



Clinical trial results:

COAST - Cisplatin Ototoxicity attenuated by Aspirin Trial

A randomised, Phase II, double-blind, placebo-controlled, two arm Trial to establish whether Aspirin can reduce hearing loss/ototoxicity for patients receiving Cisplatin chemotherapy.

Summary

EudraCT number	2012-001509-25
Trial protocol	GB
Global end of trial date	01 February 2016

Results information

Result version number	v1 (current)
This version publication date	19 July 2017
First version publication date	19 July 2017

Trial information

Trial identification

Sponsor protocol code	RHMCAN0860
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Additional study identifiers

ISRCTN number	ISRCTN83689269
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Southampton NHS Foundation Trust
Sponsor organisation address	Southampton General Hospital, Tremona Road, Southampton, United Kingdom, SO16 6YD
Public contact	Karen Martin, Senior Trials Manager, Southampton Clinical Trials Unit, 0044 2381205154, K.S.Martin@soton.ac.uk
Scientific contact	Karen Martin, Senior Trials Manager, Southampton Clinical Trials Unit, 0044 2381205154, K.S.Martin@soton.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 September 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish whether aspirin can reduce hearing loss/ototoxicity for patients receiving cisplatin based chemotherapy.

Secondary objectives:

1. To determine whether it is feasible to conduct a Phase III randomised controlled Trial of aspirin for the same patient population.
2. To quantify the extent of hearing loss in patients receiving cisplatin via the use of otoacoustic emissions (OAE).
3. To determine whether patients are able to tolerate short-term, large doses of enteric-coated aspirin taken with omeprazole without significant side-effects and with no loss of cisplatin dose-intensity

Protection of trial subjects:

The protocol stated: It may be necessary to prescribe a gastro protectant as a supportive measure during the course of the Trial. In this situation the patient should be instructed not to take the omeprazole or omeprazole-placebo from the Trial medication patient pack and should continue with the alternative gastro-protectant at the discretion of the PI or delegated responsible clinician.

There was also provision for dose modification due to toxicity:

Gastrointestinal bleeding:

Grade 1 toxicity: No intervention required.

Grade 2 toxicity at first occurrence: Stop Trial drug until toxicity resolved to grade 1 or 0.

Grade 2 toxicity at second occurrence: Stop Trial drug permanently.

Grade 3 and 4 toxicity at first occurrence: Stop Trial drug permanently.

No dose reductions of the Trial drug are allowed. Appropriate management of any bleeding event should be carried out.

Non bleeding toxicities (thought by the PI or designee to be related to the Trial drug)

Grade 1 toxicity: No intervention required, continue Trial drug

Grade 2 toxicity at first occurrence: Stop Trial drug until toxicity resolved to grade 1 or 0.

Grade 2 toxicity at second occurrence: Stop Trial drug permanently.

Grade 3 and 4 toxicity at first occurrence: Stop Trial drug permanently.

Interaction with other drugs:

A wash out period is not required for any aspirin containing medications taken prior to randomisation. Patients will be advised that additional aspirin and NSAIDs should not be taken during the treatment phase of the Trial. Patients on oral anti-coagulants such as warfarin are excluded from the trial. Details of any aspirin containing medications taken in the three weeks before randomisation should be recorded in the concomitant medication section of the CRF. Patients on therapeutic aspirin at baseline (dose of <75mg) will be eligible for Trial entry at the discretion of the PI providing the dose will not increase during the trial.

Background therapy:

Patients will receive up to 6 cycles of cisplatin chemotherapy according to tumour site, response and toxicity.

Evidence for comparator:

This is a randomised, Phase II, double-blind, placebo-controlled, two arm feasibility Trial*. Patients will be randomised into either Arm 1 or Arm 2 of the Trial. Arm 1 patients will receive cisplatin with aspirin and omeprazole. Arm 2 patients will receive cisplatin with aspirin placebo and omeprazole placebo. This

Trial design, as specified by Rubinstein et al. is not intended to replace a subsequent Phase III Trial but rather indicate if there is a reasonable probability of efficacy and to give a clearer idea of the magnitude of effect in order to better estimate the sample size for a Phase III Trial*.

*Rubinstein LV., Korn EL., Freidlin B., Hunsberger S., Ivy SP and Smith MA. Design issues of randomized phase II trials and a proposal for phase II screening trials. J Clin Oncol. 2005 Oct 1;23 (28):7199-206

Actual start date of recruitment	01 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 94
Worldwide total number of subjects	94
EEA total number of subjects	94

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	61
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

94 patients were recruited from Mar 2013 to Jul 2015 from 8 UK cancer centers. Patients were stratified at randomisation by planned cisplatin-dose using these categories: (i) $\geq 200\text{mg/m}^2$ but $< 300\text{mg/m}^2$; (ii) $\geq 300\text{mg/m}^2$ but $< 400\text{mg/m}^2$; (iii) $\geq 400\text{mg/m}^2$.

Patients were eligible if they were 18 yrs or over and deemed suitable for cisplatin chemotherapy dose

Pre-assignment

Screening details:

The SCTU will be contacted in order to register a patient and obtain a screening identification number for the trial. Once eligibility for the study is confirmed randomisation will be via an independent web-based system (TENALEA) and will be stratified by planned cisplatin-dose.

Pre-assignment period milestones

Number of subjects started	439 ^[1]
Number of subjects completed	94

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 42
Reason: Number of subjects	Not eligible - Patient to have split dose regimen: 6
Reason: Number of subjects	Not eligible - Patient has Aspirin contradictions: 9
Reason: Number of subjects	Not eligible - Has Nasopharyngeal Carcinoma: 9
Reason: Number of subjects	Not eligible - Pre-existing hearing loss: 8
Reason: Number of subjects	Not eligible - Patient not fit for chemotherapy: 28
Reason: Number of subjects	Not eligible - Due on NSAIDs during treatment: 1
Reason: Number of subjects	Not eligible - Patient receiving Aspirin $> 75\text{mg/day}$: 3
Reason: Number of subjects	Patient choice - didn't want to take part in study: 50
Reason: Number of subjects	Other reason - not specified: 46
Reason: Number of subjects	Not eligible - Other reason: 61
Reason: Number of subjects	Patient choice - Other reason: 82

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 345 subjects were actively screened and for the reasons presented in the table below, 251 did not complete the pre-assignment period.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Patients are randomised via the ALEA system to a treatment arm by means of a unique three-digit patient pack number. For subsequent cycles, a new patient pack number is requested via the ALEA system, which corresponds to the patient's randomised treatment arm. Only CTU statisticians were unblinded during the trial. Emergency unblinding for AEs were through an unblinding service at ESMS.

Arms

Are arms mutually exclusive?	Yes
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Arm title	Arm 1: Aspirin and Omeprazole
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Arm description:

Arm 1- Patients will be administered 975mg aspirin (enteric coated) three times daily, orally and 20mg omeprazole once daily, orally, for 4 days commencing the day before cisplatin administration. For patients receiving cisplatin chemotherapy on Days 1 and 2 of each cycle the treatment will be administered for a total of 5 days (commencing the day before each cisplatin treatment, and continuing for 4 days after).

Aspirin (A) and Omeprazole (O) Group

Each Cycle*

Day 1 – A + O

Day 2 – A + O + cisplatin

Day 3 – A+ O

Day 4 – A + O

The total number of cisplatin cycles varies with cancer site from up to 6 cycles

* Eligible Patients receiving cisplatin chemotherapy over a 2 day consecutive regimen will receive a total of 5 days IMP, commencing the day before starting treatment.

Arm type	Experimental
Investigational medicinal product name	aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A single batch of aspirin tablets will be manufactured into aspirin 975mg tablets. The aspirin tablet cores will be enteric coated.

The aspirin-matched placebo will be of the same appearance and size as aspirin tablets. The placebo tablets will also have the same enteric coating product as the active tablet.

The patient should take one tablet three times a day for the 4 or 5 day treatment period.

Patients on a 4 day regime should be instructed not to take IMP on day 5 and to return day 5 drug to the research nurse at their next visit (if applicable).

Investigational medicinal product name	omeprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

NuPharm will source omeprazole from a supplier and each 20mg dose will be removed from the packaging and over-encapsulated in one opaque gelatine capsule (size 0).

The omeprazole-matched placebo will be of the same size and shape as the omeprazole tablet. Each placebo tablet will be over-encapsulated in one opaque gelatine capsule (size 0).The patient should take 1 capsule a day for the 4 or 5 day treatment period.

Patients on a 4 day regime should be instructed not to take IMP on day 5 and to return day 5 drug to the research nurse at their next visit (if applicable).

Arm title	Arm 2: Placebo
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Arm description:

Arm 2- Patients will be administered aspirin matched placebo three times daily, orally, for 4 days and omeprazole matched placebo once daily, orally, for 4 days commencing the day before cisplatin administration. For patients receiving cisplatin chemotherapy on Days 1 and 2 of each cycle the aspirin and omeprazole matched placebos will be administered for a total of 5 days (commencing the day before each cisplatin treatment, and continuing for 4 days after).

Aspirin-placebo (AP) and Omeprazole-placebo (OP) Group

Each Cycle*

Day 1 – AP + OP

Day 2 – AP + OP + cisplatin

Day 3 – AP + OP

The total number of cisplatin cycles varies with cancer site from up to 6 cycles

* Eligible Patients receiving cisplatin chemotherapy over a 2 day consecutive regimen will receive a total of 5 days IMP, commencing the day before starting treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching aspirin placebo will be administered at a dose of 975mg three times daily orally for 4 days (commencing the day before each cisplatin treatment). Patients receiving cisplatin chemotherapy on days 1 and 2 of each cycle, matching aspirin placebo will be administered at a dose of 975mg three times daily orally for a total of 5 days (commencing the day before each cisplatin treatment)

Matching omeprazole placebo will be administered at a dose of 20mg, taken orally once daily for 4 or 5 days depending on the number of days of cisplatin chemotherapy per cycle.

Number of subjects in period 1	Arm 1: Aspirin and Omeprazole	Arm 2: Placebo
Started	45	49
Followed-up to Day 7 post-chemotherapy	42	42
Completed	32	34
Not completed	13	15
Adverse event, serious fatal	1	2
Consent withdrawn by subject	4	4
Physician decision	1	1
Adverse event, non-fatal	1	1
Incorrect randomisation	1	-
Lost to follow-up	4	6
Changed treatment post cycle 1	1	-
Developed recurrence disease, needed further trt	-	1

Baseline characteristics

Reporting groups

Reporting group title	Arm 1: Aspirin and Omeprazole
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Reporting group description:

Arm 1- Patients will be administered 975mg aspirin (enteric coated) three times daily, orally and 20mg omeprazole once daily, orally, for 4 days commencing the day before cisplatin administration. For patients receiving cisplatin chemotherapy on Days 1 and 2 of each cycle the treatment will be administered for a total of 5 days (commencing the day before each cisplatin treatment, and continuing for 4 days after).

Aspirin (A) and Omeprazole (O) Group

Each Cycle*

Day 1 – A + O

Day 2 – A + O + cisplatin

Day 3 – A+ O

Day 4 – A + O

The total number of cisplatin cycles varies with cancer site from up to 6 cycles

* Eligible Patients receiving cisplatin chemotherapy over a 2 day consecutive regimen will receive a total of 5 days IMP, commencing the day before starting treatment.

Reporting group title	Arm 2: Placebo
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Reporting group description:

Arm 2- Patients will be administered aspirin matched placebo three times daily, orally, for 4 days and omeprazole matched placebo once daily, orally, for 4 days commencing the day before cisplatin administration. For patients receiving cisplatin chemotherapy on Days 1 and 2 of each cycle the aspirin and omeprazole matched placebos will be administered for a total of 5 days (commencing the day before each cisplatin treatment, and continuing for 4 days after).

Aspirin-placebo (AP) and Omeprazole-placebo (OP) Group

Each Cycle*

Day 1 – AP + OP

Day 2 – AP + OP + cisplatin

Day 3 – AP + OP

Day 4 – AP + OP

The total number of cisplatin cycles varies with cancer site from up to 6 cycles

* Eligible Patients receiving cisplatin chemotherapy over a 2 day consecutive regimen will receive a total of 5 days IMP, commencing the day before starting treatment.

Reporting group values	Arm 1: Aspirin and Omeprazole	Arm 2: Placebo	Total
Number of subjects	45	49	94
Age categorical			
Units: Subjects			
Adults (18-64 years)	33	28	61
From 65-84 years	12	21	33
85 years and over	0	0	0
Age continuous			
Units: years			
median	56	62	
inter-quartile range (Q1-Q3)	52 to 65	55 to 66	-
Gender categorical			
Units: Subjects			
Female	9	13	22
Male	36	36	72

Tumour group			
Units: Subjects			
Bladder-carcinoma	9	15	24
Germ Cell	7	5	12
Head & Neck	21	14	35
Thoracic	8	14	22
Left Lung	0	1	1
PTA hearing test values in both ears - sum of 6kHz and 8kHz			
Pure tone audiogram (PTA) test at frequencies of 6 and 8kHz in both ears at baseline.			
Units: kHz			
arithmetic mean	166.1	161.6	
standard deviation	± 71.25	± 76.71	-

Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
This population includes all patients that were randomised regardless of treatment.	
Subject analysis set title	Per-protocol population
Subject analysis set type	Per protocol
Subject analysis set description:	
This population includes patients in the ITT population who have an IMP (aspirin or placebo) compliance of greater than to equal to 80% for each cycle of cisplatin chemotherapy. Also, the patient should not have any major protocol violations.	

Reporting group values	ITT population	Per-protocol population	
Number of subjects	94	53	
Age categorical			
Units: Subjects			
Adults (18-64 years)	61	36	
From 65-84 years	33	17	
85 years and over	0	0	
Age continuous			
Units: years			
median	60	60	
inter-quartile range (Q1-Q3)	52 to 66	54 to 66	
Gender categorical			
Units: Subjects			
Female			
Male			
Tumour group			
Units: Subjects			
Bladder-carcinoma			
Germ Cell			
Head & Neck			
Thoracic			
Left Lung			

PTA hearing test values in both ears - sum of 6kHz and 8kHz			
Pure tone audiogram (PTA) test at frequencies of 6 and 8kHz in both ears at baseline.			
Units: kHz			
arithmetic mean			
standard deviation	±	±	

End points

End points reporting groups

Reporting group title	Arm 1: Aspirin and Omeprazole
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Reporting group description:

Arm 1- Patients will be administered 975mg aspirin (enteric coated) three times daily, orally and 20mg omeprazole once daily, orally, for 4 days commencing the day before cisplatin administration. For patients receiving cisplatin chemotherapy on Days 1 and 2 of each cycle the treatment will be administered for a total of 5 days (commencing the day before each cisplatin treatment, and continuing for 4 days after).

Aspirin (A) and Omeprazole (O) Group

Each Cycle*

Day 1 – A + O

Day 2 – A + O + cisplatin

Day 3 – A+ O

Day 4 – A + O

The total number of cisplatin cycles varies with cancer site from up to 6 cycles

* Eligible Patients receiving cisplatin chemotherapy over a 2 day consecutive regimen will receive a total of 5 days IMP, commencing the day before starting treatment.

Reporting group title	Arm 2: Placebo
-----------------------	----------------

Reporting group description:

Arm 2- Patients will be administered aspirin matched placebo three times daily, orally, for 4 days and omeprazole matched placebo once daily, orally, for 4 days commencing the day before cisplatin administration. For patients receiving cisplatin chemotherapy on Days 1 and 2 of each cycle the aspirin and omeprazole matched placebos will be administered for a total of 5 days (commencing the day before each cisplatin treatment, and continuing for 4 days after).

Aspirin-placebo (AP) and Omeprazole-placebo (OP) Group

Each Cycle*

Day 1 – AP + OP

Day 2 – AP + OP + cisplatin

Day 3 – AP + OP

Day 4 – AP + OP

The total number of cisplatin cycles varies with cancer site from up to 6 cycles

* Eligible Patients receiving cisplatin chemotherapy over a 2 day consecutive regimen will receive a total of 5 days IMP, commencing the day before starting treatment.

Subject analysis set title	ITT population
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

This population includes all patients that were randomised regardless of treatment.

Subject analysis set title	Per-protocol population
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Subject analysis set type	Per protocol
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Subject analysis set description:

This population includes patients in the ITT population who have an IMP (aspirin or placebo) compliance of greater than to equal to 80% for each cycle of cisplatin chemotherapy. Also, the patient should not have any major protocol violations.

Primary: Total post-treatment hearing loss (first post-chemotherapy PTA test)

End point title	Total post-treatment hearing loss (first post-chemotherapy PTA test)
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End point description:

Total post treatment hearing loss = total post treatment hearing – total baseline hearing.

Where,

1 Total baseline hearing is the sum of PTA measurements at 6kHz and 8kHz in both ears prior to their first cisplatin dose.

2 Total post treatment hearing is the sum of PTA measurements at 6kHz and 8kHz in both ears from the first PTA test after their last cisplatin dose, where the first PTA test is due 7 days after last cisplatin dose.

End point type	Primary
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End point timeframe:

Difference is calculated using the first post-chemotherapy PTA hearing test (scheduled to be 7 days (+/- 3) after last cisplatin dose) and the corresponding baseline value.

End point values	Arm 1: Aspirin and Omeprazole	Arm 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39 ^[1]	40 ^[2]		
Units: kHz	39	40		

Notes:

[1] - The number of patients in arm 1 with both a baseline and one post-chemo PTA measurements.

[2] - The number of patients in arm 1 with both a baseline and one post-chemo PTA measurements.

Attachments (see zip file)	Assessment of normality/Assessment of normality - primary
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Statistical analyses

Statistical analysis title	Analysis of covariance
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Statistical analysis description:

ANCOVA model: Total post treatment hearing post-chemotherapy (the sum of PTA measurements at 6kHz and 8kHz in both ears at the first time point after their last cisplatin dose) = intercept + treatment arm + total hearing at baseline (the sum of PTA measurements at 6kHz and 8kHz in both ears prior to their first cisplatin dose) + randomisation stratification factor dose of cisplatin.

Comparison groups	Arm 2: Placebo v Arm 1: Aspirin and Omeprazole
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.233 ^[3]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	9.38
Confidence interval	
level	Other: 60 %
sides	2-sided
lower limit	-1.45
upper limit	20.22

Notes:

[3] - One-sided p-value

Primary: Total post-treatment hearing loss (first post-chemotherapy PTA test)

End point title	Total post-treatment hearing loss (first post-chemotherapy PTA test) ^[4]
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End point description:

Total post treatment hearing loss = total post treatment hearing – total baseline hearing.

Where,

1 Total baseline hearing is the sum of PTA measurements at 6kHz and 8kHz in both ears prior to their first cisplatin dose.

2 Total post treatment hearing is the sum of PTA measurements at 6kHz and 8kHz in both ears from the first PTA test after their last cisplatin dose, where the first PTA test is due 7 days after last cisplatin dose.

End point type	Primary
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End point timeframe:

Difference is calculated using the first post-chemotherapy PTA hearing test (scheduled to be 7 days (+/- 3) after last cisplatin dose) and the corresponding baseline value.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses have been specified for this primary end point. The Primary analysis was the ANCOVA model with post treatment hearing as the outcome, adjusted for the baseline hearing measure.

End point values	Arm 1: Aspirin and Omeprazole	Arm 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39 ^[5]	40 ^[6]		
Units: kHz				
arithmetic mean (standard deviation)	49 (± 61.41)	36 (± 50.85)		

Notes:

[5] - Number in arm 1 with both PTA measurements - baseline and one post-chemo

[6] - Number in arm 1 with both PTA measurements - baseline and one post-chemo

Statistical analyses

No statistical analyses for this end point

Secondary: Total post-treatment hearing loss (second post-chemotherapy PTA test)

End point title	Total post-treatment hearing loss (second post-chemotherapy PTA test)
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End point description:

Total post treatment hearing loss = total post treatment hearing – total baseline hearing.

Where,

1 Total baseline hearing is the sum of PTA measurements at 6kHz and 8kHz in both ears prior to their first cisplatin dose.

2 Total post treatment hearing is the sum of PTA measurements at 6kHz and 8kHz in both ears from the second PTA test after their last cisplatin dose, where the first PTA test is due 90 days after last cisplatin dose.

End point type	Secondary
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End point timeframe:

Difference is calculated using the first post-chemotherapy PTA hearing test (scheduled to be 90 days (+/- 7 days) after last cisplatin dose) and the corresponding baseline value.

End point values	Arm 1: Aspirin and Omeprazole	Arm 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27 ^[7]	30 ^[8]		
Units: kHz	27	30		

Notes:

[7] - Number in arm 1 with both PTA measures - at baseline and second post-chemo

[8] - Number in arm 2 with both PTA measurements - baseline and second post-chemo

Statistical analyses

Statistical analysis title	Analysis of covariance
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Statistical analysis description:

ANCOVA model: Total post treatment hearing post-chemotherapy (the sum of PTA measurements at 6kHz and 8kHz in both ears at the second time point after their last cisplatin dose) = intercept + treatment arm + total hearing at baseline (the sum of PTA measurements at 6kHz and 8kHz in both ears prior to their first cisplatin dose) + randomisation stratification factor dose of cisplatin.

Comparison groups	Arm 1: Aspirin and Omeprazole v Arm 2: Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044 [9]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	24.18
Confidence interval	
level	Other: 60 %
sides	2-sided
lower limit	12.36
upper limit	36.01

Notes:

[9] - One-sided p-value

Secondary: Total post-treatment hearing loss (second post-chemotherapy PTA test)

End point title	Total post-treatment hearing loss (second post-chemotherapy PTA test)
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End point description:

Total post treatment hearing loss = total post treatment hearing – total baseline hearing.

Where,

1 Total baseline hearing is the sum of PTA measurements at 6kHz and 8kHz in both ears prior to their first cisplatin dose.

2 Total post treatment hearing is the sum of PTA measurements at 6kHz and 8kHz in both ears from the second PTA test after their last cisplatin dose, where the second PTA test is due 90 days after last cisplatin dose.

End point type	Secondary
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End point timeframe:

Difference is calculated using the second post-chemotherapy PTA hearing test (scheduled to be 90 days (+/- 7) after last cisplatin dose) and the corresponding baseline value.

End point values	Arm 1: Aspirin and Omeprazole	Arm 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27 ^[10]	30 ^[11]		
Units: kHz				
arithmetic mean (standard deviation)	63.9 (± 52.59)	37.3 (± 49.94)		

Notes:

[10] - Number in arm 1 with the two PTA tests - one at baseline and second after chemo

[11] - Number in arm 2 with the two PTA tests - one at baseline and second after chemo

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The reporting requirement for SAEs affecting patients applies for all events occurring from date of informed consent up to 4 weeks after the last administration of trial drugs.

Adverse event reporting additional description:

At each contact with the patient, the investigator sought information on adverse events by specific questioning and, as appropriate, by examination. The clinical course of each event should be followed until resolution, stabilisation, or until it has been determined that the study treatment or participation is not the cause.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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Reporting groups

Reporting group title	Arm 1: Aspirin group
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Reporting group description: -

Reporting group title	Arm 2: Placebo group
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Reporting group description: -

Serious adverse events	Arm 1: Aspirin group	Arm 2: Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 45 (44.44%)	19 / 49 (38.78%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 45 (0.00%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight loss			
subjects affected / exposed	1 / 45 (2.22%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 45 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thromboembolic event			
subjects affected / exposed	0 / 45 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Stroke			
subjects affected / exposed	0 / 45 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders, other			
subjects affected / exposed	1 / 45 (2.22%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile neutropenia			
subjects affected / exposed	3 / 45 (6.67%)	4 / 49 (8.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	2 / 45 (4.44%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 45 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 45 (2.22%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 45 (2.22%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 45 (0.00%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 45 (4.44%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis oral			
subjects affected / exposed	2 / 45 (4.44%)	5 / 49 (10.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 45 (2.22%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral pain			
subjects affected / exposed	0 / 45 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 45 (4.44%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 45 (2.22%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Lung infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 45 (2.22%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 45 (4.44%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm 1: Aspirin group	Arm 2: Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 45 (88.89%)	47 / 49 (95.92%)	
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	1 / 45 (2.22%)	6 / 49 (12.24%)	
occurrences (all)	1	7	
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed occurrences (all)	14 / 45 (31.11%) 21	18 / 49 (36.73%) 44	
Fever subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	3 / 49 (6.12%) 4	
Pain subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 5	5 / 49 (10.20%) 5	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 5	6 / 49 (12.24%) 7	
Dyspnoea subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	5 / 49 (10.20%) 5	
Epistaxis subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 5	2 / 49 (4.08%) 2	
Respiratory, thoracic and mediastinal disorders, other subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4	3 / 49 (6.12%) 3	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	1 / 49 (2.04%) 1	
Insomnia subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	4 / 49 (8.16%) 5	
Investigations Neutrophil count decreased subjects affected / exposed occurrences (all)	8 / 45 (17.78%) 12	8 / 49 (16.33%) 14	
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 4	4 / 49 (8.16%) 4	
Weight loss			

subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	4 / 49 (8.16%) 4	
White blood cell decreased subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 6	5 / 49 (10.20%) 9	
Injury, poisoning and procedural complications Dermatitis radiation subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	0 / 49 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	6 / 49 (12.24%) 8	
Dysgeusia subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 8	7 / 49 (14.29%) 8	
Headache subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4	4 / 49 (8.16%) 8	
Lethargy subjects affected / exposed occurrences (all)	11 / 45 (24.44%) 15	15 / 49 (30.61%) 28	
Paresthesia subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	4 / 49 (8.16%) 4	
Peripheral motor neuropathy subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 5	8 / 49 (16.33%) 9	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	7 / 45 (15.56%) 15	4 / 49 (8.16%) 11	
Ear and labyrinth disorders Hearing impaired subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	3 / 49 (6.12%) 7	

Tinnitus			
subjects affected / exposed	12 / 45 (26.67%)	20 / 49 (40.82%)	
occurrences (all)	24	32	
Vertigo			
subjects affected / exposed	5 / 45 (11.11%)	2 / 49 (4.08%)	
occurrences (all)	5	2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 45 (2.22%)	4 / 49 (8.16%)	
occurrences (all)	1	6	
Constipation			
subjects affected / exposed	16 / 45 (35.56%)	19 / 49 (38.78%)	
occurrences (all)	24	30	
Diarrhoea			
subjects affected / exposed	10 / 45 (22.22%)	10 / 49 (20.41%)	
occurrences (all)	12	14	
Dry mouth			
subjects affected / exposed	4 / 45 (8.89%)	3 / 49 (6.12%)	
occurrences (all)	5	3	
Dyspepsia			
subjects affected / exposed	4 / 45 (8.89%)	12 / 49 (24.49%)	
occurrences (all)	4	18	
Mucositis oral			
subjects affected / exposed	14 / 45 (31.11%)	12 / 49 (24.49%)	
occurrences (all)	21	13	
Nausea			
subjects affected / exposed	22 / 45 (48.89%)	28 / 49 (57.14%)	
occurrences (all)	34	55	
Oral pain			
subjects affected / exposed	8 / 45 (17.78%)	4 / 49 (8.16%)	
occurrences (all)	12	6	
Vomiting			
subjects affected / exposed	11 / 45 (24.44%)	16 / 49 (32.65%)	
occurrences (all)	13	20	
Skin and subcutaneous tissue disorders			

Alopecia subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 5	11 / 49 (22.45%) 13	
Skin and subcutaneous tissue disorders, other subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 6	7 / 49 (14.29%) 8	
Musculoskeletal and connective tissue disorders Chest wall pain subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 4	1 / 49 (2.04%) 1	
Infections and infestations Mucosal infection subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 6	3 / 49 (6.12%) 6	
Urinary tract infection subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 6	3 / 49 (6.12%) 3	
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	7 / 45 (15.56%) 9	17 / 49 (34.69%) 25	
Dehydration subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4	3 / 49 (6.12%) 3	
Hypoalbuminemia subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 5	4 / 49 (8.16%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2013	<p>Protocol updated (v6)</p> <ul style="list-style-type: none"> • Clarification to exclusion criteria number 2 regarding Head & Neck patients being treated with Radiotherapy, • Change to exclusion criteria number 10 to read 'Patients with symptomatically overt hearing loss which the Principal Investigator (PI) considers should exclude the use of cisplatin'. • Change to secondary trial endpoint number 6 (PTA test frequencies) to remove tests at 10 and 12kHz as equipment cannot be calibrated at these frequencies. • GFR can now be calculated within 2 weeks prior to starting chemotherapy. • Added wording 'if the patient is too unwell to travel for the hearing assessment at 4-7 days post final Cisplatin treatment, they should be re-assessed on a weekly basis by telephone until they are well enough to re-schedule the appointment' <p>Addition of information regarding NG or PEG tube. Information on wash out prior to randomisation. Appendix II, additional information on Adverse Events for Hearing, Gastrointestinal and Renal disorders. Addition of one extra column in the schedule of observations to clarify extra pre-treatment visit</p>
24 September 2013	<p>Protocol updated (v7)</p> <ul style="list-style-type: none"> • Change in exclusion criteria from previous transient ischaemic attacks or cerebral vascular disease to previous haemorrhagic stroke • Removal of exclusion criteria severe ischaemic heart disease or myocardial infarction • Addition information on omeprazole - 'We are co-prescribing omeprazole to reduce both of these problems. Omeprazole is a proton pump inhibitor used for the treatment of gastric ulcers, duodenal ulcers, gastro-oesophageal reflux disease, acid-related dyspepsia, Zollinger-Ellison syndrome and for the eradication of Helicobacter pylori. It is also used to treat or prevent ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDs) and to reduce gastric acid before surgery. We do not expect Omeprazole to affect trial outcome.'
09 January 2014	<p>Protocol updated (v8)</p> <ul style="list-style-type: none"> • The wording related to the OAE testing has been made more generic to cover the opening of additional sites to the trial. • The OAE test cannot be performed at all hospital trusts participating in this trial. In some cases there may be the option for patients to travel outside of their region to have both their PTA and OAE tests at an alternative location. Patients who are not able to travel, or do not have the OAE testing service available to them, are still able to participate in the trial and will therefore only have the PTA assessment. • Changing the packaging of the IMP in two ways. <ul style="list-style-type: none"> • For all new shipments the bottles containing aspirin/placebo and omeprazole/placebo will be provided directly to the patient and not within a carton or outer pack. • The IMP labels have been updated to include patient pack number as this was previously on the outer carton label which will not be supplied with future shipments to existing and new sites.
03 June 2015	<p>Protocol updated (v9)</p> <ul style="list-style-type: none"> • Increase in number of patients to be recruited has required amendments to Section 3 - Trial Design; Section 8.1 - Sample size. • Amendment to the exclusion criteria – clarification regarding oral-anticoagulants • Update to section 5.3.2 – Chemotherapy delay/discontinuation • Update to section 7.1 Definition of End of Trial

28 October 2015	<p>Protocol updated (v10)</p> <p>The main purpose of this amendment is a change to the primary endpoint definition in the protocol. This change has been necessary as many patients are too ill from the side effects of the cisplatin chemotherapy to return for their second PTA hearing test assessment within the protocol defined window. The following was therefore recommended by the IDMC and agreed by the TMG committee:-</p> <ul style="list-style-type: none"> • The first available PTA assessment will be used for the primary endpoint (regardless of time frame). • Wherever possible PTA assessments will be scheduled within the protocol defined time window unless the patient is too ill to attend in which case a PTA assessment will be scheduled as soon as the patient feels well enough.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 February 2015	<p>Drug supply issue: A decision was made to suspend recruitment, and all sites were notified of this on 2-Feb-2015.</p> <p>Drug supply issue resolved: Sites were reopened to recruitment on 12 Feb 2015</p>	12 February 2015

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: