# A Double-blind, Randomized, Placebo-controlled Phase 3 Study of Orally Administered PLX3397 in Subjects with Pigmented Villonodular Synovitis or Giant Cell Tumor of the Tendon Sheath - ENLIVEN

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The primary objective of this study is to compare the response rate of Pexidartinib with that of placebo per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) at Week 25 in subjects with symptomatic, locally advanced PVNS or GCT...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Tendon, ligament and cartilage disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON47179

**Source**
ToetsingOnline

**Brief title**
PLX108-10 - ENLIVEN

### Condition

- Tendon, ligament and cartilage disorders

**Synonym**
Tumour of the tendon sheath

**Research involving**

Human

## Sponsors and support

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

## Intervention

**Keyword:** Giant Cell Tumor, Pigmented Villonodular Synovitis, PLX3397, Tendon Sheath

## Outcome measures

### Primary outcome

The proportion of subjects who achieve a complete response (CR) or partial response (PR) at the Week 25 visit based on centrally read MRI scans and RECIST 1.1.

### Secondary outcome

1. Mean change from baseline in range of motion of the affected joint, relative to a reference standard for the same joint, at the Week 25 visit

2. Proportion of responders based on centrally evaluated MRI scans and TVS at the Week 25 visit

3. Mean change from baseline score in the PROMIS Physical Function Scale at the Week 25 visit

4. Mean change from baseline score in the Worst Stiffness NRS item at the Week 25 visit

5. Protoption of responders based on the BPI Worst Pain NRS item and analgesic use by BPI-30 definition

6. Duration of response (CR or PR) based on MRI and RECIST 1.1

7. Duration of response (CR or PR) based on MRI and TVS

# Study description

### Background summary

Pigmented villonodular synovitis (PVNS) / giant cell tumor of the tendon sheath (GCT-TS) are progressive diseases with no ideal or standardized treatments. No systemic treatments and no treatments specifically directed to the recently identified pathogenetic pathways have been approved for these diseases. Although the standard of care is surgery, guidelines and evidence-based data for the timing and extent of surgical intervention are lacking. Surgical outcomes, even when curative, may result in marked patient morbidity as reflected in post-operative pain, limitation in function, and cosmetic disfigurement. In extreme or recurrent cases, the tumor may be aggressive and require limb amputation. The use of Pexidartinib, a selective kinase inhibitor that targets CSF1R (which is overexpressed in PVNS and GCT-TS), offers a promising new therapeutic option for patients with PVNS or GCT-TS. The primary objective of this study is to compare the response rate of Pexidartinib with that of placebo per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) at Week 25 in subjects with symptomatic, locally advanced PVNS or GCT-TS.

### Study objective

The primary objective of this study is to compare the response rate of Pexidartinib with that of placebo per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) at Week 25 in subjects with symptomatic, locally advanced PVNS or GCT-TS.
The secondary efficacy objectives are to evaluate: (i) patient-reported outcomes (PROs), including the Brief Pain Inventory (BPI) Worst Pain Numeric Rating Scale (NRS) item, Patient-reported Outcomes Measurement Information System (PROMIS) Physical Function Scale, and Worst Stiffness NRS item, at Week 25; (ii) response based on Tumor Volume Score (TVS) at Week 25; (iii) range of motion at Week 25; and (iv) duration of response. Other objectives are to evaluate: (i) other measures of efficacy, (ii) long-term safety, (iii) pharmacokinetics (PK), and (iv) pharmacodynamics (PDy) of Pexidartinib in treated subjects.

### Study design

This trial is a two-part multi-center Phase 3 study in subjects with symptomatic PVNS or GCT-TS for whom surgical resection would be associated with potentially worsening functional limitation or severe morbidity (locally advanced disease). In Part 1, the double-blind phase, eligible candidates will be centrally randomized in a 1:1 ratio to receive either Pexidartinib or placebo for 24 weeks. Randomization will be stratified by US versus non-US

sites and by upper extremity vs. lower extremity involvement.

## Intervention

Subjects will take five capsules a day (1000 mg/d Pexidartinib or matching placebo) divided into a morning dose of two capsules and an evening dose of three capsules for the first 2 weeks in Part 1. Thereafter, the dose will be reduced to four capsules a day (800 mg/d Pexidartinib or matching placebo) divided equally between the morning and evening doses. Doses will be taken in the fasting state at approximately the same times of the day and approximately 12 hours apart. Each treatment cycle is 28 days and subjects will be treated for up to 6 Cycles.
Dose reductions, interruptions, and re-escalations after previous reductions for toxicity are permitted according to pre-specified guidelines. Those subjects, on Pexidartinib, who complete Part 1 (ie, complete 24 weeks of dosing and the Week 25 assessments) will be eligible to advance to Part 2, a long-term treatment phase where all subjects will receive open-label Pexidartinib at a maximum starting dose of four capsules a day (800 mg/d Pexidartinib).
MRIs will be performed at Week 13 (Cycle 4, Day 1 visit of Part 1) and Week 25. For the Week 13 assessment, if clinically indicated, the investigator may request a central MRI reading for evaluation of disease progression. If a central reading confirms RECIST 1.1- defined disease progression, treatment assignment will be unblinded. Subjects receiving Pexidartinib will be discontinued from the study unless the investigator and the Sponsor*s Medical Monitor judge that the subject would potentially benefit from continued treatment with Pexidartinib. All subjects in Part 2 will continue to receive open-label Pexidartinib until all subjects have either reached at least the Week 49 visit (ie, an additional 24 weeks of open-label Pexidartinib treatment beyond the placebo-controlled phase) or withdrawn from the trial. Those subjects who complete Part 2 will be eligible to enter a separate protocol to continue receiving Pexidartinib.

## Study burden and risks

PVNS and GCT-TS are progressive diseases with no ideal or standardized treatments. No systemic treatments and no treatments specifically directed to the recently identified pathogenetic pathways have been approved for these diseases. Although the standard of care is surgery, guidelines and evidence-based data for the timing and extent of surgical intervention are lacking. Surgical outcomes, even when curative, may result in marked patient morbidity as reflected in post-operative pain, limitation in function, and cosmetic disfigurement. In extreme or recurrent cases, the tumor may be aggressive and require limb amputation. The use of Pexidartinib, a selective kinase inhibitor that targets CSF1R (which is overexpressed in PVNS and GCT-TS), offers a promising new therapeutic option for patients with PVNS or

GCT-TS. In summary, given the acceptable safety profile of the Pexidartinib at the selected dose and the promising Phase 1 data in subjects with PVNS/GCT-TS, the potential for a positive benefit/risk profile is assumed for the Phase 3 study.

Patients will have additional hospital visits, additional blood draw, MRI, ECHO/MUGA, ECGs and questionnaires/diaries to be completed. Please refer to sections E2, E4 and E6 of this ABR form for details burden with participation in this study.

# Contacts

**Public**
Daiichi Sankyo, Inc

Mt. Airy Road 211
Basking Ridge NJ 07920-2311
US
**Scientific**
Daiichi Sankyo, Inc

Mt. Airy Road 211
Basking Ridge NJ 07920-2311
US

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

1. Age * 18 years.

2. A diagnosis of PVNS or GCT-TS (i) that has been histologically confirmed either by a pathologist at the treating institution or a central pathologist, and (ii) where surgical resection would be associated with potentially worsening functional limitation or severe morbidity (locally advanced disease), with morbidity determined consensually by qualified personnel (eg, two surgeons or a multi-disciplinary tumor board).
3. Measurable disease as defined by RECIST 1.1 (except that a minimal size of 2cm is required) , assessed from MRI scans by a central radiologist
4. Symptomatic disease because of active PVNS or GCT-TS, defined as one or more of the following:
a. a worst pain of at least 4 at any time during the week preceding the screening visit (based on scale of 0 to 10, with 10 representing "pain as bad as you can imagine").
b. a worst stiffness of at least 4 at any time during the week preceding the screening visit (based on a scale of 0 to 10, with 10 representing "stiffness as bad as you can imagine").
5. Stable prescription of analgesic regimen during the 2 weeks prior to randomization.
6. During the 2 weeks prior to randomization, at least 4 of 7 consecutive days of BPI Worst Pain NRS items and Worst Stiffness NRS items completed correctly.
7. Women of childbearing potential must have a negative serum pregnancy test within the 14-day period prior to randomization. (Where demanded by local regulations, this test may be required within 72 hours of randomization.)
8. Males and females of childbearing potential are permitted in the study so long as they consent to avoid getting their partner pregnant or becoming pregnant, respectively, by using a highly effective contraception method, as described below, throughout the study and for up to 90 days after completion. Highly effective methods of contraception include: intra-uterine device (nonhormonal or hormonal), bilateral tubal occlusion, vasectomy, sexual abstinence, or barrier methods (e.g., condom, diaphragm) used in combination with hormonal methods associated with inhibition of ovulation. Women of nonchild bearing potential may be included if they are either surgically sterile or have been postmenopausal for * 1 year. Women who have documentation of at least 12 months of spontaneous amenorrhea and have an FSH level > 40 mIU/mL will be considered postmenopausal.
9. Adequate hematologic, hepatic, and renal function, defined by:
* Absolute neutrophil count * 1.5× 109 /L
* AST/ALT * 1.5× ULN
* Hemoglobin > 10 g/dL
* Total bilirubin * 1.5× ULN
* Platelet count * 100 × 109 /L
* Serum creatinine * 1.5× ULN
10. Willingness and ability to complete the BPI Worst Pain NRS item, Worst Stiffness NRS item, PROMIS Physical Function Scale, and other self-assessment instruments throughout the study.
11. Willingness and ability to use a diary.
12. Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements.

## Exclusion criteria

1. Investigational drug use within 28 days of randomization.
2. Previous use of pexidartinib or any biologic treatment targeting colony stimulating factor 1 (CSF-1) or the CSF-1 receptor; previous use of oral tyrosine kinase inhibitors, eg, imatinib or nilotinib, are allowed.
3. Active cancer (either concurrent or within the last year of starting study treatment) that requires therapy (eg, surgical chemotherapy or radiation therapy), with the exception of adequately treated basal or squamous cell carcinoma of the skin, melanoma in-situ, or carcinoma insitu of the cervix or breast or prostrate carcinoma with a prostate specific antigen value <0.2 ng/mL.
4. Known metastatic PVNS/GCT-TS.
5. Active or chronic infection with hepatitis C virus or hepatitis B virus or known active or chronic infection with human immunodeficiency virus.
6. Known active tuberculosis.
7. Significant concomitant arthropathy in the affected joint, serious illness, uncontrolled infection, or a medical or psychiatric history that, in the investigator*s opinion, would likely interfere with a candidate*s study participation or the interpretation of his or her results.
8. Women who are breastfeeding.
9. A screening Fridericia corrected QT interval (QTcF) * 450 ms (men) or * 470 ms (women).
10. MRI contraindications
11. History of hypersensitivity to any excipients in the investigational product
12. Inability to swallow capsules.

# Study design

## Design

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

## Recruitment

NL
Recruitment status: Recruitment stopped

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|---|---|
| Start date (anticipated): | 25-11-2015 |
| Enrollment: | 6 |
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Pexidartinib |
| Generic name: | Tyrosine kinase inhibitor |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 02-04-2015 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

| | |
|---|---|
| Approved WMO Date: | 23-07-2015 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

| | |
|---|---|
| Approved WMO Date: | 10-09-2015 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

| | |
|---|---|
| Approved WMO Date: | 25-09-2015 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 24-11-2015 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 06-06-2016 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 09-08-2016 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 06-09-2016 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 21-09-2016 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 27-10-2016 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 03-11-2016 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 05-12-2016 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 02-03-2017 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 19-04-2017 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 17-05-2017 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 16-06-2017 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO
Date: 11-01-2018

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 27-03-2018

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 18-09-2018

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 04-04-2019

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

Approved WMO
Date: 04-06-2019

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

## 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 | EUCTR2014-000148-14-NL |
| ClinicalTrials.gov | NCT02371369 |
| CCMO | NL51603.058.15 |