ISRCTN Document Cover Page

ISRCTN Number	ISRCTN11160449
EudraCT Number	2016-004633-24
Sponsor Protocol Number	CRUKD/17/009
Official Trial Title	A Cancer Research UK Phase I/IIa clinical trial of BT1718 (a Bicycle drug conjugate) given intravenously in patients with advanced solid tumours.
Date of Cover Page Finalisation for Upload	09 October 2024
Document Included	Redacted Reporting Analysis Plan (Version 4.0, dated 06 February 2024)

Reporting Analysis Plan v4.0 (06 February 2024) has been selected by the Sponsor (Cancer Research UK) as the most appropriate reporting analysis plan to be made available publicly, as this is the document that was most recently updated and used on the CRUKD/17/009 trial.

Cancer RESEARCH UK

Reporting Analysis Plan

Protocol Number: **CRUKD/17/009**

Protocol Name: **BT1718**

EudraCT Number: **2016-004633-24**

[redacted]

RAP Final Version:	4.0
Date:	06 Feb 2024
Replaces Version:	3.0
Date:	02 Nov 2023

Name: [redacted] Date: _____

Title: Senior Clinical Study Manager (Sponsor)

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Title: Chief Investigator

Signature: _____

SUMMARY OF CHANGES TO PREVIOUS REPORTING ANALYSIS PLAN VERSION

This summary of changes is intended to highlight the important revisions that were made during the most recent update to the reporting analysis plan (RAP) to generate the current version.

This document has been written based on information contained in the study protocol and data management plan detailed in the table below.

Protocol version	DMP version	RAP version	Revised section of RAP	Summary of changes	Date updated
9.0	4.0	N/A	N/A	Initial draft	N/A
10.0	4.0	1.0	4.0	4.1 - Update to patient population definitions	16Oct2023
			5.0	5.1 - New Table 2 included – summary of patient populations	
				5.3 Update to patient withdrawal table	
				5.4 Update to protocol deviation table	
				5.5 Update to treatment compliance tables, new table 12 (time on treatment) included	
				5.6 – Update to dose modification table	
				5.3 Update to Patient withdrawal table	
				5.8 – Update to the adverse event tables (dose escalation/expansion phase separated)	
				5.9 - Update to DLT table to split the once/twice weekly dosing.	
				5.10 – New tables included (duration of response) / progression free survival / overall survival	
				5.14 – [redacted]	

			6.0	Update to listings, tables and figures	
			7.0	Update to include trial results will now be reported on ISRCTN as opposed to ClinicalTrials.gov. Section updated to include ISRCTN reporting requirements.	
			8.0	Update to specify the HRA summaries website will also have a link to the lay summary of results on the CRUK website.	
10.0	4.0	2.0	6.1 6.2	Minor update to listings and tables	02Nov2023
10.0	4.0	3.0	5.2	Update to Table 6 – Previous Treatment for Malignant Disease to include Chemotherapy/other therapy	06Feb2024
			5.3	Update to Table 8 -Reason for patient withdrawal. Table will also be produced for the Safety Population	
			5.8	Update to Table 16 - Frequency of TEAEs by worst CTCAE Grade within an episode by Cohort. Table will also be produced for the Expansion phase/ Frequency of Patients with TEAEs by Worst CTCAE Grade by Cohort (Dose Escalation and Expansion phase)	
				Update to Table 17 – Overview of TEAEs by Cohort (Dose Escalation) updated to include Patients with ≥1 TEAE leading to mortality	
				Update to Table 18 – Overview of TEAEs by Cohort (Expansion) updated to include Patients with ≥1 TEAE leading to mortality	
			5.9.2	Update to Table 24 – Dose limiting toxicities	
			5.10	Update to include Duration of Stable Disease	

				Overall Survival and Progression Free Survival will be calculated from date of first dose Time to Progression analysis removed [redacted]	
			5.11	Time to progression analysis removed	
			6.2	Update to Tables 32 and 33 – planned tables, listings and numbering	
			6.3	Table 34 – Planned Figure Titles and Numbering removed	
Final review prior to database lock					
Protocol version	**DMP version**	**RAP version**	**Revised section of RAP**	**Summary of changes**	**Date updated**
9.0	4.0	N/A	N/A	Initial draft	N/A

Protocol amendments may be applicable during the study. The RAP will be reviewed against the amendments and updated where necessary.

The summary of changes table above should record all changes to the RAP in light of protocol amendments however if no changes were required, this should be recorded also.

CONTRIBUTORS

Senior Medical Writer: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
A	[redacted]	[redacted]
	AE	adverse event
	ALP	alkaline phosphatase
	ALT	alanine transaminase
	AST	aspartate aminotransferase
	AUC	area under the curve
C	CDD	Centre for Drug Development
	[redacted]	[redacted]
	CI	Chief Investigator
	C_{max}	maximum observed plasma concentration
	CR	complete response
	CRUK	Cancer Research UK
	CSR	Clinical Study Report
	CTA	Clinical Trial Authorisation
	CTCAE	Common Terminology Criteria for Adverse Events
D	DLT	dose limiting toxicity
E	ECG	electrocardiogram
	eCRF	electronic case report form
	EDC	electronic data capture
F	FAP	Full Analysis Population
	FFPE	formalin-fixed paraffin- embedded
	FIH	first-in-human
	FU	follow-up
G	GCP	Good Clinical Practice
	GGT	gamma-glutamyl transferase
H	HRA	Health Research Authority
I	[redacted]	[redacted]
	IMP	investigational medicinal product
	ISRCTN	International Standard Randomised Controlled Trial Number
M	MAD	maximum administered dose
	MTD	maximum tolerated dose
	MT1-MMP	membrane type I matrix metalloproteinase
N	NCI	National Cancer Institute
	NUCC	Newcastle University Centre for Cancer
O	OS	overall survival
P	PD	progressive disease [redacted]
	PI	Principal Investigator
	PFS	progression free survival
	PK	pharmacokinetic
	PR	partial response
R	RAP	Reporting Analysis Plan
	RECIST	Response Evaluation Criteria in Solid Tumours

	Abbreviation	Definition
	RP2D	recommended Phase II dose
S	SAE	serious adverse event
	SAP	Statistical Analysis Plan
	SD	stable disease
	SOP	Standard Operating Procedure
	sqNSCLC	squamous non-small cell lung cancer
T	$T_{1/2}$	terminal elimination half-life
	T_{max}	time to reach C_{max}
	TEAE	treatment emergent adverse event
V	V_{ss}	steady state volume of distribution
W	WBC	white blood cell
	WHO	World Health Organisation
Y	[redacted]	[redacted]

TABLE OF CONTENTS

1 INTRODUCTION

This document explains in detail the reporting analyses that will be carried out for the CRUKD/17/009 trial of BT1718.

The analyses described in this RAP are based upon and supplement those described in the current study protocol.

To support reproducibility of the research, a clear and comprehensive account of pre-planned reporting (or statistical) analyses must be available. This RAP will establish the essential items to be considered for interim and/or final reporting requirements.

2 TRIAL OBJECTIVES

Primary objectives	Endpoints
Dose escalation phase To propose a recommended Phase II dose (RP2D) for evaluation by establishing the maximum tolerated dose (MTD) and/or maximum administered dose (MAD), of BT1718 given in patients with advanced solid tumours, at one or more dosing schedules.	Determine a dose at which no more than one out of six patients at the same dose level experiences a probable or highly probable BT1718-related dose limiting toxicity (DLT).
Dose escalation phase and expansion phase To assess the safety and toxicity profile of BT1718 in patients with advanced solid tumours.	Determine the frequency and causality of each adverse event (AE) to BT1718 and grade severity according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.02. The causality of all AEs will be assessed by the Investigator.

Secondary objectives	Endpoints
Dose escalation phase and expansion phase To investigate the pharmacokinetic (PK) behaviour of BT1718 in humans.	Measurement of maximum observed plasma concentration (C_{max}), area under the curve (AUC), terminal elimination half-life ($t_{½}$), and other PK parameters of BT1718 in plasma, both as an intact and cleaved molecule.
Dose escalation phase and expansion phase To assess preliminary signals of BT1718 efficacy in dose escalation phase and in relevant tumour types with high expression of membrane type 1 matrix metalloproteinase (MT1-MMP) in the expansion phase.	Assess anti-tumour response according to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1. Estimate progression-free survival (PFS), PFS rate at six months, and overall survival, OS (where available). Estimate duration of response.

Tertiary objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

3 TRIAL DESIGN

Table 1: Trial Design

A	Study design	This is a multi-centre, first-in-human (FIH), Phase I/IIa, open label, dose escalation trial with an expansion phase in patients with advanced solid tumours.
B	Patient group	This clinical trial consisted of two phases, Phase I and Phase IIa: **Phase I, dose escalation phase:** Phase I consisted of Stage 1 (twice weekly dosing) and Stage 2 (once weekly dosing), where we recruited 39 patients with advanced solid tumours in escalating dose cohorts to reach our RP2D. **Phase IIa, expansion phase:** Phase IIa consisted of two expansion cohorts, a squamous non-small cell lung cancer (sqNSCLC) cohort and a basket cohort. In the expansion phase, patients were enrolled with tumour types known to commonly overexpress MT1-MMP and where MT1-MMP overexpression is confirmed during retrospective and prospective selection.
C	Sample size	Planned: 50-60 in Phase I, depending on number of dose levels explored, and up to 70 in Phase IIa. Actual: 42 in Phase I and 30 in Phase IIa.
D	Study intervention	**Phase I, Stage 1:** Patients were administered BT1718 intravenously twice weekly for three out of four weeks (dosing on Days 1, 4, 8, 11, 15 and 18 ±1 day). Each cycle of treatment consisted of 28 days, and patients were able to continue until disease progression. **Phase I, Stage 2:** Patients were administered BT1718 intravenously once weekly for three out of four weeks (dosing on Days 1, 8 and 15 ±1 day). Each cycle of treatment consisted of 28 days and patients were able to continue until disease progression. **Phase IIa:** Patients were administered BT1718 intravenously at the once weekly RP2D as defined by Phase I, Stage 2. Patients attended an off-study visit 28 days ±7 days after their last dose of BT1718. Serious adverse event (SAE) and AE collection and monitoring continued during this period or until the patient started another anti-cancer therapy. Any drug-related AEs that were still ongoing after this period were followed up monthly until resolution to baseline or stabilisation, unless the patient started another anti-cancer treatment. Information on overall and PFS was collected every 3 months until the patient started another systemic anti-cancer therapy or progressive disease (PD) occurred. All patients who provided pre-screening informed consent, regardless of whether they started BT1718 dosing or not, were followed up for survival until the end of the

		trial, where feasible. If the patient was lost to follow-up (FU) or had not progressed or died at the time of the final database lock for the clinical study report (CSR), then the information was censored as not known to have progressed/died at that time.
E	Study analysis	Dose decision meetings were to be organised by the Sponsor for review of patient data after each patient in the single patient dose escalation cohorts had completed Cycle 1 (28-day DLT observation period). When cohorts were expanded to 3+3, dose decision meetings were to be organised by the Sponsor for review of patient data once each cohort was complete. A dose decision meeting was arranged during the expansion phase in response to emerging tolerability data, including a formal assessment after the first six patients were enrolled. These meetings were attended by the Cancer Research UK Centre for Drug Development (Sponsor), Chief Investigator (CI) and Principal Investigators (PIs). The final analysis will be conducted after one of the following conditions is met: • The trial is terminated early. • The end of trial has been declared. NB: End of trial may only be declared when all patients have either withdrawn from trial, died, or completed a minimum of 12 months survival FU since their first administration of BT1718.
F	Dose escalation schedule	The study explored the earlier doses in single patient cohorts. As detailed in the protocol, on observation of related Grade 2 AEs or after the dose exceeded 6 mg/m^2 twice daily, the cohorts were expanded to 3+3. DLT definitions can be found in protocol Section 3.3. Phase I, Stage 1 twice-weekly schedule commenced and then Phase I, Stage 2 once-weekly schedule commenced later when there was an expectation of potential biological activity based on available toxicity, PK and/or [redacted] data from Stage 1.

For full details of the trial design, background and rationale for the trial, please refer to Version 10.0 of the Clinical Study Protocol.

4 PATIENT POPULATION AND ENDPOINTS

Patients must fulfil all the inclusion/exclusion criteria to be eligible for entry to the trial. Refer to the clinical study protocol for the complete list of inclusion and exclusion criteria.

4.1 Patient Populations

The analysis sets are defined as follows:

Pre-Screened Population:	Patients who signed pre-screening consent and had an archival sample analysed for the trial, whether they received BT1718 or not.
Full Analysis Population (FAP):	All enrolled patients. Patients who are enrolled in error onto the trial (due to ineligibility/administrative error) prior to receiving BT1718 will be excluded from the FAP.
Safety Population:	All enrolled patients who received at least one dose of BT1718.
Survival Population:	All eligible patients who received at least one dose of BT1718 and who completed a baseline and at least one post-treatment disease assessment (or who experienced clear disease progression without a formal post-treatment disease assessment) will be evaluable for PFS and OS (where available). Patients with a membrane MT1-MMP H-score of less than 150 are not eligible in the expansion phase and are excluded.
DLT Assessment Population:	All enrolled patients in the dose escalation phase (Phase I) who either experienced a DLT in Cycle 1 or for Phase I, Stage 1 single patient cohorts, received 100% of their dosing in Cycle 1 and for Phase I, Stage 2 escalation patients received at least 75% of their planned dose exposure of BT1718 during Cycle 1 (unless due to BT1718-related toxicity).
Response Population:	All eligible patients who received a full cycle of BT1718 or ≥66% of the planned dose exposure of BT1718 within Cycle 1 and 2, and have a baseline assessment of disease and at least one repeat assessment according to RECIST version 1.1 will be evaluable for response. Patients who develop clear evidence of PD without a formal disease assessment will be considered non-responders. Patients with a membrane MT1-MMP H-score of less than 150 are not eligible in the expansion phase and are excluded.
PK Population:	All patients who provided at least one post-treatment plasma, [redacted] samples for PK analysis will be evaluable for assessment of PK.

[redacted]

[redacted]

5 DATA CONVENTIONS AND GENERAL ANALYSIS

5.1 Patient disposition

A list of patient populations included in the summary tables will be produced.

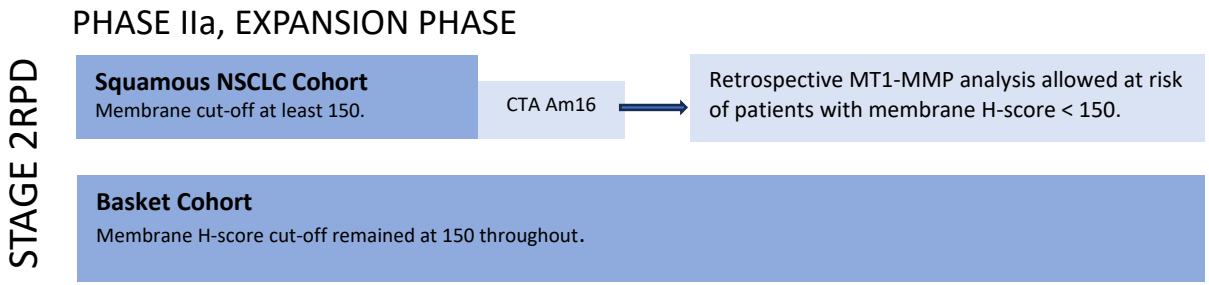
Table 2: Summary of Patient Populations

Cohort	Patient No.	Full Analysis	Safety	PFS	OS	DLT Assessment	Response
Dose Escalation (Twice weekly)	XX/XXX						
Dose Escalation (Once weekly)							
Expansion sqNSCLC Cohort							
Expansion Patients Basket Cohort							

The accrual and trial discontinuation details will be presented descriptively. This should include details of:

- Screening failure patients, including pre-screening (screening failure information is available via e-screening log).
- The number of patients in screening who were considered 'negative' for MT1-MMP overexpression in expansion phase (membrane MT1-MMP score of less than 150). See **Figure 1**.

Figure 1: Phase IIa Expansion Membrane MT1-MMP score cut-off at Screening



- Information on ineligible patients who were enrolled and/or received BT1718.
- Reasons for treatment discontinuation by number of cycles received will be described by counts and percentages. Reasons for treatment discontinuation other than disease progression will be detailed and summarised separately (Section 5.3).

5.2 Baseline characteristics

Selected demographics and baseline characteristics will be summarised for the FAP. Therefore, all tables within this section will be summarised for the FAP.

Table 3: Baseline Characteristics (Full Analysis Population)

	Overall No. of Patients (N=XX)	Dose Escalation Patients - Twice Weekly Dosing (N=XX)	Dose Escalation Patients - Once Weekly Dosing (N=XX)	Expansion Patients sqNSCLC Cohort (N=XX)	Expansion Patients Basket Cohort (N=XX)
Patients					
Male					
Female					
Age (years)					
Mean					
Median					
Min.					
Max.					
Weight (kg)					
Mean					
Median					
Min.					
Max.					
Height (cm)					
Mean					
Median					
Min.					
Max.					

WHO performance status					
0					
1					
2					
3					
4					

In case of pre-treatment characteristics with multiple measurements per patient before the start of treatment (laboratory assessments, vital signs), the baseline measurement will be considered the last value prior to or on the first day of treatment.

Baseline performance status assessments will be summarised with frequency counts.

For the cancer history, histologic diagnosis, number of baseline lesions, and involvement in the different sites will be summarised. If incomplete dates are recorded, the rules described in Section 5.11 will be used for imputation.

The primary tumour sites (and baseline lesions in trials for which tumour response is an endpoint) will be recorded in order to categorise them accurately in the analysis.

A frequency tabulation of the different types of previous oncologic surgery (excluding only diagnostic or palliative procedures), radiotherapy, or anticancer systemic therapy and a tabulation of number of prior lines of anti-cancer systemic therapy with median and range will be given, this will be produced manually for the CSR.

Table 4: Primary Diagnosis at Baseline (Full Analysis Population)

	Overall No. of Patients (N=XX)	Dose Escalation Patients - Twice Weekly Dosing (N=XX)	Dose Escalation Patients - Once Weekly Dosing (N=XX)	Expansion Patients sqNSCLC Cohort (N=XX)	Expansion Patients Basket Cohort (N=XX)
Primary tumour type					
A	N (%)				
B					
C					
Etc.					
Stage at study entry					
I					
II					
III					
IV					
Not Known					

Table 5: Summary of Baseline Disease Sites Taken From Tumour Type From Baseline Measurable and Non-Measurable Disease assessments (Full Analysis Population)

Baseline disease type	Overall No. of Patients (N=XX)	Escalation Phase No. of Patients (N=XX)	Expansion Phase sqNSCLC Cohort No. of Patients (N=XX)	Expansion Phase Basket Cohort No. of Patients (N=XX)
Target lesion location at Screening	N (%)			
Breast				
Lung				
Liver etc.				
Non-target lesion location at Screening				
Breast				
Lung				
Liver etc.				

Table 6: Previous Treatment for Malignant Disease (Full Analysis Population)

	Overall No. of Patients (N=XX)	Escalation Phase No. of Patients (N=XX)	Expansion Phase sqNSCLC Cohort No. of Patients (N=XX)	Expansion Phase Basket Cohort No. of Patients (N=XX)
Prior treatment				
Surgery	N (%)			
Radiotherapy				
Chemotherapy/other therapy				

Table 7: Lines of Previous Chemotherapy/Other Therapy (Full Analysis Population)

	Overall No. of Patients (N=XX)	Escalation Phase No. of Patients (N=XX)	Expansion Phase sqNSCLC Cohort No. of Patients (N=XX)	Expansion Phase Basket Cohort No. of Patients (N=XX)
Lines				
1	N (%)			
2				
3				
4				
5				
>5				
Median				
Min.				
Max.				

5.3 Patient withdrawal

Reasons for patient withdrawal will be provided as the data are available and presented as per the table below.

Table 8: Reasons for Patient Withdrawal/Completion (Full Analysis Population)

Reason off study	Overall No. of Patients (N=XX)	Escalation Phase No. of Patients (N=XX)	Expansion Phase sqNSCLC Cohort No. of Patients (N=XX)	Expansion Phase Basket Cohort No. of Patients (N=XX)	Expansion Phase 15mg/m^2 starting dose No. of Patients (N=XX)	Expansion Phase 20mg/m^2 starting dose No. of Patients (N=XX)
AE/SAE	XX (%)					
Withdrawal of consent						
Serious deviation of the trial protocol						
Sponsor's decision to terminate the trial						
Withdrawal by the investigator for clinical reasons not related to investigational medicinal product (IMP)						
Withdrawal from treatment by subject						
Evidence of disease progression						
Pregnancy						
Other						

Table 8 will also be produced for the Safety Population.

5.4 Protocol deviations

A protocol deviation is defined as any departure from what is described in the protocol of a clinical trial approved by an Independent Ethics Committee and Competent Authorities. Therefore, it applies to deviations related to patient inclusion and clinical procedures (e.g. assessments to be conducted or parameters to be determined), and also to other procedures described in the protocol that concern the Good Clinical Practice (GCP) guidelines or ethical issues (e.g. issues

related to obtaining the patients' Informed Consent, data reporting, the responsibilities of the Investigator, etc.).

Protocol deviations are captured throughout the trial open phase on the Sponsor's central tracker and can be filtered by study and by deviation category or on the study specific PK[redacted] deviations tracker. Standard deviation categories have been defined by the Sponsor and are further defined by those which are deemed reportable (important deviations) in the CSR. Those deviations which have been coded as CSR reportable will be summarised for all patients, according to the categories allocated at identification. Deviations are reviewed manually as per Sponsor Standard Operating Procedures (SOPs).

A summary table with the number of patients with deviations will be presented per criterion. Deviations with no effects on the risk/benefit ratio of the clinical trial (such as minimal delays in assessments or visits) will be distinguished from those that might have an effect on this risk/benefit ratio.

The following are pre-defined protocol deviations with a direct bearing on the primary outcome and, therefore, will be reported in the CSR. A summary including but not necessarily restricted to the following categories will be presented as detailed in **Table 9**.

Table 9: List of Deviations (Full Analysis Population)

Deviation Category	Number of Deviations	Number of Patients
Missed visit or investigation		
Visit or investigation conducted outside of window		
Eligibility criteria		
IMP		
Treatment error		
Other (serious breach/urgent safety measures)		

PK[redacted] deviations will be provided in the individual laboratory reports appended to the CSR.

5.5 Treatment compliance

Provided for safety population.

Treatment compliance: Treatment compliance will be calculated as patients who have managed to receive a complete dose of BT1718 with no interruptions.

- Patients in the dose escalation phase (Phase I, Stage 1 single patient cohorts) who received 100% of their planned dose exposure of BT1718 during Cycle 1 (completed DLT assessment period) will be considered to have 'completed' treatment.
- Patients in the dose escalation phase (Phase I, Stage 1 3 + 3 cohorts) who received 75% of their planned dose exposure of BT1718 during Cycle 1 (completed DLT assessment period) will be considered to have 'completed' treatment.
- Patients in the expansion phase who received a full cycle of BT1718 or ≥66% of the planned dose exposure of BT1718 within Cycle 1 and 2 will be considered to have 'completed' treatment.

Time on treatment: is the interval expressed in days, between the first infusion and the last infusion.

Table 10: Treatment Compliance in Cycle 1 (Dose Escalation Phase; Safety Population)

	All Dose Escalation (N=XX)	**Twice Weekly Dosing (N=XX)**	**Once Weekly Dosing (N=XX)**
<75%		N (%) of patients	N (%) of patients
≥75-100%			

Table 11: Treatment Compliance in Cycles 1 & 2 (Expansion Phase; Safety Population)

	All Expansion (N=XX)	**sqNSCLC Cohort (N=XX)**	**Basket Cohort (N=XX)**
<66%		N (%) of patients	N (%) of patients
≥66-100%			

Table 12: Time on Treatment (Safety Population)

	Overall No. of Patients (N=XX)	**Escalation Phase No. of Patients (N=XX)**	**Expansion Phase sqNSCLC Cohort No. of Patients (N=XX)**	**Expansion Phase Basket Cohort No. of Patients (N=XX)**
Min. (days)				
Max. (days)				
Median (days)				

5.6 Dose modifications

Provided for the safety population.

A list of all treatment modifications will be produced.

Table 13: Dosing Modifications (Safety Population)

	Dose Escalation (Twice weekly dosing) (N=XX)	**Dose Escalation (Once weekly dosing) (N=XX)**	**Expansion Patients sqNSCLC Cohort (N=XX)**	**Expansion Patients Basket Cohort (N=XX)**
Treatment Modification	No. of Pts. (N=XX)	No. of Pts. (N=XX)	No. of Pts. (N=XX)	No. of Pts. (N=XX)
Dose not given	XX (%)			
Dose delayed				
Dose given early				
Dose reduced				
Dose increased				
Infusion interrupted				
Infusion stopped				
Infusion time longer				
Infusion time shorter				

The CSR will have a summary statement of treatment modifications.

5.7 Safety

Descriptive statistics will be used for evaluation of safety. The incidence and grade of AEs and laboratory abnormalities will be calculated considering the most severe grade per patient and will be displayed in frequency tables using counts and percentages.

Deaths, SAEs and events resulting in trial discontinuation will be tabulated.

Additional safety analyses may be determined at any time in order to most clearly enumerate rates of toxicities and to further define the safety profile of BT1718.

- The safety population is composed of all patients that received at least one dose of BT1718. The safety patient population will be used for the general safety presentations.
- Events will be coded and classified according to the MedDRA dictionary. The version number will be footnoted on the listings. Toxicity evaluation (grading) will be made according to NCI CTCAE version 4.02.
- As far as the toxicities are concerned, the NCI CTCAE grade will be used wherever an NCI CTCAE grading exists.
- As a convention, the term “Grade” will always be used. Toxicities will be described according to the maximum NCI CTCAE grade.
- Maximum CTCAE grade for all AEs will be captured.

5.8 Adverse Events

Pre-treatment AEs will be defined as those where “Did this AE start prior to first dose of IMP?” is ticked in the electronic case report form (eCRF). Treatment emergent AEs (TEAEs) will be defined as those where “Did this AE start prior to first dose of IMP?” is not ticked in the CRF.

Related AEs are those where causality to IMP is considered to be Possible, Probable or Highly Probable.

The frequency of AEs will be summarised overall and by cohort in the escalation phase and expansion phase. A patient can be counted multiple times per row for the No. of Episodes but will only be counted once per row for the No. of Patients.

Table 14: Frequency of All Adverse Events by Cohort (Dose Escalation Phase; Safety Population)

			Twice weekly dosing						Once weekly dosing									
SYSTEM ORGAN CLASS Preferred Term	**All Dose Escalation**		**Cohort 1–4 (0.6 mg/m^2 – 4.8mg/m^2)**		**Cohort 5 (9.6 mg/m^2)**		**Cohort 6 (7.2 mg/m^2)**		**Cohort 1A (9.6 mg/m^2)**		**Cohort 2A (15 mg/m^2)**		**Cohort 3A (20 mg/m^2)**		**Cohort 4A (25 mg/m^2)**		**Cohort 5A (32 mg/m^2)**	
	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X
All AEs	N	N (%)	N	N (%)	N	N (%)	N	N (%)	N	N (%)	N	N (%)	N	N (%)	N	N (%)	N	N (%)
BLOOD AND LYMPHATIC																		
Anaemia																		
CARDIAC DISORDERS																		
Sinus tachycardia																		
Etc																		

There will be additional versions of the above **Table 14** based on pre-treatment AEs, related treatment emergent SAEs, non-related treatment emergent SAEs, TEAEs, treatment emergent SAEs (TE SAE; any AE that is considered Serious), treatment emergent non-serious AEs, related TEAEs, grade ≥ 3 related TEAEs.

Table 15: Frequency of All Adverse Events by Cohort (Expansion Phase, Safety Population)

SYSTEM ORGAN CLASS Preferred Term	**All Expansion**		**sqNSCLC Cohort**		**Basket Cohort**		**15mg/m^2 starting dose**	**20mg/m^2 starting dose**
	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients (N=XX)
All AEs	N	N (%)	N	N (%)	N	N (%)	N (%)	N
BLOOD AND LYMPHATIC								
Anaemia								
CARDIAC DISORDERS								
Sinus tachycardia								
Etc								

There will be additional versions of the above **Table 15** based on pre-treatment AEs, related treatment emergent SAEs, non-related treatment emergent SAEs, TEAEs, treatment emergent SAEs (any AE that is considered Serious), treatment emergent non-serious AEs, related TEAEs, grade ≥ 3 related TEAEs.

Table 16: Frequency of TEAEs by worst CTCAE Grade within an episode by Cohort (Dose Escalation, Safety Population)

	All AEs						**BT1718-related AEs**					
		Grade						**Grade**				
Adverse event	Total	1	2	3	4	5	Total	1	2	3	4	5
Overall totals												
SYSTEM ORGAN CLASS Preferred Term												
BLOOD AND LYMPHATIC…												
Anaemia												
CARDIAC DISORDERS												
Sinus tachycardia												
Etc												

Overview of TEAEs by cohort. An AE is considered to have led to withdrawal if an adverse event with “Did the AE cause the subject to be discontinued from the study?” is recorded as yes. Table 16 will also be produced for the Expansion phase.
Table 16 will also be produced for Frequency of Patients with TEAEs by Worst CTCAE Grade by **C**ohort for the Dose Escalation and Expansion phase.

Table 17: Overview of Treatment-Emergent Adverse Events by Cohort (Dose Escalation Phase; Safety Population)

		Twice weekly dosing			Once weekly dosing				
	Overall	**Cohort 1– 4 (0.6 mg/m^2 – 4.8mg/m^2)**	**Cohort 5 (9.6 mg/m^2)**	**Cohort 6 (7.2 mg/m^2)**	**Cohort 1A (9.6 mg/m^2)**	**Cohort 2A (15 mg/m^2)**	**Cohort 3A (20 mg/m^2)**	**Cohort 4A (25 mg/m^2)**	**Cohort 5A (32 mg/m^2)**
Patients with TEAEs	No. (%) of Patients N=XX	No. (%) of Patients	No. (%) of Patients	No. (%) of Patients	No. (%) of Patients	No. (%) of Patients	No. (%) of Patients	No. (%) of Patients	No. (%) of Patients
Patients with ≥1 TEAE	N (%)								
Patients with ≥1 TE SAE									
Patients with ≥ 1 related TEAE									
Patients with ≥1 related TE SAE									
Patients with ≥ 1 CTCAE Grade 3, 4 or 5 TEAE									
Patients with ≥ 1 CTCAE Grade 3, 4 or 5 related TEAE									

Patients with ≥1 TEAE leading to withdrawal									
Patients with ≥1 TEAE leading to mortality									

TEAEs leading to withdrawal of treatment will be listed by patient. Patients will be included if an adverse event has “Action taken” recorded as “Drug Withdrawn” or “Did the AE cause the subject to be discontinued from the study?” is recorded as yes.

Table 18: Overview of Treatment-Emergent Adverse Events by Cohort (Expansion Phase; Safety Population)

	Overall	**sqNSCLC Cohort**	**Basket Cohort**	**15mg/m^2 starting dose**	**20mg/m^2 starting dose**
Patients with TEAEs	No. (%) of Patients N=XX	No. (%) of Patients	No. (%) of Patients	No. (%) of Patients	No. (%) of Patients
Patients with ≥1 TEAE	N (%)				
Patients with ≥1 TE SAE					
Patients with ≥ 1 related TEAE					
Patients with ≥1 related TE SAE					
Patients with ≥ 1 CTCAE Grade 3, 4 or 5 TEAE					

Patients with ≥ 1 CTCAE Grade 3, 4 or 5 related TEAE					
Patients with ≥1 TEAE leading to withdrawal					
Patients with ≥1 TEAE leading to mortality					

TEAEs leading to withdrawal of treatment will be listed by patient. Patients will be included if an adverse event has “Action taken” recorded as “Drug Withdrawn” or “Did the AE cause the subject to be discontinued from the study?” is recorded as yes.

Table 19: Summary of TEAEs leading to Patient Withdrawal (Dose Escalation Phase; Safety Population)

	Twice weekly dosing						**Once weekly dosing**									
	Cohort 1–4 (0.6 mg/m^2 – 4.8 mg/m^2)		**Cohort 5 (9.6 mg/m^2)**		**Cohort 6 (7.2 mg/m^2)**		**Cohort 1A (9.6 mg/m^2)**		**Cohort 2A (15 mg/m^2)**		**Cohort 3A (20 mg/m^2)**		**Cohort 4A (25 mg/m^2)**		**Cohort 5A (32 mg/m^2)**	
	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X
TEAEs that led to discontinuation																
TEAEs that led to withdrawal																

Table 20: Summary of TEAEs leading to Patient Withdrawal (Expansion Phase; Safety Population)

	sqNSCLC Cohort		**Basket Cohort**		**15mg/m^2 starting dose**		**20mg/m^2 starting dose**	
	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X	No. of Episodes	No. of Patients N= X
TEAEs that led to discontinuation								
TEAEs that led to withdrawal								

5.9 Laboratory results

A summary of patients with laboratory results that are out of range and considered AEs will be produced by CTCAE grade. Results collected prior to first dose will be excluded. Patients can be counted multiple times across different CTCAE grades within a lab parameter. If a patient experienced both a high out of range value and a low out of range value, this patient will be included as both.

Table 21: Summary of Haematology Parameters by CTCAE Grade (Safety Population)

Cohort	Analyte	No. of Patients with Out of Range Values	No of Episodes/CTCAE Grade			
			Total	1	2	3 etc
Dose Escalation Once weekly	Haemoglobin	N (%)				
	Lymphocytes					
	Neutrophils					
	Platelets					
	WBC					
Dose Escalation Twice weekly	Haemoglobin					
	Lymphocytes					
	Neutrophils					
	Platelets					
	WBC					
Expansion (sqNSCLC)	Haemoglobin					
	Lymphocytes					
	Neutrophils					
	Platelets					
	WBC					
Expansion (Basket)	Haemoglobin					
	Lymphocytes					
	Neutrophils					
	Platelets					
	WBC					

Table 22: Summary of Biochemistry Parameters by CTCAE Grade (Safety Population)

	Analyte	No. of patients with out of range values Total	No. of Episodes/CTCAE Grade			
			Total	1	2	3 etc
Dose Escalation Once weekly	ALT	N (%)	N			
	AST					
	ALP					
	GGT					
	Bilirubin etc.					
Dose Escalation Twice weekly	ALT					
	AST					
	ALP					
	GGT					
	Bilirubin etc.					
Expansion (Basket)	ALT					
	AST					
	ALP					
	GGT					
	Bilirubin etc.					
Expansion (sqNSCLC)	ALT					
	AST					
	ALP					
	GGT					
	Bilirubin etc.					

There will be additional versions of the above table based on Coagulation values.

Urinalysis values that are considered AEs will be summarised in text in the CSR.

5.9.1 Bespoke additional safety analysis (Safety Population)

The following additional safety table will be produced.

Table 23: [redacted] and related toxicity summary (Safety Population)

Pt no.	[redacted]	[redacted]	[redacted]	Date of first BT1718 dose	Dose Level	Date of progression	Best response	Grade 3+ related toxicity (AEs)	Highest grade related nausea/vomiting	Highest grade related fatigue	Highest grade related peripheral neuropathy	Date of 1st dose reduction (if applicable)	Reason for discontinuation
XX/XXX													

Data in **Table 23** will present [redacted] as well as related toxicity data collected from the clinical database.

AE plots for AEs of interest including Fatigue, Nausea/Vomiting and Peripheral Neuropathy will be created for the CSR [redacted]. Please refer to Section 9.9 in the [redacted] Statistical Analysis Plan (SAP) Appendix for further information.

5.9.2 Dose limiting toxicities

For the evaluation of the primary endpoint, the total number of patients included, the number of patients evaluable for determination of DLTs, and the number of patients with any DLT (and their categorisation) will be summarised by dose level (or most adequate dose grouping). The toxicities meeting the DLT criteria in Cycle 1 and toxicities in subsequent cycles, e.g. GGT and AST, will be listed separately, and the description of laboratory abnormalities (haematology/biochemistry) will be supported by graphs depicting the evolution in time of laboratory values (including nadir calculation and median time to recovery from baseline values).

Table 24: Dose Limiting Toxicities (Dose Escalation Phase; Safety Population)

	Twice weekly dosing			**Once weekly dosing**				
	Cohort 1–4 (0.6 mg/m^2 – 4.8 mg/m^2) (N=X)	**Cohort 5 (9.6 mg/m^2) (N=X)**	**Cohort 6 (7.2 mg/m^2) (N=X)**	**Cohort 1A (9.6 mg/m^2) (N=X)**	**Cohort 2A (15 mg/m^2) (N=X)**	**Cohort 3A (20 mg/m^2) (N=X)**	**Cohort 4A (25 mg/m^2) (N=X)**	**Cohort 5A (32 mg/m^2) (N=X)**
Number of patients evaluable for DLTs								
Number of patients with DLT								
Number of DLTs								

5.10 Efficacy

The Response population will be used for the overall response analysis. Disease must be measured according to the RECIST 1.1 criteria.

Patients in the expansion phase must meet the MT1-MMP positivity rate to be evaluable for this objective.

Response rates (defined as the ratio of patients with any response (complete response, CR or partial response, PR) by the total number of patients included in the response population) will be characterised using descriptive statistics by cohort. If applicable, overall response rate, percentages for PR or CR separately and percentage of patients with stable disease (SD) ≥3 months will be analysed. Objective responses (the best tumour response achieved by each patient while on trial) will be presented in the data listings by cohort.

The characteristics of the patients achieving an objective response or SD ≥ 3 months by RECIST v.1.1, or a clinically significant improvement measured by tumour markers, will be displayed.

CR and PR need to be confirmed by a subsequent assessment at least four weeks later. SD must be met at least once and at least six weeks after the initial dose of BT1718 is given to be defined as SD. There is no requirement for repeat assessments to be performed in order for the patient to be assigned a status of SD.

Median PFS, OS,duration of response and duration of stable disease will be presented. The PFS and OS rate at 6 months (182.5 days) will also be presented.

- PFS will be calculated from trial entry (date of first dose) until the time of documented disease progression or death (whichever occurs first). Patients who are alive and progression free or lost to FU at the time of analysis will be censored at the time the patient was last known to be alive and progression free.
- OS will be calculated from trial entry (date of first dose) until the time of death from any cause. Patients who are alive or lost to FU at the time of analysis will be censored at the time the patient was last known to be alive.
- Duration of response and duration of stable disease will be measured from the date of the first scan where response was seen until date of first RECIST V1.1 progression or death. Patients will be censored at off study. Duration of response will not be calculated in the absence of any patients with confirmed PR or CR.
- The overall response rate will be calculated, please refer to Section 9.1 in the [redacted] SAP Appendix for further information.
- Low MT1-MMP will be described descriptively.

Table 25: Best Overall Response (Response Population)

Best Tumour Response	Overall No. of Patients N=XX	Dose Escalation Phase No. of Patients (N=XX)	Expansion Phase sqNSCLC Cohort No. of Patients (N=XX)	Expansion Phase Basket Cohort No. of Patients (N=XX)
CR	X (XX.X%)			
PR				
SD				
PD				
NE				

Not Done				

Table 26: Duration of Response (Response Population)

	Overall No. of Patients N=XX	**Dose Escalation Phase No. of Patients (N=XX)**	**Expansion Phase sqNSCLC Cohort No. of Patients (N=XX)**	**Expansion Phase Basket Cohort No. of Patients (N=XX)**
Median Duration of Response (days)				
Min. (days)				
Max. (days)				

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]				
[redacted]				

Table 28: Overall Survival Summary (Survival Population)

	Overall No. of Patients N=XX	**Dose Escalation Phase No. of Patients (N=XX)**	**Expansion Phase sqNSCLC Cohort No. of Patients (N=XX)**	**Expansion Phase Basket Cohort No. of Patients (N=XX)**
Median OS (days)				
Min. (days)				
Max. (days)				
OS rate at 6 months				

Table 29: Progression-Free Survival Summary (Survival Population)

	Overall No. of Patients N=XX	**Dose Escalation Phase No. of Patients (N=XX)**	**Expansion Phase sqNSCLC Cohort No. of Patients (N=XX)**	**Expansion Phase Basket Cohort No. of Patients (N=XX)**
Median PFS (days)				
Min. (days)				
Max. (days)				
PFS rate at 6 months				

5.10.1 Response for tumour markers

Any patients with elevated tumour markers at baseline will have their disease response evaluated by tumour marker. Spider plots will be created for the CSR [redacted]. Please refer to Section 9.4 in the [redacted] SAP Appendix for further information.

5.10.2 [redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

5.11 General data conventions

Data will be grouped according to the assigned dose cohort, as specified in the study protocol. Patients who deviate from the assigned dose and/or schedule will be clearly described in the CSR with regards to their treatment modification and if applicable in the list of protocol deviations (Section 5.4).

Continuous variables will be summarised and presented with summary statistics.

Categorical variables will be summarised in frequency tables. Percentages in the summary tables will be rounded and may therefore not always add up to exactly 100%.

The convention in RAVE is that an unknown day resolves to 1st of the month and an unknown month resolves to January. Dates may be ordered by this.

Durations of AEs: the start date of an AE is considered as Day 1 of the event and should be included in all duration calculations (i.e. if an AE starts and stops on same day, the duration should be reported as one day).

- For unrelated AEs, those with missing or partially completed end dates will not be excluded from analysis and the duration of the AE will be calculated from the first day of the month (if unknown) or first day of the year (based on RAVE conventions).
- For related AEs, prior to final data lock, an end date will be either i) confirmed AE end date or ii) stabilisation of AE. Cases where this is not possible are if the patient was lost to FU or the patient started a new anti-cancer therapy. If the patient starts new therapy then the AE should be recorded as recovering/resolving. If lost to FU then the AE would stay as not recovered/not resolved. In both these cases duration would not be calculated.

Time to onset of AEs from IMP administration: the time to onset should be calculated from the date of the first administration of IMP in the trial (e.g. Cycle 1, Day 1). Where multiple cycles of IMP are given, AEs occurring within a specific cycle should also have times to onset calculated from the first dose of IMP in the corresponding cycle. Onset time will be calculated as 0 if the AE occurs on the same day as the dose; however, if the start time is missing, onset time will not be calculated (only applicable when the drug admin has a start time entered).

AE assignment: AE is assigned to the cycle it begins in. This is regardless of whether the AE start time shows the AE started before the dose that day. The only exception is during Cycle 1; if 'Did AE occur prior to first dose' is checked then no cycle will be assigned.

Duration of treatment: the start date of treatment is considered as Day 1 and the duration of treatment should be inclusive of the start and end dates. For infusions of IMP (<24 hours duration) the duration should be calculated as the time elapsed between the start and end times of the infusion. Duration of treatment will be described using summary statistics.

Duration of response: the time between the initial observed response to therapy (e.g. PR) and subsequent disease progression or relapse, inclusive of the date of the initial response.

Completed cycle: a completed cycle constitutes 28 days of IMP data entered for each expected weekly visit (despite dose modifications) or if Cycle 2 data has been entered, this assumes Cycle 1 has been completed.

Treated patients: from an eCRF perspective, if drug admin form 'total administered dose' is completed, this constitutes a treated patient.

5.12 Statistical software

Medidata RAVE will be used as the Electronic Data Capture (EDC) system for the trial.

SAS version 9.4 will be used to generate data listings and summary tables/graphs.

5.13 Decimal places

When data is used in calculations it important that rounding is only conducted when the final test result is obtained (to avoid accumulation of errors).
All percentages should be presented to 1 decimal place. If a percentage value is less than 0.1% on rounding, then use '<0.1%'.

Days to be presented to 0 decimal places.

5.14 Supplementary analysis (data collected outside of the clinical database)

5.14.1 Pharmacokinetics

Patients who provided post-treatment plasma samples for PK analysis were evaluable for assessment of PK.

Intact BT1718 (parental) plasma concentration versus time data will be analysed using non-compartmental methods. The PK parameters to be determined for BT1718 include C_{max}, [redacted] AUC, $T_{1/2}$, [redacted]. Graphical summaries of individual concentration versus time curves and PK parameters will be generated.

Total DM1 (DM1 in BT1718, any peptidyl-DM1 metabolites of BT1718, and other DM1-containing mixed disulphides and free DM1) plasma concentration versus time data will be analysed using non-compartmental methods, as above.

[redacted]

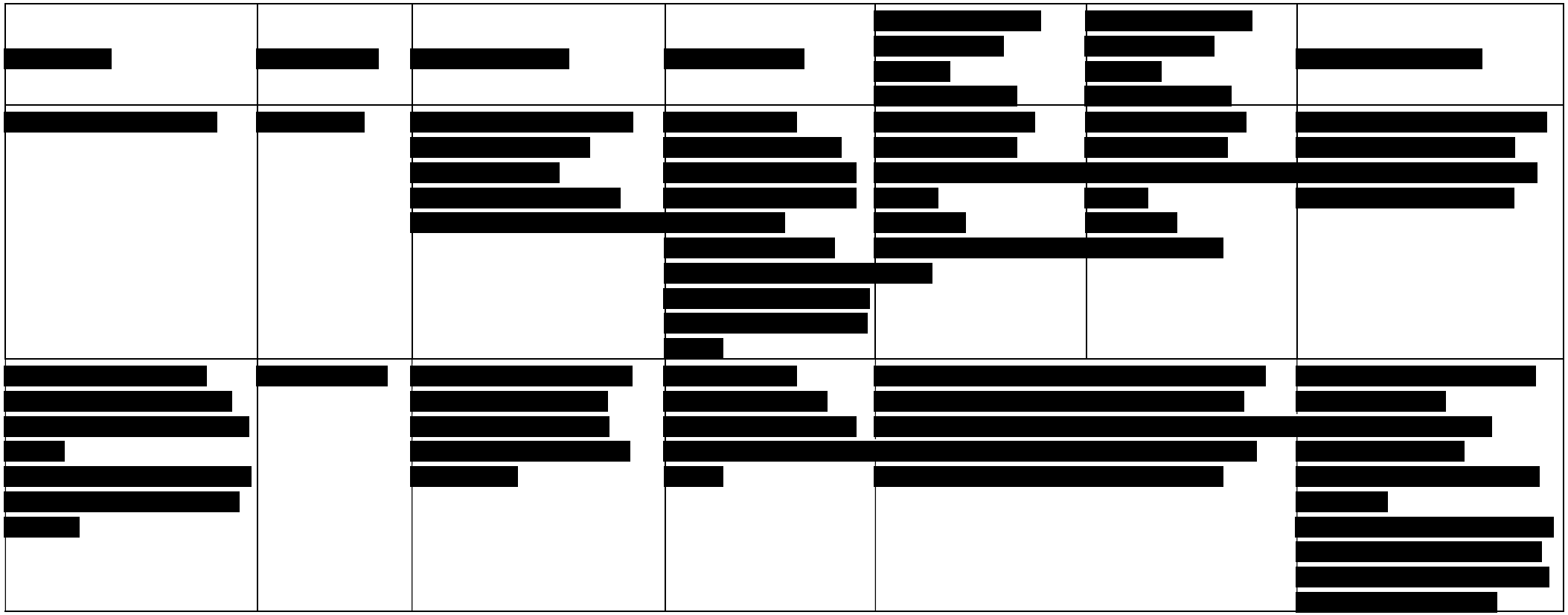
PK analyses will be described in supplementary lab reports:

- PK blood analysis report [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Data will be delivered at the end of the trial and will be reported in an appendix to the CSR or within the body of the CSR.

5.14.2 Biomarker

[redacted]



5.15 Other statistical analysis

[redacted]

Table 32: Tertiary Endpoints

Tertiary objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

6 LISTINGS, TABLES AND FIGURES

Data from the clinical database will be presented in the following listings, tables and figures.

6.1 Listings

Table 33: Planned Listing Titles and Numbering

16.2.1	**Discontinued Patients**	
16.2.1.1	Off-Study	CP_LIS
16.2.2	**Deviations**	
16.2.2.1	List of Deviations in accordance with current SOP(s)[2]	
16.2.3	**Patients Excluded from the Efficacy Analysis**	
16.2.3.1	Screen Failure Patients[2]	
16.2.3.2	Enrolment	ENR_LIS
16.2.3.3	Summary of Patient Populations	**Table *2***
16.2.4	**Demographic Data**	
16.2.4.1	Demographics	DM_LIS
16.2.4.2	Medical History	MH_LIS
16.2.4.3	Prior and Concomitant Medications	CM_LIS
16.2.4.4	Diagnosis	DG_LIS
16.2.4.5	Previous Treatment for Malignant Disease – Surgery	PTSURGERY_LIS
16.2.4.6	Previous Treatment for Malignant Disease – Chemotherapy/Other Therapy	PTCHEMOOTH_LIS
16.2.4.7	Previous Treatment for Malignant Disease – Radiotherapy	PTRADIO_LIS
16.2.4.8	Medical Procedures	MP_LIS
16.2.4.9	Pregnancy Test	PREG_LIS
16.2.4.10	Physical Examination	PE_LIS
16.2.4.11	Date of Visit	DOV_LIS
16.2.5	**Compliance and/or Drug Concentration Data**	
16.2.5.1	BT1718 Administration	EXIV_LIS
16.2.5.2	IMP Received	IMPREC_LIS
16.2.6	**Efficacy data**	

[2] Manually produced.

16.2.6.1	Target Lesions (RECIST)	TG_LIS
16.2.6.2	Non-Target Lesions (RECIST)	NT_LIS
16.2.6.3	Tumour Response (RECIST)	TR_LIS
16.2.6.4	Tumour Markers	TMCYCLE_LIS
16.2.6.5	Survival	SV_LIS
16.2.6.6	New Therapy	NEWTHER_LIS
16.2.6.7	Disease Progression	DISPROG_LIS
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
16.2.7	**Safety Data**	
16.2.7.1	Adverse Events	AE_LIS
16.2.7.2	Adverse Events by System Organ Class	AE_SOC_LIS
16.2.7.3	Follow Up	FU_LIS
16.2.7.4	WHO Performance Status	WHO_LIS
16.2.7.5	Haematology (Parameters listed - Haemoglobin, WBC, Neutrophils, Lymphocytes, Platelets)	LH_LIS
16.2.7.6	Urinalysis (Parameters listed -Glucose, Protein, Blood, pH)	LU_LIS
16.2.7.7	Coagulation (Parameters listed – Prothrombin time (PT), Activated partial thromboplastin time (APTT), International normalised ratio (INR)	LCG_LIS
16.2.7.8	Biochemistry (Parameters listed – Sodium, Potassium, Calcium (adjusted), Phosphate, Urea, Creatinine, Albumin, Bilirubin, ALP, ALT, AST, Magnesium, Fasting glucose, Random Glucose, GGT)	LC_LIS
16.2.7.9	Glucose Finger-Prick Test	GLUCOSE_LIS
16.2.7.10	Vital Signs	VSALL_LIS

16.2.7.11	ECG	EG_LIS
[redacted]	[redacted] and Related Toxicity Summary (Safety Population) [2]	[redacted]

6.2 Tables

Table 34: Planned Table Titles and Numbering

Table Number	Table Name	Section of RAP where example table is presented
14.1	**Demographic Data**	
14.1.1	Reasons for Patient Withdrawal/Completion (Full Analysis Population)	Section 5.3, Table 8
14.1.2	Reasons for Patient Withdrawal/Completion (Safety Population)	Section 5.3, Table 8
14.1.3	Participant Flow (Dose Escalation Phase and Expansion Phase; Full Analysis Population)	Section 7.1, Table 35
14.1.4	Baseline Characteristics (Full Analysis Population)	Section 5.2, Table 3
14.1.5	Primary Diagnosis at Baseline (Full Analysis Population)	Section 5.2, Table 4
14.1.6	Summary of Baseline Disease Sites Taken From Tumour Type From Baseline Measurable and Non-Measurable Disease Assessments (Full Analysis Population)	Section 5.2, Table 5
14.1.7	Previous Treatment for Malignant Disease (Full Analysis Population)	Section 5.2, Table 6
14.1.8	Lines of Previous Chemotherapy/Other Therapy (Full Analysis Population) [2]	Section 5.2, Table 7
14.1.9	Treatment Compliance in Cycle 1 (Dose Escalation Phase; Safety Population)	Section 5.5, Table 10

<table>
<tr><td>14.1.10</td><td>Treatment compliance in Cycles 1 & 2 (Expansion Phase; Safety Population)</td><td>Section 5.5, Table 11</td></tr>
<tr><td>14.1.11</td><td>Time on Treatment (Safety Population)</td><td>Section 5.5, Table 12</td></tr>
<tr><td>14.1.12</td><td>Dosing Modifications (Safety Population)</td><td>Section 5.6, Table 13</td></tr>
<tr><td>14.2</td><td>Efficacy Data</td><td></td></tr>
<tr><td>14.2.1</td><td>Best Overall Response (Response Population)</td><td>Section 5.10, Table 25</td></tr>
<tr><td>14.2.2</td><td>Duration of Response (Response Population)</td><td>Section 5.10 , Table 27</td></tr>
<tr><td>14.2.3</td><td>Duration of Stable Disease (Response Population)</td><td>Section 5.10 , Table 27</td></tr>
<tr><td>14.2.4</td><td>Overall Survival Summary (Survival Population)</td><td>Section 5.10, Error! Reference source not found.</td></tr>
<tr><td>14.2.5</td><td>Progression-Free Survival Summary (Survival Population)</td><td>Section 5.10, Table 28: Overall Survival Summary (Survival Population)
<table>
<tr><th></th><th>Overall No. of Patients N=XX</th><th>Dose Escalation Phase No. of Patients (N=XX)</th><th>Expansion Phase sqNSCLC Cohort No. of Patients (N=XX)</th><th>Expansion Phase Basket Cohort No. of Patients (N=XX)</th></tr>
<tr><td>Median OS (days)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Min. (days)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Max. (days)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>OS rate at 6 months</td><td></td><td></td><td></td><td></td></tr>
</table></td></tr>
</table>

		Table *29*
14.3	**Safety Data**	
14.3.1a	Overview of Treatment-Emergent Adverse Events by Cohort (Dose Escalation Phase; Safety Population)	Table 17
14.3.2a	Frequency of All Adverse Events by Cohort (Dose Escalation Phase; Safety Population)	Table 14
14.3.3a	Frequency of Pre-Treatment Adverse Events by Cohort (Dose Escalation Phase; Safety Population)	Based on Table 14
14.3.4a	Frequency of All Treatment-Emergent Adverse Events by Cohort (Dose Escalation Phase; Safety Population)	Based on Table 14
14.3.5a	Frequency of Related Treatment-Emergent Adverse Events by Cohort (Dose Escalation Phase; Safety Population)	Based on Table 14
14.3.6a	Frequency of Related Treatment-Emergent Adverse Events (Grade ≥3) by Cohort (Dose Escalation Phase; Safety Population)	Based on Table 14
14.3.7a	Frequency of Treatment-Emergent Adverse Events by Worst CTCAE Grade within an Episode by Cohort (Dose Escalation	Based on Table 16

	Phase; Safety Population)	
14.3.8a	Frequency of Patients with Treatment-Emergent Adverse Events by Worst CTCAE Grade by Cohort (Dose Escalation Phase; Safety Population)	Based on Table 16
14.3.9a	Frequency of All Treatment-Emergent Serious Adverse Events by Cohort (Dose Escalation Phase; Safety Population)	Based on Table 14
14.3.10a	Frequency of All Treatment-Emergent Non-Serious Adverse Events by Cohort (Dose Escalation Phase; Safety Population)	Based on Table 14
14.3.11a	Frequency of Related Treatment-Emergent Serious Adverse Events by Cohort (Dose Escalation Phase; Safety Population)	Based on Table 14
14.3.12a	Summary of Non-Related Treatment-Emergent Serious Adverse Events by Cohort (Dose Escalation Phase; Safety Population)	Based on Table 14
14.3.13a	Summary of Treatment-Emergent Adverse Events Leading to Patient Withdrawal (Dose Escalation Phase; Safety Population)	Based on Table 19
14.3.1b	Overview of Treatment-Emergent Adverse Events by	Table 18

	Cohort (Expansion Phase; Safety Population)	
14.3.2b	Frequency of All Adverse Events by Cohort (Expansion Phase; Safety Population)	Table 15
14.3.3b	Frequency of Pre-Treatment Adverse Events by Cohort (Expansion Phase; Safety Population)	Based on Table 15
14.3.4b	Frequency of All Treatment-Emergent Adverse Events by Cohort (Expansion Phase; Safety Population)	Based on Table 15
14.3.5b	Frequency of Related Treatment-Emergent Adverse Events by Cohort (Expansion Phase; Safety Population)	Based on Table 15
14.3.6b	Frequency of Related Treatment-Emergent Adverse Events (Grade ≥3) by Cohort (Expansion Phase; Safety Population)	Based on Table 15
14.3.7b	Frequency of Treatment-Emergent Adverse Events by Worst CTCAE Grade within an Episode by Cohort (Expansion Phase; Safety Population)	Based on Table 16
14.3.8b	Frequency of Patients with Treatment-Emergent Adverse Events by Worst CTCAE Grade by	Based on Table 16

	Cohort (Expansion Phase; Safety Population)	
14.3.9b	Frequency of All Treatment-Emergent Serious Adverse Events by Cohort (Expansion Phase; Safety Population)	Based on Table 15
14.3.10b	Frequency of All Treatment Emergent Non-Serious Adverse Events by Cohort (Expansion Phase; Safety Population)	Based on Table 15
14.3.11b	Frequency of Related Treatment Emergent Serious Adverse Events by Cohort (Expansion Phase; Safety Population)	Based on Table 15
14.3.12b	Summary of Non-Related Treatment-Emergent Serious Adverse Events by Cohort (Expansion Phase; Safety Population)	Based on Table 15
14.3.13b	Summary of Treatment-Emergent Adverse Events Leading to Patient Withdrawal (Expansion Phase; Safety Population)	Based on Table 20
14.3.14	Dose Limiting Toxicities (Dose Escalation Phase; Safety Population)	Table 24
14.3.15	Summary of Haematology Parameters by CTCAE Grade (Safety Population)	Table 21

14.3.16	Summary of Biochemistry Parameters by CTCAE Grade (Safety Population)	Table 22
14.3.17	Summary of Coagulation Parameters by CTCAE Grade (Safety Population)	Based on Table 22

7 PRESENTATION OF RESULTS IN ISRCTN INCLUDING ADDITIONAL TABLES

The following information will be used for presentation and upload of trial data on ISRCTN. The data presented will be consistent with the final CSR but will be tabulated in a format that fits with the ISRCTN requirements.

The tables programmed for ISRCTN will be included in Section 14 of the CSR.

7.1 Participant Flow Chart

The fields in the below flow charts will be programmed and presented as a table and the flow chart will be manually prepared for ISRCTN and the CSR.

Table 35: Table Participant Flow (Dose Escalation Phase and Expansion Phase; Full Analysis Population)

	Phase I, Escalation Phase								**Phase IIa**	
	Twice Weekly Dosing			Once Weekly Dosing					Expansion Phase	
	0.6mg/m^2 - 4.8 mg/m^2	9.6 mg/m^2	7.2 mg/m^2	9.6 mg/m^2	15 mg/m^2	20 mg/m^2	25 mg/m^2	32 mg/m^2	sqNSCLC Cohort	Basket Cohort
Enrolled										
Received BT1718										
Entered Survival FU										
Withdrew or died during treatment period										
FAP										
Safety										
Response										

Figure 2 Participant Flow Chart Escalation Phase

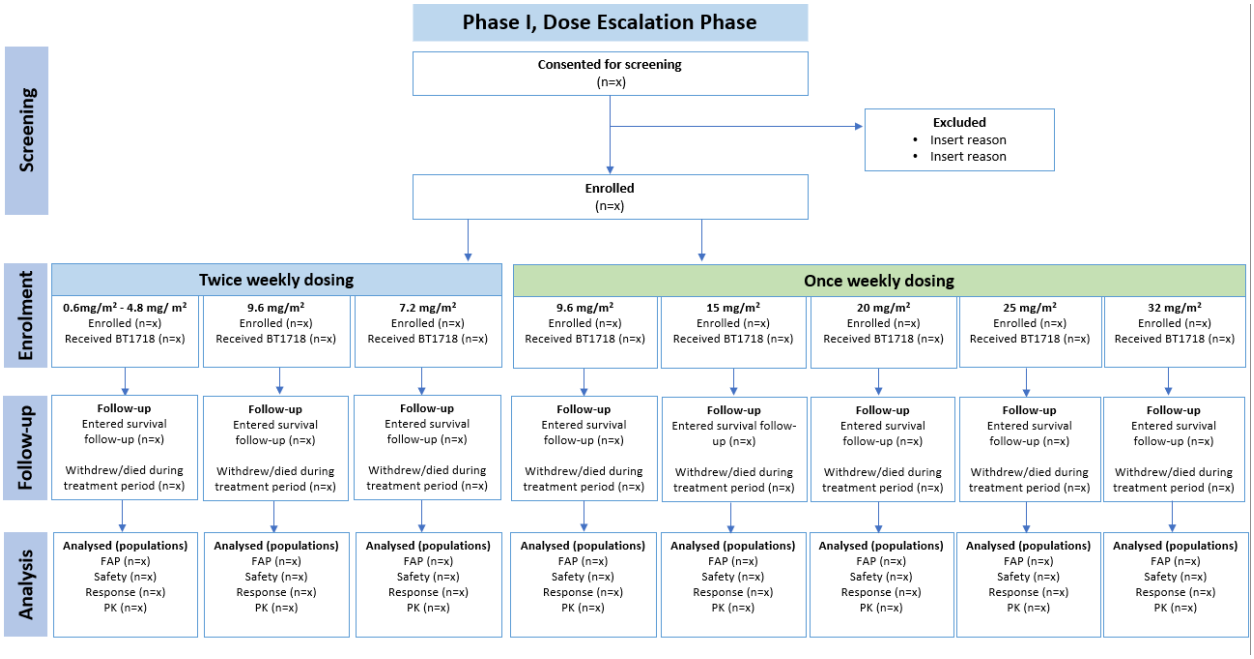
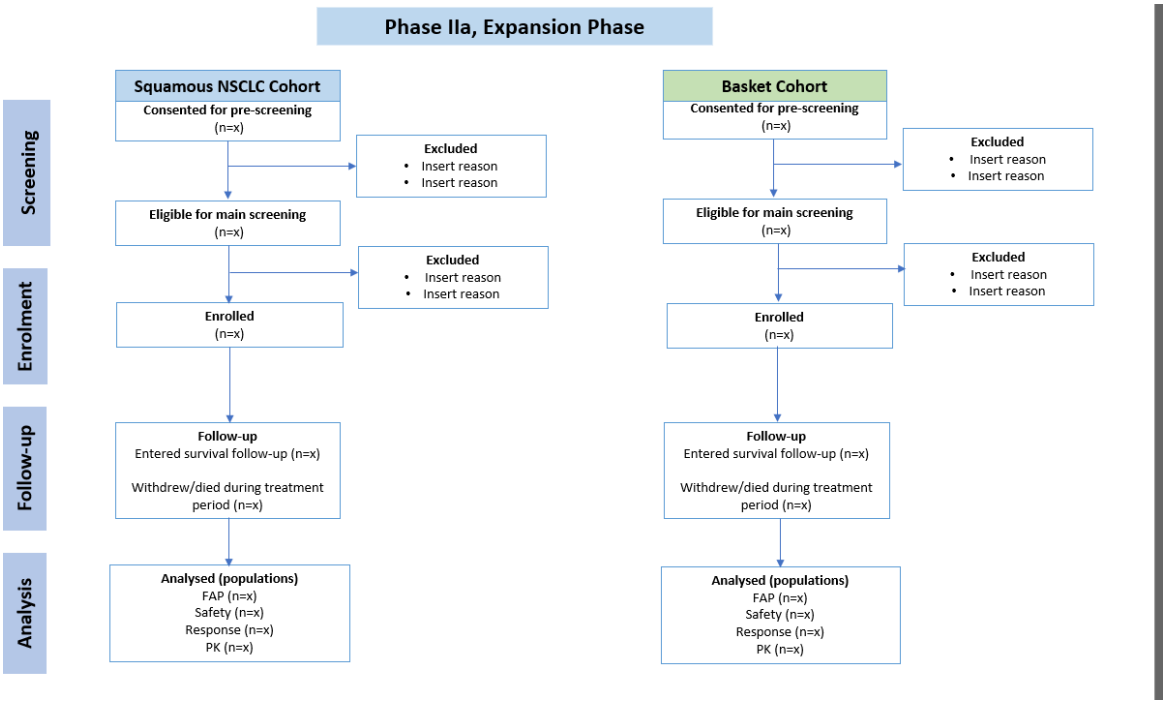


Figure 3 Participant Flow Chart Expansion Phase



7.2 Baseline Characteristics

The baseline characteristics section of the results upload will include details as per **Table 3** and **Table 4** in Section 5.2 for use on ISRCTN.

7.3 Outcome Measures

Primary and secondary endpoints will be reported on the ISRCTN website as outcome measures as follows. Results will be reported for all Primary and Secondary Endpoints.

7.3.1 Primary outcome measures

Primary Objective	Outcome measures
To propose a RP2D for evaluation by establishing the MTD and/or MAD, of BT1718 given in patients with advanced solid tumours, at one or more dosing schedules. Determine a dose at which no more than one out of six patients at the same dose level experiences a probable or highly probable BT1718-related DLT.	**MTD of BT1718 Twice weekly/Once weekly** The results for this outcome measure will be uploaded to ISRCTN as a pdf (manually prepared table for the CSR).
	MAD of BT1718 Twice weekly/Once weekly The results for this outcome measure will be uploaded to ISRCTN as a pdf (manually prepared table for the CSR).
	RP2D The results for this outcome measure will be uploaded to ISRCTN as a pdf (manually prepared table for the CSR).
	Number of participants who experienced DLTs The results for this outcome measure will use **Table 24** in Sections 5.9.2 for ISRCTN.
To assess the safety and toxicity profile of BT1718 in patients with advanced solid tumours.	The results for this outcome measure will include the following details for use on ISRCTN: • Overall AEs (Dose Escalation Phase) –will use **Table 14** in Section 5.8. • Overall AEs (Expansion Phase) –will use **Table 15** in Section 5.8. • Overall SAEs - additional versions of **Table 14** and **Table 15** will be created. • Overall Non-Serious AEs - additional versions of **Table 14** and **Table 15** will be created.

7.3.2 Secondary outcome measures

<table>
<tr><th>Secondary Objective</th><th>Outcome measures</th></tr>
<tr><td>To investigate the PK behaviour of BT1718 in humans.</td><td>Measurement of C_{max}, AUC, $t_{½}$, and other PK parameters of BT1718 in plasma, both as an intact and cleaved molecules.

The results for this outcome measure will be uploaded to ISRCTN as a pdf table(s) from the PK report(s) generated.</td></tr>
<tr><td>To assess preliminary signals of BT1718 efficacy in dose escalation and in relevant tumour types with high expression of MT1-MMP in the expansion phase.</td><td>Number of patients with each of CR, PR, SD, PD or NE according to RECIST V1.1.
The results for this outcome measure will use Table 25,
Table 28: Overall Survival Summary (Survival Population)

<table>
<tr><th></th><th>Overall No. of Patients N=XX</th><th>Dose Escalation Phase No. of Patients (N=XX)</th><th>Expansion Phase sqNSCLC Cohort No. of Patients (N=XX)</th><th>Expansion Phase Basket Cohort No. of Patients (N=XX)</th></tr>
<tr><td>Median OS (days)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Min. (days)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Max. (days)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>OS rate at 6 months</td><td></td><td></td><td></td><td></td></tr>
</table>

Table 29, Error! Reference source not found., in Section 5.10 for use on ISRCTN.</td></tr>
</table>

8 REPORTING OF CLINICAL TRIAL RESULTS TO PATIENTS AND PUBLIC

At the end of the trial summary results in lay language will be provided on the CRUK website at the following link: https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-bt1718-for-advanced-cancer

Additionally, the HRA research summaries website will also provide a link to the lay summary on the CRUK website above. CRUK CDD will provide Investigator Sites with a .pdf copy of the results

from the CRUK trials database for distribution to patients and their families (as appropriate and at the discretion of the investigator).

9 REFERENCES

- Guidelines for the Content of Statistical Analysis Alans in Clinical Trials, JAMA December 2017, Volume 318, Number 23. Gamble et al.