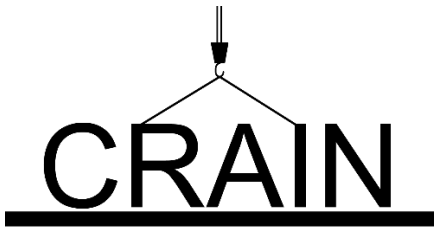

CRAIN

Statistical Analysis Plan

Trial name:	A phase 1b TiTE-CRM dose escalation clinical trial of Tolinapant (ASTX660) in combination with standard radical chemoradiotherapy in cervical cancer
Trial registration number:	EudraCT reference no: 2021-006555-34 ISCRTN: 18574865 IRAS Number: 1004372
Protocol title and version number:	CRAIN Protocol v6 12-JUL-2024
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To be approved and reviewed by:

	Name	Signature	Date
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List of Abbreviations

AE	Adverse Event
CI	Chief Investigator
eCRF	Electronic Case Report Form
CRT	Cisplatin & Radiotherapy
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
IAP	Inhibitor of Apoptosis Protein
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
PI	Principal Investigator
RECIST	Response evaluation criteria in solid tumours
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SCTU	Southampton Clinical Trials Unit
SOP	Standard operating procedure
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TiTE-CRM	Time-to-Event Continual Reassessment Method
TTL	Target Toxicity Level

KEYWORDS
Cervical cancer; Tolinapant; Chemoradiation; Chemoradiotherapy; Cisplatin;

1 Introduction

1.1 Purpose of SAP

This statistical analysis plan (SAP) describes in detail the methods that will be used to analyse the data collected as part of the Phase 1b TiTE-CRM dose escalation trial, CRAIN. It does not cover any biomarker or tissue sample analyses which will be detailed in a separate analysis plan.

The analyses described will form the basis of the final trial publication and will follow this document to ensure that they are conducted in a scientifically valid manner and to avoid post hoc decisions which may affect or influence any interpretation of the results. Any deviations from the SAP will be detailed in the final report.

1.2 Trial Personnel

CRAIN Chief Investigator:	**Professor Peter Hoskin** peterhoskin@nhs.net
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1.3 Trial background and rationale (short synopsis)

CRAIN is a phase 1b trial to determine the maximum tolerated dose (MTD) of the Inhibitor of Apoptosis Proteins (IAP) inhibitor Tolinapant combined with Cisplatin & radiotherapy (CRT) and to then determine whether there is a signal of efficacy sufficient to justify further study of the combination, in the primary treatment of cervical cancer.

Cervical cancer is the fourth most common cancer in women, with an estimated 266,000 deaths worldwide in 2012[1], where almost nine out of ten (87%) cervical cancer deaths occur in less developed countries. Current standard of care in the UK for locally advanced cervical cancer is concurrent chemoradiotherapy with weekly Cisplatin, yet 5-year overall survival rates are only around 65% with a distant relapse rate of 50%[2]. This treatment is associated with long term side effects in around half of patients with up to 15% suffering from grade 3-4 toxicity[3].

Preclinical studies performed using Tolinapant in combination with Cisplatin and radiotherapy (RT) showed an inhibition of tumour growth and enhanced survival in multiple HPV+/- head and neck squamous cell carcinoma models[4]. Additional data using a syngeneic mouse oral cancer model also showed Tolinapant in combination induced tumour growth inhibition compared to RT alone and Tolinapant alone[4]. In vitro studies by Professor Kaye Williams (co-investigator) in 4 cervical cancer models (Hela, Caski, SiHa, Me180) indicate that Tolinapant inhibits cIAP1 expression and induces co-incidental apoptosis (6-40% induction over baseline; Promega RealTime-Glo™ Annexin V Apoptosis Assay). Radiation (2Gy) or Cisplatin alone induced apoptosis in all cell lines (RT range 15-66% over baseline; Cisplatin 10-40%). The combination of Tolinapant, Cisplatin and radiation significantly enhanced apoptosis observed versus radiation alone across the panel. Induction of apoptosis correlated with significantly reduced clonogenic survival following treatment with Tolinapant, Cisplatin and radiation versus radiotherapy alone. Initial in vivo studies indicated that Tolinapant inhibited cIAP1 expression in Me180 xenografts established in Balb-c nude mice. Combining Tolinapant with chemo(Cisplatin)-radiotherapy enhanced response versus chemoradiotherapy alone whilst having no impact on acute gastro-intestinal (GI) toxicity analysed via crypt assay.

There is therefore a strong rationale to combine Tolinapant with CRT. Improvement in loco-regional control is closely related to survival improvement in cervical cancer hence this study has the potential to improve survival in a population of relatively young active women.[5]

1.4 Objectives

The objectives of Phase 1b, as set out in the CRAIN protocol are:

Primary:

- To establish the maximum tolerated safe dose (MTD) of Tolinapant in combination with Cisplatin & Radiotherapy (CRT) to aid dose selection for a phase II trial

Secondary:

- To determine the safety and tolerability of the combination of CRT+Tolinapant
- To assess the response rates to CRT+Tolinapant
- To ensure the addition of Tolinapant does not interfere with planned delivery of CRT

Tertiary (not covered by this SAP):

- To evaluate on-target effects of Tolinapant
- To explore tissue and liquid biomarkers which may predict response to Tolinapant

1.5 Definition of endpoints

A brief description of the endpoints for CRAIN Phase 1b is given below, with further detail on derivations and analyses provided in sections 3.3, 4, and 5.

1.5.1 Definition of primary endpoint

The maximum tolerated safe dose is defined as the dose where the estimated toxicity rate is closest to the target toxicity level (TTL) of 25%. The tested dose levels are modelled using a Time-to-Event Continual Reassessment Method (TiTE-CRM) which estimates the toxicity rate for each dose using the number of patients in the study experiencing a Dose Limiting Toxicity (DLT), and the cumulative amount of time spent in the study. DLTs will be categorised using the Common Terminology Criteria for Adverse Events (CTCAE) version 5 over 12 weeks from the start of treatment. See the full list of defined DLTs given in section 3.6.

1.5.2 Definition of secondary endpoints

The safety and tolerability of the combination for each dose level will be assessed using the overall number of Adverse Events (AEs) and Serious Adverse Events (SAEs), graded using CTCAE v5.
RECIST version 1.1 will be used to determine complete and partial response rates at three months from completion of chemoradiation as assessed by measurements on MRI scan.
Relative dose intensity of CRT and total chemotherapy delays will be used to ensure the addition of Tolinapant does not interfere with the planned delivery of CRT.

1.6 Analysis principles

All analyses will be reported according to CONSORT 2010 and Southampton Clinical Trials Unit (SCTU) standard operating procedure (SOP) on planning, implementing and reporting statistical analyses (CTU/SOP/5058).

2 Design considerations

2.1 Description of trial design

This is a phase 1b open-label, multi-centre study to characterise the safety and tolerability and initial evidence for clinical activity of Tolinapant when administered in combination with Cisplatin based CRT to women with newly diagnosed cancer of the cervix. The study uses a two-stage Time-to-Event Continual Reassessment Method to find the optimal dose of Tolinapant in combination with CRT.

A maximum of 42 patients will be recruited and treated according to the dose defined by the TiTE-CRM. The first patient recruited will be assigned 90mg as this will allow for a dose reduction to 60mg for future patients if the first patients experience excess toxicity. The TiTE-CRM will identify the MTD based on the assessment of dose limiting toxicities (DLTs).

The TiTE-CRM design utilises a one parameter logistic model and linear weights. Meaning that information accrued through the DLT assessment period (12 weeks from the start of treatment) is given weight equal to the proportion if the assessment period that has passed. Any patient experiencing a DLT will be included in the analysis as a full patient equivalent, regardless of the timing of the event.

The treatment schedule is planned to last 7 weeks, with an additional 5 weeks follow up for DLTs. Linear weighting will be used in the TiTE-CRM. For example:

- At trial week 12 (i.e. completion of treatment and 5 weeks of follow-up): in the absence of a DLT this would account for a full patient tolerable outcome
- At trial week 6: in the absence of a DLT this would account for 0.5 equivalent of a tolerable outcome

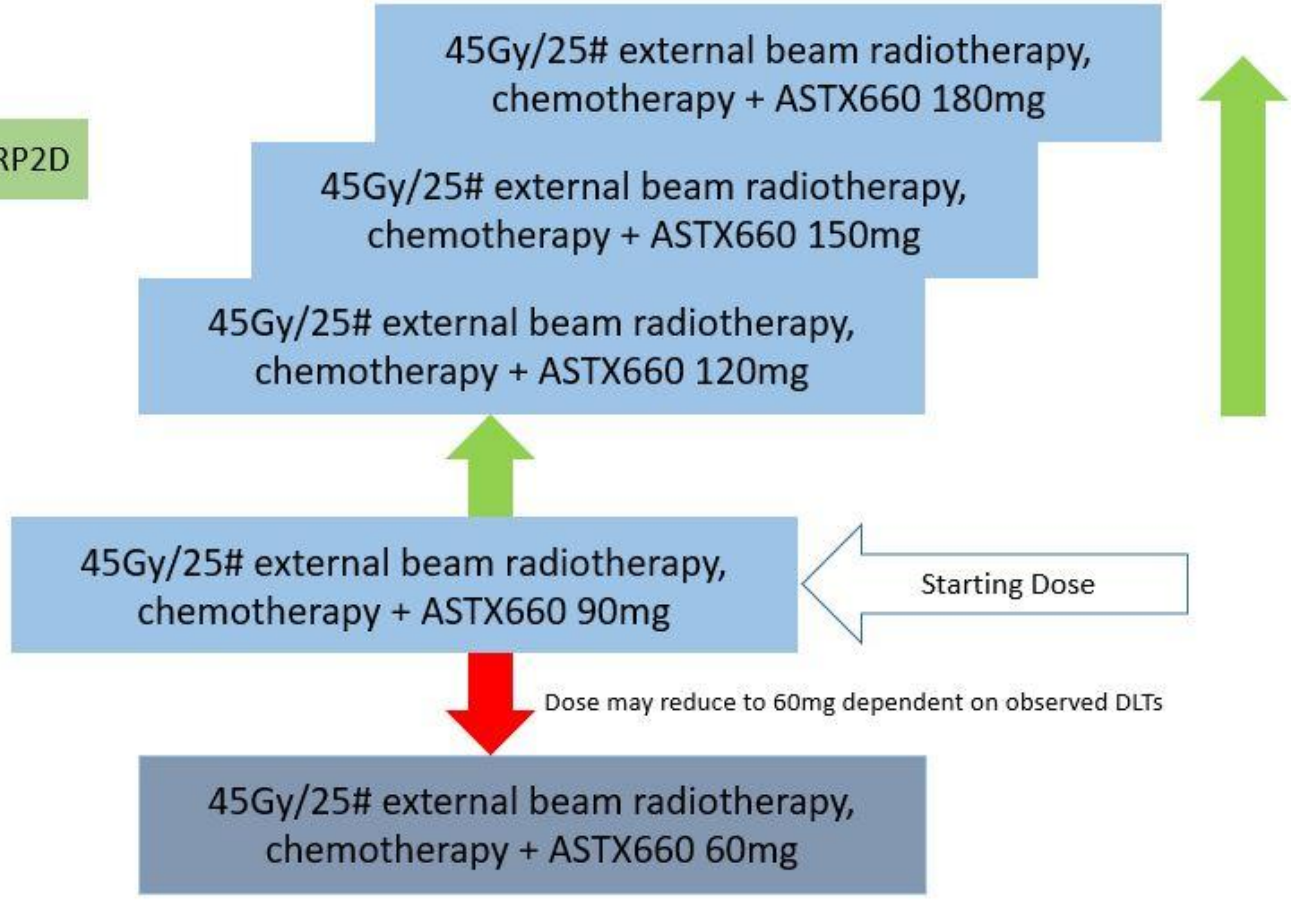
The trial will stop for success if 15 concurrent patients are treated at the current recommendation for the MTD, whilst also ensuring a total of at least 18 patients have been treated at the recommended phase II dose. The trial will stop for safety if there is sufficient evidence to suggest that dose level 1 (60mg) is too toxic i.e. a posterior probability of DLT of 35% or higher is found.

2.3.1 TRIAL SCHEMA

A phase Ib TiTE-CRM dose escalation clinical trial of tolinapant in combination with standard radical chemoradiotherapy in cervical cancer.

Ensure a minimum of n=18 at the RP2D

- First two patients will receive 90mg
- Dose for each subsequent patient based on DLTs from previous patients inputted into the TiTE-CRM model. The dose recommended by the model will be reviewed and confirmed by SRC committee
- Dose will only escalate when at least one patient has completed all treatment cycles without a DLT
- MTD will be dose closest to 25% DLT rate
- No dose skipping allowed for escalation



2.1.2 Treatment schedule

Cisplatin Administration
CRT treatment weeks should always start on a Monday, however cisplatin can be given on any day within the week. Weekly cisplatin dose should be 40mg/m^2 but, in line with local practice, can be dose banded and does not need to be given prior to radiotherapy.

External Beam Radiotherapy Administration
External beam radiotherapy administration should be a standard dose of 45Gy in 25 daily fractions over 5 weeks with nodal boosting performed using a simultaneous integrated boost (SIB) for radiologically positive nodes to a total dose of 55-60Gy in 25 daily fractions. The QA programme for the study will be co-ordinated by the National Radiotherapy Trials QA (RTTQA) Group. The CRAIN trial is streamlined through participation in the INTERLACE trial and EMBRACE.

Brachytherapy Administration
This is followed by brachytherapy for which common schedules will be a further 28Gy in 4 fractions high-dose-rate or 34Gy in 2 fractions pulsed- dose-rate, or equivalent.

Tolinapant Administration
Tolinapant in fixed dose capsules of 30 or 90mg taken orally daily for seven consecutive days as an outpatient (followed by seven consecutive days off) prior to radiotherapy on alternate weeks (weeks 1, 3, 5) during chemoradiation. Tolinapant can be taken with or without food, with the exception of PK days. On days with PK sampling, patients should refrain from eating (including soup) or drinking milk or juice for at least 2 hours prior to ingesting study drug(s) and 2 hours after ingesting study drug (4 hour fasting window). When a patient is registered, they will be allocated to a dose level of Tolinapant, they will continue to take this dose of Tolinapant throughout their participation in the CRAIN trial. The dose levels of Tolinapant that will be used in this trial are detailed in the table below.

Dose Level	**Tolinapant**
Level 1	60 mg
Level 2 (Starting level)	90 mg
Level 3	120 mg
Level 4	150 mg
Level 5	180 mg

2.2 Trial power and sample size

The sample size will vary depending on toxicities observed and dose escalation decisions. There will be a maximum of 42 patients, including 18 treated at the recommended MTD. Simulations of the study averaged 24-29 participants, with 42 deemed sufficient to both estimate the MTD and ensure that 18 were treated at the chosen dose level across a wide range of scenarios. See Appendix 1 and section 8 of the trial protocol for more details.

2.3 Timing of planned analyses

2.3.1 Safety Review committee meetings

Recruitment will be limited to three patients before the first Safety Review Committee meeting (SRC). Once two evaluable patients have received at least 7 weeks of treatment each, the SRC will review and assess the safety and toxicity of all patients.

The SRC will determine whether the trial should continue, however there will be no pause in recruitment up to the maximum of three patients whilst the review takes place. The SRC will also decide the recommended dose for future patients, the maximum number of patients to recruit on that dose and the minimum amount of data required before meeting again (this avoids too many patients being treated on the same dose).

The SRC will be guided in these decisions by the TiTE-CRM model but do not have to strictly follow its recommendations and will have the final say in all decisions. The SRC can also meet at any other time if deemed necessary, especially if there are any safety concerns raised during the study.

2.3.2 Final analysis

The final analysis will be performed once the SRC has decided that enough patients have been recruited, treated, and had their final follow-up visit as per the trial protocol or when trial funding has come to an end. The data for the final analysis will be locked once the final patient has completed their final follow-up visit and all data queries have been raised and sufficiently resolved.

3 Statistical considerations

3.1 Primary population of interest

The population of interest for the primary endpoint is defined as all eligible patients aged 16 or over with histologically proven adenocarcinoma or squamous cell carcinoma of the cervix stage IB2/IB3/IIA1/IIA2/IIB/IIIA/IIIB/IIIC1 suitable for radical treatment with radiotherapy and cisplatin, with an ECOG Performance Status 0-1.

3.2 Definition of analysis populations

3.2.1 ITT population

This population contains all eligible patients who entered the study, whether Tolinapant was received or not, analysed according to the dose level assigned.

3.2.2 Evaluable population

This population contains all eligible patients who received any amount of Tolinapant, regardless of time on the study, analysed according to the dose level assigned.

3.3 Endpoint Estimands

3.3.1 Primary endpoint

Targeted estimand

The primary clinical question of interest is:
What is the maximum tolerated dose (MTD) of Tolinapant in combination with CRT, measured by the dose limiting toxicity (DLT) risk of each dose using the TiTE-CRM Bayesian model, in eligible women aged 16 or over with histologically proven adenocarcinoma or squamous cell carcinoma of the cervix stage IB2/IB3/IIA1/IIA2/IIB/IIIA/IIIB/IIIC1 suitable for radical treatment with radiotherapy and cisplatin, with an ECOG Performance Status 0-1, allowing for patients discontinuing the trial early due to unrelated death, or withdrawing from the study completely by reducing the weight of a patient in the model accordingly.

Population

Women aged 16 or over with histologically proven adenocarcinoma or squamous cell carcinoma of the cervix stage IB2/IB3/IIA1/IIA2/IIB/IIIA/IIIB/IIIC1 suitable for radical treatment with radiotherapy and cisplatin, meeting full CRAIN eligibility criteria as fully defined in the protocol.

Treatment

Cisplatin and External beam radiotherapy over 5 weeks with assigned dose level of Tolinapant taken orally daily for seven consecutive days on alternative weeks (1, 3, 5). This is followed by brachytherapy delivered over a maximum of 2 weeks.

Endpoint

Maximum tolerated dose of Tolinapant, defined as the closest dose to the target toxicity level of 25% as modelled using the TiTE-CRM method.

Population level summary measure

The Bayesian posterior point estimates of the risk of toxicity at each dose and corresponding 95% equal tail credible intervals estimated using the TiTE-CRM model.

Intercurrent events and strategies

The intercurrent events identified for this study and the methods used for each one are detailed below.

- **Intercurrent event: Discontinued Treatment**
    - Patients who discontinue treatment early but continue to have full follow up will be included in the model and weighted according to time spent on the study as normal. A sensitivity analysis weighting patients according to the amount of treatment and follow up is detailed in the sensitivity analysis section.
    - **Strategy:** A “treatment policy” strategy will be followed in this case i.e. discontinuing treatment early is considered to be part of the treatment pathway for these patients and this reflects the ITT principle.

- **Intercurrent event: Non-compliance with treatment schedule**
    - Patients who receive treatment but do not follow the study schedule (e.g. only receive 1 week of Tolinapant but receive all other treatment) will still be included in the model and weighted according to time spent on the study as normal. A sensitivity analysis weighting patients according to the amount of treatment and follow up is detailed in the sensitivity analysis section.
    - **Strategy:** A "treatment policy" strategy will be followed in this case i.e. not following the full treatment schedule is considered to be part of the treatment pathway for these patients and thus reflects the ITT principle.

- **Intercurrent event: Withdrawal from study for any reason before any Tolinapant is taken**
    - Patients who withdraw from the study before any Tolinapant is taken do not meet the criteria for an evaluable patient and so will be excluded from the primary analysis.
    - **Strategy:** A "principle stratum" strategy is being used in this case to estimate DLT rates because these patients will not provide any useful information to the TiTE-CRM model.

- **Intercurrent event: Complete withdrawal from study for any reason after Tolinapant is taken**
    - Patients who completely withdraw from the study and do not continue to have follow up after some Tolinapant is taken will be included in the TiTE-CRM model up until the point of their complete withdrawal. The withdrawn patient's information will be weighted accordingly, e.g. if the patient withdraws at the end of week 8, then the patient will be weighted as 2/3s of a full patient equivalent (8/12 weeks).
    - **Strategy:** A "while on treatment" strategy is being used in this case because we cannot be sure if any DLTs occurred after this point.

- **Intercurrent event: Death unrelated to treatment**
    - Patients who die during the study from a cause that is deemed to be unrelated to the study treatment (and therefore not a DLT) will be included in the TiTE-CRM model up until the point of death. The patient's time on study will be weighted accordingly, e.g. if the patient dies at the end of week 8, then the patient will be weighted as 2/3s of a full patient equivalent (8/12 weeks).
    - **Strategy:** A "while on treatment" strategy is being used in this case because it is not possible for any DLTs to occur after this point and we cannot be sure if any DLTs would have occurred after this point if the patient had continued.

- **Intercurrent event: Switching away from protocol treatment**
    - Patients who switch away from the treatment defined in the protocol (e.g. switch to carboplatin instead of cisplatin) will be included in the model and weighted according to time spent on the study as normal.
    - **Strategy:** A "treatment policy" strategy will be followed in this case i.e. switching away from the protocol treatment is considered to be part of the treatment pathway for these patients and this reflects the ITT principle.

Estimator

The toxicity levels for each dose are estimated using a TiTE-CRM model based on information on dose limiting toxicities experienced by the patients. The toxicity levels are defined as the approximate percentage of patients who would expect to experience toxicity over the course of taking the dose. Information on the simulations and scenarios used to calibrate the model can be found in Appendix 1.

The TiTE-CRM design utilises a one parameter logistic model and linear weights. This means that information accrued through the DLT assessment period (12 weeks from the start of treatment) is given weight equal to the proportion of the assessment period that has passed. However, any patient experiencing a DLT will be included in the analysis as a full patient equivalent, regardless of the timing of the event. The model assumes that DLT rates increase with the dose level and data is 'shared' across the doses to provide toxicity estimates, even for doses not taken by any patients.

Interpretation

The maximum tolerated safe dose recommended by the model is defined as the dose where the estimated toxicity rate is closest to the target toxicity level (TTL) of 25%.

Sensitivity analyses

- **Follow up to 18 weeks**

To assess the impact of longer term DLTs the DLT assessment period will be extended to the full 18 weeks of trial follow-up. The same TiTE-CRM model will be run but will now include patient follow-up, and therefore any DLTs, from weeks 13-18.

- **Treatment and follow up period weighting**

The current TITE-CRM model used on the study does not account for the amount of treatment received, only the period of time a patient is followed up. To assess whether this has an impact on the model's selection of the MTD, a sensitivity analysis will be performed. Patients will be weighted according to both the proportion of time on the trial and the amount of Tolinapnt received using the following code (taken from Supplementary Appendix C in *Kong, A., Kirkham, A.J., Savage, J.S. et al. Results and lessons learnt from the WISTERIA phase I trial combining AZD1775 with cisplatin pre- or post-operatively in head and neck cancer*):

$$\text{Weight[i]} \leftarrow (\text{split}_{[1]} * (\text{DosesTaken[i]}/\text{TotalDose}) + \text{split}_{[2]} * (\text{FUpTime[i]}/\text{obswin}))$$

Where DosesTaken is the number of doses of Tolinapant taken by patient i and TotalDose is the number of Tolinapant doses that should have been taken per-protocol (3 x 7 daily doses = 21). FUpTime is the days of follow up for patient i and obswin is the number of days that a patient should have been followed up per-protocol (84 days or 12 weeks).

$\text{Split}_{[1]}$ and $\text{split}_{[2]}$ sum to 1 and are used to weight the patient's contribution to the model further towards either the number of doses taken or the follow-up period. Effectively the primary endpoint is the situation where all weight is apportioned to the follow-up time, i.e. $\text{split}_{[1]} = 0$ and $\text{split}_{[2]} = 1$.

There will be two sensitivity analyses to explore different weightings that could have been used:

1. Apportioning doses taken and follow-up time equally, assuming they are equally as important, weighting the splits 50:50 i.e. $\text{split}_{[1]} = \text{split}_{[2]} = 0.5$
2. Apportioning all weight to the number of doses taken i.e. $\text{split}_{[1]} = 1$ and $\text{split}_{[2]} = 0$

3.4 Analysis software

SAS version 9.4 or above and/or STATA version 16 or above and/or R version 3.6.0 or above will be used for analyses.

3.5 Methods for handling data

3.5.1 Withdrawal from trial

All available data up until the point of patient withdrawal from the trial will be used in analyses unless the withdrawing patient specifies that they do not wish for their data to be used.

3.5.2 Missing data

There is no imputation of missing or incomplete data planned for the primary or secondary endpoints. A missing from eCRF (electronic case report form) category will be included in summary tables if relevant to highlight the amount of missing data.

3.5.3 Outliers

Due to the nature of the primary and secondary analyses, outliers in the data are not anticipated to be an issue thus there is no method planned for their handling.

3.5.4 Data transformations

No data transformations are planned for the final analysis.

3.6 Definition of key derived variables

3.6.1 Primary endpoint – Dose limiting toxicities

Definition of Dose limiting toxicity (as per protocol section 3.3)

Any of the following events occurring after the first dose of Tolinapant will constitute a DLT if, in the opinion of the investigator, the event is defined as **definitely or probably** related to Tolinapant:

- Grade 4 neutropenia ≥7 days duration
- Grade 3 or 4 febrile neutropenia (neutrophils <1000/mm3 with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour AND/OR life-threatening consequences with urgent intervention indicated)
- Grade 3 or 4 neutropenia associated with a separate event of bacteriologically proven sepsis happening at the same time
- Grade 3 or 4 thrombocytopenia
- Death

Any other grade 3 or 4 adverse event will constitute a DLT if, in the opinion of the investigator, the event is defined as **definitely or probably** related to Tolinapant.

In all cases of a suspected DLT, clinical judgement will be the final arbiter as to whether the event should be categorised as such.

By the time of the final analysis, all possible DLTs will have been reviewed and assessed by the Safety review committee. Dose limiting toxicities will be agreed on by the SRC guided by the criteria above and clinical judgement.

3.6.2 Primary endpoint – Full patient equivalents

For the TiTE-CRM model, the number of full patient equivalents (7 weeks of treatment and 5 of follow-up) is used to calculate the toxicity estimates. Patients who experience a DLT are counted as a full patient equivalent, regardless of the timing of the event.

For patients who do not experience a DLT, the equivalent is the percentage of the 12 weeks (84 days) of the study the patient completed. For example, a patient who withdrew after 6 weeks (42 days) would be counted as the equivalent of half a full patient, 8 weeks (56 days) as 2/3 etc.

Timings are counted from the treatment start date until the latest date in the study for that patient (up to day 84), with treatment start date as day 1.

For the sensitivity analysis extending the follow up period to 18 weeks, the same principles are followed, with 18 weeks (126 days) replacing 12 weeks.

For the sensitivity analyses weighting the treatment taken and the period of follow up the principles detailed above are applied.

3.6.3 Secondary endpoint – Response assessment

Response assessment will be derived using RECIST 1.1 guidelines[6] based on the changes in measurements of lesions from screening to the 3-month scan for all evaluable patients with a 3-month scan. A combination of the responses to target and non-target lesions will be used to give an overall assessment, see the appendix for full RECIST 1.1 guidelines.

Response assessment criteria for Target lesions

Criteria	Response
Disappearance of all lesions and pathologic lymph nodes	Complete Response (CR)
≥30% decrease in sum of longest diameters & no new lesions & no progression of non-target lesions	Partial Response (PR)
No complete/partial response or progressive disease	Stable Disease (SD)
≥20% increase in sum of longest diameters or progression of non-target lesions or new lesions	Progressive Disease (PD)

Response assessment criteria for Non-Target lesions

Criteria	Response
Disappearance of all non-target lesions and pathologic lymph nodes	Complete Response (CR)
Presence of one or more non-target lesions	Non-CR/Non-PD
Unequivocal progression of existing non-target lesions or appearance of new non-target lesions	Progressive Disease (PD)

Overall Response assessment criteria

The overall response is determined using a combination of the target and non-target responses above and whether new lesions have appeared at the later scan.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete Response (CR)	Complete Response (CR)	No	Complete Response (CR)
Complete Response (CR)	Non-CR/Non-PD	No	Partial Response (PR)
Complete Response (CR)	Not evaluated	No	Partial Response (PR)
Partial Response (PR)	Non-PD or NE	No	Partial Response (PR)
Stable Disease (SD)	Non-PD or NE	No	Stable Disease (SD)
Progressive Disease (PD)	Any	Yes or No	Progressive Disease (PD)
Not all evaluated	Non-PD	No	Non Evaluable (NE)
Any	Progressive Disease (PD)	Yes or No	Progressive Disease (PD)
Any	Any	Yes	Progressive Disease (PD)

3.6.4 Secondary endpoint – Adverse events and Serious Adverse events

Adverse and Serious Adverse events will be categorised using Common Terminology Criteria for Adverse Events (CTCAE) version 5 and coded by the CTU using the Medical Dictionary for Regulatory Activities (MedDRA) and reported for all evaluable patients.

3.7 General principles for reporting and analysis

- Descriptive statistics will be presented as appropriate to the nature of the data. For example, continuous variables may be summarised by the number of observations, mean, standard deviation, median (interquartile range if appropriate), minimum, and maximum. Categorical variables may be summarised by frequency counts and percentages for each category.
- For continuous data, the mean, standard deviation, median and IQR will generally be rounded to 1 decimal place more than the accuracy of the original data. Minimum and maximum will be displayed with the same accuracy as the original data.
- Unless otherwise stated, percentages will be presented to 1 decimal place.
- Where results are split by dose level, tables may also include a total column.
- Credible intervals will be presented with the same number of decimal places as the point estimates (e.g., 1 decimal place for percentages).
- A missing from eCRF category will be included if relevant.

4 Planned analyses and reporting

All tables, listings and figures will be based on the ITT population and split by dose level unless otherwise specified.

4.1 Disposition of the study population

A CONSORT diagram (figure 1) will be produced showing an account of the following:

- Screening data - total number screened, reasons for not entering trial.
- Eligibility data - total number assessed for eligibility against the inclusion criteria.
- Recruitment information - number consented, recruited, receiving all treatment, withdrawn/lost to follow up.

A summary of inclusions/exclusions from analysis populations i.e. the number included in each population and number and reason excluded in each population will be presented in Table 1. End of Study information will be summarised in Table 2.

4.2 Protocol deviations

Any major protocol deviations will be listed in Table 3, with a description of the deviation, the patient/dose level it applies to, and any comments or actions taken.

4.3 Baseline demographic and disease characteristics

Patient demographics (e.g. age, ethnicity) and baseline disease characteristics (e.g. type of cancer, FIGO stage, and number and size of target lesions) will be summarised by dose level and overall in Table 4. Medical history and concomitant medications are summarised in Tables 5 & 6.

4.4 Primary endpoint

Table 12 will summarise the number and type (based on the protocol criteria) of DLTs experienced on each dose level up to week 12. A summary of the output from the TiTE-CRM model will be given in table 13. This will include the number of full-patient equivalents, the estimated toxicity rate, the probability of each dose being in the target toxicity range, and the probability of the toxicity rate being deemed too toxic. A plot of the estimated dose-toxicity levels and credibility intervals is given in figure 2.

4.5 Secondary endpoints

4.5.1 Complete and Partial response rates

Table 18 will show a summary of RECIST 1.1 assessments (target, non-target, and overall) comparing screening MRI scans with those repeated at three months from completion of chemoradiation. The median percentage change in the sum of Target lesions will also be calculated, along with the range and quartiles.
The overall responses will be combined to give the complete/partial response rates, along with an estimate of the 95% confidence interval using the exact (Clopper-Pearson) method.

4.5.2 Compliance to trial drug and treatment

Compliance to each component of the trial treatment (Cisplatin, External beam radiotherapy, Tolinapant, and Brachytherapy) will be summarised in Tables 7-10. For each component, the number and total dose received will be summarised by dose level, along with the number of missed/delayed/disrupted/changed doses and the reasons for these. Relative dose intensity (100% x received dose / expected dose) will also be calculated and summarised for each separately.
End of treatment summaries (number who completed the full course of each component, any reasons for not completing) will be summarised in Table 11.

4.5.3 Performance status

Performance status results will be listed by dose level and participant in Table 30.

4.5.4 Laboratory parameters

Laboratory parameters (chemistry and haematology) will be listed by dose level, participant, and parameter in Tables 31 and 32.

4.5.5 Summary of SRC Meetings for Dose Escalation Decisions

A summary of the SRC meetings will be provided in Table 33.

4.6 Safety reporting

4.6.1 Adverse events

Table 19 gives a breakdown of the number of AEs of each CTCAE grade by dose level.
The number of patients experiencing Adverse events, along with the number of individual events, will be summarised by each SOC and CTCAE classification in Table 20. This summary is repeated in Table 21 using only Adverse events graded 3+.
Tables 22 to 24 are a repeat of tables 19 to 21 but for only AEs possibly, probably or definitely related to Tolinapant.

4.6.2 Serious Adverse events

Table 25 will show a breakdown of the number of SAEs per patient, the number of each CTCAE grade, a summary of the PI Assessments, and the reasons why the events were deemed serious.
The number of patients experiencing Serious Adverse Events, along with the number of individual events, will be summarised by each SOC and CTCAE classification in Table 26.
Tables 27 and 28 are a repeat of tables 25 and 26 but for only SAEs possibly, probably or definitely related to Tolinapant.
A list of all SAEs with details including the reason for seriousness, actions taken and the assessment of causal relationship to the study drugs and expectedness will be given in Table 29.

4.7 Additional analyses

A sensitivity analysis that repeats the Primary endpoint analysis including DLTs up to week 18 will be performed and displayed in Tables 14 and 15, along with a toxicity plot in figure 3.

Two further sensitivity analyses that repeats the Primary endpoint analysis for 12 weeks, weighting patients according to both the proportion of time on the trial and the amount of Tolinapant received. These are detailed in tables 16 and 17 and figures 4 and 5.

5 Tables, listings and figures templates

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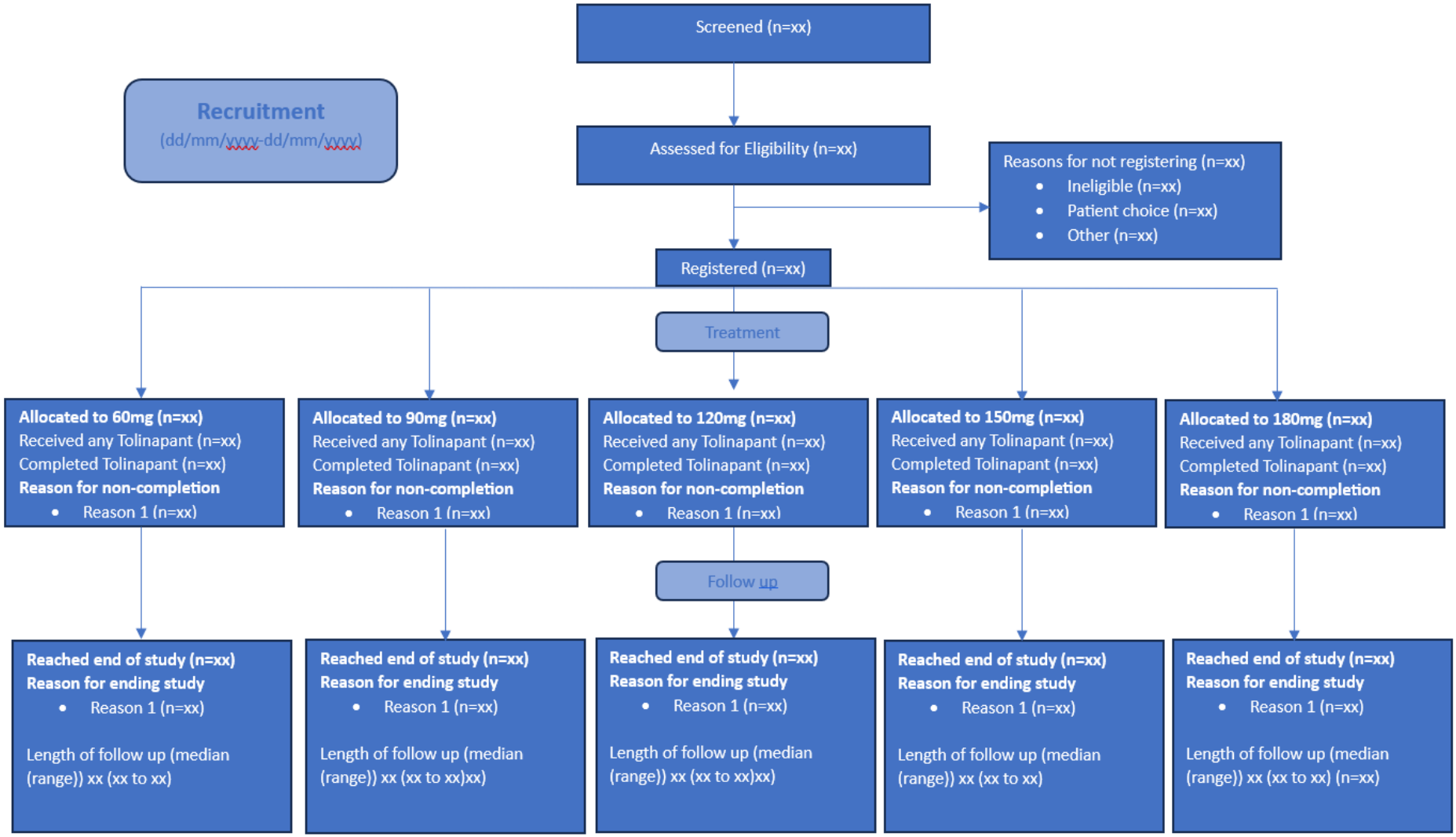
5.1 Disposition of study population

Figure 1: CONSORT Diagram



5.1.1 Summary of populations

Table 1 Summary of Populations

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of eligible patients (ITT population)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Included in Evaluable population	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Included in Primary endpoint population	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Excluded from Primary endpoint population	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 1 etc.	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are based on the number of registered patients on the dose level

5.1.2 End of Study information

Table 2 End of Study Information – ITT population

	Dose Level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of patients completed study	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of patients discontinued study early	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for discontinuation						
Subject withdrawal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc…						
Length of follow-up (days)						
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Range	xx to xx	xx to xx	xx to xx	xx to xx	xx to xx	xx to xx

Note: Percentages are based on the number of patients on the dose level, length of follow-up is (End of Study date - registration date) + 1

5.2 Protocol Deviations

Table 3 Major protocol violations

Violation	Patient (if applicable)	Dose level (if applicable)	Comments	Actions
xxxx	xxxx	xxxx	xxxx	xxxx

Programming note: this information comes from the trial management team

5.3 Baseline Demographic Characteristics

Table 4 Demographic information and Disease characteristics at baseline – ITT population

	Dose Level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Age at consent (years)						
n	xx	xx	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Ethnicity						
XXXX	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
XXXX	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ECOG Status						
0 = Fully active	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1 = Restricted in physically strenuous activity but ambulatory	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc.						
Type of Cervical Cancer						
Adenocarcinoma	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Squamous cell carcinoma	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
FIGO stage						
IA	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
IB	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc.	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

	Dose Level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Fecal urgency (RT-ARD score)						
1 = Ability to defer defecation more than 15 minutes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2 = Inability to defer defecation more than 15 minutes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Metastases Present?						
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No scan carried out	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lymph Nodes present in pelvis?						
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No scan carried out	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of Target lesions						
n	xx	xx	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Sum of Target lesions (mm)						
n	xx	xx	xx	xx	xx	xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x

Table 5 Medical History – ITT population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of patients with Medical History Term - n (%)						
Term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc.	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are based on the number of patients on the dose level.

Table 6 Concomitant Medications – ITT population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of patients taking Concomitant Medication - n (%)						
Term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc.	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are based on the number of patients on the dose level.

5.4 Compliance to trial drug and treatment

5.4.1 Study Treatment information

Table 7 Cisplatin Administration – ITT population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of doses of Cisplatin treatment received – n (%)[1]						
0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5						
Total dose received (mg)						
n	x	x	x	x	x	x
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Relative Dose Intensity (%)[2]						
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Number of patients with at least one missed dose of Cisplatin – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for missed dose – n (%)[4]						
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc.	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of patients with at least one delay/disruption to Cisplatin administration – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for delay/disruption – n (%)[5]						
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Length of delay/disruption (days)						
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Number of patients with at least one change to dose level of Cisplatin – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for changed dose – n (%)[6]						
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Denominator is the number of patients.
[2] Actual dose/expected dose *100%
[3] Denominator is the number of patients who received at least one dose of Cisplatin.
[4] Denominator is the number of patients who missed a dose of Cisplatin.
[5] Denominator is the number of patients experiencing a delay/disruption.
[6] Denominator is the number of patients experiencing a dose change.

Table 8 External beam radiotherapy Administration – ITT population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of weeks of External Beam Radiotherapy received – n (%)[1]						
0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total dose received (Gy)						
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Relative Dose Intensity (%)[2]						
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Number of patients with at least one missed administration of External Beam Radiotherapy – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for missed dose – n (%)[4]						
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc.	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of patients with at least one delay/disruption to External Beam Radiotherapy administration – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for delay/disruption – n (%)[5]						
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc.	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Length of delay/disruption (days)						
n	x	x	x	x	x	x
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Number of patients with at least one change to dose intensity – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for changed dose – n (%)[6]						
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc.	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Denominator is the number of patients.
[2] Actual dose/expected dose *100%
[3] Denominator is the number of patients who received at least one administration of External Beam radiotherapy.
[4] Denominator is the number of patients who missed an External Beam radiotherapy administration.
[5] Denominator is the number of patients experiencing a delay/disruption.
[6] Denominator is the number of patients experiencing a dose change.

Table 9 Tolinapant Administration – ITT population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of weeks of Tolinapant treatment received – n (%)[1]						
0	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total number of doses of Tolinapant taken						
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Relative Dose Intensity (%)[2]						
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Number of patients with at least one missed dose of Tolinapant – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for missed dose – n (%)[4]						
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc.	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of missed doses of Tolinapant						
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of patients with at least one delay/disruption to Tolinapant administration – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for delay/disruption – n (%)[5]						
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Length of delay/disruption (days)						
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x

[1] Denominator is the number of patients.
[2] Actual dose/expected dose *100%
[3] Denominator is the number of patients who received at least one dose of Tolinapant.
[4] Denominator is the number of patients who missed a dose of Tolinapant.
[5] Denominator is the number of patients experiencing a delay/disruption.

Table 10 Brachytherapy Administration – ITT population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of Patients who received Brachytherapy – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for not receiving Brachytherapy– n (%)[2]						
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Brachytherapy scheduled – n (%)[3]						
28Gy in 4 fractions high dose rate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
34Gy in 2 fractions pulsed-dose rate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other -	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other -	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Relative Dose Intensity (%)[4]						
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Number of patients with a delay/disruption to Brachytherapy administration – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for delay/disruption – n (%)[5]						
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc.	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Length of delay/disruption (days)						
n	x	x	x	x	x	x
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Quartiles	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x
Range	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of patients with at least one change to dose intensity – n (%)[3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for changed dose – n (%)[6]						
Reason 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Denominator is the number of patients.
[2] Denominator is the number of patients who did not receive Brachytherapy.
[3] Denominator is the number of patients who received Brachytherapy.
[4] Actual dose/expected dose *100%
[5] Denominator is the number of patients experiencing a delay/disruption.
[6] Denominator is the number of patients experiencing a change to dose intensity.

5.4.2 End of Treatment information

Table 11 End of Treatment – Evaluable population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of Patients who completed all treatment– n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of Patients who completed Cisplatin treatment– n (%)[2]	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)
Reason for non-completion of Cisplatin– n (%)[2]						
Reason 1	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)
Number of Patients who completed External Beam Radiotherapy treatment– n (%)[3]	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)
Reason for non-completion of External Beam radiotherapy– n (%)[3]						
Reason 1	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)
Reason 2	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)
Etc.	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)
Number of Patients who completed Tolinapant treatment– n (%)[4]	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)
Reason for non-completion of Tolinapant– n (%)[4]						
Reason 1	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)
Reason 2	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)
Reason 3	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)
Etc.	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of Patients who completed Brachytherapy treatment– n (%)[5]	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)
Reason for non-completion of Brachytherapy– n (%)[5]						
Reason 1	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (xx.x%)
Reason 2	x**x**/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (**xx**.x%)	xx/xx (x**x.x**%)	xx/xx (xx.x%)	xx/xx (xx.x%)
Etc.	x**x**/xx (xx.x%)	xx/xx (xx.x%)	xx/xx (**xx**.x%)	xx/xx (x**x.x**%)	xx/xx (xx.x%)	xx/xx (xx.x%)

[1] Denominator is the number of patients.
[2] Denominator is the number of patients who received Cisplatin.
[3] Denominator is the number of patients who received External Beam radiotherapy.
[4] Denominator is the number of patients who received Tolinapant.
[5] Denominator is the number of patients who received Brachytherapy.

5.5 Primary endpoint(s)

5.5.1 Primary endpoint – Toxicity estimates and maximum tolerated dose

Table 12 Summary of dose limiting toxicities (DLTs) using data up to end of week 12 – Primary endpoint population.

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of Patients included	xx	xx	xx	xx	xx	xx
Number of Patients who experienced a DLT– n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of DLTs– n (%)	xx	xx	xx	xx	xx	xx
Number of patients experiencing each type of DLT – n (%)[2] [number of events]						
Grade 4 neutropenia[3]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Grade 3 or 4 febrile neutropenia[4]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Grade 3 or 4 neutropenia[5]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Grade 3 or 4 thrombocytopenia[6]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Other Grade 3+ AE[6]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Other AE 1	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Other AE 2	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Death[6]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]

[1] Denominator is the number of patients.

[2] Denominator is the number of patients who experienced a DLT.

[3] Only a DLT if the Neutropenia lasts for greater than or equal to 7 days and clinically defined as definitely or probably related to Tolinapant

[4] Only a DLT if neutrophils <1000/mm3 with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour AND/OR life-threatening consequences with urgent intervention are indicated and the event is clinically defined as definitely or probably related to Tolinapant

[5] Only a DLT if associated with a separate event of bacteriologically proven sepsis happening at the same time and clinically defined as definitely or probably related to Tolinapant.

[6] Only a DLT if in the opinion of the investigator, the event is defined as definitely or probably related to Tolinapant.

Table 13 Bayesian dose toxicity model summary using all data up to end of week 12 – Primary endpoint population

Using the DLT data up to 12 weeks, the estimated risk of toxicity for the model-recommended MTD is xx.x%. The probability that the MTD toxicity level is 35% or more (i.e. too toxic) is xx.x%. The probability that this dose lies in the target interval of 20-30% is xx.x%. A summary of the estimated toxicity rates based on the 12-week data are given below and the estimated dose-toxicity model is shown in figure 2.

	Dose level				
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**
Number of patients included in the model	xx	xx	xx	xx	xx
Number of full patient assessment equivalents[1]	xx	xx	xx	xx	xx
Number of DLTs	xx	xx	xx	xx	xx
Estimated DLT rate[2] (95% Credible interval)[3]	xx.x% (xx.x to xx.x)	xx.x% (xx.x to xx.x)	xx.x% (xx.x to xx.x)	xx.x% (xx.x to xx.x)	xx.x% (xx.x to xx.x)
Target dose probability[4]	x.xx%	x.xx%	x.xx%	x.xx%	x.xx%
Probability of being too toxic[5]	x.xx%	x.xx%	x.xx%	x.xx%	x.xx%

Highlighted dose is the suggested maximum tolerated dose level.

[1] A full patient assessment equivalent is defined as 12 weeks (84 days). Once a patient has reached day 84 or experienced a DLT they count as one full assessment. Otherwise, the equivalent is calculated as number of days since treatment start/84 for each patient. This figure is the sum of all patients who have received treatment.

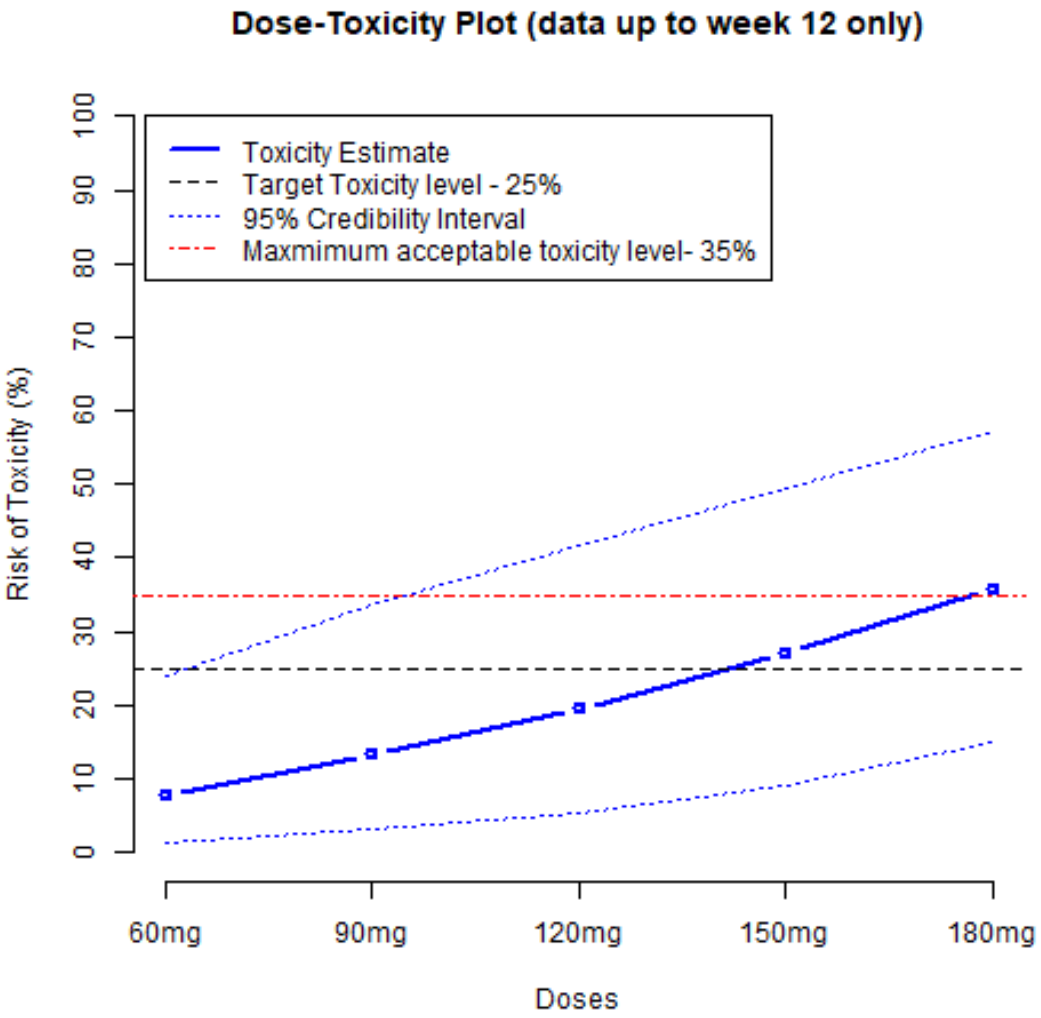
[2] Estimated using the TiTE-CRM model – all information for each dose is used to modal toxicity for all levels, even if no patients have actually been assigned to the dose.

[3] Credible intervals are equal tail intervals.

[4] Probability the dose lies within the target toxicity level (20-30%), estimated using the model.

[5] Probability the dose is too toxic, i.e. greater than 35%.

Figure 2: Dose toxicity curve estimated using all data up to end of week 12



5.5.2 Primary endpoint (Sensitivity Analysis) – Toxicity estimates and maximum tolerated dose for 18 weeks

Table 14 Summary of dose limiting toxicities (DLTs) using all data up to 18 weeks – Primary endpoint population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of Patients included	xx	xx	xx	xx	xx	xx
Number of Patients who experienced a DLT– n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of DLTs– n (%)	xx	xx	xx	xx	xx	xx
Number of patients experiencing each type of DLT – n (%)[2] [number of events]						
Grade 4 neutropenia[3]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Grade 3 or 4 febrile neutropenia[4]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Grade 3 or 4 neutropenia[5]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Grade 3 or 4 thrombocytopenia[6]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Other Grade 3+ AE[6]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Other AE 1	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Other AE 2	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Death[6]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]

[1] Denominator is the number of patients.

[2] Denominator is the number of patients who experienced a DLT.

[3] Only a DLT if the Neutropenia lasts for greater than or equal to 7 days and clinically defined as definitely or probably related to Tolinapant

[4] Only a DLT if neutrophils <1000/mm3 with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour AND/OR life-threatening consequences with urgent intervention are indicated and the event is clinically defined as definitely or probably related to Tolinapant

[5] Only a DLT if associated with a separate event of bacteriologically proven sepsis happening at the same time and clinically defined as definitely or probably related to Tolinapant.

[6] Only a DLT if in the opinion of the investigator, the event is defined as definitely or probably related to Tolinapant.

Table 15 Bayesian dose toxicity model summary for all data up to 18 weeks – Evaluable population

Using the DLT data up to 18 weeks, the estimated risk of toxicity for the model-recommended MTD is xx.x%. The probability that the MTD toxicity level is 35% or more (i.e. too toxic) is xx.x%. The probability that this dose lies in the target interval of 20-30% is xx.x%. A summary of the estimated toxicity rates based on all data are given below and the estimated dose-toxicity model is shown in figure 3.

	Dose level				
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**
Number of Patients assessed	xx	xx	xx	xx	xx
Number of full patient assessment equivalents[1]	xx	xx	xx	xx	xx
Number of DLTs	xx	xx	xx	xx	xx
Estimated DLT rate[2]	x.xx%	x.xx%	x.xx%	x.xx%	x.xx%
Target dose probability[3]	x.xx%	x.xx%	x.xx%	x.xx%	x.xx%
Probability of being too toxic[4]	x.xx%	x.xx%	x.xx%	x.xx%	x.xx%

Highlighted dose is the suggested maximum tolerated dose level.

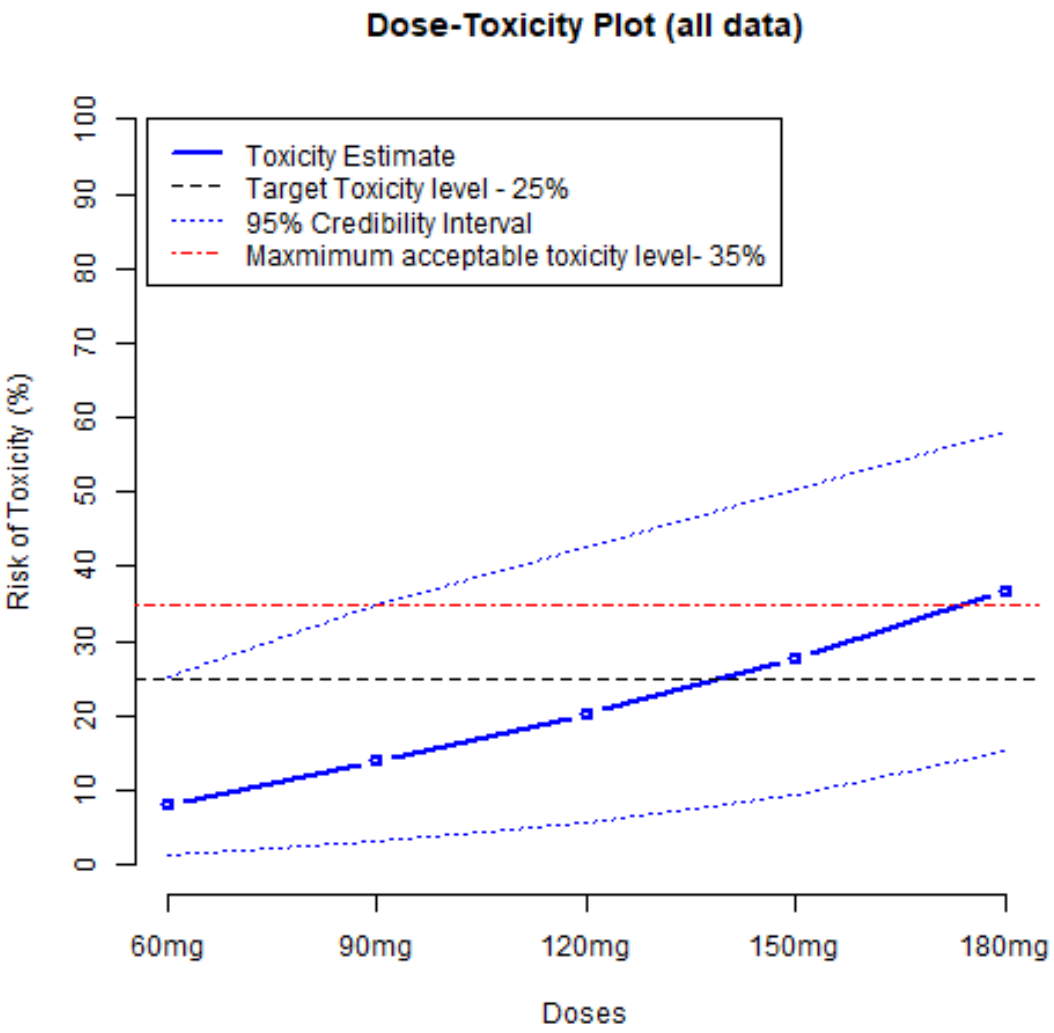
[1] A full patient assessment equivalent is defined as 18 weeks (126 days). Once a patient has reached day 126 or experienced a DLT they count as one full assessment. Otherwise, the equivalent is calculated as number of days since treatment start/126 for each patient. This figure is the sum of all patients who have received treatment.

[2] Estimated using the TiTE-CRM model – all information for each dose is used to modal toxicity for all levels, even if no patients have actually been assigned to the dose.

[3] Probability the dose lies within the target toxicity level (20-30%), estimated using the model.

[4] Probability the dose is too toxic, i.e. greater than 35%.

Figure 3: Dose toxicity curve estimated using all data up to 18 weeks



5.5.3 Primary endpoint (Sensitivity Analysis) – Toxicity estimates and maximum tolerated dose using treatment and follow up period weighting

Table 16 Bayesian dose toxicity model summary for data up to the end of week 12 using equal weighting for doses taken and follow-up time – Evaluable population

Using the DLT data up to 12 weeks and using equal weighting for doses taken and follow-up time, the estimated risk of toxicity for the model-recommended MTD is xx.x%. The probability that the MTD toxicity level is 35% or more (i.e. too toxic) is xx.x%. The probability that this dose lies in the target interval of 20-30% is xx.x%. A summary of the estimated toxicity rates based on all data are given below and the estimated dose-toxicity model is shown in figure 4.

	Dose level				
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**
Number of Patients assessed	xx	xx	xx	xx	xx
Number of full patient assessment equivalents[1]	xx	xx	xx	xx	xx
Number of DLTs	xx	xx	xx	xx	xx
Estimated DLT rate[2]	x.xx%	x.xx%	x.xx%	x.xx%	x.xx%
Target dose probability[3]	x.xx%	x.xx%	x.xx%	x.xx%	x.xx%
Probability of being too toxic[4]	x.xx%	x.xx%	x.xx%	x.xx%	x.xx%

Highlighted dose is the suggested maximum tolerated dose level.

[1] A full patient assessment equivalent is defined as 18 weeks (126 days). Once a patient has reached day 126 or experienced a DLT they count as one full assessment. Otherwise, the equivalent is calculated as number of days since treatment start/126 for each patient. This figure is the sum of all patients who have received treatment.

[2] Estimated using the TiTE-CRM model – all information for each dose is used to modal toxicity for all levels, even if no patients have actually been assigned to the dose.

[3] Probability the dose lies within the target toxicity level (20-30%), estimated using the model.

[4] Probability the dose is too toxic, i.e. greater than 35%.

Figure 4: Dose toxicity curve estimated using data up to 12 weeks using equal weighting for doses taken and follow-up time

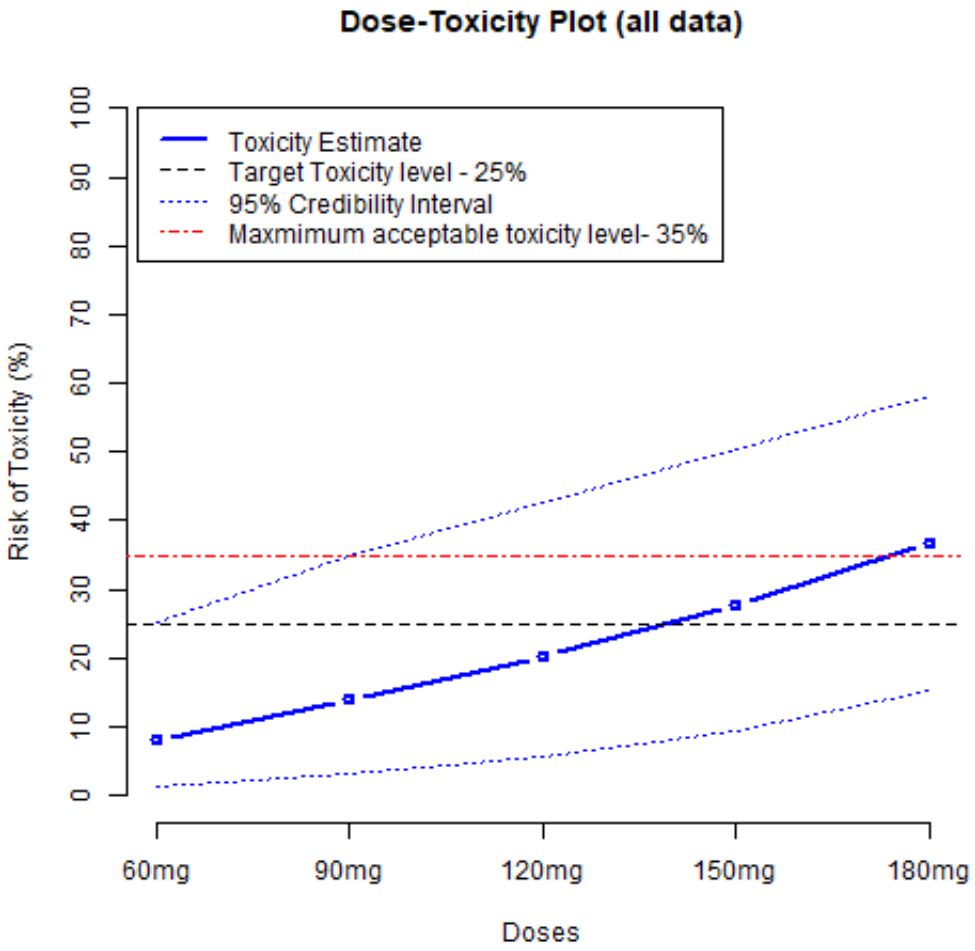


Table 17 Bayesian dose toxicity model summary for data up to the end of week 12 apportioning all weight to the number of doses taken – Evaluable population

Using the DLT data up to 12 weeks and apportioning all weight to the number of doses taken, the estimated risk of toxicity for the model-recommended MTD is xx.x%. The probability that the MTD toxicity level is 35% or more (i.e. too toxic) is xx.x%. The probability that this dose lies in the target interval of 20-30% is xx.x%. A summary of the estimated toxicity rates based on all data are given below and the estimated dose-toxicity model is shown in figure 5.

	Dose level				
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**
Number of Patients assessed	xx	xx	xx	xx	xx
Number of full patient assessment equivalents[1]	xx	xx	xx	xx	xx
Number of DLTs	xx	xx	xx	xx	xx
Estimated DLT rate[2]	x.xx%	x.xx%	x.xx%	x.xx%	x.xx%
Target dose probability[3]	x.xx%	x.xx%	x.xx%	x.xx%	x.xx%
Probability of being too toxic[4]	x.xx%	x.xx%	x.xx%	x.xx%	x.xx%

Highlighted dose is the suggested maximum tolerated dose level.

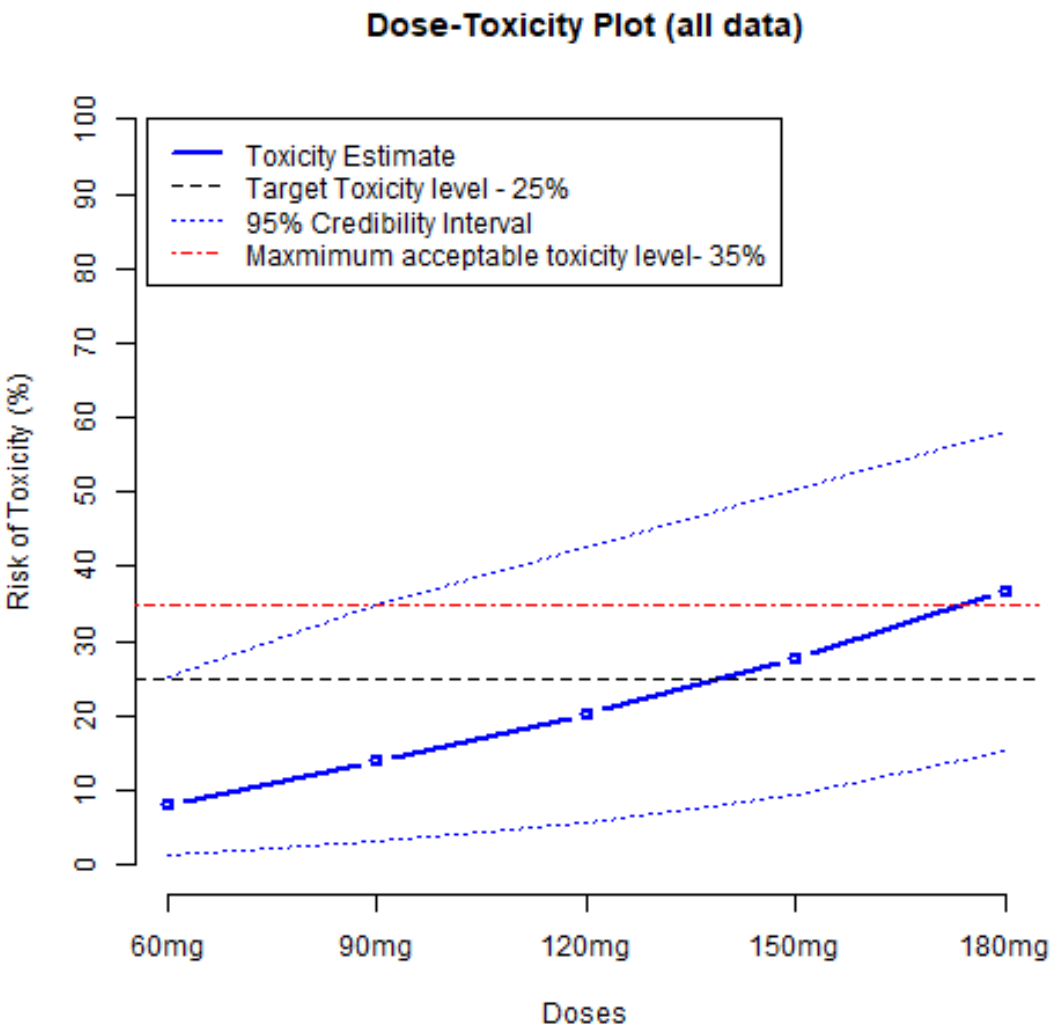
[1] A full patient assessment equivalent is defined as 18 weeks (126 days). Once a patient has reached day 126 or experienced a DLT they count as one full assessment. Otherwise, the equivalent is calculated as number of days since treatment start/126 for each patient. This figure is the sum of all patients who have received treatment.

[2] Estimated using the TiTE-CRM model – all information for each dose is used to modal toxicity for all levels, even if no patients have actually been assigned to the dose.

[3] Probability the dose lies within the target toxicity level (20-30%), estimated using the model.

[4] Probability the dose is too toxic, i.e. greater than 35%.

Figure 5: Dose toxicity curve estimated using data up to 12 weeks apportioning all weight to the number of doses taken



5.6 Response to study treatment

5.6.1 Response rate at 3 months

Table 18 Summary of disease assessment responses at 3 months – ITT population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of Patients who had a 3-month MRI– n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Response of target lesions according to RECIST 1.1 – n (%)[2]						
Complete response	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Partial Response	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Stable Disease	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Progressive Disease	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not evaluable	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Response of non-target lesions according to RECIST 1.1 – n (%)[2]						
Complete response	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-CR/Non-PD	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Unequivocal Progressive Disease	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not evaluable	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Overall Response according to RECIST 1.1 – n (%)[2]						
Complete response	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Partial Response	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Stable Disease	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Progressive Disease	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not evaluable	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Percentage change in sum of target measurements from screening scan Median Quartiles Range	 xx.x xx.x to xx.x xx.x to xx.x	 xx.x xx.x to xx.x xx.x to xx.x	 xx.x xx.x to xx.x xx.x to xx.x	 xx.x xx.x to xx.x xx.x to xx.x	 xx.x xx.x to xx.x xx.x to xx.x	 xx.x xx.x to xx.x xx.x to xx.x
Total responses[2,3]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Response rate (95% CI)[4]	(xx.x%) (xx.x to xx.x)	(xx.x%) (xx.x to xx.x)	(xx.x%) (xx.x to xx.x)	(xx.x%) (xx.x to xx.x)	(xx.x%) (xx.x to xx.x)	(xx.x%) (xx.x to xx.x)

[1] Denominator is the number of patients.
[2] Denominator is the number of patients with 3-month MRI.
[3] Calculated as the sum of partial and complete overall responses.
[4] CI (confidence interval) is based on the exact (Clopper-Pearson) method.

5.7 Safety Reporting

5.7.1 Adverse Events

Table 19 Overall toxicity by CTCAE Grade – Evaluable population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Adverse events – n (%)						
CTCAE 5.0 Grade 1 – Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 5.0 Grade 2 – Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 5.0 Grade 3 – Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 5.0 Grade 4 – Life-threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 5.0 Grade 5 - Fatal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**

Note: Percentages are based on the number of Adverse events.

Table 20 Overall toxicity summary by SOC and CTCAE term – Evaluable population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of patients that experienced at least one AE – n (%) [no. of events]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Summary of AEs – n (%)[1]						
Classification group 1 name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Classification group 2 name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Classification group XX name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Classification group XX name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]

[1] Percentages are based on the number of patients on the dose level

Table 21 Overall toxicity summary by SOC and CTCAE term (Grade 3+) – Evaluable population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of patients that experienced at least one AE – n (%) [no. of events]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Summary of AEs – n (%)						
Classification group 1 name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Classification group 2 name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]

5.7.2 Adverse Events Related to Tolinapant

Table 22 Overall toxicity by CTCAE Grade for AEs possibly, probably or definitely related to Tolinapant – Evaluable population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Adverse events – n (%)						
CTCAE 5.0 Grade 1 – Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 5.0 Grade 2 – Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 5.0 Grade 3 – Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 5.0 Grade 4 – Life-threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE 5.0 Grade 5 - Fatal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**

Note: Percentages are based on the number of Adverse events.

Table 23 Overall toxicity summary by SOC and CTCAE term for AEs possibly, probably or definitely related to Tolinapant – Evaluable population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of patients that experienced at least one AE – n (%) [no. of events]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Summary of AEs – n (%)[1]						
Classification group 1 name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Classification group 2 name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Classification group XX name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Classification group XX name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]

[1] Percentages are based on the number of patients on the dose level

Table 24 Overall toxicity summary by SOC and CTCAE term for AEs possibly, probably or definitely related to Tolinapant (Grade 3+) – Evaluable population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of patients that experienced at least one AE – n (%) [no. of events]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Summary of AEs – n (%)						
Classification group 1 name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Classification group 2 name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]

5.7.3 Serious Adverse Events

Table 25 Reported Serious Adverse Events (SAEs)/Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) – Evaluable population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of patients experiencing at least one SAE/SAR/SUSAR – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of SAE/SAR/SUSAR per patient (for patients with at least one SAE/SAR/SUSAR) – median (range)	xx (xx.x to xx.x)	xx (xx.x to xx.x)	xx (xx.x to xx.x)	xx (xx.x to xx.x)	xx (xx.x to xx.x)	xx (xx.x to xx.x)
Overall Assessment – n (%)[2]						
SUSAR (Suspected Unexpected Serious Adverse Reaction)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SAR (Serious Adverse Reaction)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SAE (Serious Adverse Event)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not SAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE v5.0 grade – n (%)[2]						
1 – Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2 – Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3 – Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4 – Life threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5 – Death related to AE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Why was the event serious – n (%)[2]						
1 – Resulted in death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2 – Life threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3 – Required hospitalisation or prolongation of existing hospitalisation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4 – Persistent or significant disability/incapacity	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5 – Congenital anomaly/birth defect	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Percentages are based on the number of patients on the dose level

[2] Percentages are based on the number of SAEs/SARs/SUSARs.

Table 26 Summary of the main symptom(s) as reported on the SAE form – Evaluable population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of patients that experienced at least one SAE – n (%) [no. of events]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Summary of SAEs – n (%)						
Classification group 1 name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Classification group 2 name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]

5.7.4 Serious Adverse Events Related to Tolinapant

Table 27 Reported Serious Adverse Events (SAEs)/Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) possibly, probably or definitely related to Tolinapant – Evaluable population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of patients experiencing at least one SAE/SAR/SUSAR – n (%)[1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of SAE/SAR/SUSAR per patient (for patients with at least one SAE/SAR/SUSAR) – median (range)	xx (xx.x to xx.x)	xx (xx.x to xx.x)	xx (xx.x to xx.x)	xx (xx.x to xx.x)	xx (xx.x to xx.x)	xx (xx.x to xx.x)
Overall Assessment – n (%)[2]						
SUSAR (Suspected Unexpected Serious Adverse Reaction)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SAR (Serious Adverse Reaction)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SAE (Serious Adverse Event)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not SAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
CTCAE v5.0 grade – n (%)[2]						
1 – Mild	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2 – Moderate	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3 – Severe	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4 – Life threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5 – Death related to AE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Why was the event serious – n (%)[2]						
1 – Resulted in death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2 – Life threatening	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3 – Required hospitalisation or prolongation of existing hospitalisation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4 – Persistent or significant disability/incapacity	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5 – Congenital anomaly/birth defect	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pending	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

[1] Percentages are based on the number of patients on the dose level

[2] Percentages are based on the number of SAEs/SARs/SUSARs.

Table 28 Summary of the main symptom(s) as reported on the SAE form possibly, probably or definitely related to Tolinapant – Evaluable population

	Dose level					
	60mg (n=xx)	**90mg (n=xx)**	**120mg (n=xx)**	**150mg (n=xx)**	**180mg (n=xx)**	**Total (n=xx)**
Number of patients that experienced at least one SAE – n (%) [no. of events]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Summary of SAEs – n (%)						
Classification group 1 name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
Classification group 2 name	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]	**xx (xx.x%)** [xx]
xxxx	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]
…	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]	xx (xx.x%) [xx]

Table 29 List of all SAEs reported, table sorted by PI assessment, SOC, arm, patient ID, and date SAE reported – Evaluable population

Patient ID	Overall assessment	PI assessment	CR assessment	Dose level	Date of onset of SAE	Date treatment last received		Main symptom (MedDRA)	SOC	CTCAE Grade[1]	Serious[2]	Action[3]	Casuality[4]	Expectedness[5]
						Tolinapant	Other							
													Tolinapant: **Cisplatin:** **Brachytherapy:**	**Tolinapant:** **Cisplatin:** **Brachytherapy:**

[1]CTCAE v5.0 Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life-threatening, or 5=Death related to AE.

[2]Why was the event serious: 1=Resulted in death, 2=Life-threatening, 3=Required hospitalisation or prolongation of existing hospitalisation, 4=Persistent or significant disability/incapacity, or 5=Congenital anomaly/birth defect 6 = Other important medical event

[3]Action taken due to SAE: 0=None, 1=Dose reduction, 2=Treatment delayed, 3=Treatment reduced & delayed, 4=Treatment stopped

[4]Investigator's Opinion - Causal relationship to SAE: 1 = Definitely, 2 = Probably, 3 = Possibly, 4 = Unlikely, 5 = Not related

[5]Investigator's Opinion – Expectedness: 1 = Expected, 2 = Unexpected

5.8 Performance Status and Laboratory Parameters

5.8.1 Performance status

Table 30 Performance status – ITT population

Dose level	Patient ID	Timepoint & date	Status and description
xxmg	CR1-1001001	Screening dd-mmm-yy	0 - Fully active, able to carry on all pre-disease performance without restriction

Note: Row is omitted where results missing

5.8.2 Laboratory chemistry

Table 31 Laboratory chemistry by timepoint – ITT population

Dose level	Patient ID	Timepoint and date	Parameter	Value	Unit	Abnormal result?	Clinical significance
xxmg	CR1-1001001	Screening dd-mmm-yy	Potassium	x.xx	mmol/L	y/n/not measured	y/n/not measured

Note: Row is omitted where results missing

5.8.3 Laboratory haematology

Table 32 Laboratory haematology by timepoint – ITT population

Dose level	Patient ID	Timepoint and date	Parameter	Value	Unit	Abnormal result?	Clinical significance
xxmg	CR1-1001001	Screening dd-mmm-yy	Haemoglobin	xxx	g/L	y/n/not measured	y/n/not measured

Note: Row is omitted where results missing

5.9 Summary of SRC meetings

Table 33 Summary of SRC Meetings for Dose Escalation Decisions

Date of Meeting	Current dose level	Number of participants reviewed by SRC	Number of evaluable participants	Number of DLTs	Details of DLTs	SRC decision
xx-xxx-xx	XXX	xx	xx	xx	xxxxxx	Text to explain main decisions of SRC and details of dose escalation if appropriate
xx-xxx-xx	XXX	xx	xx	xx	xxxxxx	xxxxxx
xx-xxx-xx	XXX	xx	xx	xx	xxxxxx	xxxxxx
xx-xxx-xx	XXX	xx	xx	xx	xxxxxx	xxxxxx
...						

SRC = Safety Review Committee; DLT = Dose-Limiting Toxicity.

6 References

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7 SAP revision history

Version number	Revision history	Author	Date
0.1	First draft of SAP based on template, SRC reports, and Protocol version 5.	Joshua Northey	15APR2024
0.2	Updates following review by Senior Statistician Geoff Saunders	Joshua Northey	02 JUL 2024
0.3	Addition of Estimands framework & definitions of evaluable patients	Joshua Northey	01 AUG 2024
0.4	Addition of sensitivity analyses by treatment and follow up weighting and addition of AE & SAE tables related to Tolinapant. Also addition of line listing tables for laboratory parameters and performance status and added a table for the SRC meetings summary.	Geoff Saunders	03 SEP 2024
0.5	General tidying of formatting etc. and consort diagram	Joshua Northey	13 SEP 2024
0.6	Minor updates following review by PH	Joshua Northey	21 OCT 2024
1	Finalised to version 1	Joshua Northey	24 OCT 2024

APPENDIX 1


CRAIN TiTE CRM simulations summar


RECISTGuidelines.pdf