/ ASCOLT

STATISTICAL ANALYSIS PLAN

Aspirin for Dukes C and High Risk Dukes B Colorectal Cancers (ASCOLT)

An International, Multi-centre, Double Blind, Randomised Placebo Controlled Phase III Trial

Investigational Product: Aspirin

Indication: Dukes C and High Risk Dukes B Colorectal Cancers

Phase: III

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APPROVAL

The undersigned hereby declare that they have prepared/examined the Statistical Analysis Plan and agree to its form and content. In addition, they confirm that to the best of their knowledge the Statistical Analysis Plan contains all information relevant for the conduct of Statistical Analysis of the study.

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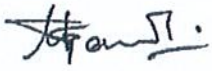

20-Feb-2023

Sign *Date*

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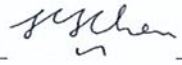

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REVISION HISTORY

Version	Author	Date of Implementation	Description of Modification
2.0	Mihir Gandhi	20-Feb-2023	Updated to reflect protocol V7.0, improve analysis methods and incorporate comments from steering committee.

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1 INTRODUCTION

Colorectal cancer is the third most common cancer worldwide with almost 1 million new cases diagnosed each year. It is now also the third leading cause of cancer mortality in men and women with more than half of diagnosed patients dying from the disease. Mortality rates in Asian countries have risen concomitantly and in Singapore rates have doubled over the same period, with incidence rates amongst the highest in Asia. Colon cancer has recently surpassed lung cancer as the commonest cancer diagnosed in Singapore.

The utility of Aspirin and NSAIDs in preventing cancer, especially colon cancer is the subject of intense pre-clinical and clinical interest and investigation. Whereas high quality evidence (randomised controlled studies) indicates that Aspirin is effective in reducing colorectal adenomatous polyps; and numerous studies point towards an ability to prevent colorectal cancer; the role of Aspirin as an adjuvant agent in patients with established cancers remains to be defined. A nested cohort study (NURSES Health Study) suggested that the initiation of Aspirin after the diagnosis of colon cancer was able to reduce colorectal cancer specific mortality (HR 0.53, CI 0.33-0.86). Further, a pre-planned analysis of patients in the CALGB 89810 adjuvant Irinotecan trial suggested that patients who used Aspirin or a Cox-2 inhibitor regularly had half the risk of recurrence and death. Although this data is supportive of Aspirin's biological activity in this disease and possible role in adjuvant therapy, it needs to be confirmed in a randomised prospective trial. Two large randomised Cox-2 inhibitor studies had been undertaken to answer the same question, but were suspended prematurely, due to concerns of cardiovascular toxicity. In contrast, Aspirin is cardio-protective and is one of the most widely used drugs with a well-established safety profile.

We hypothesise through this randomised, placebo-controlled adjuvant study, that Aspirin in patients with Dukes C or high risk Dukes B colorectal cancer (ASCOLT) can improve survival in this patient population over placebo control. If indeed found to be beneficial, Aspirin will positively impact the lives of many individuals in Asia and the whole world as it is cheap and easy to administer.

2 STUDY OBJECTIVES

Primary objective

Null hypothesis: Among subjects with Dukes C or high risk Dukes B colorectal cancer, Disease Free Survival (DFS) between those randomised to Aspirin and those randomised to placebo control is equal.

Alternative hypothesis: Among subjects with Dukes C or high risk Dukes B colorectal cancer, DFS between those randomised to Aspirin and those randomised to placebo is not equal.

Primary objective: To compare DFS between the group randomised to Aspirin with the group randomised to placebo control in subjects with Dukes C or high risk Dukes B colorectal cancer.

Secondary objectives

1. To compare the DFS between the group randomised to Aspirin with the group randomised to placebo control in subjects with high risk Dukes B and Dukes C colon cancer.
2. To compare the overall survival (OS) between the group randomised to Aspirin with the group randomised to placebo control in subjects with Dukes C or high risk Dukes B colorectal cancer.

Exploratory objectives

1. To compare the DFS and OS between the group randomised to Aspirin with the group randomised to placebo control in subjects with Dukes C or high risk Dukes B colorectal within the following subgroups:
    a. Baseline variables
        i. Country.

Countries with small sample size (less than 25) will be pooled under 'Others' or with countries with similar ethnic population.

ii. Resected high risk Dukes B colon cancer, Dukes C colon cancer, colon cancer and rectal cancer.

iii. Exposed to Oxaliplatin, not exposed to Oxaliplatin.

iv. Ethnicity (East Asian, South Asian, Caucasian and Others).

v. Type of surgery (laparoscopic surgery, open surgery).

vi. Chemotherapy duration (<3 months, 3-6 months, >6 months).

vii. Age group (<70, ≥70).

b. Translational variables

i. Compliant subjects, non-compliant subjects.

Compliant subject is defined as an individual who is on the study drug for at least 70% of days in first year from randomisation or up to treatment discontinuation or recurrence, whichever is earlier.

ii. Duration of exposure to study drug (<1 year, 1-2 years, >2 years).

The duration of exposure to study drug during the treatment period is defined as the number of days from the first dose to the last dose excluding days of interruptions, i.e. "duration of exposure" = "last dosing date" – "first dosing date" – "days off medication" + "1 day".

iii. PIK3CA mutations (mutant PIK3CA, wild-type PIK3CA)

iv. COX-2 expression (positive for COX-2 overexpression, negative for COX-2 overexpression)

2. To compare the recurrence free survival between the group randomised to Aspirin with the group randomised to placebo control in subjects with Dukes C or high risk Dukes B colorectal cancer, taking into account competing risks of death due to other cancers and death due to other causes.

Subgroup analyses on PIK3CA mutations and COX-2 are restricted to subjects from Australia, New Zealand, Taiwan (Shuang Ho Hospital), Singapore (National Cancer Centre)

and Malaysia (University Malaya Medical Centre) sites who consented to tumour sample collection.

3 STUDY ENDPOINTS

Primary endpoint

DFS is defined as the time from randomisation to the time of documentation of first disease recurrence or death from any cause. If there is no disease recurrence or death by the time when a subject is last followed up, it will be censored at that time.

The disease recurrence is defined as any one of the followings:

- Unequivocal radiological evidence of colorectal cancer recurrence
- Recurrence detected by digital rectal examination (DRE)
- Positive histology or cytology (i.e. peritoneal or pleural cytology)
- Colonoscopic evidence of local cancer recurrence at the previous operation site
- Detection of a new colon or rectal primary tumour

Secondary endpoints

OS is defined as the time from randomisation to the time of death from any cause. If there is no death by the time when a subject is last known to be alive, it will be censored at that time.

Exploratory endpoints

Exploratory endpoints involve DFS and OS in subgroups, as well as recurrence free survival. Recurrence free survival is defined as time from randomisation to first disease recurrence.

1 TRIAL DESIGN

1.1 Study Population

The study population consists of Dukes C colon cancer, high risk Dukes B colon cancer, Dukes B rectal cancer or Dukes C rectal cancer subjects who have completed the resection of primary tumour. The population will be treated with standard therapy (chemotherapy ± radiotherapy). During the last cycle of standard therapy, patients would be invited to

participate in this study. Once informed consent is taken and within 120 days of completion of the standard therapy, they would be checked for trial eligibility.

Inclusion Criteria

- Male or female outpatient of ≥18 years of age or ≥ country's legal age for adult consent
- Dukes C colon cancer, high risk Dukes B colon cancer, Dukes B rectal cancer or Dukes C rectal cancer
- Undergone complete resection of primary tumour
- Completed standard therapy (at least 3 months of chemotherapy ± radiotherapy)
- Within 120 days of completion of standard therapy (surgery, chemotherapy ± radiotherapy)
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2
- Satisfactory haematological or biochemical functions (tests should be carried out within 8 weeks prior to randomisation): Results of clinical investigations carried out within 8 weeks prior to randomisation can be used in place of the required screening investigations. Patients with mild laboratory abnormalities can be included at the discretion by the site principal investigator, and after approval by ASCOLT Trial Management Group
    - ANC ≥ 1.0 x 10^9/L
    - Platelets ≥ 100 x 10^9/L
    - Creatinine clearance ≥ 30 mL/min
    - Total bilirubin ≤ 2.0 x the upper limit normal
    - AST & ALT ≤ 5 x the upper limit normal

Completed the following investigations

- Colonoscopy (or CT colonogram (within 16 months prior to randomization))
- Imaging of abdomen (CT or CT colonogram or MRI or PET or Ultrasound) within 16 months prior to randomization

- Written informed consent

Exclusion Criteria

- Pre-existing familial adenomatous polyposis, inflammatory bowel disease or ulcerative colitis
- Active gastritis or active peptic ulcer
- History of continuous daily use of proton pump inhibitor (PPI) more than 1 year prior to consent
- Gastrointestinal bleeding within the past one year
- Haemorrhagic diathesis (i.e. haemophilia)
- Uncontrolled hypertension (untreated systolic blood pressure > 160 mmHg, or diastolic blood pressure > 95 mmHg)
- History of recent cancers (except for colorectal cancers, non melanoma skin cancers, basal cell carcinomas, squamous cell carcinomas) in the past 5 years
- History of stroke, coronary arterial disease, angina, or vascular disease
- Patients who are on current long term treatment (≥ 4 consecutive weeks) with Aspirin, NSAID or Cox-2 inhibitors
- History of erosive GERD or active erosive GERD on gastroscopy.
- Patient on active current treatment with antiplatelet agents (i.e. off-study Aspirin, clopidogrel, ticlopidine)
- Patient receiving current treatment with anticoagulants (i.e. warfarin, low molecular weight heparins)
- Pregnant, lactating, or not using adequate contraception
- Patient having known allergy to NSAID or Aspirin
- Unexplained rise of CEA (i.e. smoker with elevated CEA will not be excluded)
- Patient on other investigational drug
- Patient with HNPCC (Lynch Syndrome)

3.1 Randomisation

Randomisation will occur within 120 days of completion of standard therapy. After informed consent is signed and subject's eligibility is confirmed, the subject can be randomised in a 1:1

allocation ratio (Aspirin group: 200 mg Aspirin once a day for 3 years or placebo group: 200 mg matching placebo once a day for 3 years), stratified by

- Study centre
- Tumour type (Dukes C colon, high risk Dukes B colon cancer, or rectal cancer sub-groups) and
- Type of adjuvant chemotherapy received (exposed/ not exposed to Oxaliplatin)

All randomisations will be done via direct web randomisation. Authorised study centre personnel will randomise the subjects via a password-protected internet web site provided by Singapore Clinical Research Institute.

3.2 Treatment Schedule

A total of 1587 subjects will be randomised from multinational centres. After randomisation, subject will have 3-monthly assessments for 3 years (month 3 to month 36) followed by 6-monthly assessments for additional 2 years (month 42 to month 60). Subjects who consent to continue information collection after month 60 will have vital data captured via review of medical records or phone call.

The study drug, oral Aspirin 200 mg/ placebo 200 mg once a day, should begin immediately but no later than 2 weeks of randomisation. The study drug will be stopped immediately if there is a disease recurrence confirmed by CT, histology or cytology. In the event of SAE related to the study drug, the study drug will be stopped immediately.

The investigator has the right to discontinue study treatment if he/she feels that it is in the best interests of the subject or due to safety concerns. The reasons for treatment discontinuation will be documented. All subjects, including subjects who discontinued from study treatment, will continue to be followed for 5 years after randomisation, unless the subject is lost to follow up, died or withdrew consent.

3.3

3.4 Assessment Schedule

The table below gives an overview of study follow-up and assessment schedule. Phone assessments are allowed at alternate 3-monthly assessments should the subject is unable to return for a follow-up. In the first 3 years, subjects with early treatment discontinuation but without recurrence will only continue with 3-monthly visit. Haemogoblin assessment will not be required for these subjects. In the first 3 years, subjects with recurrence will be assessed at 6-monthly intervals in the clinic or via phone assessments if they are unable to return for 3-monthly clinic follow up. Haemogoblin, CEA and concomitant medication assessments are not required after recurrence. In the last 2 years, subjects with recurrence may have their 6-monthly assessments via phone should they are unable to return for clinical follow up. CEA assessments are not part of these subjects' 6-monthly assessments.

Assessments	Screening*	Baseline	Follow-up month (+/- 1 month)			Follow-up month (+/-1 month) after recurrence	Follow-up month (+/- 1 month) after early treatment discontinuation but without recurrence	Post month (
			3-monthly in first 3 years		6-monthly in last 2 years	3-monthly followed by 6 monthly	3-monthly	
			3, 9 ,15, 21, 27, 33	6,12, 18, 24, 30, 36	42, 48, 54, 60	3 to 60	3 to 36	
Written informed consent	x							
Demography, colorectal cancer surgery and tumour history, risk factors, medical history, family history of colorectal cancer		x						
Record surgical measurements (for rectal cancer only) and synchronous tumours characteristics		x						
Adjuvant therapy		x						
Vital signs (body weight, height, blood								

pressure), ECOG		x						
Haemoglobin		x (Within 8 weeks prior to randomisation)		x				
Laboratory investigations (platelet count, creatinine, serumbilirubin, AST, ALT)	x (Within 8 weeks prior to randomisation)							
CEA		x	x	x	x		x	
Imaging of abdomen (CT or CT colonogram or MRI or PET or Ultrasound)	x (Within 16 months prior to randomisation)		x (Month 6, 18 and 30) Optional; or frequency according to institutional practice					
Radiological examination of the chest (including but not restricted to chest X-ray, CT thorax or PET scan)	x (Within 16 months prior to randomisation)							
Colonoscopy / CT colonogram	x (Within 16 months prior to randomisation)		x (Month 6 and 30) Optional; or frequency according to institutional practice					
Protocol treatment compliance			x	x	x			
Adverse event and serious adverse event			x	x				
Death			x	x	x	x	x	x
Medical events			x	x	x	x	x	x
Concomitant NSAIDs		x	x	x	x	x	x	x
Concomitant treatment/ medication			x	x				
Recurrence, salvage chemotherapy			x	x	x	x	x	x

3.5 Sample Size Calculation

Initial sample size calculation (before start of the study)

The initial total trial size was 2660 subjects, with 1330 randomised to Aspirin group and 1330 randomised to Placebo group. In the sub-groups, there should be at least 2000 high risk Dukes B or Dukes C colon cancer patients, others are rectal cancer patients.

It was assumed that 3-year DFS rate for Dukes B colon cancer, Dukes C colon cancer and rectal cancer are 65% after standard adjuvant chemotherapy; and the attrition rate is 5%. The total trial size (2660) would be sufficient to detect an absolute difference of 6% in DFS rate between the two groups amongst all subjects, with a two-sided log-rank test of 5% type I error and 90% power. For the main sub-group analysis, the 3-year DFS rate for colon cancer patients is assumed to be 65% under standard care, which is similar to the entire group as a whole, the size of colon cancer group (2000) would be sufficient to detect a 6% absolute difference in DFS rate for colon cancer between the two groups, with a two-sided logrank test of 5% type I error and 80% power.

Subsequent sample size calculation (20 March 2013)

Based on recent studies of Aspirin in colorectal cancer patients, with a reported hazard ratio (HR) or risk ratio ranging from 0.67 to 0.77, we assumed a HR of 0.72 for DFS between Aspirin and the placebo group. The corresponding absolute difference in DFS rate between the two groups was about 8.5% instead of 6% for a 3-year DFS rate of 65% in the placebo group. To detect a HR of 0.72, a total of 300 recurrences (or deaths if occur without recurrence) is required for a two-sided logrank test of 5% type I error and 80% power. This translates to a total sample size of 1200 subjects if the DFS rate is 65% in the placebo group and attrition rate is 15%.

Latest sample size calculation (9 May 2018)

A recent review of pooled trial interim data (i.e. not stratified by treatment group), after enrolment of at least 1140 subjects and 3 years of follow-up being completed in 430 subjects,

revealed a pooled DFS rate of 79% at 5-year. With a total sample size of 1200, an estimate of only 240 recurrences would be observed, a shortfall of 60 recurrences to maintain the study power at 80%. To observe 300 recurrences (or deaths) at the end of study, a sample size of 1587 subjects would be required with attrition rate reduced from 15% to 10%, while the rest remains unchanged.

4 STATISTICAL ANALYSIS

4.1 General

Continuous variables will be summarised using descriptive statistics, i.e., mean, standard deviation, median, interquartile range (IQR), minimum and maximum. Categorical variables will be summarised by frequency and percentage. All statistical significance tests and confidence intervals are two-sided. A p-value <0.05 is considered statistically significant. All confidence intervals (CIs) are at 95% level. All statistical analyses will be conducted using SAS version 9.2 or higher (Statistical Analysis System software, SAS Institute, North Carolina, USA).

4.2 Analysis Populations

All efficacy analyses will be carried out on modified intention-to-treat (mITT) basis, i.e., all subjects who signed the informed consent form for the study enrolment and commenced study treatment after the randomisation are to be analysed as randomised.

As part of sensitivity analysis, efficacy analysis on per-protocol basis will also be performed. Per-protocol analysis consists of subjects included in the mITT population after excluding those with major protocol deviation and those who were compliant <70% of the days in the first year from randomisation. Compliance has been defined in section 2.

Subjects included in safety data analysis are those who received at least one dose of the study treatment drug. These subjects will be grouped and analysed as actually treated.

The number of subjects screened, randomised to the study treatment, completing each subsequent study period including up to 3-year treatment and 5-year follow-up will be summarised in a CONSORT flow chart.

4.3 Major Protocol Deviations

All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment will be identified and categorised as major or minor by trial management team while blinded to subject's treatment group allocation. The following protocol deviations will be categorised as major protocol deviations:

Any of the below inclusion criteria not met but subject enrolled into the study

1. Male or female outpatient of ≥ 18 years of age or ≥ country's legal age for adult consent
2. Dukes C colon cancer, high risk Dukes B colon cancer, Dukes B rectal cancer or Dukes C rectal cancer
3. Undergone complete resection of primary tumour
4. Completed standard therapy (at least 3 months of chemotherapy ± radiotherapy)
5. Written informed consent

Any of the below exclusion criteria met but subject enrolled into the study

6. Gastrointestinal bleeding within the past one year
7. Haemorrhagic diathesis (i.e. haemophilia)
8. History of recent cancers (except for colorectal cancers, non-melanoma skin cancers, basal cell carcinomas, squamous cell carcinomas) in the past 5 years
9. History of stroke, coronary arterial disease, angina, or vascular disease
10. Patient on active current treatment of antiplatelet agents (i.e. off-study Aspirin, clopidogrel, ticlopidine)
11. Patient receiving active treatment of anticoagulants (i.e. warfarin, low molecular weight heparins)

12. Patient having known allergy to NSAID or Aspirin

Others

13. Recurrence diagnosed before randomisation but subject was randomised

These major protocol deviations will be provided in two listings together with corresponding subject ID, treatment group, site, country, description and the following three major protocol deviation categories: Inclusion criteria, exclusion criteria and others. Minor protocol deviations relating to eligibility criteria will also be provided.

4.4 Discontinuation and Exposure to Study Treatment

Numbers and percentages of subjects who permanently discontinued the study drug will be presented by randomised treatment group. Reasons for treatment discontinuation will be summarised together with follow up completion rate and time. Duration of exposure to study drug will be further summarised using descriptive statistics by group. Definition of duration of exposure can be found in section 2.

4.5 Demographics and Baseline Characteristics

Demographics and baseline characteristics including details of colorectal cancer, adjuvant therapy, risk factors, medical and family history, vital signs, and laboratory investigations for the subjects will be summarised using descriptive statistics. No significance tests will be performed for between groups comparison. Clinical comparability will be assessed based on only the summary statistics presented.

4.6 Time-to-event Endpoints

For primary outcome of DFS, survival curves will be constructed using the Kaplan-Meier method. Product-limit estimates of 3- and 5-year survival rates will be calculated. Median survival times will also be reported. The complementary log-log transformation will be used for deriving the median survival times corresponding 95% CIs. The primary analysis will be a mITT analysis which uses stratified logrank test adjusting for trial stratification factor

(centre pooled by country (categorical), type of tumour (Dukes C colon vs. high risk Dukes B colon vs. rectal; categorical) and type of adjuvant chemotherapy (exposed vs. not exposed to Oxaliplatin; categorical)) to generate p-value comparing the treatment groups, followed by multivariate Cox proportional hazard (PH) regression model to estimate adjusted HR and its corresponding 95% CI. The multivariate Cox PH regression model will also include the the trial stratification factors used in the stratified logrank test as covariates. Additional covariates such as time from surgery to first chemotherapy in days (continuous), type of surgery (laparoscopic surgery vs, open surgery; categorical), chemotherapy duration (<3 months vs. 3-6 months vs. >6 months; categorical) and age group (<70 vs. ≥70 years old; categorical) will be added as part of sensitivity analysis. The CI of the HR will be based on profile-likelihood. Firth's correction may be used if monotone likelihood phenomenon is observed. Unadjusted HR and p-value from non-stratified logrank test will also be reported as supplementary results.

As part of secondary objective, the same analysis on DFS will be repeated for sub-population of colon cancer except that the covariate, type of tumour, will consists of only two categories: Dukes C colon vs. high risk Dukes B colon.

The secondary outcome of OS will be analysed in a similar manner as the primary endpoint, except that repeated analysis on colon cancer sub-population will not be done.

For all subgroup analyses of DFS and OS by different countries, tumour types (high risk Dukes B colon, Dukes C colon, colon, rectal), adjuvant chemotherapy types (exposed to Oxaplatin, not exposed to Oxaliplatin), ethnic groups (East Asian, South Asian, Caucasian, Others), type of surgery (laparoscopic surgery, open surgery), chemotherapy duration (<3 months, 3-6 months, >6 months), age group (<70, ≥70), levels of compliance (<70%, ≥70%), duration of exposure to drug (<1 year, 1-2 years, >2 years), PIK3CA mutations (mutant PIK3CA, wild-type PIK3CA) and COX-2 expression (positive for COX-2 overexpression, negative for COX-2 overexpression), tests for interactions between treatment group and the subgroup variable of interest will be conducted first. As the subgroups under tumour types are not mutually exclusive, the test for interaction will be based on the original mutually

exclusive groups. Results of subgroup analyses will be presented in forest plots. Subgroup analyses will be considered as exploratory.

Appropriateness of Cox PH regression model will be checked using graphical method of log-log survival curves for treatment indicator and each covariate. Continous covariate will be dichotomised at mean value to check for the PH assumption. PH assumption will be considered not satisfied if there is strong evidence of non-parallelism in the log-log survival curves. Should there be at least one covariate not satisfying the PH assumption, "no-interaction" (i.e. estimated coefficients not varying by stratum) stratified Cox regression model will be used instead. The model will be stratified by stratas formed after combining categories of all covariates which did not satisfy the PH assumption. Covariate(s) which satisfies the PH assumption will remain included in the stratified model. If the treatment indicator is found to not satisfy the PH assumption, time-varying HR will be obtained by partitioning the follow-up time into 1-year intervals.

In addition, cumulative incidence curves for recurrence free survival will be estimated for the two treatment groups after considering competing risks of death due to other cancers and death due to other causes. Recurrence free survival is defined as time from randomisation to first disease recurrence. The cumulative incidence curves will be constructed for first disease recurrence using Fine and Gray's model, adjusting for the trial stratification factors (centre pooled by country (categorical), type of tumour (Dukes C colon vs. high risk Dukes B colon vs. rectal; categorical) and type of adjuvant chemotherapy (exposed vs. not exposed to Oxaliplatin; categorical)). Cause-specific sub-distribution hazard ratios together with its corresponding 95% CIs will also be reported.

For all the survival analyses performed, Breslow's method will be used for handling of ties.

4.7 Safety Endpoints

The evaluation of drug safety is based on clinical adverse events and laboratory abnormalities reported during the study. All safety presentations will be based on actually-treated subject dataset.

AEs and SAEs will be summarised using the following method:

Number and percentage of subjects who ever reported adverse event (AE) and serious adverse event (SAE) together with the number of AEs and SAEs will be presented by treatment group. The severity and outcome of AEs and SAEs, relationship to treatment and action taken will be summarised.

Same AE term reported at multiple level of severities by a single subject will be counted for each level of severity, not just the highest severity. Under subject counts at each severity category, only unique subject will be counted. The same method will also be applied for summaries by relationship, treatment given, outcome, and action taken.

All on-study adverse events will be further summarised by MedDRA terminology. Summaries of AEs will be based on the resulting system organ class (SOC) and preferred terms (PT). All reported SAEs will be listed indicating the subject ID, SAE criteria, randomisation date, onset date, resolution date, relationship to study treatment and outcome of causality.

The term "AEs" used in the summaries would cover severe AEs and SAEs as well.

Number of subjects who ever experienced the following medical events including acute myocardial infarct, ischaemic stroke, new cancer (non-colorectal), major GI bleeding (requiring blood transfusion), haemorrhagic stroke and major nervous system bleeding throughout the study will be counted and its corresponding percentages will be respectively compared between the two treatment groups using Fisher's exact test.

4.8 Interim Analysis

Interim analyses were scheduled every year as long as there is subject still on study treatment. An independent Data Monitoring Committee (DMC) was established to review the interim results of the study. Ideally, the first interim analysis should be done after 540 subjects have been recruited or at the midpoint (end of Year 2012) of the targeted recruitment period, whichever comes earlier. The second interim analysis should be done once 540 subjects have

been followed up for 3 years (approximately between fifth to sixth years). Treatment allocations in all the interim analyses were masked with the label "Group A" and "Group B".

Safety was the main aspect for review in the first DMC meeting. A report containing non-confidential data was sent to the Study Steering Committee. Randomisation, compliance, CRF received and processed, AE and SAE were included in this DMC report. The study endpoints reviewed in the second interim analysis were DFS and OS, as well as safety profiles. Subsequent reviews of DFS and OS were done upon request of DMC.

The analysis results of the interim analyses were not the sole criteria for deciding whether to early terminate the study. Rather they provided a guideline to aid in the decision, which also took into account the characteristics of the subjects, nature of toxicities, relevant external results. Another goal of this monitoring was to review the number of events needed for the primary analysis and whether the sample size needed to be adjusted to achieve the targeted number of events.

4.9 Final Analysis

Final analysis will be performed after pre-determined number of recurrences (or deaths) has been observed (i.e. 300 recurrences or death) and all subjects have completed a minimum follow-up of 1 year. The date for last patient last visit is 31 March 2023.

APPENDICES

Appendix 1: Mock-up tables

Table 1: Subject status and demographics

	Modified intention-to-treat			Per-protocol		
	Aspirin	Placebo	Total	Aspirin	Placebo	Total
Number of subjects randomised	xxx	xxx	xxx	xxx	xxx	xxx
Number of subjects ineligible but randomised, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects discontinued study treatment, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed protocol treatment	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AE/SAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol violation/ ineligibility	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Clinical decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Recurrence	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)
Others	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects who did not complete study, n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Subject withdrew consent	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawn from study by investigator	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow-up	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)
Others	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Subject follow-up completion, n (%)						
1 year follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2 year follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3 year follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4 year follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
5 year follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject follow-up time, month						
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Demographics						
Age, year						
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Age group, n (%)						
<70	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
≥70	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Gender, n (%)						
Male	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Female	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Ethnicity, n (%)						
East Asian	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
South Asian	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Caucasian	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Others	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Country, n (%)						
Country 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Country 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
…	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Country Y	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Diet, n (%)						
Vegetarian (including egg)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Non-vegetarian	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

n: number of subjects; %: percentage of respective population pool treatment group; AE: adverse event; SAE: serious adverse event; SD: standard deviation; IQR: interquartile range.

Table 2: Study treatment exposure

	Modified intention-to-treat			Per-protocol		
	Aspirin	Placebo	Total	Aspirin	Placebo	Total
Number of compliant subjects, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Duration of exposure to study drug, n (%)						
<1 year	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1-2 years	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>2 years	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Duration of exposure to study drug, day						
N	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

Note: Compliant subject is defined as an individual who is on study drug for at least 70% of days in first year from randomisation or up to study discontinuation or recurrence, whichever is ealier. Duration of exposure is defined using the following formula: "duration of exposure" = "last dosing date" – "first dosing date" – "days off medication" + "1 day".
n: number of subjects; %: percentage of respective population pool treatment group; AE: adverse event; SAE: serious adverse event; SD: standard deviation; IQR: interquartile range.

Table 3: Colorectal cancer status and adjuvant therapy received

	Modified intention-to-treat		Per-protocol	
	Aspirin (N=xxxx)	Placebo (N=xxxx)	Aspirin (N=xxxx)	Placebo (N=xxxx)
Colorectal cancer status				
Time from surgery to randomisation, day				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Type of surgery, n (%)				
Laparoscopic surgery	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Open surgery	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Tumour location, n (%)				
Caecum	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Ascending colon	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Hepatic flexure	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Transverse colon	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Splenic flexure	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Descending colon	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Sigmod colon/ rectosigmoid colon	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Rectum	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
T-staging, n (%)				
T1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

T2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
T3	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
T4	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Tumour type, n (%)				
Dukes C colon cancer	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
High risk Dukes B colon cancer	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Rectal cancer (Dukes B or Dukes C)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Proximal margin involved	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Distal margin involved	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Circumferential margin involved	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Histology, n (%)				
Mucinous	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Adenocarcinoma	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Signet ring type	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Others	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Any synchronous tumours, n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Adjuvant therapy received				
First chemo regimen, n (%)				
Capecitabine	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
5-fu bolus	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Infusional 5-fu	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Folfox	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Capecitabine – oxaliplatin	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Others	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Cycle duration, weeks				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
No. of cycles completed				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Time from surgery to first chemotherapy, days				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Time from last chemotherapy to randomisation, days				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

Duration of chemotherapy, n (%)					
<3 months		xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
3-6 months		xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
>6 months		xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
RT regimen (for rectal cancer only), n (%)*					
Neoadjuvant chemo RT		xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Tumour regression grade:	Grade 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Grade 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Grade 3	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Grade 4	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Grade 5	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
	Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Neoadjuvant RT		xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Adjuvant RT		xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Adjuvant chemo RT		xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No RT		xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Time from first RT to randomisation, days					
n		xxx	xxx	xxx	xxx
Mean (SD)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max		xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Dose of RT (for rectal cancer only), Gy					
n		xxx	xxx	xxx	xxx

Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
No. of fractions (for rectal cancer only)				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

n: number of subjects; %: percentage of respective population pool treatment group; SD: standard deviation; IQR: interquartile range; RT: radiotherapy.
*Percentage of total rectal cancer subjects.

Table 4: Risk factors

	Modified intention-to-treat		Per-protocol	
	Aspirin (N=xxxx)	Placebo (N=xxxx)	Aspirin (N=xxxx)	Placebo (N=xxxx)
Tumour grade, n (%)				
Grade 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Grade 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Grade 3/ 4	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Lymphatic invasion, n (%)				
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Vascular invasion, n (%)				
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Perineural invasion, n (%)				
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Bowel obstruction, n (%)				
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Perforation, n (%)				
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Apical lymph nodes involved, n (%)				
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Alcohol history, n (%)				
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Current social drinker	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Current habitual drinker	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Ex-drinker	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Smoking history, n (%)				
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Number of years smoking, mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

n: number of subjects; %: percentage of respective population pool treatment group; SD: standard deviation.

Table 5: Medical history, family history, and vital signs

	Modified intention-to-treat		Per-protocol	
	Aspirin (N=xxxx)	Placebo (N=xxxx)	Aspirin (N=xxxx)	Placebo (N=xxxx)
Medical history				
Asthma, n (%)				
Current active	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Past history	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Diabetes, n (%)				
Current active	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Past history	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Coronary arterial disease, n (%)				
Current active	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Past history	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Angina, n (%)				
Current active	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Past history	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Vascular disease, n (%)				
Current active	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Past history	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Stroke, n (%)				
Current active	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Past history	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Gastrointestinal ulcer, n (%)				
Current active	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Past history	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Gastrointestinal bleeding, n (%)				
Current active	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Past history	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Other cancers, n (%)				

Current active	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Past history	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
ECOG at screening, n (%)				
0: Asymptomatic	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
1: Symptomatic but completely ambulatory	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
2: <50% in bed during the day	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
3: >50% in bed, but not bedbound	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
4: Bedbound	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Family history				
Number of family members with colorectal cancer (1st and 2nd degree relatives only), n (%)				
Nil	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
One	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Two	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Three	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
≥ Four	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Vital signs at screening				
Weight, kg				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

Height, cm				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Systolic blood pressure, mmHg				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Diastolic blood pressure, mmHg				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

n: number of subjects; %: percentage of respective population pool treatment group; SD: standard deviation; IQR: interquartile range.

Table 6: Laboratory investigations at screening

	Modified intention-to-treat		Per-protocol	
	Aspirin (N=xxxx)	Placebo (N=xxxx)	Aspirin (N=xxxx)	Placebo (N=xxxx)
Haematology				
Haemoglobin, g/dL				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Clinically significant, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Platelet count, 10^9/L				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Clinically significant, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Biochemistry				
Creatinine, µmol/L				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Clinically significant, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Serum bilirubin, µmol/L				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Clinically significant, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AST, µ/L				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Clinically significant, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ALT, µ/L				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Clinically significant, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
CEA, µg/L				
n	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Clinically significant, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

n: number of subjects; %: percentage of respective population pool treatment group; SD: standard deviation; IQR: interquartile range.

Table 7: Disease free survival and overall survival

	Modified intention-to-treat		Per-protocol	
	Aspirin (N=xxxx)	Placebo (N=xxxx)	Aspirin (N=xxxx)	Placebo (N=xxxx)
First recurrence, n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Site of recurrence, n (%)				
Local	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Anastomotic site	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Lymph node	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Peritoneum	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Liver	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Lungs	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
New primary	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Others	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Method of first recurrence diagnosis, n (%)				
Radiological imaging	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Histology / cytology	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Scope	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Digital rectal examination	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Others	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Death, n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Cause of death, n (%)				

Colorectal cancer	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Other cancer	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Other causes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Presence of colon/rectal cancer at death, n (%)				
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Median follow-up time (95% CI), month	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
All tumour types				
Subjects with recurrence or who died without recurrence, n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Median DFS time (95% CI), month	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
DFS rate at 3 years (95% CI), %	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
Difference in DFS rate at 3 years (95% CI), %	xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
DFS rate at 5 years (95% CI), %	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
Difference in DFS rate at 5 years (95% CI), %	xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
DFS hazard ratio (95% CI); p-value[1]	xx.x (xx.x-xx.x); 0.xxx		xx.x (xx.x-xx.x); 0.xxx	
Adjusted DFS hazard ratio 1 (95% CI); p-value[2]	xx.x (xx.x-xx.x); 0.xxx		xx.x (xx.x-xx.x); 0.xxx	
Adjusted DFS hazard ratio 2 (95% CI); p-value[3]	xx.x (xx.x-xx.x); 0.xxx		xx.x (xx.x-xx.x); 0.xxx	
Median OS time (95% CI), month	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
OS rate at 3 years (95% CI), %	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
Difference in OS rate at 3 years (95% CI), %	xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
OS rate at 5 years (95% CI), %	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)

Difference in OS rate at 5 years (95% CI), %	xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
OS hazard ratio (95% CI); p-value[1]	xx.x (xx.x-xx.x); 0.xxx		xx.x (xx.x-xx.x); 0.xxx	
Adjusted OS hazard ratio 1 (95% CI); p-value[2]	xx.x (xx.x-xx.x); 0.xxx		xx.x (xx.x-xx.x); 0.xxx	
Adjusted OS hazard ratio 2 (95% CI); p-value[3]	xx.x (xx.x-xx.x); 0.xxx		xx.x (xx.x-xx.x); 0.xxx	
Colon cancer only				
Subjects with recurrence or who died without recurrence, n (%)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
Median DFS time (95% CI), month	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
DFS rate at 3 years (95% CI), %	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
Difference in DFS rate at 3 years (95% CI), %	xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
DFS rate at 5 years (95% CI), %	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)	xx.x (xx.x-xx.x)
Difference in DFS rate at 5 years (95% CI), %	xx.x (xx.x-xx.x)		xx.x (xx.x-xx.x)	
DFS hazard ratio (95% CI); p-value[1]	xx.x (xx.x-xx.x); 0.xxx		xx.x (xx.x-xx.x); 0.xxx	
Adjusted DFS hazard ratio 1 (95% CI); p-value[2]	xx.x (xx.x-xx.x); 0.xxx		xx.x (xx.x-xx.x); 0.xxx	
Adjusted DFS hazard ratio 2 (95% CI); p-value[3]	xx.x (xx.x-xx.x); 0.xxx		xx.x (xx.x-xx.x); 0.xxx	
Sub-distribution hazard ratio for first recurrence (95% CI); p-value[4]	xx.x (xx.x-xx.x); 0.xxx		xx.x (xx.x-xx.x); 0.xxx	
Sub-distribution hazard ratio for death due to other cancers (95% CI); p-value[4]	xx.x (xx.x-xx.x); 0.xxx		xx.x (xx.x-xx.x); 0.xxx	
Sub-distribution hazard ratio for death due to other causes (95% CI); p-value[4]	xx.x (xx.x-xx.x); 0.xxx		xx.x (xx.x-xx.x); 0.xxx	

n: number of subjects; %: percentage of respective population pool treatment group; CI: confidence interval; DFS: disease free survival; OS: overall survival.
[1]P-values from log-rank test.
[2]Adjusted hazard ratio was estimated using Cox proportional hazard model with trial stratification factors (centre pooled by country (categorical), type of tumour (categorical) and type of adjuvant chemotherapy (categorical)) as covariates. P-values from stratified log-rank test stratified by the factors included as covariates in the Cox proportional hazard model.

[3]Adjusted hazard ratio was estimated using Cox proportional hazard model with trial stratification factors (centre pooled by country (categorical), type of tumour (categorical) and type of adjuvant chemotherapy (categorical)), time from surgery to first chemotherapy in days (continuous), type of surgery (categorical), chemotherapy duration (categorical) and age group (categorical) as covariates. P-values from stratified log-rank test stratified by the factors included as covariates in the Cox proportional hazard model.
[4]P-value from Fine and Gray's model.

Table 8: Results of multivariate Cox proportional hazard models on disease free survival and overall survival

	Modified intention-to-treat		Per-protocol	
	Adjusted Hazard Ratio (95% CI)	P-value	Adjusted Hazard Ratio (95% CI)	P-value
Disease free survival				
Treatment (Aspirin vs. placebo)	xx.x (xx.x-xx.x)	0.xxx	xx.x (xx.x-xx.x)	0.xxx
Country		0.xxx		0.xxx
Country 1 vs. Reference Country	xx.x (xx.x-xx.x)	0.xxx	xx.x (xx.x-xx.x)	0.xxx
Country 2 vs. Reference Country	xx.x (xx.x-xx.x)	0.xxx	xx.x (xx.x-xx.x)	0.xxx
Country Y vs. Reference Country	xx.x (xx.x-xx.x)	0.xxx	xx.x (xx.x-xx.x)	0.xxx
Tumour type		0.xxx		0.xxx
Rectal cancer vs. Dukes C colon cancer	xx.x (xx.x-xx.x)	0.xxx	xx.x (xx.x-xx.x)	0.xxx
High risk Dukes B colon cancer vs. Dukes C colon cancer	xx.x (xx.x-xx.x)	0.xxx	xx.x (xx.x-xx.x)	0.xxx
Adjuvant chemotherapy (exposed vs. not exposed to Oxaliplatin)	xx.x (xx.x-xx.x)	0.xxx	xx.x (xx.x-xx.x)	0.xxx
Overall survival				
Treatment (Aspirin vs. placebo)	xx.x (xx.x-xx.x)	0.xxx	xx.x (xx.x-xx.x)	0.xxx
Country		0.xxx		0.xxx
Country 1 vs. Reference Country	xx.x (xx.x-xx.x)	0.xxx	xx.x (xx.x-xx.x)	0.xxx
Country 2 vs. Reference Country	xx.x (xx.x-xx.x)	0.xxx	xx.x (xx.x-xx.x)	0.xxx
Country Y vs. Reference Country	xx.x (xx.x-xx.x)	0.xxx	xx.x (xx.x-xx.x)	0.xxx

Tumour type		0.xxx		0.xxx
Rectal cancer vs. Dukes C colon cancer	xx.x (xx.x-xx.x)	0.xxx	xx.x (xx.x-xx.x)	0.xxx
High risk Dukes B colon cancer vs. Dukes C colon cancer	xx.x (xx.x-xx.x)	0.xxx	xx.x (xx.x-xx.x)	0.xxx
Adjuvant chemotherapy (exposed vs. not exposed to Oxaliplatin)	xx.x (xx.x-xx.x)	0.xxx	xx.x (xx.x-xx.x)	0.xxx

Note: Adjusted hazard ratio was estimated using Cox proportional hazard model with trial stratification factors (centre pooled by country (categorical), type of tumour (categorical) and type of adjuvant chemotherapy (categorical)) as covariates.

Table 9: Summary of adverse events

Population: Safety population

	Number of Subjects		Number of Events	
	Aspirin (N=xxxx)	Placebo (N=xxxx)	Aspirin	Placebo
Subjects ever experienced any AE, n (%)	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Severity, n (%)				
Mild	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Moderate	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Severe	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Unknown	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Treatment related, n (%)				
Not related	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Unlikely related	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Possibly related	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Probably related	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Definitely related	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Unknown	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Treatment given, n (%)				
Yes	xxx (xx.x)	xxx (xx.x)	xxx	xxx
No	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Outcome, n (%)				
Recovered	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Recovered with sequelae	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Ongoing	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Death	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Unknown	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Action taken to study treatment, n (%)				
None	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Modified	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Temporarily interrupted	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Permanently discontinued	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Unknown	xxx (xx.x)	xxx (xx.x)	xxx	xxx

AE: adverse event.
Note: Under number of events, the same AE term of multiple severities, relationships, treatments, actions reported by a single subject will be counted separately. Under number of subjects, only unique subjects will be counted.

Table 10: Summary of serious adverse events

Population: Safety population

	Number of Subjects		Number of Events	
	Aspirin (N=xxxx)	Placebo (N=xxxx)	Aspirin	Placebo
Subjects ever experienced any SAE, n (%)	xxx (xx.x)	xxx (xx.x)	xxx	xxx
SAE criteria, n (%)				
Death	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Life-threatening	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Inpatient hospitalization	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Hospitalization prolonged	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Disability / incapacity	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Congenital anomaly	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Others	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Action taken, n (%)				
None	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Modified to 100mg OD	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Temporarily interrupted	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Permanently discontinued	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Unknown	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Treatment related, n (%)				
Not related	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Unlikely related	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Possibly related	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Probably related	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Definitely related	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Unknown	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Outcome, n (%)				
Recovered	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Recovered with sequalae	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Ongoing	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Death	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Unknown	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Withdrawn due to SAE, n (%)				
Yes	xxx (xx.x)	xxx (xx.x)	xxx	xxx
No	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Causality, n (%)				
Study treatment	xxx (xx.x)	xxx (xx.x)	xxx	xxx

Disease under study	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Other illness	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Concurrent medication / treatment	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Others	xxx (xx.x)	xxx (xx.x)	xxx	xxx
Unknown	xxx (xx.x)	xxx (xx.x)	xxx	xxx

SAE: serious adverse event.
Note: Under number of events, the same SAE term of multiple SAE criteria, actions, relationships, outcomes and causalities reported by a single subject will be counted separately. Under number of subjects, only unique subjects will be counted.

Table 11: Adverse events by system organ class and severity grade

Population: Safety population

	Aspirin (N = xxx)							
	MILD		MODERATE		SEVERE		UNKNOWN	
System Organ Class Preferred Term	n (%)	nAE	n (%)	nAE	n (%)	nAE	n (%)	nAE
System organ class 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term 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	xx (xx.x)	xx	xx (xx.x)	xx
System organ class X	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term X	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
	Placebo (N = xxx)							
	MILD		MODERATE		SEVERE		UNKNOWN	
System Organ Class Preferred Term	n (%)	nAE	n (%)	nAE	n (%)	nAE	n (%)	nAE
System organ class 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

Preferred term 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term 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	xx (xx.x)	xx	xx (xx.x)	xx
System organ class X	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term X	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

n (%) = number (percent) of subjects.
nAE = number of adverse events.

Table 12: Serious adverse events by system organ class

Population: Safety population

	Aspirin (N = xxx)		Placebo (N = xxx)	
System Organ Class Preferred Term	n (%)	nAE	n (%)	nAE
System organ class 1	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term 1	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term 2	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term 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
System organ class X	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term X	xx (xx.x)	xx	xx (xx.x)	xx

n (%) = number (percent) of subjects.
nAE = number of adverse events.

Table 13: Severe adverse events related to treatment by system organ class

Population: Safety population

	Aspirin (N = xxx)		Placebo (N = xxx)	
System Organ Class Preferred Term	n (%)	nAE	n (%)	nAE
System organ class 1	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term 1	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term 2	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term 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
System organ class X	xx (xx.x)	xx	xx (xx.x)	xx
Preferred term X	xx (xx.x)	xx	xx (xx.x)	xx

Related adverse events are defined as those with "Unknown", "Possible", "Probable", "Definite" relationship with study treatment.
n (%) = number (percent) of subjects.
nAE = number of adverse events.

Table 14: Medical events

Population: Safety population

n (%)	Aspirin (N=xxxx)	Placebo (N=xxxx)	P-value[1]
Acute myocardial infarct			0.xxx
Yes	xx (xx.x)	xx (xx.x)	
No	xx (xx.x)	xx (xx.x)	
Ischaemic stroke			0.xxx
Yes	xx (xx.x)	xx (xx.x)	
No	xx (xx.x)	xx (xx.x)	
New cancer (non-colorectal)			0.xxx
Yes	xx (xx.x)	xx (xx.x)	
No	xx (xx.x)	xx (xx.x)	
Major GI bleeding			0.xxx
Yes	xx (xx.x)	xx (xx.x)	
No	xx (xx.x)	xx (xx.x)	
Hemorrhagic stroke			0.xxx
Yes	xx (xx.x)	xx (xx.x)	
No	xx (xx.x)	xx (xx.x)	
Major nervous system bleeding			0.xxx
Yes	xx (xx.x)	xx (xx.x)	
No	xx (xx.x)	xx (xx.x)	

n: number of subjects; %: percentage of randomised in each treatment group; GI: gastrointestinal bleeding.
[1]Fisher's exact test.

Appendix 2: Mock-up figures

Figure 1: CONSORT diagram

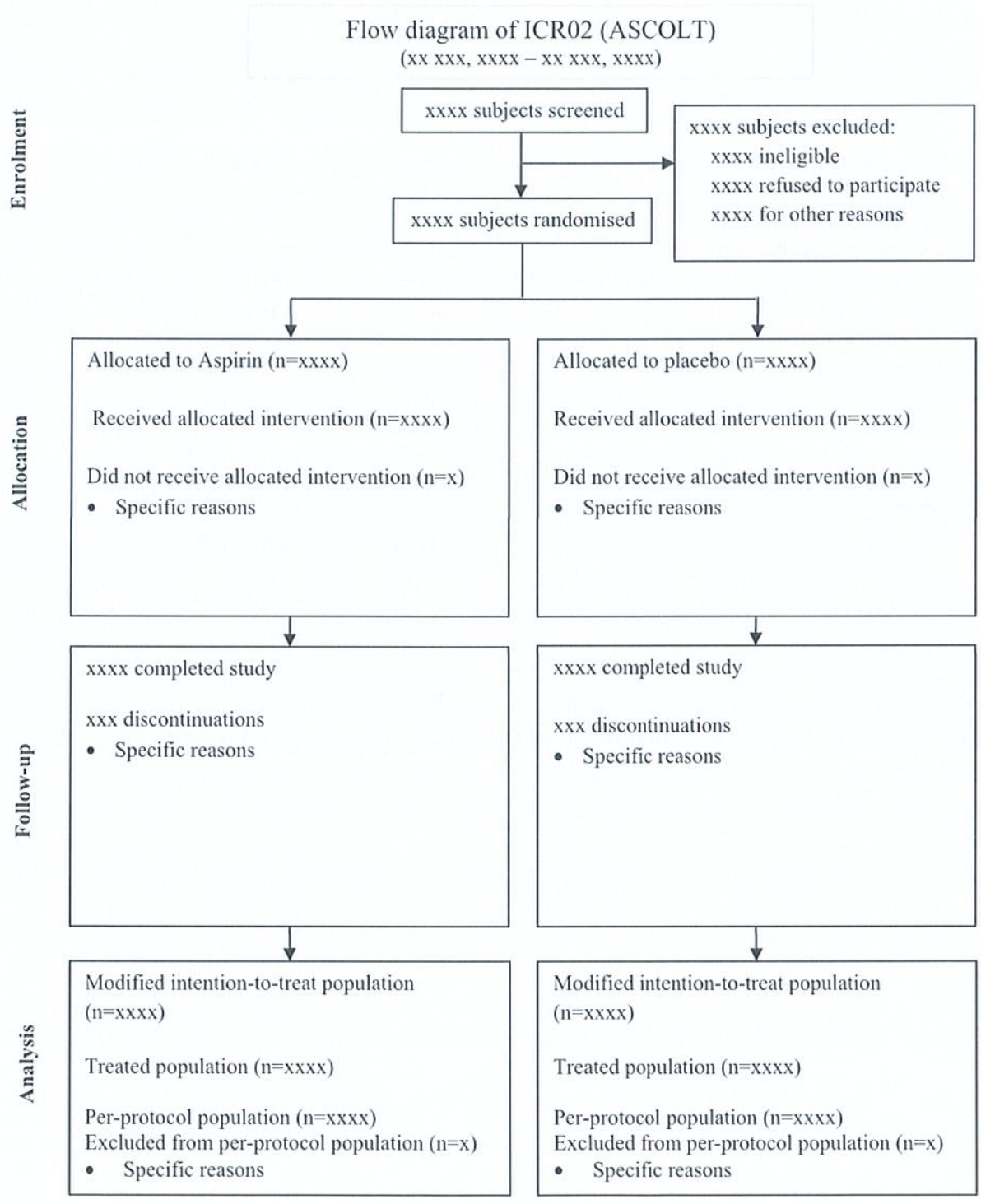

Figure 2: Kaplan-Meier estimate of disease free survival

Modified Intention-to-treat Population

Per-protocol Population

Figure 3: Kaplan-Meier estimate of disease free survival among colon cancer subjects

Modified Intention-to-treat Population

Per-protocol Population

Figure 4: Kaplan-Meier estimate of overall survival

Modified Intention-to-treat Population

Per-protocol Population

Figure 5: Forest plots for subgroup analysis on disease free survival (DFS)

Modified Intention-to-Treat Population Subgroup (N=Aspirin, Placebo)	Events/ No. of Subjects	Median DFS Aspirin	 Placebo	Hazard Ratio (95% CI)	p-value	Hazard Ratio	p-value Interaction
Country							0.559
Country 1 (N= 20, 20)	6/40	32.0	28.0	0.80 (0.63, 0.86)	0.559		
Country 2 (N= 30, 30)	3/60	34.0	30.1	0.70 (0.48, 0.76)	0.622		
Country 3 (N= 20, 20)	6/40	30.0	24.3	0.80 (0.77, 1.05)	0.055		
Country Y (N= 30, 30)	3/60	40.0	36.8	0.90 (0.71, 0.99)	0.493		
Tumour Type							0.124
Rectal Cancer (N= 20, 20)	6/40	41.0	39.8	1.20 (1.14, 1.34)	0.124		
Dukes C Colon Cancer (N= 30, 30)	3/60	30.0	26.9	1.00 (0.76, 1.02)	0.427		
High Risk Dukes B Colon Cancer (N= 20, 20)	6/40	22.0	19.2	0.80 (0.63, 0.98)	0.995		
Colon Cancer (N= 50, 50)	9/99	52.0	42.8	0.70 (0.66, 0.91)	0.800		
Adjuvant Chemotherapy							0.379
Exposed to Oxaliplatin (N= 30, 30)	3/60	40.0	32.6	0.70 (0.64, 0.96)	0.379		
Not Exposed to Oxaliplatin (N= 20, 20)	6/40	32.0	31.1	0.80 (0.70, 0.98)	0.594		
Ethnic Group							0.740
East Asian (N= 30, 30)	3/60	50.0	48.4	0.90 (0.62, 1.09)	0.740		
South Asian (N= 20, 20)	6/40	60.0	58.3	1.20 (1.12, 1.25)	0.765		
Caucasian (N= 30, 30)	3/60	20.0	18.3	1.00 (0.99, 1.04)	0.738		
Others (N= 20, 20)	6/40	44.0	42.5	0.80 (0.74, 0.99)	0.217		
Surgery Type							0.501
Laparoscopic (N= 30, 30)	3/60	10.0	7.5	1.10 (0.83, 1.33)	0.501		
Open (N= 20, 20)	6/40	30.0	21.4	0.30 (0.28, 0.52)	0.601		
Chemotherapy Duration							0.217
<3 Months (N= 20, 20)	6/40	44.0	41.0	0.70 (0.41, 0.94)	0.217		
3-6 Months (N= 30, 30)	3/60	10.0	1.2	0.80 (0.74, 1.01)	0.501		
>6 Months (N= 20, 20)	6/40	30.0	23.3	1.10 (0.98, 1.36)	0.601		
Age Group							0.555
Less than 70 (N= 30, 30)	3/60	22.0	19.6	1.20 (1.04, 1.43)	0.555		
At least 70 (N= 20, 20)	6/40	30.0	29.0	1.00 (0.73, 1.19)	0.666		
Compliance							0.540
Compliant (N= 30, 30)	3/60	30.0	23.8	0.70 (0.41, 0.72)	0.540		
Non-compliant (N= 20, 20)	6/40	40.0	37.8	0.80 (0.68, 0.98)	0.052		
Drug Duration							0.272
<1 Year (N= 30, 30)	3/60	30.0	21.5	0.90 (0.81, 1.15)	0.272		
1-2 Years (N= 30, 30)	6/60	34.0	30.5	1.20 (1.09, 1.30)	0.619		
>2 Years (N= 30, 30)	6/60	34.0	31.2	1.40 (1.29, 1.57)	0.719		
PIK3CA Mutation							0.540
Mutant (N= 30, 30)	3/60	30.0	26.9	0.70 (0.64, 0.96)	0.540		
Wild-type (N= 20, 20)	6/40	40.0	37.5	0.80 (0.62, 0.99)	0.052		
COX-2 Overexpression							0.540
Positive (N= 30, 30)	3/60	30.0	25.9	0.70 (0.45, 0.96)	0.540		
Negative (N= 20, 20)	6/40	40.0	33.1	0.80 (0.62, 1.04)	0.052		

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