IDANAT2: A double-blind, multicentre, parallel group, randomised, controlled trial to evaluate the possible benefit of isoniazid dose adjustment according to the genotype for NAT2 (arylamine N-acetyltransferase type 2) in patients with pulmonary tuberculosis

CLINICAL TRIAL REPORT

Sponsor	University of Cologne Albertus-Magnus-Platz D-50923 Köln, Germany
Sponsor representative / responsible project leader:	Prof. Dr. med. Uwe Fuhr Institute of Pharmacology University Hospital, University of Cologne Gleueler Straße 24 D-50931 Köln, Germany Phone: +49-221-478-5230, Fax: +49-221-478-7011 E-mail: uwe.fuhr@uk-koeln.de
Coordinating investigator:	Prof. Dr. med. Gerd Fätkenheuer Department I of Internal Medicine University Hospital, University of Cologne Joseph-Stelzmann-Str. 9 D-50931 Köln, Germany Phone +49-221-478-4886, Fax +49-221-478-6733 E-mail : g.faetkenheuer@uni-koeln.de
EUDRACT Number	2007-000224-41
Internal study number	Uni-Koeln-310
ClinicalTrials.gov Identifier:	NCT00571753
Study phase:	III

Study initiation date:	12 August, 2008 (first subject screened)
Follow-up of the last subject:	02 September 2010
Study termination date by Sponsor:	15 September, 2010

Responsible for clinical study report: Dr. med. Dorota Tomalik-Scharte, Dr. Jeremy Franklin

The study was performed in compliance with Good Clinical Practice guidelines, including the archiving of essential documents.

Date of report: Final Version as of 15 September 2011

2 Synopsis

Title of the study:	**IDANAT2:** A double-blind, multicentre, parallel group, randomised, controlled trial to evaluate the possible benefit of isoniazid dose adjustment according to the genotype for NAT2 (arylamine N-acetyltransferase type 2) in patients with pulmonary tuberculosis.
Sponsor	University of Cologne Albertus-Magnus-Platz D-50923 Köln, Germany
Sponsor representative / responsible project leader:	Prof. Dr. med. Uwe Fuhr Institute of Pharmacology University Hospital, University of Cologne Gleueler Straße 24 D-50931 Köln, Germany Phone: +49-221-478-5230, Fax: +49-221-478-7011 E-mail: uwe.fuhr@uk-koeln.de
Coordinating investigator:	Prof. Dr. med. Gerd Fätkenheuer Department I of Internal Medicine University Hospital, University of Cologne Joseph-Stelzmann-Str. 9 D-50931 Köln, Germany Phone +49-221-478-4886, Fax +49-221-478-6733 E-mail : g.faetkenheuer@uni-koeln.de

Involved centres with the responsible principal investigators	
Study centre	Principle Investigator
Department I of Internal Medicine, University Hospital, University of Cologne Joseph-Stelzmann-Str. 9, 50931 Köln, Germany	Prof. Dr. med. G. Fätkenheuer
Abteilung Innere Medizin/ Pneumologie, Thoraxklinik am Universitätsklinikum Heidelberg, Amalienstr.5 69126 Heidelberg, Germany	Prof. Dr. med. F. Herth
Zentralkrankenhaus Bad Berka GmbH Robert-Koch-Allee 9 99437 Bad Berka, Germany	Prof. Dr. med. R. Bonnet
Medizinische Klinik I, Abteilung Pneumologie/Allergologie, Universitätsklinikum Frankfurt am Main, Theodor-Stern-Kai 7 60590 Frankfurt am Main, Germany	Prof. Dr. med. T. Wagner
Diakoniekrankenhaus Rotenburg Verderer Str. 200, 27356 Rotenburg, Germany	Prof. Dr. med. T. Schaberg
Lungenfachklinik Immenhausen	Prof. Dr. med. S. Andreas

Robert-Koch-Str. 3, 34376 Immenhausen, Germany	
Helios Klinikum Emil von Behring GmbH Lungenklinik Heckeshorn Klinik für Pneumologie Walterhöferstraße 11 14165 Berlin	PD Dr. med. T. Bauer
Karl-Hansen-Klinik, Klinik für Lungen- und Bronchialkrankheiten Allergie und Umweltmedizin, Infektionskrankheiten/Tbc, Antoniusstr. 19 33175 Bad Lippspringe	Prof. Dr. med. habil. H. Schweisfurth till the end of 2009, then Dr. med. D. Specht
Division of Infectious Diseases and Clinical Immunology, Department of Internal Medicine, University of Ulm Robert-Koch-Straße 8, 89081 Ulm, Germany	Prof. Dr. med. P. Kern
Department of Pulmonal Diseases, K. Marcinkowski University of Medical Sciences, ul. Szamarzewskiego 84 60-569 Poznan, Poland	Prof. Dr. med. H. Batura-Gabryel
Specialized Hospital of Lung Diseases and Tuberculosis in Wielkopolska in Chodzież, ul. Strzelecka 32, 64-800 Chodzież, Poland	Dr. med. Tomasz Przysiecki
Prof. Dr. med. Donka Stefanova Clinic for Tuberculosis, Medical University Sofia, Buleward "Akademik I. Geschov" No: 17, Sofia 1431 Bulgaria	Prof. Dr. med. Donka Stefanova

IDANAT2 Steering Committee:

- Prof. Dr. med. Uwe Fuhr, Department of Pharmacology, University Hospital, University of Cologne, Gleueler Straße 24, D-50931 Köln, Germany, Phone: +49-221-478-5230, Fax: +49-221-478-7011, E-Mail: uwe.fuhr@uk-koeln.de
- Prof. Dr. med. Gerd Fätkenheuer, Department I of Internal Medicine, University Hospital, University of Cologne, Joseph-Stelzmann-Str. 9, D-50931 Köln, Phone +49-221-478-4886, Fax +49-221-478-6733, E-mail : g.faetkenheuer@uni-koeln.de
- Dr. rer. nat. Ursula Paulus, Clinical Trial Center, University of Cologne, Gleueler Straße 269, D-50935 Köln, Germany, Phone: +49-221-478-88120, Fax : +49-221-478-7983,

E-Mail: ursula.paulus@kksk.de

- Prof. Dr. Walter Lehmacher, University Hospital, Institute of Medical Statistics, Informatics and Epidemiology, University of Cologne, Joseph-Stelzmann-Str. 9, D-50931 Köln, Germany, Phone: +49-221-478-6500, Fax: +49-221-478-6520, E-mail: Walter.Lehmacher@uni-koeln.de

- PD Dr. med. Walter Haas, Head of Division for Respiratory Diseases and Immunisation, Department for Infectious Disease Epidemiology, Robert Koch Institute, Seestr. 10, 13353 Berlin, Germany. Phone +49-30-4547-3431, Fax: +49-30-4547-3533, E-Mail: HaasW@rki.de

- Prof. Dr. med. Donka Ivanova Stefanova, Head of Clinic for Tuberculosis, Medical University Sofia, Buleward "Akademik I. Geschov" No: 17, Sofia 1431 Bulgaria, Phone: +359 2 80 54 277, Fax: +359 852 8572 E-Mail: profstefanova@mbox.digsys.bg

- Prof. Dr. med. Halina Batura-Gabryel, Department of Pulmonal Diseases of the K.M Marcinkowski University of Medical Sciences, ul. Szamarzewskiego 84, 60-569 Poznan, Poland. Phone: +48-61-8417061, Fax: +48-61-8417061, E-Mail: halinagabryel@wp.pl

- Prof. Dr. Junichi Azuma, Department of Clinical Evaluation of Medicines and Therapeutics Graduate School of Pharmaceutical Sciences, Osaka University, 1-6, Yamadaoka, Suita, 565-0871 Osaka, Japan. Phone:+81-6-6879-8258, Fax: +81-6-6879-8259, Email: azuma@phs.osaka-u.ac.jp

- Prof. Dr. med. Tom Schaberg, Diakoniekrankenhaus Rotenburg, Verderer Str. 200, 27356 Rotenburg, Germany. Phone: +49-4261-776235, Fax: +49-4261-776208, E-mail: schaberg@diako-online.de

- Prof. Dr. med. Robert Loddenkemper, Secretary General of the German Central Committee against Tuberculosis, Lungenklinik Heckeshorn, HELIOS Klinikum Emil von Behring, Walterhöferstr. 11, 14165 Berlin, Germany. Phone: +49-030-8102-1164/-1522, Fax: +49-030-8102-1362, E-mail: rloddenkemper@dzk-tuberkulose.de

IDANAT2 Data Monitoring and Safety Committee

- Prof. Dr. Wolfgang Köpcke, Institute of Medical Informatics and Biomathematics, Westfälischen Wilhelms-Universität Münster, Domagkstraße 9, 48129 Münster, Germany, Phone: +49-251-83-55261/62, Fax: +49-251-83-55277, E-Mail: kopcke@uni-muenster.de

- Prof. Dr. med. Hartmuth Lode, Research Centre for Medical Studies, Hohenzollerndamm 2, 10717 Berlin-Wilmersdorf, Germany, Phone: +49-30-8871-9792, Fax: +49-30-8871-9386, E-Mail: haloheck@zedat.fu-berlin.de

- Prof. Dr. med. Gerd Goeckenjan, Am Ziegenberg 95, 34128 Kassel, Germany. Phone: +49-561-9885655, Fax: +49-561-98850752, E-mail: GGoeckenjan@t-online.de

International consulting member:

• Dr. Masako Ohno, PhD, Graduate School of Pharmaceutical Sciences, Osaka University, 1-6, Yamadaoka, Suita 565-0871 Osaka, Japan, Phone:+81-6-6879-8258, Fax: +81-6-6879-8259, E-mail: ohno@phs.osaka-u.ac.jp	
Publication (reference)	Not applicable
Study period:	date of screening in the first subject: 12 August 2008 date of follow-up in the last subject: 02 September 2010 study termination: 15 September 2010
Clinical Phase:	Phase III
Objectives	Main objectives: The study was conducted to compare safety and efficacy of isoniazid administered as an adjusted dose based on NAT2 genotype and as a standard dose Additional objectives • Population pharmacokinetics/pharmacodynamics of isoniazid and (optional) other antituberculosis drugs. • Optional: to obtain data on other factors and their relationship to treatment success and/or NAT2, including early bactericidal activity (EBA), specification of Mycobacterium tuberculosis (M. tuberculosis) strains, pharmacogenetics of the first-line antituberculosis drugs other than isoniazid, utility of the interferon-gamma test (Interferon-Gamma-Release-Assay) • Optional: to evaluate cost-effectiveness of NAT2-based isoniazid dose adjustment
Design:	The study had a prospective, parallel groups, double blind, multicentre, randomised controlled design (phase III– therapeutic use) comparing a standard isoniazid dose (Control) to an isoniazid dose modified according to NAT2 genotype (Test) in 5 parallel groups.
Study Scheme and methods	<u>Visits:</u> • Pre-study recruitment screen • Active clinical phase • End-of-study evaluation <u>Investigations on recruitment screen:</u> • Informed consent; • Medical history; • Demographics (age, sex, body height, race); • Physical examination (including body weight and body temperature); • Sputum collection with smear slide preparation, bacterial culture and susceptibility testing to isoniazid, rifampicin, ethambutol, and pyrazinamide (*optional*: for assessment of EBA by colony-forming units (cfu) and total

	acid-fast bacilli counting, specification of *M. tuberculosis* strains); Alternatively, other appropriate specimens like bronchoalveolar lavage fluid, pus, gastric washings, biopsied tissue etc. could be examined and cultured and drug susceptibility testing was done; • Pulmonary radiograph; • Routine laboratory screen: haematology (haematocrit, haemoglobin, RBC, total and differential leukocyte count, platelet count), clinical chemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [AP], total and conjugated bilirubin, creatinine, glucose); • Blood analysis for serology of hepatitis B and C, HIV 1/2; by HIV-positive patients: $CD4^+$ lymphocytes count; • Pregnancy test in female subjects prior to menopause; • Blood sampling for NAT2 and cytochrome P450 enzyme 2E1 (CYP2E1) genotyping; optional: for genotyping of CYP3A5, PXR, RXR and other enzymes and targets related to antituberculosis drugs; • *Optional*: Blood sampling for CYP3A4/5 phenotyping; • *Optional*: Blood sampling for IFN-gamma test (Interferon-Gamma-Release-Assay). <u>Investigations on active clinical phase:</u> • Administration of isoniazid study medication in standard dose (Control) or in adjusted dose according to NAT2 genotype (Test; treatment was started with the standard dose, adjustment was scheduled for day 3 [time needed for NAT2 genotyping] and should not be later than on day 7 of treatment) with other antituberculosis drugs administered in standard dose; • Compliance check; • Determination of adverse events; • Medical history update; • In patients included with a positive sputum smear. Sputum collection with smear slide preparation and bacterial culture to monitor treatment; • *Optional*: Sputum collection for assessment of EBA by cfu and total acid-fast bacilli counting after the first and the second isoniazid dose; • Clinical chemistry (ALT, AST, AP, total and conjugated bilirubin); • Blood sampling for measurements of isoniazid concentrations (*optional*: concentrations of other antituberculosis drugs): 3 blood samples per patient will be collected during the study at dispersed points of time within given time intervals 0-2 hours, 2-12 hours and 12-24 hours post-dose, respectively; • *Optional*: Blood sampling for CYP3A4/5 phenotyping; • *Optional*: Blood sampling for IFN-gamma test (Interferon-Gamma-Release-Assay). <u>Investigations at the end-of-study evaluation (after 8 weeks of therapy):</u> • Medical history update;

	• Physical examination (including body weight and body temperature); • Sputum collection with smear slide preparation and bacterial culture; • Clinical assessment of the response to the treatment • Susceptibility testing of *M. tuberculosis* to isoniazid, rifampicin, ethambutol, and pyrazinamide in patients with positive culture, *optional*: specification of *M. tuberculosis* strains; • Routine laboratory screen: haematology (haematocrit, haemoglobin, RBC, total and differential leukocyte count, platelet count), clinical chemistry (ALT, AST, AP, total and conjugated bilirubin, creatinine); • For females only, pregnancy test; • Determination of adverse events; • Compliance check; • *Optional*: Blood sampling for IFN-gamma test (Interferon-Gamma-Release-Assay)
Diagnosis:	Newly diagnosed pulmonary tuberculosis
Inclusion criteria	According to the final version of the study protocol (Amendment III as of 22 April 2010) • Patient is informed and given ample time and opportunity to think about her/his participation and has given her/his written informed consent; • Patient is willing and able to comply with all trial requirements, inclusive genotyping procedure; • Patient is between 18 and 75 years of age (inclusive) during the whole trial, male or female; • Patient has newly diagnosed pulmonary tuberculosis for whom daily antituberculosis therapy is indicated; Patient has radiological evidence of a pulmonary infiltrate.
Exclusion criteria	According to the final version of the study protocol (Amendment III as of 22 April 2010), patients of any of the following categories were excluded from allocation: • Patients with known contraindications for isoniazid: acute hepatitis, macroscopic hematuria, allergy to isoniazid, peripheral neuritis, coagulopathy, severe haemorrhagic diathesis, seizure disorders, psychosis; • Patients with advanced or unstable chronic liver disease which is confirmed on results of biochemical or serological tests by eligibility assessment (relevant abnormalities of the following liver tests: ALT, AST, AP, total and conjugated bilirubin; positive serology for hepatitis), if the assessed risk-benefit ratio for the participation in the study is unfavourable (inclusion upon a decision of clinical investigator); • Patients with a severe, life-threatening disease with a life expectancy of less than 2 years; • Patients known to have AIDS ($CD4^+$ count <200/μl) or HIV-seropositive patients who are receiving HAART (highly active antiretroviral therapy). Note: HIV-positive patients may be included;

	• Patients with diabetes mellitus; • Patients with renal insufficiency (creatinine clearance < 30mL / min / 1.73m^2) and patients on hemodialysis; • Patients with any other clinical conditions suggesting that he/she should not be included (decision of the clinical investigator); • Patients with chronic infections requiring concomitant systemic antibacterial agents that are also active against *M. tuberculosis* (i.e. fluoroquinolones, aminoglycosides, macrolides) • Patients with intake of systemic antibacterial agents that are also active against *M. tuberculosis* (i.e. fluoroquinolones, aminoglycosides, macrolides) within 4 weeks prior to antituberculosis treatment; • Patients who have ever received antituberculosis chemotherapy; • Patients who take any hepatotoxic agent on regular basis or have taken it within 3 month before study onset; • Patients with known drug abuse • Patients with known / continuous severe alcohol abuse (drinking more than 60 g and less than 200 g alcohol daily) presenting with relevant (more than 20%) abnormalities of the following liver tests: ALT and/or AST and/or AP and/or bilirubin • -Patients with known / continuous very severe alcohol abuse (drinking equal to or more than 200 g alcohol daily) irrespective of the results of the following liver tests: ALT and/or AST and/or AP and/or bilirubin • Patients who participate in other interventional clinical studies; • Female patients who are pregnant or lactating; • Female patients not willing and capable to use two different contraceptive methods throughout the study, e.g. double barrier methods (e.g. diaphragm and condom by the partner, intrauterine device and condom, sponge and condom, spermicide and condom). Acceptable alternatives of effective contraception are also sexual abstinence or vasectomized partner. In contrast, oral contraceptives are not recommended, since the effectiveness of them may be reduced due to a possible interaction with rifampicin; • Patients who are placed in a closed institution as a result of a court or any other authorities' decision • Patients who are known or suspected not to comply with the study directives and/or known or suspected not to be reliable or trustworthy; Patients who are known or suspected not to be capable of understanding and evaluating the information that is given to them as part of the formal information policy (informed consent), in particular regarding the foreseeable risks to which they will be exposed. Exclusion criteria after allocation: Patients with any of followings will not be included into evaluation for efficacy: • Infection with Mycobacterium avium complex; • Resistance of *M. tuberculosis* to isoniazid at the first screening test (initial culture);

<table>
<tr><td></td><td>• Negative bacterial culture</td></tr>
<tr><td>Groups / interventions</td><td>Prior to treatment, a blood sample for NAT2 genotyping was drawn. Treatment was started with standard isoniazid dose (appr. 5 mg/kg b.w.) in all patients as described for the Control group (s. table). Within maximal 6 days (time required for NAT2 genotyping, randomisation) the dose was adapted according to NAT2 status in the Test group only (modified daily isoniazid dose is appr. 2.5 mg/kg, 5 mg/kg and 7.5 mg/kg for slow, intermediate and rapid acetylators, respectively). Other medications were given with no group differences.
<table>
<tr><td>NAT2 status</td><td colspan="3">Control group (mg)</td><td colspan="3">Test group (mg)</td></tr>
<tr><td>Body weight (kg)</td><td><40</td><td>40-<60</td><td>≥60</td><td><40</td><td>40-<60</td><td>≥60</td></tr>
<tr><td>no highly active allele</td><td>200</td><td>300</td><td>400</td><td>100</td><td>150</td><td>200</td></tr>
<tr><td>one highly active allele</td><td>(200)</td><td>(300)</td><td>(400)</td><td colspan="3">not applicable</td></tr>
<tr><td>two highly active alleles</td><td>200</td><td>300</td><td>400</td><td>300</td><td>450</td><td>600</td></tr>
</table>
Clinical chemistry was done weekly until week 4 and every second week until week 8. In patients included with a positive sputum smear, sputum was collected weekly, starting two weeks after therapy onset until 3 negative samples were examined and, independently from the sputum result, also after 8 weeks of treatment. Patient's adverse events, well-being of the patients, and compliance were monitored. During therapy 3 blood samples per patient were collected at dispersed points of time within given time intervals (0-2 hours, 2-12 hours and 12-24 hours post-dose, respectively).</td></tr>
<tr><td>Endpoints / primary outcome(s)</td><td>• <u>Incidence of hepatotoxicity</u> occurring up to week 8 of therapy, defined according to the following criteria:
- in patients with normal results of liver tests before treatment: increase to more than 2-fold above upper limit of normal range in ALT or conjugated bilirubin or combined increase in AST, AP and total bilirubin provided one of them is more than 2-fold;
- in patients with abnormal results of liver tests before treatment: increase to more than 2-fold above the levels before administration (baseline) in ALT or conjugated bilirubin or combined increase in AST, AP and total bilirubin provided one of them is more than 2-fold.

• <u>Incidence of early treatment failure,</u> defined in patients included with a positive sputum smear as continuous or recurrently positive sputum cultures up to 8 weeks of therapy or, in patients without a positive sputum smear upon inclusion/producing no sputum assessed on the basis of clinical evaluation indicating lack of response to the given treatment</td></tr>
<tr><td>Further characteristics</td><td>Secondary outcome measures:
• Further adverse events of isoniazid
• Time course of sputum conversion
• Duration of hospital stay

Further characteristics:
• Population pharmacokinetic/pharmacodynamic parameters of isoniazid and (optional) other antituberculosis drugs including covariate analysis</td></tr>
</table>

	• *Optional*: EBA of drug treatment including isoniazid during the first 2 days of treatment measured by counting of colony-forming units (cfu) and total acid-fast bacilli in sputum • *Optional*: specification of *M.tuberculosis* strains • *Optional*: T-cell-based IFN-gamma test (Interferon-Gamma-Release-Assay) • *Optional*: genotype for cytochrome P450 enzyme 3A5 (CYP3A5), pregnane X receptor (PXR), retinoid X receptor (RXR), and for other enzymes and targets related to antituberculosis drugs • *Optional*: phenotype for CYP3A4/5
Planned sample size:	According to the final version of the study protocol (Amendment III as of 22 April 2010), the sample size of 242 (2x121) patients with slow acetylator genotype was assumed appropriate to test (with a power of 80%) the hypothesis that the genotype-adjusted dose is superior to the standard dose with regard to hepatotoxicity in slow acetylators. The hypothesis regarding early treatment failure was intended to be evaluated in an IPD meta-analysis together with the Japanese sister trial. To this end, in Europe approximately 599 patients were intended to be screened; 402 patients should have been included in the trial (eligibility fraction: 85%; only 50% of intermediate acetylators was intended to be included); 382 patients were expected to complete the trial (loss to follow-up: 5%); 242 of these were expected to be slow acetylators (based on actual distribution of NAT2 genotypes in Caucasians). Based on results of interim analysis the sample size could have been adapted. In this case, it was planned to include up to 50% additional patients in the trial.
Statistics	A two-fold confirmatory strategy was initially planned, (i) superiority regarding hepatotoxicity for slow acetylators, and (ii) superiority regarding early treatment failure for rapid acetylators. Both null hypotheses were to be assessed by the Cochran-Mantel-Haenszel test stratified by country and HIV-status following a three-stage group-sequential design with O'Brien-Fleming boundaries with Bonferroni corrected one-sided α=1.25%. The interim analyses (possibly adaptive using the 'inverse normal method') were to be performed after 2×40 and 2×81 randomized and evaluable slow acetylators. Exploratory Analysis: Due to lack of power, for slow acetylators [rapid acetylators] the primary endpoint treatment failure [hepatotoxicity] would be analyzed for non-inferiority with margin Δ=0.05. Exploratory analyses would also be done to compare all 4 groups of slow and rapid acetylators to that of intermediate acetylators and to compare the combined endpoint 'hepatotoxicity or treatment failure' between the combined dose adjusted groups of slow and rapid acetylators and the respective combined standard therapy groups.
Summary of the study conduct, results, and conclusion	

Conduction of the study

The study was at first intended to be performed in tuberculosis centres in three countries Germany, Russia and Poland. According to the Protocol version which was initially approved by the Ethics Committee (EC) and the National Competent Authority (NCA) in Germany (Study Protocol, amended version as of September 10, 2007), the patients' observation time in the study was 24 weeks. However, an adjustment of the study design was subsequently required due to a pronounced delay in the course of the study and an unsatisfied patient recruitment. Thus, a reduction of the observation time to 8 weeks as well as recruitment of only 50% of intermediate acetylators, who are non-informative with respect to the primary objective, was introduced by the Amendment II to the Protocol as of July 9, 2009. This version of the protocol was also the initially submitted and approved document in Poland and Bulgaria. The latter country was involved in the performance of the project after an unfavourable opinion of the Ethics Committee in Russia had been obtained. Since the changes applied in the course of the study did not bring about any significant improvement in patient recruitment, the Sponsor decided to perform further adjustments, mainly concerning the inclusion and exclusion criteria Thus, the Amendment III as of April 22, 2010 was submitted to and approved by EC and NCA of the participating countries. Unfortunately, this step was not satisfactory either. Thus, in view of the low patient recruitment rate and lack of perspectives indicating possible improvement of the problem, the Sponsor decided to terminate the study on September 15, 2010.

Characterisation of study population

19 patients were randomised, but 6 of these had intermediate genotype and 4 had unknown genotype, thus these 10 patients could only be assigned to the control group. An effective randomisation between test and control treatment strategies was performed for 7 slow acetylators (test: n=3; control: n=4) and two rapid acetylators (test:n=0; control: n=2). Median age at recruitment was 45 years (range: 24 to 71). 6 patients (32%) were female and 13 were male. Median body weight was 58 kg (range: 50 to 101). There were 15 smokers (79%; median 20 cigarettes per day, range 8 to 40), 3 non-smokers and one ex-smoker. 4 patients (21%) discontinued the study prematurely: one due to an adverse event (hepatotoxicity), the others because of their own decision. (All statistics calculated for the complete dataset, n=19.)

Primary outcome results:

Early treatment failure (based on sputum culture at week 8): In the entire cohort (n=19), 5 patients were evaluated as responders at week 8, 10 as non-responders and 4 were not evaluable, yielding an early treatment failure rate of 67%. According to NAT2 genotype, response rates were: rapid acetylators 2/2, slow acetylators 2/5 (plus 2 missing values), intermediate acetylators 1/5 (plus 1 missing value) and unknown genotypes 0/3 (plus 1 missing value).

Hepatotoxicity (up to week 8): one of 19 patients (intermediate acetylator) suffered the defined hepatotoxicity (5%).

Safety results:

There were altogether 26 adverse events (AE) during the course of the study, which were

reported by 12 of 19 subjects. One adverse event was evaluated as serious (SAE). This SAE was described as hepatitis medicamentosa (drug-induced hepatitis) and was certainly related to the treatment with isoniazid. The reason for the classification of SAE in this case was repeated increase of the liver enzymes ALT and AST to more than ten-fold above the upper limit of the normal range, which corresponded to the seriousness criterion “other medically important condition”. It is noteworthy that the hepatotoxic reaction occurred on two occasions in this patient. First, the disorder was classified as a usual AE and gave reason to the withdrawal of isoniazid for a short period of time. After normalization of the liver enzymes and isoniazid re-challenge, another strong hepatotoxic reaction occurred and was classified as SAE. Since hepatotoxic effects are a known adverse reaction in patients treated with isoniazid, this SAE did not fulfil criteria of suspected unexpected serious adverse drug reaction (SUSAR). At the discretion of the investigator, the index patient was discontinued from isoniazid treatment and the further participation in the study. The SAE completely resolved by the follow-up examination.

Most of the other observed AE were characterized by a mild intensity and only 3 were moderate. The art of AE ranged from different pain complaints such as back or joint pain or headache and toothache (all in all 9 cases) followed by different skin problems (5 cases), gastrointestinal disorders (4 cases) to various complaints, each of them was observed only once in the study population (tongue irritation, rhinitis, increase of uric acid, depression, cough, insomnia, and drug-induced hepatitis, see above). Three AE were certainly related to isoniazid (hepatotoxic reaction, vomiting), 5 were classified as possibly (increase of uric acid, exanthema, joint pain in two subjects, and nausea) and 2 (skin lesions, depression) as unlikely related to isoniazid, whereas 16 were not related. All but 2 AE recovered by the follow-up examination. Since the studied population was very small, no comparison of the frequency of AE with respect to NAT2 treatment groups is possible.

Conclusions:

The study treatment was well tolerated. In view of the very low recruitment, comparative evaluation of efficacy between the randomised treatment groups or the genotype groups is not appropriate; the planned statistical tests have no worthwhile power. The overall rate of early treatment failure was 67% and the rate of hepatotoxicity 5%.

The study had to be terminated early because of low recruitment rates, suggesting that the anticipated samples size could not be reached within the budget and within a reasonable time period. The low number of patients included precludes the evaluation of the study according to the outcome parameters.

Date of the report: 15 September 2011