CLINICAL STUDY REPORT

PenVe

A prospective 2 arm randomised controlled trial comparing the use of open label pentoxifylline and tocopherol versus current standard of care for the prevention of fibrosis related outcomes in irradiated head and neck oncology patients (Feasibility Study)

Sponsor Protocol Code:	223295
EudraCT Number:	2018-001153-27
ClinicalTrials.gov Identifier:	N/A
ISRCTN number:	74484952
REC Number:	18/LO/1910
Investigational Drugs (IMPs):	Pentoxifylline and tocopherol
Indication:	Irradiated head and neck oncology patients
Development Phase:	Phase II feasibility
Study Begin (FPFV):	05/08/2019
Study End (LPLV):	02/08/2023
Report Version & Issue Date:	V1 05 August 2024
Co-sponsor Name and Address:	Guy's and St. Thomas' NHS Foundation Trust King's Health Partners Clinical Trials Office, F16 Tower Wing Guys Hospital, Great Maze Pond, London SE1 9RT
Co-sponsor contact details:	qm.khpcto@kcl.ac.uk
Chief Investigator:	Mr. Vinod Patel

SIGNATURE PAGE

By signing below I approve the contents of this Clinical Study Report, and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. The clinical trial reported herein was conducted in accordance with the principles contained in the Declaration of Helsinki, Good Clinical Practice (GCP) and all applicable laws and regulations.

This was a non-commercial academic trial, the results of this study are not intended to be used or a licensing application.

Chief Investigator:

Printed name Vinod Patel **Signature** **Date** 14/08/24

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APPENDICES

1. Ethics

Independent Ethics Committee or Institutional Review Board
The study protocol and amendments were reviewed and approved by a National Research Ethics Service (London - Harrow Research Ethics Committee).

Ethical conduct of the study
The trial was conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki (1996) as amended, the principles of Good Clinical Practice (GCP) and in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, the Research Governance Framework for Health and Social Care, the Data Protection Act 1998 and other regulatory requirements as appropriate. The trial protocol and substantial amendments were reviewed by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA)

Subject information and consent
This was a single centre study based at Guy's & St Thomas NHS Foundation Trust. Participants were recruited between July 2019 and July 2022 from a dedicated and specialist clinic (pre-head and neck radiation dental assessment clinic) at Guy's Hospital (London, UK). Study visits were conducted at the Dental Hospital and the Oral Clinical Research Unit, both located at Guy's Hospital.

Participants were screened during multi-disciplinary meetings following a biopsy-proven diagnosis of cancer. All cancer patients are discussed through this route where the treatment plan is decided. Patients who were to receive radiotherapy were informed of the PenVe study and introduced to the dedicated research nurse. Patients were provided a participant information sheet and given time to decide to take part. At this stage the oncology team referred the patient to have their mandatory oral and dental check before they are approved to proceed to radiotherapy. Upon attendance to the dedicated head and neck radiotherapy dental assessment clinic (Guy's Dental Hospital), patients underwent a clinical review. The inclusion/exclusion criteria were checked and following this the patient was invited to participate in the trial. Written informed consent was obtained by a study doctor and baseline measures were completed.

2. Data Monitoring
Oversight of this feasibility study was provided by a Trial Steering Committee with two independent clinicians, one independent statistician and one patient representative. The Chief Investigator, Trial Manager and Trial Administrator also sat on the committee.

3. Sponsors, Investigators and Trial Sites

Sponsor	
Name: Guy's and St. Thomas' NHS Foundation Trust Address: King's Health Partners Clinical Trials Office, Floor 16 Tower Wing Guys Hospital, Great Maze Pond, London SE1 9RT Sponsor Contact: Amy Holton Telephone: 020 7188 5732 Fax: 020 7188 8330 Email: amy.holton@kcl.ac.uk	

Chief Investigator

Name: Vinod Patel
Address: Floor 23, Oral Surgery Dept, Tower Wing,
Guy's Dental Hospital,
Great Maze Pond,
London, SE1 9RT
Telephone: 0207 188 3885
Email: vinod.patel@gstt.nhs.uk

4. Co-Investigator(s), Statistician, Laboratories, Database Management

Name: Professor Mark McGurk
Address: University College Hospital,
6th Floor
235 Euston Road
London, NW1 2BU
Telephone: 020 3447 2159
Fax: 020 3447 9855
Email: mark.mcgurk@ucl.ac.uk

Name: Teresa Guerro Urbano
Address: Guy's and St Thomas' Hospitals
Oncology Offices,
Ground Floor, Lambeth Wing
St Thomas' Hospital
Westminster Bridge Rd
London SE1 7EH
Telephone: 02071884219
Fax: 02079289968
Email: Teresa.GuerreroUrbano@gstt.nhs.uk

Name: Abdel Douiri
Address: School of Population Health & Environmental Sciences
Faculty of Life Sciences & Medicine
King's College London
4.16 Addison House
Guy's Campus,
London SE1 1UL
Telephone: 0207 848 6635
Email: abdel.douiri@kcl.ac.uk

Name: Angela Cape
Address: King's Clinical Trial Unit
Research Management and Innovation Directorate
Institute of Psychiatry, Psychology and Neuroscience
16 de Crespigny Park
London, SE5 8AF
Telephone: 020 7848 5164
Email: Angela.Cape@gstt.nhs.uk

5. Study Synopsis

Title of clinical trial	A prospective 2 arm randomised controlled trial comparing the use of open label pentoxifylline and tocopherol versus current standard of care for the prevention of fibrosis related outcomes in irradiated head and neck oncology patients (Feasibility Study)
Protocol Short Title/Acronym	PenVe trial
Study Phase	Phase II
Sponsor name	Guy's and St Thomas' NHS foundation Trust
Chief Investigator	Mr Vinod Patel
Eudract number	2018-001153-27
REC number	18/LO/1910
IRAS project ID:	223295
Medical condition or disease under investigation	Osteoradionecrosis (ORN) of the jaws Trismus Dysphagia
Purpose of clinical trial	A feasibility study to determine the logistical possibility of successfully running a larger multi centre clinical trial to establish whether the prophylactic use of pentoxifylline and tocopherol can avoid the radiation fibrous related outcomes
Primary objective	Feasibility of the trial • To assess patient's preference of drug formulation and subsequent side effects • To assess the recruitment and retention to the trial, and patient adherence to the drugs • To assess the appropriateness and acceptability of the outcome measurement tools
Secondary objective (s)	• To assess the presence of osteoradionecrosis in both intervention and control arms • To assess an improved mouth opening in both intervention and control arms • To assess an improved swallowing capacity in both intervention and control arms • To assess an improved quality of life in both intervention and control arms
Trial Design	This was a feasibility study consisting of two arms, single-centre, randomised controlled, open labelled trial investigating outcomes following the prophylactic use of pentoxifylline and tocopherol in irradiated head and neck oncology patients.
Endpoints	Primary Endpoints: • The time point that the participant agrees to swap from liquid to tablet formulation of pentoxifylline and of vitamin E • Patient's self-reported preference for tablet

	or liquid • The presence and number of side effects using the standard adverse event reporting • Number of participants consented, as a proportion of the number of patients eligible and invited • Number of participants randomised, as a proportion of the number of patients consented • Number of participants who attend their month 6 visit (visit 4), as a proportion of the number of patients randomised • Number of patients recruited • Number of visits attended • Number of phone calls answered • Participants self-reported adherence (number of doses missed) • Number of questionnaires completed by participants Secondary Endpoints: Completion of the following at 6 months: • Proportion of patients with osteoradionecrosis at month 6 post trial randomisation • Difference in mouth opening measurements from baseline to month 6 post randomisation • Difference in swallowing scores from baseline to month 6 post randomisation • Difference in quality of life scores from baseline to month 6 post randomisation
Planned number of subjects	68
Summary of eligibility criteria	Inclusion criteria: • Patients (≥18yrs) presenting with a primary head and neck (H&N) tumour requiring radiotherapy treatment and placing them in the highest risk group for developing osteoradionecrosis, trismus and dysphagia. These include: o Oropharynx (Tonsil, Base of Tongue) o Nasopharynx o Oral Cavity o Maxillary sinus o Salivary glands o Unknown primary of the neck o Hypopharynx • Oncology treatment aiming for the intent to cure • Patients able to consent and willing to participate Exclusion criteria: • Previous history of H&N cancer • Patients treated with any drug implicated to cause medication related osteonecrosis of the jaw (MRONJ). These include bisphosphonates, denosumab, radium 223, tyrosine kinase inhibitors

	and bevacizumab • Any patient with significant medical history where taking part in this study may potentially compromise their health. • Women who are pregnant or breast feeding or of child bearing age not on adequate contraception • Patients lacking capacity to consent. • Oncology treatment for palliative care • Patients deemed to have a high risk of recurrent tumour • Patients with a previous history of cerebral haemorrhage, extensive retinal haemorrhage, acute myocardial infarction, severe cardiac arrhythmias and / or impaired renal function, impaired liver function which in the expert opinion of the principal investigator present a risk to the patient • Known drug allergy or sensitivity to pentoxifylline (or methyl xanthines) and alpha-tocopheryl or any constituents of the medication (e.g. methyl and propyl hydroxybenzoates and / or a rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency) • Patients taking theophylline or oestrogens • Patients with metastatic disease • Patient participating in other drug (CTIMP) trials
IMP, dosage and route of administration	Pentoxifylline 400mg BD (liquid or tablet formulation) Vitamin E 1000IU OD (liquid or tablet formulation)
Active comparator product(s)	N/A
Maximum duration of treatment of a subject	6 Months
Version and date of protocol amendments	Version 1.1 09/11/2018: Amendment to section 9.2- changed from abstinence to true abstinence and when this is in line with the preferred and usual lifestyle of the participant. Version 1.2 08/01/2019: Amendment to title Version 2.0 06/05/2020: Amendment to patient commencement in the study. Amendment to the eligibility criteria with expansion of head and neck cancers. Minor formatting amendments throughout. Version 2.1 11/08/2021: inconsistencies within the protocol were corrected throughout the document, typos and formatting issues fixed. Update to co-investigators due to staff turnover. Added to the withdrawal section about ORN development as this information was in the PIS but not in the protocol. Version 3.0 18/11/2022: Amendment to patient randomisation in the study. Change in sponsor contact.

6. Glossary of terms

CI - Chief Investigator

CRF- Case Report Form/ Clinical Research Facility

ICF - Informed Consent Form

IMP - Investigational Medicinal Product

KHP CTO – Kings Health Partners Clinical trial office

MRONJ - Medication Related Osteonecrosis of the Jaw

PVe – Pentoxifylline in combination with vitamin E

REC - Research Ethics Committee

HRA - Health Research Authority

H & N cancer – Head and neck cancer

HRQOL – Health Related Quality Of Life

IMRT – Intensity Modulated Radiation Therapy

ORN - Osteoradionecrosis

PI - Principal Investigator

RIF – Radiation induced fibrosis

SAE – Serious adverse event

SAR – Serious Adverse reaction

SUSAR - Suspected Unexpected Serious Adverse Reaction

SSQ - Sydney Swallow Questionnaire

Tocopherol - (also known as *Vitamin E*)

7. Publication (reference)

Publications are pending.

8. Study period (years)

The study period ran from 29/04/2019 until 30/11/2023. The end of study was defined as the date of database lock.

Patient recruitment started on 05/08/2019 with the recruitment of the first participant until 13/07/2022 when recruitment was closed.

9. Phase of development

Phase II

10. Objectives

Primary Objectives	Primary Endpoints	Method
To assess patient's preference for pentoxifylline formulation and vitamin E (tocopherol) formulation, in a tablet vs liquid format (Intervention group only)	• The time point that the participant agrees to swap from liquid to tablet formulation of a) pentoxifylline and b) vitamin E • Patient's self-reported preference for tablet or liquid	Through patient contact: Daily telephone call in the first 2 weeks, 3 weekly telephone calls (+/- 1 week) in conjunction with patient diary, 3 monthly clinical follow up post randomisation 6 monthly clinical follow up post randomisation This will be recorded in the patient notes and transcribed to the eCRF Independent and reflective patient feedback at focus groups
To assess patient's subsequent side effects related to the pentoxifylline and vitamin E (Intervention group only)	The presence and number of side effects using standard adverse event reporting.	Through patient contact: Daily telephone call in the first 2 weeks, 3 weekly telephone calls (+/- 1 week) in conjunction with patient diary, 3 monthly clinical follow up (+/- 1 month) 6 monthly clinical follow up (+/- 1 month) This will be recorded in the patient notes and transcribed to the eCRF
To assess the recruitment into the trial	• Number of participants consented, as a proportion of the number of patients eligible and invited	Through the screening and enrolment log which is overseen by the PI and research nurse. The numbers

	• Number randomised, as a proportion of the number of patients consented	consented and randomised will be recorded in the eCRF.
To assess retention of the participants in the trial	• Number of participants who attend their month 6 post randomisation visit (visit 4), as a proportion of the number of patients randomised • Number of patients recruited	Through patient contact: 6 monthly clinical follow up post randomisation This will be recorded in the patient notes and transcribed to the eCRF
To assess the participation in the trial follow up visits and phone calls (intervention group only)	• Number of visits attended • Number of phone calls answered	Through patient contact: Daily telephone call in the first 2 weeks, 3 weekly telephone calls (+/- 1 week) in conjunction with patient diary, 3 monthly clinical follow up post randomisation visit (+/- 1 month) 6 monthly clinical follow up post randomisation visit (+/- 1 month) This will be recorded in the patient notes and transcribed to the eCRF
To assess patient adherence to pentoxifylline and Vitamin E (Intervention group only)	• Sustained and elevated levels of Vitamin E levels (higher than natural variation / standard range) at months 3 and months 6 in comparison to participant's baseline, through blood test for Vitamin E and recording levels of Vitamin E present. • Participants self-reported adherence	Vitamin E blood test taken at baseline, 3 months post randomisation and 6 months post randomisation. Patients asked to bring any remaining Pentoxifylline and vitamin E for measurement of liquid or tablets left at formulation changeover and at month 6 Patients asked about adherence (number of doses missed) through patient contact:

		Daily telephone call in the first 2 weeks, 3 weekly telephone calls (+/- 1 week) in conjunction with patient diary, 3 monthly clinical follow up (+/- 1 month) 6 monthly clinical follow up (+/- 1 month) This will be recorded in the patient notes and transcribed to the eCRF
To assess the acceptability to participants of the outcome measurement tools	Number of questionnaires completed by participants	Through completed questionnaires at trial visits. Through focus groups
Secondary objectives	**Secondary endpoints**	**Method**
To assess presence of osteoradionecrosis	Proportion of patients with osteoradionecrosis at month 6 post randomisation	Clinical review including an oral examination to determine or exclude the presence of ORN at month 3 post randomisation, month 6 post randomisation
To assess improvement in mouth opening	Difference in mouth opening measurements from baseline to month 6 post randomisation	Ruler measurements taken at baseline, month 3 post randomisation, month 6 post randomisation
To assess improvement in swallowing capacity	Difference in swallowing scores from baseline to month 6 post randomisation	Sydney swallow questionnaire taken at baseline, month 3 post randomisation, month 6 post randomisation
To assess improvement in quality of life	Difference in quality of life scores from baseline to month 6 post randomisation	Washington quality of life questionnaire taken at baseline, month 3 post randomisation, month 6 post randomisation

11. Background and Context

The use of radiotherapy to treat head and neck cancer is a well-established treatment method. Most recently there has been a rise in the use of chemotherapy as it provides better outcome against the original cancer diagnosis. Unfortunately, radiotherapy is not without its side effects. Its use often leads to radiation induced fibrosis and affects tissue at every level. For head and neck oncology patients this frequently leads to scarring of the facial and throat muscles meaning lifelong restriction in mouth opening that continues to worsen as well as difficulty in swallowing. There are no established treatments to improve or eliminate these outcomes.

Osteoradionecrosis (ORN) is a lifelong complication associated with head and neck radiotherapy. The condition is not new and since its initial mention in the 1920s, a century on, the condition is still rife amongst this vulnerable group.

Attempts through the decades have been made to manage the condition but no interventions have shown outstanding results. In recent times, the priority remains avoidance and hence a concerted effort is made through pre-radiotherapy dental assessment with extraction of poor and dubious prognosis of teeth. Good oral hygiene and high fluoride dental products are reinforced. Following radiotherapy, dental extractions should be avoided and restoration and maintenance of teeth remains critical.

Unfortunately, these interventions have not been able to eliminate or reduce the incidence of ORN even with the change to Intensity Modulated Radiation Therapy (IMRT), a novel radiation delivery system aimed at reducing collateral radiation damage. The increased use of chemotherapy to supplement radiotherapy is one reason for the sustained incidence of ORN. Dry mouth and high calorific diets have continued to lead to radiation dental decay which eventually leads to the need for dental extractions.

Furthermore, pilot data now shows that ORN is no longer weighted towards an induced cause (dental extraction, dental infection, dentures, dental implants) following our concerted efforts of pre-radiotherapy dental assessment and treatment. Now spontaneous ORN appears to be the predominant cause and worryingly how can you avoid a non-intervention cause?

ORN remains an important area in the NHS. As treatment for cancer and general medicine improves it is well recognised patients are living for longer. The risk of ORN remains life-long and hence sadly many patients who overcome their head and neck cancer are then be blighted with this complication. Refractory ORN is difficult to treat with no guaranteed intervention for cure. Severe ORN can only be treated with major surgery of resection +/- reconstruction which itself carries both morbidity and mortality. With an ageing population can such cohort undergo such major surgery with such co-morbidities? If so the financial implications for the NHS are huge with an estimated average cost of £50,000 for a seamless ORN surgical case. Away from the finances, the patient is left with a poor quality of life. Unable to eat and function their reserve is lessened, and many patients die with their ORN unresolved.

These complications are here to stay and will burden both the patient and NHS resources. It remains key to avoid their occurrence. Most recently the use of 2 medicines (pentoxifylline and tocopherol) have shown positive results in the management of established ORN. They have been successfully used in other cancer specialities to deal with radiation induced fibrosis. It is now proposed that the prophylactic use of these medicines may help prevent ORN, restricted mouth opening and swallowing difficulties. Its financial burden on the NHS will be less than the surgical cost and overall if it can prevent ORN then the quality of life implications for patients remains very important.

Unfortunately, the tablet formulation of pentoxifylline is deemed quite large even for the average patient. It is enterically coated to reduce the side effect of stomach irritation. This remains a very important problem if this drug is to be administered to head and neck radiotherapy patients. Having recognised that head and neck radiotherapy patients have restricted mouth opening, dry mouth and fibrosis of the throat making swallowing difficult, compliance for pentoxifylline maybe difficult. The tablet if crushed and mixed with water would then lose its enteric coating potentially leading to increase gastric irritation and hence poor compliance. It is primarily on this basis that a feasibility trial was required before considering a substantive trial.

12. Methodology

Study setting

The feasibility trial took place at Guys & St Thomas NHS Foundation Trust within the Head and Neck Cancer (H&N) service.

Design

A single-centre, prospective parallel 2-arm, open labelled randomised (3:1 ratio) controlled trial investigating Radiation induced fibrosis (RIF) outcomes following the prescription of prophylactic Pentoxifylline in combination with vitamin E (PVe) versus current best standard of care.

Study summary

Participants were assessed for eligibility at baseline, prior to starting radiotherapy. Questionnaires and assessments were completed at this timepoint once written informed consent had been obtained. Participants then underwent their radiotherapy treatment and routine care. Once participants had been deemed cancer-free and no longer needing further radiotherapy, they were contacted by the research team to confirm they are willing to continue in the PenVe study. Participants who wished to continue were re-assessed for eligibility and were randomised into the active or control arm within 3 to 9 months after their last radiotherapy treatment.

Participants allocated to the active group started the IMP within 1 week of randomisation. They were contacted on a daily basis for two weeks by a research nurse to document adherence and any adverse events. After these two weeks, the phone calls continued once every three weeks while the participants were taking the IMP.

All participants were seen at 3 months and 6 months post-randomisation to complete questionnaires and assessments for outcome measures. At the end of the study, participants were invited to provide feedback on the trial in the form of a focus group or online form. Options were provided to accommodate different preferences.

Table 1: PenVe Schedule of Events

	Screening Visit / enrolment Pre radiotherapy (Baseline)	**Randomisation*; 3 months post radiotherapy completion Phone call (Day 0) +6 month window**	**1-day post randomisation (Day 1)** ***IMP arm only*** **+ 7 days window**	**Daily phone calls for 2 weeks** ***IMP arm only***	**3-weekly phone calls; 5 weeks post randomisation** ***IMP arm only*** **+/- 7 days**	**Month 3 post randomisation +/- 1 month**	**Month 6 post randomisation +/- 1 month**
Informed consent	X						
Review Inclusion / exclusion criteria	X	X					
Demographics	X						
Medical History	X						
Concomitant diseases / concomitant treatment	X	X	X			X	X
Oral Examination	X					X	X
Measurement of trismus Willis Bite Gauge (If no teeth present)	X					X	X
The Sydney Swallow Questionnaire (SSQ)	X					X	X
The University of Washington Quality of Life Revised V4 (UW-QOL-R4)	X					X	X
First Dosage of IMP			X				
Pregnancy test (where necessary – women of child bearing age randomised to the study IMP's)	X		X			X	X
Vitamin E Blood Test	X					X	X
Randomisation Group A) Best standard of care		X					

	Screening Visit / enrolment Pre radiotherapy (Baseline)	**Randomisation*; 3 months post radiotherapy completion Phone call (Day 0) +6 month window**	**1-day post randomisation (Day 1)** *IMP arm only* **+ 7 days window**	**Daily phone calls for 2 weeks** *IMP arm only*	**3-weekly phone calls; 5 weeks post randomisation** *IMP arm only* **+/- 7 days**	**Month 3 post randomisation +/- 1 month**	**Month 6 post randomisation +/- 1 month**
B) Pentoxifylline 400mg BD & Tocopherol 1000IU OD							
Dispensing IMP			X			X	
Adverse Event Monitoring			X				
Concomitant medication monitoring	X						
Compliance check IMP				X	X	X	X
Dispensing patient centred diary			X			X	
Patient Diary Compliance				X			
Completion of Patient's End of Study Form							X
Invitation for optional Focus group [a]							X
Discussion of treatment preference			X	X	X	X	X
Adhoc phone calls as necessary	X						

*Patient was be randomised to one of the following allocations

A. Best standard of care
B. Pentoxifylline 400mg BD & Tocopherol 1000IU OD (Subject preference for liquid or tablet formulation was discussed at each telephone call and visit)

[a] If the patient withdrew from study visits before month 6, they were still invited to attend the focus group.

13. Number of patients (planned and analysed)

13.1 Planned

The planned sample size was 68 participants.

13.2 Analysed

Table 2: Participant flow in the PenVe trial

Arm	**Total**		
# patients screened	1652		
# patients consented	54		
	Active	**Control**	**Total**
# patients randomised/ study arm	22	7	29
# patients completed study/ study arm	16	6	22
# patients completed treatment/ study arm (completion defined as at least 5 months of treatment)	11	6	17
Reasons for non-completion if applicable	N=1 no longer wished to take part, N=1 had recurrence of cancer, N=3 lost to follow-up, N=1 treatment failure	N= 1 No longer wished to take part	

Table 3: The reasons for patient withdrawal from the study

PIN	**Study arm**	**Withdrawal Reason**
P010001	IMP	Treatment Failure
P010003	not randomised	Ineligible

PIN	Study arm	Withdrawal Reason
P010004	not randomised	COVID
P010005	IMP	No longer wishes to take part
P010006	not randomised	Ineligible
P010007	not randomised	COVID
P010009	not randomised	Ineligible
P010010	control	No longer wishes to take part
P010011	not randomised	COVID
P010012	not randomised	COVID
P010013	not randomised	Ineligible
P010014	not randomised	Ineligible
P010015	not randomised	Ineligible
P010016	not randomised	No longer wishes to take part
P010017	not randomised	Lost to contact
P010018	not randomised	Ineligible
P010020	IMP	Lost to contact
P010022	IMP	Adverse Event
P010023	not randomised	COVID
P010027	not randomised	Death of participant
P010028	not randomised	Ineligible
P010029	IMP	Lost to contact
P010031	IMP	Lost to contact
P010033	not randomised	Ineligible
P010035	not randomised	No longer wishes to take part
P010038	not randomised	Lost to contact
P010039	not randomised	Other
P010040	not randomised	Other
P010041	not randomised	Other
P010042	not randomised	Ineligible
P010044	not randomised	ineligible
P010050	not randomised	Did not want to take medication

14. Diagnosis and main criteria for inclusion

Inclusion Criteria

- Patients (≥18yrs) presenting with a primary head and neck (H&N) tumour requiring radiotherapy treatment and placing them in the highest risk group for developing osteoradionecrosis, trismus and dysphagia. These include:
  - Oropharynx (Tonsil, Base of Tongue)
  - Nasopharynx
  - Oral cavity
  - Maxillary sinus
  - Salivary glands
  - Unknown primary of the neck

  - Hypopharynx
- Oncology treatment aiming for the intent to cure
- Patients able to consent and willing to participate

6.2 Exclusion Criteria

- Previous history of H&N cancer
- Patients treated with any drug implicated to cause medication related osteonecrosis of the jaw (MRONJ). These include bisphosphonates, denosumab, radium 223, tyrosine kinase inhibitors and bevacizumab
- Any patient with significant medical history where taking part in this study may potentially compromises their health.
- Women who are pregnant or breast feeding or of child bearing age not on adequate contraception
- Patients lacking capacity to consent.
- Oncology treatment for palliative care
- Patients deemed to have a high risk of recurrent tumour
- Patients with cerebral haemorrhage, extensive retinal haemorrhage, acute myocardial infarction, severe cardiac arrhythmias and /or impaired renal function, impaired liver function which in the expert opinion of the principal investigator present a risk to the patient
- Known drug allergy or sensitivity to pentoxifylline (or methyl xanthines) and alpha-tocopheryl and /or any constituents of the medication (e.g. methyl and propyl hydroxybenzoates and / or a rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency)
- Patients taking theophylline or oestrogens
- Patients with metastatic disease
- Patients participating in other drug (CTIMP) trials

15. Test product, dose and mode of administration

The following products were classed as Investigational Medicinal Products (IMPs) in this trial:

Pentoxifylline 200mg/5ml solution. This was supplied in 200ml amber glass bottles with child resistant closures. The product was manufactured by the Pharmacy Manufacturing Unit (PMU) at Guys and St Thomas' NHS Foundation Trust (GSTFT) in accordance with EU GMP.

The solution was a clear, colourless, aqueous solution containing a methyl hydroxybenzoate and propyl hydroxybenzoate preservative system with a shelf-life of 12 months. The product was labelled, QP certified and distributed by the Pharmacy Manufacturing Unit in accordance with its MIA(IMP) licence.

Pentoxyfylline 400mg modified release tablets (Trental®). The tablet form of the IMP was supplied in a 90-tablet blister pack. Hospital supplies of commercially available, licenced product were used in the study.

Alpha- tocopherol acetate 500mg/5ml suspension (Vitamin E suspension – equivalent to 500 IU in 5ml). Supplied in 100ml amber glass bottles with an HDPE child resistant and tamper evident cap. Hospital supplies of commercially available, licenced product were used in the study.

dl-alpha-tocopheryl acetate 200 IU capsules (equivalent to 200 IU of vitamin E). Supplied in a 60 capsule blister pack. An EU licenced product from Spain was sourced and used in the study (Auxina E, Chiesi).

Dosing Regimen

Patients randomised to the investigational arm received 6 months of treatment of pentoxifylline and tocopheryl, starting 3 - 9 months after completion of radiotherapy. Patients had the option to start with either the liquid or tablet formulations of either IMP. They had the option to switch to a different formulation throughout the trial.

Pentoxifylline dose: 400mg orally TWICE a day.

Vitamin E (alpha-tocopheryl) dose: 1000 IU orally ONCE a day.

16. Duration of treatment

Patients randomised to the investigational arm received 6 months of daily treatment of pentoxifylline and tocopheryl, starting 3 - 9 months after completion of radiotherapy.

17. Reference therapy, dose and mode of administration

No reference therapy was used. Participants in the control arm received no study treatment, only standard care.

18. Criteria for evaluation: Endpoints

18.1 *Primary end-point - Feasibility*

Primary Endpoints
The time point that the participant agrees to swap from liquid to tablet formulation of pentoxifylline and of vitamin E Patient's self-reported preference for tablet or liquid
The presence and number of side effects using the standard adverse event reporting
Number of participants consented, as a proportion of the number of patients eligible and invited
Number of participants randomised, as a proportion of the number of patients consented
Number of participants who attend their month 6 post randomisation visit (visit 4), as a proportion of the number of patients randomised Number of patients recruited
Number of visits attended Number of phone calls answered
Sustained and elevated levels of Vitamin E levels (higher than natural variation / standard range) at month 3 post randomisation and month 6 post randomisation in comparison to participant's baseline, through blood test for Vitamin E and recording levels of Vitamin E present.

Participants self-reported adherence (number of doses missed)
Number of questionnaires completed by participants

18.2 Secondary end points – clinical outcomes

Secondary endpoints
Proportion of patients with osteoradionecrosis at month 6 post randomisation
Difference in mouth opening measurements from baseline to month 6 post randomisation
Difference in swallowing scores from baseline to month 6 post randomisation
Difference in quality of life scores from baseline to month 6 post randomisation

19. Statistical Methods

The analyses were primarily descriptive in nature in line with the objectives of this feasibility study. All estimates of study endpoints are presented with 95% confidence intervals. No tests for significant differences between treatment groups were performed.

Baseline data are presented as means (SD), medians (IQR) and frequencies (%) as appropriate.

Recruitment: The number of patients who agree to participate is reported as a percentage of the total number invited, with 95% confidence interval.

Retention: The number of patients who attend their month 6 visit is reported as a proportion of the total number recruited, with 95% confidence interval.

Adherence: The number of patients who adhere to the Vitamin E study medication, as confirmed by blood test, is reported as a proportion of the total number recruited, with 95% confidence interval (treatment arm only).

Patient's preference for medication formulation: The time between starting treatment and moving from liquid to tablet formulation is recorded for each patient, and reported as mean (SD) or median (IQR) and range (treatment arm only).

Side effects: The tolerance and safety of treatment was examined by tabulating adverse drug reactions for the treatment group; this included all gastric irritation events which were recorded as a separate category.

Secondary endpoints: The proportion of participants with fibrosis related events (trismus, dysphagia, ORN) and significant change in quality of life by 6 months was calculated by treatment arm, along with the mean score (SD) or number (%) of all clinical assessments.

Every effort was made to obtain all follow up data for all participants randomised including those that have stopped treatment. Missing data in questionnaires and outcome data was summarised by treatment arm. Participants with missing outcome data were investigated by comparing baseline

characteristics (using descriptive comparisons) with participants who have complete follow-up measurements.

20. Changes in the Trial Plan

Major changes to the trial protocol included:

A change in the inclusion criteria was made to widen the patient pool and target more patients who had risk of osteoradionecrosis. The criteria were changed to include all oral cavity cancers, rather than restricting to the floor of mouth and tongue.

The timing of randomisation was changed following patient feedback. Originally patients were to be randomised and start IMP the day after completion of radiotherapy. Patients found it difficult to start on the trial when recovering from treatment. A window of 3 to 5 months post radiotherapy treatment was added to the protocol to allow for some time to heal and rest from hospital visits.

Other changes were made to include randomisation over the phone to remove one of the visits to the hospital and to allow for a 7-day window to start treatment after randomisation.

The randomisation window was changed again to 3 to 9 months post completion of radiotherapy. Patients were falling out of the randomisation window due to changes implemented in standard care after COVID. More patients required scans to ensure that they were cancer-free, and the timing of these scans were pushing participants out of the randomisation window. The extension of the window was to allow for this additional clinical step. Unfortunately, this amendment was approved too late to have an impact on our participants as we were approaching the end of the study.

20.1 Protocol Deviations

No serious breaches or deviations occurred during the trial.

21. Summary – Conclusions

21.1 Demographic data

The following tables summarise the demographics of the study population:

Table 4: Number of participants included in the PenVe

Number of Participants			
Age (years)	**Male**	**Female**	**Total**
Pre-term new-born infants (<37 weeks)	0	0	0
New-borns (0-27 days)	0	0	0

Number of Participants			
Age (years)	**Male**	**Female**	**Total**
Infants and toddlers (28 days – 23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	18	4	22
Elderly (≥65 years)	6	1	7
Total	**24**	**5**	**29**

Table 5: Demographic data for all patients (safety population)

	Control (N=7)	**Pentoxifylline & Vitamin E (N=22)**	**Total (N=29)**
Age (years)			
Mean (SD)	56.9 (6.64)	59.3 (8.60)	58.7 (8.12)
Median	55.0	60.3	60.1
Min, Max	50.8, 68.8	40.6, 74.2	40.6, 74.2
Sex n (%)			
Male	6 (85.7%)	18 (81.8%)	24 (82.8%)
Female	1 (14.3%)	4 (18.2%)	5 (17.2%)
Ethnicity n (%)			
White	6 (85.7%)	18 (81.8%)	24 (82.8%)
Asian	0 (0%)	1 (4.5%)	1 (3.4%)
Black	0 (0%)	1 (4.5%)	1 (3.4%)
Mixed	0 (0%)	0 (0%)	0 (0%)
Other	1 (14.3%)	2 (9.1%)	3 (10.3%)
Missing	0 (0%)	0 (0%)	0 (0%)
Smoking Status Prior to Cancer Diagnosis n (%)			
Current smoker	1 (14.3%)	2 (9.1%)	3 (10.3%)
Ex-smoker	4 (57.1%)	15 (68.2%)	19 (65.5%)
Never smoked	2 (28.6%)	5 (22.7%)	7 (24.1%)
Missing	0 (0%)	0 (0%)	0 (0%)
Type of Head and Neck Cancer n (%)			

	Control (N=7)	Pentoxifylline & Vitamin E (N=22)	Total (N=29)
Oropharynx (Tonsil, Base of Tongue)	4 (57.1%)	14 (63.6%)	18 (62.1%)
Nasopharynx	2 (28.6%)	1 (4.5%)	3 (10.3%)
Oral cavity	0 (0%)	3 (13.6%)	3 (10.3%)
Maxillary sinus	0 (0%)	1 (4.5%)	1 (3.4%)
Salivary glands	1 (14.3%)	2 (9.1%)	3 (10.3%)
Unknown primary of the neck	0 (0%)	0 (0%)	0 (0%)
Hypopharynx	0 (0%)	1 (4.5%)	1 (3.4%)
Not applicable	0 (0%)	0 (0%)	0 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)
Oncology Treatment n (%)			
Radiotherapy	0 (0%)	1 (4.5%)	1 (3.4%)
Radiotherapy and chemotherapy	6 (85.7%)	16 (72.7%)	22 (75.9%)
Radiotherapy and surgery	1 (14.3%)	3 (13.6%)	4 (13.8%)
Radiotherapy and chemotherapy and surgery	0 (0%)	2 (9.1%)	2 (6.9%)
Not applicable	0 (0%)	0 (0%)	0 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)
Note: N = number of patients in the treatment group analysis set, n = Number of subjects in the specified category with non-missing values.			
Abbreviation: SD = Standard Deviation.			

Table 6: Baseline characteristics of the per protocol population Frequency (%) is displayed unless otherwise specified.

	No IMP (N=10)	Pentoxifylline & Vitamin E (N=19)
Age (years)		
Mean (SD)	58.21 (10.27)	63.6 (5.54)
Median	60.35	63.0
Min, Max	40, 74.2	54.0, 78.1
Sex n (%)		
Male	7 (70.0%)	17 (89.5%)
Female	3 (30.0%)	2 (10.5%)
Ethnicity n (%)		
White	9 (90.0%)	15 (78.9%)
Asian	0 (0%)	1 (5.3%)
Black	0 (0%)	1 (5.3%)
Mixed	0 (0%)	0 (0%)
Other	1 (10.0%)	2 (10.5%)
Missing	0 (0%)	0 (0%)

21.2 Primary outcome

Primary Objectives

1. To assess patient's preference for pentoxifylline formulation and vitamin E (tocopherol) formulation, in a tablet vs liquid format (Intervention group only)
2. To assess patient's subsequent side effects related to the pentoxifylline and vitamin E (Intervention group only) (see section 21.3 Safety Measures)
3. To assess the recruitment into the trial
4. To assess retention of the participants in the trial
5. To assess the participation in the trial (a) follow up visits and (b) phone calls
6. To assess patient adherence to pentoxifylline and Vitamin E (Intervention group only)
7. To assess the acceptability to participants of the outcome measurement tools

Table 7: Primary outcome 1: Patient's preference for pentoxifylline formulation and vitamin E (tocopherol) formulation, in a tablet vs liquid format (Intent-to-treat population)

	Control (N=7)	Pentoxifylline & Vitamin E (N=22)	Total (N=29)
Requested formulation change for Pentoxifylline or Vitamin E n (%)			
Yes	0 (0%)	0 (0%)	0 (0%)
No, never requested to change formulation during trial	0 (0%)	22 (100%)	22 (75.9%)
No, participant is not in intervention arm	5 (71.4%)	0 (0%)	5 (17.2%)
Not applicable	2 (28.6%)	0 (0%)	2 (6.9%)
Missing	0 (0%)	0 (0%)	0 (0%)
Note: n = Number of subjects in the specified category with non-missing values			

Table 8: Primary Outcomes 3 and 4: Assessment of recruitment and retention in the trial (Intent-to-treat population)

	Total (N=54)
Number of Patients Consented n (%)	54 (100%)

	Total (N=54)
Number of Eligible Patients n (%)	53 (98.1%)
Number of Patients Randomised n (%)	29 (53.7%)
Completers of the Study (a) n (%)	22 (40.7%)
Note: N = number of patients consented, n = Number of subjects in the specified category with non-missing values. (a) Completers for study are defined as patients who attended their 6-month post randomisation assessment>.	

Table 9: Primary Outcome 5a: Participation in the trial follow-up visits (Intent-to-treat population)

	Control (N=7)	Pentoxifylline & Vitamin E (N=22)	Total (N=29)
Visit 1			
Absent	0 (0%)	0 (0%)	0 (0%)
Present	7 (100%)	22 (100%)	29 (100%)
Visit 2			
Absent	0 (0%)	0 (0%)	0 (0%)
Present	7 (100%)	22 (100%)	29 (100%)
Visit 3			
Absent	0 (0%)	0 (0%)	0 (0%)
Present	7 (100%)	22 (100%)	29 (100%)
Visit 4			
Absent	1 (14.3%)	1 (4.5%)	2 (6.9%)
Present	6 (85.7%)	21 (95.5%)	27 (93.1%)
Visit 5			
Absent	1 (14.3%)	3 (13.6%)	4 (13.8%)
Present	6 (85.7%)	19 (86.4%)	25 (86.2%)
Visit 6			
Absent	0 (0%)	0 (0%)	0 (0%)
Present	7 (100%)	22 (100%)	29 (100%)
Note: N = Number of patients in the treatment group analysis set, n = Number of subjects in the specified category with non-missing values			

Table 10: Primary Outcome 5b: Participation in trial follow-up visits (Intent-to-treat population)

	Pentoxifylline & Vitamin E (N=22)
Day 1	
Study team contacted participant - Successful	19 (86.4%)
Study team contacted participant - Not successful	0 (0%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	3 (13.6%)
Day 2	
Study team contacted participant - Successful	18 (81.8%)
Study team contacted participant - Not successful	1 (4.5%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	3 (13.6%)
Day 3	
Study team contacted participant - Successful	19 (86.4%)
Study team contacted participant - Not successful	0 (0%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	3 (13.6%)
Day 4	
Study team contacted participant - Successful	19 (86.4%)
Study team contacted participant - Not successful	0 (0%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	3 (13.6%)
Day 5	
Study team contacted participant - Successful	19 (86.4%)
Study team contacted participant - Not successful	0 (0%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	3 (13.6%)
Day 6	
Study team contacted participant - Successful	17 (77.3%)
Study team contacted participant - Not successful	2 (9.1%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	3 (13.6%)
Day 7	

	Pentoxifylline & Vitamin E (N=22)
Study team contacted participant - Successful	19 (86.4%)
Study team contacted participant - Not successful	0 (0%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	3 (13.6%)
Day 8	
Study team contacted participant - Successful	18 (81.8%)
Study team contacted participant - Not successful	1 (4.5%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	3 (13.6%)
Day 9	
Study team contacted participant - Successful	17 (77.3%)
Study team contacted participant - Not successful	2 (9.1%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	3 (13.6%)
Day 10	
Study team contacted participant - Successful	19 (86.4%)
Study team contacted participant - Not successful	0 (0%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	3 (13.6%)
Day 11	
Study team contacted participant - Successful	17 (77.3%)
Study team contacted participant - Not successful	1 (4.5%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	4 (18.2%)
Day 12	
Study team contacted participant - Successful	16 (72.7%)
Study team contacted participant - Not successful	2 (9.1%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	4 (18.2%)
Day 13	
Study team contacted participant - Successful	17 (77.3%)
Study team contacted participant - Not successful	1 (4.5%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)

	Pentoxifylline & Vitamin E (N=22)
Missing	4 (18.2%)
Day 14	
Study team contacted participant - Successful	17 (77.3%)
Study team contacted participant - Not successful	1 (4.5%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	4 (18.2%)
Week 5	
Study team contacted participant - Successful	15 (68.2%)
Study team contacted participant - Not successful	3 (13.6%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	4 (18.2%)
Week 8	
Study team contacted participant - Successful	14 (63.6%)
Study team contacted participant - Not successful	2 (9.1%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	6 (27.3%)
Week 11	
Study team contacted participant - Successful	14 (63.6%)
Study team contacted participant - Not successful	2 (9.1%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	6 (27.3%)
Week 14	
Study team contacted participant - Successful	11 (50.0%)
Study team contacted participant - Not successful	5 (22.7%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	6 (27.3%)
Week 17	
Study team contacted participant - Successful	10 (45.5%)
Study team contacted participant - Not successful	3 (13.6%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	9 (40.9%)
Week 20	
Study team contacted participant - Successful	10 (45.5%)
Study team contacted participant - Not successful	3 (13.6%)

	Pentoxifylline & Vitamin E (N=22)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	9 (40.9%)
Week 23	
Study team contacted participant - Successful	9 (40.9%)
Study team contacted participant - Not successful	2 (9.1%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	11 (50.0%)
Week 26	
Study team contacted participant - Successful	5 (22.7%)
Study team contacted participant - Not successful	2 (9.1%)
Participant contacted study team	0 (0%)
Not applicable	0 (0%)
Missing	15 (68.2%)
Note: N = Number of patients in the treatment group analysis set, n = Number of subjects in the specified category with non-missing values	

Table 11: Primary Outcome 6: Patient adherence as measured by blood vitamin E levels at Baseline, Month 3 and Month 6 time points (Intent-to-Treat Population)

	Control (N=7)	Pentoxifylline & Vitamin E (N=22)	Total (N=29)
Baseline			
N	7	21	28
Mean (SD)	29.6 (7.34)	35.2 (10.6)	33.8 (10.1)
Median	26.9	34.2	32.4
Min, Max	22.2, 43.8	16.0, 59.3	16.0, 59.3
Missing	0 (0%)	1 (4.5%)	1 (3.4%)
Month 3			
N	6	16	22
Mean (SD)	31.8 (5.36)	91.8 (184)	75.4 (158)
Median	31.8	45.4	38.6
Min, Max	22.8, 38.1	26.3, 778	22.8, 778
Missing	1 (14.3%)	6 (27.3%)	7 (24.1%)
Month 6			
N	5	15	20
Mean (SD)	31.6 (8.41)	55.2 (22.3)	49.3 (22.1)
Median	33.6	46.2	42.7
Min, Max	22.1, 43.1	27.0, 91.5	22.1, 91.5
Missing	2 (28.6%)	7 (31.8%)	9 (31.0%)

	Control (N=7)	Pentoxifylline & Vitamin E (N=22)	Total (N=29)
Note: N = Number of patients in the treatment group analysis set, n = Number of subjects in the specified category with non-missing values			

Table 12: Primary Outcome 6: Patient adherence to IMP measured by self-report (only intervention arm of Intent-to-Treat Population)

	Pentoxifylline & Vitamin E (N=22)
Number of missed Vitamin E doses n (%)	
N	10.0
Mean (SD)	0.455 (0.963)
Min, Max	0, 3.00
Number of missed Pentoxifylline doses n (%)	
N	25.0
Mean (SD)	1.14 (1.81)
Min, Max	0, 6.00
Note: N = number of patients in the treatment group analysis set, n = Number of subjects in the specified category with non-missing values.	
Number of missed doses are reported whilst the patient is enrolled in the study. If a patient discontinued, they are not deemed to have missed a dose post discontinuation	

Table 13: Primary Outcome 7: Acceptability of questionnaires as measures by the number (%) of Questionnaires Completed by Participants by Treatment (Intent-to-Treat Population)

	Baseline		Month 3		Month 6	
	Control (N=7)	Pentoxifylline & Vitamin E (N=22)	Control (N=7)	Pentoxifylline & Vitamin E (N=22)	Control (N=7)	Pentoxifylline & Vitamin E (N=22)
University of Washington Quality of Life Questionnaire (UW-QOL) n (%)						
Incomplete	2 (28.6%)	4 (18.2%)	2 (28.6%)	6 (27.3%)	2 (28.6%)	10 (45.5%)
Complete	5 (71.4%)	18 (81.8%)	5 (71.4%)	16 (72.7%)	5 (71.4%)	12 (54.5%)
Sydney Swallow Questionnaire (SSQ) n (%)						
Incomplete	0 (0%)	2 (9.1%)	1 (14.3%)	9 (40.9%)	1 (14.3%)	8 (36.4%)
Complete	7(100%)	20 (90.9%)	6 (85.7%)	13 (59.1%)	6 (85.7%)	14 (63.6%)

Note: N = Number of patients randomised in the treatment group analysis set, n = Number of subjects in the specified category with non-missing values.

21.3 Safety results

Table 14: Summary of adverse events in the PenVe trial

Adverse Events	Treatment Arm (n=22)	Control arm (n = 7)	Total (n = 29)
Total Number of AEs per Study Arm	62	1	63
Subjects affected by non-serious adverse events:	11	1	12
Total number of SAEs	1	0	1
Total number of SARs	0	0	0
Total number of SUSARs	0	0	0

Table 15: Listing of Adverse Events for all participants in the PenVe trial

System Organ Class	Preferred Term	Number of Subjects Experiencing the AE who took the IMP (22 participants)	Total Number of Occurrences of the AE in Active Arm	Number of Subjects Experiencing the AE in the control arm (7 participants)	Total Number of Occurrences of the AE in control arm
Blood and lymphatic system disorders	NA	0	0	0	0
Cardiac disorders	Atrial flutter	1/22 (4.5%)	1	0	0
Congenital, familial and genetic disorders	NA	0	0	0	0
Ear and labyrinth disorders	NA	0	0	0	0
Eye Disorders	NA	0	0	0	0
Gastrointestinal disorders	Gastric Irritation	3/22 (13.6%)	4	0	0
	Vomiting	1/22 (4.5%)	10	0	0
	Constipation	1/22 (4.5%)	1	0	0
	Abdominal pain	2/22 (9.1%)	2	0	0
	Diarrhoea	2/22 (9.1%)	2	0	0
	Nausea	1/22 (4.5%)	1	0	0
	Oesophagitis	1/22 (4.5%)	1	0	0
	Abdominal noises	1/22 (4.5%)	2	0	0
General disorders and administration site conditions	Muscle Pain	1/22 (4.5%)	1	0	0
	Dizziness	3/22 (13.6%)	6	0	0
	Dry mouth	3/22 (13.6%)	3	0	0
	Pyrexia	1/22 (4.5%)	1	0	0
	Saliva decreased	0	0	1/22 (4.5%)	1
	NG tube fell out	1/22 (4.5%)	1	0	0
	Purulent phlegm	1/22 (4.5%)	1	0	0
	Tremor	1/22 (4.5%)	1	0	0
	Dyspnoea	1/22 (4.5%)	1	0	0
	Pain in jaw	1/22 (4.5%)	1	0	0
	Tongue pain	1/22 (4.5%)	1	0	0

	Mouth ulceration	1/22 (4.5%)	2	0	0
	Headache	3/22 (13.6%)	6	0	0
	Migraine	1/22 (4.5%)	1	0	0
	Paraesthesia (leg)	1/22 (4.5%)	1	0	0
	Dysphagia	1/22 (4.5%)	1	0	0
Hepatobiliary disorders	NA	0	0	0	0
Immune system disorders	NA	0	0	0	0
Infections and infestations	NA	0	0	0	0
Injury, poisoning and procedural complications	NA	0	0	0	0
Investigations	NA	0	0	0	0
Metabolism and nutritional disorders	Hypothyroidism	1/22 (4.5%)	1	0	0
Musculoskeletal and connective tissue disorders	NA	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Recurrent head and neck cancer	1/22 (4.5%)	1	0	0
Nervous system disorders	NA	0	0	0	0
Pregnancy, puerperium and perinatal conditions	NA	0	0	0	0
Product issues	NA	0	0	0	0
Psychiatric disorders	Depression	1/22 (4.5%)	1	0	0
Renal and urinary disorders	NA	0	0	0	0
Reproductive system and breast disorders	NA	0	0	0	0
Respiratory, thoracic and mediastinal disorders	Pneumonia	1/22 (4.5%)	1	0	0
	Nasopharyngitis	1/22 (4.5%)	1	0	0
	Cough	1/22 (4.5%)	1	0	0
	Dry throat	1/22 (4.5%)	1	0	0
	Throat irritation	1/22 (4.5%)	1	0	0
	COVID	1/22 (4.5%)	1	0	0

Skin and subcutaneous tissue disorders	NA	0	0	0	0
Social circumstances	*NA*	0	0	0	0
Surgical and medical procedures	Radiography to replace NG tube	1/22 (4.5%)	1	0	0
Vascular disorders	*NA*	0	0	0	0

Table 16: Listing of Serious Adverse Events for all patients

Serious Adverse Events	**Treatment Arm**	**Control Arm**
Total Number of SAEs per Study Arm	1	0
Total number of all cause deaths per Study Arm	0	0
Total number of deaths resulting from adverse events per Study Arm	0	0

Within the per protocol population (n= 29), a total of 63 AEs, including 1 SAE, were identified as treatment-emergent and included in the safety analysis. Summary tables for AEs in the per protocol population and SAEs are presented in the appendix of this synopsis.

Overall, 12 patients (41.4%) patients experienced at least one AE. The proportion that experienced at least one SAE was 3.4% (n=1).

Incidence of adverse drug reactions (ADRs): 11 / 63 AEs (17.5%) were assessed as related to at least one study drug and 4 / 29 patients (13.8 %) experienced an ADR.

There were 0 Serious Adverse Reactions (SARs), 0 unexpected SARs and 0 SUSARs.

22. Conclusion

The data achieved from the feasibility study is exactly what was required and in line with our primary outcomes. This valuable information will now assist hugely in formulating trial calculations for the future larger trial and for the various trial and participant challenges to be addressed.

23. Date of Report

This is version 1.0 of the Clinical Study Report synopsis, dated 05/08/2024.

APPENDICES

i) Summary of treatment-emergent AEs in the per protocol population

For per protocol allocation, participants remained in the IMP arm if they took at least one dose of either pentoxifylline or vitamin E.

System Organ Class	**Preferred Term**	**Number of Subjects Experiencing the AE who took the IMP** (n = 19)	**Total Number of Occurrences of the AE in Active Arm**	**Number of Subjects Experiencing the AE who did not take the IMP (from control arm and from IMP arm)** (n = 10)	**Total Number of Occurrences of the AE in control arm**
Blood and lymphatic system disorders	NA	0	0	0	0
Cardiac disorders	Atrial flutter	1/19 (5.3%)	1	0	0
Congenital, familial and genetic disorders	NA	0	0	0	0
Ear and labyrinth disorders	NA	0	0	0	0
Eye Disorders	NA	0	0	0	0
Gastrointestinal disorders	Gastric Irritation	3/19 (15.8%)	4	0	0
	Vomiting	1/19 (5.3%)	10	0	0
	Constipation	1/19 (5.3%)	1	0	0
	Abdominal pain	2/19 (10.5%)	2	0	0
	Diarrhoea	2/19 (10.5%)	2	0	0
	Nausea	1/19 (5.3%)	1	0	0
	Oesophagitis	1/19 (5.3%)	1	0	0
	Abdominal noises	1/19 (5.3%)	2	0	0

General disorders and administration site conditions	Muscle Pain	1/19 (5.3%)	1	0	0
	Dizziness	3/19 (15.8%)	6	0	0
	Dry mouth	3/19 (15.8%)	3	0	0
	Pyrexia	1/19 (5.3%)	1	0	0
	Saliva decreased	0	0	1/10 (10.0%)	1
	NG tube fell out	1/19 (5.3%)	1	0	0
	Purulent phlegm	1/19 (5.3%)	1	0	0
	Tremor	1/19 (5.3%)	1	0	0
	Dyspnoea	1/19 (5.3%)	1	0	0
	Pain in jaw	1/19 (5.3%)	1	0	0
	Tongue pain	1/19 (5.3%)	1	0	0
	Mouth ulceration	1/19 (5.3%)	2	0	0
	Headache	3/19 (15.8%)	6	0	0
	Migraine	1/19 (5.3%)	1	0	0
	Paraesthesia (leg)	1/19 (5.3%)	1	0	0
	Dysphagia	1/19 (5.3%)	1	0	0
Hepatobiliary disorders	NA	0	0	0	0
Immune system disorders	NA	0	0	0	0
Infections and infestations	NA	0	0	0	0
Injury, poisoning and procedural complications	NA	0	0	0	0
Investigations	NA	0	0	0	0
Metabolism and nutritional disorders	Hypothyroidism	1/19 (5.3%)	1	0	0
Musculoskeletal and connective tissue disorders	NA	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Recurrent head and neck cancer	1/19 (5.3%)	1	0	0
Nervous system disorders	NA	0	0	0	0
Pregnancy, puerperium and perinatal conditions	NA	0	0	0	0
Product issues	NA	0	0	0	0

Psychiatric disorders	Depression	1/19 (5.3%)	1	0	0
Renal and urinary disorders	NA	0	0	0	0
Reproductive system and breast disorders	NA	0	0	0	0
Respiratory, thoracic and mediastinal disorders	Pneumonia	1/19 (5.3%)	1	0	0
	Nasopharyngitis	1/19 (5.3%)	1	0	0
	Cough	1/19 (5.3%)	1	0	0
	Dry throat	1/19 (5.3%)	1	0	0
	Throat irritation	1/19 (5.3%)	1	0	0
	COVID	1/19 (5.3%)	1	0	0
Skin and subcutaneous tissue disorders	NA	0	0	0	0
Social circumstances	NA	0	0	0	0
Surgical and medical procedures	Radiography to replace NG tube	1/19 (5.3%)	1	0	0
Vascular disorders	NA	0	0	0	0

ii) Summary of treatment-emergent ARs in the per protocol population

System Organ Class	**Preferred Term**	**Number of Subjects Experiencing the AE who took the IMP** (n=19)	**Total Number of Occurrences of the AE in Active Arm**	**Number of Subjects Experiencing the AE who did not take the IMP (control arm and from IMP arm)** (n = 10)	**Total Number of Occurrences of the AE in control arm**
Gastrointestinal disorders	Gastric Irritation	3/19 (5.3%)	4	0	0
	Vomiting	1/19 (5.3%)	3	0	0
	Diarrhoea	1/19 (5.3%)	1	0	0
	Abdominal noises	1/19 (5.3%)	1	0	0
General disorders and administration	Tremor	1/19 (5.3%)	1	0	0

site conditions					
Respiratory, thoracic and mediastinal disorders	Throat irritation	1/19 (5.3%)	1	0	0

iii) Summary of treatment-emergent SAEs in the study population

System Organ Class	Preferred Term	Number of Subjects Experiencing the AE who took the IMP (n = 22)	Total Number of Occurrences of the AE in Active Arm	Number of Subjects Experiencing the AE in the control arm (n = 7)	Total Number of Occurrences of the AE in control arm
General disorders and administration site conditions	Pyrexia	1/22 (4.5%)	1	0	0

iv) Summary of treatment-emergent SARs in the study population

None to report.