# AIPAC (Active Immunotherapy PAClitaxel): A multicentre, Phase IIb, randomised, double blind, placebo-controlled study in hormone receptor-positive metastatic breast carcinoma patients receiving IMP321 (LAG-3Ig fusion protein) or placebo as adjunctive to a standard chemotherapy treatment regimen of paclitaxel.

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Primary objectives:* Safety run-in stage: determine the recommended phase two dose for therandomised phase* Randomised stage: to determine efficacy of IMP321 combined with weekly paclitaxel compared to weekly paclitaxel plus placebo in hormone...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Breast neoplasms malignant and unspecified (incl nipple) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON55556

**Source**
ToetsingOnline

**Brief title**
AIPAC

## Condition

- Breast neoplasms malignant and unspecified (incl nipple)

**Synonym**
hormone receptor-positive metastatic breast carcinoma, metastatic breast cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Immutep S.A.S.
**Source(s) of monetary or material Support:** Immutep S.A.S.

## Intervention

**Keyword:** HR positive, Immunotherapy, IMP321, Metastatic breast carcinoma

## Outcome measures

### Primary outcome

Progression Free survival

### Secondary outcome

Secondary Efficacy Endpoints

* To assess overall survival (OS)

* To assess adverse events according to the current National Cancer Institute

(NCI) Common Terminology Criteria for Adverse Events (CTCAE) and other safety

parameters

* To assess the time to next treatment (TTNT), objective response rate (ORR)

according to RECIST 1.1, time to and duration of response and duration of

stable disease

* To assess the plasma concentration time profile of IMP321 and derived PK

parameters

* To assess the quality of life (QOL)

* To assess development of anti-drug (IMP321) antibodies (ADA)

# Study description

**Background summary**

Lymphocyte activation gene 3 protein (LAG-3) is a transmembrane protein found on activated T and natural killer (NK) cells and a key mediator of immune responses. IMP321 is a recombinant soluble human LAG-3Ig fusion protein which is under development as a cancer immunotherapeutic agent. Like endogenous LAG-3, IMP321 binds to major histocompatibility complex (MHC) class II antigen presenting cells (APCs) such as dendritic cells (DCs), and triggers a T helper (Th)1 response and T cell proliferation.

Nine clinical studies with IMP321 have been conducted to date, including three evaluating IMP321 as a monotherapy or as part of chemo-immunotherapy (one each in metastatic renal cell carcinoma [MRCC], metastatic breast cancer [MBC], and pancreatic cancer) and six evaluating IMP321 as a vaccine adjuvant (two in healthy volunteers, three in melanoma, and one in prostate cancer).

The proposed Phase IIb clinical study aims to investigate the safety and efficacy of the active immunotherapy IMP321 in combination (adjunctive) with paclitaxel chemotherapy in patients with hormone receptor-positive metastatic breast cancer.

**Study objective**

Primary objectives:
* Safety run-in stage: determine the recommended phase two dose for therandomised phase
* Randomised stage: to determine efficacy of IMP321 combined with weekly paclitaxel compared to weekly paclitaxel plus placebo in hormone receptor-positive metastatic breast cancer patients

Secondary Objectives
* to further characterise the anti-tumour activity of IMP321 in combination with weekly paclitaxel in terms of clinical responses and clinical outcomes and compare it to placebo
* to examine the safety and tolerability of IMP321 in combination with weekly paclitaxel and compare it to placebo
* to characterise the pharmacokinetic (safety run-in only) and immunogenic properties of IMP321

* to assess the quality of life related to IMP321 compared to placebo

Exploratory Objectives
* To characterise the immune response of patient and identify biomarkers

**Study design**

Multicentre, placebo-controlled, double-blind, 1:1 randomised Phase IIb study in female hormone receptor-positive metastatic breast cancer patients.

The study comprises of two stages. In the open-label, safety run-in stage the Recommended Phase 2 Dose (RPTD) of IMP321 in combination with paclitaxel will be confirmed. In the placebo-controlled, double-blind randomisation stage, paclitaxel + IMP321 at the RPTD will be compared to paclitaxel + placebo.

Stage 1 - open label, safety run-in (dose optimization): The study will be initiated with an open-label, safety run-in stage to assess the comparative safety, tolerability, pharmacokinetics and induction of immune responses of 6 mg (cohort 1) and 30 mg (cohort 2) of IMP321 as adjunctive to paclitaxel chemotherapy.

Stage 2 - placebo-controlled, double-blind randomisation: In the second stage of the study a total number of 226 patients will be randomised 1:1 to receive either paclitaxel + IMP321 at the RPTD or paclitaxel + placebo in a double-blinded fashion. Patients will be stratified by ECOG performance status (0 versus 1).

IIn both study stages, treatment consists of a chemo-immunotherapy phase followed by a maintenance phase. The chemo-immunotherapy phase consists of 6 cycles of 4 weeks. During each cycle the patient will receive weekly paclitaxel (80 mg/m$^2$) at Days 1, 8 and 15 with adjunctive treatment of study agent, either IMP321 or placebo, on Days 2 and 16 of each 4-week cycle. After completion of the 6-cycle chemo-immunotherapy phase, responding or stable patients will receive study agent (IMP321 or placebo) every 4 weeks during the maintenance phase for additional 12 injections.
A patient will stay on treatment until disease progression, unacceptable toxicity, completion of the maintenance phase or discontinuation for any other reason.

Screening should occur during the 3 weeks prior to start of paclitaxel treatment (Cycle 1/ Day 1). Upon start of study treatment, patients will be followed for PFS and OS. PFS will be radiologically assessed at the study sites until progressive disease (PD), death, withdrawal of consent, loss to follow-up, or until the end of the study, whichever occurs first. Radiological assessment will be performed at interval of 8 weeks while patients are on study treatment and every 12 weeks during follow-up (after week 73). OS will be monitored until death, withdrawal of consent, loss to follow-up or until the

end of the study, whichever occurs first. Radiological scans will be evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 at the clinical sites for treatment decisions. Independent blinded read will be performed for primary analysis.

### Intervention

IMP321 or placebo as adjunctive to standard chemotherapy with paclitaxel.

Repeated subcutaneous doses of study agent (IMP321 or placebo) will be administered, at Day 2 (D2) and Day 16 (D16) of each 4-week cycle during the 6 cycles of weekly paclitaxel chemotherapy (chemo-immunotherapy phase). A total of 12 SC injections of study agent will be administered during this chemo-immunotherapy phase.

After completion of this chemo-immunotherapy phase, responding or stable patients will receive study agent every 4 weeks during the maintenance phase for an additional period of 48 weeks. A patient will stay on treatment until disease progression, unacceptable toxicity, death, completion of the maintenance phase or discontinuation for any other reason. Up to 12 further SC injections of study agent will be administered during this phase.

### Study burden and risks

The anticipated risks are based on IMP321 non-clinical and clinical experience and are well tolerated and have an acceptable safety profile. Patients will be monitored closely for the occurrence of any significant clinical events and treatment will only continue if it is considered safe and appropriate to do so. The early clinical development program of IMP321demonstrated that its use is generally safe and well tolerated and can justify evaluation in a larger patient population. These studies also demonstrated that IMP321 can elicit a targeted cellular immune response and has a strong potential for anti-tumour activity. In summary, the expected benefit definitely outweighs the expected risks for the patients.

## 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

1. Able to give written informed consent and to comply with the protocol
2.1 Metastatic oestrogen receptor positive and/or progesterone receptor positive breast adenocarcinoma,
histologically proven by biopsy of the primary tumour and/or a metastasis
3. Female of age 18 years or above
4. Patients who are indicated to receive first line chemotherapy with weekly paclitaxel
5.1 All patients of childbearing potential must have a negative highly sensitive pregnancy test at
screening and agree to use highly effective method for contraception according to the EU Clinical
Trial Facilitation Group guidance from time of study entry until at least 6 months after the last
administration of study drug. The partners of patients with childbearing potential must also apply
contraceptive methods. Patients who are either,
o postmenopausal (>= 60 years of age, or < 60 years of age and amenorrhoeic for 12 months in the
absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression with folliclestimulating
hormone (FSH) above 40 U/L and oestradiol below 30 ng/L; or if taking tamoxifen or toremifene, and age < 60 years, then FSH and oestradiol in the

postmenopausal range),
permanently sterilized (e.g., bilateral tubal occlusion, hysterectomy),
o or otherwise be incapable of pregnancy are not considered to be of childbearing potential
6. ECOG performance status 0-1
7. Expected survival longer than three months
8. Resolution of toxicity of prior therapy to grade < 2 (except for alopecia and transaminases in case of
liver metastases)
9. Evidence of measurable disease as defined by RECIST version 1.1
10.1 Laboratory criteria:
* Total white cell count >= 3 x 10^9/L
* Platelet count >= 100 x 10^9/L
* Haemoglobin >= 9 g/dL or 5.58 mmol/L
* Absolute Neutrophil Count (ANC) >= 1.5 x 10^9/L
* Serum creatinine <= 1.5 × ULN
* Total bilirubin <= 20 µmol/L, except for familial cholaemia (Gilbert*s disease)
* Serum ASAT and ALAT <= 3 times ULN or <=5 times ULN if liver metastases are present

## Exclusion criteria

1. Prior chemotherapy for metastatic breast adenocarcinoma
2. Disease-free interval of less than twelve months from the last dose of adjuvant chemotherapy
3. Prior high-dose chemotherapy requiring hematopoietic stem cell rescue
4.1 Inflammatory carcinoma at time of screening
5.1 Candidate for treatment with trastuzumab (or other Her2/neu targeted agents) or endocrine based
therapy according to the applicable treatment guidelines
6.2 Systemic chemotherapy, radiation therapy or any other investigational agent within 4 weeks,
endocrine therapy within 1 week or CDK4/6 inhibitors within 5 times half-life (acc. to SPC) prior
to first dose of study treatment
7.1 Symptomatic known cerebral and/or leptomeningeal metastases
8. Women who are pregnant or lactating
9. Serious intercurrent infection within 4 weeks prior to first dose of study treatment
10. QTcF >480 ms, family or personal history of long or short QT syndrome, Brugada syndrome or
known history of QTc prolongation, or Torsade de Pointes (TdP)
11. Uncontrolled electrolyte disorders that can worsen the effects of a QTc-prolonging drug (e.g.,
hypocalcaemia, hypokalaemia, hypomagnesemia)

12.1 Evidence of severe or uncontrolled cardiac disease (NYHA III-IV) within 6 months prior to first
dose of study treatment including: myocardial infarction, severe/unstable angina, ongoing cardiac
dysrhythmias of NCI CTCAE version 4.03 Grade >=2, atrial fibrillation, coronary/peripheral artery
bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient
ischemic attack, ventricular arrhythmias requiring medication or symptomatic pulmonary embolism
13. Active acute or chronic infection
14. Active autoimmune disease requiring immunosuppressive therapy
15.1 Positive test for HIV
16.1 Positive test for Hepatitis B (anti-HBc) or C (Patients who are anti-HBc+ and HBsAg negative are eligible and are not excluded from participation in this study)
17. Life threatening illness unrelated to cancer
18. Previous malignancies within the last three years other than breast carcinoma, except successfully
treated squamous cell carcinoma of the skin, superficial bladder cancer, and in situ carcinoma of the
cervix
19. Any current disorder that would impede the patient*s ability to provide informed consent or to
comply with the protocol
20. Any condition requiring continuous systemic treatment with either corticosteroids (>10 mg daily
prednisone equivalents) or other immunosuppressive medications within 4 weeks prior to first dose
of study treatment. Inhaled or topical steroids and physiological replacement doses of up to 10 mg
daily prednisone equivalent are permitted in the absence of active autoimmune disease
21. Past history of severe allergic episodes and/ or Quincke*s oedema
22. Alcohol or substance abuse disorder
23. Known hypersensitivity to any of the components of the study agents
24.1 Participation in an interventional clinical study within 4 weeks prior to first dose of study
treatment, with intervention not covered by exclusion criterion 6.2
25. Unwilling or unable to follow protocol requirements
26. In the clinical judgment of the Investigator, the patient is unsuitable for participation in this study
27. Persons with any kind of dependency on the Investigator or employed by the sponsor or Investigator
28. Persons held in an institution by legal or official order
29. Patients with prior organ or stem cell transplantation
30. Patients having received a live, attenuated vaccine within 4 weeks prior to

the first administration of
study treatment
31. Patients treated with systemic immune stimulatory agents within 6 weeks or
five half lives of the
drug prior to first administration of study treatment

# Study design

## Design

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| 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

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 19-02-2016 |
| Enrollment: | 44 |
| Type: | Actual |

# Ethics review

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|---|---|
| Approved WMO Date: | 12-10-2015 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 21-12-2015 |
| Application type: | First submission |

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|---|---|
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 27-07-2016 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 11-08-2016 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 20-02-2017 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 14-03-2017 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 11-04-2017 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 14-06-2017 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 28-06-2017 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO | |

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|---|---|
| Date: | 26-02-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 06-03-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 01-08-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 02-08-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 15-11-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 28-11-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 10-12-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 19-12-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam |

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| | (Rotterdam) |
| Approved WMO Date: | 20-05-2019 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 24-05-2019 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 07-10-2019 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 28-10-2019 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 20-01-2020 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 22-01-2020 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 09-04-2021 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 21-04-2021 |

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|---|---|
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

# 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 | EUCTR2015-002541-63-NL |
| ClinicalTrials.gov | NCT02614833 |
| CCMO | NL54895.078.15 |

# Study results

Results posted: 23-06-2022

**First publication**
08-06-2022