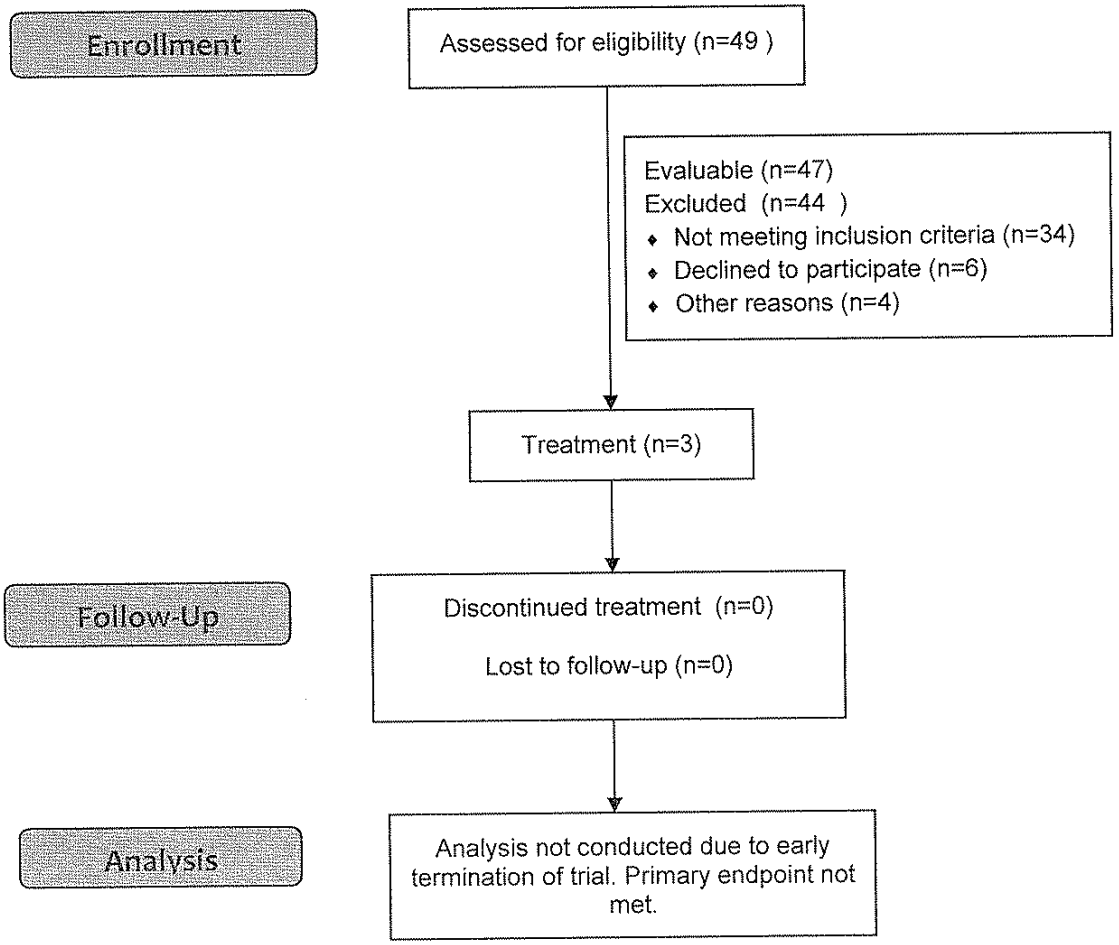
END OF TRIAL REPORT

Trial Identification and Report Information	
Title	Proof of Mechanism Study of an Oral Hedgehog Inhibitor (GDC-0449) in Patients with Resectable Pancreatic Ductal Adenocarcinoma in the Pre-operative Window Period
Chief Investigator:	David A. Tuveson, MD/PhD
EudraCT no.:	2010-018776-24
REC Ref no.:	10/H0304/76
H0304/76	A091941
Sponsor:	Cambridge University Hospitals NHS Foundation Trust
Sponsor's Address:	R&D Manager, R&D Department (Box 277) Addenbrooke's Hospital Hills Road Cambridge CB2 0QQ
Trial Statistician:	Dr. Adrian Mander
Final Data Analysis carried out by:	No final data analysis has been conducted due to the early termination of the trial.
Author of the report:	Dr. Aarthi Gopinathan


Enrollment
Assessed for eligibility (n=49)
Evaluable (n=47)
Excluded (n=44)
Not meeting inclusion criteria (n=34)
Declined to participate (n=6)
Other reasons (n=4)
Treatment (n=3)
Follow-Up
Discontinued treatment (n=0)
Lost to follow-up (n=0)
Analysis
Analysis not conducted due to early termination of trial. Primary endpoint not met.

Trial Summary	
Final Protocol version:	Protocol Version 6.0, Dated 24 January 2012
Study Design:	This was a single-centre, non-randomised, open-label, proof of mechanism study. The study was based on preclinical data showing that inhibition of the hedgehog pathway in a mouse model of pancreatic cancer markedly altered the structure of the stromal compartment of pancreatic tumours. The trial was designed to determine whether GDC-0449 modulated hedgehog signalling in stromal and/or tumour cells. In addition, the trial evaluated the safety of GDC-0449 in the pre-operative setting. 20 patients with resectable pancreatic cancer were meant to be entered onto the study and to be treated with GDC-0449, in the window period prior to surgery. Initially, the expected recruitment period was 12 months.
No. of participants:	Target Recruitment: 20 patients Actual Recruitment: 3 patients The study was terminated early due to poor recruitment.
Investigational Medicinal Products:	GDC-0449, 150mg once daily (No dose adjustment for body surface area or body weight), hard gelatine size1 capsules of 150mg strength.
Date of End of Trial:	10 August 2012
Reported Serious Breaches:	No serious breaches reported
Significant deviations identified during the trial:	No significant deviations detected/reported. Any deviations identified during the trial were classed as minor, with no impact on the trial data.

Statistical Analysis and Main Findings	
Trial objectives and endpoints:	Primary Objectives: • To study the effect of GDC-0449 treatment on the stromal cell and tumour cell hedgehog signalling in patients with PDAC. • To study the safety and tolerability of pre-operative GDC-0449 treatment in patients who undergo Whipple's or distal pancreatectomy surgery for PDAC. Secondary Objectives: • To study the effect of GDC-0449 treatment on stromal architecture in patients with PDAC. • To evaluate GDC-0449 tissue and plasma concentrations in patients with PDAC. • To study the treatment effect of GDC-0449 on the perfusion and elasticity of the tumour in patients with PDAC. • To study the treatment effect of GDC-0449 on circulating biomarkers of PDAC. Primary Endpoints: • Extent of Gli1 signalling inhibition (Gli1 signalling reflects the activity of

	the hedgehog signalling pathway) as measured by qRT-PCR of Gli1 in microdissected stromal tissue derived from biopsies and surgical material. • Toxicity as measured by post-operative mortality, post-operative pancreatic leakage and any unexpected excess complications after surgery and adverse events during treatment and post-operatively as defined by NCI CTCAE v3.0. <u>Secondary Endpoints:</u> • Evidence of hedgehog inhibition in tumour tissue taken from surgery, looking at stromal content, proliferation, apoptosis and microvessel density. • Plasma conentrations of GDC-0449. • Intra-tumoral concentrations of GDC-0449. • Changes in dynamic contrast-enhanced ultrasound and elastography ultrasound using EUS. • Changes in CA19.9 after treatment. Changes in Circulating Tumour Cells (CTC) and Circulating Nucleic Acids (CNA) after treatment.
Trial Analysis Population:	Patients with documented tissue diagnosis of pancreatic ductal adenocarcinoma with a sufficient amount of tissue for Laser Capture Micro-dissection (LCM) of the stromal and tumour compartments and confirmed eligibility for Whipple's or distal pancreatectomy. Due to the difficulty in recruiting patients to this study, several amendments were made to the inclusion criteria over the course of the study to enable recruitment. These amendments were as follows: • Inclusion of patients undergoing distal pancreatectomy. • Estimated creatinine clearance reduced to ≥ 50ml/min. • Inclusion of an optional tissue biopsy during the screening period, in cases where insufficient tissue was available for analysis. • Albumin level reduced from >30mg/dL to ≥ 25 mg/dL. Despite these protocol amendments, a total of 3 patients were enrolled in the study, and the study was terminated early.
Statistical Methods:	Statistical analysis was not carried out, as insufficient patients were enrolled to assess the endpoints.
Results:	No results are currently available. No analyses of tissue samples have been conducted thus far. The tissue analysis for the primary endpoint and pharmacokinetics was meant to be conducted at Genentech and Tandem Laboratories, respectively. Due to the early stoppage of the trial, Roche declined to financially support these analyses. We have worked on determining the feasibility of conducting these analyses without their financial support, and identifying the amount of funding available to do so. Although we will not be carrying out the above-mentioned measurements, ilt is intended that the pre- and post-treatment tissue and blood samples available from the three patients who completed the trial will still be analysed as specified in the protocol, particularly by immunohistochemical evaluation to evaluate the effect of the drug on these tumours.

Conclusion:	The objectives of the trial were not met due to the problems with recruitment. The attached flowchart outlines the reasons for non-enrolment. As a field of research, this type of trial is essential since more therapies need to be developed to support the treatment of pancreatic cancer patients prior to resection given the very high rates of early relapse. However, this trial has demonstrated the difficulty in enrolling this population of patients who often deteriorate whilst awaiting investigations. In addition, obtaining sufficient tissue via EUS micro-cores for tissue-related endpoints and basing eligibility on this has proven a challenge from patients with operable pancreatic tumours, which tend to be smaller. This should be taken into consideration in the design of future studies in this patient population.

Dissemination of Research Findings and Publications	
To participants:	There is currently no plan to inform participants of any findings from the study.
Publications:	None.

Chief Investigator's Signature	
	pp Prof Thirlwall Signature: _____ Date: 8/8/13.

HIPPoS
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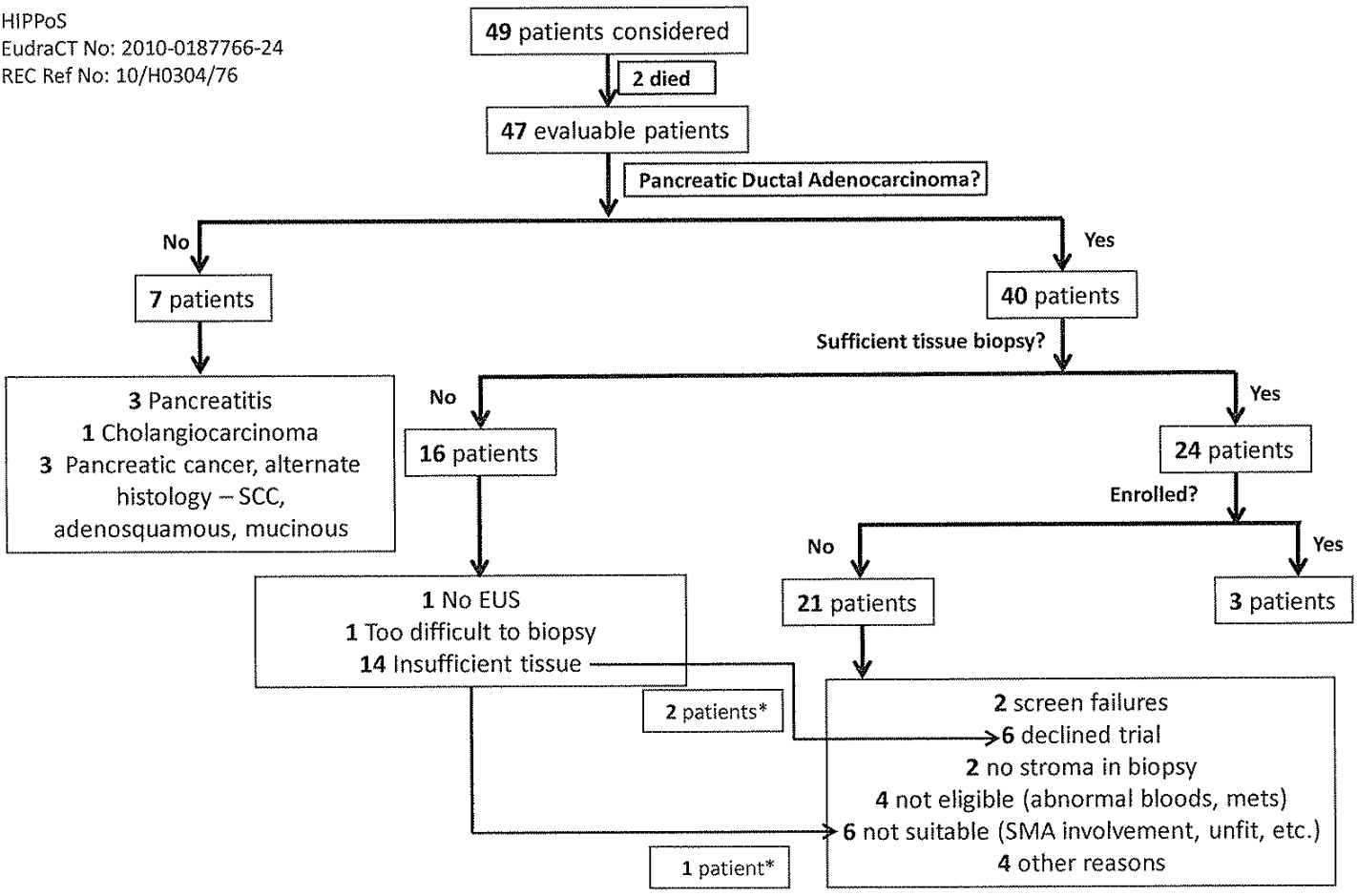

* These patients could have been enrolled, but would have required a second biopsy.