A multicenter, randomized, double-blind, placebo-controlled study of enzastaurin for the prevention of arterial events in patients with vascular Ehlers-Danlos Syndrome (vEDS) confirmed with COL3A1 mutations, followed by an open label extension (OLE)

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The aim of this study is to evaluate the efficacy, safety, and pharmacokinetics (PK) of enzastaurin in preventing new arterial events (rupture, dissection, pseudoaneurysm, carotid-cavernous sinus fistula, or aneurysm, fatal or not) leading to...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Connective tissue disorders (excl congenital)
Study type	Interventional

Summary

ID

NL-OMON51515

Source
ToetsingOnline

Brief title
AR-101-PREVEnt

Condition

- Connective tissue disorders (excl congenital)

Synonym
connective tissue disorder, vascular Ehlers-Danlos Syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Aytu BioPharma, Inc
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Enzastaurin, Phase 3, Vascular Ehlers-Danlos Syndrome (vEDS)

Outcome measures

Primary outcome

Primary efficacy endpoint

• Time to intervention for an arterial event (rupture, dissection, pseudoaneurysm, carotid-cavernous sinus fistula, or aneurysm, fatal or not) or mortality attributable to an arterial event, as adjudicated by an Event Committee and analyzed for difference in the time-to-composite-event of active vs. placebo treatments, using survival analysis until end of study

Secondary outcome

Secondary safety and tolerability endpoint

• Safety assessments include adverse events (AEs), vital signs, physical examinations, ophthalmological examinations, clinical laboratory values, and electrocardiograms (ECGs)

• Number of patients who discontinue study drug due to AEs

Secondary efficacy endpoint

• Time to intervention for repair (to include catheter-based procedures) of an arterial event (rupture, dissection, pseudoaneurysm, carotid-cavernous sinus

fistula, or aneurysm, fatal or not), as adjudicated by an Event Committee

• Reduction in the rate of intestinal rupture, pneumothorax, retinal

detachment, as adjudicated by an Event Committee

• Emergent hospitalization for management of an arterial event

• Time to arterial event

• Rate of arterial event

• Time to arterial rupture

• Rate of arterial rupture

• Time to arterial dissection

• Rate of arterial dissection

• Time to pseudoaneurysm

• Rate of pseudoaneurysm

• Time to carotid-cavernous sinus fistula

• Rate of carotid-cavernous sinus fistula

• Time to aneurysm

• Rate of aneurysm

• Change in Health-Related Quality of Life (HRQL) SF-36

• Change in Ped-QL (Pediatric Quality of Life Inventory

Study description

Background summary

vEDS is an autosomal-dominant inherited connective tissue disorder caused by heterozygous mutations in the COL3A1 gene, which encodes the pro-α 1 chain of collagen III. vEDS is a sub-type of Ehlers-Danlos Syndrome (EDS). vEDS is a rare disease, with a prevalence of 1 in 50,000 to 1 in 200,000 (Byers et al,

2017). Initial diagnosis depends on the recognitions of clinical features (thin, translucent skin, easy bruising, and a characteristic facial appearance) including family history. Most critically, patients are at risk for spontaneous rupture of the major arteries, hollow organs, and gravid uterus. About 25% of patients have a first complication by the age of 20 and more than 80% have at least one complication by the age of 40 (Pepin et al, 2000). The life span for affected individuals is a median age of about 51 years (49 for males and 53 for females) (Pepin et al, 2014; Frank et al, 2019). There are no currently approved therapies, and management is complex and requires multiple specialists who can respond to and manage the major vascular complications. Various antihypertensive agents may be prescribed.
Two mouse models were created for vEDS that carry heterozygous mutations in COL3A1 that encode glycine substitutions analogous to those found in humans with vEDS and showed that signaling abnormalities in the phospholipase C/inositol 1,4,5-triphosphate/protein kinase C/extracellular signal-regulated kinase pathway (PLC/IP3/PKC/ERK) are major mediators of
vascular pathology. Treatment with pharmacologic inhibitors of ERK1/2 or PKCβ prevented death due to spontaneous aortic rupture (Bowen et al, 2020). The results provide evidence that targetable signaling abnormalities contribute to the pathogenesis of vEDS, highlighting unanticipated therapeutic opportunities.
Enzastaurin is an orally available investigational first-in-class small molecule, serine/threonine kinase inhibitor of the PKCβ, phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT) pathways.
In the murine model, pharmacologic inhibition using a specific PKCβ inhibitor, enzastaurin
(60 mg/kg/d), reduced the risk of death from aortic dissection by 60%, with 80% of enzastaurin treated vEDS mice surviving after 40 days of treatment compared to only 50% of untreated vEDS mice ($p = 0.0305$) (WO2020/081741). Further elucidating that aberrant cellular signaling is the driver of disease, phosphorylated PKCβ was found in two human vascular tissue samples of patients who died from genetically confirmed vEDS.

Study objective

The aim of this study is to evaluate the efficacy, safety, and pharmacokinetics (PK) of enzastaurin in preventing new arterial events (rupture, dissection, pseudoaneurysm, carotid-cavernous sinus fistula, or aneurysm, fatal or not) leading to intervention or mortality attributable to arterial events in patients with vEDS confirmed with pathogenic variant of COL3A1 gene mutations, compared to placebo. As adjudication will be performed independently by an Event Committee, intervention is denoted as (i) emergent hospitalization for management of an arterial event (ii) surgery for repair (to include catheter-based procedures), and (iii) symptom-based investigations where intervention is potentially indicated but the risk of intervention exceeds the risk of the disease thus precipitating no intervention.

Study design

4.1 Overall Design (page 35 PA3)
This is a multicenter, randomized, double-blind, placebo-controlled study with patients with vEDS receiving enzastaurin 500 mg QD compared to placebo, in addition to background standard of care, followed by an open label extension (OLE) phase.
The study will consist of two arms and patients with vEDS will be randomized in a 1:1 ratio to receive 500 mg enzastaurin QD plus background standard of care or matching placebo QD plus background standard of care for up to 30 months. The study will also include a 6 month OLE phase. The objectives and endpoints will be to evaluate the ongoing efficacy of enzastaurin compared to placebo in preventing new arterial events (rupture, dissection, pseudoaneurysm, carotid cavernous sinus fistula or aneurysm) leading to intervention or mortality attributable to an arterial event, time to intervention for repair of an arterial event, reduction in rates of intestinal rupture, pneumothorax, and retinal detachment as well as evaluation of the safety and tolerability of enzastaurin.
Approximately 220 to 240 adult patients with vEDS are planned to be randomized in a 1:1 ratio of enzastaurin or placebo, and approximately 20 to 40 adolescent patients with vEDS are planned to be randomized in a 1:1 ratio of enzastaurin or placebo. Patients with vEDS will be enrolled in the trial if they meet the inclusion criteria consisting of age between 18-60 years (for adults) and 12 17 years (adolescent patients) at the time of pivotal study start.
As part of the assessment of inclusion and exclusion criteria, all COL3A1 genetic variants will be reviewed by the Genetic Variant Adjudication Committee. The diagnosis of vEDS, and inclusion in the study, rests on the identification of a pathogenic variant in one allele of COL3A1 that is shown or predicted to result in production of an abnormal protein. Individuals with these *dominant-negative* variants tend to have more severe clinical presentations of vEDS. This is the most common class of variants that causes vEDS and includes: (i) Missense variants that result in substitution of glycines at the +1 position in the Gly-Xaa-Yaa repeat of the triple helical domain of COL3A1; (ii) Splice site variants (excluding G>A at the -1 position); and (iii) In-frame insertions or deletions. Individuals with reduced amount of COL3A1 protein that results from *haploinsufficient* alleles tend to have milder clinical presentations of vEDS and are excluded from this study because these patients are at a reduced risk of arterial events. The use of anti-hypertensive medications and other chronic care medications such as vitamin C will be allowed as long as there are no specific contraindications with enzastaurin.
Patients with vEDS will be ineligible for the study if they are pregnant, are a woman of childbearing potential on inadequate contraception, or have contraindications related specifically to enzastaurin or PKC isoform inhibitor.
At the time of interim analysis, safety findings in adults will be utilized to inform the beginning of enrollment of adolescent patients.

Over the course of the up to 30-month study duration in the double-blind phase, visits will take place at baseline (Day 1), Day 15, Month 3, and then every 3 months thereafter up to EOS visit at Month 30; vascular imaging will be conducted at baseline and every 12 months. Periodic imaging analysis will be conducted via magnetic resonance angiography (MRA) to potentially include use of intravenous contrast. If contraindicated, then computed tomography (CT) scan can be utilized and potentially supplemented with ultrasound for selected arterial segments. For each patient, the same imaging modality will be used throughout the study. Standardized telephone or videoconference interviews may also be performed at interim timepoints. Data will be collected to allow for analysis including number of patients with an event, time to event, and total number of events for rate calculations.
An electrocardiogram (ECG) monitoring protocol will be utilized to exclude patients with a prolonged QT interval corrected for heart rate (QTc), and will consist of ECGs at baseline, 4 to 6 hours post-dose at Day 1, pre dose after steady state concentrations are reached (Day 15 [Month 0.5]), 4 to 6 hours post-dose at every visit to include Months 3, 6, 12, 18, 24, and 30. Upon completion, patients will be automatically rolled over in the OLE phase part of the study.
The OLE will be a single arm of patients treated with 500 mg enzastaurin QD starting at Month 30 and continuing for up to 6 months. Over the course of the 6-month OLE phase, visits will take place at the OLE baseline and at Month 6. At both visits, a full physical examination, drug monitoring, and events recorded during standardized questionnaires. Standardized telephone or videoconference interviews may also be performed at interim dates. Data will be collected to allow for analysis of efficacy as well as safety and tolerability endpoints.
An overview of study design is provided in the study schema (Section 1.2) and assessments to be performed in the study are provided in the SoA (Table 1 1).

Intervention

• Enzastaurin: 500 mg QD orally in the form of four 125 mg tablets with background standard of care
• Matching placebo with background standard of care

Study burden and risks

The study lasts 30 months
Blood samples and urine release
Risks of the procedures
Side effects of the medication

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

1. Adult patients must be 18-60 years of age inclusive, at the time of screening may be considered to enroll pending interim analysis.
2. Adolescent patients must be 12-17 years of age inclusive, at the time of screening.
3. Confirmed pathogenic COL3A1 genetic mutation via validated Laboratory Development Test (LDT) performed in a Clinical Laboratory Improvement Amendments (CLIA) laboratory or regulatory equivalent outside of the United States or an assay performed by a laboratory accredited according to the ISO 15189 standard by a national or regional accreditation body. As part of the assessment of inclusion and exclusion criteria, all COL3A1 genetic variants will be reviewed by the Genetic Variant Adjudication Committee. The diagnosis

of vEDS, and inclusion in the study, rests on the identification of a pathogenic variant in one allele of COL3A1 that is shown or predicted to result in production of an abnormal protein. Individuals with these *dominant-negative* variants tend to have more severe clinical presentations of vEDS. This is the most common class of variants that causes vEDS and includes:
• Missense variants that result in substitution of glycines in the Gly-Xaa-Yaa repeat of the triple helical domain of COL3A1:
o The triple helical domain extends from amino acid positions 168-1196 of the protein. Eligible variants will cause the replacement of the invariant glycines at every 3rd amino acid position of this domain, following the sequence Gly-Xaa-Yaa-Gly-Xaa-Yaa-Gly-Xaa-Yaa*etc. where Xaa and Yaa represent any other amino acid. Substitutions of Gly residues that happen to occur at the Xaa or Yaa position are not eligible for inclusion as they are unlikely to cause vEDS.
• Splice site variants:
o A few nucleotides that precede and follow the coding regions (exons) in flanking regions called introns specify the site of the cleavage that removes the introns between exons to create a full-length mRNA. These nucleotides occur at the -2, -1 (before the exon), +1 and +2 (after the exon) positions of the introns that flank each block of coding sequence (called exons). Substitutions at these sites will alter correct splicing. The one exception that will generally not be eligible is the -1G>A substitution because it usually will result in mRNA instability.
• In-frame insertion or deletion:
o Insertions or deletions that are entirely within the coding sequence and are a multiple of 3 nucleotides (i.e., 3, 6, 9, etc.) will result in an *in-frame* mRNA that will be stable and give rise to an abnormal protein. Such variants will only be eligible if they occur in the triple helical domain of type III collagen (amino acids 168-1196).
4. The patient should be stable with no vEDS-related events in the within 3 months before screening.
5. Patients must have a negative SARS-CoV-2 test, regardless of vaccination status prior to starting treatment.
6. Sexually active female patients: unless surgically sterile or post-menopausal for at least 12 months, use 2 forms of contraception with failure rate of <1% per year continuously from the first administration of study drug until 3 months after last study drug administration.
• Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal)
• Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
• An intra-uterine device (IUD)
• An intra-uterine hormone releasing system
• Bilateral tubal occlusion
• Vasectomized partner
• Sexual abstinence
7. Male patient agrees to use barrier contraception (condom) during sexual intercourse with women of childbearing potential from the first administration

of study drug until 3 months after last study drug administration. The male patient is willing to ensure that the female sexual partner unless surgically sterile (i.e., after hysterectomy or bilateral oophorectomy) or postmenopausal for at least 12 months uses at least 1 additional method of contraception with a low failure rate defined as <1% per year as follows:
• Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal).
• Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable).
• An intra-uterine device (hormone-free).
• An intra-uterine deice (IUD).
• An intra-uterine hormone releasing system
• Bilateral tubal occlusion
• Vasectomy
• Sexual abstinence
8. Patients and/or appropriate legal guardian must sign an informed consent form and/or assent, as described in Appendix 1, Section 10.1.3, according to local, regional and/or country-specific guidance for study participation.

Exclusion criteria

1. Individuals with reduced amount of COL3A1 protein which are the result of *haploinsufficient* alleles tend to have milder clinical presentations of vEDS and are excluded from this study because these patients are at a reduced risk of arterial events. These variants are rarer and include:
• Variants that change the codon for an amino acid to one that encodes a premature termination codon (a *nonsense* variant).
• Splice site variants that are predicted or have been shown to lead to an unstable mRNA (due to *frameshift").
• *Frameshift* variants that involve the insertion or deletion of a block of nucleotides that is not a multiple of 3 nucleotides (i.e., 1, 2, 4, 5, 7, etc.). Such variants will *shift* the reading frame of the mRNA and will predictably lead to a premature termination codon and an unstable mRNA.
2. Currently being treated with strong or moderate inducers of cytochrome P450 3A4 (CYP3A4), such as carbamazepine and phenytoin or strong CYP3A4 inhibitors, such as ketoconazole, within 4 weeks prior to Visit 1. (FDA 2020)
3. Currently being treated with QTc prolonging medication within 4 weeks prior to Visit 1 (see Appendix 5).
4. Contraindications related to enzastaurin (known allergy or hypersensitivity to enzastaurin or any of its components or required use of a medication that is contraindicated in combination with enzastaurin).
5. Unable to swallow tablets or receive intact tablets.
6. Prior participation in any interventional clinical study in which patient received investigational therapeutic within 4 weeks prior to Visit1.
7. QTc interval by Fridericia*s formula is > 450 msec in males and > 470 msec

in females or if the patient has a known personal or family history of long QT syndrome during Screening.
8. The patient has one of the following conditions:
a. Any of the following clinical laboratory parameters exceeding the upper limit of normal (ULN): alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine and/or total bilirubin (>1.5 x ULN total bilirubin if known Gilbert*s syndrome). If a patient has elevations only in total bilirubin that are >1 x ULN and <1.5 x ULN, bilirubin will be fractionated to identify possible undiagnosed Gilbert*s syndrome (i.e., direct bilirubin <35%).
b. Thyroid-stimulating hormone outside the normal range.
9. Patient with a prior diagnosis of liver cancer or cirrhosis, chronic viral hepatitis, or some other defined etiology for chronic liver inflammation known to predispose to hepatocellular carcinoma.
10. Patient who is pregnant or breast feeding.
11. Women of childbearing potential on inadequate contraception.
12. An individual who has a medical, psychological or social condition that, in the opinion of the Principal Investigator, would interfere with the patient*s safety, obtaining informed consent, or compliance to the study procedures.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	50
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Enzastaurin
Generic name:	DB102

Ethics review

Approved WMO Date:	25-04-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-10-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-01-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-01-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2021-006574-23-NL
CCMO	NL80923.091.22

Study results

Summary results
Trial never started