at least one dose of study drug.	
End point type	Primary
End point timeframe: Up to Cycle 1 Day 28	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	Pooled Analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	39			
Units: mg/m ² /day				
number (not applicable)	40			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment Emergent DLTs During Cycle 1

End point title	Number of Subjects with Treatment Emergent DLTs During Cycle 1 ^[3]
End point description: DLTs were defined as non-haematological or haematological drug-related treatment-emergent adverse events (TEAEs). TEAEs are defined as events which started or worsened on or after the first dose of study drug administration up to 30 days (gap period) after the last dose of study drug administration. Any TEAE assessed as not drug-related that required a dose reduction in Cycle 1 was also considered a DLT. The Safety population included all subjects who received at least one dose of study drug.	
End point type	Primary
End point timeframe: Up to Cycle 1 Day 28	

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	21	12	
Units: Subjects with DLTs during Cycle 1	0	5	3	

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Plasma Concentration (C_{max}) of XL184 on Days 1 and 21 of Cycle 1

End point title	Maximum Plasma Concentration (C _{max}) of XL184 on Days 1 and 21 of Cycle 1 ^[4]
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End point description:

The PK analysis was performed on subjects who received at least one oral administration of XL184, without major protocol deviation affecting the PK, who did not experience emesis during the dosing interval and who had sufficient number of plasma concentrations to estimate the main PK parameters. 'n' denotes number of subjects analysed for each category.

End point type	Primary
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End point timeframe:

Cycle 1 Day 1 (pre-dose and 4 hours post-dose) and Cycle 1 Day 21 (pre-dose and 2, 4, 8, and 24 hours post-dose)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	16	12	
Units: nanograms per millilitre				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (n= 6, 16, 12)	278 (± 67.6)	350 (± 73.9)	585 (± 39.1)	
Cycle 1 Day 21 (n= 6, 13, 9)	1854 (± 33.4)	1552 (± 53.0)	2160 (± 37.8)	

Statistical analyses

No statistical analyses for this end point

Primary: Time to Reach C_{max} (T_{max}) of XL184 on Cycle 1 Day 21

End point title	Time to Reach C _{max} (T _{max}) of XL184 on Cycle 1 Day 21 ^[5]
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End point description:

The PK analysis was performed on subjects who received at least one oral administration of XL184, without major protocol deviation affecting the PK, who did not experience emesis during the dosing interval and who had sufficient number of plasma concentrations to estimate the main PK parameters.

End point type	Primary
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End point timeframe:

Cycle 1 Day 21 (pre-dose and 2, 4, 8, and 24 hours post-dose)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	13	9	
Units: hours				
median (full range (min-max))	2.00 (0.00 to 4.00)	4.00 (1.85 to 24.03)	2.00 (1.08 to 25.45)	

Statistical analyses

No statistical analyses for this end point

Primary: Time of the last observed plasma concentration (Tlast) of XL184 on Cycle 1 Day 21

End point title	Time of the last observed plasma concentration (Tlast) of XL184 on Cycle 1 Day 21 ^[6]
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End point description:

The PK analysis was performed on subjects who received at least one oral administration of XL184, without major protocol deviation affecting the PK, who did not experience emesis during the dosing interval and who had sufficient number of plasma concentrations to estimate the main PK parameters.

End point type	Primary
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End point timeframe:

Cycle 1 Day 21 (pre-dose and 2, 4, 8, and 24 hours post-dose)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	13	9	
Units: hours				
median (full range (min-max))	23.74 (8.05 to 24.92)	24.00 (7.98 to 26.83)	23.92 (7.08 to 25.45)	

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-time Curve from 0 to 24 Hours Post-dose (AUC₀₋₂₄ hours) of XL184 on Cycle 1 Day 21

End point title	Area Under the Plasma Concentration-time Curve from 0 to 24 Hours Post-dose (AUC ₀₋₂₄ hours) of XL184 on Cycle 1 Day 21 ^[7]
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End point description:

The PK analysis was performed on subjects who received at least one oral administration of XL184, without major protocol deviation affecting the PK, who did not experience emesis during the dosing interval and who had sufficient number of plasma concentrations to estimate the main PK parameters.

End point type	Primary
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End point timeframe:

Cycle 1 Day 21 (pre-dose and 2, 4, 8, and 24 hours post-dose)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	11	6	
Units: nanograms*hours per millilitre				
geometric mean (geometric coefficient of variation)	29872 (± 35.8)	30230 (± 52.1)	37058 (± 29.8)	

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Total Clearance (CL/F) of XL184 on Cycle 1 Day 21

End point title	Apparent Total Clearance (CL/F) of XL184 on Cycle 1 Day 21 ^[8]
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End point description:

The PK analysis was performed on subjects who received at least one oral administration of XL184, without major protocol deviation affecting the PK, who did not experience emesis during the dosing interval and who had sufficient number of plasma concentrations to estimate the main PK parameters.

End point type	Primary
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End point timeframe:

Cycle 1 Day 21 (pre-dose and 2, 4, 8, and 24 hours post-dose)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No additional statistical analysis was pre-specified for this endpoint.

End point values	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	11	6	
Units: Litres per hour (L/ h)				
geometric mean (geometric coefficient of variation)	1.64 (± 34.8)	2.04 (± 47.4)	2.11 (± 38.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response (BOR)

End point title	Best Overall Response (BOR)
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End point description:

Disease response was assessed according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria (Version 1.1) for subjects with solid tumours. BOR was the best post-baseline response recorded from the start of the treatment until disease progression or recurrence. Central review evaluation of BOR for subjects who responded (Complete Response [CR], Partial Response [PR]) to therapy or have long term stable disease (≥ 6 cycles) on protocol therapy. The Evaluable population included all subjects who received at least 85% of the prescribed dose or experienced a DLT.

End point type	Secondary
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End point timeframe:

Up to the end of the treatment period, approximately 4 years

End point values	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	19	11	
Units: Subjects				
CR	0	0	0	
PR	0	2	2	
Stable Disease	2	5	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)
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End point description:

Disease response was assessed according to RECIST V1.1 criteria for subjects with solid tumours. DoR was measured from when the time measurement criteria were met for CR or PR (whichever was recorded first) that was subsequently confirmed until the first date that progressive disease was objectively documented, date of death, or censoring date. '9999' denotes no subjects had a partial response in that study arm; '99999' denotes standard deviation cannot be calculated when only one is subject analysed; 'n' denotes number of subjects analysed for each category. The Evaluable population included all subjects who received at least 85% of the prescribed dose or experienced a DLT.

End point type	Secondary
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End point timeframe:

Up to the end of the treatment period, approximately 4 years

End point values	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	19	11	
Units: days				
arithmetic mean (standard deviation)				
Partial Response or Stable Disease (n= 2, 7, 3)	195.0 (± 1.41)	457.0 (± 399.46)	340.7 (± 242.71)	
Partial Response (n= 0, 2, 2)	9999 (± 9999)	868.5 (± 617.30)	346.5 (± 342.95)	
Stable Disease (n= 2, 5, 1)	195.0 (± 1.41)	292.4 (± 159.87)	329.0 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline in Pharmacodynamic Biomarkers on Days 21 and 28 of Cycle 1

End point title	Percentage Change from Baseline in Pharmacodynamic Biomarkers on Days 21 and 28 of Cycle 1
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End point description:

Pharmacodynamic biomarkers included hepatocyte growth factor receptor protein (c-MET), vascular endothelial growth factor receptor 2 (VEGF-R2), hepatocyte growth factor (HGF), GAS 6 receptor (AXL), carbonic anhydrase 9 (CA9), erythropoietin (EPO), osteopontin (OPN), placenta growth factor (PIGF), interleukin-6 (IL-6), and tissue inhibitors of metalloproteinase-1 (TIMP-1). Baseline is the last non-missing result prior to first study drug administration, including unscheduled assessments (where applicable). 'n' denotes number of subjects analysed for each category. The Evaluable population included all subjects who received at least 85% of the prescribed dose or experienced a DLT.

End point type	Secondary
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End point timeframe:

Baseline; Days 21 and 28 of Cycle 1

End point values	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	15	10	
Units: Percentage change from baseline (%)				
median (full range (min-max))				
AXL: Cycle 1 Day 21 (n= 6, 15, 10)	23.92 (8.3 to 48.8)	21.17 (0.0 to 56.9)	-8.62 (-31.0 to 56.9)	
AXL: Cycle 1 Day 28 (n= 5, 15, 10)	24.24 (-1.7 to 93.0)	18.73 (-10.1 to 58.7)	-1.99 (-26.5 to 81.6)	
CA9: Cycle 1 Day 21 (n= 6, 15, 10)	163.05 (36.1 to 1234.1)	128.37 (-58.4 to 1276.0)	175.19 (-7.5 to 542.5)	
CA9: Cycle 1 Day 28 (n= 5, 15, 10)	140.21 (21.1 to 865.3)	205.52 (-33.8 to 1308.4)	185.01 (-50.1 to 784.4)	

PIGF: Cycle 1 Day 21 (n= 6, 15, 10)	81.91 (7.4 to 165.9)	94.37 (-10.3 to 288.8)	115.29 (-0.2 to 292.1)
PIGF: Cycle 1 Day 28 (n= 5, 15, 10)	86.83 (4.8 to 149.3)	115.07 (26.8 to 219.0)	91.20 (-2.6 to 938.7)
OPN: Cycle 1 Day 21 (n= 6, 15, 10)	-20.43 (-48.6 to -7.3)	-12.60 (-54.5 to 22.6)	-19.13 (-76.2 to 42.0)
OPN: Cycle 1 Day 28 (n= 5, 15, 10)	-14.02 (-39.7 to 11.4)	-10.46 (-54.0 to 128.6)	-22.00 (-58.9 to 59.8)
TIMP-1: Cycle 1 Day 21 (n= 6, 15, 10)	-35.79 (-49.3 to 17.3)	-36.01 (-64.2 to 37.0)	-15.10 (-59.5 to 17.9)
TIMP-1: Cycle 1 Day 28 (n= 5, 15, 10)	-30.07 (-38.9 to 0.4)	-24.82 (-69.5 to 31.7)	-19.71 (-41.7 to 1.5)
VEGF-R2: Cycle 1 Day 21 (n= 6, 15, 10)	-12.50 (-24.1 to 5.1)	-16.61 (-29.9 to -3.2)	-33.49 (-49.9 to -7.9)
VEGF-R2: Cycle 1 Day 28 (n= 5, 15, 10)	-13.44 (-17.9 to -4.1)	-22.96 (-38.4 to -3.8)	-37.20 (-49.8 to -2.0)
c-MET: Cycle 1 Day 21 (n= 6, 15, 10)	14.70 (4.9 to 40.6)	11.81 (-23.7 to 39.8)	-1.70 (-33.3 to 64.1)
c-MET: Cycle 1 Day 28 (n= 5, 15, 10)	20.36 (5.8 to 55.6)	10.96 (-13.4 to 25.2)	2.63 (-20.9 to 29.1)
EPO: Cycle 1 Day 21 (n= 6, 15, 10)	85.99 (2.3 to 229.7)	5.49 (-56.4 to 204.2)	27.27 (-74.5 to 183.7)
EPO: Cycle 1 Day 28 (n= 5, 15, 10)	99.37 (23.1 to 173.9)	28.61 (-49.9 to 166.8)	89.16 (-67.9 to 372.2)
HGF: Cycle 1 Day 21 (n= 6, 15, 10)	-23.25 (-54.1 to 12.8)	-17.32 (-64.4 to 123.9)	-23.57 (-56.2 to 34.3)
HGF: Cycle 1 Day 28 (n= 5, 15, 10)	-6.92 (-52.9 to 53.4)	-10.76 (-86.1 to 149.1)	-23.67 (-64.5 to 66.4)
IL-6: Cycle 1 Day 21 (n= 6, 15, 10)	8.70 (-93.8 to 504.6)	0.00 (-76.8 to 6653.0)	-48.78 (-97.2 to 4972.0)
IL-6: Cycle 1 Day 28 (n= 5, 15, 10)	5.01 (0.0 to 224.8)	0.00 (-90.7 to 7660.6)	-36.30 (-97.2 to 2859.6)

Statistical analyses

Statistical analysis title	AXL: Change from Baseline at Cycle 1 Day 21
Statistical analysis description:	
Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction.	
Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0349
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	AXL: Change from Baseline at Cycle 1 Day 28
Statistical analysis description:	
Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction. Number of subjects included in analysis= 30.	
Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55

	mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0245
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	CA9: Change from Baseline at Cycle 1 Day 21
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Statistical analysis description:

Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction.

Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	CA9: Change from Baseline at Cycle 1 Day 28
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Statistical analysis description:

Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction. Number of subjects included in analysis= 30.

Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	PIGF: Change from Baseline at Cycle 1 Day 21
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Statistical analysis description:

Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction.

Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
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Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	PIGF: Change from Baseline at Cycle 1 Day 28
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Statistical analysis description:

Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction. Number of subjects included in analysis= 30.

Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	OPN: Change from Baseline at Cycle 1 Day 21
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Statistical analysis description:

Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction.

Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0039
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	OPN: Change from Baseline at Cycle 1 Day 28
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Statistical analysis description:

Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction. Number of subjects included in analysis= 30.

Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0322
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	TIMP-1: Change from Baseline at Cycle 1 Day 21
Statistical analysis description: Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction.	
Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0003
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	TIMP-1: Change from Baseline at Cycle 1 Day 28
Statistical analysis description: Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction. Number of subjects included in analysis= 30.	
Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	VEGF-R2: Change from Baseline at Cycle 1 Day 21
Statistical analysis description: Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction.	
Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	VEGF-R2: Change from Baseline at Cycle 1 Day 28
Statistical analysis description: Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the	

Bonferroni correction. Number of subjects included in analysis= 30.

Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title

c-MET: Change from Baseline at Cycle 1 Day 21

Statistical analysis description:

Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction.

Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7091
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title

c-MET: Change from Baseline at Cycle 1 Day 28

Statistical analysis description:

Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction. Number of subjects included in analysis= 30.

Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5472
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title

EPO: Change from Baseline at Cycle 1 Day 21

Statistical analysis description:

Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction.

Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
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Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2837
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	EPO: Change from Baseline at Cycle 1 Day 28
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Statistical analysis description:

Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction. Number of subjects included in analysis= 30.

Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0498
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	HGF: Change from Baseline at Cycle 1 Day 21
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Statistical analysis description:

Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction.

Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7872
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	HGF: Change from Baseline at Cycle 1 Day 28
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Statistical analysis description:

Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction. Number of subjects included in analysis= 30.

Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.9999
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	IL-6: Change from Baseline at Cycle 1 Day 21
Statistical analysis description: Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction.	
Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.9999
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	IL-6: Change from Baseline at Cycle 1 Day 28
Statistical analysis description: Testing the null hypothesis of whether the overall median difference between each post-baseline and baseline visit is zero using Wilcoxon signed-rank test adjusted for multiple comparisons using the Bonferroni correction. Number of subjects included in analysis= 30.	
Comparison groups	XL184 30 mg/m ² /day v XL184 40 mg/m ² /day v XL184 55 mg/m ² /day
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.9999
Method	Wilcoxon (Mann-Whitney)

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description: The OS was defined as the time from the start of study treatment until death due to any cause. Survival times were censored at the time when the subject was last known to be alive i.e. at the last recorded visit date. '99999' denotes that the value was not calculable (not reached). The Evaluable population included all subjects who received at least 85% of the prescribed dose or experienced a DLT.	
End point type	Secondary
End point timeframe: Up to the end of the follow-up period, a maximum of approximately 8.5 years	

End point values	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	19	11	
Units: months				
median (confidence interval 95%)	18.93 (1.61 to 22.75)	34.02 (6.28 to 99999)	8.48 (5.16 to 99999)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 30 of the follow-up period, approximately 4 years

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	XL184 30 mg/m ² /day
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Reporting group description:

Subjects received XL184 30 mg/m²/day administered orally.

Reporting group title	XL184 40 mg/m ² /day
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Reporting group description:

Subjects received XL184 40 mg/m²/day administered orally.

Reporting group title	XL184 55 mg/m ² /day
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Reporting group description:

Subjects received XL184 55 mg/m²/day administered orally.

Serious adverse events	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	13 / 21 (61.90%)	6 / 12 (50.00%)
number of deaths (all causes)	3	6	5
number of deaths resulting from adverse events	1	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Tumour pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 6 (16.67%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 21 (9.52%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Agitation			

subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 21 (14.29%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Lipase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Urine output decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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

Mitral valve disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Tricuspid valve disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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			
Depressed level of consciousness			
subjects affected / exposed	1 / 6 (16.67%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyskinesia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (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
Cerebral ischaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Hydrocephalus			

subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Peripheral motor neuropathy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Abdominal pain			

subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Gastritis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 6 (16.67%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Musculoskeletal and connective tissue disorders			
Bone pain			

subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Enterocolitis infectious			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Lung infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	2 / 12 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypernatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			

subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	0 / 12 (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

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

Non-serious adverse events	XL184 30 mg/m ² /day	XL184 40 mg/m ² /day	XL184 55 mg/m ² /day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	21 / 21 (100.00%)	12 / 12 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 6 (33.33%)	12 / 21 (57.14%)	6 / 12 (50.00%)
occurrences (all)	4	20	8
Flushing			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	1 / 12 (8.33%)
occurrences (all)	0	4	2
Hot flush			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Deep vein thrombosis			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 21 (0.00%) 0	1 / 12 (8.33%) 1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 6 (50.00%)	14 / 21 (66.67%)	7 / 12 (58.33%)
occurrences (all)	3	22	8
Pyrexia			
subjects affected / exposed	2 / 6 (33.33%)	6 / 21 (28.57%)	7 / 12 (58.33%)
occurrences (all)	2	10	9
Pain			
subjects affected / exposed	1 / 6 (16.67%)	4 / 21 (19.05%)	1 / 12 (8.33%)
occurrences (all)	2	12	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	3 / 21 (14.29%)	4 / 12 (33.33%)
occurrences (all)	0	4	5
Oedema peripheral			
subjects affected / exposed	1 / 6 (16.67%)	3 / 21 (14.29%)	2 / 12 (16.67%)
occurrences (all)	1	3	2
Gait disturbance			
subjects affected / exposed	1 / 6 (16.67%)	2 / 21 (9.52%)	1 / 12 (8.33%)
occurrences (all)	1	2	1
Face oedema			
subjects affected / exposed	1 / 6 (16.67%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	1	5	0
Malaise			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Hypothermia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Immune system disorders			

Hypersensitivity subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	0 / 21 (0.00%) 0	0 / 12 (0.00%) 0
Reproductive system and breast disorders			
Menstruation irregular subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 21 (9.52%) 5	0 / 12 (0.00%) 0
Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 21 (0.00%) 0	1 / 12 (8.33%) 1
Genital rash subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 21 (0.00%) 0	1 / 12 (8.33%) 1
Testicular pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 21 (0.00%) 0	0 / 12 (0.00%) 0
Vaginal haemorrhage subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 21 (0.00%) 0	1 / 12 (8.33%) 1
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 3	9 / 21 (42.86%) 16	6 / 12 (50.00%) 8
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	7 / 21 (33.33%) 9	4 / 12 (33.33%) 6
Nasal congestion subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 3	5 / 21 (23.81%) 8	2 / 12 (16.67%) 2
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 3	5 / 21 (23.81%) 5	3 / 12 (25.00%) 4
Dyspnoea subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	4 / 21 (19.05%) 4	2 / 12 (16.67%) 2
Hypoxia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	3 / 21 (14.29%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Atelectasis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Rhinorrhoea			
subjects affected / exposed	1 / 6 (16.67%)	1 / 21 (4.76%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Tachypnoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Haemoptysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pneumothorax			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Sinus disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Sinus pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 6 (16.67%)	3 / 21 (14.29%)	1 / 12 (8.33%)
occurrences (all)	1	4	1

Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	4 / 21 (19.05%)	2 / 12 (16.67%)
occurrences (all)	0	7	3
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	5 / 21 (23.81%)	0 / 12 (0.00%)
occurrences (all)	0	7	0
Irritability			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Depression			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Confusional state			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Personality change			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 6 (83.33%)	15 / 21 (71.43%)	8 / 12 (66.67%)
occurrences (all)	9	33	8
Alanine aminotransferase increased			
subjects affected / exposed	3 / 6 (50.00%)	17 / 21 (80.95%)	8 / 12 (66.67%)
occurrences (all)	4	48	14
Weight decreased			
subjects affected / exposed	2 / 6 (33.33%)	11 / 21 (52.38%)	8 / 12 (66.67%)
occurrences (all)	4	17	11
Platelet count decreased			
subjects affected / exposed	1 / 6 (16.67%)	14 / 21 (66.67%)	5 / 12 (41.67%)
occurrences (all)	1	24	12
Lymphocyte count decreased			
subjects affected / exposed	3 / 6 (50.00%)	11 / 21 (52.38%)	5 / 12 (41.67%)
occurrences (all)	5	22	10
White blood cell count decreased			

subjects affected / exposed	5 / 6 (83.33%)	9 / 21 (42.86%)	5 / 12 (41.67%)
occurrences (all)	8	18	20
Neutrophil count decreased			
subjects affected / exposed	3 / 6 (50.00%)	7 / 21 (33.33%)	4 / 12 (33.33%)
occurrences (all)	5	16	15
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 6 (50.00%)	7 / 21 (33.33%)	3 / 12 (25.00%)
occurrences (all)	6	11	3
Lipase increased			
subjects affected / exposed	1 / 6 (16.67%)	7 / 21 (33.33%)	5 / 12 (41.67%)
occurrences (all)	2	12	6
Haemoglobin increased			
subjects affected / exposed	1 / 6 (16.67%)	7 / 21 (33.33%)	0 / 12 (0.00%)
occurrences (all)	4	25	0
Blood bilirubin increased			
subjects affected / exposed	2 / 6 (33.33%)	1 / 21 (4.76%)	3 / 12 (25.00%)
occurrences (all)	3	1	6
Amylase increased			
subjects affected / exposed	0 / 6 (0.00%)	4 / 21 (19.05%)	2 / 12 (16.67%)
occurrences (all)	0	8	3
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 21 (14.29%)	1 / 12 (8.33%)
occurrences (all)	0	10	1
Blood cholesterol increased			
subjects affected / exposed	1 / 6 (16.67%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Blood urea increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Blood creatinine decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	3

Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences (all)	0	4	1
Carbon dioxide increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
International normalised ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Weight increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Blood chloride decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood chloride increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood phosphorus increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood urea decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Glucose urine present			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Haptoglobin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Lipase decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Neutrophil count increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pancreatic enzymes decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Protein total decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Protein total increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	3
Prothrombin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	5 / 21 (23.81%)	1 / 12 (8.33%)
occurrences (all)	0	7	1
Fall			
subjects affected / exposed	0 / 6 (0.00%)	3 / 21 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	5	0
Skin abrasion			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Sunburn			
subjects affected / exposed	1 / 6 (16.67%)	1 / 21 (4.76%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Wound complication			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	7 / 21 (33.33%)	3 / 12 (25.00%)
occurrences (all)	0	8	5
Sinus bradycardia			

subjects affected / exposed	0 / 6 (0.00%)	3 / 21 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Palpitations			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Left ventricular hypertrophy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pericardial effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 6 (33.33%)	13 / 21 (61.90%)	4 / 12 (33.33%)
occurrences (all)	4	30	4
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	6 / 21 (28.57%)	0 / 12 (0.00%)
occurrences (all)	0	9	0
Paraesthesia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 21 (14.29%)	1 / 12 (8.33%)
occurrences (all)	1	4	1
Dysarthria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Dysgeusia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Lethargy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Memory impairment			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

hydrocephalus subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 21 (0.00%) 0	0 / 12 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	8 / 21 (38.10%) 13	9 / 12 (75.00%) 18
Haemolysis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 21 (0.00%) 0	1 / 12 (8.33%) 1
Eye disorders			
Vision blurred subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	3 / 21 (14.29%) 3	0 / 12 (0.00%) 0
Eye irritation subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 21 (0.00%) 0	1 / 12 (8.33%) 1
Scleral hyperaemia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 21 (0.00%) 0	0 / 12 (0.00%) 0
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	5 / 6 (83.33%) 11	15 / 21 (71.43%) 41	9 / 12 (75.00%) 18
Vomiting subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 3	16 / 21 (76.19%) 42	7 / 12 (58.33%) 13
Nausea subjects affected / exposed occurrences (all)	4 / 6 (66.67%) 7	13 / 21 (61.90%) 34	8 / 12 (66.67%) 13
Abdominal pain subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	10 / 21 (47.62%) 18	3 / 12 (25.00%) 6
Constipation subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 4	8 / 21 (38.10%) 17	4 / 12 (33.33%) 5
Stomatitis			

subjects affected / exposed	0 / 6 (0.00%)	3 / 21 (14.29%)	4 / 12 (33.33%)
occurrences (all)	0	3	4
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	4 / 21 (19.05%)	1 / 12 (8.33%)
occurrences (all)	0	7	1
Abdominal pain upper			
subjects affected / exposed	1 / 6 (16.67%)	2 / 21 (9.52%)	1 / 12 (8.33%)
occurrences (all)	1	6	1
Oral pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 21 (4.76%)	2 / 12 (16.67%)
occurrences (all)	1	2	2
Anal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Mouth haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Cheilitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Eructation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Proctalgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			

Hair colour changes			
subjects affected / exposed	2 / 6 (33.33%)	8 / 21 (38.10%)	5 / 12 (41.67%)
occurrences (all)	2	8	5
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 6 (16.67%)	8 / 21 (38.10%)	5 / 12 (41.67%)
occurrences (all)	1	21	6
Dry skin			
subjects affected / exposed	1 / 6 (16.67%)	7 / 21 (33.33%)	2 / 12 (16.67%)
occurrences (all)	1	8	2
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)	5 / 21 (23.81%)	2 / 12 (16.67%)
occurrences (all)	0	6	2
Rash maculo-papular			
subjects affected / exposed	0 / 6 (0.00%)	7 / 21 (33.33%)	0 / 12 (0.00%)
occurrences (all)	0	7	0
Skin hypopigmentation			
subjects affected / exposed	1 / 6 (16.67%)	3 / 21 (14.29%)	3 / 12 (25.00%)
occurrences (all)	1	3	4
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	4 / 21 (19.05%)	1 / 12 (8.33%)
occurrences (all)	2	7	1
Dermatitis acneiform			
subjects affected / exposed	1 / 6 (16.67%)	3 / 21 (14.29%)	1 / 12 (8.33%)
occurrences (all)	1	3	1
Skin ulcer			
subjects affected / exposed	1 / 6 (16.67%)	3 / 21 (14.29%)	0 / 12 (0.00%)
occurrences (all)	1	5	0
Pain of skin			
subjects affected / exposed	1 / 6 (16.67%)	2 / 21 (9.52%)	1 / 12 (8.33%)
occurrences (all)	1	3	1
Rash			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Skin irritation			

subjects affected / exposed	1 / 6 (16.67%)	1 / 21 (4.76%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Skin induration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	3 / 6 (50.00%)	13 / 21 (61.90%)	9 / 12 (75.00%)
occurrences (all)	8	40	15
Haematuria			
subjects affected / exposed	1 / 6 (16.67%)	3 / 21 (14.29%)	3 / 12 (25.00%)
occurrences (all)	2	7	5
Urinary tract pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Chromaturia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Haemoglobinuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Micturition urgency			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 6 (33.33%)	12 / 21 (57.14%)	7 / 12 (58.33%)
occurrences (all)	3	15	10
Delayed puberty			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	3 / 6 (50.00%)	7 / 21 (33.33%)	5 / 12 (41.67%)
occurrences (all)	4	9	6
Pain in extremity			
subjects affected / exposed	3 / 6 (50.00%)	9 / 21 (42.86%)	3 / 12 (25.00%)
occurrences (all)	5	22	6
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 21 (14.29%)	1 / 12 (8.33%)
occurrences (all)	2	3	2
Joint range of motion decreased			
subjects affected / exposed	2 / 6 (33.33%)	3 / 21 (14.29%)	0 / 12 (0.00%)
occurrences (all)	2	5	0
Neck pain			
subjects affected / exposed	1 / 6 (16.67%)	2 / 21 (9.52%)	2 / 12 (16.67%)
occurrences (all)	1	2	2
Myalgia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 21 (4.76%)	2 / 12 (16.67%)
occurrences (all)	1	2	3
Flank pain			
subjects affected / exposed	0 / 6 (0.00%)	3 / 21 (14.29%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Bone pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Joint effusion			
subjects affected / exposed	1 / 6 (16.67%)	1 / 21 (4.76%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	2	0

Bone lesion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Sinusitis			
subjects affected / exposed	1 / 6 (16.67%)	3 / 21 (14.29%)	1 / 12 (8.33%)
occurrences (all)	2	8	1
Skin infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 21 (4.76%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	2 / 12 (16.67%)
occurrences (all)	0	1	3
Enterocolitis infectious			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Mucosal infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 21 (4.76%)	0 / 12 (0.00%)
occurrences (all)	2	5	0
Gastroenteritis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Lymph gland infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Penile infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vulvitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 21 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 6 (16.67%)	12 / 21 (57.14%)	7 / 12 (58.33%)
occurrences (all)	1	19	13
Hypocalcaemia			
subjects affected / exposed	3 / 6 (50.00%)	10 / 21 (47.62%)	7 / 12 (58.33%)
occurrences (all)	14	34	11
Hyponatraemia			
subjects affected / exposed	2 / 6 (33.33%)	10 / 21 (47.62%)	4 / 12 (33.33%)
occurrences (all)	2	16	8
Hyperglycaemia			
subjects affected / exposed	2 / 6 (33.33%)	8 / 21 (38.10%)	5 / 12 (41.67%)
occurrences (all)	2	21	12
Hypoalbuminaemia			
subjects affected / exposed	1 / 6 (16.67%)	10 / 21 (47.62%)	4 / 12 (33.33%)
occurrences (all)	1	27	9
Hypokalaemia			
subjects affected / exposed	1 / 6 (16.67%)	7 / 21 (33.33%)	6 / 12 (50.00%)
occurrences (all)	1	18	10
Hypophosphataemia			
subjects affected / exposed	1 / 6 (16.67%)	10 / 21 (47.62%)	3 / 12 (25.00%)
occurrences (all)	1	20	4
Hypoglycaemia			
subjects affected / exposed	1 / 6 (16.67%)	7 / 21 (33.33%)	5 / 12 (41.67%)
occurrences (all)	2	13	9
Hypomagnesaemia			
subjects affected / exposed	2 / 6 (33.33%)	5 / 21 (23.81%)	5 / 12 (41.67%)
occurrences (all)	3	14	12
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	5 / 21 (23.81%)	3 / 12 (25.00%)
occurrences (all)	0	6	3

Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 21 (14.29%)	4 / 12 (33.33%)
occurrences (all)	0	3	5
Hypercalcaemia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 21 (14.29%)	0 / 12 (0.00%)
occurrences (all)	1	5	0
Hypermagnesaemia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences (all)	2	1	1
Hypernatraemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 21 (4.76%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 21 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Hypochloraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 21 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2012	<p>Added information was given about XL184, that it had been associated with prolonged QTc, and that medications prolonging QTc were prohibited and medications that may prolong QTc should be avoided where possible. Electrocardiogram assessments were added.</p> <p>It was clarified that subjects were to fast for 2 hours before and 1 hour after taking XL184, and informed consent form was updated accordingly. A definition was added for dose-limiting cardiac toxicity based on QT prolongation: "QTc prolongation >500 milliseconds that persists despite correction of serum electrolyte abnormalities".</p> <p>A statement was added clarifying that corticosteroids "are not routinely recommended on the study unless deemed absolutely necessary or when used in stable or decreasing doses from the time of study enrolment."</p> <p>Revised the dosing nomogram to allow for smaller dosing deviations between the calculated and administered doses of XL184 and to reduce the BSA eligibility requirement to 0.35 mg/m² for all subjects enrolled on Dose Levels 1, 2, or 3.</p>
23 April 2013	<p>For subjects who were removed from protocol treatment, annual follow-up evaluations for 5 years were added.</p>
22 May 2013	<p>Added evaluation of OS from study entry through a 5-year follow-up period as a trial objective.</p> <p>Clarified follow-up evaluations were to be performed 30 days, 6 months, and then annually up to 5 years after receiving the last dose of study drug.</p> <p>Clarified that OS would be analysed using the Kaplan-Meier method.</p>
21 January 2014	<p>Updated the Comprehensive Adverse Event and Potential Risk and informed consent document risk profile for XL184.</p>
16 April 2014	<p>The amendment divided the protocol into a PK expansion cohort (Part A) and a separate MTC cohort of Part B. Based on DLTs observed during the dose escalation phase that was already completed before this amendment, the RP2D was determined to be 40 mg/m². The Part B MTC subjects were considered as a separate cohort in the toxicity assessment.</p> <p>An expansion cohort was added to acquire additional PK data at Dose Level 2 (40 mg/m²), the RP2D. Six evaluable subjects were to be enrolled to Part A of the study for a total of 12 evaluable subjects at Dose Level 2 (six subjects < 12 years of age and six subjects ≥ 12 years of age).</p> <p>The PK schedule was updated to collect additional trough samples at pre-Day 1 before Cycle 4 and pre-Day 1 with each disease evaluation.</p>
06 August 2015	<p>The requirement to collect trough PK samples with each disease assessment and PK samples at the time of a DLT for subjects remaining on study was removed, because adequate PK sample had been obtained and the commercial sponsor support of PK sample evaluation ended.</p>
02 May 2016	<p>The Protocol was amended to reflect modified risk information for XL184 and to update the Comprehensive Adverse Events and Potential Risks (CAEPR) list to Version 2.2, 18 December 2015.</p>
24 January 2017	<p>The Protocol was amended to reflect modified risk information for XL184 and to update the CAEPR list to Version 2.3, 04 October 2016. The amendment was being submitted in response to a Request for Rapid Amendment.</p>
02 June 2017	<p>The Protocol was amended to modify disease evaluation requirements for the remaining subjects on the study.</p>

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.

Given the limitation of the dosing schedule, PK parameters on Day 21 (AUC, CL/F) may not represent the PK parameters at steady-state.

Notes: