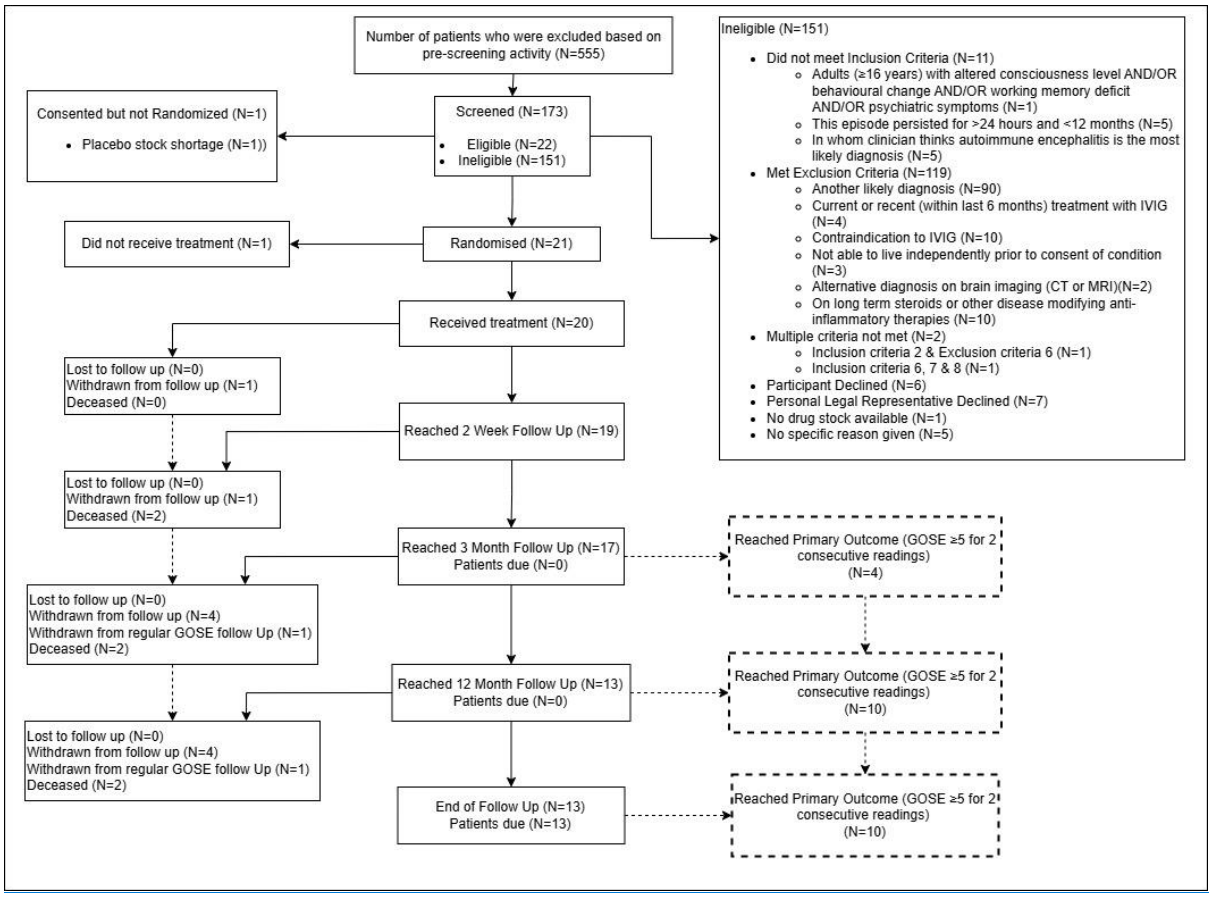
ENCEPH-IG Basic Results

Participant Flow:



Baseline Characteristics

	Trial Arm		
	Placebo	**IVIG**	**Total**
N	11 (52.4%)	10 (47.6%)	21 (100.0%)
Age at randomisation	61.0 [48.0, 72.0] N=11	71.0 [70.0, 72.0] N=9	70.0 [60.0, 72.0] N=20
Biological sex			
Female	5 (45.5%)	5 (50.0%)	10 (47.6%)
Male	6 (54.5%)	5 (50.0%)	11 (52.4%)
Ethnicity			
White	11 (100.0%)	9 (90.0%)	20 (95.2%)
Missing	0 (0.0%)	1 (10.0%)	1 (4.8%)
Time from symptom onset to randomisation			
24 hours to 1 week	0 (0.0%)	1 (10.0%)	1 (4.8%)
1 to 3 weeks	3 (27.3%)	2 (20.0%)	5 (23.8%)
3 to 5 weeks	3 (27.3%)	1 (10.0%)	4 (19.1%)
5 to 8 weeks	0 (0.0%)	0 (0.0%)	0 (0.0%)
8 to 12 weeks	4 (36.4%)	6 (60.0%)	10 (47.6%)
12 weeks to 12 months	1 (9.1%)	0 (0.0%)	1 (4.8%)

On the day of randomisation patient in ITU/HDU			
No	8 (72.7%)	9 (90.0%)	17 (81.0%)
Yes	3 (27.3%)	0 (0.0%)	3 (14.3%)
Missing	0 (0.0%)	1 (10.0%)	1 (4.8%)
Reason for admission to HDU/ITU (denominator: those admitted to HDU/ITU)			
Uncontrolled seizures/status epilepticus	1 (33.3%)	0 (0.0%)	1 (33.3%)
Decreased conscious level	1 (33.3%)	0 (0.0%)	1 (33.3%)
Transferred from external ITU	1 (33.3%)	0 (0.0%)	1 (33.3%)
Days between ITU/HDU admission and randomisation	8.0 [1.0, 16.0] N=3	N/A N=0	8.0 [1.0, 16.0] N=3
Ventilatory support at randomisation			
No	10 (90.9%)	8 (80.0%)	18 (85.7%)
Yes	1 (9.1%)	1 (10.0%)	2 (9.5%)
Missing	0 (0.0%)	1 (10.0%)	1 (4.8%)
Previous episodes of encephalitis			
No	10 (90.9%)	8 (80.0%)	18 (85.7%)
Yes	1 (9.1%)	1 (10.0%)	2 (9.5%)
Missing	0 (0.0%)	1 (10.0%)	1 (4.8%)
Aetiology of previous encephalitis (denominator: those with a previous episode of encephalitis)			
NMDA encephalitis	0 (0.0%)	1 (100.0%)	1 (50.0%)
HSV infection (site unspecified)	1 (100.0%)	0 (0.0%)	1 (50.0%)
Days between previous encephalitis and randomisation	102.0 [102.0, 102.0] N=1	10.0 [10.0, 10.0] N=1	56.0 [10.0, 102.0] N=2
Previous diagnosis of epilepsy			
No	11 (100.0%)	7 (70.0%)	18 (85.7%)
Yes	0 (0.0%)	2 (20.0%)	2 (9.5%)
Missing	0 (0.0%)	1 (10.0%)	1 (4.8%)
Number of hospital admissions due to epilepsy in the past 12 months	N/A N=0	1.0 [0.0, 2.0] N=2	1.0 [0.0, 2.0] N=2
On at least one antiepileptic drug before hospital admission			
No	10 (90.9%)	5 (50.0%)	15 (71.4%)
Yes	1 (9.1%)	4 (40.0%)	5 (23.8%)
Missing	0 (0.0%)	1 (10.0%)	1 (4.8%)
Previously treated for a comorbidity			
No	10 (90.9%)	5 (50.0%)	15 (71.4%)
Yes	1 (9.1%)	4 (40.0%)	5 (23.8%)

Missing	0 (0.0%)	1 (10.0%)	1 (4.8%)
Number of comorbidities previously treated for	7.0 [7.0, 7.0] N=1	1.5 [1.0, 3.5] N=4	2.0 [1.0, 5.0] N=5
Fever (>37.5 °C)			
No	8 (72.7%)	6 (60.0%)	14 (66.7%)
Yes	2 (18.2%)	1 (10.0%)	3 (14.3%)
Missing	1 (9.1%)	3 (30.0%)	4 (19.0%)
Headache			
No	6 (54.5%)	5 (50.0%)	11 (52.4%)
Yes	2 (18.2%)	2 (20.0%)	4 (19.0%)
Missing	3 (27.3%)	3 (30.0%)	6 (28.6%)
Seizures			
No	0 (0.0%)	2 (20.0%)	2 (9.5%)
Yes	10 (90.9%)	7 (70.0%)	17 (81.0%)
Missing	1 (9.1%)	1 (10.0%)	2 (9.5%)
Olfactory hallucinations			
No	7 (63.6%)	7 (70.0%)	14 (66.7%)
Yes	1 (9.1%)	0 (0.0%)	1 (4.8%)
Missing	3 (27.3%)	3 (30.0%)	6 (28.6%)
Behavioural/Personality Change			
No	3 (27.3%)	1 (10.0%)	4 (19.0%)
Yes	7 (63.6%)	7 (70.0%)	14 (66.7%)
Missing	1 (9.1%)	2 (20.0%)	3 (14.3%)
Alteration in cognition			
No	1 (9.1%)	1 (10.0%)	2 (9.5%)
Yes	10 (90.9%)	8 (80.0%)	18 (85.7%)
Missing	0 (0.0%)	1 (10.0%)	1 (4.8%)
Alteration in consciousness			
No	4 (36.4%)	5 (50.0%)	9 (42.9%)
Yes	6 (54.5%)	2 (20.0%)	8 (38.1%)
Missing	1 (9.1%)	3 (30.0%)	4 (19.0%)
Abbreviated Mental Test Score	9.0 [9.0, 9.0] N=1	4.5 [3.0, 6.0] N=2	6.0 [3.0, 9.0] N=3
Photophobia			
No	1 (9.1%)	3 (30.0%)	4 (19.0%)
Missing	10 (90.9%)	7 (70.0%)	17 (81.0%)
Neck stiffness/Signs of Meningism			
No	0 (0.0%)	3 (30.0%)	3 (14.3%)
Yes	1 (9.1%)	0 (0.0%)	1 (4.8%)
Missing	10 (90.9%)	7 (70.0%)	17 (81.0%)
Dysphasia (speech abnormalities)			
No	1 (9.1%)	3 (30.0%)	4 (19.0%)
Missing	10 (90.9%)	7 (70.0%)	17 (81.0%)

Total Glasgow Coma Scale	14.0 [7.0, 14.0] N=11	15.0 [14.0, 15.0] N=9	14.0 [14.0, 15.0] N=20
White Blood Cell count (10^9/L)	10.8 (2.2) N=11	8.7 (2.3) N=9	9.9 (2.4) N=20
Sodium (mmol/L)	134.5 (7.7) N=11	133.2 (4.4) N=9	133.9 (6.3) N=20
IgA (g/l)	1.8 [1.6, 2.7] N=7	3.7 [3.0, 28.6] N=3	2.5 [1.7, 3.4] N=10
IgG (g/l)	8.5 [7.5, 9.6] N=10	12.5 [8.4, 13.2] N=7	8.8 [8.3, 11.4] N=17
IgM (g/l)	0.8 [0.5, 0.9] N=7	1.0 [0.8, 1.3] N=3	0.8 [0.5, 1.0] N=10
Baseline GOSE grade			
Severely Disabled pre-injury	2 (18.2%)	0 (0.0%)	2 (9.5%)
Lower severe disability	9 (81.8%)	5 (50.0%)	14 (66.7%)
Upper severe disability	0 (0.0%)	4 (40.0%)	4 (19.0%)
Missing	0 (0.0%)	1 (10.0%)	1 (4.8%)

Continuous data summarised by median [Q25, Q75]. IVIG = Intravenous Immunoglobulin, ITU = Intensive Therapy Unit, HDU = High Dependency Unit, NMDA = N-methyl-D-aspartate, HSV = Herpes Simplex Virus, IgA = Immunoglobulin A, IgG = Immunoglobulin G, IgA = Immunoglobulin M, GOSE = Glasgow Outcome Scale – Extended.

Outcome Measures

Primary Outcome Measure

	Trial Arm		
	Placebo	**IVIG**	**Total**
N	11 (52.4%)	10 (47.6%)	21 (100.0%)
Participant status at 12-months			
Recovered	5 (45.5%)	5 (50.0%)	10 (47.6%)
Not recovered	1 (9.1%)	1 (10.0%)	2 (9.5%)
Died	1 (9.1%)	1 (10.0%)	2 (9.5%)
Withdrew	3 (27.3%)	2 (20.0%)	5 (23.8%)
Not recovered at time of study closure	1 (9.1%)	1 (10.0%)	2 (9.5%)
Weeks to recovery (GOSE form timepoints)	20.0 [16.0, 32.0] N=5	10.0 [8.0, 16.0] N=5	16.0 [8.0, 28.0] N=10
Actual weeks to recovery (when the GOSE forms were completed)	20.5 [13.4, 28.1] N=4	12.0 [8.3, 16.7] N=5	16.7 [8.3, 22.1] N=9

Secondary Outcome Measure

	Trial Arm		
	Placebo	**IVIG**	**Total**
N	11 (52.4%)	10 (47.6%)	21 (100.0%)

EQ5D3L score at 3-months	0.6 [0.4, 0.7] N=9	0.7 [0.3, 0.8] N=8	0.7 [0.4, 0.7] N=17
Health rating (0-100) at 3-months	50.0 [34.0, 75.0] N=9	75.0 [55.0, 87.5] N=8	70.0 [40.0, 80.0] N=17
EQ5D3L score at 12-months	0.8 [0.6, 0.9] N=6	0.7 [0.5, 0.8] N=5	0.8 [0.5, 0.9] N=11
Health rating (0-100) at 12-months	67.5 [60.0, 83.0] N=6	80.0 [80.0, 85.0] N=5	80.0 [60.0, 85.0] N=11
Treatment administered as outlined in protocol			
No	0 (0.0%)	2 (20.0%)	2 (9.5%)
Yes	11 (100.0%)	8 (80.0%)	19 (90.5%)
Reason for changes to protocol treatment (denominator: treatment not administered as outlined in protocol)			
Other	N/A	1 (50.0%)	1 (50.0%)
Patient refused	N/A	1 (50.0%)	1 (50.0%)
Change to protocol treatment (denominator: treatment not administered as outlined in protocol)			
Patient had full course of IMP but declined 4&5 of IV methylprednisolone	N/A	1 (50.0%)	1 (50.0%)
Patient withdrew before treatment commenced	N/A	1 (50.0%)	1 (50.0%)
Received additional treatment			
No	3 (27.3%)	4 (40.0%)	7 (33.3%)
Yes	4 (36.4%)	2 (20.0%)	6 (28.6%)
Missing	4 (36.4%)	4 (40.0%)	8 (38.1%)
Additional treatment received (denominator: those who received additional treatment)			
Plasma Exchange	1 (25.0%)	0 (0.0%)	1 (16.7%)
IVIG	0 (0.0%)	1 (50.0%)	1 (16.7%)
Rituximab	2 (50.0%)	0 (0.0%)	2 (33.3%)
Anti-epileptic	0 (0.0%)	1 (50.0%)	1 (16.7%)
IVIG & plasma exchange	1 (25.0%)	0 (0.0%)	1 (16.7%)
Reason for additional treatment (denominator: those who received additional treatment)			
Lack of patient improvement	4 (100.0%)	1 (50.0%)	5 (83.3%)
Control of seizures	0 (0.0%)	1 (50.0%)	1 (16.7%)
Clinically defined relapse since baseline (returning symptoms of encephalitis after starting to recover)			
No	8 (72.7%)	8 (80.0%)	16 (76.2%)
Yes	3 (27.3%)	1 (10.0%)	4 (19.0%)
Missing	0 (0.0%)	1 (10.0%)	1 (4.8%)
Admitted to ITU or HDU between baseline and 3-months			
No	10 (90.9%)	9 (90.0%)	19 (90.5%)

Yes	1 (9.1%)	0 (0.0%)	1 (4.8%)
Missing	0 (0.0%)	1 (10.0%)	1 (4.8%)
Experienced seizures between baseline and 3-months			
No	6 (54.6%)	6 (60.0%)	12 (57.1%)
Yes	5 (45.5%)	3 (30.0%)	8 (38.1%)
Missing	0 (0.0%)	1 (10.0%)	1 (4.8%)
Required ventilatory support between baseline and 3-months			
No	10 (90.9%)	8 (80.0%)	18 (85.7%)
Yes	1 (9.1%)	1 (10.0%)	2 (9.5%)
Missing	0 (0.0%)	1 (10.0%)	1 (4.8%)
Mortality (while in the trial)			
No	7 (63.6%)	6 (60.0%)	13 (61.9%)
Yes	1 (9.1%)	2 (20.0%)	3 (14.3%)
Withdrew	3 (27.3%)	2 (20.0%)	5 (23.8%)
Time until death (days)	77.0 [77.0, 77.0] N=1	441.5 [107.0, 776.0] N=2	107.0 [77.0, 776.0] N=3
Death related to Encephalitis (denominator: those who died)			
No	1 (100.0%)	0 (0.0%)	1 (33.3%)
Yes	0 (0.0%)	1 (50.0%)	1 (33.3%)
Missing*	0 (0.0%)	1 (50.0%)	1 (33.3%)
Cause of death related to IVIG (denominator: those who died)			
No	1 (100.0%)	1 (50.0%)	2 (66.7%)
Missing*	0 (0.0%)	1 (50.0%)	1 (33.3%)
Cause of death (denominator: those who died)			
Disseminated intravascular coagulation & Autoimmune encephalitis	0 (0.0%)	1 (50.0%)	1 (33.3%)
Ischaemic heart disease, Pneumonia & Crohn's disease	1 (50.0%)	0 (0.0%)	1 (33.3%)
Missing*	0 (0.0%)	1 (50.0%)	1 (33.3%)
Adherent (commenced treatment within 5 days)			
No	0 (0.0%)	1 (10.0%)	1 (4.8%)
Yes	11 (100.0%)	9 (90.0%)	20 (95.2%)
Received additional IVIG			
No	8 (72.7%)	7 (70.0%)	15 (71.4%)
Yes	1 (9.1%)	1 (10.0%)	2 (9.5%)
Missing	2 (18.2%)	2 (20.0%)	4 (19.0%)
% of doses received (denominator: those who received additional IVIG)			
+/- 55g stopped mid infusion on day 4	0 (0.0%)	1 (100%)	1 (50.0%)
Missing	1 (100%)	0 (0.0%)	1 (50.0%)

Number of days on treatment	N/A (missing) N=0	4 [4,4] N=1	4 [4, 4] N=1
Contaminated (received IVIG within 14 days in placebo arm)			
No	11 (100.0%)	N/A	11 (100.0%)
Days to first discharge from hospital	25.0 [14.0, 53.0] N=9	13.0 [11.5, 16.0] N=8	14.0 [13.0, 43.0] N=17
Days to last discharge from hospital	58.0 [25.0, 81.0] N=6	14.5 [13.0, 30.5] N=8	21.5 [13.0, 63.0] N=14

*Cause of death could not be ascertained for one participant who died in the community and the death certificate was not accessible. Continuous data summarised by median [Q25, Q75]. EQ5D3L = EuroQol 5-Dimension 3-Level version, IVIG = Intravenous Immunoglobulin, ITU = Intensive Therapy Unit, HDU = High Dependency Unit.

Adverse Events

	Arm		
	Placebo	**IVIG**	**Total**
N	11 (52.4%)	10 (47.6%)	21 (100.0%)
Experienced an adverse event			
No	1 (9.1%)	1 (10.0%)	2 (9.5%)
Yes	10 (90.9%)	8 (80.0%)	18 (85.7%)
Missing	0 (0.0%)	1 (10.0%)	1 (4.8%)
Number of AEs per participant	1.8 (1.3) N=10	3.1 (2.0) N=8	2.4 (1.8) N=18
Gastrointestinal bleed*	0 (0.0%)	3 (37.5%)	3 (16.7%)
New onset severe depression or worsening depression*	1 (10.0%)	2 (25.0%)	3 (16.7%)
New onset severe paranoia or worsening paranoia*	1 (10.0%)	1 (12.5%)	2 (11.1%)
New visual or auditory hallucinations*	1 (10.0%)	0 (0.0%)	1 (5.6%)
New onset delusions*	1 (10.0%)	0 (0.0%)	1 (5.6%)
Hyperglycemia*	1 (10.0%)	1 (12.5%)	2 (11.1%)
Gastrointestinal tract infection*	0 (0.0%)	1 (12.5%)	1 (5.6%)
Intraabdominal infection*	1 (10.0%)	0 (0.0%)	1 (5.6%)
Soft tissue infection*	1 (10.0%)	0 (0.0%)	1 (5.6%)
Clostridium difficile infection*	1 (10.0%)	1 (12.5%)	2 (11.1%)
Urinary tract infection*	3 (30.0%)	2 (25.0%)	5 (27.8%)
Blood stream infection*	1 (10.0%)	1 (12.5%)	2 (11.1%)
Pneumonia*	4 (40.0%)	0 (0.0%)	4 (22.2%)
Herpes Virus*	0 (0.0%)	1 (12.5%)	1 (5.6%)
Venous thromboembolism*	0 (0.0%)	1 (12.5%)	1 (5.6%)
Other*	4 (40.0%)	6 (75.0%)	10 (55.6%)