A phase 2, 12-week, randomized, double-blind, placebo-controlled study of DS-1211b in individuals with pseudoxanthoma elasticum

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Primary:To assess the safety and tolerability of DS-1211b compared with placebo in subjects with PXE.To assess the dose response by assessing the treatment changes in PD endpoints.

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON51483

Source
ToetsingOnline

Brief title
DS1211-A-U201

Condition

- Other condition

Synonym
tissue-nonspecific alkaline phosphatase (TNAP) inhibition

Health condition

pseudoxanthoma elasticum

Research involving
Human

Sponsors and support

Primary sponsor: Daiichi Sankyo, Inc
Source(s) of monetary or material Support: Daiichi Sankyo Inc.

Intervention

Keyword: 12-week, DS-1211b, pseudoxanthoma elasticum

Outcome measures

Primary outcome

Safety parameters: Incidence of adverse events(AEs), including serious adverse events (SAEs), and treatment-emergent AEs, physical examination/assessment findings including vital sign measurements, standard clinical laboratory parameters, and electrocardiograms.

Secondary outcome

PD endpoints: AProfiles of ALP, inorganic pyrophosphate (PPi), and pyridoxal 5*-phosphate (PLP)

PK endpoints: Plasma concentration and PK parameters of DS-1211a Include, but are not limited to, maximum plasma concentration, time to reach maximum plasma concentration, trough plasma concentration, area under the plasma concentration-time curve during dosing interval, area under the plasma concentration-time curve up to the last uantifiable time, and area under the plasma concentration-time curve up to infinity (if possible to calculate).

Study description

Background summary

The molecular basis of PXE is the inactivating mutations in the gene encoding ABCC6, an ATPdependent efflux transporter that is present mainly in the liver.3 Extracellularly, the excreted nucleoside triphosphate is hydrolyzed by ectonucleotidases to nucleoside monophosphate and
inorganic pyrophosphate (PPi), the latter a potent endogenous inhibitor of mineralization. In PXE, the absence of ABCC6-mediated adenosine triphosphate release from the liver results in
reduced PPi levels, leading to ectopic calcification.
Pyrophosphate is rapidly degraded to inorganic phosphate by tissue-nonspecific alkaline phosphatase (TNAP), encoded by the ALPL gene. It has been hypothesized that inhibition of TNAP activities would increase endogenous substrate PPi levels, leading to amelioration of the ectopic mineralization phenotype in PXE. Indeed, a growing number of in vitro and in vivo pharmacology studies (including animal models of PXE) have confirmed and supported this approach.

Although not acutely life threatening, PXE is associated with significant risks of visual impairments including blindness, comorbidity from peripheral and cardiovascular diseases, and adverse impacts on the quality of life in afflicted individuals. No specific treatment is currently available for PXE in retarding or reversing the disease progression or its complications in multiple organs, except for the off-label use of anti-VEGF therapy against ocular complications of choroidal neovascularization.

DS-1211b is a potent small-molecule inhibitor of TNAP being developed by Daiichi Sankyo for the treatment of ectopic calcification diseases such as PXE. In vitro and in vivo animal studies have shown that it is effective in inhibiting TNAP activities, increasing PPi levels, and reducing ectopic calcification.

To date, Daiichi Sankyo has conducted 3 Phase 1 healthy volunteer studies to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of DS-1211b. Oral administration in the single- and repeat-dose Phase 1 clinical studies in healthy volunteers over a wide dose range has shown that DS-1211b is safe and well tolerated, has a predicable PK profile, inhibits ALP activities, and raises PPi levels. Therefore, Daiichi Sankyo is proceeding with this study in individuals with an established diagnosis of PXE to continue the development of DS-1211b for the treatment of PXE and potentially other progressive ectopic calcification diseases.

Study objective

Primary:
To assess the safety and tolerability of DS-1211b compared with placebo in subjects with PXE.
To assess the dose response by assessing the treatment changes in PD endpoints.

Study design

Study DS1211-A-U201 is a 12-week, randomized, double-blind, placebo-controlled, parallelgroup study that aims to assess the safety, tolerability, and pharmacokinetic (PK) and pharmacodynamic (PD) dose response of DS-1211b in individuals with Pseudoxanthoma Elasticum (PXE) by using biomarkers relating to tissue-nonspecific alkaline phosphatase (TNAP) inhibition.

Eligible individuals with established diagnosis of PXE will be randomized to 1 of 4 arms in a 1:1:1:1 ratio, to receive 20 mg, 40 mg, or 60 mg of DS-1211b or placebo in tablet form for once daily dosing (Figure 3.1 of the protocol), for a total of 12-week dosing, followed by a postdose biomarker assessment and a 2-week follow-up safety check. Approximately 12 to 16 individuals with PXE will be enrolled in each group for a total of approximately 48 to 64 enrolled study participants.

Intervention

The study drugs for this study are:
• DS-1211b film-coated tablet in 20-mg dose strength for study dose levels of 20 mg,40 mg, and 60 mg
• Matching placebo tablets

Study burden and risks

This safety, tolerability, and dose-ranging study will evaluate DS-1211b doses that will inhibit TNAP sufficiently to give rise to peak inorganic pyrophosphate (PPi) increases of approximately 2-fold from baseline while allowing alkaline phosphatase (ALP) activity and pyridoxal 5*- phosphate (PLP) levels to return towards normal after cessation of dosing.
Safety, tolerability, PK, and mechanism of action (MOA)-related PD biomarkers (ALP, PPi, and PLP) will be assessed from the 3 active doses, 20 mg, 40 mg, and 60 mg, of DS-1211b versus placebo. TNAP inhibition increases PPi levels, the MOA by which DS-1211b is proposed to reduce ectopic calcification. However, excessive TNAP inhibition increases the risk of recapitulating clinical manifestations of hypophosphatasia, a genetic mineralization disorder of TNAP deficiency accompanied by abnormally and persistently elevated PPi and PLP levels.
Therefore, a careful benefit-to-risk characterization of the extent of TNAP inhibition that achieves a balance between increases in PPi versus increases in PLP is critical for selecting a target DS-1211b dose for later studies.

Nonclinical studies demonstrated that the potassium salt of DS-1211a significantly reduced the ectopic calcium deposition in the murine model of PXE, KK/HIJ mice. Significant inhibition of ectopic calcification was observed at a DS-1211a concentration of approximately 15.6 nmol/L.

The exposure at this pharmacological active dose could be estimated to be 0.374 µmol·h/L (0.137 µg·h/mL) in AUC24h, assuming a relatively stable drug exposure throughout treatment under food admixture route of administration.
Data from nonclinical toxicology studies suggest a potential risk for a reversible nephrotoxicity at high concentration of DS-1211b. The observed nephrotoxicity correlated with DS-1211b dose and systemic exposure and was accompanied by an increase in serum UN and serum CRE, suggesting that occurrence of nephrotoxicity may be monitorable in clinical trials. The NOAEL was established in nonclinical toxicology studies, and the drug exposure at the NOAEL in most sensitive species, monkeys (36.4 µg·h/mL in AUC24h), was 266-fold above the corresponding exposure that retarded calcium deposition in KK/HIJ mice and 95-fold above with adjustment of species differences in IC50 (factor = 36.3 / 13.0 = 2.79). The margin of exposure between the NOAEL in monkeys and the estimated high dose of 50 mg in humans is approximately 20-fold.

Besides the potential renal toxicity identified from animal toxicity studies, hypophosphatasia is a potential safety risk for DS-1211b, based on the known mechanism of action of TNAP inhibition. Hypophosphatasia is a rare, inherent, metabolic disorder characterized by low activity of TNAP due to mutations on ALPL gene encoding TNAP. The disease manifestation and severity are varied in a broad range from very severe type in infant to milder form in adult.
The elevated levels of TNAP substrates, PLP, PPi and PEA, have been reported and among those, PLP is used as a sensitive marker which correlate with hypophosphatasia severity. In Ph2 study, PLP will be measured as one of safety monitoring measures.

In the SAD and MAD studies, 96 healthy volunteers were given doses of 3 to 3000 mg. There were no deaths, SAEs, severe TEAEs, apparent renal toxicity detected by serum UN or CRE increases, or urinary kidney impairment markers. There were no safety signals that were severe or dose-related trends observed in TEAE occurrences. In the rBA/FE study, multiple doses were evaluated in tablet and equivalent PIB dose under fasting and fed conditions in 18 healthy subjects. The subjects had an acceptable safety profile, and the study drug was well tolerated.

In conclusion, a wide dose range of DS-1211b was evaluated in the SAD (1000-fold), MAD (30-fold), and rBA/FE studies in healthy volunteers. DS-1211b doses from 3 mg to 3000 mg (a single dose), 30 mg to 300 mg once daily, and 150 mg twice daily for 10 days were generally safe and well tolerated. The PD effects were observed on PPi, PLP, PEA, and ALP activity, which corroborates the proposed mechanism of action of DS-1211b as a TNAP inhibitor in human subjects. Thus far, the human experience of DS-1211b in healthy volunteers (18 to 45 years old) did not reveal safety concerns with single and multiple oral doses up to 3000 mg.
In addition, the nonclinical safety profile demonstrated monitorable and reversible target organ toxicities with adequate safety margins. Given the totality of clinical and nonclinical data, the benefit/risk assessment is

favorable for further clinical development.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Sign and date the ICF prior to the start of any study-specific qualification procedures.
2. Are male or female participants aged 18 to 75 years at screening.
3. Have an established diagnosis of PXE, with typical ocular and dermatological clinical features:
a. Ocular findings - angioid streaks or peau d*orange
b. Skin findings - characteristic PXE papules and plaques or diagnostic histopathological changes in lesional skin
4. Are fully vaccinated for coronavirus disease 2019 (COVID-19) per current

Center for Disease Control and Prevention guidelines
5. For women of childbearing potential (not postmenopausal as a result of either natural or postsurgery cessation of menses), must have a negative serum pregnancy test at screening and must be willing to use an effective method of birth control, as detailed in Section 17.1.2 of the protocol upon entering study screening, during the treatment period, and up until the time of the follow-up visit.
6. Are willing and able to comply with scheduled visits, drug administration plan,
laboratory tests, other study procedures, and study restrictions.

Exclusion criteria

1. Have a history of bone fracture in the past 6 months.
2. Have a history of active metabolic bone disease that significantly affect the interpretation of study biomarker results, excluding osteopenia or osteoporosis without fragility fracture.
3. Have a history of calcium pyrophosphate deposit disease such as chondrocalcinosis, pseudogout, and pyrophosphate arthropathy.
4. Have a history of hypophosphatasia.
5. Have a history of untreated hyperparathyroidism.
6. Participated in another interventional research study in the past 60 days.
7. Are participating or have participated within the last 12 months in PXE trials (eg, trials with PPi, PPi analogues such as bisphosphonate, or ENPP1 and its analogues) or in clinical trials relating to bone mineralization.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	10-10-2022
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	DS-1211b
Generic name:	DS-1211b

Ethics review

Approved WMO Date:	23-06-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-07-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2022-000676-19-NL
CCMO	NL80994.056.22