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A clinical study to learn whether a new drug, TPN-101, is safe when given to AGS patients

Submission date 29/07/2022	**Recruitment status** Stopped	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 07/11/2022	**Overall study status** Stopped	
Last Edited 17/10/2023	**Condition category** Nervous System Diseases	

Plain English summary of protocol

Background and study aims
Aicardi-Goutières Syndrome (AGS) is a genetic disorder characterised by weak or stiffened muscles, the loss of brain cells (cerebral atrophy) and can lead to intellectual and physical impairments. There are currently no approved medications for AGS making it very important to evaluate new and alternative approaches. The purpose of this study is to discover if the experimental medication, TPN-101 can inhibit the accumulation of harmful DNA copies in the nerve cells in the brain, a characteristic of AGS; this, in turn would ameliorate symptoms in AGS patients.

Who can participate?
This is a multi-centre, open-label single dose level study taking place in roughly 3-5 sites in France, Italy, the United Kingdom or the United States.
Approximately 10-16 patients will be enrolled. Male and female participants will be grouped into cohorts based on age;
Cohort 1: Adults 18 years and above
Cohort 2: Adolescents (12-17 years of age)
Cohort 3: Children 5-11 years of age
Cohort 4: Children under 5 years of age

What does the study involve?
Participants must provide written informed consent prior to undergoing study procedures. After Screening assessments are complete, all eligible subjects will receive TPN-101 daily by oral administration for 48 weeks during the open-label treatment period.
This study includes blood sampling, physical and neurological examinations, health questionnaires and optional MRI scans. The study will involve ionising radiation, even if this will only apply in the small minority of participants who undergo image-guided lumbar puncture.
Participants' total time in the study will be approximately 66 weeks: a screening period of up to 6 weeks, a treatment period of up to 48 weeks and a follow-up period of 12 weeks after lost dose of study medication. A data safety monitoring board (DSMB), consisting of experts in rare neurological disorders, drug safety and statistics will monitor the emerging safety data throughout the study.

What are the possible benefits and risks of participating?
Benefits:
The potential benefits of TPN-101 and taking part in this clinical study are unknown. However, the knowledge gained from this study may help the study doctor and other physicians participating in this clinical study determine what treatment to provide other AGS patients in the future. We cannot and do not guarantee or promise that participants will receive any benefits from this study.
Risks:
The potential risks and burdens for this study are provided in the Participant Information Sheet and Informed Consent Form(s) (PIS-ICF(s)). The participants will therefore know about these risks and burdens prior to taking part in the study. Due to the character limit for this question please refer to the PIS-ICF(s) for the risks and burdens. The management of these risks and burdens is presented below.

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements at various time points during the study, and by the documentation of AEs.

A Data Safety Monitoring Board (DSMB), consisting of external experts in rare neurological disorders, drug safety, and statistics will monitor the emerging safety data throughout the study and will meet after age cohort has been fully enrolled and all participants have completed the Week 4 visit, after all participants in the first age cohort have completed the Week 12 visit, and approximately every 12 weeks or for cause thereafter to review available safety data. The DSMB will review the available safety data and recommend whether dosing should be terminated, continued, altered or if any additional monitoring procedures or safety precautions need to be initiated.

Where is the study run from?
Transposon Therapeutics, Inc (USA)

When is the study starting and how long is it expected to run for?
July 2022 to January 2025

Who is funding the study?
Transposon Therapeutics, Inc (USA)

Who is the main contact?
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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-000064-21

Integrated Research Application System (IRAS)
1005838

Central Portfolio Management System (CPMS)
52954

Protocol serial number
TPN-101-AGS-201

Study information

Scientific Title
A phase 2a study of TPN-101 in patients with Aicardi-Goutières Syndrome (AGS)

Study objectives
Primary objectives:
1. To demonstrate proof-of-mechanism for TPN-101 in AGS, as evidenced by reduction in interferon (IFN) score
2. To assess the safety and tolerability of TPN-101 in patients with (AGS)

Secondary objectives:
1. To assess PK of TPN-101 in plasma and CSF
2. To assess the PD effects of TPN-101 in blood and CSF
3. To assess effect of TPN-101 on cerebral blood flow
4. To assess clinical and functional status

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/11/2022, Scotland A REC (2ndFloor, Waverley Gate, 2-4 Waterloo Place, Edinburgh, EH1 3EG, UK; +44 (0)131465 5680; Manx.Neill@nhslothian.scot.nhs.uk), ref: 22/SS/0068

Study design
Interventional non randomized

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Aicardi-Goutières Syndrome (AGS)

Interventions
In this study, all participants will receive TPN101. The participant, their caregiver, and the study team will know the dose of TPN101 the participant receives. If the participant qualifies for enrolment and decides to take part in this research study, their total participation will last for up to 66 weeks. This includes:
• A Screening Period of up to 6 weeks (to confirm eligibility for the study)
• A Treatment Period of 48 weeks (when participants will receive TPN101)
• A Follow-up Period of 12 weeks after participants' last dose of the study medication

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
TPN-101 [Censavudine]

Primary outcome(s)
1. Determine the reduction in innate immune signalling, as assessed by the expression of 24 ISG, used to calculate an IFN score in whole blood from screening (Day -42) through to Day 420 (follow-up)
2. Determine the incidence and severity of treatment-emergent adverse events (TEAEs) with TPN-101 administered for up to 48 weeks in patients with AGS

Key secondary outcome(s))
1. Determine concentrations of TPN-101 in plasma and CSF from screening (Day -42) , day 84 and day 336
2. Determine L1 expression, including L1 RNA on days 1, 28, 84, 168, 252 and 336.
3. Determine IFN status in blood and CSF, including IFN-alpha and IFN-gamma, as well as by measuring antiviral protective capacity (IFN activity) in patient serum and CSF, and genome-wide RNA Seq expression analysis in whole blood from screening (Day -42) through to Day 420 (follow-up
4. Determine other inflammatory biomarkers in blood and CSF, (e.g., neopterin) from screening (Day -42) through to Day 420 (follow-up)
5. Determine neurodegeneration biomarkers, including NfL, UCHL-1, tau, and GFAP in blood and CSF from screening (Day -42) through to Day 420 (follow-up)
6. Determine brain magnetic resonance imaging (MRI) including arterial spin labelling for measurement of cerebral blood flow at Days 1 and 336
7. Determine clinical and functional status, as measured by Vineland-3, AGS Scale, Caregiver Diary Score, BSID III, WPPSI-IV, WISC-V, WAIS-IV, GMFM-88, and classification according to 5 systems: GMFCS, MACS, CFCS, EDACS, and VFCS at days 1, 168, 336 and 420

Completion date
01/01/2025

Reason abandoned (if study stopped)
Lack of staff/facilities/resources

Eligibility

Key inclusion criteria
1. Male or female participants of the following ages:
1.1. Cohort 1: Adults (≥18 years of age)
1.2. Cohort 2: Adolescents (12 to 17 years of age)
1.3. Cohort 3: Children 5 to 11 years of age
1.4. Cohort 4: Children <5 years of age and >=6 kg in weight
2. Molecular diagnosis of AGS due to biallelic mutations in 1 of the following 5 genes: TREX1, RNASEH2A, RNASEH2B, RNASEH2C, or SAMHD1, or due to a recognized dominant mutation in TREX1.
3. IFN score in peripheral blood >2 standard deviations above the mean score of healthy controls measured on 3 occasions, approximately 2 weeks apart, during the 6-week Screening Period. The IFN score, determined on a Nanostring panel, is the median fold change in expression of a panel of 24 interferon-stimulated genes (ISGs) compared with the median IFN score of healthy controls.
4. Clinical syndrome consistent with AGS diagnosis based on clinical, CSF, and radiological findings. The following are examples of such findings (none of these are required for inclusion):
4.1. Early onset encephalopathy with psychomotor delay, spasticity, extrapyramidal signs, and

microcephaly, the latter appearing in the first year of life
4.2. Calcifications particularly visible at basal ganglia level (putamen, pallidus, and thalamus), but also extending to the periventricular white matter
4.3. Cerebral white matter abnormalities
4.4. Cerebral atrophy
4.5. Important systemic symptoms in the early stages of the disease including irritability, feeding and sleeping difficulties, unexplained fevers, and the appearance of chilblain-like skin lesions on the fingers, toes, and ears
5. Women of childbearing potential (WOCBP) must be surgically sterilized (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), or agree to use highly effective methods of contraception, e.g., combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of
ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner (provided that the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success); or sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments), from Screening through 3 months after the last dose of the study medication. Women who are pregnant or breastfeeding are not eligible for enrollment.
6. Has a reliable caregiver to accompany the patient to all study visits. Caregiver must have frequent contact with patient and be willing to monitor the patient's health and concomitant medications throughout the study.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Sex
All

Key exclusion criteria
1. Mutation in IFIH1, ADAR1, LSM11, or RNU7-1.
2. Pre-/perinatal infections, in particular the TORCH complex (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus)
3. Presence of other significant neurological disorders; brain tumor or other space-occupying lesion; history of severe head injury
4. Clinically significant intercurrent illness, medical condition (e.g., hematological, endocrine, cardiovascular, renal, hepatic, or gastrointestinal disease) or medical history (including neurological or mental illness) that would jeopardize the safety of the patient, limit participation, or compromise the interpretation of the data derived from the patient
5. Autoimmune disease requiring treatment or management (quiescent rheumatoid arthritis, psoriasis, treated autoimmune thyroiditis, or controlled Type 1 diabetes are acceptable)
6. History of human immunodeficiency virus (HIV), hepatitis B, or any active infection during Screening, unless the patient will have been symptom-free for at least 30 days prior to study drug administration. Patients with treated hepatitis C with no laboratory evidence of active disease and liver enzymes <2 × upper limit of normal (ULN) are allowed

7. History of cancer within 5 years of Screening, with the exception of fully treated non-melanoma skin cancers
8. Receipt of an experimental agent within 30 days or 5 half-lives prior to Screening, whichever is longer
9. Prior treatment with an immunomodulator other than a JAK inhibitor within 6 months of Screening; patients taking JAK inhibitors for AGS must have been on a stable dose for one month prior to Screening
10. Current treatment with a nucleoside reverse transcriptase inhibitor (NRTI) or other antiviral drug
11. Receipt of systemic corticosteroids within 30 days prior to Screening
12. Any vaccination within 30 days prior to Screening
13. Any major surgery within 30 days of Screening or any planned major surgery during the study
14. For patients who agree to the optional lumbar puncture (LP), any contraindication to undergoing an LP including, but not limited to:
14.1. Inability to tolerate an appropriately flexed position for the time necessary to perform an LP; international normalized ratio (INR) >1.4 or other coagulopathy; platelet count of <120,000 /µL
14.2. Infection at the desired LP site
14.3. Taking anti-platelet or anti-coagulant medication within 30 days of Screening (Note: low dose aspirin is permitted but should be stopped 5 days prior to the LP)
14.4. Severe deformity or abnormality of the lumbar spine
14.5. Suspected non-communicating hydrocephalus or intracranial mass
14.6. Prior history of spinal mass or trauma
15. History of any significant drug allergy (such as anaphylaxis or hepatotoxicity)
16. Physical and laboratory test findings, including the following:
16.1. Evidence of organ dysfunction or any clinically significant deviation from normal physical examination or vital signs that are not specific to AGS and that could interfere with the conduct of the study, the interpretation of the data, or increase patient risk, in the opinion of the investigator
16.2. Clinically significant abnormality on 12-lead ECG prior to study drug administration, confirmed by repeat testing
16.3. Total alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2× ULN, confirmed by repeat testing
16.4. Total bilirubin >1.2 × the ULN (unless due to Gilbert's syndrome)
16.5. Serum creatinine >168 µmol/L (1.9 mg/dL), confirmed by repeat testing
16.6. Hemoglobin less than 7.5 g/dL or absolute neutrophil cell count of <1500/µL
16.7. Positive blood screen for HIV or hepatitis B surface antigen
16.7. Positive urine drug screen

Date of first enrolment
01/10/2023

Date of final enrolment
01/01/2025

Locations

Countries of recruitment
United Kingdom

Scotland

France

Italy

Study participating centre
Royal Hospital for Children and Young People
Edinburgh Bio Quarter
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Sponsor information

Organisation
Transposon Therapeutics, Inc

Funder(s)

Funder type
Industry

Funder Name
Transposon Therapeutics, Inc

Results and Publications

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary
Published as a supplement to the results publication