2. SYNOPSIS

Due to strategic portfolio review within AstraZeneca, the decision was made to terminate enrolment to study D6500C00001 and subjects were not recruited into Part B. As only partial data were obtained from the study, these data were summarised as a synopsis format Clinical Study Report.

Study centres

This study took place at 5 centres in 4 countries: Spain, United Kingdom, United States, and South Korea.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	• To investigate the safety and tolerability of AZD0156 when given orally to subjects with advanced malignancies, as a monotherapy and in combination with olaparib, cytotoxic chemotherapies, or novel anti-cancer agents	• Adverse events • Physical examinations and body weight • 12-lead ECG • Vital signs • Laboratory safety assessments
Secondary	Safety	• To define the MTD, if possible, or a lower biologically effective dose(s) (if decided by the SRC and AstraZeneca), as a monotherapy or in combination with either cytotoxic chemotherapies, or novel anti-cancer agents	• Dose-Limiting Toxicities

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	• To obtain a preliminary assessment of the anti-tumour activity of AZD0156 either as monotherapy alone or in combination with either olaparib, cytotoxic chemotherapies, or novel anti-cancer agents.	According to RECIST version 1.1 by investigator assessment: • Objective response rate • Durable response rate • Duration of response • Non-progressive disease at Week 12 • Best percentage change in the sum of the target lesions and percentage change in the sum of the target lesions at Week 12 • Progression-free survival
Secondary	PK	• To characterise the PK of AZD0156 at steady state after multiple dosing when given orally as a monotherapy and/or also in combination with either cytotoxic chemotherapies, or novel anti-cancer agents	• Single-dose and steady-state plasma and urine PK parameters for AZD0156 and AZ13824692 (M1) (AZD0156 metabolite) and for olaparib were assessed (see details in Section 9 of SAP version 3.0, dated 27 September 2019 located in Appendix 16.1.9).
Secondary	PDc	• To obtain a preliminary assessment of AZD0156 activity in the tumour by evaluation of PDc biomarker changes which may include, but were not limited to functional ATM inhibition, ctDNA and CTCs.	• AZD0156 PDc (PDc biomarkers used to inform the extent and duration of ATM target inhibition) • Biomarkers that might have been included but were not limited to functional ATM inhibition ctDNA and CTCs
Exploratory	PK	• To investigate the presence, and/or identity of drug metabolites of AZD0156 and, if appropriate, characterise their PK. • To confirm the PK of cytotoxic chemotherapy and novel anti-cancer agents, when given in combination with AZD0156, where relevant. • To explore the relationship between PK and efficacy, safety, and blood borne and tissue biomarkers.	• Metabolite identification/PK • PK of cytotoxic chemotherapy and other novel anti-cancer agents when given in combination with AZD0156

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Biobanking for exploratory research on biomarkers and pharmacogenetics	• To collect and store an optional pre-dose plasma and serum sample and/or analyse surplus blood or tissue including patient specific archival tumour tissue, if available, for potential future exploratory research into factors that may influence the development of agents to treat human disease and/or response to AZD0156 (where response is defined broadly to include efficacy, tolerability or safety). This may include the analysis of tumour specific and circulating biomarkers, such as tumour DNA, mRNA, proteins or metabolites. In the event that additional tumour molecular profiling is required to understand further any response to AZD0156, AstraZeneca may request a sample of the most recent tumour biopsy for additional research.	• Predictive Markers and acquired resistance to AZD0156 observed in ctDNA • Predictive Markers and acquired resistance to AZD0156 observed in tumour • Exploratory biomarkers • Pharmacogenetics
Exploratory	Biobanking for exploratory research on biomarkers and pharmacogenetics	• To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD0156 treatment. • To investigate predictive markers and acquired resistance to AZD0156 that may be observed in tumour from patients treated with AZD0156 either as monotherapy or in combination with cytotoxic chemotherapy and novel anti-cancer agents.	

Abbreviations: ATC = Anatomical Therapeutic Chemical; ATM = Ataxia Telangiectasia Mutated; AUC = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time zero up to the time of last quantifiable sample; AUC_{0-72} = area under the plasma concentration-time curve from time zero to 72 hours post-dose; AUC_{ss} = area under the concentration-time curve across the dosing interval; $C_{ss\ max}$ = maximum plasma concentration at steady state; $C_{ss\ min}$ = minimum plasma concentration at steady state; ctDNA = circulating tumour deoxyribonucleic acid; CTC = circulating tumour cell; DNA = deoxyribonucleic acid; DDI = drug-drug interaction; ECG = electrocardiogram; mRNA = messenger ribonucleic acid; MTD = maximum tolerated dose; PDc = pharmacodynamics; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumours; SRC = safety review committee; $t_{ss\ max}$= time of maximum concentration at steady state; $V_{ss/F}$ = volume of distribution.
Note: The secondary PDc endpoints and the exploratory endpoints were not analysed as a part of this CSR.

Study design

This was a modular, phase I, 2-part, open-label, multicentre study of AZD0156, administered orally, alone, or in combination with either cytotoxic chemotherapies or novel anti-cancer agents in subjects with advanced/metastatic solid malignancies. The study design allowed an escalation of the dose of AZ0156 alone or in combination with the chosen dose and schedule of either cytotoxic chemotherapies or novel anti-cancer agents, with intensive safety monitoring to ensure the safety of the subjects.

There were originally 2 parts to each module of this study; Part A: dose escalation/schedule selection and part B: Response Evaluation Criteria in Solid Tumours cohort expansions in particular subject groups. Part B of this study was not conducted for either module as a result of a strategic portfolio review within AstraZeneca. The decision was made to terminate enrolment, and subjects were not recruited into Part B expansions.

This study used a Bayesian adaptive design approach to dose escalation to improve the efficiency and precision of the maximum tolerated dose estimation compared to a traditional 3 + 3 or rolling 6 design. Dose escalation decisions were made by the Safety Review Committee (SRC) based on emerging preclinical data and the emerging safety and tolerability information from the clinical programme on a minimum of 3 evaluable subjects.

Target subject population and sample size

This study was conducted in adult subjects with advanced/metastatic solid malignancies. Key inclusion criteria were ≥18 years of age unless local country regulations stated subjects had to be older; histological or cytological confirmation of a locally advanced or metastatic specified solid malignancy which was refractory or resistant to the standard therapy or had no appropriately effective standard therapy; and Eastern Cooperative Oncology Group (ECOG) or World Health Organization performance status 0 to 1 with no deterioration during the previous 2 weeks and a minimum life expectancy of >12 weeks.

The planned sample size was determined based on the desire to obtain adequate tolerability, safety, pharmacokinetic (PK), and pharmacodynamic (PDc) data while exposing as few subjects as possible to the investigational product and procedures. For Part A (dose escalation), cohorts of 3 to 6 evaluable subjects were required with the total number of subjects dependant on the number of dose escalations necessary. For Module 1, it was estimated that up to 20 cohorts would be required across all schedules; while for Module 2, it was estimated that up to 6 cohorts would be needed.

Investigational product and comparators: dosage, mode of administration, and batch numbers

Investigational product

The investigational product, AZD0156, was administered by oral tablet either as a monotherapy or in combination with cytotoxic chemotherapy and/or novel anti-cancer agents. The treatment in Module 1 was AZD0156 + olaparib and in Module 2 was AZD0156 + irinotecan/FOLFIRI (5-fluorouracil/folinic acid and irinotecan).

The dose and schedules to be explored in parallel were determined by the SRC based on emerging data. In particular, the type of schedule involved intermittent or continuous dosing with AZD0156 alongside continuous olaparib or irinotecan as described below.

Module 1

The first 3 subjects in Cohort 1 of Module 1 each received a single dose of AZD0156 monotherapy, followed by a 72 hour washout period, before completing the subsequent 5 to 7 days' monotherapy dosing, in order to profile the PK of AZD0156. All other subjects in Module 1 received 5 to 7 days' continuous dosing with AZD0156 as a monotherapy at each dose level prior to Cycle 1.

Intermittent Dosing Schedules

Weekly Intermittent Schedule (Schedule 1) – AZD0156 was dosed on weekly repeating intermittent basis – for example, 3 days on, 4 days off each week of the cycle. Olaparib was dosed twice daily on a continuous daily basis throughout the cycle.

Cycle Intermittent Schedule (Schedule 2) – This was an initial period of daily AZD0156 dosing at the start of the cycle (for example, 7 days) in combination with olaparib, followed by dosing with olaparib alone (300 mg twice daily continuously) for the remainder of the cycle with no AZD0156 – for example, 7 days on, 21 days off.

Continuous Dosing Schedules

Daily Continuous Schedule (Schedule 3) – AZD0156 was dosed daily on a continuous basis in combination with olaparib, which was also dosed twice daily on a continuous daily basis throughout the cycle.

Module 2

AZD0156 + irinotecan/FOLFIRI (5-fluorouracil/folinic acid and irinotecan) Dosing Schedule

In Module 2, AZD0156 was to initially be dosed alongside a reduced dose of irinotecan (150 mg/m^2) only. Once AZD0156 had been successfully dosed alongside the standard dose level of irinotecan in the FOLFIRI regimen 180 mg/m, Folinic acid and 5-FU were to be

introduced to the combination and the dose of AZD0156 was to be escalated. The AZD0156 program was discontinued following the dosing with 150 mg/m^2 Irinotecan.

AZD0156 was supplied by AstraZeneca R&D supply chain as individual bottles of tablets. Combination agents were supplied by local sourcing (either directly or local supply with reimbursement) or directly by AstraZeneca R&D supply chain.

Individual batch numbers used in this study are provided in Appendix 16.1.6.

Duration of treatment

Subjects received AZD0156 in combination with olaparib in Module 1 and with irinotecan in Module 2 until they experienced unacceptable toxicity, withdrew voluntarily, or the investigator believed they were no longer deriving benefit from treatment.

For each subject, the screening period was up to 28 days, and the follow-up period was at least 28 days after the last dose of study treatment. Each cycle of treatment was 21 days for Module 1 Schedule 1 (the M1S1 group), 28 days for Module 1 Schedule 2 (the M1S2 group), 21 days for Module 1 Schedule 3 (the M1S3 group), and 14 days for Module 2 Schedule 1 (the M2S1 group). Subjects were to continue on treatment until disease progression, unacceptable toxicity, or withdrawal for other reasons.

Statistical methods

Analysis sets

The following analysis sets were used:

- **All Subjects Set**: All subjects who were enrolled in the study or were screening failures. The All Subjects Set was used for the summaries of subject disposition and screening failures.

- **Safety Analysis Set**: All subjects who received at least 1 dose of AZD0156. The Safety Analysis Set was used for the summaries of the demographic, exposure, and safety data. The efficacy endpoint of progression-free survival also used the Safety Analysis Set.

- **Pharmacokinetics Set**: All dosed subjects who received at least 1 dose of AZD0156 with reportable AZD0156 plasma concentrations and no important adverse events (AEs) (for instance, vomiting post dose) that occurred the same day as PK sampling or protocol deviations that might impact PK (see Section Pharmacokinetics).

- **Evaluable-for-Response Set**: Dosed subjects who had measurable disease at baseline. The Evaluable-for-Response Set was used for the summaries and analysis of the tumour response data.

The data were summarised using standard summary statistics (mean, standard deviation, median, minimum, and maximum for continuous variables and frequency and percentages for categorical variables). Please see Section 9 of the SAP version 3.0, dated 27 September 2019 (Appendix 16.1.9) for information on the summary statistics for the PK data. No formal statistical analysis was carried out for this study.

For Module 1, data analysis was performed 6 months after the last subject from any module/schedule/cohort completed the dose-limiting toxicity (DLT) assessment period. For Module 2, data analysis was performed once the last subject had completed their last visit in the study.

Safety

AEs were collected throughout the study, from the time of informed consent until the end of the follow-up period that was defined as 28 days after study treatment was discontinued. AEs were summarized by system organ class (SOC) and preferred term (PT) based on the Medical Dictionary for Regulatory Activities Version 21.0.

The Common Terminology Criteria for Adverse Events (CTCAE) grades were summarized by SOC and PT, using the National Cancer Institute CTCAE Version 4.03.

Treatment-emergent AEs were defined as any AEs that occurred after the administration of the first dose of study drug and through 28 days after the last dose of study drug or combination drug.

Treatment-emergent AEs were characterized based on the onset date relative to each subject's participation in the study.

A DLT was defined as any toxicity not attributable to the disease or disease-related processes under investigation, which occurred from the first dose of study treatment (Day 1, Cycle 0 or Cycle 1) up to the last day of the DLT assessment period inclusive of non-dosing days in dose escalation cohorts and which might manifest as one of the AEs, despite optimal therapeutic intervention (see Section 3.3 of Protocol version 6.0, dated 01 Mar 2019 located in Appendix 16.1.1).

An evaluable subject for DLT was defined as having completed minimum safety evaluation requirements and

Module 1:

- Had received the 5 to 7 days AZD0156 monotherapy dosing if enrolled during the initial part of the study (Part A)

  AND

- Had received at least 75% of the specified dose of AZD0156 and olaparib in the first cycle of dosing in the absence of a DLT

  OR

- Had experienced a DLT either during the 5-7 days AZD0156 monotherapy dosing or in the first cycle of dosing with the combination therapy of AZD0156 and olaparib.

Module 2:

- Had received at least 75% of the specified doses of AZD0156 and irinotecan/FOLFIRI in the two cycles of dosing (28 days dosing)

  OR

- Had experienced a DLT during days during the first 2 cycles (28 days) of dosing with the combination therapy of AZD0156 and irinotecan/FOLFIRI

Results of laboratory evaluations, vital signs, 12-lead electrocardiograms (ECG), physical examinations, ECOG status, pulmonary function tests, and other safety (chest x-ray, blood transfusions and use of granulocyte colony-stimulating factor/growth factors) variables and changes from baseline were summarised with descriptive statistics. Abnormal laboratory values were flagged. Shifts in the overall results of ECG from baseline to the end of treatment were summarized by module, dose level, and overall.

Efficacy

The efficacy endpoints that were summarised and analysed included objective response rate, durable response rate, duration of response, non-progressive disease at Week 12, best percentage change in the sum of the target lesions, percentage change in the sum of the target lesions at Week 12, and progression-free survival.

Pharmacokinetics

The plasma and urine PK parameters for AZD0156, metabolite (M1), and olaparib were calculated using non-compartmental methods in Phoenix WinNonlin Version 8.1 (Certara USA, Inc., Princeton, New Jersey) from available concentration data using methods as detailed in Section 9 of the SAP version 3.0, dated 27 September 2019 (Appendix 16.1.9).

All available AZD0156, M1, and olaparib plasma concentration data are listed in Section 14.2 and Appendix 16.2. Any concentration data not used in the PK analysis and any concentrations or parameters not included in the summary statistics were agreed by the PK Scientist and AZ Clinical Pharmacology Scientist and are flagged in the listings with a reference to the justification detail which are presented in Appendix 16.2 (Listing 16.2.6.6.1).

The PK analysis set was originally defined at the time of database lock, based upon PK-related protocol deviations registered in the database. However, during the PK analysis undertaken post database lock, it was agreed with the specialist PK team that exclusions from the PK outputs should only be based upon their assessment whilst conducting the PK analysis. This generally considered exclusion of individual PK concentration and parameter data values, rather than subject level exclusions. In order to avoid confusion with the 'PK analysis set' as originally defined in the Tables, Figures and Listings, the decision was taken to label all PK outputs (both individual data listings and summary tables and figures) as the 'Safety Analysis Set'.

Study Results

For Module 1, data analysis was performed 6 months after the last subject from any module/schedule/cohort completed the DLT period. For Module 2, data analysis was performed once the last subject had completed their last visit in the study period. The primary data cut-off occurred on 28 November 2019.

Subject population

- In total, 84 subjects were enrolled: 57 subjects with AZD0156 + olaparib (weekly intermittent AZD0156, 21 day cycle) in the M1S1 group; 17 subjects with AZD0156 + olaparib (cycle intermittent AZD0156, 28 day cycle) in the M1S2 group; 3 subjects with AZD0156 + olaparib (continuous, 21 day cycle) in the M1S3 group; and 7 subjects with AZD0156 + irinotecan/FOLFIRI (14 day cycle) in the M2S1 group (Table 14.1.1).

- Of the 84 enrolled subjects, 83 subjects received study treatment. Of the 57 subjects who were assigned to study treatment in the M1S1 group, 3 (5.3%) subjects received AZD0156 as monotherapy only, 53 (93.0%) subjects received it as combination therapy, and 1 subject did not receive AZD0156. Of the 17 subjects in the M1S2 group, 2 (11.8%) subjects received AZD0156 as monotherapy only, and 15 (88.2%) subjects received it as combination therapy. All 3 (100%) subjects in the M1S3 group received AZD0156 as combination therapy. Similarly, all 7 (100%) subjects in the M2S1 group received AZD0156 as combination therapy (Table 14.1.1).

- Of the 83 treated subjects, all the subjects terminated the study with the exception of 4 subjects who continued on the study treatment as part of a post-reporting drug access program: 2 subjects in the M1S1 group, 1 subject in the M1S2 group, and 1 subject in the M2S1 group. The main reason for the study termination was confirmed disease progression reported by 48 (84.2%) subjects, 13 (76.5%) subjects, and 1 (33.3%) subject in the M1S1, M1S2, and M1S3 groups, respectively. In the M2S1 group, 4 (57.1%) subjects reported confirmed disease progression as the most common reason

to terminate the study. There were only 2 subjects in the M1S1 group who reported AEs as the reason for the study termination (Table 14.1.1).

Table S2 presents subject disposition through the data cut-off date of 28 November 2019.

Table S1 Subject Disposition (All Subjects Set)

	Number (%) of Subjects			
	Module 1			Module 2
	Schedule 1[a] AZD+OLA Total N = 57	Schedule 2[b] AZD+OLA Total N = 17	Schedule 3[c] AZD+OLA Total N = 3	Schedule 1[d] AZD+IRI Total N = 7
Subjects enrolled	57	17	3	7
Safety analysis set	56	17	3	7
Evaluable-for-response set	52	16	3	7
Subjects assigned to treatment	57 (100)	17 (100)	3 (100)	7 (100)
Received AZD0156	56 (98.2)	17 (100)	3 (100)	7 (100)
As monotherapy only	3 (5.3)	2 (11.8)	0	0
As combination therapy	53 (93.0)	15 (88.2)	3 (100)	7 (100)
Did not receive AZD0156	1 (1.8)	0	0	0
Discontinued AZD0156 treatment	**56 (100)**	**17 (100)**	**3 (100)**	**7 (100)**
Confirmed disease progression	46 (82.1)	13 (76.5)	3 (100)	4 (57.1)
Adverse event	4 (7.1)	1 (5.9)	0	0
Subject decision	2 (3.6)	0	0	1 (14.3)
Risk to subjects as judged by the investigator and/or sponsor	0	2 (11.8)	0	0
Death	0	0	0	1 (14.3)
Other	4 (7.1)	1 (5.9)	0	1 (14.3)
Discontinued OLA	**54 (96.4)**	**16 (94.1)**	**3 (100)**	**-**
Confirmed disease progression	45 (80.4)	13 (76.5)	3 (100)	-
Adverse event	3 (5.4)	1 (5.9)	0	-
Subject decision	1 (1.8)	0	0	-
Risk to subjects as judged by the investigator and/or sponsor	0	1 (5.9)	0	-
Other	5 (8.9)	1 (5.9)	0	-
Discontinued IRI	**-**	**-**	**-**	**7 (100)**
Confirmed disease progression	-	-	-	4 (57.1)
Subject decision	-	-	-	1 (14.3)
Death	-	-	-	1 (14.3)
Other	-	-	-	1 (14.3)
Terminated the study	**57 (100)**	**17 (100)**	**3 (100)**	**7 (100)**
Confirmed disease progression	48 (84.2)	13 (76.5)	1 (33.3)	4 (57.1)
Adverse event	2 (3.5)	0	0	0
Subject decision	2 (3.5)	1 (5.9)	0	1 (14.3)
Sponsor decision	0	1 (5.9)	0	0
Death	2 (3.5)	1 (5.9)	2 (66.7)	1 (14.3)
Subjects continued on treatment with study drug as part of post reporting drug access program	2 (3.5)	1 (5.9)	0	1 (14.3)
Other	1 (1.8)	0	0	0

Abbreviations: AZD = AZD0156, AE = adverse event, IRI = irinotecan, OLA = olaparib.

[a] Module 1 (AZD0156 + olaparib) Schedule 1 (M1S1) [Weekly Intermittent AZD0156, 21 day cycle].

[b] Module 1 (AZD0156 + olaparib) Schedule 2 (M1S2) [Cycle Intermittent AZD0156, 28 day cycle].

[c] Module 1 (AZD0156 + olaparib) Schedule 3 (M1S3) [Continuous, 21 day cycle]. Only 1 cohort was included in this schedule.

[d] Module 2 (AZD0156 + irinotecan/FOLFIRI) Schedule 1 (M2S1) [14 day cycle]. Only 1 cohort was included in this schedule.

Note: Twenty subjects were screen failures: 18 subjects did not meet eligibility criteria and 2 subjects experienced AEs.

Table S3 presents subject disposition for the M1S1 group through the data cut-off date of 28 November 2019.

Table S2 Subject Disposition for the Module 1 Schedule 1 (All Subjects Set)

	Number (%) of Subjects									
AZD0156	**2 mg QD**	**8 mg QD**	**30 mg QD**	**30 mg BID**	**15 mg BID**	**30 mg BID**	**60 mg BID**	**30 mg BID**	**120 mg BID**	**60 mg BID**
Olaparib	**100 mg BID**	**100 mg BID**	**100 mg BID**	**100 mg BID**	**200 mg BID**	**200 mg BID**	**200 mg BID**	**300 mg BID**	**200 mg BID**	**300 mg BID**
	N = 6	**N = 5**	**N = 7**	**N = 6**	**N = 6**	**N = 4**	**N = 4**	**N = 7**	**N = 4**	**N = 8**
Subjects assigned to treatment	6 (100)	5 (100)	7 (100)	6 (100)	6 (100)	4 (100)	4 (100)	7 (100)	4 (100)	8 (100)
Received AZD0156										
As monotherapy only	0	0	1 (14.3)	0	0	0	0	1 (14.3)	0	1 (12.5)
As combination therapy	6 (100)	5 (100)	6 (85.7)	6 (100)	6 (100)	4 (100)	4 (100)	6 (85.7)	4 (100)	6 (75.0)
Did not receive AZD0156	0	0	0	0	0	0	0	0	0	1 (12.5)
Discontinued AZD0156 treatment	6 (100)	5 (100)	7 (100)	6 (100)	6 (100)	4 (100)	4 (100)	7 (100)	4 (100)	7 (100)
Confirmed disease progression	5 (83.3)	4 (80.0)	5 (71.4)	5 (83.3)	5 (83.3)	4 (100)	4 (100)	6 (85.7)	3 (75.0)	5 (71.4)
Adverse event	1 (16.7)	0	2 (28.6)	0	1 (16.7)	0	0	0	0	0
Subject decision	0	0	0	0	0	0	0	1 (14.3)	0	1 (14.3)
Other	0	1 (20.0)	0	1 (16.7)	0	0	0	0	1 (25.0)	1 (14.3)
Discontinued OLA	6 (100)	5 (100)	6 (85.7)	6 (100)	6 (100)	4 (100)	4 (100)	7 (100)	4 (100)	6 (85.7)
Confirmed disease progression	5 (83.3)	4 (80.0)	4 (57.1)	5 (83.3)	5 (83.3)	4 (100)	4 (100)	6 (85.7)	3 (75.0)	5 (71.4)
Adverse event	1 (16.7)	0	1 (14.3)	0	1 (16.7)	0	0	0	0	0
Subject decision	0	0	0	0	0	0	0	1 (14.3)	0	0
Other	0	1 (20.0)	1 (14.3)	1 (16.7)	0	0	0	0	1 (25.0)	1 (14.3)
Terminated the study	6 (100)	5 (100)	7 (100)	6 (100)	6 (100)	4 (100)	4 (100)	7 (100)	4 (100)	8 (100)
Confirmed disease progression	6 (100)	4 (80.0)	5 (71.4)	5 (83.3)	6 (100)	4 (100)	4 (100)	5 (71.4)	4 (100)	5 (62.5)
Adverse event	0	0	1 (14.3)	0	0	0	0	0	0	1 (12.5)
Subject decision	0	0	0	0	0	0	0	1 (14.3)		1 (12.5)
Death	0	0	1 (14.3)	0	0	0	0	1 (14.3)	0	0
Subjects continued on treatment with study drug as part of post reporting drug access program	0	0	0	1 (16.7)	0	0	0	0	0	1 (12.5)
Other	0	1 (20.0)	0	0	0	0	0	0	0	0

Abbreviations: AE = adverse event, BID = twice daily, OLA = olaparib, QD = once daily

Note 1: Module 1 (AZD0156 + olaparib) Schedule 1 [Weekly Intermittent AZD0156, 21 day cycle]

Note 2: Twenty subjects were screen failures: 18 subjects did not meet eligibility criteria and 2 subjects experienced AEs.

Table S4 presents subject disposition for the M1S2 group through the data cut-off date of 28 November 2019.

Table S3 Subject Disposition for Module 1 Schedule 2 (All Subjects Set)

	Number (%) of Subjects		
AZD0156	**40 mg BID**	**80 mg BID**	**60 mg BID**
Olaparib		**300 mg BID**	
	N = 7 n (%)	**N = 3 n (%)**	**N = 7 n (%)**
Subjects assigned to treatment	7 (100)	3 (100)	7 (100)
Received AZD0156			
As monotherapy only	1 (14.3)	1 (33.3)	0
As combination therapy	6 (85.7)	2 (66.7)	7 (100)
Did not receive AZD0156	0	0	0
Discontinued AZD0156 treatment	**7 (100)**	**3 (100)**	**7 (100)**
Confirmed disease progression	6 (85.7)	1 (33.3)	6 (85.7)
Adverse event	0	1 (33.3)	0
Risk to subjects as judged by the investigator and/or sponsor	1 (14.3)	1 (33.3)	0
Other	0	0	1 (14.3)
Discontinued OLA	**6 (85.7)**	**3 (100)**	**7 (100)**
Confirmed disease progression	6 (85.7)	1 (33.3)	6 (85.7)
Adverse event	0	1 (33.3)	0
Risk to subjects as judged by the investigator and/or sponsor	0	1 (33.3)	0
Other	0	0	1 (14.3)
Terminated the study	**7 (100)**	**3 (100)**	**7 (100)**
Confirmed disease progression	6 (85.7)	1 (33.3)	6 (85.7)
Adverse event	0	0	0
Subject decision	0	1 (33.3)	0
Sponsor decision	1 (14.3)	0	0
Death	0	1 (33.3)	0
Subjects continued on treatment with study drug as part of post reporting drug access program	0	0	1 (14.3)

Abbreviation: AE = adverse event, BID = twice daily, OLA = olaparib

Note 1: Module 1 (AZD0156 + olaparib) Schedule 2 [Cycle Intermittent AZD0156, 28 day cycle]

Note 2: Twenty subjects were screen failures: 18 subjects did not meet eligibility criteria and 2 subjects experienced AEs.

The M1S3 group consisted of 1 dosing cohort at 10 mg AZD0156 BID/300 mg olaparib BID (Table S2). The M2S1 group also consisted of 1 dosing cohort at 30 mg AZD0156 BID/150 mg/m^2 irinotecan (Table S2).

- Overall, the median age of the subjects in the M1S1 group was 56 years (range: 30 to 76 years), in the M1S2 group was 57 years (range: 40 to 73 years), in the M1S3 group was 65 years (range: 63 to 79 years), and in the M2S1 group was 62 years (range: 46 to 73 years). A total of 66.1%, 58.8%, 100%, and 28.6% of subjects were females in the M1S1, M1S2, M1S3, and M2S1 groups, respectively; while 82.1%, 58.8%, 100%, and 85.7% of subjects were white in the M1S1, M1S2, M1S3, and M2S1 groups, respectively. There were 16.1% and 35.3% of Asian subjects in the M1S1 and M1S2 groups, respectively, while no Asian subjects were included in the M1S3 and M2S1 groups (Table 14.1.4.1).

- At baseline, the most commonly reported sites of local disease were other locally advanced sites (14 [25.0%] subjects), and breast and skin/soft tissue (3 [5.4%] subjects each) in the M1S1 group; breast (5 [29.4%] subjects) and other locally advanced sites (3 [17.6%] subjects) in the M1S2 group; pancreas (2 [66.7%] subjects) in the M1S3 group; and colon and pancreas (3 [42.9%] subjects each) in the M2S1 group (Table 14.1.4.2.1).

- At baseline, the commonly reported sites of metastatic disease were other metastatic sites (17 [30.4%] subjects), lymph nodes (11 [19.6%] subjects), and respiratory (10 [17.9%] subjects) in the M1S1 group; other metastatic sites and liver (4 [23.5%] subjects each), and bone and locomotor, lymph nodes, and breast (2 [11.8%] subjects each) in the M1S2 group; liver (2 [66.7%] subjects) in the M1S3 group; and other metastatic sites (3 [42.9%] subjects) and hepatic (including gall bladder) (2 [28.6%] subjects) in the M2S1 group (Table 14.1.4.2.1).

- There were 9 deaths reported. In Module 1, 8 subjects died: 5 subjects in the M1S1 group, 1 subject in the M1S2 group, and 2 subjects in the M1S3 group; while in Module 2, 1 subject in the M2S1 group died (Table 14.3.3.1.1).

Summary of treatment duration

Module 1 (AZD0156 + olaparib)

- Median duration of the actual treatment was 1.12 months (range: 0, 16.72) in the M1S1 group, 0.69 months (range: 0.16, 2.99) in the M1S2 group, and 2.53 months (range: 1.15, 3.45) in the M1S3 group. Median duration of the actual treatment and the total treatment were comparable across the 3 groups (Table 14.3.1.1.1). Median relative dose intensity was 100% (range: 38%, 108%) in the M1S1 group, 78% (range: 50%, 100%) in the M1S2 group, and 100% (range: 67%, 100%) in the M1S3 group (Table 14.3.1.1.2).

Module 2 (AZD0156 + irinotecan/FOLFIRI)

- Median duration of the actual treatment and the total treatment was 0.59 months (range: 0.10, 2.00) in the M2S1 group (Table 14.3.1.1.1). Median relative dose intensity was 100% (range: 75%, 100%) in the M2S1 group (Table 14.3.1.1.2).

Summary of safety results

Module 1 (AZD0156 + olaparib)

Categories of Adverse Events

- Of the 76 treated subjects in Module 1, the majority of subjects (73 [96.1%]) experienced any AE, while 42 (55.3%) subjects had any AE ≥ CTCAE Grade 3. There were 3 (3.9%) subjects with AEs leading to death, 29 (38.2%) subjects with serious adverse events (SAEs), and 7 (9.2%) subjects experienced AEs leading to discontinuation of study treatment (Table 14.3.2.1.1).

Adverse Events by System Organ Class and Preferred Term

- Among the 73 subjects who experienced any AE: 54 (96.4%) subjects in the M1S1 group, 16 (94.1%) subjects in the M1S2 group, and 3 (100%) subjects in the M1S3 group reported AEs (Table 14.3.2.1.1).

- The system organ class (SOC) with the highest incidence of subjects reporting AEs was gastrointestinal disorders (63 [82.9%] subjects), followed by general disorders and administration site conditions and investigations (41 [53.9%] subjects each), and blood and lymphatic system disorders (39 [51.3%] subjects) (Table 14.3.2.2).

- The most commonly reported AEs by preferred term (PT) were nausea (47 [61.8%] subjects), anaemia (37 [48.7%] subjects), and vomiting (29 [38.2%] subjects). Overall, nausea was reported in 31 (55.4%) subjects in the M1S1 group, 13 (76.5%) subjects in the M1S2 group, and 3 (100%) subjects in the M1S3 group. Anaemia in the M1S1, M1S2, and M1S3 groups was reported in 24 (42.9%), 11 (64.7%), and 2 (66.7%) subjects, respectively. Vomiting in the M1S1, M1S2, and M1S3 groups was reported in 23 (41.1%), 5 (29.4%), and 1 (33.3%) subject, respectively. Other frequently reported AEs in >20% of subjects included constipation, diarrhoea, fatigue, and decreased appetite (Table 14.3.2.3).

- There were 58 (76.3%) subjects with any AE causally related to study treatment: 40 (71.4%) subjects in the M1S1 group, 15 (88.2%) subjects in the M1S2 group, and 3 (100%) subjects in the M1S3 group. The most commonly reported AE assessed by investigator as possibly related to study treatment was nausea in 22 (39.3%) subjects in the M1S1 group, 10 (58.8%) subjects in the M1S2 group, and 3 (100%) subjects in the M1S3 group; followed by anaemia in 9 (16.1%), 7 (41.2%), and 1 (33.3%) subjects, respectively; vomiting in 15 (26.8%), 3 (17.6%), and 1 (33.3%) subjects, respectively; and diarrhoea in 10 (17.9%), 1 (5.9%), and 2 (66.7%) subjects, respectively (Table 14.3.2.6).

- There were 42 (55.3%) subjects with any AE ≥ CTCAE Grade 3: 29 (51.8%) subjects in the M1S1 group, 10 (58.8%) subjects in the M1S2 group, and 3 (100%) subjects in the M1S3 group (Table 14.3.2.5).

- The most commonly reported AEs of ≥ CTCAE Grade 3 by PT in all the subjects in Module 1 included anaemia (8 [10.5%] subjects), neutrophil count decreased or platelet count decreased (6 [7.9%] subjects each), neutropenia (5 [6.6%] subjects), intestinal obstruction or gamma-glutamyl transferase (GGT) increased (4 [5.3%] subjects each), febrile neutropenia, lymphopenia, lymphocyte count decreased, or aspartate aminotransferase (AST) increased (3 [3.9%] subjects each), abdominal pain, constipation, vomiting, thrombocytopenia, alanine aminotransferase increased, blood alkaline

phosphatase (ALP) increased, blood bilirubin increased or device occlusion (2 [2.6%] subjects each) (Table 14.3.2.4).

- There were 18 (23.7%) subjects with any AE ≥ CTCAE Grade 3 causally related to study treatment: 9 (16.1%) subjects in the M1S1 group, 8 (47.1%) subjects in the M1S2 group, and 1 (33.3%) subject in the M1S3 group (Table 14.3.2.1.1).

- There were 3 subjects, all in the M1S1 group, who had an AE with an outcome of death. These AEs included intestinal obstruction in 2 subjects and biliary obstruction in 1 subject (Table 14.3.3.1.1 and Listing 16.2.7.3). None of these deaths were considered causally related to study treatment. Narratives for subjects who died are provided in Section 14.4.1.

- There were 29 (38.2%) subjects with SAEs: 23 (41.1%) subjects in the M1S1 group, 5 (29.4%) subjects in the M1S2 group, and 1 (33.3) subject in the M1S3 group (Table 14.3.4.1). The most commonly reported SAEs was intestinal obstruction (4 [5.3%] subjects), followed by febrile neutropenia, thrombocytopenia, platelet count decreased, and device occlusion (2 [2.6%] subjects each). Detailed narratives for the subjects who experienced SAEs are provided in Section 14.4.2.

- No subject experienced any SAE causally related to study treatment (Table 14.3.4.2).

- There were 7 (9.2%) subjects with any AE leading to discontinuation of study treatment: 6 (10.7%) subjects in the M1S1 group including intestinal obstruction (3 [5.4%] subjects) and transaminases increased, bile duct obstruction, and upper gastrointestinal haemorrhage (1 [1.8%] subject each). Any AE leading to discontinuation of study treatment was reported by 1 (5.9%) subject in the M1S2 group (neutropenic colitis) and it was reported to be causally related to study treatment. No subject in the M1S3 group experienced any AE that led to discontinuation of study treatment (Table 14.3.5.1). Detailed narratives for the subjects who experienced AEs leading to discontinuation of study treatment are provided in Section 14.4.3.

- In the M1S1 group, no DLTs were observed in dosing cohorts up to 30 mg AZD0156 BID/300 mg olaparib BID; however, DLTs were observed in 1 subject at 120 mg AZD0156 BID/200 mg olaparib BID with the reported AE of Grade 3 raised AST and in 1 subject at 60 mg AZD0156/300 mg olaparib BID with the reported AE of Grade 4 thrombocytopenia (Table 14.3.2.7). It was subsequently decided by AstraZeneca to stop dose escalation in this schedule and as a result, an MTD was not determined.

- In the M1S2 group, no DLTs were observed at 40 mg AZD0156 BID/300 mg olaparib BID; however, DLTs were observed in 2 subjects at 80 mg AZD0156 BID/300 mg olaparib BID and the reported AEs included Grade 3 and Grade 4 febrile neutropenia,

Grades 4 thrombocytopenia, Grade 4 neutrophil count decreased, and Grade 4 platelet count decreased. DLTs at 60 mg AZD0156/300 mg olaparib BID were observed in 2 subjects and the reported AEs included a Grade 3 febrile neutropenia and Grade 3 and Grade 4 platelet count decreased. Note that at the time of database lock, 3 subjects in this cohort were deemed to have experienced DLTs. However, the Grade 2 tooth infection which was experienced by subject 0101-127, was determined not to be a DLT case by the SRC (see Note to File in Section 16.1.9) and as such a footnote was included in the relevant outputs to explain this (Table 14.3.2.7).

- In the M1S2 group, the MTD of AZD0156 was established as 40 mg AZD0156 BID/300 mg olaparib BID for 7 days, followed by olaparib 300 mg BID alone for 21 days (28-day cycle) (see Safety Review Committee Meeting Minutes, dated 18 March 2019, located in Appendix 16.1.9).

- In the M1S3 group, no DLTs were observed at 10 mg AZD0156 BID/300 mg olaparib BID (Table 14.3.2.7). However, subsequently it was decided by AstraZeneca to stop dose escalation in this schedule and as a result, an MTD was not determined.

- There were no confirmed cases of Hy's law (Table 14.3.6.6).

- The haematological AEs in all subjects in Module 1 included anaemia in 37 (48.7%) subjects, neutropenia in 6 (7.9%) subjects, thrombocytopenia in 3 (3.9%) subjects, lymphopenia in 4 (5.3%) subjects, and leukopenia in 1 (1.3%) subject (Table 14.3.2.4).

- Overall, there were no specific trends in the laboratory parameters over time; however, Grade 3 AST changed from Grade 1 at baseline in 1 of 5 subjects at 8 mg AZD0156 QD/100 mg olaparib BID and 1 of 7 subjects at 40 mg AZD0156 BID/300 mg olaparib BID. Grade 3 creatine kinase changed from Grade 1 at baseline in 1 of 6 subjects at 2 mg AZD0156/100 mg olaparib BID. No concurrent musculoskeletal AEs were reported. No subject showed Grade 4 changed from Grade 1 at baseline in haematology, coagulation, and clinical chemistry (Table 14.3.6.3).

- Overall, there were no specific trends in the vital signs; however, a decrease in weight over time from baseline was observed in subjects in some dosing cohorts (Table 14.3.7.1.1).

- Overall, there were no specific trends in the ECG results: however, a clinically significant abnormality in the ECG at the end of treatment was observed in 1 subject at 60 mg AZD0156 BID/300 mg olaparib BID in the M1S2 group. This subject had abnormal but not clinically significant ECG at baseline (Table 14.3.7.2.3). This subject experienced a nonserious AE of Grade 1 atrioventricular block first degree on Study Day 5 and this event resolved 2 days after the onset, which was considered to be not related to study treatment

by the investigator, and the study treatment continued unchanged (Listing 16.2.7.1 and Listing 16.2.10.1).

- Overall, there were no specific trends in the physical examination results (Listing 16.2.10.2).

Module 2 (AZD0156 + irinotecan/FOLFIRI)

Categories of Adverse Events

- All subjects (7 [100%]) experienced any AE, while 6 (85.7%) subjects had any AE ≥ CTCAE Grade 3. There was 1 (14.3%) subject with an AE leading to death, 3 (42.9%) subjects with SAEs, and 1 (14.3%) subject experienced AEs leading to discontinuation of study treatment.

Adverse Events by System Organ Class and Preferred Term

- All 7 (100%) subjects in the M2S1 group experienced an AE (Table 14.3.2.1.1).
- The SOC with the highest incidence of subjects reporting AEs was gastrointestinal disorders (7 [100%] subjects), followed by investigations (6 [85.7%] subjects), blood and lymphatic system disorders (5 [71.4%] subjects), and general disorders and administration site conditions (4 [57.1%] subjects) (Table 14.3.2.2).
- The most commonly reported AEs by PT were nausea (6 [85.7%] subjects), followed by diarrhoea (5 [71.4%) subjects), and anaemia and vomiting (4 [57.1%] subjects each) (Table 14.3.2.3).
- There were 6 (85.7%) subjects with any AE ≥ CTCAE Grade 3 (Table 14.3.2.5).
- The most commonly reported AEs of ≥ CTCAE Grade 3 by PT included GGT increased, neutropenia, or neutrophil count decreased (2 [28.6%] subjects each), and abdominal pain, lymphocyte count decreased, and haemorrhage intracranial (1 [14.3%] subject each) (Table 14.3.2.5).
- There were 4 (57.1%) subjects with any AE ≥ CTCAE Grade 3 causally related to study treatment (Table 14.3.2.1.1).
- There were 6 (85.7%) subjects with any AE causally related to study treatment. The most commonly reported AEs assessed by investigator as possibly related to study treatment were diarrhoea and vomiting (3 [42.9%] subjects, each), followed by nausea, anaemia, neutropenia, fatigue, myoglobin urine present, neutrophil count decreased, and decreased appetite (2 [28.6%] subjects, each) (Table 14.3.2.6).

- There was 1 subject who had an SAE with a fatal outcome of Grade 5 intracranial haemorrhage that was considered by the investigator to be related to treatment with AZD0156 and unrelated to treatment with irinotecan (Listing 16.2.7.1 and Listing 16.2.7.4). Detailed narrative for this subject is provided in Section 14.4.1.

- There were 3 (42.9%) subjects with SAEs. The SAEs included abdominal pain, dizziness, neutropenia, and haemorrhage intracranial (Table 14.3.4.1). Detailed narratives for subjects who experienced SAEs are provided in Section 14.4.2.

- There were 2 (28.6%) subjects with an SAE causally related to study treatment (Table 14.3.2.1.1).

- There was 1 subject with any AE leading to discontinuation of study treatment. The AE was a fatal outcome of intracranial haemorrhage (Table 14.3.5.3). Detailed narrative for this subject who experienced AEs leading to discontinuation of study treatment is provided in Section 14.4.3.

- DLTs were observed in 3 subjects at 30 mg AZD0156 BID/150 mg/m^2 irinotecan. The 3 subjects experienced 1 DLT each, which included Grade 4 neutropenia and Grade 3 abdominal pain (Table 14.3.2.7). The MTD was therefore not determined.

- There were no confirmed cases of Hy's law (Table 14.3.6.6).

- The haematological AEs in total subjects included anaemia in 4 (57.1%) subjects and neutropenia in 2 (28.6%) subjects. No subject reported thrombocytopenia, lymphopenia, and leukopenia in Module 2 (Table 14.3.2.4).

- Overall, there were no specific trends in the laboratory parameters over time; however, Grade 3 bilirubin changed from Grade 1 at baseline in 1 subject at 30 mg AZD0156 BID/150 mg/m^2 irinotecan dosing and no concurrent hepatic AEs were reported in this subject (Table 14.3.6.3 and Listing 16.2.7.1).

- Overall, there were no specific trends in the vital signs (Table 14.3.7.1.1).

- Overall, there were no specific trends in the ECG results (Table 14.3.7.2.3), or physical examination results (Listing 16.2.10.2).

Summary of pharmacokinetics results

The pharmacokinetic results for AZD0156 showed that:

- AZD0156 was rapidly absorbed with a median t_{max} across all treatments and dose levels of approximately 1 to 2 hours (range 0.5 to 4.2 hours).

- Where the terminal half-life ($t_{1/2}$, λ_z), apparent clearance (CL/F) and apparent volume of distribution ($V_{z/F}$) could be adequately determined it appeared to be similar across all dose levels and treatments.

- Exposure (C_{max} and AUC) generally increased with increasing dose for the dose range investigated on each of the PK Days in what appeared to be an approximately dose proportional manner.

- There was a small amount of accumulation observed in AZD0156 exposure when dosed alone in Cycle 0, with accumulation ratio values on PK Day Last Weekly Dose just > 1 (slightly higher for BID than QD doses).

- There was no evidence of time-dependant kinetics from single dose to multiple dose for AZD0156 when dosed alone in Cycle 0, with TCP values for AZD0156 close to 1 for the QD cohorts and a little higher for the BID cohorts at the higher dose levels.

- The presence of olaparib did not appear to make a clinically relevant difference to the PK of AZD0156.

The plasma PK data for metabolite and the urine PK data for AZD0156 were not summarised in the study results.

Summary of efficacy results

The objective response rate was based on the percentage of subjects who had a best objective response of confirmed complete or partial response.

- In Module 1, 7 subjects had a confirmed partial response: 5/52 (9.6%) subjects in the M1S1 group and 2/16 (12.5%) subjects in the M1S2 group. No subject reported a confirmed partial response in the M1S3 group. Also, in Module 2 (the M2S1 group), there was no confirmed partial response reported (Table 14.2.1).

- The majority of subjects reported non-response status (Table 14.2.1).

- For the best objective response in total, non-response in Module 1 was reported by 47/52 (90.4%) subjects in the M1S1 group, 14/16 (87.5%) subjects in the M1S2 group, and 3/3 (100%) subjects in the M1S3 group. In Module 2 (the M2S1 group), 7/7 (100%) subjects reported non-response (Table 14.2.1).

- The objective response rate for each module/schedule with the 80% confidence interval (CI) based on the percentage of subjects who had a best objective response of confirmed complete or partial response in Module 1 was 9.6% (80% CI 4.8 - 17.1) in the M1S1 group; 12.5% (80% CI 3.4 - 30.0) in the M1S2 group; and 0% (0.0 - 53.6) in the M1S3 group. In Module 2 (the M2S1 group), it was 0% (0.0 - 28.0) (Table 14.2.1).

Other efficacy outcomes are reported in Tables 14.2.2, 14.2.3, 14.2.4, 14.2.5.1, 14.2.6.1, 14.2.6.2, 14.2.7, and 14.2.8.1 in Section 14.2.

Conclusions

Module 1

Results from Module 1 of this study suggested that AZD0156 in combination with olaparib was generally well tolerated and had an acceptable safety profile in the study population. The safety data observed were consistent with the known safety profiles of AZD0156 or olaparib. Overall, 73 (96.1%) subjects experienced any AE in Module 1 during the study. The most commonly reported AEs were nausea, anaemia, and vomiting. Of these, 42 (55.3%) subjects reported AEs ≥ CTCAE Grade 3 which included anaemia, neutrophil count decreased or platelet count decreased, neutropenia, and intestinal obstruction or GGT increased.

In the M1S1 group, DLTs were observed in 1 subject at 120 mg AZD0156 BID/200 mg olaparib BID with the reported AE of Grade 3 raised AST and in 1 subject at 60 mg AZD0156/300 mg olaparib BID with the reported AE of Grade 4 thrombocytopenia. In the M1S2 group, DLTs were observed in 2 subjects at 80 mg AZD0156 BID/300 mg olaparib BID and the reported AEs included Grade 3 and Grade 4 febrile neutropenia, Grades 4 thrombocytopenia, Grade 4 neutrophil count decreased, and Grade 4 platelet count decreased. DLTs at 60 mg AZD0156/300 mg olaparib BID were observed in 2 subjects and the reported AEs included a Grade 3 febrile neutropenia and Grade 3 and Grade 4 platelet count decreased. In the M1S3 group, no DLTs were observed at 10 mg AZD0156 BID/300 mg olaparib BID.

In the M1S2 group, the MTD of AZD0156 was established as 40 mg AZD0156 BID/300 mg olaparib BID for 7 days, followed by olaparib 300 mg BID alone for 21 days (28-day cycle). In the M1S1 and M1S3 groups, the MTD was not determined.

There were 8 deaths reported in Module 1, which were attributed to disease progression (4 subjects), intestinal obstruction (2 subjects), biliary obstruction (1 subject), and metastatic ampullary carcinoma (1 subject).

Three subjects had an AE with a fatal outcome. These AEs included intestinal obstruction in 2 subjects and biliary obstruction in 1 subject. None of these deaths were considered causally related to study treatment.

In total, 29 (38.2%) subjects reported SAEs. The commonly reported SAEs included intestinal obstruction, febrile neutropenia, thrombocytopenia, platelet count decreased, and device occlusion.

Seven (9.2%) subjects had AEs leading to discontinuation of the study treatment. These mainly included events of intestinal obstruction.

There were no confirmed cases of Hy's law.

Overall, there were no specific trends in the laboratory parameters; however, a decrease in weight over time from baseline was observed in subjects in some dosing cohorts.

Overall, there were no specific trends in the results of ECG and physical examination over time.

Module 2

Module 2 of this study was discontinued due to the 3 subjects experiencing DLTs at 30 mg AZD0156 BID/150 mg/m^2 irinotecan. The reported AEs included Grade 4 neutropenia and Grade 3 abdominal pain.

In Module 2, overall, 7 (100%) subjects experienced AEs during the study. The most commonly reported AEs were nausea, diarrhoea, anaemia, and vomiting. Of these, 6 (85.7%) subjects reported AEs ≥ CTCAE Grade 3 which included gamma-glutamyl transferase increased, neutropenia, neutrophil count decreased, and abdominal pain, lymphocyte count decreased, and haemorrhage intracranial.

One subject had an SAE of intracranial haemorrhage with a fatal outcome. The event was considered by the investigator to be related to treatment with AZD0156 and unrelated to irinotecan. The laboratory data showed normal platelets and no clotting abnormality. A CT scan revealed a high-density cerebellar area likely to be haematoma, but could not exclude haemorrhagic metastasis.

In total, 3 (42.9%) subjects reported SAEs. The SAEs included abdominal pain, dizziness, neutropenia, and haemorrhage intracranial.

One subject had an AE that leading to the discontinuation of the study treatment (intracranial haemorrhage as noted above).

There were no confirmed cases of Hy's law.

Overall, there were no specific trends in the laboratory parameters and vital signs over time.

Overall, there were no specific trends in the results of ECG and physical examination over time.