RINGSIDE: A Phase 2/3, Randomized, Multicenter Study to Evaluate AL102 in Patients with Progressing Desmoid Tumors

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This study has been transitioned to CTIS with ID 2024-515909-26-00 check the CTIS register for the current data. Main objective: Part A: To evaluate the safety and tolerability of AL102 in subjects withprogressing desmoid tumorsPart B: To evaluate...

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

Summary

ID

NL-OMON56437

Source
ToetsingOnline

Brief title
AL-DES-01

Condition

- Other condition

Synonym
desmoid, desmoid tumors

Health condition

Desmoid tumors

Research involving

Human

Sponsors and support

Primary sponsor: Immunome, Inc
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: AL102, Phase 2/3, Progressing Desmoid Tumors, Randomized

Outcome measures

Primary outcome

Part A: Frequency and severity of TEAEs and SAEs; time to treatment

discontinuation due to TEAE

Part B: Progression free survival

OLE: Frequency and severity of TEAEs and SAEs

Secondary outcome

Part A: change from baseline to week 16 in tumor volume

Part B:

1. proportion of subjects with ORR;

2. duration of response;

3. PFS as defined as the time from randomization until the date of radiographic

progression by BICR or clinical progression

4. change from baseline to WK28 in quality of life;

5. change from baseline to Week 28 in the worst pain intensity (WPI);

6. frequency and severity of TEAEs and SAEs;

7. time to treatment discontinuation due to TEAE

OLE:

1. PFS as defined as the time of radiographic progression

2. Proportion of subjects with ORR (CR and PR) by Investigator based on RECIST v1.1

3. DOR as defined by the time from CR or PR (by BICR based on RECIST v1.1) until the earlier of the first documentation of disease progression or death from any cause

4. PFS as defined as the time to radiographic progression as assessed by BICR based on RECIST v1.1, OR clinical progression

5.Change from baseline (defined as from the start of AL102 treatment) in

* Quality of life as determined by GODDESS DTSS Total Symptom Score

* GODDESS DTIS Physical Functioning Domain Score

* WPI using BPI short form

Part A: from baseline to week 16

Part B:

1, 6-7. baseline and throughout study duration

2. time from CR or PR until the earlier first documentation of disease progression or death from any cause

3. from randomization until the date of radiographic progression by BICR or clinical progression 4-5. from baseline to week 28

OLE: baseline and throughout OLE duration

Study description

Background summary

Desmoid tumor is a rare monoclonal, fibroblastic proliferation that arises in the deep soft tissues characterized by infiltrative growth and a tendency toward local recurrence but an inability to metastasize. The incidence of desmoid tumors is 5-6 cases per 1 million people per year with a peak age of 30-40 years. The treatment of desmoid tumor per current guidelines includes active surveillance as the first step after diagnosis in a majority of the patients. A decision towards an active treatment should be postponed until the occurrence of progression or increase of symptom burden. Active treatments may include surgery, radiotherapy and systemic therapy. There are no approved drugs for the treatment of desmoid tumors. Systemic therapy for patients impending threat to life or function include tyrosine kinase inhibitors (TKIs) such as sorafenib or pazopanib. While shown to be effective, these treatments have known toxicities (such as fatigue) which influence tolerability and compliance. If the tumor is slow-growing, non-steroidal anti-inflammatory drugs (NSAIDs) or hormonal therapy such as tamoxifen may be considered, although there is limited evidence to support the use of these treatments. AL102 is a potent, orally available, selective gamma secretase inhibitor (GSI) mediated Notch signaling that is currently under development as an anti-tumor/anti-angiogenic agent. Nonclinical and clinical data provide rationale for evaluating the potential clinical benefits of AL102 in subjects with desmoid tumors for whom available standard of care is not providing durable response as defined by complete response (CR) or PR. It is estimated, based on the published literature, that treatment with AL102 may have a positive impact in patients with progressing desmoid tumors, who may thus derive benefit from this treatment.

Study objective

This study has been transitioned to CTIS with ID 2024-515909-26-00 check the CTIS register for the current data.

Main objective:
Part A: To evaluate the safety and tolerability of AL102 in subjects with progressing desmoid tumors
Part B: To evaluate effects of AL102 on disease progression in subjects with progressing desmoid tumors
OLE: To evaluate the safety and tolerability of AL102 in subjects with progressive desmoid tumors

Secondary objective:
Part A: change from baseline to week 16 in tumor volume

Part B:,1. proportion of subjects with ORR;
2. duration of response;
3. PFS as defined as the time from randomization until the date of radiographic progression by BICR or clinical progression
4. change from baseline to WK28 in quality of life;
5. change from baseline to Week 28 in the worst pain intensity (WPI);
6. frequency and severity of TEAEs and SAEs;
7. time to treatment discontinuation due to TEAE

OLE:
1. PFS as defined as the time of radiographic progression
2. Proportion of subjects with ORR (CR and PR) by Investigator based on RECIST v1.1
3. DOR as defined by the time from CR or PR (by BICR based on RECIST v1.1) until the earlier of the first documentation of disease
progression or death from any cause
4. PFS as defined as the time to radiographic progression as assessed by BICR based on RECIST v1.1, OR clinical progression
5.Change from baseline (defined as from the start of AL102 treatment)in
* Quality of life as determined by GODDESS DTSS Total Symptom Score
* GODDESS DTIS Physical Functioning Domain Score
* WPI using BPI short form

Part A: from baseline to week 16
Part B: 1, 6-7. baseline and throughout study duration
2. time from CR or PR until the earlier first documentation of disease
progression or death from any cause
3. from randomization until the date of radiographic progression by BICR or clinical progression
4-5. from baseline to week 28
OLE: baseline and throughout OLE duration

Study design

Part A is a randomized, open-label, 3-arm study in adult subjects with progressing desmoid tumors. Part A will also include a food effect/pharmacokinetics (PK) sub study on the first 12 subjects and a lead-in cohort.

Part B is a double-blind, placebo-controlled, 2-arm study evaluating the recommended dose
regimen from Part A in patients with progressing desmoid
tumor

OLE is the part of the study into which certain Part A and Part B subjects transfer, to receive

AL102.

Intervention

On Part A Main study Day 1, eligible subjects will be randomized in a 1:1:1 ratio to receive AL102 1.2 mg once daily (QD) or AL102 2mg in a weekly intermittent regimen or AL102 4 mg in a weekly intermittent regimen. Subjects will receive AL102 until progression, intolerable toxicity, or withdrawal of consent.

On Part B, study Day 1, eligible subjects will be randomized in a 1:1 ratio to receive AL102 mg QD or placebo. Part B is an event-based study with no fixed treatment duration. Part B will be completed after the event-based analysis is completed.

The estimate duration of the Open Label extension part where patients from part A or Part B could be crossed over, is estimated to 12 months

Study burden and risks

Subject's participation in Part A will consists of a screening period (up to 4 weeks), a treatment period and a follow-up period (up to 4 weeks). During the study, subject will attend 10 scheduled (telephone) visits.

Subject's participation in part B will consists of a screening period up to 4 weeks, a treatment period and a follow up period up to 4 weeks. During this part of the study subject will attend around 20 visits.
In case the subjects will be rolled over to Open Label Extension study, they will come for additional 8-10 visits during one year

Aside from the intervention above, participation in the study involves blood draws and urine collection at multiple visits, and tumor biopsy, if no archival biopsy is present. Subjects will also be subjected to questions regarding medical history, use of concomitant medications/procedures and adverse events; MRI scans; urine sampling; measurement of vital signs; physical examination; holter monitoring; ECGs and patient reported outcomes questionnaires. Subjects will be expected to come to some visits in fasted state, to not take part in other medical studies, keep their appointments for visits, follow instructions from the study team, keep a patient card with them at all times, not donate blood/sperm/ova and to use appropriate forms of contraception, avoid exposure to sunlight, avoid consuming grapefruit or oranges.

Based on a previous study, the following side effect are considered very common (may affect more than 1 in 10 people): Diarrhea; Nausea (feeling sick); Vomiting (being sick); Hypophosphatemia (low level of phosphate in the blood); Decreased appetite; Hypokalemia (low level of potassium in the blood); Fatigue

(feeling tired); Rash; Pruritus (itchy skin). Based on previous studies, the following side effects may also be possible: Reproduction risks; Liver failure; Skin cancers.

Although a rare condition, there is a significant unmet medical need for treatment of desmoid tumors in both adult and pediatric population. It is estimated, based on published literature, that treatment with AL102 may have a positive impact in patients with progressing desmoid tumors, who may thus derive benefit from this treatment.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Part A

1. At least 18 years of age (inclusive) at the time of signing the ICF.
2. Histologically confirmed desmoid tumor (aggressive fibromatosis) by local pathologist (prior to informed consent).
3. Disease progression, assessed by the investigator, defined as having at least one of the following:
a) Unidimensional growth of desmoid tumor(s) by >=10%, using the sum of the largest diameters of target lesion(s), within 18 months of the screening MRI
b) Having desmoid tumor-related pain that is not adequately controlledwith non-opioid medication
4. At least 1 measurable lesion amenable to volume measurements byMRI at screening
5. One of the following:
• Treatment naïve subjects for whom, in the opinion of the investigator, the IP is deemed appropriate; OR
• Recurrent/refractory disease following at least one line of therapy (including surgery, radiation, or systemic therapy).
6. A desmoid tumor in which continued progressing disease will not result in immediate significant risk to the subject.
7. Agrees to provide formalin-fixed paraffin embedded (FFPE) archival or fresh tumor tissue.
8. Must be able to swallow whole capsules with no GI condition affecting absorption (not including history of colectomy); nasogastric or G-tube administration is not allowed.
9. Male or female subjects.
10. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) within 24 hours prior to the start of investigational product (IP). An extension up to 72 hours is permissible in situations where results cannot be obtained within the standard 24 hour window.
11. WOCBP and men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of the treatment with IP plus 120 days post-treatment completion.
Contraception methods should be consistent with local regulations.
12. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Part B
1. >=12 years of age (inclusive) in countries which allow participation of adolescents and >= 40 kg at the time of signing the ICF.
2. Histologically confirmed desmoid tumor (aggressive fibromatosis) by local pathologist (prior to informed consent) that has progressed per RECIST v1.1 (>=20% or new lesion) by investigator within 12 months of the screening visit scan.
3. Evidence of measurable disease by CT/MRI scan. Measurable lesions are defined according to RECIST v1.1.

4. One of the following:
• Recurrent/refractory disease following at least one line of therapy (including surgery, radiation, or systemic therapy); OR
• Treatment naïve subjects for whom, in the opinion of the investigator, surgery or radiation therapy is not deemed appropriate;
5. A desmoid tumor in which continued progressing disease will not result in immediate significant risk to the subject.
6. Agrees to provide FFPE archival or fresh tumor tissue.
7. Must be able to swallow whole capsules with no GI condition affecting absorption (not including history of colectomy or proctocolectomy); nasogastric or G-tube administration is not allowed.
Gender and Reproductive Considerations
8. Male or female subjects.
9. Premenstrual female subjects with a history of ovulatory dysfunction may be enrolled
10.WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to the start of IP.
11. WOCBP and men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of the treatment with IP plus 120 days post-treatment completion.
Contraception methods should be consistent with local regulations.
12. Subject and/or legally authorized representative (i.e. parent/guardian) must be capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF.
14.Minor subjects must be capable of giving written assent as appropriate per the applicable age (per local regulatory requirements).

OLE
1. One of the following:
a. Participated in Part A (including MRI at Week 16) and were still on study at time that Part B/OLE dose selection was made, OR
b. Participating in Part B and were noted to have radiographic progressive disease by BICR, OR
c. Are on study after completion of Part B
2. Must be able to swallow whole capsules with no GI condition affecting absorption; nasogastric or G-tube administration is not allowed.
3. Subject and/or legally authorized representative (i.e. parent/guardian) must be capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF.
4. Minor subjects must be capable of giving written assent as appropriate per the applicable age (per local regulatory requirements)

Exclusion criteria

1. Diagnosed with a malignancy in the past 2 years, unless for protocol defined allowed malignancies
2. Current or recent (within 2 months of IP administration) GI disease or disorders that increase the risk of diarrhea, such as inflammatory bowel disease and Crohn's disease
3. Evidence of uncontrolled, active infection, requiring systemic antibacterial, anti-viral or anti-fungal therapy <=7 days prior to administration of IP
4. Myocardial infarction within 6 months prior to enrollment, greater than Class 1 angina pectoris, or has NYHA Class III or IV heart failure, symptomatic ventricular arrhythmias, sustained ventricular tachycardia, TdP, the long QT syndrome, pacemaker dependence, or electrocardiographic evidence of acute ischemia
5. History of additional risk factors for TdP
6. Unstable or severe uncontrolled medical condition or any important medical illness or abnormal laboratory finding
7. Pregnant or breastfeeding or expecting to conceive children during the study
8. ECOG performance status >=2
9. Abnormal organ and marrow function at Screening defined as: a. Neutrophils <1500/mm3; b. Platelet count <100,000/mm3; c. Hemoglobin <9 g/dL; d. Electrolytes (potassium, calcium, magnesium, and phosphorus, using corrected value if low serum albumin level is
present) outside the normal limits of the local laboratory; e. Total bilirubin >1.5x ULN (except known Gilbert's syndrome >3x ULN); f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >2.5x ULN; g. Serum or plasma creatinine > ULN and creatinine clearance (CrCl) <60 mL/min; h. Uncontrolled triglyceride >=Grade 2 elevations per CTCAE v5.0 (>300 mg/dL or >3.42 mmol/L)
10. ECG Exclusions : a. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) >=450 msec; b. QRS duration > 110 ms; c. PR interval > 240 ms; d. Marked ST-T wave abnormalities which would make it difficult to measure the QT interval
11. Any treatments for desmoid tumors within 4 weeks prior to first dose
12. Chronic NSAIDs for the treatment of desmoid tumors within 4 weeks of first dose
13. Prior treatment with GSI or other agents targeting the Notch pathway
14. Use of strong inhibitors of CYP3A4 or strong inducers of CYP3A4
18. Contraindication to MRI

Part B
1. Diagnosed with a malignancy in the past 2 years, unless for protocol defined allowed malignancies
2. Current or recent (within 2 months of IP administration) GI disease or disorders that increase the risk of diarrhea, such as inflammatory bowel disease and Crohn's disease
3. Evidence of uncontrolled, active infection, requiring systemic antibacterial, anti-viral or anti-fungal therapy <=7 days prior to

administration of IP
4. Myocardial infarction within 6 months prior to enrollment, greater than Class 1 angina pectoris, or has NYHA Class III or IV heart failure, symptomatic ventricular arrhythmias, sustained ventricular tachycardia, TdP, the long QT syndrome, pacemaker dependence, or electrocardiographic evidence of acute ischemia
5. History of additional risk factors for TdP
6. Unstable or severe uncontrolled medical condition or any important medical illness or abnormal laboratory finding
7. Pregnant or breastfeeding or expecting to conceive children during the study
8. ECOG performance status >=2
9. Abnormal organ and marrow function at Screening defined as: a. Neutrophils <1500/mm3; b. Platelet count <100,000/mm3; c. Hemoglobin <9 g/dL; d. Electrolytes (potassium, calcium, magnesium, and phosphorus, using corrected value if low serum albumin level is present) outside the normal limits of the local laboratory; e. Total bilirubin >1.5x ULN (except known Gilbert's syndrome >3x ULN); f. AST and ALT >2.5x ULN; g. Serum or plasma creatinine > ULN and CrCl <60 mL/min (calculation of CrCl will be based on acceptable institution standard); h. Uncontrolled triglyceride >=Grade 2 elevations per CTCAE v5.0 (>300 mg/dL or >3.42 mmol/L); i.Any other laboratory abnormality >=Grade 3
10. ECG Exclusions: a. Mean QTcF >=450 msec; b. Second or third degree AV block
11. Any treatments for desmoid tumors within 4 weeks prior to first dose
12. Chronic NSAIDs for the treatment of desmoid tumors within 4 weeks of first dose
13. Prior treatment with GSI or other agents targeting the Notch pathway
14. Use of strong inhibitors of CYP3A4 or strong inducers of CYP3A

OLE
1. Unstable or severe uncontrolled medical condition or any important medical illness, abnormal ECG or laboratory finding.
2. Ongoing TEAE from Part A or Part B that requires discontinuation.
3. Breastfeeding or expecting to conceive children within the projectedduration of the study.
4. Use of any therapy that is prohibited in Part A or Part B of the study.
5. Concurrent enrollment in another clinical study unless it is an observational (non-interventional) clinical study.
6. Hypersensitivity to AL102 and any of its excipients.
Other protocol defined criteria could apply

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-02-2022
Enrollment:	10
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	NA
Generic name:	AL102 1.2mg milligram(s)
Product type:	Medicine
Brand name:	NA
Generic name:	AL102 2mg milligram(s)

Ethics review

Approved WMO Date:	21-07-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-10-2021

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-10-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	05-02-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-05-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-08-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-08-2024
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
EU-CTR	CTIS2024-515909-26-00
EudraCT	EUCTR2020-005833-34-NL

Register	ID
ClinicalTrials.gov	NCT2020-005833-34
CCMO	NL78146.056.21