Clinical trial results:
SPRING - Seizure PRophylaxis IN Glioma

Summary

EudraCT number	2018-001312-30
Trial protocol	GB
Global end of trial date	08 September 2023

Results information

Result version number	v1 (current)
This version publication date	23 October 2026
First version publication date	23 October 2026

Trial information

Trial identification

Sponsor protocol code	Spring

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Public Health Scotland
Sponsor organisation address	Gyle Square, 1 South Gyle Crescent, Edinburgh, United Kingdom, EH12 9EB
Public contact	phs.researchoffice@phs.scot, Public Health Scotland, phs.researchoffice@phs.scot
Scientific contact	phs.researchoffice@phs.scot, Public Health Scotland, phs.researchoffice@phs.scot

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	03 November 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 September 2023
Global end of trial reached?	Yes
Global end of trial date	08 September 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This aim of the study is to investigate whether use of levetiracetam before surgery will help to prevent patients with suspected brain tumours developing seizures after their surgery.

The patients will have surgery planned and will have not experienced a seizure.

We will give half of these patients current standard care (no anti-epileptic drug) and the other half will receive an anti epileptic drug called levetiracetam before surgery and for up to one year after to see if this drug will reduce their risk of having seizures. Using a drug in this manner is called prophylactic use.

Protection of trial subjects:

TBC?

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2019
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: 107
Worldwide total number of subjects	107
EEA total number of subjects	0

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)	69
From 65 to 84 years	38
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

107 patients screened. 5 found to be ineligible on ASM arm and 8 on no ASM arm. Withdrawn due to various reasons including already on ASM, patient withdrawal prior to surgery, consent issues and patient death prior to completion.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Anti-Seizure Medication

Arm description:

Levetiracetam 500mg twice daily for 2 weeks, then increasing to 750mg twice daily thereafter for 1 year. Patients should have a minimum of 2 doses of 500mg prior to surgery. (In those with moderate chronic kidney disease stage 3 estimated Glomerular Filtration Rate (eGFR 30-59 mL/min/1.73 m2) a starting dose of 250mg twice a day for 2 weeks, then increasing to 500mg twice a day thereafter).

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

Dosage and administration details:

Levetiracetam will be taken orally twice a day at approximately the same times each day, spaced as close to 12 hours apart as possible. Patients with impaired renal function (CKD 3, eGFR 30-59 ml/min/1.73m2) will have a different dose schedule consistent with the European levetiracetam label.
Normal treatment
Randomisation-2 weeks
1 tablet of 500 mg AM
1 tablet of 500 mg PM
Next 12 months
1 tablet of 500 mg + 1 tablet of 250 mg = 750 mg AM
1 tablet of 500 mg + 1 tablet of 250 mg = 750 mg PM
Impaired Renal Function treatment
Randomisation-2 weeks
1 tablet of 250 mg AM
1 tablet of 250 mg PM
Next 12 months
1 tablet of 500 mg AM 1 tablet of 500 mg PM

Arm title	No ASM (standard care)

Arm description:

no AED(anti-epileptic drug) treatment (standard care)

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Anti-Seizure Medication	No ASM (standard care)
Started	54	53
Completed	49	45
Not completed	5	8
Adverse event, serious fatal	-	1
Physician decision	1	-
Withdrew prior to surgery	2	2
Protocol deviation	2	5

Baseline characteristics

Reporting groups

Reporting group title	Anti-Seizure Medication

Reporting group description:

Levetiracetam 500mg twice daily for 2 weeks, then increasing to 750mg twice daily thereafter for 1 year. Patients should have a minimum of 2 doses of 500mg prior to surgery. (In those with moderate chronic kidney disease stage 3 estimated Glomerular Filtration Rate (eGFR 30-59 mL/min/1.73 m2) a starting dose of 250mg twice a day for 2 weeks, then increasing to 500mg twice a day thereafter).

Reporting group title	No ASM (standard care)

Reporting group description:

no AED(anti-epileptic drug) treatment (standard care)

Reporting group values	Anti-Seizure Medication	No ASM (standard care)	Total
Number of subjects	54	53	107
Age categorical Units: Subjects			
Adults (18-64 years)	34	35	69
Adults (65-84 years)	20	18	38
Gender categorical Units: Subjects			
Female	16	18	34
Male	38	35	73

Subject analysis sets

Subject analysis set title	Analysis Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients randomised who completed the trial and survived to 12 months.

Reporting group values	Analysis Population		
Number of subjects	72		
Age categorical Units: Subjects			
Adults (18-64 years)	52		
Adults (65-84 years)	20		
Gender categorical Units: Subjects			
Female	25		
Male	47		

End points

End points reporting groups

Reporting group title	Anti-Seizure Medication
Reporting group description:	
Levetiracetam 500mg twice daily for 2 weeks, then increasing to 750mg twice daily thereafter for 1 year. Patients should have a minimum of 2 doses of 500mg prior to surgery. (In those with moderate chronic kidney disease stage 3 estimated Glomerular Filtration Rate (eGFR 30-59 mL/min/1.73 m2) a starting dose of 250mg twice a day for 2 weeks, then increasing to 500mg twice a day thereafter).	
Reporting group title	No ASM (standard care)
Reporting group description:	
no AED(anti-epileptic drug) treatment (standard care)	
Subject analysis set title	Analysis Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Patients randomised who completed the trial and survived to 12 months.	

Primary: Seizure within 12 months

End point title	Seizure within 12 months
End point description:	
We are interested in the occurrence of a seizure within one year of randomisation for patients in each arm of the study. This is a binary response variable, with patients either having a seizure or not having a seizure within one year of randomisation.	
End point type	Primary
End point timeframe:	
Within one year of randomisation	

End point values	Anti-Seizure Medication	No ASM (standard care)	Analysis Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	36	36	72	
Units: No of Patients having Seizure				
Yes	17	15	32	
No	19	21	40	

Statistical analyses

Statistical analysis title	Logistic Regression Model
Statistical analysis description:	
We are interested in the occurrence of a seizure within one year of randomisation for patients in each arm of the study. This is a binary response variable, with patients either having a seizure or not having a seizure within one year of randomisation.	
Comparison groups	Anti-Seizure Medication v No ASM (standard care)

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	3.21
Variability estimate	Standard deviation

Notes:

[1] - Compared to a p-value of 0.05.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First patient randomised 06 December 2019 through to 30 days after last patient last visit (08 September 2023) to 9th October 2023.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	29.0

Reporting groups

Reporting group title	ASM (Study Drug)

Reporting group description:

Levetiracetam 500mg twice daily for 2 weeks, then increasing to 750mg twice daily thereafter for 1 year. Patients should have a minimum of 2 doses of 500mg prior to surgery. (In those with moderate chronic kidney disease stage 3 estimated Glomerular Filtration Rate (eGFR 30-59 mL/min/1.73 m2) a starting dose of 250mg twice a day for 2 weeks, then increasing to 500mg twice a day thereafter).

Reporting group title	No ASM (standard care)

Reporting group description:

no AED(anti-epileptic drug) treatment (standard care)

Serious adverse events	ASM (Study Drug)	No ASM (standard care)	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 52 (21.15%)	12 / 51 (23.53%)	
number of deaths (all causes)	27	25	
number of deaths resulting from adverse events	0	0	
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium decreased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications			
Hip fracture			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis postoperative			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure chronic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 52 (0.00%)	2 / 51 (3.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 52 (1.92%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ASM (Study Drug)	No ASM (standard care)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 52 (63.46%)	32 / 51 (62.75%)	
Surgical and medical procedures			
Hospitalisation	Additional description: Modified Safety reporting for Elective hospitalisation for any surgery for brain cancer or its complications and Elective hospitalisation for pre-existing conditions (not exacerbated by trial treatment).		
subjects affected / exposed	4 / 52 (7.69%)	5 / 51 (9.80%)	
occurrences (all)	5	6	
Nervous system disorders			
Seizure	Additional description: Modified safety reporting for seizure.		
subjects affected / exposed	15 / 52 (28.85%)	12 / 51 (23.53%)	
occurrences (all)	33	24	
General disorders and administration site conditions			
Disease progression	Additional description: Modified safety reporting for Progressive neurological deficit.		
subjects affected / exposed	5 / 52 (9.62%)	6 / 51 (11.76%)	
occurrences (all)	6	6	
Death	Additional description: Modified safety reporting for death due to disease progression.		
subjects affected / exposed	25 / 52 (48.08%)	22 / 51 (43.14%)	
occurrences (all)	25	22	
Psychiatric disorders			
Mental status changes	Additional description: Modified safety reporting for Reported change in memory/mood/personality/fatigue.		
subjects affected / exposed	3 / 52 (5.77%)	2 / 51 (3.92%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2015	The following changes were requested: 1) Incorporation into the protocol that should a patient lose capacity throughout the trial, they will be given the opportunity to remain the trial. 2) Reformatting of some sections within the protocol 3) Addition of Section 1.5 (Disease Progression) – incorporation of allowing participants to stay in the study should they lose capacity after consenting 4) More detailed description of LAEP and EQ-5D-5L (Section 2.5) 5) Addition of PHQ9 questionnaire which is used as a screening tool for depressive symptoms. This was a recommendation from the MHRA following their protocol review (Section 2.5). The protocol has also been updated to remove patients with severe depression as defined by a PHQ-9 score of 20+ 6) Addition of Cognitive/capacity monitoring section (Section 2.6) 7) Addition of Treatment Breaks section (Section 4.4)
29 May 2019	This amendment encompasses the following: Addition of sites and PIs: 1) Poole Hospital NHS Foundation Trust – PI - Dr Maxine Flubacher 2) Portsmouth Hospitals NHS Trust – PI - Dr Yogeshkumar Nishchal 3) The Clatterbridge Cancer Centre NHS Foundation Trust - PI - Dr Shaveta Mehta 4) South Tees Hospitals NHS Trust – PI - Dr KS Manjunath Prasad Change of PI: 5) The Leeds Teaching Hospitals NHS Trust - Mr Ryan Mathew Furthermore, there have been some minor updates to the protocol including: 1) KEY CONTACTS - Removal of Kirsten Murray as Senior Trial Coordinator 2) Section 5.3 – Modified Safety Reporting section has been updated to provide further clarification 3) Section 7.3.5 – (2 - 2) Assessment of utility associated with seizures) has been updated to clarify the analysis that will be performed 4) Appendix 3 – References have been updated where appropriate
09 March 2020	Addition of new sites: Pietro D'Urso Salford Royal Hospital, Stott Lane, Salford, M6 8HD Isaac Phang Royal Preston Hospital, Sharoe Green Lane, Preston, PR2 9HT Puneet Plaha John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU Patrick Mitchell Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP

07 April 2020	Summary of changes 1. SmPC 14 March 2019 - Section 4.8 Undesirable Effects: A new adverse reaction of gait disturbance has been added to the list of Nervous System Disorders, affecting between 1 in 1000 and 1 in 10000 people. 2. SmPC 01 April 2019 - Section 4.8 Undesirable Effects: A new adverse reaction of delirium has been added to the list of Psychiatric Disorders, affecting between 1 in 1000 and 1 in 10000 people. 3. SmPC 01 April 2019 - Section 4.8 Undesirable Effects: A new adverse reaction of encephalopathy has been added to the list of Nervous System Disorders, affecting between 1 in 1000 and 1 in 10000 people. 4. SmPC 04 October 2019 - Section 4.4 Special warnings and precautions for use of Keppra has been updated to include abnormal thoughts, feeling irritable or reacting more aggressively than usual or if patient or family or friends notice important changes in mood or behaviour. The protocol and PIS have been updated to reflect these changes to the SmPC. Amendments to section 4.8 of the SmPC has resulted in amendments to the protocol and the PIS. (
18 June 2020	Sponsorship of the SRING trial has transferred from the Common Services Agency to Public Health Scotland on 01 April 2020. This is due to the formal transfer of the staff and functions responsible for overseeing sponsorship and research governance of clinical trials managed by the Scottish Clinical Trials Research Unit, transferring to Public Health Scotland.
30 June 2020	This substantial amendment has been created in order to:1. Bring all documentation in line with the change to Sponsor in substantial amendment 062. Remove pregnancy testing for IMP patients at follow up, justification for this is covered within the covering letter3. Enable a 2 step consent process to allow patients additional time for consideration and to minimise requirement for hospital visits4. Allow nominated patient Carers to collect IMP, in the event that patients may be shielding or are too unwell to collect their IMP. 5. Add collection of data for the COVID-19 pandemic, in order to capture any COVID-19 related effect on the analysis. 6. Amend PHQ-9 withdrawal and exclusion criteria from 20+ to ≥20 in order to improve clarity
03 March 2021	Addition of a new site: Principal Investigator: Mr Andrew McEvoy Site Name: National Centre for Neurology and Neurosurgery Address: National Hospital for Neurology & Neurosurgery, Queen SquareLondon, WC1N 3BG
25 May 2021	Updated SmPC documents are included for the IMP.The protocol has been updated in line with changes to the Reference Safety Information; QT prolongation and aggravated seizures have been added to the rare side effects. As such post randomisation ECG has been introduced for patients on the IMP arm. Patients that have QT prolongation will not start IMP. In addition the protocol has other changes:1.Introduction of Standard Gamble exercise within Health Economics2.Electronic patient reported outcomes to help reduce the burden for patients3.Other minor changes to improve clarity for sites. The Patient Information sheet has been redesigned based on patient feedback and to help simplify information. Patient documentation updated in line with the changes
19 January 2022	This amendment is to update the reference safety information (RSI), section 4.8 of the SmPC, to add wording regarding predisposition of Neuroleptic Malignant syndrome in the the Japanese population. This is not a contraindication but rather, something clinicians are to be aware of.
04 November 2022	This amendment is to update the Carer information sheet and consent form. Carers will be given the option to provide their email address in order to complete Quality of Life questionnaires online. This was omitted in error in the submission of substantial amendment 09.

11 April 2023	This amendment is to notify of the change of Chief Investigator from Dr Robert Grant to Professor Michael Jenkinson, as Dr Grant is retiring.
12 July 2023	This amendment is to notify of the early closure of the SPRING trial due to the early withdrawal of funding.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/42111024