Clinical trial results:
A phase III multi-centre randomised, double blind, placebo controlled trial to assess the role of intravenous immunoglobulin in the management of children with encephalitis (The IgNiTE study)

Summary

EudraCT number	2014-002997-35
Trial protocol	GB
Global end of trial date	10 January 2024

Results information

Result version number	v1 (current)
This version publication date	19 May 2024
First version publication date	19 May 2024

Trial information

Trial identification

Sponsor protocol code	OVG2014/05

Additional study identifiers

ISRCTN number	ISRCTN15791925
ClinicalTrials.gov id (NCT number)	NCT01640652
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Research Governance, Ethics & Assurance Team (RGEA)
Sponsor organisation address	Boundary Brook House, Oxford, United Kingdom, OX3 7GB
Public contact	Andrew J Pollard, University of Oxford, 44 1865611400, andrew.pollard@paediatrics.ox.ac.uk
Scientific contact	Andrew J Pollard, University of Oxford, 44 1865611400, andrew.pollard@paediatrics.ox.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	09 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to investigate whether intravenous immunoglobulin improves neurological outcomes in children with all-cause encephalitis when administered early in the illness (within 5 working days from the suspicion of an encephalitis diagnosis)

Protection of trial subjects:

1. The study was conducted in strict accordance with GCP
2. The study protocol and all amendments, the informed consent form, and any accompanying materials provided to participants were reviewed and approved by an Independent Ethics Committee
3. Participants were monitored during administration of the study treatment and for 20 minutes after each dose for adverse events
4. Participants had a mandatory full blood count check 24-48 hours after the second dose of the study treatment as a mitigation measure to monitor for haemolysis that can happen with high doses of IVIG.
5. Safety data were collected throughout the study: adverse events and AESIs (within 5 days of each dose of study treatment), SAEs (until 6 months post randomisation), SARs, deaths, and pregnancy (all through study period)
6. Brain MRIs were conducted in line with site specific safety protocols
7. The trial had a DSMC that reviewed study safety data at specified intervals.

Background therapy:

Not Applicable

Evidence for comparator:

Intravenous Immunoglobulins (IVIG) is a formulation of a ready-to -use natural antibodies (Privigen) made from blood donations. The active substance in Privigen is human normal immunoglobulin (antibodies of the type IgG). Privigen contains human protein of which at least 98% is IgG. The approximate percentage of IgG subclasses is as follows: IgG - 67.8% IgG2 - 28.7% IgG3 - 2.3% IgG4 - 1.2% Privigen contains trace amounts of IgA (not more than 25 micrograms/ml) and is essentially sodium free. The other ingredients (excipients) are the amino acid proline and water for injections. Privigen® solution for infusion is for single-use only.

In the study, the Privigen formulation was compared with a placebo which was made up of 0.1% human albumin in 0.9% Sodium Chloride solution.

Study medication was prescribed according to the protocol. Two doses of 1g/kg/dose of either IVIG or a matching volume of placebo were given 24–36hours apart, with the first dose administered as soon as possible after enrolment and within five working days from the suspicion of an encephalitis diagnosis. Participants were followed up for 12 months after randomisation, with outcomes assessed during the acute admission, at 4–8 weeks after discharge from acute care, at 6 months after randomisation, and 12 months after randomisation.

Actual start date of recruitment	23 December 2015
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: 18
Worldwide total number of subjects	18
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)	5
Children (2-11 years)	8
Adolescents (12-17 years)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment of hospitalised children (between 6 months to 16 years) who met the case definition for encephalitis based on the consensus definition by the International Encephalitis Consortium, commenced in July 2015 across 21 NHS hospitals; by identifying and approaching eligible parents for enrolment by members of the study research team.

Pre-assignment

Screening details:

A total of 884 patients were screened for eligibility; of these, 52 were eligible for enrolment. 34 eligible subjects withheld consent and only 18 participants were enrolled across 12 hospital. 10 participants were assigned to IVIG treatment arm, and 8 patients were assigned to placebo arm.

Period 1

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

Blinding implementation details:

This was a double blinded study as the participants, their parents or guardians, clinical staff and all study staff (including staff involved in recruitment, administration of study treatment, data collection and entry, and laboratory analyses) were blinded to the treatment allocation through the entire study period. Study monitors who were independent of the study and all site pharmacists were unblinded to ensure dispensing of the correct allocation and robust IMP management at each study site

Arms

Are arms mutually exclusive?	Yes
Arm title	Human normal IVIG (Privigen) Solution

Arm description:

- The intravenous immunoglobulin (IVIG) arm received two doses of 1g/kg/dose of the privigen (100 mg/mL solution) in addition to routine standard of care; given 24–36hours apart, with the first dose administered as soon as possible after enrolment and within five working days from the suspicion of an encephalitis diagnosis.

Arm type	Experimental
Investigational medicinal product name	Privigen
Investigational medicinal product code	
Other name	Not Applicable
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

Two doses of 1g/kg/dose of IVIG were given 24–36hours apart, with the first dose administered as soon as possible after enrolment and within five working days from the suspicion of an encephalitis diagnosis.

Arm title	Placebo (0.1% human albumin in 0.9% Sodium Chloride solution)

Arm description:

Two doses of 0.1% human albumin in 0.9% Sodium Chloride solution (the addition of albumin was to make the placebo visually identical to IVIG to maintain blinding); given 24–36hours apart, with the first dose administered as soon as possible after enrolment and within five working days from the suspicion of an encephalitis diagnosis. The volume of placebo given per dose was equivalent to 1g/kg of IVIG.

Arm type	Placebo

Investigational medicinal product name	0.1% human albumin in 0.9% Sodium Chloride solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

Two doses of 0.1% human albumin in 0.9% Sodium Chloride solution (the addition of albumin was to make the placebo visually identical to IVIG to maintain blinding); given 24–36hours apart, with the first dose administered as soon as possible after enrolment and within five working days from the suspicion of an encephalitis diagnosis. The volume of placebo given per dose was equivalent to 1g/kg of IVIG.

Number of subjects in period 1	Human normal IVIG (Privigen) Solution	Placebo (0.1% human albumin in 0.9% Sodium Chloride solution)
Started	10	8
Completed	9	6
Not completed	1	2
Consent withdrawn by subject	1	1
Refused second dose	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Human normal IVIG (Privigen) Solution

Reporting group description:

- The intravenous immunoglobulin (IVIG) arm received two doses of 1g/kg/dose of the privigen (100 mg/mL solution) in addition to routine standard of care; given 24–36hours apart, with the first dose administered as soon as possible after enrolment and within five working days from the suspicion of an encephalitis diagnosis.

Reporting group title	Placebo (0.1% human albumin in 0.9% Sodium Chloride solution)

Reporting group description:

Two doses of 0.1% human albumin in 0.9% Sodium Chloride solution (the addition of albumin was to make the placebo visually identical to IVIG to maintain blinding); given 24–36hours apart, with the first dose administered as soon as possible after enrolment and within five working days from the suspicion of an encephalitis diagnosis. The volume of placebo given per dose was equivalent to 1g/kg of IVIG.

Reporting group values	Human normal IVIG (Privigen) Solution	Placebo (0.1% human albumin in 0.9% Sodium Chloride solution)	Total
Number of subjects	10	8	18
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	3	2	5
Children (2-11 years)	4	4	8
Adolescents (12-17 years)	3	2	5
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	5.55	4.09	
inter-quartile range (Q1-Q3)	1.52 to 11.8	2.71 to 9.64	-
Gender categorical Units: Subjects			
Female	6	4	10
Male	4	4	8

End points

End points reporting groups

Reporting group title	Human normal IVIG (Privigen) Solution

Reporting group description:

- The intravenous immunoglobulin (IVIG) arm received two doses of 1g/kg/dose of the privigen (100 mg/mL solution) in addition to routine standard of care; given 24–36hours apart, with the first dose administered as soon as possible after enrolment and within five working days from the suspicion of an encephalitis diagnosis.

Reporting group title	Placebo (0.1% human albumin in 0.9% Sodium Chloride solution)

Reporting group description:

Two doses of 0.1% human albumin in 0.9% Sodium Chloride solution (the addition of albumin was to make the placebo visually identical to IVIG to maintain blinding); given 24–36hours apart, with the first dose administered as soon as possible after enrolment and within five working days from the suspicion of an encephalitis diagnosis. The volume of placebo given per dose was equivalent to 1g/kg of IVIG.

Primary: GOS-E Peds scores at 12 months after randomisation

End point title	GOS-E Peds scores at 12 months after randomisation[1]

End point description:

GOS- E Peds (Glasgow Outcome Score Extended) is the paediatric version of the GOS-E. It is a validated tool for use in children, and provides a developmentally appropriate structured interview necessary to evaluate children across different age groups.
Two doses of 1g/kg/dose of either IVIG or a matching volume of placebo were given 24–36hours apart, with the first dose administered as soon as possible after enrolment and within five working days from the suspicion of an encephalitis diagnosis.
No statistical analysis was performed for this endpoint due to unmet sample size (only 18 participants had been recruited); and the trial was therefore underpowered to perform hypothesis testing of outcomes, subgroup comparisons or sensitivity analyses. Therefore, all analyses performed were descriptive. The analyses were performed on the intention-to-treat population; this included all 18 participants who were randomized.

End point type	Primary

End point timeframe:

Participants were followed up for 12 months after randomisation, with outcomes assessed during the acute admission, at 4–8 weeks after discharge from acute care, at 6 months after randomisation, and 12 months after randomisation.

Notes:

[1] - 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: At the time the trial was halted, only 18 participants had been recruited. The trial was therefore underpowered to perform hypothesis testing of outcomes, subgroup comparisons or sensitivity analyses. Therefore, all analyses performed were descriptive. The analyses were performed on the intention-to-treat population; this included all 18 participants who were randomised. In the analysis of the AEs, the population analysed were the 16 participants who received study treatment.

End point values	Human normal IVIG (Privigen) Solution	Placebo (0.1% human albumin in 0.9% Sodium Chloride solution)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: Percentage				
Upper Good Recovery	4	1		
Lower Good Recovery	1	0		
Upper Severe Disability	1	1		

Lower severe Disability	2	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Five days following each doses of study drug administration

Adverse event reporting additional description:

Collection of adverse events of special interest was carried out in the first five days from each dose of study drug, serious adverse events is collected up to 6months post randomization, serious adverse reactions is collected between 6- and 12-months post randomization and information on any death occurring up to 12months after randomization.

Assessment type	Systematic

Dictionary used

Dictionary name	PROTOCOL
Dictionary version	v7.0

Reporting groups

Reporting group title	Human normal IVIG (Privigen) solution

Reporting group description:

- The intravenous immunoglobulin (IVIG) arm received two doses of 1g/kg/dose of the privigen (100mg/mL solution) in addition to routine standard of care; given 24–36hours apart, with the first dose administered as soon as possible after enrolment and within five working days from the suspicion of an encephalitis diagnosis.

Reporting group title	Placebo (0.1% human albumin in 0.9% Sodium Chloride solution)

Reporting group description:

Placebo arm received two doses of 0.1% human albumin in 0.9% Sodium Chloride solution (the addition of albumin made the placebo visually identical to the IVIG); given 24–36hours apart, with the first dose administered as soon as possible after enrolment and within five working days from the suspicion of an encephalitis diagnosis.

Serious adverse events	Human normal IVIG (Privigen) solution	Placebo (0.1% human albumin in 0.9% Sodium Chloride solution)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	3 / 8 (37.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgery for PEG insertion, fundoplication, upper limb botox and muscle and skin biopsies			

subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
prolonged Seizure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Allergic reaction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cortical Blindness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Ventilation and intubation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bilateral achilles tenotomy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Sepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
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: 1 %

Non-serious adverse events	Human normal IVIG (Privigen) solution	Placebo (0.1% human albumin in 0.9% Sodium Chloride solution)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2014	• SUSAR reporting section was modified to permit delegation of SUSAR reporting responsibilities by the CI. • Clinical trial identifier was added. • Study short title was added
21 January 2015	• Changes to study design. • Addition of text relating to the recruitment of non-English speakers. • Amendment to text relating to the unblinding process. • Changes relating to the cellular immunology aspects of the protocol. • Clarification of level of training required for administration of the study drug. • Clarification of text relating to the treatment of reaction occurring during study drug administration. • Clarification of text relating to exposure to the study drug during pregnancy. • Correction made to SAE definition • Clarification of time points for obtaining research blood samples. • Several minor administrative changes made to text for clarity
05 August 2015	• Change to the timing of completion of discharge questionnaires. • Removal of GOSEPeds at discharge • Amendment to text relating to one of the exploratory objectives and clarification of outcome measures to achieve this objective • Change to and addition of new study time point for research blood sampling • Removal of 'region' as a stratification factor for randomization • Amendment of information relating to documentation of participant Study ID • Clarification on the process of questionnaire completion • Amendment to text relating to blood processing for clarity • Amendment to the Study Flow Chart and Schedule of Study Procedures • Several minor amendments made to text for clarity.
17 September 2015	• Clarification of time window for administration of first dose of the study drug. • Clarification of exclusion criterion relating to IgA deficiency. • Clarification to text relating to research sample type being collected. • Clarification of text relating to withdrawal of participant from study treatment. • Clarification of the role of DSMC relating to review of data quality. • Amendment to the risk of anaphylaxis following general anaesthesia. • Minor amendment made to schedule of study procedures to clarify timing of research blood sampling.
04 November 2015	• Addition of mandatory full blood count check 24-48 hours following the 2nd dose of the study drug as a risk mitigation measure to monitor for signs of haemolysis with IVIG treatment. • Amendment to age ranges that define which of the neuropsychology assessments will be done.

10 March 2016	• Page 36: Time point 'T6 Around 12 months post randomisation' was incorrectly documented as 'T5 Around 12 months post randomisation'. This has been corrected to read T6. • Page 42: Section 9.5 Concomitant Medications - The sentence 'Participants should not be enrolled if they are still being actively followed up in another study that involves an IMP' has been removed, consistent with similar changes in version 3.0 of the protocol, as per the decision at the previous DSMC meeting.
09 October 2016	• Clarification on reporting of serious adverse events beyond the 6 months post randomisation time point. • Clarification of what age to use for ex premature infants when assessing eligibility. • Modification of the exclusion criterion relating to co-enrolment to other IMP trials to make this in line with the changes made in the last amendment. • Clarification of the process of obtaining consent from 16 year old participants beyond the initial hospital admission period. • Clarification of the processes around the time of randomization. • Clarification on the role of the PI in unblinding. • Clarification of the age groups for the different cognitive scales for participants in the IgNiTE trial. • Clarification on the process of obtaining the safety FBC result for participant's transferred to a non-IgNiTE participating hospital before the test is due. • Amendment to the description of the study time points to provide clarity. • Clarification on the procedure for recording adverse events. • Clarification of the process of reporting serious adverse events and follow up of these where ongoing at the end of the participant's time in the study. • Minor change to the wording of the exclusion criterion relating to recruitment within the study time window to improve clarity. • For consistency of terminology, we have used 4instead of SAEs judged to be related to the IMP throughout the protocol. • Update to the versions of the WPPSI and WISC to be used. Note that REC approval to update the WPPSI to version 4 was obtained in SA5 but this change was not effected in the protocol. • Correction to the spelling of 'Behaviors' in the text 'Adaptive Behaviors Assessment System'. • For consistency and where appropriate, we have replaced the term 'IMP' with 'study drug'. • Addition of a window around the T2+7d time point. • Extension of the 4-6 week post discharge from acute care time point by 2 weeks to allow an additional time for completion of study questionnaires.
05 July 2017	• Extension of the time window for administration of the first dose of study drug. • Clarification on the starting point for calculating the time window for administering the first dose of study treatment. • Deletion of the exclusion criterion relating to the time window for administering the first dose of study drug . • Increase in the number of recruiting sites to 40. • Inclusion of additional clinical endpoints 6. Modification of text relating to an inclusion criterion to provide clarity. • Addition of text explaining the rationale for inclusion of clinically improving patients to the IgNiTE trial. • Correction to the protocol version number for the last substantial amendment in the amendment history section of the protocol. • Clarification of patients to be recorded on the screening log.

22 March 2022	• Update to details of key trial contacts. • Reference to UK GDPR added to the protocol alongside the reference to the Data Protection Act. • Removal of endpoints which cannot be derived from the data collected. • Removal of Biobank approach and consent in section 8.8. • Updates to section numbering where subsections have been deleted due to the changes made to study design. • Update to version number and date throughout. • Removal of information on blood processing related to exploratory endpoints. • Minor change to text for clarity. • Update the statisticians on the trial. • Update the statistical analysis section due to the early termination. • Addition of text relating to early trial termination. • Post study completion clarification of study activities at the T2 +7d time point, allowing this to be completed by telephone should it be required and clarification that AESIs and SAEs can be collected at this timepoint. • At the time that funding was withdrawn, the NIHR continued to fund completion of study activities for all enrolled participants unless they had withdrawn consent. They completed the trial activities as planned

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Primary study objective was not achieved due to unmet sample size. Recruitment to the trial was impacted by strict inclusion and exclusion criteria; with limited time window for enrolment, even when the study had clinically meaningful endpoints.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37945292

http://www.ncbi.nlm.nih.gov/pubmed/27810972