High-dose rifampicin for the Treatment of TB Meningitis: a dose-finding study

NCT no: 02169882

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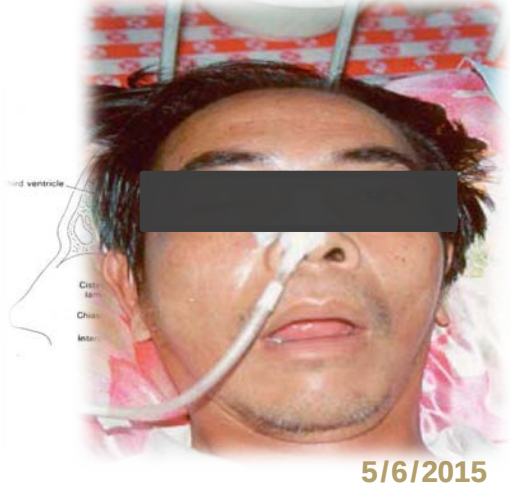
Background & Rationale

- Meningitis is the most severe manifestation of TB
- Difficult to diagnose, high mortality

- Current treatment regimens:
  - Not evidence-based
  - Follow Pulmonary TB treatment
  - Rifampicin (RIF) is keystone drug fro TBM
  - BUT its penetration to the BBB is limited



HIGHER DOSE OF RIFAMPICIN: MORE EFFECTIVE?

- How high can we go? (besides PK, safety)
- How long?

Our previous study

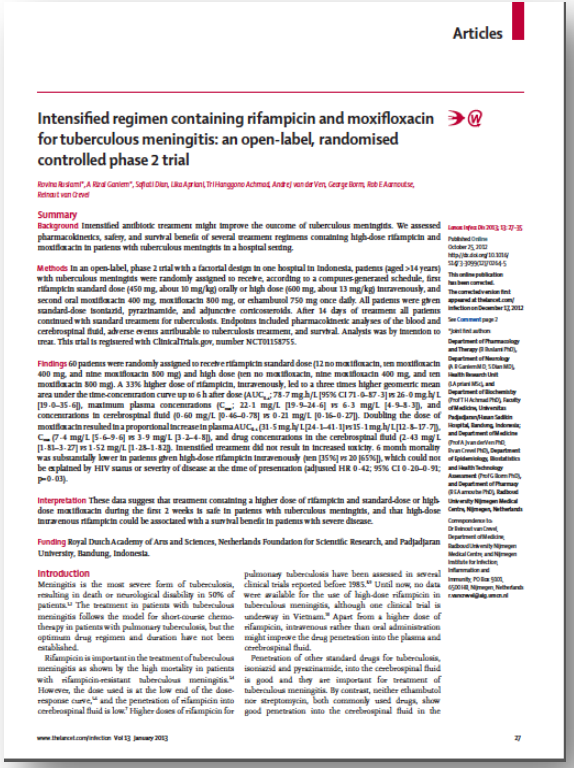
(Lancet Infectious Disease, 2013)

Phase 2 RCT (1st worldwide)

- RIF 600 mg iv vs. 450 mg p.o (14 days)
- drug levels, safety, outcome

- a better PK profiles of RIF (3 times higher)
- no increasing of adverse events

- decrease of mortality by 50%
  (35% vs. 65%, p<0.001)



Articles

Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial

Rovina Ruslami*, A Rinal Ganiem*, Sofiati Dian, Lika Apriani, TH Hanggono Achmad, Andrej van der Ven, George Borm, Rob E Aarnoutse, Reinout van Crevel

Summary

Background Intensified antibiotic treatment might improve the outcome of tuberculous meningitis. We assessed pharmacokinetics, safety, and survival benefit of several treatment regimens containing high-dose rifampicin and moxifloxacin in patients with tuberculous meningitis in a hospital setting.

Methods In an open-label, phase 2 trial with a factorial design in one hospital in Indonesia, patients (aged >14 years) with tuberculous meningitis were randomly assigned to receive, according to a computer-generated schedule, first rifampicin standard dose (450 mg, about 10 mg/kg) orally or high dose (600 mg, about 13 mg/kg) intravenously, and second oral moxifloxacin 400 mg, moxifloxacin 800 mg, or ethambutol 750 mg once daily. All patients were given standard-dose isoniazid, pyrazinamide, and adjunctive corticosteroids. After 14 days of treatment all patients continued with standard treatment for tuberculosis. Endpoints included pharmacokinetic analyses of the blood and cerebrospinal fluid, adverse events attributable to tuberculosis treatment, and survival. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01158755.

Findings 60 patients were randomly assigned to receive rifampicin standard dose (12 no moxifloxacin, ten moxifloxacin 400 mg, and nine moxifloxacin 800 mg) and high dose (ten no moxifloxacin, nine moxifloxacin 400 mg, and ten moxifloxacin 800 mg). A 33% higher dose of rifampicin, intravenously, led to a three times higher geometric mean area under the time-concentration curve up to 6 h after dose (AUC_{0-6}: 78·7 mg·h/L [95% CI 71·6–87·3] vs 26·0 mg·h/L [19·0–35·6]), maximum plasma concentrations (C_{max}: 22·1 mg/L [19·9–24·6] vs 6·3 mg/L [4·9–8·3]), and concentrations in cerebrospinal fluid (0·60 mg/L [0·46–0·78] vs 0·21 mg/L [0·16–0·27]). Doubling the dose of moxifloxacin resulted in a proportional increase in plasma AUC_{0-6} (31·5 mg·h/L [24·1–41·1] vs 15·1 mg·h/L [12·8–17·7]), C_{max} (7·4 mg/L [5·6–9·6] vs 3·9 mg/L [3·2–4·8]), and drug concentrations in the cerebrospinal fluid (2·43 mg/L [1·81–3·27] vs 1·52 mg/L [1·28–1·82]). Intensified treatment did not result in increased toxicity. 6 month mortality was substantially lower in patients given high-dose rifampicin intravenously (ten [35%] vs 20 [65%]), which could not be explained by HIV status or severity of disease at the time of presentation (adjusted HR 0·42; 95% CI 0·20–0·91; p=0·03).

Interpretation These data suggest that treatment containing a higher dose of rifampicin and standard-dose or high-dose moxifloxacin during the first 2 weeks is safe in patients with tuberculous meningitis, and that high-dose intravenous rifampicin could be associated with a survival benefit in patients with severe disease.

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Introduction

Meningitis is the most severe form of tuberculosis, resulting in death or neurological disability in 50% of patients.[1,2] The treatment in patients with tuberculous meningitis follows the model for short-course chemotherapy in patients with pulmonary tuberculosis, but the optimum drug regimen and duration have not been established.

Rifampicin is important in the treatment of tuberculous meningitis as shown by the high mortality in patients with rifampicin-resistant tuberculous meningitis.[3,4] However, the dose used is at the low end of the dose-response curve,[5,6] and the penetration of rifampicin into cerebrospinal fluid is low.[7] Higher doses of rifampicin for pulmonary tuberculosis have been assessed in several clinical trials reported before 1985.[8,9] Until now, no data were available for the use of high-dose rifampicin in tuberculous meningitis, although one clinical trial is underway in Vietnam.[10] Apart from a higher dose of rifampicin, intravenous rather than oral administration might improve the drug penetration into the plasma and cerebrospinal fluid.

Penetration of other standard drugs for tuberculosis, isoniazid and pyrazinamide, into the cerebrospinal fluid is good and they are important for treatment of tuberculous meningitis. By contrast, neither ethambutol nor streptomycin, both commonly used drugs, show good penetration into the cerebrospinal fluid in the

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However...

- RIF iv is not easy
  - Invasive, impractical
  - more expensive, and not widely available
- alternative for RIF iv?
  - oral dose (15 or 20 mg/BW **or even higher**)
  - with similar PK/PD profile
- RIF is a friendly drug, tolerated well by patients
- Higher oral dose of RIF → 35 mg/kg in PTB: ☺ → In Africa

then...**Remover study**

RIF 600 mg iv vs. 750 mg & 900 mg p.o (10 days)

Still tolerable and safe

RIF 900 mg p.o had **less optimum PK profile** than 600 mg

We need to go higher

Next…**ReDEFINe study**

To explore if higher dose of oral rifampicin

- 2x SD (900 mg)
- 3x SD (1350 mg)
- compared to standard dose (SD)

more effective in treating TBM

AND

still tolerated well by the patients.

Other problem in TBM management

- Bacterial confirmation: still difficult!
  - Gene-expert?
- Pathogenesis of TBM is still limited
  - Underlying susceptibility
  - Poor outcome
- Clinical, neurological, neuroradiology, inflammatory response

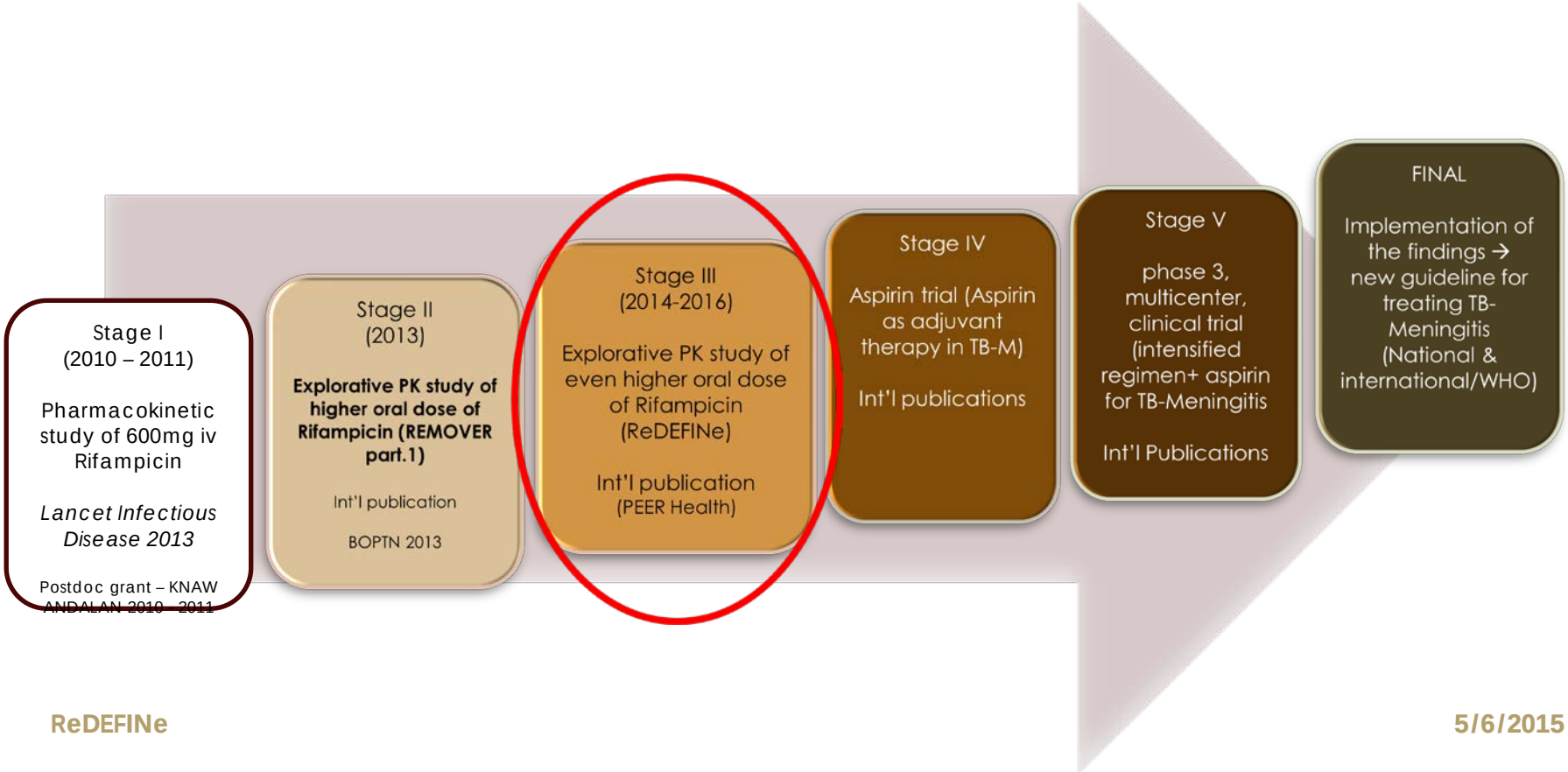
ReDEFINe Study

Our next step

Overall aim of the study

To establish the optimal oral dose of RIF for TBM

Roadmap of Research Project



Primary objective & endpoint

Objective

To generate PK data of higher dose of RIF in TBM patients

Primary objective & endpoint

Objective	Endpoints
To generate PK data of higher dose of RIF in TBM patients	PK data of Rif in the blood & the CSF
	At the first 3-critical day & after steady state (>10 days of treatment)

Secondary objectives & endpoints

Objectives

- safety and tolerability
- Efficacy → clinical & neurological response
- Gene-expert for TBM?
- Biorepository of blood, CSF for future research

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Endpoints

- Grade 3&4 and SAE by 60 days
- Mortality at 180 days
- Clinical & neurological response
- Neuroradiological response at day 60
- Resolution of blood & CSF imnflammatory response at day 7
- Sensitivity geneXpert vs. culture

Expected Outcomes

Data on PK & safety of high dose RIF in TBM patients

Additional data on efficacy if high dose RIF in TBM patients

Bio repository (blood & CSF) for future studies related to TBM

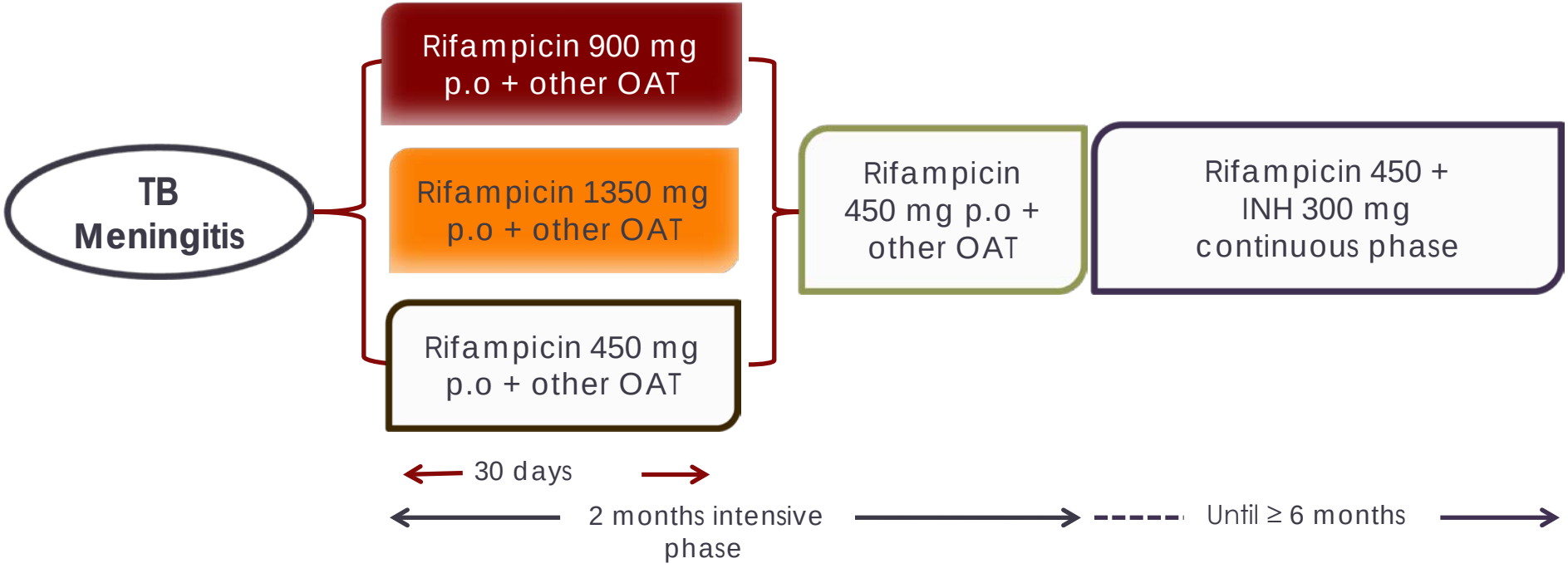
Detailed phenotyping of TBM patients → improve patient care (clinical guidelines)

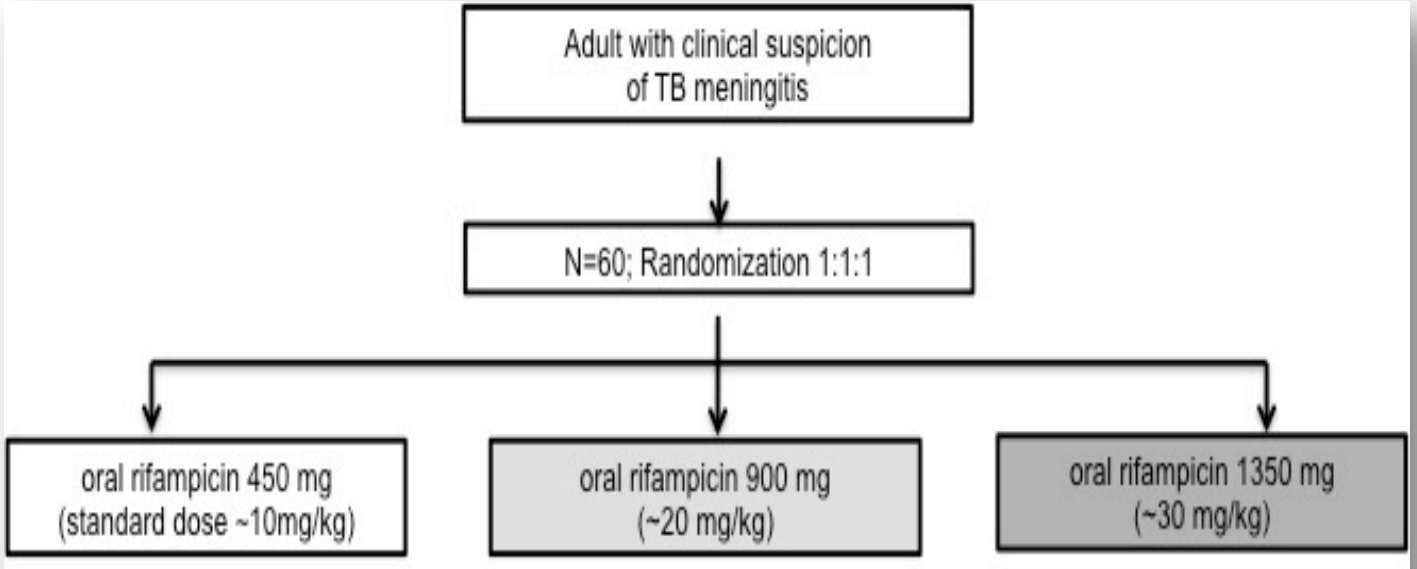
STUDY DESIGN, SUBJECTS, & DRUGS

- Prospective, single-center, **double-blinded**, 1:1:1, **randomized**, **placebo** controlled trial
- Phase 2b clinical trial (dose-finding study)

What?	**450 mg vs. 900 mg vs. 1350 mg oral RIF among other TB meds**
Who?	Adult TBM patient, hospitalized at RSHS
How many?	60 subjects in total (≈ 20subjects/group)
How long?	180 days follow up of subjects

Study design





Follow up: every other day until discharge. At day 30, 45, 60. Final follow up 180 days

Primary pharmacokinetic endpoint: rifampicin AUC in blood; rifampicin concentration in CSF (day 2 +/-1 and day 10 +/-1)

Safety endpoint: grade III and IV and serious adverse event (by 60 days)

Other Secondary endpoints: neurological response; neuroradiological response, mortality up till 180 days

Study subjects:

adult TBM patients hospitalized at Neurology dept., RSHS

- Male/female, ≥15 years
- Clinical susp. of TBM AND CSF/blood glucose ratio <0.5
- None or ≤3 days of OAT
- ICF ☺
- Reproductive age female → to hold being pregnant
- Storage specimens ☺

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- Storage specimens ☺

- LFT >5 ULN, eGFR <50ml/min
- Pregnancy or breastfeeding
- Confirmed cryptococcal or bacterial meningitis
- Rapid clinical deterioration
- History of RIF hypersensitivity/intolerance

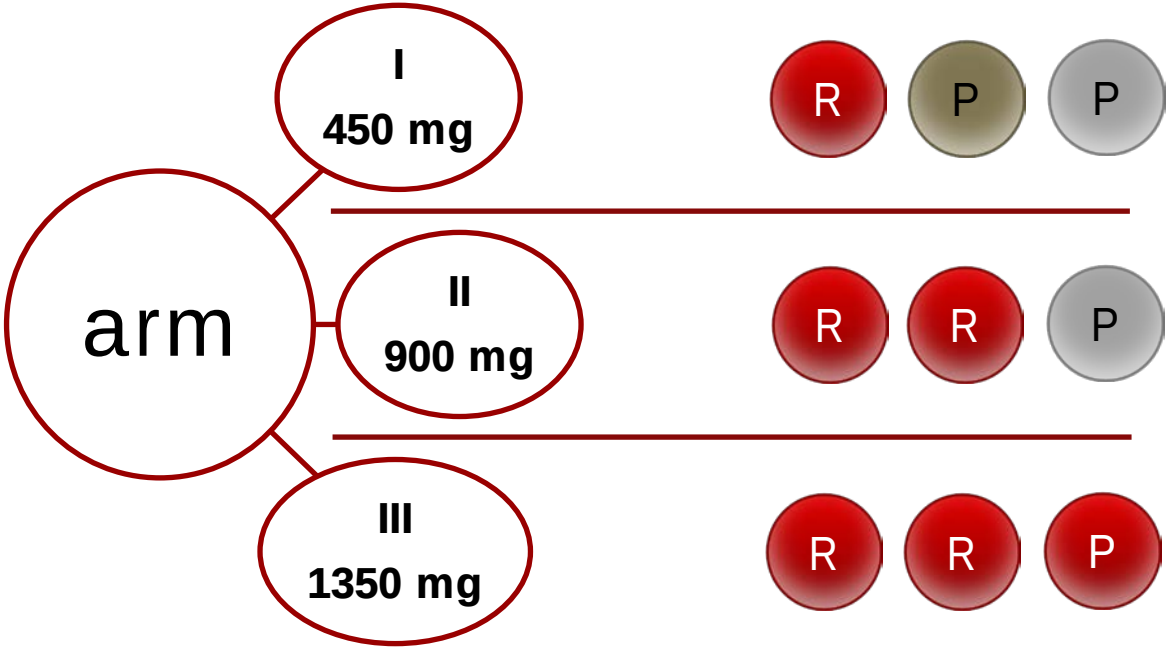
Study drug & treatment

- Rifarmpicin 450 mg – PT. Kimia Farma, Indonesia
- Placebo – PT. Kimia Farma, Indonesia

- Other TB drugs (INH, EMB and PZA)
- B6, adjunctive dexamethasone (for 6-8 weeks)

- 2 months RHEZ + 4 month RH

Treatment regimen



Blinding: use placebo

Randomized

30 days

STUDY PROCEDURES

RECRUITMENT

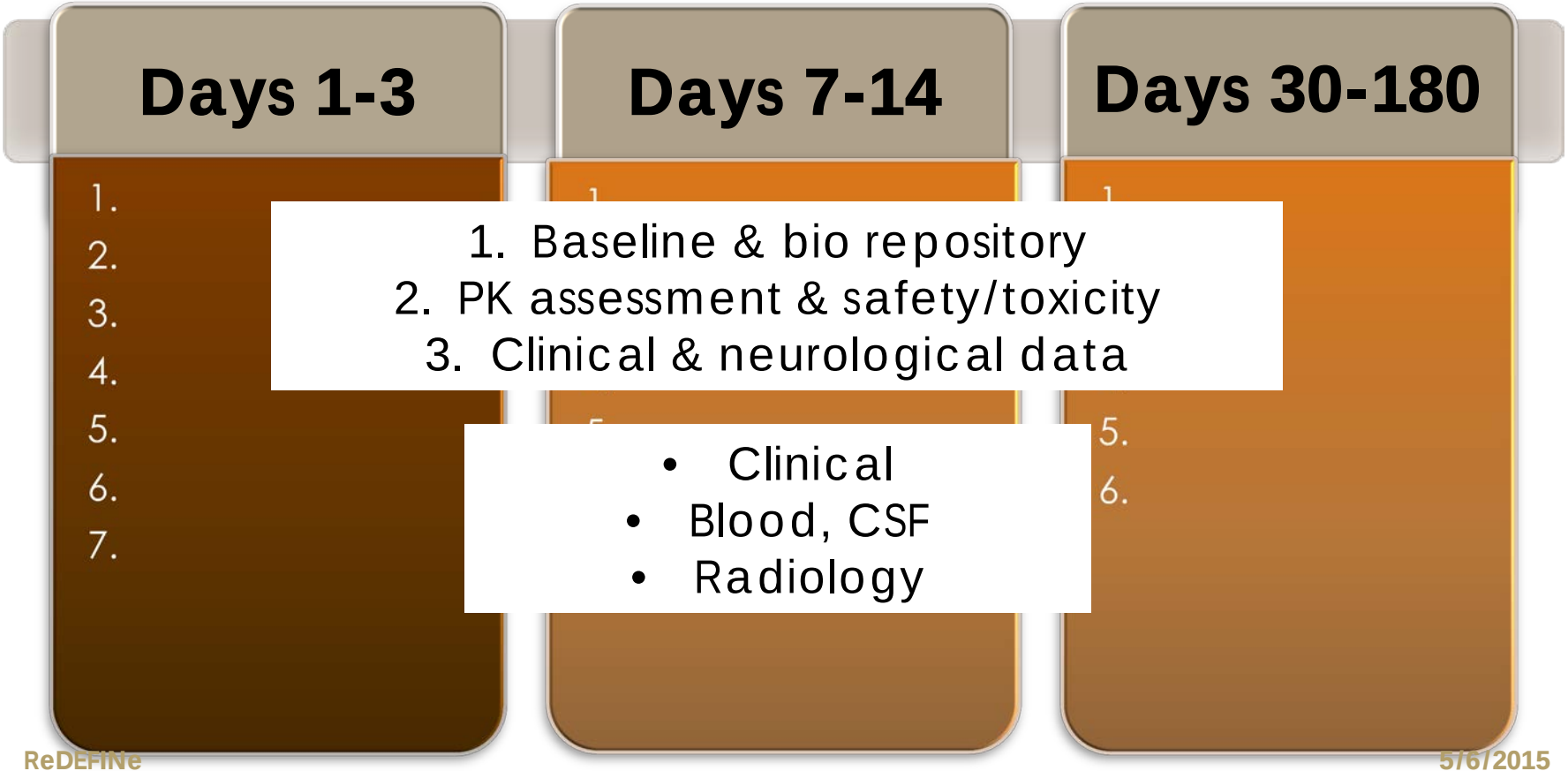
- Screening
- Eligibility: IC & EC
- IC

RANDOMIZATION & BLINDING

- 1:1:1
- Stratified for disease severity grade

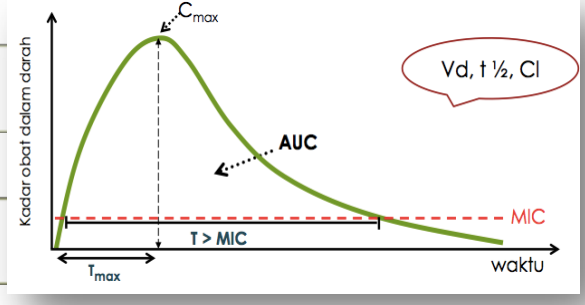
DATA COLLECTION

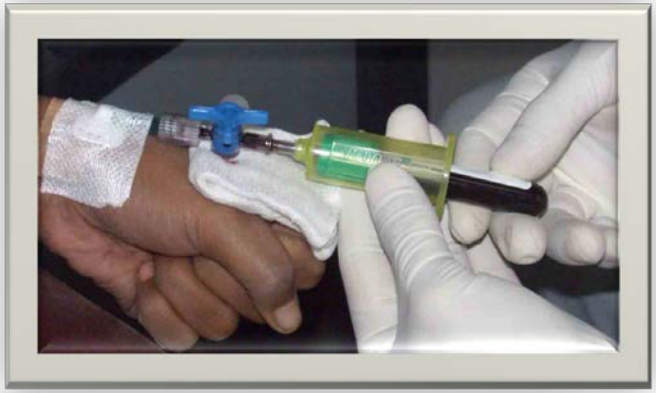
- PK data
- Safety and tolerability
- Clinical & neurological


Days 1-3
Days 7-14
Days 30-180
1.
2.
3.
4.
5.
6.
7.
1. Baseline & bio repository
2. PK assessment & safety/toxicity
3. Clinical & neurological data
5.
6.
• Clinical
• Blood, CSF
• Radiology

PK assessment

- 2x, first 3-critical day & ≥10 days
- Sample: blood & CSF
- Blood: 6 time points in 12 h
  CSF: 1 time point at the same day
- Bio-analysis: at the PK lab, Bandung
- PK analysis: winNonlin software



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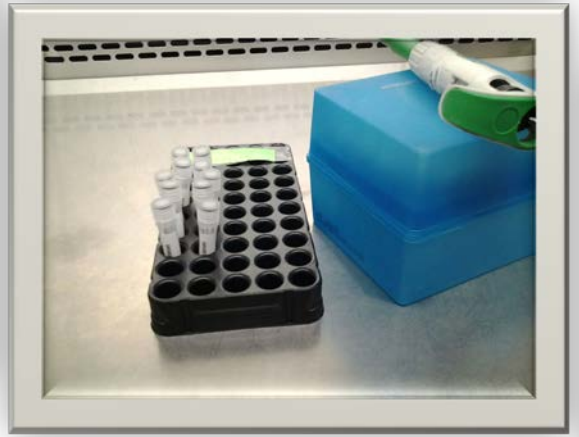


QA/QC of data collection

- Patient compliance to treatment → diary

- Clinical monitoring & audit
  - Monitor: INA-RESPOND → scheduled
  - Audit from int'l researchers during the first year of the study

- Data collection & entry
  - SDW
  - e-CRF (using RedCap)
  - SOPs (10 SOPs)

GCP compliance

Data retention: 15 yrs

PATIENT SAFETY CONSIDERATION

- AE and SAE
- Detail:
  - clinical & laboratory
  - Scheduled time
- CTCAE version 4.0 (2010) - grading
- *Pregnancy – Rifampicin: category C*
- DSMB

Progress Report

5-month recruitment

Suspected TB Meningitis (n= 68)

Excluded (n=14)
- Contraindicated to be LP (n=4)
- Refused to be LP (n=3)
- No CSF sample (n=1)
- SOL (n=3)
- Meningitis bakterialis (n=2)
- Criptococcus meningitis (n=1)

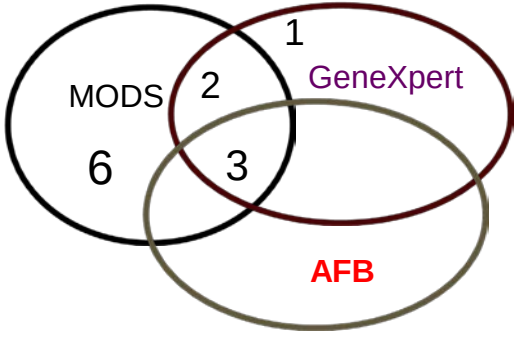
TBM (n=54)

Not eligible for ReDEFINe (n= 34)
- 3 days or more of anti-tuberculosis chemotherapy (n=7)
- Not willing to give ICF (n=2)
- History of hypersensitivity to rifampicin (n=1)
- Rapid clinical deterioration (n=3)
- EGFR <50 (n=1)
- CSF/blood glucose ratio >0.5 (n=19)
- Aged < 15 years old (n=1)

ReDEFINe (n =20)
- Probable: n=8 (40%)
- Definite: n=12 (60%)

(MODS positive 11, GeneXpert 6; AFB 3)

Withdrawn from the study (n=1)



Still on ReDEFINe study (n=19)
- Still on study drug (n=3)
- Died before finish study drug (n=3)
- Completed 30 days study drug (n=2)
- Completed 45 days FU (n=2)
- Completed 60 days FU (n=9)
- Completed 180 days FU (n=0)

Table 1. Subject Demographics Distribution (n=20)

	ReDEFINe (N=20)
Age (y)—median (IQR)	32.5 (22.25-45.75)
Gender (M)—n/N (%)	11/20 (55%)
Chief complaint	
Lowered of consciousness	16/20 (80%)
Severe headache	2/20 (10%)
Seizure	0/20 (0%)
Motor deficit or other neurological complaint	2/20 (10%)
Duration of chief complaint (d)—median (IQR)	5 (2-13)
Duration of TBM symptom (d)—median (IQR)	14 (7-30)
Glascow coma scale—median (IQR)	13 (11-13)
Body temperature (°C)—median (IQR)	37.5 (37-38.6)
TBM grade—n/N (%)	
Grade I	1/15 (6.7%)
Grade II	17/15 (86.7%)
Grade III	2/15 (6.7%)

AEs during study period

24 AEs

- Grade 1= 20
- Grade 2 = 3
- Grade 3 = 1

5 SAEs

- Death = 3: unlikely related
- Hospitalization = 2
  - Decubitus
  - Seizure ec. Paradoxical reaction post TB treatment

Frequency of Adverse Events
by Severity

Term of AEs	Total AEs (n= 19)	Grade 1	Grade 2	Grade 3	Grade 4
		Mild	Moderate	Severe	Potentially Life Threatening
Purpura	1	1	0	0	0
Thrombocytopenia	2	2	0	0	0
Leukopenia	2	2	0	0	0
Hepatotoxicity	8	5	2	1	0
Anemia	2	2	0	0	0
Respiratory Failure	3	0	0	0	3
Gastric toxicity	1	1	0	0	0

QC/QA of data collection

- 2 monitoring visits
- DSMB meeting






We need another 40 subjects & have 2 years to go

Thank you…