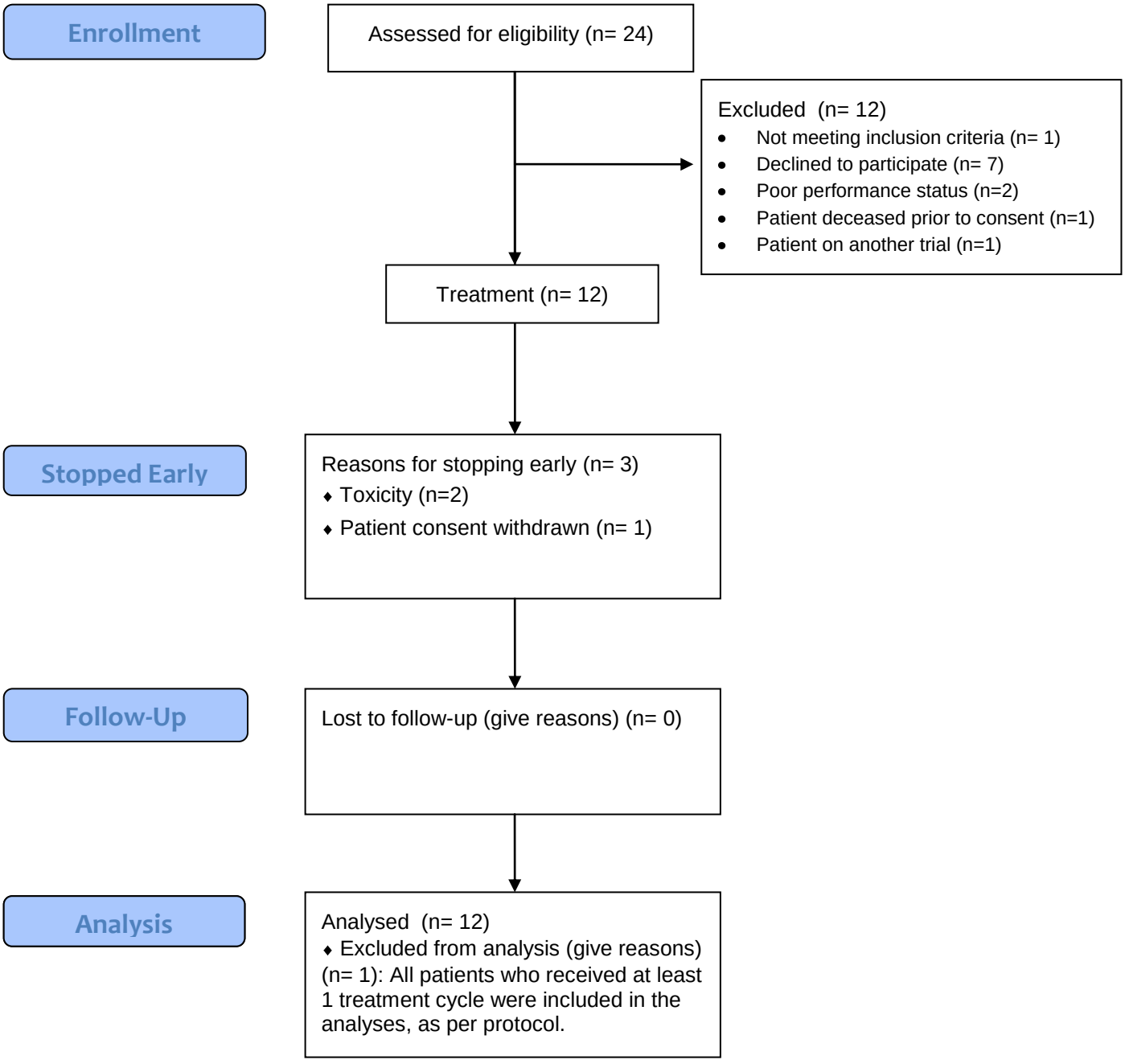
END OF TRIAL REPORT

Trial Identification and Report Information	
Title	A pharmacokinetic study of adjuvant capecitabine in patients who have undergone proximal pancreatico-dudenectomy for resection of pancreatic adenocarcinoma
Chief Investigator:	Professor Duncan Jodrell
EudraCT no.:	2008-008476-14
REC Ref no.:	09/H0718/27
R&D no.:	A091361
Sponsor:	Cambridge University Hospitals NHS Foundation Trust
Sponsor's Address:	Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge Biomedical Campus, Hill's Road, Cambridge, CB2 0QQ
Trial Statistician:	Deepak Parashar
Final Data Analysis carried out by:	Deepak Parashar
Authors of the report:	Nicola Ramenatte (compilation) Deepak Parashar (statistics) Donna Michelle Smith (PK)


Enrollment
Assessed for eligibility (n= 24)
Excluded (n= 12)
Not meeting inclusion criteria (n= 1)
Declined to participate (n= 7)
Poor performance status (n=2)
Patient deceased prior to consent (n=1)
Patient on another trial (n=1)
Treatment (n= 12)
Stopped Early
Reasons for stopping early (n= 3)
Toxicity (n=2)
Patient consent withdrawn (n= 1)
Follow-Up
Lost to follow-up (give reasons) (n= 0)
Analysis
Analysed (n= 12)
Excluded from analysis (give reasons) (n= 1): All patients who received at least 1 treatment cycle were included in the analyses, as per protocol.

Trial Summary	
Final Protocol version:	Version 4.0, dated 01 June 2011
Study Design:	This was a multicentre, non-randomised, pharmacokinetic study. Twelve patients with fully resected adenocarcinoma of the pancreas, who had undergone proximal pancreatico-duodenectomy were to be entered into this study. Patients failing to complete PK sampling during Cycle 1 were replaced. The expected recruitment period was 12 months (expected accrual rate of 1 patient per month). This study aimed to address the issue of whether proximal pancreatico-duodenectomy resection impacts on the availability of capecitabine for systemic absorption.
No. of participants:	Target recruitment: 12 participants Actual recruitment: 12 participants This is a single arm trial.
Investigational Medicinal Products:	Capecitabine, 1250 mg/m^2, Per Oral, twice daily for 14 days, every 3 weeks for 8 cycles. Film-coated tablet, MA numbers: EU/1/00/163/001 and EU/1/00/163/002
Date of End of Trial:	16 August 2012
Reported Serious Breaches:	No serious breaches reported
Significant deviations identified during the trial:	No significant deviations detected/reported. All deviations were classed as minor with no impact on the trial data.

Statistical Analysis and Main Findings	
Trial objectives and endpoints:	**Primary Objective** • To establish the pharmacokinetics (PK) of capecitabine in patients who have undergone proximal pancreatico-duodenectomy. **Secondary objectives** • To establish the toxicity profile of capecitabine in these patients and to identify any dose limiting toxicities (DLT). • To ensure equivalent capecitabine exposure when compared to previous studies using patients who have not undergone such surgery. **Tertiary objectives** • To collect blood samples for future pharmacogenetic analysis. Endpoints: PK parameters Safety
Trial Analysis Population:	Initially, 13 participants were enrolled out of which 1 was found ineligible. Therefore, recruitment of 12 participants matched with the target recruitment. All 12 patients received at least one cycle of protocol treatment. In this study, the full analysis population is the same as the safety population.

Statistical Methods:	All analyses were carried out in accordance with the protocol, and there was no deviation. A statistical analysis plan was drafted before the final data analysis was performed. **Clinical Data** Baseline Variables were summarized using descriptive statistics: mean, standard deviation, median, minimum and maximum for continuous variables, and frequency and percentages for categorical measures. There were a total of 8 cycles of chemotherapy of 3 weeks duration each. Per patient, number of cycles of chemotherapy received were summarised along with any reasons for stopping and reduction. Daily dose received was tabulated against daily dose expected for Day 1 on Cycles 1 & 3. Total dose received and expected for all cycles was also tabulated. All Adverse Events (AE) graded according to the NCI CTCAE Toxicity Criteria (version 3.0) were summarised as incidence rates or percentages broken down by grades, and per patient. Serious Adverse Events (SAE) were listed as well as number of patients experienced SAE. A compliance check was performed to confirm if the SAEs had been recorded as AEs. AEs occurred during Cycle 1 were also tabulated and summarised to establish the DLTs. The PK parameters of interest – namely, the Area Under concentration-time Curve (AUC) and the Maximum plasma Concentration (Cmax) were summarised descriptively for Capecitabine and its metabolites (DFCR, DFUR, 5-FU and FBAL). List of AEs per patient upon administration of CAP dose on Day 1 Cycle 1 were listed. AUC and Cmax distributions graphs for Treatment Cycle 1 and PK Cycle 1 by NCI Grade categories – Grade 2 vs. Grade (<2) were drawn individually for each of the Capecitabine analytes. Correlation of enzyme data (Gem Vmax, Gem km, DFCR Vmax, DFCR km) with Neutrophils on Day 1 Cycle 1 (or Pre-treatment where data was not taken within 3 days) were detailed via scatter graphs, and significant correlations were identified. A p-value of <0.01 was considered as significant. Correlation of the ratio of AUC-DFUR/AUC-DFCR with AUC-DFCRVmax enzyme was also detailed. The above analyses was carried out using the statistical software STATA version 11.2. **PK Data** Non-compartmental PK analysis was performed using WinNonLin® v5.1 software on non-rounded bioanalytical data. Dose times and bleed times were provided by the sponsor and the actual times used to determine the PK parameters in plasma.

Results:

Summary

- Capecitabine median T_{max} = 0.5 hours (0.28 – 2)
- Capecitabine median C_{max} = 9900 ng/ml
- Capecitabine median $AUC_{(0\text{-}inf)}$ = 7600 hr.µg/mL
- DFCR and DFUR median T_{max} = 1 hours (1-4)
- 2/12 patients had delayed T_{max} (3 and 4 hours)
- No apparent differences between cycles 1 and 3

Clinical data

- Treatment summary:
  - 9 patients received 8 cycles
  - 2 patients discontinued treatment after 3 and 5 cycles, due to toxicity
  - 1 patient withdrew consent (after receiving 1 cycle) due to abdominal pain of uncertain causality
- Dose modification:
  - 7 patients had at least one dose modification.
  - 5 patients required dose reduction at some point during treatment .
  - Out of a total of 81 cycles, 9 (11%) had dose modification.
- Toxicity summary:
  - No unexpected toxicities were identified.
  - There were a total of 10 Grade 3 or 4 AEs in 6 patients (Diarrhoea – 3 (30%), Rash: hand-foot skin reaction – 3 (30%)), and 2 SAEs in 2 patients (Grade 2 Infection and Grade 3 diarrhoea).
  - A total of 43 Cycle 1 AEs were recorded. Most common were: Diarrhea (8), Fatigue (asthenia, lethargy, malaise) (3), Rash: hand-foot skin reaction (3). No Cycle 1 DLTs (as generally defined in Phase I trials) were identified.
  - The incidence of toxicity was not significantly different from previous reports.

Toxicity comparator (Van Cutsem Phase III trial)[i]

Grade 3 or 4 toxicity		
	Diarrhoea	10.7%
	Stomatitis	1.3%
	HFS	16.2%
Hospitalisation for AEs		
	All	11.8%
	Diarrhoea	4.4%
Dose Reduction		27%

Correlation of CDA activity with PK parameters and clinical data.

On Day 1 of Cycle 1, Gem Vmax was found to be significantly correlated with DFCR Vmax (Correlation Coefficient = 0.938, p-value < 0.001) as well as with neutrophils (Correlation Coefficient = 0.73, p-value = 0.007) at the 1% significance level.

Conclusion:	Whipple's procedure does not appear to lead to impaired capecitabine absorbtion: AUC is not changed. However, administration with food, after a Whipple's procedure is more akin to dosing in the starved state (Reigner et al): Tmax is reduced and Cmax is increased.

Dissemination of Research Findings and Publications	
To participants:	Results will be discussed with participants, where possible, during their routine follow-up visits.
Publications:	Publication being prepared for submission. Results will be presented in a peer reviewed publication. A link to this publication will be posted on the Cambridge Pancreatic Cancer Centre website. A summary of the results will be published on the CRUK CancerHelp UK website.

Chief Investigator's Signature	
	 29.7.13 Signature: _____ Date: _____

[i] Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol. 2001 Nov 1;19(21):4097-106. Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, Bugat R, Findlay M, Frings S, Jahn M, McKendrick J, Osterwalder B, Perez-Manga G, Rosso R, Rougier P, Schmiegel WH, Seitz JF, Thompson P, Vieitez JM, Weitzel C, Harper P; Xeloda Colorectal Cancer Study Group.