A Phase 2a Study of TPN-101 in Patients with C9ORF72 ALS/FTD (Amyotrophic Lateral Sclerosis and/or Frontotemporal Dementia)

Published: 04-10-2021
Last updated: 05-04-2024

The primary objective of this study is:* To assess the safety and tolerability of TPN-101 in patients with C9ORF72 ALS/FTDThe exploratory objectives of this study are:* To assess the concentrations of TPN-101 in plasma and cerebrospinal fluid (CSF…

Ethical review	Not approved
Status	Will not start
Health condition type	Spinal cord and nerve root disorders
Study type	Interventional

Summary

ID

NL-OMON52346

Source
ToetsingOnline

Brief title
TPN-101-C9-201

Condition

- Spinal cord and nerve root disorders

Synonym
Amyotrophic lateral sclerosis, motor neurone disease; Frontotemporal dementia, Pick's disease

Research involving
Human

Sponsors and support

Primary sponsor: Transposon Therapeutics, Inc
Source(s) of monetary or material Support: Transposon Therapeutics

Intervention

Keyword: amyotrophic lateral sclerosis, frontotemporal dementia, neurodegenerative diseases

Outcome measures

Primary outcome

The primary endpoint is:

* Incidence and severity of treatment-emergent AEs (TEAEs) of TPN-101

administered for

up to 48 weeks in patients with C9ORF72 ALS/FTD

Secondary outcome

Exploratory Efficacy Endpoints

* Concentrations of TPN-101 in plasma and CSF

* Target engagement of TPN-101 in blood as measured by L1 cDNA

* Disease-related biomarkers

* Disease modification-related neuro-biomarkers, including neurofilament light

chain

(NfL) and neurofilament heavy chain (pNfH) in blood and CSF

* Inflammatory biomarkers in blood and/or CSF

* Clinical and functional status, as measured by ALS Functional Rating

Scale-Revised

(ALSFRS-R), ALS Assessment Questionnaire-40 item (ALSAQ-40), slow vital capacity

Transposon Therapeutics, Inc. Clinical Protocol TPN-101-C9-201

(SVC), CDR Dementia Staging Instrument plus National Alzheimer's Coordinating Center Behavior and Language Domains * Sum of Boxes (CDR plus NACC FTLD-SB), FTD Rating Scale, Color Trails, Stroop Color and Word Test, Montreal Cognitive Assessment (MoCA), Cortical Basal Ganglia Functional Scale (CBFS), Center for Neurologic Study * Bulbar Function Scale (CNS-BFS), ALS Cognitive Behavioral Scale

(ALS-CBS), and Neuropsychiatric Inventory*Questionnaire (NPI-Q)

* Survival

* Other safety assessments, including clinically significant changes in physical examinations, neurological examinations, vital sign measurements, body weight, clinical

laboratory tests, electrocardiograms (ECGs), and assessments of suicidality

(i.e., Columbia Suicide Severity Rating Scale [C-SSRS])

Study description

Background summary

TPN-101 is a 4*-substituted nucleoside analog of the commercially available antiretroviral drug
d4T and has a chemical name of 2*,3*-didehydro-2*,3*-deoxy-4*-ethynylthymidine (4*- ethynyld4T). TPN-101 is an inhibitor of the hL1 ORF2 RT enzyme, and therefore inhibits reverse
transcription of L1 RNA to generate cDNA copies of the hL1 genome.
TPN-101 has been developed through clinical Phase 2b studies as an oral, once daily nucleoside
reverse transcriptase inhibitor (NRTI) for human immunodeficiency virus-type 1 (HIV-1)

infection. TPN-101 was well tolerated in clinical studies in healthy volunteers (n=84) and HIV-1
infected patients (n =222) and showed evidence of efficacy in a Phase 2b study in patients with
HIV-1. However, the human immunodeficiency virus (HIV) program was terminated for
strategic reasons by the prior sponsor and ownership of the Investigational New Drug (IND) was
transferred to Transposon (IND 74750) on June 30, 2020.
The sponsor is developing TPN-101 for the treatment of neurodegenerative diseases,
including C9ORF72 ALS/FTD. Nonclinical pharmacology studies demonstrate that TPN-101
inhibits hL1 RT-dependent retrotransposition in cultured cells with a potency directly
comparable to its antiviral half maximal effective concentration (EC50) for HIV-1.
The attendant effects of hL1 ORF2 inhibition are anticipated to be a reduction in the cDNA
burden in affected cells of neuronal and glial origin in which overexpression of hL1 is occurring.
There are no validated and predictive disease relevant animal models that can be used to reliably
assess the potential effects of TPN-101 in diseased human brain. There is an abundance of
mechanistic support in model organism studies to support the hypothesis that successful
suppression of hL1 ORF2 will mitigate hL1driven neuropathology.
A battery of other studies (completed and ongoing) indicates TPN-101 has low potential for
off-target and, particularly, mitochondrial toxicities. Based on extensive in vitro assessments, it

has been determined that the likelihood of cytochrome P450- or transporter-mediated drug-drug
interactions with TPN-101 is negligible.

Study objective

The primary objective of this study is:
* To assess the safety and tolerability of TPN-101 in patients with C9ORF72 ALS/FTD

The exploratory objectives of this study are:
* To assess the concentrations of TPN-101 in plasma and cerebrospinal fluid

(CSF)
* To assess target engagement of TPN-101 in blood
* To assess disease-related biomarkers
* To assess the PD effects of TPN-101 in blood and CSF
* To assess inflammatory biomarkers in blood and/or CSF
* To assess clinical and functional status
* To assess survival

Study design

This is a Phase 2a multi-center, randomized, double-blind, placebo-controlled parallel-group,
2-arm study with a long-term, open-label treatment phase in patients with C9ORF72 ALS and/or
FTD. This study includes a 6-week Screening Period, a 24-week Double-blind Treatment Period,
a 24-week Open-label Treatment Period, and a Follow-up Visit 4-weeks post-treatment.
After providing written informed consent, patients will undergo screening assessments. Patients
must meet all inclusion criteria and none of the exclusion criteria to be enrolled in this study.
Approximately 40 patients will be enrolled in the study, with a target enrollment of roughly
equal numbers of patients with C9ORF72 ALS (with or without FTD) and FTD.
Eligible patients will be randomly assigned in the Double-blind Treatment Period in a 3:2 ratio to
one of the following two treatment arms:
* TPN-101, 400 mg/day
* placebo
Patient randomization will be stratified by clinical phenotype into the following 2 strata:
1) patients who meet ALS criteria with or without FTD symptoms and 2) patients with pure FTD
or primarily FTD symptoms who do not meet ALS criteria.
Blinded study drug will be taken daily for 24 weeks. Patients and their caregivers will return to
the study site at Weeks 2, 4, 8, 12, 18, and 24 for clinical and neurologic testing, safety
assessments, and TPN-101 concentration/PD sample collection.
During the Open-label Treatment Period, all patients who complete the Double-blind Treatment
Period will receive TPN-101 (400 mg/day) for 24 weeks. Patients who do not tolerate the
400 mg/day dose may have their dose reduced to 200 or 100 mg/day at the investigator*s
discretion. Patients and their caregivers will return to the clinic at Weeks

26, 32, 40, and 48 for
clinical and neurologic testing, safety assessments, and TPN-101
concentration/PD sample
collection.
A Follow-up Visit will occur approximately 4 weeks after the end of treatment
(i.e., Week 52)

This study is designed to evaluate the safety and tolerability of TPN-101 (400
mg/day) compared
with placebo in patients with C9ORF72 ALS/FTD. This study is also designed to
evaluate
exposure of TPN-101 in plasma and CSF, as well as identify evidence of target
engagement, PD
biomarkers indicative of effects of TPN-101 on disease activity, and the
effects of TPN-101 on
relevant clinical endpoints. This study is designed to provide data on PD
effects that, in
aggregate, may provide proof-of-concept for the treatment hypothesis and inform
decision-making about future development plans.

Intervention

Study drug will consist of capsules of placebo or TPN-101 (100 mg), which will
be identical in appearance.
Study drug will be taken by mouth each morning with or without food. The first
dose of study drug will be
administered in the clinic on Day 1. Study drug should be taken in the morning
at home on all other days.
During the Double-blind Treatment Period, patients will receive either placebo
or TPN-101 (400 mg/day).
During the Open-label Treatment Period, all patients will receive TPN-101 (400
mg/day). Patients who do not
tolerate the 400 mg/day dose may have their dose reduced to 200 or 100 mg/day
at the investigator*s discretion.

Study burden and risks

NA

Contacts

Public
Transposon Therapeutics, Inc

2765 Sand Hill Road c/o Canaan Partners na
Menlo Park 94025 CA
US
Scientific
Transposon Therapeutics, Inc

2765 Sand Hill Road c/o Canaan Partners na
Menlo Park 94025 CA
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Males or females * 18 years of age at the time of informed consent
2. Have documentation of a clinical genetic test demonstrating the presence of a confirmed repeat expansion in the C9orf72 gene from a CLIA certified laboratory
3. Body weight range of * 41 kg (90 lbs) to * 118 kg (260 lbs)
4. Score * 18 on the Mini-Mental State Exam (MMSE) at Screening
5. If female, must be postmenopausal (for at least 2 years), surgically sterilized (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), or agree to use highly effective methods of contraception from Screening through Week 52
6. If male, with a partner who is not postmenopausal (for at least 2 years) or surgically sterilized (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), the patient must agree that he and his partner will use highly effective methods of contraception from Screening through Week 52
7. Able to perform all protocol-specified assessments, including neuropsychological tests; and comply with taking study medication and the study visit schedule, as judged by the investigator
8. Have a reliable caregiver to accompany the patient to all study visits.

Caregiver must be able to read, understand, and speak local language fluently to ensure comprehension of informed consent and informant-based assessments of the patient. Caregiver must also have frequent contact with patient (at least 3 hours per week at one time or at different times) and be willing to monitor the patient's health and concomitant medications throughout the study
9. Able to understand and provide written informed consent at Screening
10. Agree to allow data sharing across observational longitudinal and interventional studies using an encrypted global unique identifier (GUID) so that potential prior or future data on biomarkers and disease progression can be made accessible to the sponsor
11. Stable doses of all concomitant medications for 1 month prior to Screening (e.g., edaravone, riluzole, dextromethorphan/quinidine, psychotropic medications, cognitive enhancers, etc.)

For patients with ALS (with or without FTD):
12. Diagnosis of ALS (probable, possible, laboratory-supported probable or definite) according to the World Federation of Neurology revised E1 Escorial criteria
13. Onset of weakness within 3 years prior to Screening
14. SVC * 60% of predicted normal adjusted for sex, age, and height (from the sitting position)
15. Able to perform reproducible pulmonary function tests
16. ALSFRS-R * 30 at Screening

For patients with FTD:
17. A gradual, progressive decline in behavior, language, or motor function consistent with C9orf72 hexanucleotide expansion-related syndrome such as behavioral variant FTD, primary progressive aphasia, or amnestic syndrome
18. CDR plus NACC FTLD global score of 0.5-2.0 at Screening

Exclusion criteria

1. Presence of other significant neurological or psychiatric disorders including (but not limited to) biomarker confirmed Alzheimer's disease; dementia with Lewy bodies; prion disease; Parkinson's disease; multiple sclerosis; a primary or severe psychotic disorder; severe bipolar or unipolar depression; prior history of suicidal thoughts or behavior that are believed to represent a current safety risk; seizure; brain tumor or other space-occupying lesion; history of stroke; or history of severe head injury within the past 20 years
2. History of significant brain abnormality, including, but not limited to, prior hemorrhage or infarct, cerebral contusion, encephalomalacia, aneurysm, vascular malformation, subdural hematoma, hydrocephalus, space-occupying lesion (e.g., abscess or brain tumor such as meningioma); symptoms or signs of elevated intracranial pressure, e.g., symptoms or history of head injury or

abnormal funduscopic exam. If there is history or evidence on neurologic exam suggesting possible subdural hematoma (SDH), patients should be fully evaluated, including magnetic resonance imaging (MRI) if indicated, to exclude significant, new SDH
3. Active alcohol, drug abuse or substance abuse, or any other reason that makes it unlikely that the patient will comply with study procedures in the opinion of the investigator
4. Clinically significant findings on Screening laboratory testing, physical examination or vital signs that are not specific to ALS/FTD that could interfere with the conduct of the study, the interpretation of the data, or increase patient risk
5. Clinically significant intercurrent illness or medical condition (e.g., hematological, endocrine, cardiovascular, renal, hepatic, or gastrointestinal disease) that would jeopardize the safety of the patient, limit participation, or compromise the interpretation of the data derived from the patient
6. History of HIV infection, hepatitis B or hepatitis C, or any active infection
7. History of cancer within 5 years of Screening, with the exception of fully excised non-melanoma skin cancers
8. Receipt of an investigational agent within 30 days or 5 half-lives prior to Screening, whichever is longer
9. Prior treatment with any monoclonal antibody within 6 months of Screening
10. Receipt of systemic corticosteroids within 30 days prior to Screening
11. Any vaccination within 30 days prior to study drug administration
12. Has smoked or used tobacco products within 6 months prior to study drug administration
13. Hypertension, defined as confirmed systolic blood pressure (SBP) > 170 mmHg and/or diastolic blood pressure (DBP) > 100 mmHg at Screening
14. Hypotension, defined as confirmed SBP < 90 mmHg and/or DBP < 60 mmHg at Screening
15. Any major surgery within 4 weeks of Screening
16. Females who are pregnant (positive pregnancy test at Screening or prior to administration of study drug), breastfeeding, or unable or unwilling to use highly effective methods of contraception throughout the study
17. Contraindication to undergoing a lumbar puncture (LP) including, but not limited to: 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/*L; infection at the desired LP site; taking anti-platelet or anti-coagulant medication within 30 days of Screening (Note: aspirin is permitted); severe degenerative arthritis of the lumbar spine; suspected non-communicating hydrocephalus or intracranial mass; prior history of spinal mass or trauma
18. Allergy to any of the components of the study drug
19. History of any significant drug allergy (such as anaphylaxis or hepatotoxicity)
20. Physical and laboratory test findings, including the following:
a. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory

determinations beyond what is consistent with the target population
b. Clinically significant abnormality on 12-lead ECG prior to study drug administration, confirmed by repeat testing
c. Total bilirubin, alanine aminotransferase (ALT), or aspartate aminotransferase (AST) > 2 × upper limit of normal (ULN), confirmed by repeat testing
d. Serum creatinine > 168*mol/L (1.9mg/dL), confirmed by repeat testing
e. Hematocrit < 35% for males and < 32% for females, absolute neutrophil cell count of < 1500/*L
f. Clinically significant abnormal thyroid stimulating hormone (TSH) test
g. Abnormally increased number of white blood cells (> 7 cells/mm3) in the CSF obtained at the Screening Visit; if there is evidence that the spinal tap was traumatic, patients with > 7 cells/mm3 must be discussed with the medical monitor to determine if they may be eligible
h. Hemoglobin A1C >7%, confirmed by repeat testing
i. Positive blood screen for HIV, hepatitis C antibody, or hepatitis B surface antigen

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Brand name:	TPN-101
Generic name:	Censavudine

Ethics review

Approved WMO Date:	04-10-2021
Application type:	First submission
Review commission:	METC NedMec
Not approved Date:	05-07-2022
Application type:	First submission
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-002251-11-NL
ClinicalTrials.gov	NCT04993755
CCMO	NL78812.041.21