

# Oseltamivir for treatment of thrombocytopenia and plasma leakage in dengue

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|--|--|---|
| <b>Submission date</b><br>08/01/2018   | <b>Recruitment status</b><br>No longer recruiting        | <input checked="" type="checkbox"/> Prospectively registered<br><input type="checkbox"/> Protocol |
| <b>Registration date</b><br>12/01/2018 | <b>Overall study status</b><br>Completed                 | <input type="checkbox"/> Statistical analysis plan<br><input checked="" type="checkbox"/> Results |
| <b>Last Edited</b><br>10/01/2022       | <b>Condition category</b><br>Infections and Infestations | <input type="checkbox"/> Individual participant data  |

## Plain English summary of protocol

### Background and study aims

Dengue is a virus caused by mosquitos. Symptoms include high fever, heaches, vomiting, muscle pains and skin rashes. Low platelets counts (thrombocytopenia) are very common in dengue. Having a low blood platelet count means that the body cannot form blood clots to stop bleeding. Increasing evidence suggests that low platelet numbers play a role in plasma leakage and the bleeding complications of dengue. Patients with dengue can remove certain acids causing a lower amount of platelets. This can be reversed by the neuraminidase inhibitor called oseltamivir. This medication is an approved drug for treatment of influenza. It is speculated that oseltamivir may fasten platelet recovery in dengue-induced thrombocytopenia and prevent plasma leakage. The aim of this study is to investigate whether oseltamivir reduces the time needed for platelet numbers to recover and/or prevent plasma leakage in patients with acute dengue with moderate to severe thrombocytopenia.

### Who can participate?

Adults aged 16 and older who go to the hospital for dengue.

### What does the study involve?

Participants are randomly allocated to one of two groups. Those in the first group continue with their standard level of care. Those in the second group receive oseltamiriv phosphate twice a day taken by mouth for a maximum of 5 days or when their platelet number reaches a certain level. Platelet numbers are determined twice a day using an ultrasound (using sound waves to create images) and blood tests. Participants are followed three weeks after the start of the study to assess if there are any complications.

### What are the possible benefits and risks of participating?

Participation in this study is associated with possible risks and benefits. Possible benefits for participants are that daily laboratory tests are covered by the study and that daily ultrasonography for plasma leakage will be performed. In case the hypothesis that oseltamivir promotes recovery of dengue-associated thrombocytopenia is true, participants randomized to the oseltamivir may be discharged from hospital earlier. There is extensive clinical experience with oseltamivir and severe side effects are uncommon. Nonetheless, the current study employs oseltamivir for a new, unregistered indication and side effects cannot be excluded.

Where is the study run from?

1. RS Nasional Diponegoro (Indonesia)
2. RSUD K.R.M.T. Wongsonegoro (Indonesia)
3. William Booth Hospital (Indonesia)
4. RSUD Kartini (Indonesia)
5. RSAU Salamun (Indonesia)
6. RSUP Dr. Hasan Sadikin (Indonesia)
7. RSUD Al-Ihsan (Indonesia)

When is the study starting and how long is it expected to run for?

September 2017 to December 2019

Who is funding the study?

ZonMw (Netherlands)

Who is the main contact?

1. Dr Rahageng Tunjunputri (Public)
  2. Dr Quirijn de Mast (Scientific)
- quirijn.demast@radboudumc.nl

## Contact information

### Type(s)

Public

### Contact name

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### Contact details

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Indonesia

50111

### Type(s)

Scientific

### Contact name

Dr Quirijn de Mast

### ORCID ID

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## Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

650/EC/FK-RSDK/XI/2017

## Study information

### Scientific Title

Treatment Of Thrombocytopenia with Oseltamivir in acute dengue virus infection (TOTO-trial): a randomized, placebo controlled, multicenter trial

### Acronym

TOTO

### Study objectives

1. Oseltamivir phosphate given to patients with thrombocytopenia in acute dengue reduces the time to platelet recovery (platelets  $>100 \times 10^{12}/L$ )
2. Oseltamivir phosphate given to patients with thrombocytopenia in dengue reduces the incidence of dengue-associated plasma leakage

### Ethics approval required

Old ethics approval format

### Ethics approval(s)

Ethics Committee of the Faculty of Medicine Diponegoro University and Dr Kariadi Hospital, 27/12/2017, ref: 650/EC/FK-RSDK/XI/2017

### Study design

Phase 2 multicentre randomized placebo-controlled double-blinded interventional trial

### Primary study design

Interventional

### Secondary study design

Randomised controlled trial

### Study setting(s)

Hospital

## Study type(s)

Treatment

## Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

## Health condition(s) or problem(s) studied

Dengue

## Interventions

The study is designed as a phase 2, multicentre, randomized, placebo-controlled, double-blinded intervention trial.

Participants will be randomized using block randomization in a 1:1 allocation ratio.

The trial is double-blinded, i.e. both researchers/study personnel, physicians and participants are blinded.

The intervention tested is oseltamivir phosphate 75 mg BID orally (intervention group) or placebo (control group) until platelet number reaches  $>100 \times 10^9/L$  or for a maximum of 5 days. Patients are randomised using block randomization with variable block size.

Platelet numbers are determined 2 times/daily in all participants and plasma leakage are assessed daily using ultrasonography and by twice daily haematocrit.

Participants will be followed up daily until discharge from hospital or until their platelet count has reached  $\geq 100 \times 10^9/L$ . A follow-up visit at home will be performed three weeks after randomization to assess for late complications and to obtain convalescence laboratory measurements.

## Intervention Type

Drug

## Phase

Phase II

## Drug/device/biological/vaccine name(s)

Oseltamivir phosphate

## Primary outcome measure

Current primary outcome measures as of 25/02/2019:

1. Time to platelet recovery (platelet count  $\geq 100 \times 10^9/L$ ) is measured using twice daily platelet count measurement from enrollment until discharge or until platelet count  $\geq 100 \times 10^9/L$
2. Plasma leakage is measured by twice daily haematocrit, daily ultrasonography (looking for gall bladder wall thickness, ascites and pleural fluid) and plasma markers (e.g. Syndecan-1) from enrollment until discharge or until platelet count  $\geq 100 \times 10^9/L$

Previous primary outcome measures:

1. Time to platelet recovery (platelet count  $\geq 100 \times 10^9/L$ ) is measured using twice daily platelet count measurement from enrollment until discharge or until platelet count  $\geq 100 \times 10^9/L$

2. Plasma leakage is measured by twice daily haematocrit and daily ultrasonography (looking for gall bladder wall thickness, ascites and pleural fluid) from enrollment until discharge or until platelet count  $\geq 100 \times 10^9/l$

### **Secondary outcome measures**

Current secondary outcome measures as of 25/02/2019:

1. Safety of oseltamivir use in dengue is measured using daily measurement of creatinine and liver enzymes from enrollment until discharge or until platelet count  $\geq 100 \times 10^9/l$  for a maximum of five days and at week 3 post-enrollment
2. Rate of change of platelet count is measured twice daily using platelet count measurement at 24, 48 and 5 days
3. Number of participants developing severe thrombocytopenia measured using platelet count measurement at enrollment until discharge or until platelet count  $\geq 100 \times 10^9/l$ .
4. Dengue-related complications, especially clinical bleeding is assessed daily using WHO bleeding scores at enrollment until discharge or until platelet count  $\geq 100 \times 10^9/l$
5. Markers of inflammation, coagulation and endothelial perturbation is measured using daily plasma samples

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4. Dengue-related complications, especially clinical bleeding is assessed daily using WHO bleeding scores at enrollment until discharge or until platelet count  $\geq 100 \times 10^9/l$
5. Flow cytometric platelet studies, including platelet activation and reactivity assays as well as platelet sialic acid expression is measured daily using antibodies against P-selectin and the binding of fibrinogen to platelets in unstimulated samples and after stimulation with platelet agonists. Platelet sialic acid content is measured using the lectins SNA, MAL-II and RCA.
6. Markers of inflammation, coagulation and endothelial perturbation is measured using daily plasma samples

### **Overall study start date**

01/09/2017

### **Completion date**

31/12/2019

## **Eligibility**

### **Key inclusion criteria**

1. Admission to hospital
2. Aged 18 years and above; Updated 01/11/2018: Aged 16 years and above
3. Positive result of NS1 rapid test (proven dengue) or positive for acute dengue serology with probable dengue criteria as defined in WHO 2009 criteria
4. Fever  $\leq 6$  days
5. Platelet count  $< 70 \times 10^9/L$

**Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

70

**Total final enrolment**

70

**Key exclusion criteria**

1. Symptoms or signs of another infectious disease
2. Pregnancy or breastfeeding
3. Persistent or recurrent clinical bleeding such as epistaxis, haematemesis, haematochezia, melena, intermenstrual bleeding
4. Chronic liver or kidney disease or active haematological disease
5. Estimated creatinine clearance at moment of enrolment <70 ml/min
6. ALT value > 3x the upper limit of normal
7. Use of platelet function inhibitors or anticoagulants
8. Platelet transfusion during the current hospitalization
9. In patients with earlier platelet count available in past days: platelet number already recovering

**Date of first enrolment**

13/01/2018

**Date of final enrolment**

31/07/2019

**Locations****Countries of recruitment**

Indonesia

**Study participating centre**

**RS Nasional Diponegoro**

Jl. Professor Haji Soedarto S.H.

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**Study participating centre**  
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# Sponsor information

## Organisation

Center for Tropical and Infectious Diseases (Centrid)

## Sponsor details

Fakultas Kedokteran Universitas Diponegoro-RSUP Dr Kariadi  
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Semarang  
Indonesia  
50111

## Sponsor type

Hospital/treatment centre

# Funder(s)

## Funder type

Charity

## Funder Name

ZonMw

## Alternative Name(s)

Netherlands Organisation for Health Research and Development

## Funding Body Type

Private sector organisation

## Funding Body Subtype

Other non-profit organizations

## Location

Netherlands

# Results and Publications

## Publication and dissemination plan

The results of this phase II trial will be published in one manuscript at the end of 2020.

## Intention to publish date



31/12/2020

### Individual participant data (IPD) sharing plan

After publication of the trial results, data will be stored in DANS repository (<https://dans.knaw.nl>). The type of data stored are quantitative data, including allocation to treatment arm, demographics of the study participants (age, sex), platelet data (counts, activation and reactivity, sialic acid content), data on plasma leakage and safety data (renal and liver function). Data will be available on request (restricted access). Data will be stored anonymized. Participants have given consent for anonymized data to be stored in a repository.

### IPD sharing plan summary

Stored in repository

### Study outputs

| Output type                     | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---------------------------------|---------|--------------|------------|----------------|-----------------|
| <a href="#">Results article</a> |         | 07/01/2022   | 10/01/2022 | Yes            | No              |