PROTOCOL TITLE: "Phase 2b Randomized double-blind, placebo controlled trial to estimate the potential efficacy and safety of two repurposed drugs, acetylsalicylic acid and ibuprofen, for use as adjunct therapy added to, and compared with, the standard WHO recommended TB regimen (SMA-TB)"

Protocol ID	SMA TB 001
Short title	Adjunctive Acetylsalicylic Acid and Ibuprofen for Tuberculosis (SMA TB)
ClinicalTrial.gov ID	NCT04575519
Version	4.0
Date	6th August, 2020
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Sponsor	**Fundació Institut Germans Trias i Pujol (IGTP)** Cristina Vilaplana, MD PhD (See contact details above)

PROTOCOL SIGNATURE SHEET

Name	**Signature**	**Date**
Sponsor or its legal representative: Fundació Institut Germans Trias i Pujol (IGTP)		
Coordinating Investigator: Cristina Vilaplana, MD PhD		

SIGNATURE PAGE- DECLARATION

PHASE 2B RANDOMIZED DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL TO ESTIMATE THE POTENTIAL EFFICACY AND SAFETY OF TWO REPURPOSED DRUGS, ACETYLSALICYLIC ACID AND IBUPROFEN, FOR USE AS ADJUNCT THERAPY ADDED TO, AND COMPARED WITH, THE STANDARD WHO RECOMMENDED TB REGIMEN (The SMA-TB trial)

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, local laws and regulations; and other applicable requirements

Principal Investigator: _____

Signed: _____Date: _____

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ACRONYMS LIST

ASA	Acetylsalicylic acid	KTHC	Klerksdorp-Tshepong Hospital Complex
AE	Adverse Events	M	Month
ALT	Alanine aminotransferase	MDR-TB	Multi-Drug Resistant Tuberculosis (Resistance to both isoniazid and rifampicin)
ART	AntiRetroviral Therapy	MDSCs	myeloid-derived suppressor cells
AST	Aspartate aminotransferase	MMP	Matrix metalloproteinases
CAB	local Community Advisory Board	Mtb	*M. tuberculosis*
CDC	Centers for Disease Control a Prevention	NCTLD	National Centre for Tuberculosis and Lung Diseases Ethics Committee of Georgia
CHBAH	Chris Hani Baragwanath Academic Hospital	NF-kB	Nuclear Factor kB
CI	Confidence Interval	NGS	Next Generation Sequencing
COX	Cyclooxygenase	NRL	National Reference Laboratory
CPT	Cell Preparation Tube	NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
CRF	Case Record Form	OTC	Over The Counter
CRP	C-reactive protein	OUS	Oslo Universittetssykehus
CT	Clinical Trial	PBMC	Peripheral Blood Mononuclear Cells
DMP	Data Management Plan	PHRU	Perinatal and HIV Research Unit
DMSO	Dimethyl sulfoxide	PI	Principal Investigator
DPO	Data Protection Officer	PK	Pharmacokinetic
DSMB	Data Safety Management Board	qPCR	quantitative Polymerase Chain Reaction

DST	Drug Susceptibility Testing	RNA	Ribonucleic acid
DOT	Directly Observed Therapy		
DS-TB	Drug-Sensitive Tuberculosis	RT-MLPA	Reverse Transcriptase Multiplex Ligation-dependent Probe Amplification
EAB	Ethics Advisory Board	Rx	X-ray
eCRF	electronic Case Report Form	SAE	Serious adverse events
ECRIN	European Network for clinical Trials	SC	Steering Committee
ELISA	Enzyme-Linked ImmunoSorbent Assay	SCC	Sputum Culture Conversion
EMA	European Medicines Agency	SCReN	Spanish Clinical Research Network
ESR	Erythrocytes sedimentation rate	SGRQ	St. George's Respiratory Questionnaire
EU	European Union	SJS	Stevens-Johnson syndrome
FBS	Fetal Bovine Serum	SoC	Standard of Care
FPFV	First Patient, First Visit	TB	Tuberculosis
GI	Gastrointestinal	TBTC	Tuberculosis Trials Consortium
H2020	Horizon 2020	TEN	Toxic Epidermal Necrolysis
Hb	Hemoglobin	TNF	Tumor Necrosis Factor
HDT	Host-Directed Therapies	Tregs	T regulatory cells
HIV	Human Immunodeficiency Virus	TSC	Trial Steering Committee
HQoL	Health-related Quality of Life	ULN	Upper Limit of Normal
HuGTiP	Hospital Universitari Germans Trias i Pujol	WHC	Wits Health Consortium

ICMJE	International Committee of Medical Journal Editors	WHO	Word Health Organization
IGTP	Institut de Recerca Germans Trias i Pujol	WP	Work Package
IRF	Interferon-Regulatory Factor	XDR-TB	Extensively Drug-Resistant Tuberculosis
IBU	Ibuprofen		

1. PROTOCOL SUMMARY

1.1. ABSTRACT

Protocol Synopsis	
Protocol Title:	Phase 2b Randomized double-blind, placebo-controlled trial to estimate the potential efficacy and safety of two repurposed drugs, acetylsalicylic acid and ibuprofen, for use as adjunct therapy added to, and compared with, the standard WHO recommended TB regimen (The SMA-TB trial)
Treatment Indication:	Pulmonary Tuberculosis (TB)
Trial Objective:	To assess the efficacy and safety of 2 repurposed drugs (acetylsalicylic acid and ibuprofen), for use as adjunct therapy added to, and compared with, the standard of care (SoC) WHO-recommended TB regimen in drug sensitive (DS) and multi-drug resistant (MDR) TB patients.
Trial Design:	Multicentre**,** phase IIB, placebo-controlled, randomized, 3-arm trial in DS and MDR TB patients.
Patient Population:	A total of 354 evaluable, newly diagnosed, pulmonary TB patients (300 DS and 54 MDR-TB) will be enrolled.
Stratification	Enrolment will be stratified according to country.

Treatment arms:	If eligible and informed consent obtained, patients will be randomized 1:1:1 into one of the following 3 arms, to receive: 1. Standard of Care (SoC) TB treatment + **placebo twice daily during first 4 weeks of TB treatment followed by placebo once daily for an additional 4 weeks.** (control group). 2. SoC TB treatment + **acetylsalicylic acid 300mg twice daily during first 4 weeks of TB treatment followed by acetylsalicylic acid 300mg once daily for an additional 4 weeks.** 3. SoC TB treatment + **ibuprofen 400mg twice daily during first 4 weeks of TB treatment followed by ibuprofen 400mg once daily for an additional 4 weeks.**

Criteria for evaluation:

Primary Endpoints:

1. Time to ≥ 67% sustained reduction in the TB score over the course of TB treatment
2. Hazard ratio for time to stable culture conversion (SCC) (at least 2 consecutive negative cultures for *M. tuberculosis* at least 4 weeks apart during the first 24 weeks of TB treatment.

Secondary Endpoints:

- Hazard ratio for stable culture conversion (SCC) at week 8 and week 16 after treatment start. Difference between each intervention arm and control group.
- Proportion of patients with improvement or resolution of clinical signs and symptoms at end of treatment (TB score). Difference between each intervention arm and control group.
- Proportion of patients with improvement of lung function impairment as change from baseline at week 8, 24 and end of treatment in the 1-second forced expiratory volume (FEV1) expressed as FEV1. Difference between each intervention arm and control group.
- Improvement in CXR (measured with the BCN-SA score) using the x-ray taken at baseline as the comparator compared with subsequent x-rays over the course of TB therapy [Time Frame: at week 8, week 24 and for MDR TB patients at the end of treatment]. Difference between intervention and control group.

- Number of patients with improvement of Health-related Quality of Life comparing baseline measure with that over the course of therapy [Time Frame: 8, week 24 and for DR TB patients at the end of treatment]. Difference between each intervention arm and control group.

Safety Endpoints:

- Safety: the proportion with serious adverse events (SAEs),) between each intervention arm and the control group.
- Tolerability: the proportion of patients in each arm who either
  a. Permanently discontinued either placebo, acetylsalicylic acid or ibuprofen;
  b. And/or had TB treatment interruption for longer than seven days/doses, prescribed either by a listed investigator, or a non-study physician up to two weeks after scheduled or unscheduled permanent discontinuation of placebo/NSAID.

Exploratory Endpoints:

- Host and pathogen biomarkers [Time Frame: at baseline, weeks 1, 2, 4, 8 and 24 and at end of treatment]. Difference between intervention and control group.
- Machine learning of clinical, quality of life, digital, and other composite markers of TB treatment response.

Study sites:

South Africa:

- The Perinatal and HIV Research Unit's (PHRU) clinical research clinic at Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto (Site PI: Dr. Ziyaad Waja)
- PHRU satellite clinical research site at the Klerksdorp-Tshepong Hospital Complex (KTHC) in the Matlosana Municipality around Klerksdorp (Site PI: Dr Tumelo Moloantoa)

PHRU is a division of the Wits Health Consortium (Pty) Ltd a wholly owned company of the University of the Witwatersrand.

Georgia:

- The National Center for Tuberculosis and Lung Disease (NCTLD) in Tbilisi

Study duration: 52 months as follows:

- Start up (M1-M6, including obtaining ethical and regulatory approvals)
- Participant recruitment (M6-M36)
- Participant follow-up (M6-M48)
- Analysis of results and dissemination (M30-M52)

1.2. SCHEMATIC OF STUDY DESIGN

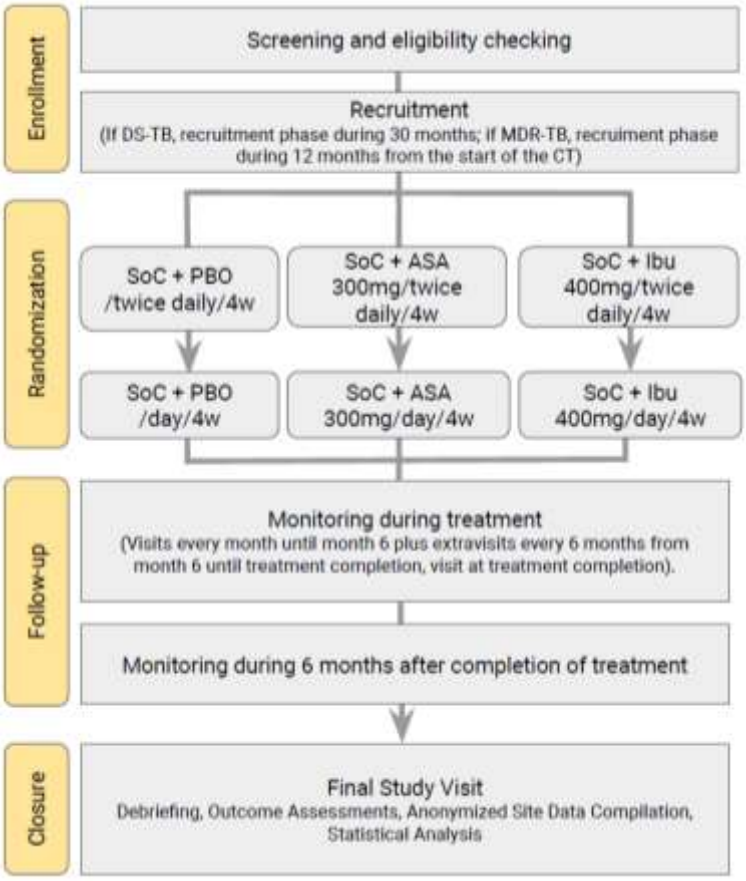

Figure 1: Schematic of the study design.

2. PURPOSE AND OBJECTIVES

2.1.BACKGROUND AND RATIONALE FOR CONDUCTING THE SMA-TB CLINICAL TRIAL.

TB is a chronic, life-threatening infectious disease which caused 1.6 million deaths and around 10 million cases in 2018 [1]. The TB disease burden is still unacceptably high worldwide. Although much of the burden is concentrated in high-burden settings in Asia and Sub-Saharan Africa, TB continues to be of concern also in high-income nations including Europe[2], where reaches high endemicity in big cities and affects vulnerable populations (children, elderly, patients with comorbidities, undernourished, homeless, drug-abusers, refugees) which often present more complicated clinical cases [1]. South Africa and Georgia are included in the list of 18 high-priority countries for TB, bearing the 85% of the TB burden. Moreover, the increasing number of MDR-TB cases poses a problem for national health systems worldwide, which suffer from the increased complications associated to these forms of the disease, and their high-rate of negative outcomes and sequelae.

The duration and regimen of TB treatment is currently based predominantly on whether the *M. tuberculosis (Mtb)* strain is a) DS or b) MDR with doses adjusted by patients' weight only [3]. Staging or patients stratification is the determination of distinct phases or periods in the course of a disease, or the specific extent

of a disease process in an individual patient, and is used to tailor and fine-tune treatment and to predict outcomes in several medical fields including cancer, cirrhosis and some infectious diseases [4,5]. The systematic stratification of patients for personalized treatment does not exist for TB even if it would significantly improve TB control. As each TB case is different, individualized treatment regimens should be applied to obtain better outcomes, as it has been shown in a recent study analyzing the Clinical Management of MDR-TB [6]. However, no individualized treatment is possible without stratifying the patients by integrating pathogen and host factors that will predict the course of the disease and the response to the intervention. As new candidate biomarkers are numerous in TB, but validation and independent confirmation are rare, clinical validation of pathogen and host biomarkers able to predict the response to treatment are needed [7] and should be included in any stratifying strategy.

In this scenario, novel therapeutic approaches are urgently needed to 1) improve outcomes and 2) shorten treatment duration; and Host-Directed Therapies (HDT) might be the best solution. The TB drug pipeline remains sparse, with repurposed antibiotics (levofloxacin, moxifloxacin, clofazimine, cycloserine, terizidone, imipenem-cilastatin, meropenem) and only 2 new drugs (Delamanid and Bedaquiline) having been proposed with success in the last 50 years and incorporated in the WHO TB treatment guidelines update [8].

There is growing evidence that repurposed drugs – drugs with indications for diseases other than TB – can significantly improve patient outcomes, particularly for XDR-TB. Unfortunately, these drugs are not yet readily accessible either for further research or to treat patients, and there are many barriers to wider use, including cost, regulatory issues and a lack of incentives for industry to promote access [9]. Repurposed medicines with proven efficacy in TB or potential efficacy in highly resistant TB cases can fill important gaps in DR-TB treatment, and are of increasing importance in both trial and operational research for DR-TB. But they need to be made accessible [9].

HDTs have emerged as a great alternative with the potential to modulate the immune system and improve treatment outcomes while reducing the duration of treatment [10,11]. Even if there is an expanding portfolio of HDT for use as adjunct treatments to TB therapy, we here focus on HDT modulating inflammation, as the latter has been related to worse health outcomes: tissue destruction and permanent lung damage (4). Importantly, as they target the host immune response instead of the pathogen, they do not increase the risk of generating drug-resistance. Within HDT, repurposed drugs represent a shortcut in drug development and can be implemented at short-term. As hyperinflammation is associated to worse outcomes, HDT with anti-inflammatory effect might improve outcomes by reducing tissue damage and thus the risk of permanent sequelae. However, the variability between patients should be considered when considering to treat patients with HDT, as patients may not all benefit equally [12].

Evaluation of a cheap, worldwide available HDT drug to be administered as co-adjuvant to standard treatment in order to enhance its efficacy: by reducing the length of TB treatment, increasing the curation rate and

improving the outcomes of TB patients, both in DS-TB and MDR-TB. In SMA-TB we propose to use 2 common NSAID, acetylsalicylic acid(ASA) and ibuprofen (Ibu), cheap, suitable, acceptable, safe, worldwide available and considered an essential medicine by the WHO, as an HDT to enhance the current TB drug therapeutic regimen[13–16].

ASA and Ibu are Non-Steroidal Anti-Inflammatory Drug (NSAID), 'repurposed' drug with anti- inflammatory effect and potential anti-TB activity which is cheap, have a reasonable safety profile and have been widely used for decades as anti-inflammatory drugs for pain, and inflammatory diseases. They have been used since 1899 (ASA) and 1960 (Ibu); approved for Over-The-Counter sale (OTC) without prescription and included in the 18th WHO Essential Medicines List [17]. Available over the counter in many jurisdictions, its safety profile is well known. ASA is a salicylate, which unselectively inhibits the 2 isoforms of COX (COX-1 and COX-2), as other non-selective NSAIDs, but does it in an irreversible manner and also has an antiplatelet effect [18]. ASA increases lipoxin A4 production to reduce TNFα levels and achieve eicosanoid balance during chronic inflammation. ASA has been successfully used as acute and long-term treatment of chronic inflammatory diseases as pericarditis or those with an autoimmune etiology (i.e. rheumatoid arthritis, systemic lupus erythematosus) with limited Adverse Effects (AE) [19,20]. Ibu is also a nonselective COX inhibitor that is used for treating pain, fever, and inflammation including painful menstrual periods, migraines, and rheumatoid arthritis [21]. It blocks the production of prostaglandins possibly by inhibiting cyclooxygenase activity and might have less adverse effects than other NSAIDs such gastrointestinal bleeding [22]. Ibu has been previously shown to achieve a reduced lung pathology and mycobacterial burden in a highly susceptible mouse model of tuberculosis, increasing its survival [23]. ASA and Ibu were chosen for its potential benefit on TB (based on scientific literature), its safety profile, price and availability, major assets when considering an intervention to be globally implemented for the maximum best interest of both the patients and Health Systems.

2.2. PRIMARY OBJECTIVE

To evaluate the potential benefit of ASA and Ibu used as HDT when administered concurrently with standard of care TB treatment (SoC).

3. STUDY DESIGN AND ENDPOINTS

3.1. DESCRIPTION OF THE STUDY DESIGN

3.1.1. Primary Efficacy Endpoints

3.1.1.1. Time to ≥ 67% sustained reduction in TB score over the course of TB treatment.

3.1.1.2. Hazard ratio for stable culture conversion (SCC) (at least 2 consecutive negative cultures for *Mtb* at least 4 weeks apart.

3.1.2. Safety and Tolerability Endpoints

3.1.2.1. Safety. The proportion of participants with at least one serious adverse event (SAEs) by arm until the end of TB treatment; and the serious event rate expressed in person time – starting the

day of the first dose of NSAID or placebo until one month (30 days) after the last placebo or NSAID taken, including all adverse events recorded in each arm.

3.1.2.2. Tolerability: The proportion of patients in each arm who permanently discontinued either placebo, ASA or Ibu; and/or had a TB treatment interruption for longer than seven days/doses, prescribed either by a listed investigator, or a non-study physician up to two weeks after scheduled or unscheduled permanent discontinuation of placebo/NSAID. This will be reported as a composite measure of both but each constituent of this endpoint will be reported separately.

3.1.3. Secondary Endpoints

The secondary endpoints include:

- Hazard ratio for stable culture conversion (SCC) at week 8 and week 16 after treatment start. Difference between each intervention arm and control group.
- Proportion of patients with improvement or resolution of clinical signs and symptoms at end of treatment (TB score). Difference between each intervention arm and control group.
- Proportion of patients with improvement of lung function impairment as change from baseline at week 8, 24 and end of treatment in the 1-second forced expiratory volume (FEV1) expressed as FEV1. Difference between each intervention arm and control group.
- Improvement in CXR (measured with the BCN-SA score) using the x-ray taken at baseline as the comparator compared with subsequent x-rays over the course of TB therapy [Time Frame: at week 8, week 24 and for MDR TB patients at the end of treatment]. Difference between intervention and control group.
- Number of patients with improvement of Health-related Quality of Life comparing baseline measure with that over the course of therapy [Time Frame: 8, week 24 and for DR TB patients at the end of treatment]. Difference between each intervention arm and control group.

3.1.4. Exploratory Endpoints

3.1.4.1. Host and pathogen biomarkers: we will collect specimens of a variety of human body fluids and mycobacterial isolates to identify novel biomarkers of TB treatment and host directed therapy responses.

3.1.4.2. Using machine learning techniques to developing and test novel composite markers that include clinical, quality of life, digital, and other biological markers of TB treatment response.

4. STUDY INTERVENTION PRODUCT

4.1. STUDY PRODUCT DESCRIPTION

ASA and Ibu are two ‘repurposed’ drugs with anti-inflammatory effects and potential anti-TB activity which are cheap, have an established, well supported safety profile and have been widely used for decades as

anti-inflammatory drugs for pain and inflammatory diseases. It has been used for more than 50 years; approved for over-the-counter sale (OTC) without prescription and included in the 18th World Health Organisation (WHO) Essential Medicines List [17]. Available over the counter in many jurisdictions, their safety profiles are well known.

ASA is a salicylate, which unselectively inhibits the 2 isoforms of COX (COX-1 and COX-2), as other non-selective NSAIDs, but does it in an irreversible manner and also has an antiplatelet effect [18]. ASA increases lipoxin A4 production to reduce TNFα levels and achieve eicosanoid balance during chronic inflammation. ASA has been successfully used as acute and long-term treatment of chronic inflammatory diseases such as pericarditis or those with an autoimmune etiology (i.e. rheumatoid arthritis, systemic lupus erythematosus) with limited adverse effects [24]. The effect obtained in vivo also depends on the doses used. Based on published literature and in vivo studies, the benefit of ASA in TB could be through 2 mechanisms. While low doses have antithrombotic effect, intermediate doses (500mg to 3g) inhibit COX-1 and COX-2 and likely do have a COX-independent anti-inflammatory effect on the neutrophils. The dampening of TNFα-induced hyperinflammation will aid tissue repair and control burden of *M. tuberculosis*, as experimentally shown by Marzo et al and others [25,26]. A recent publication has also demonstrated in vivo that low-doses of ASA will also have a potential positive effect on TB. Hortle et al showed how mycobacteria drive host haemostasis through the formation of granulomas, and how the treatment with ASA markedly reduced mycobacterial burden in a zebrafish model [13]. As ASA has an antithrombotic effect from very low doses, we can expect that inhibition of thrombocyte activation leads to reduced bacterial burden.

It is rapidly absorbed in stomach and upper intestine; readily distributes into most body fluids and tissues (V_d: 10 L;); and hydrolyzed to salicylate (active) by esterases in the GI mucosa, red blood cells, synovial fluid and blood. Metabolism of salicylate occurs primarily by hepatic conjugation; metabolic pathways are saturable. Its excretion is through urine, 75% as salicyluric acid and 10% as salicylic acid. Time to peak is 3 to 4 hours if using enteric-coated tablets. Its action lasts 4-6 hours and the platelet inhibitory effects lasts the lifetime of the platelet (~10 days) due to its irreversible inhibition of platelet COX-1[18].

Ibu was derived from propionic acid, and its active ingredient is (±)-2-(*p*-isobutylphenyl) propionic acid. It's a nonselective COX inhibitor, in that it inhibits two isoforms of cyclooxygenase, COX-1 and COX-2. Ibu is a NSAID used for treating mild to moderate pain, fever and inflammation (juvenile idiopathic arthritics, rheumatoid arthritis, pericarditis)[19,21]. The analgesic, antipyretic, and anti-inflammatory activity of ibu appears to operate mainly through inhibition of COX-2, which decreases the synthesis of prostaglandins involved in mediating inflammation, pain, fever, and swelling. Antipyretic effects may be due to action on the hypothalamus, resulting in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation. As stated in Kroesen et al. [26], Ibu increased survival and significantly decreased the number and size of lung lesions consistent with decreased bacillary loads in the lungs in a murine model of active TB [23], even if its good results on controlling *Mtb* infection might be dependent on timing of administration [27]. According to

other studies' results, Ibu was suggested as a good candidate to be administered to enhance isoniazid and pyrazinamide effect [28].

Ibu is rapidly absorbed. Peak serum Ibu levels are generally attained one to two hours after administration. With single doses up to 800 mg, a linear relationship exists between amount of drug administered and the integrated area under the serum drug concentration vs time curve. Above 800 mg, however, the area under the curve increases less than proportional to increases in dose. There is no evidence of drug accumulation or enzyme induction. The bioavailability of the drug is minimally altered by the presence of food. Ibu is rapidly metabolized and eliminated in the urine. The excretion of Ibu is virtually complete 24 hours after the last dose. The serum half-life is 1.8 to 2.0 hours [21].

4.2.PRODUCT SUPPLY, DISTRIBUTION, AND ACCOUNTABILITY

ASA and Ibu will be obtained by IGTP for all sites, prepacked and labelled with a study ID according to the randomisation schedule, and sent to sites. The clinical investigator or designee is responsible for ensuring that ASA and Ibu received at clinical trial sites are inventoried and accounted for throughout the trial. The dispensing of trial drug to the patient will be documented on the drug accountability form. The medication will be sent upon approval of the ethics and regulatory authorities to the study site. The pharmacist of record for this trial will receive the study drugs. The trial drugs must be handled strictly in accordance with the protocol and the container label and will be stored in a limited access area under appropriate environmental conditions. Unused and used trial drug must not be disposed of until the sponsor's monitor has completed drug accountability during the close out visit. All used and unused drugs will be returned back to Sponsor or destroyed at the site after written confirmation. The trial drug will be dispensed under the supervision of the investigator, or a qualified member of the investigational staff. Trial drug will be supplied only to patients participating in the trial. Trial drug will not be re-labelled or reassigned for use by other patients.

4.3. ADMINISTRATION OF STUDY DRUG

ASA will be administered orally in a gastro-resistant tablet with a dose of 300mg twice daily during the first 4 weeks of treatment followed by one dose daily for 4 additional weeks (arm 2).

Ibu will be administered orally in a film-coated tablet with a dose of 400mg twice daily during the first 4 weeks of treatment followed by one dose daily for 4 additional weeks (arm 3).

All drugs will be administered as Direct Observational Treatment (DOTS) in accordance with each site's standard of practice.

4.4. THE RATIONALE FOR CHOICE OF INTERVENTIONAL DRUGS AND DOSES

This proposal intends to evaluate an already-approved drug, which has previously been used in humans; thus, in theory the dose selection should rely on safety and previous use rather than to scale the dose from animal studies.

ASA doses used commonly as immunosuppressive (in autoimmune diseases mostly: autoimmune pericarditis, rheumatoid arthritis, systemic lupus erythematosus and other rheumatologic diseases) are higher

than those proposed here, as it is accepted that low doses have antithrombotic effect while intermediate doses (500mg to 3g) inhibit COX-1 and COX-2 and likely do have a COX-independent anti-inflammatory effect on the neutrophils. However, based on the murine experiments, maintained low-doses achieved better results than the higher doses [14,15,29].

There are 3 other clinical trials using ASA for TB, even if only for the meningitis form. One of these trials has already been completed and its results are shown to be safe (see Table 1).

Table 1: Summary of the CT using ASA for TB, the doses evaluated and safety results (if any).

Clinicaltrials.gov code	Title	Drug and dosage	Safety results
NCT02237365	A Pilot Study Of Adjunctive ASA For The Treatment Of HIV Negative Adults With Tuberculous Meningitis (Aspirin TBM)	ASA: 81mg/day/60 days 1000mg day/60 days	Combining dexamethasone with aspirin did not significantly increase gastrointestinal bleeding of any severity or any other category of grade 3 or 4 AE. There was a non-significant increase in non-severe gastro-intestinal bleeding events in the ASA-treated participants. [30]
NCT03927313	Linezolid, Aspirin and Enhanced Dose Rifampicin in HIV-TBM (LASER-TBM)	1000mg/day/56 days	Unknown, CT ongoing
NCT04145258	Intensified Tuberculosis Treatment to Reduce the Mortality of Patients With Tuberculous Meningitis (INTENSE-TBM)	200mg/day/8weeks	Unknown, CT ongoing

Ibu recommended oral doses when used for treating Inflammatory Diseases, as osteoarthritis or rheumatoid Arthritis are 1.2–3.2 g daily, given as 300 mg 4 times daily, and the maximum prescribing limit established as 3.2 g daily [21].

Table 2: Summary of the CT using Ibu for TB, the doses evaluated and safety results (if any).

Clinicaltrials.gov code	Title	Drug and dosage	Safety results
NCT02781909	Potential Efficacy and Safety of Using Adjunctive Ibuprofen for XDR-TB Tuberculosis (NSAIDS-XDRTB)	400mg/daily/8 weeks	Results analysis still ongoing, but preliminary results showed no SAE reported and ibuprofen well-tolerated.

On the other hand, the published literature indicating the adverse effects of NSAIDs (ASA and Ibu included) are dose-related and depending on their chronic intake, occurring with doses of 1,800 to 3,200 mg daily (>100 mg/kg) in case of ASA [16,18,31,32] and with doses of >1800mg/day in case of Ibu [19]. Because of this, it is considered that to avoid/reduce this risk the lowest effective dose during the shortest time should be given. According to this premise and as we do consider the experimental drug should be given at least during the

intensive phase to achieve any effect, we have been conservative in the doses selected to be evaluated in this trial, establishing them as 500mg daily (maximum of 4 weeks) for ASA, and 800mg daily (maximum of 4 weeks) for Ibu.

4.5. TOLERABILITY

Both ASA and Ibu have been used for more than 50 years and approved for over-the-counter sale (OTC) without prescription. More than 50 years' experience with them in clinical practice worldwide suggests their safety and both drugs are considered an essential medicine by the WHO [17]. However, there are some safety concerns for the subjects involved in the proposed trial, as NSAIDs are not innocuous.

The most frequent types of Adverse Events (AE) are gastrointestinal (GI) damage or bleeding complications (new episodes or aggravated pre-existing conditions). Most systematic reviews that have been done considering short-term administration, confirmed an acceptable safety profile of ASA with doses ranging 375-2000 mg/day [29,33]. Forder et al showed in a meta-analysis reviewing several manuscripts showed that OTC ASA taken at doses of 2,5-3 g/day during up to a week was well-tolerated. Even if the incidence of gastrointestinal AEs was elevated in ASA users compared with placebo users, the risk of these AEs was not statistically significantly different, and there were no reports of serious gastrointestinal complications in either of the groups. In another meta-analysis, Lanas et al showed similar results for short-term doses of ASA up to 4g/day in which GI AE were more frequent with ASA but only one serious AE was reported [34]. Low-doses maintained ASA also showed an increased risk for bleeding GI events, especially when combined with other NSAIDS, clopidogrel and selective serotonin reuptake inhibitors; a risk which diminished with the concomitant use of proton pump inhibitors [35]. Finally, a prospective study on long-term use of ASA also showed an increased risk of GI bleeding, but more strongly related to dose (325mg versus 81 mg) than to duration of use (>5 years vs <5 years)[36].

Very common GI AE for ibu (>10%) include nausea (57%), vomiting (22%), flatulence (16%) and diarrhea (up to 10%); while dyspepsia, abdominal discomfort, constipation and GI hemorrhage happen commonly (1-10%) [21]. A CT registered at clinicaltrials.gov as NCT01822665 evaluated the gastrointestinal safety of Ibu and compared it to placebo. When giving Ibu 400 mg liquid gel capsules twice daily for 7 days, the results showed no significant difference in mean endoscopy score of gastric mucosal damage between the Ibu and placebo. The percentage of presence of AE were as follows: 0% SAE; 20.83% AE (abdominal pain, 12.50% (3/24); flatulence 4.17% (1/24), chest pain 4.17% (1/24), arthralgia 4.17% (1/24), back pain 4.17% (1/24).

Short-term use (less than 14 days) demonstrates dose-dependent gastric lesions resulting for all NSAIDs; while long-term (3 months or more) endoscopy studies in patients showed ulcer rates from 15%-35% with various NSAIDs, but serious outcomes are rare as confirmed by other studies [16,31].

Chronic Ibu use has been found correlated with risk of arterial thrombotic events, namely hypertension, stroke and myocardial infarction, particularly among those treated chronically using high doses (>2400mg/day) and which can be fatal, especially in patients with pre-existing cardiovascular disease or risk

factors [37][38]. Because of this, the European Medicines Agency (EMA) issued warnings on using doses >2400mg/day, especially in patients with stablished ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, congestive heart failure or uncontrolled hypertension [39].

Patients on long term, moderate-to-high dose (doses of 1,800 to 3,200 mg daily (>100mg/kg)) ASA therapy can show elevations in serum ALT levels, with or without mild increases in alkaline phosphatase and bilirubin. The hepatotoxicity of ASA is usually mild and asymptomatic, and although with higher doses symptoms of nausea, abdominal pain and even signs of hepatic dysfunction can occur. Very rarely, a special form of ASA hepatotoxicity (Reye syndrome) can occur in children or young adults after a prodromal febrile illness, typically influenza B or varicella. Liver injury from high doses of ASA is usually mild and self-limited, and signs and symptoms resolve rapidly with discontinuation. ASA can often be continued in lower doses safely [18,40]. Hepatotoxicity due to Ibu is very rare (<0.01%). Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs but elevations of aspartate transaminase (ALT) or alanine transaminase (AST) (approximately three or more times the upper limit of normal) occur in 1% patients, especially at doses of 2,400-3,200mg of Ibu, but these resolve rapidly with discontinuation [40].

Water and electrolyte imbalances have been reported for both drugs. Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury, especially in those with renal disease. NSAIDs can cause serious rashes: exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. The drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity. Asthma and other hypersensitivity responses can occur with NSAIDs and anaemia is sometimes seen with NSAID treatment [18].

Most AE's of ASA and Ibu are dose-related and the doses used in our study will be relatively low (600mg maximum daily for ASA and 800mg for Ibu), thus we do expect a reasonably good safety profile of the experimental drugs in our CT. However, we have taken these risks into account when designing the protocol, especially for the exclusion criteria, and we will implement a process of symptom and objective screening for AE in order to ensure patients' safety.

5. STUDY START-UP

5.1. PROTOCOL REGISTRATION

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity.

The protocol will be registered at Clinicaltrials.gov database prior to the implementation of this protocol.

5.2.SCREENING AND ENROLLMENT

There will be minimal pre-screening of participants. Patients diagnosed with TB in clinics will be approached by a recruiter to assess their interest in volunteering for a clinical trial. If there is interest, potential participants will be invited to the study clinic, where consent is administered. Once consent is obtained, additional information is obtained from the participant to assess eligibility and screening bloods are taken.

This screening process may take more than one visit. At the first visit after obtaining informed consent we will collect the following information from participants.

- Relevant demographic and clinical data including medical history, alcohol and drug use and concomitant medication. Medical history will be collected from medical records and interviewing the participant.
- Health-related Quality of Life questionnaires will be administered to assess how participants feel and how the disease and the treatments are affecting daily life.
- At each study visit we will ask participants if they are feeling better or worse and check if they have any new symptoms.
- Women who are able to become pregnant will be asked about what type of birth control they are using.

If a participant provisionally meets eligibility criteria based on their medical history, we will collect blood and sputum specimens as outlined in Section 6.

Once laboratory results are available, the participant will return to the site for their results. At this visit, they will have their vital signs checked and be examined by a doctor who will confirm eligibility. Participants who are eligible for the study will be randomised to one of the study treatment arms and initiated on treatment. Those that do not qualify will be referred back to their local clinics to receive TB treatment.

5.2.1. Eligibility criteria

Prior to randomization, all participants must have source documentation showing clearly that they fulfil all inclusion and exclusion criteria. Eligibility criteria are listed in Table 3.

Table 3: Inclusion and exclusion criteria.

Inclusion criteria	**Exclusion criteria**
1. Adults, 18- 60 years of age	1. Has a **comorbid condition where treatment with ASA, Ibu or other NSAID is indicated** (e.g. cardiovascular disease, rheumatic fever, chronic pain, etc.)
2. Written informed consent in a language they understand. **This includes informed consent to be in the trial and informed consent to collect specimens**	2. People **institutionalized** (incarceration in jail or prison, or due to chronic mental illness). If incarcerated during the study, participants may be terminated, those incarcerated in the first 8 weeks of follow up will be late exclusions and replaced*. Patients either who are planned to be hospitalized or currently hospitalized whilst treated for MDR TB in a TB hospital or ward may be enrolled.
3. **Laboratory confirmed pulmonary TB** (with or without extrapulmonary involvement) defined as a hard copy of a sputum laboratory result that reports *Mtb* detection by a WHO recommended assay - both rapid molecular assays or mycobacterial culture with subsequent speciation are acceptable as inclusion criteria.	3. **Receipt of multi-drug TB treatment** (including rifamycin plus isoniazid preventive treatment regimens) for ≥3 days in the 6 months prior to randomization. Participants who have received ≥3 days TB preventive treatment in the month prior to TB treatment initiation will also be excluded.

Inclusion criteria	Exclusion criteria
*Patients who are subsequently found to be culture negative for Mtb at baseline will be late exclusions; and not included in the analysis**	
4. Women of childbearing potential (including females <2 years post-menopausal) **must have a negative pregnancy test at enrolment.** *Women who become pregnant during the first 8 weeks of the study will have the study drug stopped immediately. If pregnancy occurs during the first 4 weeks, the participant will be excluded from the analysis***	4. Currently **Pregnancy/breastfeeding**. *Women who conceive and are found to be pregnant in the first 4 weeks of the trial will be terminated from the trial and excluded from the analysis*.*
5. **Participant must be willing to have an HIV test done unless there is compelling evidence that the patient is HIV-infected at the time of randomisation**. Compelling evidence of HIV infection is: • Hard copy of an unsuppressed viral load • Hard copy of a prescription for antiretroviral therapy • Documentation in clinical record of two rapid tests positive for HIV infection • Hard copy of a laboratory ELISA or Western blot test positive for HIV	5. Any of the following laboratory parameters taken prior to randomization: • Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN); • Total bilirubin > 2 x ULN; • Neutrophil count ≤ 700 neutrophils /mm^3; • Platelet count < 50,000 cells / mm^3 • Haemoglobin concentration less than 8 g/dL • Serum creatinine concentration more than twice the upper limit of normal
	6. Co-treatment in the three months prior to randomization, or planned treatment over the course of the trial follow up with any one of the following agents: • anticoagulant therapy • immune modulating therapy (cancer treatments, any oral or daily use of inhaled steroids; • Antacids or proton pump inhibitors – including self-treatment and prescription
	7. History or clinical record of sensitivity, asthma or allergy that could be attributed to NSAIDs
	8. Weight < 45kg at baseline.
	9. A history or clinical record suggestive of any of the following in past two years: • peptic ulcer disease or gastro-intestinal bleeding, • coagulopathy or other bleeding disorder, • renal disease requiring hospitalization - in addition, any prior record at any time of acute kidney injury will be an exclusion criterion.

Inclusion criteria	Exclusion criteria
	• liver disease requiring further investigation or hospitalization, • underlying cardiovascular disease or risk factors for cardiovascular disease.
	10. Patients with HIV infection (irrespective of ART status) if: • CD4 <350 cells/mm^3 • if on ART, unsuppressed (>200 copies/ml) viral load • if not on ART, either in the opinion of the attending doctor, or according to local ART guidelines, the patient should initiate ART during the 8 week initial placebo or NSAID treatment phase.
	11. Alcohol use: potential participant either self-reports or in the investigator's opinion that the patient drinks more than an average of four units/day over a usual week or is a binge drinker (men: 5 or more drinks; women: consume 4 or more drinks, in about 2 hours).**
	12. Major co-morbid conditions or any other finding which in the opinion of the investigator would compromise the protocol compliance or significantly influence the interpretation of results.
*Late exclusion criteria: These are criteria which become apparent after randomization (and after likely receipt of study drug). Where possible, participants who are late exclusions during the initial 8 weeks placebo or NSAID treatment phase will be replaced by another eligible participant. ** 1 unit of alcohol is equivalent to 8g of ethanol, the amount that can be processed by the average adult in in hour (UK specifications). One tot (25ml) of alcoholic spirits, half a glass of wine, 284ml of beer are roughly equivalent to one unit of alcohol. *** In South Africa, pregnancy tests will be done at every visit for the first 8 weeks due to high rates of pregnancy	

5.2.2. Special populations

Children, Pregnant Women, and Breast-Feeding Women

Pregnant and breastfeeding women at baseline will be excluded. women of childbearing potential (including females less than 2 years post-menopausal) must have a negative pregnancy test at enrolment and must agree to use effective methods of birth control, recorded in the source document. Pregnancy tests should be repeated during the first 10 weeks of the trial if there is clinical suspicion of conception. In South Africa, pregnancy tests will be done at each study visit until all 8 weeks of exposure to placebo or NSAID therapy is completed due to high rates of pregnancy. Subjects found to be pregnant during pre-randomisation testing or during the first four weeks of placebo or NSAID treatment will be excluded. Those found to be pregnant after the first four weeks will be censored at that time and have the NSAID or placebo stopped immediately but

will continue follow up to one month after the birth of the infant. We will only recruit adults 18 years and older.

Prisoners

This study will not enrol prisoners. However, it is possible that a participant will be incarcerated after enrolment. If an enrolled individual is incarcerated during the initial 8 weeks of the trial, and adherence to treatment cannot be assured, they will be terminated from the trial and replaced.

HIV-Infected Individuals

We plan to include HIV-infected individuals who at baseline are either on suppressive ART or who are not considered candidates for ART initiation in the first 8 weeks of their participation in the trial. However, HIV co-infected TB patients with a CD4 count at screening of ≥ 350 cells/mm3 will be considered for participation in this study. (See table 1, inclusion and exclusion criteria).

5.2.3. Management of participants deemed ineligible

Patients deemed ineligible to participate in the clinical trial will be referred to their local clinic with results of their screening investigations, and treated for TB according to standard of care guidelines in each country.

5.3. RECRUITMENT

5.3.1. Recruiting sites and capacity

A total of 354 evaluable participants (300 DS-TB and 54 MDR-TB) will be recruited and followed-up, in the ratio of approximately one third each at the two South African sites and one third at the site in Tbilisi, Georgia.

South Africa

Soweto and Klerksdorp are 160km apart and annual TB incidence in the Dr Kenneth Kaunda District, within which Matlosana is located, is 800/100,000; approximately twice that of the Johannesburg Metropolitan Council within which Soweto is located. Both sites have similar HIV prevalence (~30% in pregnant women). PHRU has extensive experience in conducting clinical trials of tuberculosis treatment and has support functions for regulatory and data management and a research pharmacy currently overseeing ~30 clinical trials. Established in Soweto in 1996 the PHRU has over 20 years' experience in conducting complex clinical trials and Dr Martinson is the site PI for several TB-related clinical trials. Dr Martinson and Prof Variava established the Matlosana research site in 2007 and Prof Variava is the site PI of several studies sponsored by the TB Alliance in both multi-drug and drug sensitive TB patients, and is the national PI of Otsuka Pharmaceuticals clinical trial of Delamanid. Dr Moloantoa is a co-investigator on several prior clinical trials and has been the site PI for two large clinical trials. Dr Waja is a co-investigator and has been the lead clinician on three multinational clinical trials.

Georgia

National Center of Tuberculosis and Lung Disease (NCTLD) is a lead facility for TB control in Georgia, which administers and implements the National Tuberculosis Program, aimed to decrease spreading of

Tuberculosis in Georgia. The NTLD is subordinate to the Ministry of Labor, Health and Social Affairs, which in general is responsible for TB control in the country. TB management actions are fulfilled though a network of specialized TB service institutions and Primary Health Care services. TB program has a vertical structure and consists of three levels: I) National level – NCTLD, II) Regional level – Regional TB Facilities including TB Dispensaries in Tbilisi and III) District level – TB Units and PHC Facilities. In the past 2-3 years, the building of National Center for TB and Lung Disease has been renovated, including MDRTB and departments for sensitive TB treatment and the overall environmental improvements are sorted. Distributions of different categories of patients between the building rooms are currently in use. The NCTLD houses the National TB Reference Laboratory, a key asset in the country's ability to conduct state of the art TB clinical research. The NRL works on TB culture, DST, molecular diagnostic methods and is involved in various research projects. NCTLD focuses on NDR/XDR TB problems in its clinical practice and research. The Center has 270 beds in 5 departments: 4 therapeutic, 1 paediatric and 1 surgical (pulmonary and extrapulmonary). It is involved in several clinical trials.

5.3.2. Recruitment strategy

Patients with newly diagnosed TB will be identified by recruiters at each site – both in-patients and out-patients newly diagnosed with TB will be screened. We anticipate that most eligible patients will have a hard copy of a positive, sputum Xpert result; but there may be some identified by having a sputum culture positive for *Mtb*. Recruiters will engage with potential participants who have laboratory confirmation of TB and who either have yet to initiate TB treatment or who have taken less than three doses of TB treatment at the time of screening, for this episode of TB disease. They will be invited to attend the research clinic to obtain informed consent and further assessment of eligibility. We will attempt to ensure similar numbers of DS TB participants are recruited at each site but will allow competitive enrolment after a minimum of 50 DS participants have been recruited at each site. In addition, 18 participants with MDR TB will be recruited at each site.

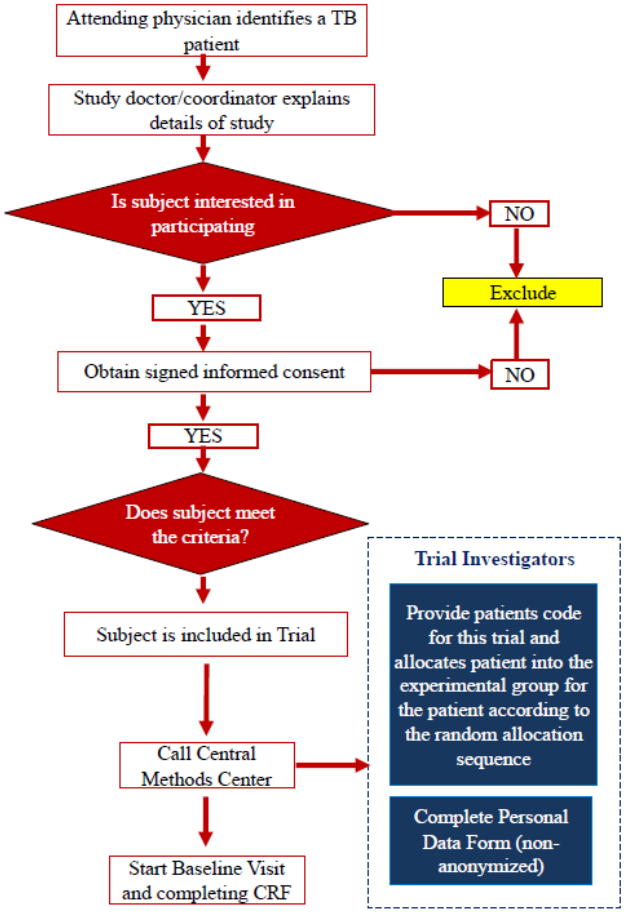

Figure 2: Summary of the flow process from identifying a patient and his/her inclusion in the trial.

Table 4: Recruitment strategy, timeline in order to ensure feasibility.

TB cases	Recruitment phase	Potential last patient first visit	Treatment duration	Treatment completion of last patient	End of follow-up of last patient
DS-TB	M6-M36	M36	6 months	M42	Up to M48
MDR-TB	M6-M18	M18	Up to 20 months (exact duration depending on drug sensitivity testing and WHO treatment guidelines)	Up to M42	Up to M48

Participants with sputum GeneXpert positive pulmonary TB will be approached. Site PI will be reachable for any questions. The clinical history will be taken and inclusion and exclusion criteria will be assessed. After exclusion of patients that cannot participate in this study and informed consent of participating patients, these consenting patients will be enrolled. Written informed consent, using IRB-approved consent forms, will be obtained by trained study personnel prior to performing any study-specific procedures. All consented participants will be cautioned against the use of over-the-counter analgesia whilst taking the NSAID/placebo.

Once recruited, patients will be randomized to one of the experimental groups as follows, the trial being stratified by site:

1. SoC TB treatment + placebo daily in 2 doses during first 4 weeks of treatment followed by placebo daily in 1 dose for an additional 4 weeks (control group, arm 1).
2. SoC TB treatment + ASA 600mg daily in 2 doses during first 4 weeks of treatment followed by ASA 300mg daily for an additional 4 weeks (arm 2).
3. SoC TB treatment + Ibu 800mg daily in 2 doses during first 4 weeks of treatment followed by Ibu 400mg daily for an additional 4 weeks (arm 3).

All pulmonary DS -TB cases with or without extrapulmonary involvement, regardless of their HIV status will be included in all sites. DS-TB cases will receive SoC TB treatment (2HREZ/4HR) at all study sites plus additional Ibu/ASA/placebo as randomised. Chronic comorbidities as HIV infection, diabetes, extrapulmonary involvement, lung cancer, history of smoking, Chronic Obstructive Pulmonary Disease, and chronic renal disease and other major comorbidities will be recorded for further analysis. The trial has been powered for DS-TB patients only. However, we will also include 54 MDR-TB (n=18/site, n=18 in each arm) to have an exploratory analysis. If we can find clear markers of response to HDT in the DS group, we will assess if the MDR patients have similar markers but the sample is not capable of distinguishing if these markers can be used in patients with MDR TB. For this, MDR will be based on being rifampicin resistant from Gene Xpert. Only rifampicin monoresistant or rifampicin + Isoniazid resistant participants will be included. As the SoC for DR-TB is tailored to each patient depending on the sensitivity pattern of the responsible pathogen strain, we will not standardize but consider the optimal combinatorial treatment regimen according to WHO guidelines and drug availability in the country [3,8].

In order to detect any possible trend in efficacy/safety depending on special populations, we will include all adult cases of pulmonary TB. We will exclude children, as the efficacy and safety should be proved first in adults; and those presenting with major co-morbid conditions as it could compromise the protocol compliance or significantly influence the interpretation of results.

5.4. RANDOMIZATION AND BLINDING

This study will be a double-blind, randomised, placebo-controlled trial. Both the investigator and participant will be blinded to the treatment regimen. Participants will be randomly allocated to one of the experimental arms at an allocation ratio of 1:1:1, according to an allocation sequence generated prior to first recruitment, Allocation to study arms will use variable length block randomization, stratified by site. The random allocation sequence will remain concealed from the clinical sites and those enrolling patients into the study; the individual recruiting the patient will contact a central data centre electronically immediately after eligibility criteria have been confirmed. The central data centre will receive age, gender, site and the screening identity number (SID) and will provide a pre-specified randomization number which will double as the trial identification number (TIN) that corresponds to a prepacked and prelabelled study drug kit in the site pharmacy.

Prepacked Ibu, ASA and placebo will be identical in shape, size and color.. Neither clinicians nor patients will be unblinded to treatment received unless there is a specific indication to unblind (see unblinding rules below).

6. STUDY VISITS

6.1. SCHEDULE OF EVENTS.

Table 5: Schedule of events plan with planned visits and study procedures.

	BL	Follow Up															
		Intervention								**DS and MDR Follow up on Rx**						**MDR on Rx**	**Final visit**
Week/Visit	0	1	2	3	4	5	6	7	8	9	10	12	16	20	24*	Extravisits until treatment completion every 8 weeks	End of FU@
Study Visit (N)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16, 17, 18…	Depends on treatment completion date
TB Score (TBS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Eligibility	X																
Informed Consent	X																
Randomization	X																
Clinical examination	X	X	X		X				X			X	X	X	X	X	X
HIV test if required	X																
CD4 and HIV RNA	X																
Pregnancy test if female	X				X				X								
Sputum culture	X	X	X		X		X		X			X	X	X	X	X	X
12-lead ECG If MDR	X				X				X								
Pulse Oximetry, Hb, Symptom check, weight, abdominal circumference, MUAC and anonymised photo	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray	X								X						X		
6 minute walk	X								X						X		
Spirometry	X								X						X		
HQoL Questionnaires	X				X				X						X		X
Sample collections for host and pathogen biomarkers study	X	X	X		X				X						X	X#	X
Safety evaluation	X	X	X		X		X		X			X	X	X	X	X	X
Safety lab tests	X	X	X		X		X		X			X	X	X	X	X	X
PK studies			X						X			X					
Adherence check		X	X		X				X			X	X	X	X	X	X

BL means Baseline. *In DS-TB patients, week 24 will coincide with treatment completion. $ If treatment is extended beyond week 24, extra visits will be performed every 24 weeks until end of treatment, when last visit will be conducted. @All patients will be followed-up for 6 months (24 weeks) after treatment completion, to investigate relapse. #Only at the treatment completion visit. &PK studies will be performed at week 2, only for the first 10 patients.

Screening and Baseline

The screening evaluation will occur on days up to 4 days before the baseline visit. Patients will be asked to provide informed consent. If consent is provided, demographic and medical history questions will be examined, including concomitant medications, and vital signs assessment and full physical exam conducted. For women, a pregnancy test will be performed. Lab safety tests will be performed (including hematology, chemistry, liver enzymes and bilirubin). 12-lead ECG and chest X-ray will be performed. HIV testing will be performed; patients found to be positive will have CD4 and HIV RNA tests performed. Sputum specimens will be obtained for Gene Xpert TB/RIF or TB/RIF ULTRA, Ziehl-Neelsen staining and cultures on solid and liquid media. Cultures will be reserved for routine DST (using molecular and/or phenotypic testing) and pathogen biomarkers study if participant is considered eligible for the study. Patients may advance to day 0 once screening activities are completed as ensuring inclusion and exclusion criteria are met may be spread over at least two visits within the indicated time window. Patients meeting all inclusion criteria and no

exclusion criteria will enter the study and undergo randomization and will receive the appropriate treatment according to the randomization list. At baseline, weight and height will be recorded for BMI calculation and spirometry will also be performed. Samples for host biomarkers study will be collected and HQoL questionnaires will be administered. Patients will be given an empty sputum container for collection of a first-morning specimen on the day of the next visit for sputum culture and Ziehl-Neelsen staining.

Weeks 1-8

A physical exam with vital signs assessment will be conducted, and weight recorded for BMI calculation. Study procedures will be conducted as indicated in Table 5. Adherence and concomitant medications will be assessed. Safety evaluation will be conducted, with AE reviewed and samples from safety laboratory tests collected as per the visit event table. Samples for host and pathogen biomarkers study will also be collected according to Table 5. Sputum will be collected for culture and Ziehl-Neelsen staining and patients will be given an empty sputum container for collection of a first-morning specimen on the day of the next visit. Patients will attend the site to receive correspondent medication according to DOTS schedule. Samples for Pharmacokinetics (PK) studies will be collected at week 2 and week 8.

Weeks 9-10

We will conduct post investigational treatment follow up, to ascertain if there are residual effects of the NSAIDs. Similar evaluations will be done at these visits as were done whilst participants were receiving placebo/NSAID. Study procedures will be conducted as indicated in Table 5.

Week 11-20

A physical exam with vital signs assessment will be conducted, and weight recorded for BMI calculation. Adherence and concomitant medications will be assessed. Safety evaluation will be conducted, with AE reviewed and samples from safety laboratory tests collected. Sputum will be collected for culture and Ziehl-Neelsen staining and patients will be given an empty sputum container for collection of a first-morning specimen on the day of the next visit. Samples for Pharmacokinetics (PK) studies will be collected at week 12. Study procedures will be conducted as indicated in Table 5.

Last visit -end of Follow-Up

A physical exam with vital signs assessment will be conducted, and weight recorded for BMI calculation. Safety evaluation will be conducted, with AE reviewed and samples from safety laboratory tests collected. Samples for host and pathogen biomarkers study will also be collected. HQoL questionnaires will be administered. Final treatment outcomes assessment will be performed and recorded.

6.2. DETAILED STUDY PROCEDURES

Clinical examination will be done at treatment initiation then as recommended per clinical routine in the clinic, or as required. The TB Score will be measured and recorded. Our outcome measure will be comparison of the times taken to reach 67% reduction in TB score between patients in each intervention arm with those in

the control arm and number of patients with improvement or resolution of clinical signs and symptoms at end of treatment. This TB score has been described to be useful to monitor good response to TB treatment, regardless of HIV status. Moreover, failure to decrease TB score by 25% was associated with subsequent failure and mortality (3). It consists of 5 symptoms and 6 signs and is scored as indicated in Table 6. The TB score used in the SMA TB trial is based on two studies which have demonstrated that TB score provides important information on the subsequent health status (45, 46). Having few symptoms or a reduction on the symptoms can be used as measure of good health or improvement. Scores will not be calculated by study staff but will be collected in such a way to allow scores to be calculated using data in the CRF.

Table 6: List of signs and symptoms to calculate the TB score.

Sr. No.	**Variable**	**Score**
1	Cough	1
2	Haemoptysis	1
3	Dyspnoea	1
4	Chest Pain	1
5	Night Sweats	1
6	Anaemia	1
7	Pulse > 80 beats / min	1
8	Positive finding on lung auscultation	1
9	Temperature >37°C	1
10	BMI < 18	1
11	BMI < 16	1
12	MUAC < 220 mm	1
13	MUAC < 200 mm	1
Total points		13

Directly Observed Therapy (DOT):

Doses of study drug will be given as directly observed therapy (DOT) by study personnel, or by a health care worker or lay treatment supervisor who is aware of the study protocol and trained regarding the study protocol according to the standard practices of each study site. Alternatively, doses of study drug can be given via DOT by a family member or employer who has been trained by the study team. For this study DOT dosing implies that the dose has been taken, swallowed and retained for at least half an hour after ingestion. Study operating procedures will detail documentation of DOT and also processes to follow for vomiting of doses.

Adherence will be confirmed by review of the participant's treatment card, and retraining of the DOT provider will be provided if treatment card is poorly completed. Adherence will be defined as the number of prescribed doses taken. DOT may be administered at the TB clinic or other health care facility, or, with the participant's permission, at the participant's residence, workplace, or other mutually agreed upon location

convenient for the participant. Video DOT - where participants video themselves with their phone taking their tablets and then WhatsApp the video to the research site - will also be acceptable, provided the participant concurs and understands the process.

Daily, brief symptom screens to ascertain potential gastric, hepatic and other AE will be administered prior to that day's dose. The presence of symptoms will direct the study physician to review the patient that day and determine if further dosing of placebo/NSAID is warranted and/or if further investigations or treatment are required. DOT of the first daily dose should occur at least 5 days a week during the first 8 weeks of treatment with weekend doses given as self-administered treatment (SAT). No more than 3 consecutive doses of SAT will be allowed. The second daily dose of NSAID/placebo may be taken as SAT. TB treatment may be self-administered or given as DOT after the participant has completed the intervention phase of the study (after 8 weeks). All doses taken will be recorded on a treatment card and reviewed by study staff at the next scheduled visit.

Additional Study Measures at scheduled Study Visits whilst on TB Treatment

At each study visit, the following additional checks will be conducted to assess any changes from baseline as an indicator of improvement in TB disease:

- Participants will be asked questions related to demographics, current and past medical history, concomitant medications, alcohol and drug use and TB symptoms.
- **Symptom check**: Participants will be asked if they feel any better since the last visit and if they have developed any new symptoms. TB symptoms will be graded to assess improvement or worsening. We will also add other questions to those of the score to ensure score questions are not overly weighted.
- **Weight**: participants will be weighed at each visit (shoes and jackets will be removed and pockets should be emptied). Because the TB score is somewhat subjective, we will weigh each participant weekly using the same scale and process.
- **Pulse Oximetry**: Pulse rate will be electronically measured using a pulse oximeter device. We will also record value of oxygen saturation on pulse oximetry. For the purpose of this study; tachycardia will be defined as pulse rate of ≥100 beats per minute
- **Finger prick Haemoglobin**: A single drop of blood will be used to detect point of care Hb levels using the HemoCue Hb 201 analyser bought new for this study, at each site. For the purpose of this study; anaemia will be defined as haemoglobin ≤10 g/dL.
- **Abdominal circumference** will be measured as follows: Start at the top of the hip bone, then bring the tape measure all the way around the participant's body, level with the belly button making sure it's not too tight and that it's straight, even at the back. The circumferential distance of the abdomen will be recorded immediately after exhalation.

- **Mid Upper Arm Circumference** (MUAC): The circumference of the left upper arm, measured at the mid-point between the tip of the shoulder and the tip of the elbow (olecranon process and the acromion). MUAC is used for the assessment of nutritional status.
- **Anonymised photo** for digital estimation of BMI and response to treatment. Participants will be asked to wear a face mask (either full face mask such as a hockey goalkeepers mask, or surgical mask with sunglasses) so that they cannot be identified. They will be asked to remove any jackets and shoes. A digital photograph will be taken and analysed. Participants will be asked to provide consent to have their photograph taken and used for analysis.
- **Six-minute walk**. All participants capable of walking will be supervised to do the six-minute walk to monitor their performance capacity. This will be standardized using a pre-measured course and overseen by a trained staff member in each clinic facility. The distance walked by the patient will be accurately measured in metres until patients have completed their treatment.
- Lung functional impairment will be measured by **Spirometry** at baseline, month 2, month 6 and end of treatment (week 24 or at treatment completion visit if extra visits are scheduled). Spirometry will not be conducted during the Covid-19 pandemic. Once it is considered safe to conduct spirometry tests and after communication with the relevant ethics authorities, spirometry will be conducted by trained and qualified study personnel. Spirometry will be conducted using appropriate filters and disposable apparatus to ensure infection control.

Sputum conversion monitoring:

Sputum will be taken as per the visit schedule, more frequently early on in treatment and less frequently as treatment progresses. Additional specimens will be taken if clinically indicated. The Median time to SCC (at least 2 consecutive negative cultures for *Mtb* at least 4 weeks apart, with no positive intermediate cultures), as well as percentage of patients with SCC at weeks 8 and 24 after treatment start will be used, as SSC has been identified as a potential predictor to end-of-treatment outcome and relapse [41]. Time to positivity in liquid media culture will also be recorded.

Radiology:

Post-Anterior erect chest X-rays will be performed: at baseline within 7 days of starting of TB chemotherapy, at the end of 8 weeks' post-enrolment; and at treatment completion (week 24 or at treatment completion visit if extra visits are scheduled). The BCN-SA score developed jointly by the IGTP and the PHRU will be used to monitor the mean of improvement or resolution of chest X-ray image associated with active TB. This score measures activity and chronicity signs. All X-rays will be retained for future use for machine learning algorithms once de-identified, this is included in the Informed Consent. We will be collaborating with international stakeholders to analyze study X-rays. They will develop software to compare radiological improvements of patients on TB treatment. All X-rays are anonymized (names, date of birth and hospital numbers are deletes from the images) before being analyzed. PhD and master's students will be involved in these analyses. We plan to make these anonymized images together with anonymized clinical data

available to other researchers, on application. We envisage that these digital images will be an important resource to improve electronic analysis of chest-x-rays in people with confirmed tuberculosis and to identify electronic methods to identify clinical improvement.

Blood and urine tests monitoring:

The following tests will be done at screening to assess eligibility. Some of these will be repeated at each study visit for safety monitoring:

- All participants will undergo HIV testing and counselling at the **screening** visit unless there is compelling evidence that the patient is HIV-infected at the time of randomisation. Compelling evidence of HIV infection is:
    - Hard copy of an unsuppressed viral load
    - Hard copy of a prescription for antiretroviral therapy
    - Documentation in clinical record of two rapid tests positive for HIV infection
    - Hard copy of a laboratory ELISA or Western blot test positive for

  HIV testing will be carried out with two rapid tests (the second test will be to confirm the result of the first); only one test need be carried out if the participant is known to have HIV, the single test will be confirmatory. Should there be a discrepancy between the two rapid tests, blood will be sent to the laboratory for enzyme-linked immunosorbent assay ELISA and Western Blot test in order to confirm the diagnosis. For HIV-positive participants, a CD4 count and HIV Viral load should be performed unless written results are available from a test done within the preceding 3 months.

- Serum/Urine β-HCG: Urine will be collected for pregnancy testing if a woman is of child-bearing potential. A pregnancy test will also be done at each study visit during the intervention phase (up to week 8).
- HBA1c if clinically indicated
- Safety Laboratory Assessments: (At every study visit).
    - Full Blood Count (Leukocytes, Hemoglobin, red blood cell count, with differential, ESR and platelets.)
    - Clinical Chemistry (Total protein, albumin, total globulin, glucose, urea, electrolytes, creatinine, total bilirubin (direct and indirect), ALT, AST, alkaline phosphatase.

Health Quality of Life (HQoL) will be measured at scheduled time points with 3 questionnaires:

1) SGRQ questionnaire to measure the impact on the respiratory system, designed by St. George's School of London University (SGQR);

2) A validated basic questionnaire to detect mental illness at the care level (Kessler-10,); and

3) A questionnaire designed by Vilaplana et al (BCN-Q, not published) that evaluates sociological data and the psychological state of the patients. This questionnaire includes questions about the patient's burden of

the patient, the stigma suffered by the patient by the illness, the impact this has had on his or her person and family, support received by institutions or family and friends, through to infect other people, impact of the disease on the development and activities of the patient including sleep, eating habits and their mood.

Sampling for Host and Pathogen biomarkers and Pharmacokinetics studies

The study offers a unique opportunity to identify pathogen and host factors that could act as biomarkers in terms of predicting disease outcomes and/or treatment response. Samples from TB patients will be used to identify biomarkers by studying relevant pathogen and host factors in TB patients' samples, and clinically validating biomarkers identified in SMA-TB project or in previously established cohorts.

The different clinical isolates obtained from the sputum samples will be studied in terms of their lipid content and NF-kB and IRF signalling activation. The cording capacity of *Mtb* strains, which is considered as a virulence factor, will also be studied. The levels of cytokines, chemokines, inflammatory proteins and general biomarkers related to systemic inflammation will be measured in plasma and urine samples, as well as the ex vivo frequency, phenotype and COX-2i expression of various cells subsets.

The samples will be also used to measure the expression of 200 human genes from the innate, adaptive, regulatory and inflammatory compartments by the dcRT-MLPA test; the levels of CD5L, an innate protein related to inflammation status in plasma and urine samples with an ICT test; and IP-10 will be quantified by ELISA from blood spotted directly onto Whatman filter paper cards.

Other potential biomarkers are expected to be identified though a system biology approach identifying key molecular enclaves that behave differently.

All this information will provide hints on the different biological processes involved in responders vs non-responders. Samples to be collected are detailed in Table 7, along with the recipient collaborators that will receive them to perform the study of host and pathogen biomarkers (Table 8). The total planned phlebotomy volume will be 200.2 ml over at least 6 months, with maximum volume of 99.4 mL over a 1-month period. Phlebotomy volumes are detailed in Table 9. Work procedures will be issued as documents and specific training will be done to the sites' staff in order to minimize errors and biases among the trial sites. Samples will be collected at scheduled time points and will be stored at CT sites until shipped in at least 2 batches. Copies of import/export authorisations will be kept as required by national/EU legislation.

Pharmacokinetics

Intensive PK sampling: Samples for Pharmacokinetics (PK) studies will be collected for determination of TB drug concentrations in plasma. Up to 45 evaluable participants (15 from each group) will have PK assessments at the week 2 and week 8 study visits (sampling will be immediately prior to dose administration and at 30 minutes after the dose, then 1, 2, 4 and 8 hours' post-dose).

Sparse PK assessment at the week 12 visit (trough level immediately before the TB treatment dose and at 1, and 2 hours post-dose). Samples will consist of 2ml of blood collected via an indwelling catheter or by direct venipuncture. At least 3 consecutive doses by DOT given at approximately the same time each day

should be administered prior to PK collection. Specimens will be obtained, processed, and assayed according to the PK standard operating procedures manual.

Table 7: Samples for the host and pathogens biomarkers study. *Baseline before starting any treatment.

Sample type	BL*	W1	W2	W4	W8	End of TT	6 M after end of TT
Samples for Host biomarkers studies							
Whole blood in 1 PaxGene tube	X	X	X	X	X	X	X
Whole blood in 2 8mL-CPT tubes	X		X	X	X	X	X
Blood spot dried on Whatman filter paper card	X		X	X	X	X	X
Urine in 15mL tubes	X	X	X	X	X	X	X
CD5L kit[&]	X	X	X	X	X	X	X
Samples for Pathogen biomarkers studies							
DS-MTB strains[$]	X						
MDR-TB strains[$]	X						
ZN stains	X						
Exhaled Breath	X	X	X	X	X	X	

Table 8: Samples for host and pathogen biomarkers' studies: recipients and collaborators.

Sample type	Recipient	Recipient's contacts
Samples for Host biomarkers studies		
Whole blood in 1 PaxGene tube	LUMC	Pr. Tom Ottenhoff/Dr. Mariëlle Haks, LUMC, M.C.Haks@lumc.nl, M.C.Haks@lumc.nl
Whole blood in 2 8mL-CPT tubes	plasma: IGTP; PBMCs: OUS	Dr. Cris Vilaplana, UTE, IGTP. cvilaplana@igtp.cat/cvilaplana@gmail.com
Blood spot dried on Whatman filter paper card	OUS	Pr. Anne-Ma Dyrhol-Riis,OUS, a.m.d.riise@medisin.uio.no
Urine in 15mL tubes	IGTP	Dr. Cris Vilaplana, UTE, IGTP. cvilaplana@igtp.cat/cvilaplana@gmail.com
CD5L kit[&]	to be performed on site, results to be sent to IGTP	Dr. MR Sarrias, Innate Immunity Lab, IGTP. msarrias@igtp.cat
Samples for Pathogen biomarkers studies		
DS-MTB strains[$]	CNRS	Dr. Jerôme Nigou/Dr. Emilie Layre, IPBS, CNRS. jerome.nigou@ipbs.fr, emilie.layre@ipbs.fr
MDR-TB strains[$]	IGTP	Pr. P-J Cardona, UTE, IGTP. pjcardona@igtp.cat
ZN stains	IGTP	Pr. P-J Cardona, UTE, IGTP. pjcardona@igtp.cat
Exhaled Breath	CNRS	Dr. Jerôme Nigou/Dr. Emilie Layre, IPBS, CNRS. jerome.nigou@ipbs.fr, emilie.layre@ipbs.fr

Table 9: Phlebotomy volumes.

Weeks (W)	W0	W1	W2	W4	W6	W8	W12	End of treatment	6 months after completing treatment	**Total**
HIV Test	0,1									0,1
CD4	2,5									2,5
HIV RNA	2,5									2,5
Lab Safety Tests	9		9	9	9	9			9	54,0
Host biomarkers study	18,6	2,5	18,6	18,6		18,6		18,6	18,6	114,1
Pharmacokinetics			9			9	9			
Total per weeks	32,7	2,5	36,6	27,6	9	36,6	9	18,6	27,6	200,2
Total per month				99,4		45,6	9	18,6	27,6	200,2

6.3. SAMPLE MANAGEMENT

Blood and urine samples from the subjects enrolled at the PHRU/NCTLD sites as well as the *Mtb* strains isolated and Ziehl-Neelsen stained slides will be collected at the scheduled time points (see Table 5). Samples

will remain and be kept at [PHRU/NCTLD] or associated laboratories until shipped and processed by the SMA-TB consortia partners as agreed according to the SMA-TB project proposal.

Samples will always be handled according to the Convention on Biological Diversity website and its "*Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity" and* the Regulation (EU) No 511/2014 and the EU Directive 2004/23/EC on the obligations when handling and using human material for research. They will be pseudonymized, thus labelled with their corresponding participant's code (*SMA-TB*-XXX), and they will only be used for the study's purposes.

Some of the samples collected (whole blood in PaxGene tubes) will be used for a genetic test. We will perform the dcRT-MLPA test, which uses a multiplex qPCR platform for 200 human genes covering innate and adaptive immunity as well as a larger set of inflammatory and signalling genes), and which has shown clear signals correlating with successful TB therapeutic responses in 3 different previous cohorts[42]. This platform will be used to profile immune gene expression only in relation to TB therapy outcome including the interventional arms.

Human material will be kept for at least 10 years at biobanks. if considered appropriate, data and samples could be used (secondary use) for studies related to biomarkers of TB response, promoted by the sponsor or SMA-TB partners.

Samples collected within the project might be used for future research related by SMA-TB investigator teams or their collaborators if considered appropriate, previously approved by an Ethics Committee, as indicated in the patient consent information sheet and consent form. This secondary use will be limited to future relevant projects with the aim to study tuberculosis disease, how to treat it or how to prevent it.

After the period of 10 years, all remaining samples will be destroyed.

6.4. UNSCHEDULED VISITS

In the event of an unscheduled patient visit, the subject will undergo safety screening. Depending on the reason for the visit, the subject may be referred to the appropriate service for possible AE follow-up. Blood specimens may be collected as per investigators discretion. All AE reported by the subject or observed by the investigator will be documented and reported. Aside from AE, information gathered at these unscheduled visits will not be included in the statistical analysis.

6.5. CONCOMITANT MEDICATIONS

All patients will be treated with the Standard of Care (SoC) TB regimen by the investigation sites as per WHO consolidated guidelines (1)(2), relevant national guidelines for treating TB and the investigator's best clinical judgment.

Fixed dose combination TB treatment or equivalent will be obtained in South Africa and Georgia from each sites National TB Control Programme as per routine, and given in doses consistent with local guidelines.

Vitamin B6 obtained from a commercial distributor will be administered according to each site's national guidelines. Rifafour or the equivalent fixed dose combination TB treatment will be given in doses consistent with local guidelines.

All other concomitant prescription and over the counter medications taken during study participation will be recorded on the case report forms (CRFs) at baseline and at each follow-up visit. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

6.6. UNBLINDING AND TREATMENT INTERRUPTION

All patients will be treated with the Standard of Care (SoC) WHO-recommended TB regimen (1)(2). As SoC is tailored to each patient according to the sensitivity profile of the causing *Mtb* strain and, in order to minimize bias, we will consider SoC as the optimal combinatorial treatment regimen according to WHO guidelines and drug availability in the country. Whilst they are taking the investigational products, we will provide all treatment via DOT at least five days on most weeks. At each DOT visit we will implement a standardized symptom questionnaire that elicits symptoms associated with most likely adverse effects of the interventional drugs and also TB treatment. Participants responding positively will be assessed by a study investigator who will make a decision whether further investigations are required or whether investigational drug or TB treatment should be withheld or if proton pump inhibitor should be co-administered. These decisions will be documented n the source document and also in the database.

We anticipate that prematurely unblinding a participant's allocation while they are on treatment will be done only occasionally, if at all, in this study. If any patient is due for emergency, or scheduled major surgery or other invasive procedure that may require halting of ASA or Ibu, that cannot be delayed to the end of the NSAID or placebo treatment period, unblinding would be automatically condoned. Similarly, for any serious adverse event where the receipt of ASA or Ibu may have contributed to the condition, unblinding would be automatically condoned. For any other unblinding to occur, the site principal investigator would present the clinical context and reason to unblind to the other two site principal investigators and request their opinion. If all three concur, unblinding will be allowed. The study statistician will provide the treatment allocation for that participant only.

6.7. JUSTIFICATION FOR INCLUSION OF A PLACEBO OR NON-TREATMENT GROUP.

All patients will be treated with the Standard of Care (SoC) WHO-recommended TB regimen as stated in section 6.6. The difference between arms will be the addition or not of co-adjuvant treatment with interventional drugs. Placebo group will be used as control group (arm 1).

7. ASSESSMENT OF SAFETY

7.1. SAFETY AND TOLERABILITY ENDPOINTS

Safety and tolerability (physical examination, serious adverse events (SAEs), routine laboratory, chest radiography) between the interventions and control group.

7.2. SAFETY AND TOLERABILITY EVALUATION

The safety of the study medication will be continually assessed by:

- Symptom screening on every weekday when patients taking placebo of NSAID attend for their DOT visit.
- We will accurately record the adverse events occurring during the course of the study. All patients will undergo routine safety monitoring that will include symptom and adverse event reviews, safety laboratory tests, 12 lead ECG, and serial chest X-rays. The intervals for these tests are specified in the schedule of events (Table 5).
- We will document if placebo or NSAIDs are stopped temporarily or permanently by either the patient, an investigator, or by a non-study physician. We will obtain underlying reasons for the stopping of placebo or NSAIDs. Similarly, we will document if, and when TB treatment was withheld for any duration. For study purposes we will ascertain the reasons for TB treatment being withheld for longer than two days.
- The DSMB will cyclically review all SAEs, and stopping of placebo or NSAIDs and stopping of TB medication. The sponsor will suspend the study if the DSMB recommends that there are sufficient grounds that suggest continuation of the study will jeopardise participants' health or safety. The sponsor will notify the Institutional Ethics Committee without undue delay of temporary halt including the reason for such an action.
- Investigators at each study site will ensure that all patients are kept informed of new data that becomes apparent either in this or in other trials.

7.3. ADVERSE EVENTS (AE)

All abnormalities found during the physical examination (including vitals) or routine laboratory investigations during the routine visits will be dealt as AE. Any other adverse event occurring during the study period (unsolicited) will also be recorded. If any events are reported, patients will be asked for complete evaluation.

All observed or volunteered AE regardless of the study group or suspected causal relationship to the study drugs will be recorded on the "Adverse Event" page of the CRF.

Temporary and permanent discontinuation of treatments will be fully documented in the source document with reasons. Additionally, any self-treatment or prescriptions of antacids and/or proton pump inhibitors will be documented.

Safety laboratory tests at various time points during follow up for safety evaluation will be performed according to what is explained in Table 5 and section 6.1. and 6.2.

7.3.1. Definitions

Adverse Event (AE).

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered an intervention and which does not necessarily have to have a causal relationship with this intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory

finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol specified procedure, whether or not considered related to the medicinal product or protocol specified procedure. The AE recoded during the study period will be recorded and graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events [43].

Unanticipated problems (UP)

Unanticipated problems (UP) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3.2. Reporting procedures

Reporting AE

For each AE it will be recorded:

- Severity: The adverse events recoded during the study period will be recorded and graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events [43].
- Causal relationship with intervention: Relatedness (causality) of adverse events to vaccine will also be assessed by the Investigator. The relationship of each AE, including solicited systemic AEs (solicited local AEs are considered as related) to trial medication will be addressed using the following categories: not related, unlikely related, possibly related, probably related, definitely related to ASA, not assessable.
- Action taken regarding treatment: It will be recorded using the following categories: none, TB treatment modification, medical intervention, hospitalization, treatment discontinued, intervention discontinued (withdrawn), other.
- Outcome: resolved, recovered with minor sequelae, recovered with major sequelae, ongoing/continuing treatment, condition worsening, death, unknown.

Reporting of SAE

In case of the presence of a SAE will be immediately reported to CT site PI and coordinator. The latter will notify the event to the Data Safety Management Board (DSMB), providing a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality who will take the correspondent decisions (withdrawal, notification to the competent Regulatory Authorities, etc.). All subjects with SAEs will be followed up for outcome.

In addition to the expedited reporting of SAEs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the Institutional Ethics Committee and DSMB.

- This safety report consists of:a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;a report concerning the safety of the patients, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

Reporting unanticipated problems

All possible unanticipated problems will be reported to the IRB within three (3) working days of receiving notice of the event if the event requires immediate intervention to prevent serious harm to participants or others. All other possible unanticipated problems will be reported to the IRB as soon as possible and no later than ten (10) business days from the date of the event or from the date the investigator is notified of the event. Investigators must promptly report (according to the above schedule) the following events to the IRB if the events occur within thirty (30) days of participants' active participation:

• AE which in the opinion of the principal investigator are both unexpected and related.

• An unanticipated event related to the research that exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to potential risk

• Information that indicates a change to the risks or potential benefits of the research. For example:

• An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.

• A paper is published from another study that shows that the risks or potential benefits of your research may be different than initially presented to the IRB.

• A breach of confidentiality.

• Incarceration of a participant in a protocol not approved to enrol prisoners.

• Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant.

• Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.

• Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm.

• Event that requires prompt reporting to the sponsor.

• Sponsor imposed suspension for risk.

• Any other event that indicates participant or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

7.3.3. Follow up of AE

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported until the end of study as defined in the protocol.

8. ETHICAL ISSUES

8.1. ETHICS COMPLIANCE

SMA-TB will perform one CT covering different aspects and involving different health centres outside EU member states. Patients will be recruited in South African and Georgian sites in parallel. The CT will be conducted in these two countries mainly for scientific reasons**:** both hold high endemicity of TB, and of MDR-TB cases, while having different human and tuberculous genetic background and different social conditions. We ensure:

- the feasibility of the project by being able to complete the study in a reasonable amount of time, based on available data;
- the richness of the data generated;
- the access to the populations which need the most an improvement in the TB treatment and who can benefit the most of SMA-TB outputs.

TB patients show very different characteristics in terms of comorbidities and susceptibility to drugs in both countries. South Africa has a high percentage of TB-patients are also Human Immunodeficiency Virus (HIV)-co-infected [44]; while in Georgia HIV-coinfection rates are low, but there are a high percentage of strains resistant to more than two common TB drugs (MDR/XDR-TB)[44]. New treatment regimens that substantially improve TB treatment (shorten and/or simplify therapy) are critically needed in these settings. Conducting the trial in these 2 countries will allow us to show any effect of the repurposed drug in 2 different populations which for their high TB incidence, can benefit most of an enhanced treatment. To comply with all the ethical requirements according to H2020 Guidelines, we will ensure that the research activities carried out in these 2 countries is compatible with EU and international law and that it could have been legally conducted in at least one of the EU Member States by submitting the protocol of the Clinical Trial and associated documents to the Ethics Committee of the Hospital Germans Trias i Pujol (Badalona, Spain) (FW00001930, IRB00002131), the IGTP correspondent regulatory authority.

8.2. DSMB

A DSMB will be constituted before the start of the study to provide oversight. It will comprise at least 4 members including one trials statistician. The DSMB will review the proposed protocol prior to its finalization – including scheduling interim analyses and stopping rules. The committee will meet at least twice annually electronically, and will have a face to face meeting when approximately half of all participants have completed their initial 8 weeks of placebo or NSAID. Additional meetings requested by the DSMB will be arranged by the study team. At each meeting the study statistician will generate a DSMB report that describes progress,

reports unanticipated problems, and reports rates of SAEs and premature stopping of placebo or NSAID or interruption of TB medication. Once sufficient patients have a final primary outcome interim analyses of the outcomes will be shared with the DSMB only, retaining blinding of the investigator team.

Whenever a safety problem will be encountered, the PI coordinator will notify the event to the DSMB, who will meet to take the correspondent decisions. Any advice or recommendations of the DSMB will only be communicated to the sponsor and study team. Should the study team decide not to fully implement the advice of the DSMB, the Principal Investigator will notify the DSMB, and all Ethics Committees, including a note to substantiate why the advice of the DSMB was not be followed.

The DSMB will review preliminary safety and efficacy signals at regular intervals during the trial. The DSMB will be directed to discontinue enrolment and treatment for arms in which safety or efficacy appears likely to be worse than in the control arm. Criteria based on which the DSMB can decide to put the study on hold include the occurrence of multiple grade 3 or 4 events which are found to be related to the study drug/s.

9. PARTICIPANT WITHDRAWAL OR TERMINATION

9.1. REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request and an investigator may terminate participation in the study. It will be documented whether or not each patient completed the clinical study. If, for a patient, study treatment or observations are discontinued, the primary reason for discontinuation will be recorded. Primary reasons for discontinuation included:

- Late exclusion.
- Adverse event (AE): Any significant AE that, in the opinion of the Investigator or concerned patient, is not compatible with study continuation.
- Death of a participants.
- Lost to follow-up: the loss or lack of continuation of a patient to follow-up.
- Non-compliance with study drug: an indication that a patient has not agreed with or followed the instructions related to the study medication.
- Physician decision: a position, opinion or judgment reached after consideration by a physician with reference to the patient.
- Pregnancy
- Protocol violation: an event or decision that stands in contrast to the guidelines set out by the protocol.
- Study terminated by the Sponsor: an indication that a clinical study was stopped by its Sponsor.
- Withdrawal by patient: study discontinuation requested by a patient for whatever reason.
- Other: different than the ones previously specified. Need to be specified when recorded.

For any patient discontinuing the study, the Investigator will:

- Clearly document the reason for discontinuation in the study

- Offer, a final clinical visit to document the patient's health condition at exit from the trial. This examination will verify that all values tested at screening have remained within a clinically acceptable range (i.e., not clinically significant changes compared to screening)
- Arrange, with a detailed referral letter, alternative medical care for the withdrawn patient, if necessary.
- Report in the eCRF the date and time of the last dose administration, and date and primary reason of study discontinuation.
- Offer the patient a subsequent follow up visit at the research site, if appropriate.

Discontinued patients will not be replaced unless they are discontinued in the initial ASA/ibu treatment phase.

9.2. STUDY TERMINATION

The participant will be considered terminated at the date of the last visit of the last patient or upon completion of any follow-up procedure described in the protocol. The Investigator and the Sponsor have the right to discontinue the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation. Reasons for discontinuation have to be documented appropriately. In this event, no further patients will receive doses of the study drugs, and patients already having received a dose of study drug will not receive any further doses of the study drug but will undergo all safety assessments scheduled after the last dose of study drug, up to an including the end of study examination.

10. STUDY STATISTICS

10.1. HYPOTHESIS

We hypothesised that there would be a statistically significant difference in the time to 67% reduction in TB score for DS TB patients between the SoC arm and the two intervention arms, separately, during follow-up.

10.2 SAMPLE SIZE

We determined the sample size for DS TB patients, comparing the standard arm of TB treatment versus two intervention arms, each pair being compared separately but under the same assumptions. We assumed that the control arm will have a TB score reduction of at least 67% by week 15 of follow-up, whereas the NSAID arms would have a TB score reduction of at least 67% by week 8 of follow-up. Using these estimates, we determined the hazard for these events using the formula $Hazard = -\ln(1-e)/t$ where e is the percentage drop. Additionally, we determined the hazard ratio for the intervention arm using the expression $Hazard\ Ratio = Hazard\ Intervention/Hazard\ Control$ and also assumed a 15% loss to follow-up. Our calculation used an accrual period of 2 years plus a 1-year follow-up.

We varied the difference in time to TB score reduction between the SoC and intervention arms estimating the difference at 20% and 25%, and varied the power to detect the difference (80%, 82.5%, 85% and 90%) and used a two-sided significance level of 0.05. Under these conditions, it is envisaged that to detect at least a 25% difference between the SoC and intervention arms, the study would recruit at least 91 participants per arm and a total of 273 participants overall (Table 1). Because there is little data on which to estimate relative reductions in TB score we have further escalated the sample size to 300 (approximately 100 per arm) DS TB

patients. We anticipate that each study site will recruit at least 50 DS TB patients and that in the event a study site was unable to complete the full recruitment of 100 DS participants per site other sites would competitively enrol until the sample size is met.

Table 10: Sample size estimation

Power	Rate Control	No event control	Treatment	No event Treatment	Difference	SS Control & Treatment	Adjust for 15% LTFU	Sample size per arm	Total Sample size
0.8	0.5	0.5	0.7	0.3	0.2	224	258	112	336
0.825	0.5	0.5	0.7	0.3	0.2	240	276	120	360
0.85	0.5	0.5	0.7	0.3	0.2	256	294	128	384
0.9	0.5	0.5	0.7	0.3	0.2	300	345	150	450
0.8	0.5	0.5	0.75	0.25	0.25	136	156	68	204
0.825	0.5	0.5	0.75	0.25	0.25	146	168	73	219
0.85	0.5	0.5	0.75	0.25	0.25	156	179	78	234
0.9	0.5	0.5	0.75	0.25	0.25	182	209	91	273
0.8	0.6	0.4	0.8	0.2	0.2	178	205	89	267
0.825	0.6	0.4	0.8	0.2	0.2	190	219	95	285
0.85	0.6	0.4	0.8	0.2	0.2	204	235	102	306
0.9	0.6	0.4	0.8	0.2	0.2	238	274	119	357
0.8	0.6	0.4	0.85	0.15	0.25	102	117	51	153
0.825	0.6	0.4	0.85	0.15	0.25	110	127	55	165
0.85	0.6	0.4	0.85	0.15	0.25	118	136	59	177
0.9	0.6	0.4	0.85	0.15	0.25	138	159	69	207

We will also include 54 MDR TB patients. These patients have not been included in the sample size estimations and will not be included in the formal assessment of primary outcomes, but will be compared by their clinical responses to treatment to their DS peers, and their biomarker responses to DS TB patients by arm.

Accrual rates will closely be monitored by the statistics and data management centre (SDMC) to ensure that each site is recruiting as per the study plan. In the event that accrual rates are lower than expected in some sites, the SDMC will recalculate the sample size to ensure appropriate redistribution that introduces no bias.

10.3 DATA ANALYSIS

Primary objective 1: Time to detect at least a 25% difference in the reduction in TB score reaching 67% of baseline score between the intervention and control arms.

Statistical analysis: We will use a stratified Kaplan-Meier curve and the log rank test statistic. Any emerging differences will be quantified using the Cox proportional hazards regression and plotted graphically on the Kaplan-Meier curves.

Primary objective 2: Hazard ratio for stable culture conversion (SCC) (at least 2 consecutive negative cultures for M. tuberculosis at least 4 weeks apart. [Time Frame: Up to Week 24]. Difference between intervention and control group.

Statistical analysis: The hazard rates for stable culture up to week 24 will be determined using the Cox proportional hazards regression. These will be plotted using the Kaplan-Meier and the confirmatory visit date.

Secondary objective 1: Time to a stable culture conversion (SCC) at week 8 and week 16 after treatment start. Difference between each intervention arm and control group.
Statistical analysis: The Cox proportional hazards regression will be used to compare the time to a stable culture conversion at week 8 and week 16. Their survival curves will be plotted using the Kaplan-Meier test

Secondary objective 2: Proportion of patients with improvement or resolution of clinical signs and symptoms at end of treatment (TB score). Difference between each intervention arm and control group.
Statistical analysis: The proportion of patients with improvement or resolution of clinical signs and symptoms at the end of treatment will be compared between groups using the chi-square test or the Fishers Exact test as appropriate. Predictors of the TB score will be determined using the last measure by way of a logistic regression and during follow-up time using the generalized estimating equations.

Secondary objective 3: Proportion of patients with improvement of lung function impairment as change from baseline at week 8, 24 and end of treatment in the 1-second forced expiratory volume (FEV1) expressed as FEV1. Difference between each intervention arm and control group.
Statistical analysis: The difference in FEV1 measurements between baseline and follow-up will be determined and plotted graphically. The difference between study arms will be compared using linear mixed modeling with a p-value determined for each visit and an overall global p-value.

Secondary objective 4: Improvement in CXR (measured with the BCN-SA score) using the x-ray taken at baseline as the comparator compared with subsequent x-rays over the course of TB therapy [Time Frame: at week 8, week 24 and for MDR TB patients at the end of treatment]. Difference between intervention and control group.
Statistical analysis: The difference in BCN-SA Scores between baseline and follow-up will be determined and plotted graphically. The difference between study arms will be compared using linear mixed modeling with a p-value determined for each visit and an overall global p-value.

Secondary objective 5: Number of patients with improvement of Health-related Quality of Life comparing baseline measure with that over the course of therapy [Time Frame: 8, week 24 and for DR TB patients at the end of treatment]. Difference between each intervention arm and control group.
Statistical analysis: The difference between study arms in the Health-related Quality of Life Questionnaire between baseline and follow-up will be determined and plotted graphically. Additionally, this difference will be compared between groups using linear mixed modeling with a p-value determined for each visit and an overall global p-value.

Secondary objective 6: Safety and tolerability, proportion with serious adverse events (SAEs),) between each intervention arm and the control group.

Statistical analysis: Safety endpoints will be classified using the MedDRA coding dictionary and presented as System Organ Class and Preferred Terms. Frequencies for each study arm will be determined for AEs and SAEs and their incidence rates per 100 person years. Time to the first SAE will be determined using the logrank rank test and their hazards by the Cox proportional hazards regression models.

All statistical analysis will be conducted in SAS Enterprise Guide 7.15 and STATA 15 software.

11. MONITORING AND DATA HANDLING

Site Monitoring will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet Sponsor, PHRU, NCTLD and regulatory guidelines, and that the study is conducted in accordance with the protocol and site SOPs. Site monitoring will be performed according to details in a written monitoring plan.

11.1. SOURCE DOCUMENTS AND ACCESS TO SOURCE DOCUMENTS

All data will be coded to preserve patients' identity, according to the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 and equivalent local regulations in South Africa and Georgia on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. The clinical history information of patients enrolled will be strictly confidential and their identity will be kept anonymous.

Once enrolled, a sequential code for each patient will be generated as *SMA-TB-* XXX (XXX meaning the correspondent number of patient) which will be used to match patient's samples with clinical data without need to use patient's name & surname.

For each patient, a pseudonymized form created ad-hoc for this project will correlate him/her with his/her projects' code. This form will be to be kept together with the Medical Record of each patient as the Hospital Records copy. A spreadsheet file will be filled-in with the following data of each patient included: name, the Hospital Record Number and the correspondent Project's code (*SMA-TB*-XXX). Only persons involved in the study and after prior training will receive access to the data. A paper CRF will be created ad-hoc and filled-in for each patient included with all the data required: Project's code (*SMA-TB-XXX*), clinical characteristics and monitoring data. In order to comply with the patients' rights of confidentiality, this form will be pseudonymized, without the name and surnames of the patient and where only the project's code will be recorded, together with all the clinical data associated to the specific case. In order to comply with the ethics requirements of samples' collections, both documents will be kept as 2 different documents and stored in 2 different computers.

All the data collected and intended to process will be relevant and limited to the purposes of the SMA-TB project (in accordance with the 'data minimisation 'principle).

Data from the study will be collected in the created ad-hoc CRF. The WHC and NCTLD sites recruiting patients will use paper copies of the CRF to record the data, and will periodically enter it into the eCRF created in the Redcap system of the WHC. During the study the Coordinating Investigator will visit the investigational sites to confirm that the facilities remain acceptable, that the investigational team is adhering to the protocol and that data are being accurately recorded in the CRFs. Source data verification (a comparison of the data in the CRF with the subject's laboratory test results and other source documents) will also be performed. Authorized representatives of the regulatory authority may visit the center to perform inspections, including source data verification. Clean File for the final database will be declared when all data have been entered and a quality check on a sample of the data has been performed. The database will be locked after Clean File has been declared and data extracted for statistical analysis. Study committee meetings will be held as needed prior to or during the study. The medical, nursing and other staff involved in the study will receive proper education/information on how to conduct the study according to the protocol.

11.2. STUDY RECORDS RETENTION AND DATA ACCESS

The data collected in a database will be kept for the period of 25 years, as required by the EU Clinical Trial Regulation No 536/2014 and complying with all applicable local South African and Georgian regulatory requirements.

As the anonymized data generated could be very useful to other researchers, physicians and clinical managers of TB patients, we do plan to give open-access to at least some of them. Within the SMA-TB project we will draw up a Data Management Plan (DMP) within the first 6 months of the project including which data generated by the action, whether and how it will be made accessible and how it will be maintained and preserved. DPO (Data Protection Officer) at IGTP will support IGTP on this task who will work with the DPO (or person responsible of Data protection at the institution) of the Partners involved.

All data collected and generated and samples collected within the project might be used for future research related by SMA-TB investigator teams or their collaborators if considered appropriate, previously approved by an Ethics Committee. Their reuse will be limited to future relevant projects with the aim to study tuberculosis disease, how to treat it or how to prevent it. By consenting to participate, patients will be consenting to the secondary use of samples in this related future research.

12. QUALITY MANAGEMENT

The principal investigator of each site shall select a Monitor(s) qualified by training and experience to monitor the study. A Monitor may be an employee of the principal investigator's organization or an organization contracted by the principal investigator. The Monitor shall assure that the investigators are complying with the signed investigator agreement, the Clinical Investigation Plan/Protocol, IDE regulations and any conditions of approval imposed by the Investigation Site IRB/EC.

To ensure patient's rights, wellbeing and safety, compliance as well as quality of data, the monitors will visit the sites on a regular basis. Frequency of the visits depends on the actual patient inclusion rate and the observed events and deviations on a site.

Routine monitoring will occur to:

- verify that subject enrollment is being achieved;
- verify that the inclusion/exclusion criteria have been met at enrollment;
- verify that the correct version of the informed consent has been signed by the subject;
- review the medical records of all enrolled subjects to ensure all adverse events have been captured and properly reported;
- verify that the data and imaging are accurate, complete and backed up by source documents;
- verify that all contracts, certifications, and medical licenses for each site are valid through the duration of the study.

The monitor will verify the compliance to study procedures, Standard Operating Procedures and other instructions. The presence of certificates, Standard Operating Procedures and instructions related to devices, facilities, laboratories, pharmacy and other departments involved will be checked.

Findings from the monitoring visits will be reported by the monitor to the sponsor-investigator through a monitoring visit report. It is the responsibility of the sponsor-investigator to follow up on findings, deviations, queries or other issues where required.

13. PROTOCOL DEVIATIONS AND AMENDMENTS

13.1. PROTOCOL DEVIATIONS

Investigator-Sponsor or site investigator must not make any changes to or deviate from the protocol, except to protect the life and physical well-being of a subject in an emergency. A site investigator shall notify the Investigator-Sponsor and the reviewing IRB of any deviation from the protocol to protect the life or physical wellbeing of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days. All deviations from the protocol, with the reason for the deviation and the date of occurrence, must be documented and reported to the Investigator-Sponsor using the appropriate case report form. Sites are also required to report deviations to the IRB per local requirements. Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, center retraining, or discontinuation) will be put into place by the Investigator-Sponsor.

For the purpose of consistency and reporting, deviations will be classified according to the scheme outlined below:

- Type A - Deviation to protect the life or physical well-being of a subject in an unforeseen emergency
- Type B - Deviation based on medical judgment
- Type C - Deviation due to misunderstanding of protocol requirements (training was an issue and retraining may be required)
- Type D - Deviation due to a situation that is beyond control
- Type E - Deviation due to an oversight, error or protocol non-compliance.

In the event of trend or pattern observed in a particular deviation type, the Investigator-Sponsor will perform compliance visit. Documentation of such a visit and any subsequent training will be documented.

13.2. PROTOCOL AMENDMENTS

A 'substantial amendment' is defined as an amendment to the terms of the Ethics Committee application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the patients of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be submitted to the Ethics Committee and to the competent authorities for approval.

Non-substantial amendments will be submitted to the authorities and ethics committees as notification, i.e. approval is not needed.

14. RISKS

14.1. INSTITUTIONAL REVIEW BOARD INVOLVEMENT

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by nationally and internationally registered and certified ethics review committee of the University of the Witwatersrand and the National Centre for Tuberculosis and Lung Diseases Ethics Committee of Georgia (IRB00007705 NCTLD Georgia #1 IORG 0006411). In order to confirm the research conducted outside the EU is legal in at least one EU Member State, we will obtain the Ethical Clearance from the Ethics Committee of the Hospital Germans Trias i Pujol (Badalona, Spain), the IGTP correspondent regulatory authority; which already issued a document notifying its favourable opinion on the activities proposed in the SMA-TB proposal.

14.2. DATA SAFETY MONITORING BOARD

We have established a data safety monitoring board comprising a biostatistician, a trialist and a person with extensive clinical experience in TB and its treatment. The DSMB will formally meet once the protocol has been approved and will develop a plan for future meetings. The meetings will be formatted in a standardised fashion: there will be an open section where the overall PI presents the progress and conduct of the trial, with recruitment, retention, adherence and other metrics of progress, and line listings of adverse events and serious adverse events, and the number of participants who have had to have their randomization allocation unblinded – all this data will be reported overall without comparison by allocated treatment arm.

Included in the open report will be a tolerability report of all participants. Once any queries of the DSMB have been addressed by the investigators, the DSMB will be offered a closed report. Once we have sufficient outcomes of the trial, the DSMB will be offered the opportunity to view analyses by arm at pre-specified and DSMB-agreed upon timings. Intermittently, but at least annually, once the trail has recruited sufficient

participants, and has safety on NSAID/placebo data, and other outcome data, the DSMB will meet and will make recommendation to investigators regarding the conduct and progress of the trial as well as on whether the trial should continue to recruit. If the DSMB recommends the premature halting of the trial due either to futility or due to reaching its objective sooner than anticipated, discussions will be held with the DSMB and investigators on how best to do this.

14.3. MEDICAL RISKS.

The potential medical risks and their expected frequency due to ASA and Ibu have been listed in Table 11.

Table 11: Potential medical risks identified [18].

Medical risk	Expected frequency
Dyspepsia	1-10%
Increased bleeding tendency	1-10%
Urticaria	0.1-1%
Dermatologic AE (Steven-Johnson syndrome, Lyell's syndrome, erythema nodosum, erythema multiforme)	0.01-0.1%
Anaphylactic reactions including shock	0.01-0.1%
Aplastic anemia agranulocytosis, thrombocytopenia	0.01-0.1%

There is additional risk to staff and participants during the Covid-19 pandemic. Study sites have implemented multiple processes to minimise the risk of participants being infected with SARS-CoV-2.

At both South African sites, we have installed wash hand basins in the waiting areas of the TB clinic and multiple containers of hand sanitisers are affixed to the wall. Participants must wash their hands-on entry to the clinic. We do a temperature check, and symptom screen for TB and COVID-19 at entry. Those with symptoms or a high fever ≥37.7C will be assessed by the study doctor. All staff and participants wear masks at all times. Staff wear appropriate personal protective equipment when interacting with participants and collecting specimens. Our clinics have extractor fans, capable of ensuring 12 room changes per hour, and have Ultra Violet germicidal irradiation lamps in every consultation room. Table and counter surfaces will be wiped down with a dilute bleach solution between patients. We will give masks to patients for other family members and provide information on how to reduce risk of acquisition of SARS-CoV-2.

14.4. LEGAL RISKS.

There are no identifiable legal risks to the participants besides a potential breach in patients' confidentiality.

14.5. FINANCIAL RISKS TO THE PARTICIPANTS.

There are no financial risks to the participants. Treatment for TB is routine and free in South Africa and in Georgia. There will be no other costs to the participants.

14.6. STEPS TAKEN TO MINIMIZE THE RISKS

In order to minimize the medical risks, we will exclude all patients having a history of conditions that might increase the presence of the medical risks due to interventional drugs (see Table of inclusion and exclusion criteria, Table 3). In order to minimize the risk of a potential breach in patients' confidentiality, all data will be coded to preserve patients' identity, according to the Regulation (EU) 2016/679 of the European

Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. The clinical history information of patients enrolled will be strictly confidential and their identity will be kept anonymous.

15. BENEFITS

There is no direct benefit to patients with TB to enrol in this study. Their involvement in this study may be of great help to understand and manage TB and will contribute to provide valuable information on how to help in a short future other TB patients.

This study has the potential to improve tuberculosis patient's outcomes through better therapeutically approaches. It will also help to validate new tests to monitor TB disease and to predict its outcomes which might be further commercially exploited.

16. PAYMENT AND RE-NUMERATION

An insurance cover will be issued in favor of the patients participating in the CT. The insurance will be in compliance with the local regulation and with the requirements of the Health Authorities.

In case of an injury occurring to the patient during the clinical trial, the patients will be provided with free medical management as long as required or till such time it is established that the injury is not related to the clinical trial. A financial compensation will be provided in the case of CT related injury or death for which patients are entitled to compensation as per each country's national guidelines.

Participants will not be paid for their participation but will receive compensation for their transport and time as per each country's regulatory guidelines.

17. COSTS

There are no costs to the participants.

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