



Universitätsklinikum  
Hamburg-Eppendorf

## STUDY PROTOCOL

<b>Phase IIa proof-of-principle study for the induction treatment of autoimmune hepatitis using infliximab AIH-MAB</b>	
EudraCT No.	2017-003311-19
Protocol No.	AIH-MAB
Version/Date	Version 2.0, 17.08.2017
Sponsor	University Medical Centre Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg Germany
Coordinating Principal Investigator	Dr. Christina Weiler-Normann, MD I. Department of Medicine, University Medical Centre Hamburg-Eppendorf  Prof. Dr. Ansgar W. Lohse, MD (Deputy-LKP) I. Department of Medicine, University Medical Centre Hamburg-Eppendorf
Executive Committee	<p><u>Chairs:</u> Prof. Dr. Ansgar W. Lohse (Academic PI) Dr. Christina Weiler-Normann (Academic Co-PI)</p> <p><u>Executive Committee Members:</u> Prof. Dr. Christoph Schramm Prof. Dr. Marilyn Addo Dr. Marcial Sebode</p> <p><u>Comment:</u> Members of the executive committee will also be members of the steering committee. The latter will include also Prof. Wegscheider as trial statistician, and all members of the steering committee trial.</p>

**CONFIDENTIALITY STATEMENT**

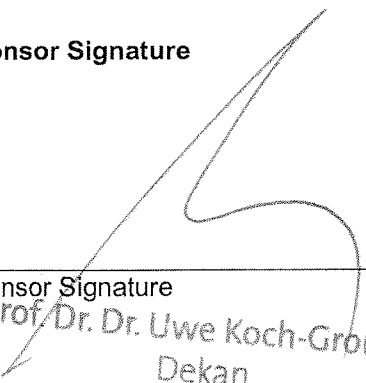
The information provided in the following document is confidential and is only available for review to Principal Investigators, the Ethics Committee and the Competent Authorities. No disclosure should take place without the written authorisation from the Sponsor, except to the extent necessary to obtain informed consent from potential patients or to obtain approval of this protocol by an Ethics Committee or Regulatory Authorities.

Protocol No. AIH-MAB

**SIGNATURES**

This protocol has been approved by the Sponsor:

**Sponsor Signature**

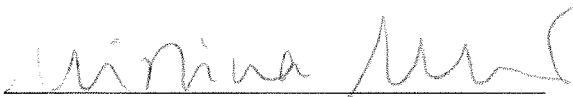
  
\_\_\_\_\_  
Sponsor Signature  
Prof. Dr. Dr. Uwe Koch-Gromus  
Dekan

18.8.2017  
\_\_\_\_\_  
Date

\_\_\_\_\_  
Sponsor Name  
Prof. Dr. Dr. Uwe Koch-Gromus  
Dekan


**Coordinating Principal Investigator**

I hereby confirm that I have acknowledged the protocol and agree to conduct the study in compliance with the protocol.

  
\_\_\_\_\_  
Coordinating Principal Investigator Signature

AUG 17<sup>th</sup>, 2017  
\_\_\_\_\_  
Date

CHRISTINA WEILER-NORFANN  
\_\_\_\_\_  
Coordinating Principal Investigator Name

  
\_\_\_\_\_  
Deputy-Coordinating Principal Investigator Signature

18.08.2017  
\_\_\_\_\_  
Date

Ausgar W. Coly  
\_\_\_\_\_  
Deputy-Coordinating Principal Investigator Name

**Statistician Signature**

\_\_\_\_\_  
Statistician Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Statistician Name

Protocol No. AIH-MAB

**3 SYNOPSIS**

<b>Title of Study:</b>	Phase IIa proof of principle study for the induction treatment of auto-immune hepatitis using infliximab AIH-MAB
<b>Coordinating Principal Investigators</b>	Dr. Christina Weiler-Normann Prof. Dr. Ansgar W. Lohse (Deputy-LKP)
<b>Executive Committee</b>	<p><u>Chairs:</u> Prof. Dr. Ansgar W. Lohse (Academic PI) Dr. Christina Weiler-Normann (Academic Co-PI)</p> <p><u>Executive Committee Members:</u> Prof. Dr. Christoph Schramm Prof. Dr. Marilyn Addo</p> <p><u>Comment:</u> Members of the executive committee will also be members of the steering committee. The latter will include also Prof. Wegscheider as trial statistician, and all members of the steering committee of the AIH-MAB trial</p>
<b>Study centre:</b>	I. Department of Medicine University Medical Centre Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg, Germany
<b>Protocol-No.</b>	AIH-MAB
<b>EudraCT-No.</b>	2017-003311-19
<b>Study Period</b>	<p>First patient in to last patient out (months): 24 Duration of the entire trial (months): 24 Recruitment period (months): 12 FPFV: Q1/2018 LPLV: Q4/2019</p>
<b>Phase of development:</b>	Phase IIa
<b>Primary Objective:</b>	The primary objective of the AIH-MAB trial is to show that infliximab induces biochemical remission in treatment-naïve patients with auto-immune hepatitis
<b>Secondary Objectives:</b>	Secondary objectives include quality of life during the trial, decreasing liver elastography as a marker for intrahepatic inflammation and the absence of weight gain
<b>Tertiary Objectives:</b>	Tertiary objectives include immunological analysis of immune activation of peripheral blood mononuclear cells
<b>Study Design:</b>	Proof-of-principle single-armed monocentric pilot study.

<p><b>Treatment:</b></p>	<p><b><u>Test product:</u></b>                  Inflectra® (Infliximab)</p> <p><b><u>Experimental intervention:</u></b>                  A total of 12 patients will receive a dose of 5mg/kg bodyweight infliximab at time points 0, 2 weeks, 6 weeks and every 4 weeks thereafter for a total period of 6 months. Infliximab is administered intravenously. All patients will receive standard maintenance treatment according to clinical practice guidelines starting in week 2.</p> <p><b><u>Follow-up per patient:</u></b>                  Follow-up for all patients will be until the individual patient recruited has completed 6 months' follow-up.</p> <p><b><u>Duration of intervention per patient:</u></b>                  Infliximab is administered as infusion over a time of 1-2 hours. Additionally, 2 hours of monitoring is warranted after the infusion. Emergency equipment as well as trained personell will be present.</p> <p><b><u>Experimental and/or control off label or in label in Germany:</u></b>                  Infliximab is not approved for the induction treatment in autoimmune hepatitis, therefore, treatment is off label.</p>
<p><b>Number of patients:</b></p>	<p><u>To be assessed for eligibility</u> (n = 50)  <u>To be allocated to trial</u> (n = 12)  <u>To be analysed</u> (n = 12)</p>

<p><b>Diagnosis and main criteria for inclusion:</b></p>	<p><b><u>Key inclusion criteria:</u></b></p> <ol style="list-style-type: none"> <li>1. Patients with untreated autoimmune hepatitis diagnosed in accordance to the „simplified criteria for the diagnosis of autoimmune hepatitis“</li> <li>2. Female patients: Female subjects must be postmenopausal, surgically sterile, or if premenopausal and not surgically sterile, be prepared to use <math>\geq 1</math> effective method of contraception during the study and for 6 months after the end of treatment visit*.</li> <li>3. Must provide written informed consent and agree to comply with the study protocol</li> </ol> <p>*Effective methods of contraception are considered to be double barrier method (i. e. condom or diaphragm with spermicide), intrauterine device, vasectomy (partner), hormonal (contraceptive pill, patch, intramuscular implant or injection or abstinence if in line with the preferred lifestyle of the subject.</p> <p><b><u>Key exclusion criteria:</u></b></p> <ol style="list-style-type: none"> <li>1. Age younger than 18 years old or older than 65 years</li> <li>2. History of severe heart disease or heart failure</li> <li>3. Active or latent tuberculosis or history of past tuberculosis</li> <li>4. Active viral, bacterial or parasitemic infection</li> <li>5. Additional liver disease other than autoimmune hepatitis (including, but not limited to alcoholic liver disease, viral hepatitis, primary sclerosing cholangitis, primary biliary cholangitis, non-alcoholic steatohepatitis), history of alcohol abuse</li> <li>6. History of decompensation of cirrhosis (ascites, variceal bleeding, encephalopathy)</li> <li>7. Positive anti HBc-Titre</li> <li>8. Known or suspected hepatocellular carcinoma</li> <li>9. Presence of transjugular intrahepatic portosystemic shunt procedure</li> <li>10. Hepatorenal syndrome or creatinine <math>&gt;2\text{mg/dl}</math> at screening</li> <li>11. Subjects that have undergone bariatric surgery</li> <li>12. Pregnancy or planned pregnancy</li> <li>13. Chronic obstructive pulmonary disease</li> <li>14. Other medical conditions that may diminish life expectancy, including known cancers</li> <li>15. Participation in another investigational product, biologic or medical device study within 30 days prior to screening</li> <li>16. Mental instability and lack of capability of giving consent.</li> <li>17. History of known or suspected clinically significant hypersensitivity to azathioprine or bone marrow disease</li> <li>18. History of the use of infliximab</li> <li>19. Liver failure (INR <math>&gt; 1,5</math>)</li> <li>20. Body weight <math>&lt; 40\text{kg}</math> or above <math>90\text{kg}</math>, BMI <math>&lt; 18\text{kg/m}^2</math> or <math>&gt; 30\text{kg/m}^2</math></li> <li>21. Patients not willing or able to comply with the study procedures</li> <li>22. Transaminase elevation <math>&gt; 1000\text{ U/l}</math></li> <li>23. Application of life vaccines 4 weeks prior to treatment or planned application of life vaccines during the treatment</li> </ol>
--	--

<p><b>Criteria for evaluation:</b> <b>Efficacy:</b></p>	<p><b><u>Primary Endpoints:</u></b></p> <ul style="list-style-type: none"> <li>Biochemical remission of autoimmune hepatitis defined as normalization of AST, ALT and IgG at month 6.</li> </ul> <p><b><u>Secondary Endpoints:</u></b></p> <ul style="list-style-type: none"> <li>Stable Quality of life (using standardized tools including the GAD-7, PHQ-9 and SF-12) at week 0, 4, 12, 24 and 48.</li> <li>Decrease in Elastography</li> <li>Absence of weight gain</li> </ul> <p><b><u>Tertiary Endpoints:</u></b></p> <ul style="list-style-type: none"> <li>Reduction of immune activation as shown in in-vitro experiments performed on peripheral blood mononuclear cells</li> </ul>
<p><b>Safety:</b></p>	<p>Percentage of patients meeting key safety endpoints, as well as assessment of adverse drug reactions.</p>
<p><b>Statistical methods:</b></p>	<p><b><u>Efficacy / test accuracy:</u></b></p> <p>The primary endpoint “biochemical remission” is a composite endpoint including the normalization of AST, ALT and IgG. As this is a proof-of-principle study, efficacy of at least 50%, but more likely 80% will be assumed.</p> <p><b><u>Description of the primary efficacy / test accuracy analysis and population:</u></b></p> <p>The primary analysis will be intention-to-treat. All details on the analyses, including the definition of the analysis populations, will be detailed in a statistical analysis plan, which will be finalised prior to database.</p> <p><b><u>Effect size assumed for power calculation:</u></b></p> <p>To assess the main hypotheses of the phase IIa study, the required sample size to achieve 80% power with a one-sided Binomial test at a significance level of 10% a total number of 12 patients are required (calculated with the Software ADDPLAN, Version 6.1.1). The above null hypothesis can be rejected at the level of 10% whenever at least 9 out of 12 patients show a response. In this case the estimated response rate is given by 75.0% and the one-sided 90%-confidence interval would be given as [52.5%; 100.0%] All other performed analyses will be of descriptive nature and therefore no formal sample size calculation can be made,</p> <p><b><u>Safety:</u></b></p> <p>Will be ascertained via the assessment of key safety endpoints.</p> <p><b><u>Secondary endpoints:</u></b></p> <p>Only descriptive analyses will be performed, no formal sample size can be made.</p>

STUDY SCHEDULES: Table 1:

Phase of study	Screening	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11 Follow-up	Visit 12/ End of Study
Point in time	- 2 wks to Day -1	2 wks to Day -1	Day 0	Week 1 +/- 1 day	Week 2 +/- 1 day	Week 4 +/- 3 days	Week 6 +/- 3 days	Week 8 +/- 3 days	Week 12 +/- 3 days	Week 16 +/- 3 days	Week 20 +/- 3 days	Week 24 +/- 3 days	Week 36 +/- 1 week1	Week 48 +/- 1 week1
Informed Consent	✓													
I/E Criteria	✓	✓												
Medical History & Demographics	✓													
Physical Examination <sup>a</sup>	✓	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓
Height & Weight	✓	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>
Vital Signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood tests as routine in AIH	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
12-lead ECG	✓													
Urine Pregnancy (if applicable)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Quantiferon® test	✓													
Blood test for immunological analysis	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Infusion of infliximab			✓				✓				✓			
Elastography		✓	✓											
QoL Questionnaire		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Events/Severe adverse event & Hospitalisation & Concomitant medication			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

<sup>a</sup> Symptom-targeted physical examination;

<sup>b</sup> Only weight

**Table 2 (detailed Trial Timeline Flow):**

Year 1												Year 2												Year 3												Year 4																	
Preparation of study protocol, submission to authorities																																																					
↓												Recruitment of patients																																									
												Data acquisition																																									
MS1: Submission to authorities												Database Cleaning												Analysis publication																													
↓												MS2: First patient in						MS3: Last patient in						MS4: Last patient out						MS5: Final analysis of primary end point																							
↓												↓												↓												↓																	
1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12						

<b>4</b>	<b>TABLE OF CONTENTS</b>	
1	TITLE PAGE.....	1
2	SYNOPSIS.....	5
3	TABLE OF CONTENTS.....	11
4	LIST OF ABBREVIATIONS.....	13
5	ETHICS.....	14
5.1	Ethics Committee or Institutional Review Board.....	14
5.2	Ethical Conduct of the Study.....	14
5.3	Patient Information and Informed Consent.....	14
5.4	Confidentiality.....	14
5.5	Insurance.....	14
5.6	Publication Policy.....	14
5.7	Qualification of the Investigator.....	15
6	INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE.....	16
7	INTRODUCTION AND BACKGROUND.....	18
7.1	The Medical Problem.....	18
7.1.1	Prevalence, Incidence, Mortality.....	18
7.1.2	Burden of Disease.....	18
7.1.3	Improvement of Therapy / Impact of the Trial.....	18
7.2	Pharmacological Classification.....	18
7.3	Clinical Use.....	18
7.4	Human Pharmacodynamics.....	18
7.5	Human Pharmacokinetics.....	19
7.6	Preclinical Results.....	19
7.7	Cautions and Tolerability.....	19
7.7.1	Contraindications.....	19
7.7.2	Special Warnings and Preventive Measures for the Treatment.....	19
7.7.3	Side Effects.....	22
7.7.4	Overdose.....	25
7.8	Rationale.....	25
7.9	Risk-Benefit Considerations.....	25
8	STUDY OBJECTIVES.....	26
8.1	Primary Objective.....	26
8.2	Primary Endpoints.....	26
8.3	Secondary Objectives.....	26
8.4	Secondary Endpoints.....	26
8.5	Safety Endpoints.....	26
9	INVESTIGATIONAL PLAN.....	27
9.1	Overall Study Design and Plan-Description.....	27
9.2	Discussion of Study Design, Including the Choice of Control Groups.....	27
9.3	Selection of Study Population.....	27
9.3.1	Inclusion Criteria.....	27

## Protocol No. AIH-MAB

9.3.2	Exclusion Criteria.....	27
9.3.3	Removal of Patients from Therapy or Assessment.....	28
9.4	Treatments.....	29
9.4.1	Treatments Administered.....	29
9.4.2	Identity of Investigational Medicinal Product(s).....	30
9.4.3	Selection of Doses in the Study.....	31
9.4.4	Prior and Concomitant Therapy.....	31
9.4.5	Treatment Compliance.....	31
9.5	Efficacy and Safety Variables.....	31
9.5.1	Efficacy and Safety Measurement Assessed and Flow Chart.....	31
9.5.2	Appropriateness of Measurements.....	31
9.5.3	Primary efficacy variable(s).....	37
9.6	Data Quality Assurance.....	38
9.6.1	Quality Assurance System.....	38
9.6.2	Monitoring.....	38
9.6.3	Documentation and Data Collection.....	38
9.6.4	Data Management.....	38
9.6.5	Archival of documents.....	39
9.7	Statistical Methods Planned in the Protocol and Determination of Sample Size.....	39
9.7.1	Statistical and Analytical Plan.....	39
9.7.2	Determination of Sample Size.....	40
9.8	Changes in the conduct of the study or planned analysis.....	40
9.9	DSMB.....	40
10	REPORTS.....	41
10.1	Clinical Study Report.....	41
11	REFERENCES.....	41

**5 LIST OF ABBREVIATIONS**

AE	Adverse event
AIH	Autoimmune Hepatitis
ALT	Alanine-Aminotransferase
AST	Aspartate-Aminotransferase
BCG	Bacillus Calmette-Guerin
BMI	Body Mass Index
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
DMP	Data management plan
DNA	Desoxyribonuclease
ECG	Electrocardiogramme
e.g.	for example
FOCP	Females of child bearing potential
FSH	Follicle stimulating hormone
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
I/E	Inclusion/Exclusion
IgG	Immunoglobulin G
IMP	Investigational Medical Product
i.e.	that is
INR	International normalized ratio
kPa	kiloPascal
PI	Principal investigator
QoL	Quality of Life
SAE	Severe adverse event
SAR	Serious adverse reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TNF	Tumor necrosis factor alpha

## 6 ETHICS

### 6.1 Ethics Committee or Institutional Review Board

This study will be planned and performed in accordance with

- The Declaration of Helsinki in its version of Fortaleza, 2013 as well as AMG and GCP
- The EU Clinical Trial Directive 2001/20/EC;
- The EU Clinical Trial Directive 2001/83/EC;
- The "Note for Guidance on Good Clinical Practice" (CPMP/ICH/135/95 of January 17, 1997);

and other applicable laws.

### 6.2 Ethical Conduct of the Study

The Sponsor authorises CTC North or one of its designees to make all necessary applications.

CTC North or a designee will submit, among other documents, the study protocol, the patient information and the informed consent form to the Ethics Committee and request for approval (favourable opinion). CTC North or a designee will provide the clinical trial application to the Competent Authority. The approval of both, the Ethics Committee and the Competent Authority must be obtained prior to the start of any study related intervention.

### 6.3 Patient Information and Informed Consent

An Investigator will explain to the patients the nature, significance and implications of the study prior to the clinical examination. He will explain all methods, rules of conduct and any restrictions which may apply. Possible effects and side effects will be discussed. Patients will be informed that they are free to withdraw from the study at any time, without giving any reason for doing so. They must be able to understand the full implications of their decision.

All participants will sign an informed consent form as evidence of consent. The patient information sheet and the informed consent form of each participant will be filed in the ISF. A second original of the signed consent form and a copy of the information sheet will be handed to the patients after signature and before enrolment.

If a patient withdraws consenting to participating in the study after blood sampling and before the analysis in the laboratory has taken place, the laboratory has to be informed immediately.

### 6.4 Confidentiality

The Principal Investigator (PI) must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorised parties. Only an identification code (i.e., consists of identification number, sex and year of birth) should be recorded on any form or biological sample submitted to the laboratory, Sponsor, Competent Authorities' or Ethics Committee. The PI must keep a screening and enrolment log showing codes and names for all patients screened and for all patients enrolled in the trial.

### 6.5 Insurance

The Sponsor is responsible for the appropriate insurance coverage for the patients.

### 6.6 Publication Policy

The Sponsor has to publish the result of this study in accordance with § 42b AMG. Beside it is in the sole discretion of the Sponsor whether or not to publish the results of this study. The trial will be registered at [clinicaltrials.gov](http://clinicaltrials.gov).

**6.7 Qualification of the Investigator**

The PI and Investigators of the study site fulfil the requirements of applicable national law. Curriculum vitae of the PI and Investigators will be filed in the TMF.

For conducting the study, the PI may delegate tasks to Investigators (or other qualified staff). This is to be documented properly. The PI is responsible for the adequate training and supervision of all delegates. No study related procedure must be performed by personnel which is not properly trained and delegated.

In the present document the mere term "Investigator" refers to the PI or Investigator.

**7 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE**

<b>Sponsor:</b>	University Medical Centre Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg Germany
<b>Coordinating Principal Investigator:</b>	Dr. Christina Weiler-Normann I. Department of Medicine University Medical Centre Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg Germany Phone: +49 40-7410-50238 Fax: +49 40-7410-58531 Email: cweiler@uke.de
<b>Deputy:</b>	Prof. Dr. Ansgar W. Lohse I. Department of Medicine University Medical Centre Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg Germany Phone: +49 40-7410-53910 Fax: +49 40-7410-58531 Email: alohse@uke.de
<b>Medical Monitor:</b>	Prof. Dr. Christoph Schramm I. Department of Medicine University Medical Centre Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg Germany Phone: +49 40-7410-52545 Fax: +49 40-7410-40272 Email: cschramm@uke.de
<b>Clinical Trial Management:</b>	Project Management, Monitoring, Data Query and Safety Management CTC North GmbH & Co. KG at the University Medical Centre Hamburg-Eppendorf Martinistrasse 64 20251 Hamburg Germany Phone: +49 40-524719-200 Fax: +49 40-524719-129
<b>Safety Management</b>	Safety Management CTC North GmbH & Co. KG at the University Medical Centre Hamburg-Eppendorf Phone: +49 40-524719-225 Fax: +49 40-524719-222 Email: <a href="mailto:pharmacovigilance@ctc-north.com">pharmacovigilance@ctc-north.com</a>

Protocol No. AIH-MAB

**Statistician:**

Prof. Dr. Karl Wegscheider  
Institut für Biometrie  
University Medical Center Hamburg-Eppendorf  
Germany  
Phone: +49 40-7410-56110  
Fax: +49 40-7410-57485  
E-Mail: k.wegscheider@uke.uni-hamburg.de

**Executive Committee**

Dr. Christina Weiler-Normann  
Prof. Dr. Marylin Addo  
Prof. Dr. Ansgar W. Lohse  
Prof. Dr. Christoph Schramm  
I. Department of Medicine  
University Medical Center Hamburg-Eppendorf  
Martinistrasse 52  
20246 Hamburg  
Germany

**Data Safety Monitoring Board**

Dr. Marcial Sebode  
Prof. Dr. Marylin Addo  
Prof. Dr. Christoph Schramm  
I. Department of Medicine  
University Medical Center Hamburg-Eppendorf  
Martinistrasse 52  
20246 Hamburg  
Germany

## 8 INTRODUCTION AND BACKGROUND

### 8.1 The Medical Problem

#### 8.1.1 Prevalence, Incidence, Mortality

Autoimmune Hepatitis (AIH) is a rare inflammatory liver disease associated with elevated transaminases, elevated Immunoglobulin G, the presence of autoantibodies and interface hepatitis in liver histology (1). If left untreated, AIH progresses to liver fibrosis and cirrhosis with its complications. Historical placebo-controlled studies could show a mortality of around 70% in the placebo-treated group(2). Today, effective immunosuppressive treatment is available and mortality is approximately twice as high as in a control population.

The prevalence of AIH is low, per definition AIH is a rare disease. Recent population-based studies have shown a rising prevalence (3).

#### 8.1.2 Burden of Disease

AIH is a rare disease with an estimated incidence rate of 1,68 per 100000 population/year (3). Clinical controlled studies are rare as AIH is a rare disease. Since incidence is rising, it is becoming an increasing health problem. Most patients are in need of medical treatment life-long.

#### 8.1.3 Improvement of Therapy / Impact of the Trial

Standard induction treatment of autoimmune hepatitis includes high doses of corticosteroids. This treatment is associated with numerous side effects that are often very bothersome for the patient and consecutively leads to reduced treatment adherence in these patients. Especially weight gain, cushingoid changes in habitus and facial appearance, hirsutism and edema are often problematic in these often young and female patients. Additionally, the potential psychological side effects as sleep disturbance, depression and development of steroid-induced psychosis can be very wearing.

In this trial, we seek to replace steroid induction treatment by treatment with the TNF-blocker infliximab.

### 8.2 Pharmacological Classification

Infliximab (Inflixtra<sup>®</sup>), is a chimeric human-murine monoclonal IgG1-antibody. It is produced with the help of recombinant DNA Technology in murine hybridoma cells. Other ingredients: Sucrose, Polysorbate 80, Sodiumdihydrogenphosphate-Monohydrate, Disodiumphosphate-Dihydrate. It will be reconstituted in *Aqua ad injectabile*.

This medication is licenced in the EU: EU/1/13/854/001, EU/1/13/854/002, EU/1/13/854/003, EU/1/13/854/004, EU/1/13/854/005. Initial licensing occurred September 10th, 2013.

### 8.3 Clinical Use

Inflixtra<sup>®</sup> is licensed for the use in ulcerative colitis, Crohn's disease, rheumatoid arthritis (in combination with Methotrexate), ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. It was first licensed as Remicade<sup>®</sup> in the United States in 1998 and in the European Union in 1999. There is broad clinical experience with the use of Infliximab

### 8.4 Human Pharmacodynamics

Elevated concentrations of TNF $\alpha$  have been found in involved tissues and fluids of patients with rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. In rheumatoid arthritis, treatment with infliximab products reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, chemoattraction [IL-8 and monocyte chemoattractant protein (MCP-1)] and tissue degradation [matrix metalloproteinase 1 and 3]. In Crohn's disease, treatment with infliximab products reduced infiltration of inflammatory cells and TNF $\alpha$  production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNF $\alpha$  and interferon. After treatment with infliximab products,

patients with rheumatoid arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein compared to baseline. Peripheral blood lymphocytes from infliximab product-treated patients showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients. In psoriatic arthritis, treatment with infliximab products resulted in a reduction in the number of T-cells and blood vessels in the synovium and psoriatic skin lesions as well as a reduction of macrophages in the synovium. In plaque psoriasis, infliximab products treatment may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which infliximab products exert their clinical effects is unknown.

## 8.5 Human Pharmacokinetics

In adults, single intravenous infusions of 3 mg/kg to 20 mg/kg of infliximab showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg to 10 mg/kg in rheumatoid arthritis, 5 mg/kg in Crohn's disease, and 3 mg/kg to 5 mg/kg in plaque psoriasis indicate that the median terminal half-life of infliximab is 7.7 to 9.5 days. Following an initial dose of infliximab, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8 week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8 weeks after a maintenance dose of 3 to 10 mg/kg of infliximab, median infliximab serum concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender. It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.

## 8.6 Preclinical Results

Preclinical data revealed and published in the manufacturer's information.

## 8.7 Cautions and Tolerability

### 8.7.1 Contraindications

The use of infliximab is contraindicated in

- Patients with moderate to severe heart failure
- Patients who have developed a severe hypersensitivity reaction to infliximab

### 8.7.2 Special Warnings and Preventive Measures for the Treatment

#### 8.7.2.1 Serious infections

Infliximab should not be initiated in patients with an active infection, including clinically relevant localized infections. Patients greater than 65 years of age, patients with comorbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with infliximab, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection

may also be falsely negative while on therapy with infliximab. Treatment should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

#### 7.7.2.2 Malignancies

Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF blocking agents (initiation of therapy  $\leq 18$  years of age), including infliximab products. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported postmarketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports. In the controlled portions of clinical trials of all the TNF blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of infliximab clinical trials, 5 patients developed lymphomas among 5707 patients treated with infliximab (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately four-fold higher than expected in the general population. Patients with Crohn's disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blocking therapy. Cases of acute and chronic leukemia have been reported with postmarketing TNF blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia. Post-marketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including infliximab products. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males. It is uncertain whether the occurrence of hepatosplenic T-cell lymphoma is related to TNF blockers or TNF blockers in combination with these other immunosuppressants. When treating patients, consideration of whether to use infliximab alone or in combination with other immunosuppressants such as azathioprine or 6-mercaptopurine should take into account a possibility that there is a higher risk of hepatosplenic T-cell lymphoma with combination therapy versus an observed increased risk of immunogenicity and hypersensitivity reactions with infliximab product monotherapy from the clinical trial data from studies with infliximab.

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including infliximab products. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. In the controlled portions of clinical trials of some TNF blocking agents, including infliximab products, more malignancies (excluding lymphoma and nonmelanoma skin cancer) have been observed in patients receiving those TNF blockers compared with control patients. During the controlled portions of trials with infliximab, in patients with moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 14 patients were diagnosed with malignancies (excluding lymphoma and non-melanoma skin cancer) among 4019 infliximab-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among infliximab-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for infliximab-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among infliximab-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected. In a clinical trial exploring the use of infliximab in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in inflix-

imab-treated patients compared with control patients. All patients had a history of heavy smoking. Psoriasis patients should be monitored for nonmelanoma skin cancers, particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for infliximab, NMSCs were more common in patients with previous phototherapy. The potential role of TNF blocking therapy in the development of malignancies is not known. Rates in clinical trials for infliximab cannot be compared to rates in clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering infliximab treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving infliximab.

#### **7.7.2.3 Hepatitis B Reactivation**

Use of TNF blockers, including infliximab products, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients should be tested for HBV infection before initiating TNF blocker therapy. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and anti-viral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF blocker therapy in this situation and monitor patients closely.

#### **7.7.2.4 Hepatotoxicity**

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis, have been reported rarely in postmarketing data in patients receiving infliximab products. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between 2 weeks to more than 1 year after initiation of infliximab; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g.,  $\geq 5$  times the upper limit of normal) develop, infliximab should be discontinued, and a thorough investigation of the abnormality should be undertaken. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving infliximab products without progression to severe hepatic injury.

#### **7.7.2.5 Patients with Heart Failure**

Infliximab products have been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of infliximab in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg infliximab, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking infliximab. There have also been rare postmarketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer infliximab to patients with mild or moderate heart failure, they should be closely monitored during therapy, and infliximab should be discontinued if new or worsening symptoms of heart failure appear.

#### **7.7.2.6 Hematologic Reactions**

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving infliximab products. The causal relationship to infliximab therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised

in patients who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever). Discontinuation should be considered in patients who develop significant hematologic abnormalities.

#### **7.7.2.7 Hypersensitivity**

Infliximab products have been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of infusion. However, in some cases, serum sickness-like reactions have been observed in patients after initial therapy with infliximab products (i.e., as early as after the second dose), and when therapy with infliximab products was reinstated following an extended period without treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with a marked increase in antibodies to infliximab product, loss of detectable serum concentrations of infliximab products, and possible loss of drug efficacy. Infliximab should be discontinued for severe hypersensitivity reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction. In rheumatoid arthritis, Crohn's disease and psoriasis clinical trials, readministration of infliximab after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment. In general, the benefit- risk of readministration of infliximab after a period of no-treatment, especially as a reinduction regimen given at weeks 0, 2 and 6, should be carefully considered.

#### **7.7.2.8 Neurologic Reactions**

Agents that inhibit TNF have been associated in rare cases with CNS manifestation of systemic vasculitis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of infliximab in patients with these neurologic disorders and should consider discontinuation of infliximab if these disorders develop.

#### **7.7.2.9 Autoimmunity**

Treatment with infliximab products may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with infliximab, treatment should be discontinued.

#### **7.7.2.10 Live Vaccines/Therapeutic Infectious Agents**

In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with infliximab is not recommended. Fatal outcome due to disseminated BCG infection has been reported in an infant who received a BCG vaccine after *in utero* exposure to infliximab products. Infliximab products are known to cross the placenta and have been detected up to 6 months following birth. At least a six month waiting period following birth is recommended before the administration of any live vaccine to infants exposed *in utero* to infliximab products. Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with infliximab. It is recommended that all patients be brought up to date with all vaccinations prior to initiating infliximab therapy. The interval between vaccination and initiation of infliximab therapy should be in accordance with current vaccination guidelines.

### **8.7.3 Side Effects**

Due to long-standing clinical experience, side effects are well known and summarized in table 3 and in the summary of product characteristics.

**Table 3: Adverse drug reactions observed during clinical trials and post-marketing experience**

<i>Infections and infestations</i>	
Very common:	Viral infection (e.g. influenza, herpes virus infection).
Common:	Bacterial infections (e.g. sepsis, cellulitis, abscess).
Uncommon:	Tuberculosis, fungal infections (e.g. candidiasis).
Rare:	Meningitis, opportunistic infections (such as invasive fungal infections [pneumocystosis, histoplasmosis, aspergillosis, coccidioidomycosis, cryptococcosis, blastomycosis], bacterial infections [atypical mycobacterial, listeriosis, salmonellosis], and viral infections [cytomegalovirus]), parasitic infections, hepatitis B reactivation.
Not known:	Vaccine breakthrough infection (after <i>in utero</i> exposure to infliximab)*.
<i>Neoplasms benign, malignant and unspecified (including cysts and polyps)</i>	
Rare:	Lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia, melanoma, cervical cancer.
Not known:	Hepatosplenic T-cell lymphoma (primarily in adolescents and young adults with Crohn's disease and ulcerative colitis), Merkel cell carcinoma.
<i>Blood and lymphatic system disorders</i>	
Common:	Neutropenia, leucopenia, anaemia, lymphadenopathy.
Uncommon:	Thrombocytopenia, lymphopenia, lymphocytosis.
Rare:	Agranulocytosis (including infants exposed <i>in utero</i> to infliximab), thrombotic thrombocytopenic purpura, pancytopenia, haemolytic anaemia, idiopathic thrombocytopenic purpura.
<i>Immune system disorders</i>	
Common:	Allergic respiratory symptom.
Uncommon:	Anaphylactic reaction, lupus-like syndrome, serum sickness or serum sickness-like reaction.
Rare:	Anaphylactic shock, vasculitis, sarcoid-like reaction
<i>Psychiatric disorders</i>	
Common:	Depression, insomnia.
Uncommon:	Amnesia, agitation, confusion, somnolence, nervousness.
Rare:	Apathy.
<i>Nervous system disorders</i>	
Very common:	Headache.
Common:	Vertigo, dizziness, hypoaesthesia, paraesthesia.
Uncommon:	Seizure, neuropathy.
Rare:	Transverse myelitis, central nervous system demyelinating disorders (multiple sclerosis-like disease and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy).
<i>Eye disorders</i>	
Common:	Conjunctivitis
Uncommon:	Keratitis, periorbital oedema, hordeolum
Rare:	Endophthalmitis
Not known:	Transient visual loss occurring during or within 2 hours of infusion
<i>Cardiac disorders</i>	
Common:	Tachycardia, palpitation
Uncommon:	Cardiac failure (new onset or worsening), arrhythmia, syncope, bradycardia
Rare:	Cyanosis, pericardial effusion
Not known:	Myocardial ischaemia/myocardial infarction

## Protocol No. AIH-MAB

<i>Vascular disorders</i>	
Common	Hypotension, hypertension, ecchymosis, hot flush, flushing
Uncommon	Peripheral ischaemia, thrombophlebitis, haematoma
Rare	Circulatory failure, petechia, vasospasm
<i>Respiratory, thoracic and mediastinal disorders</i>	
Very common	Upper respiratory tract infection, sinusitis
Common	Lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, epistaxis
Uncommon	Pulmonary oedema, bronchospasm, pleurisy, pleural effusion
Rare	Interstitial lung disease (including rapidly progressive disease, lung fibrosis and pneumonitis)
<i>Gastrointestinal disorders</i>	
Very common:	Abdominal pain, nausea
Common:	Gastrointestinal haemorrhage, diarrhoea, dyspepsia, gastroesophageal reflux, constipation
Uncommon	Intestinal perforation, intestinal stenosis, diverticulitis, pancreatitis, cheilitis
<i>Hepatobiliary disorders</i>	
Common:	Hepatic function abnormal, transaminases increased.
Uncommon:	Hepatitis, hepatocellular damage, cholecystitis.
Rare:	Autoimmune hepatitis, jaundice.
Not known:	Liver failure.
<i>Skin and subcutaneous tissue disorders</i>	
Common:	New onset or worsening psoriasis including pustular psoriasis (primarily palm & soles), urticaria, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia.
Uncommon:	Bullous eruption, onychomycosis, seborrhoea, rosacea, skin papilloma, hyperkeratosis, abnormal skin pigmentation.
Rare:	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, furunculosis.
Not known:	Worsening of symptoms of dermatomyositis.
<i>Musculoskeletal and connective tissue disorders</i>	
Common:	Arthralgia, myalgia, back pain.
<i>Renal and urinary disorders</i>	
Common:	Urinary tract infection.
Uncommon:	Pyelonephritis.
<i>Reproductive system and breast disorders</i>	
Uncommon:	Vaginitis.
<i>General disorders and administration site conditions</i>	
Very common:	Infusion-related reaction, pain.
Common:	Chest pain, fatigue, fever, injection site reaction, chills, oedema.
Uncommon:	Impaired healing.
Rare:	Granulomatous lesion.
<i>Investigations</i>	
Uncommon:	Autoantibody positive.
Rare:	Complement factor abnormal.

\* including bovine tuberculosis (disseminated BCG infection)

#### **8.7.4 Overdose**

No case of overdose has been reported. Single doses up to 20 mg/kg have been administered without toxic effects

#### **8.8 Rationale**

Steroid treatment is often wearing and may reduce treatment adherence due to multiple side effects. Currently, there is no alternative treatment available for induction treatment of AIH. There are small case series using cyclophosphamide or intravenous cyclosporine A as an induction treatment, but due to toxic side effects, this only serves as an emergency treatment. The rationale of this trial is to show the efficacy of infliximab in the induction treatment for AIH.

#### **8.9 Risk-Benefit Considerations**

There is substantial need to improve therapeutic options AIH. Previous data has shown treatment effect of infliximab in heavily pre-treated and difficult-to-treat AIH patients. Weighing steroid side effects and side effects by infliximab, it seems defensible to treat patients with AIH with infliximab for a period of 6 months under close monitoring. All aspects of the trial will be conducted in accordance with the Declaration of Helsinki principles, ICH-GCP rules and local laws. The study protocol will be submitted for ethical approval to the responsible ethics committee. All participants must provide written informed consent prior to any study interventions.

Therefore, it appears ethical to test infliximab in treatment-naïve AIH patients. If infliximab shows efficacy in this patient cohort, it will be a treatment alternative for patients with this condition and contraindications towards a high-dose steroid treatment.

## 9 STUDY OBJECTIVES

The primary endpoint: "biochemical remission" is justified as:

- It has been shown in the past, that biochemical remission is associated with increased survival

The primary and secondary endpoints will be determined by primary and secondary measures:

- Laboratory values for AST, ALT and IgG
- Quality of life measured by standardized and validated tools
- Weight
- Elastography in kPa

### 9.1 Primary Objective

The primary objective of the AIH-MAB trial is to show the efficacy of infliximab in inducing remission in treatment-naïve patients with autoimmune hepatitis.

### 9.2 Primary Endpoints

Primary efficacy endpoint: Biochemical remission 6 months after treatment initiation.

### 9.3 Secondary Objectives

Secondary objectives include quality of life, weight and elastography.

### 9.4 Secondary Endpoints

- Changes in quality of life
- Weight changes
- Changes in elastography

### 9.5 Safety Endpoints

Safety endpoints for tolerability will include all adverse events, serious adverse events and clinically relevant adverse laboratory results (including deaths and hospitalisations with date-change – all to be adjudicated), observation of episodes of anaphylactoid reactions or severe infections.

## 10 INVESTIGATIONAL PLAN

### 10.1 Overall Study Design and Plan-Description

The clinical trial is designed as monocentric single armed proof-of-principle study.

I.v. administration of infliximab will be carried out according to standard procedures, infusion will be given at a dose of 5mg/kg bodyweight every 4 weeks.

### 10.2 Discussion of Study Design, Including the Choice of Control Groups

A single-armed study design was chosen as high-dose steroid treatment leads to visible and reported side effects after 4 weeks in the vast majority of patients. Further on, good historical and own data is available from patients treated with standard treatment for comparison. All patients will receive standard treatment with azathioprine and induction treatment with infliximab will be administered instead of steroid treatment.

### 10.3 Selection of Study Population

Autoimmune hepatitis is a rare disease. As only untreated patients are eligible for this study, patients presenting with untreated autoimmune hepatitis meeting the inclusion and exclusion criteria will be offered study participation.

#### 10.3.1 Inclusion Criteria

1. Patients with untreated autoimmune hepatitis diagnosed in accordance to the „simplified criteria for the diagnosis of autoimmune hepatitis“
2. Female patients: Female subjects must be postmenopausal, surgically sterile, or if premenopausal and not surgically sterile, be prepared to use  $\geq 1$  effective method of contraception during the study and for 6 months after the end of treatment visit\*. Accepted methods of contraception are given in section 9.3.2.1.
3. Patients must provide written informed consent and agree to comply with the study protocol.

#### 10.3.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria are met at screening or on Day-1:

1. Age younger than 18 years old or older than 65 years
2. History of severe heart disease or heart failure
3. Active or latent tuberculosis or history of past tuberculosis
4. Active viral, bacterial or parasitemic infection
5. Additional liver disease other than autoimmune hepatitis (including, but not limited to alcoholic liver disease, viral hepatitis, primary sclerosing cholangitis, primary biliary cholangitis, non-alcoholic steatohepatitis), history of alcohol abuse
6. History of decompensation of cirrhosis (ascites, variceal bleeding, encephalopathy)
7. Presence of anti-HBc Titre
8. Known or suspected hepatocellular carcinoma
9. Presence of transjugular intrahepatic portosystemic shunt procedure
10. Hepatorenal syndrome or creatinine  $>2\text{mg/dl}$  at screening
11. Having undergone bariatric surgery
12. Pregnancy or planned pregnancy
13. Chronic obstructive pulmonary disease
14. Other medical conditions that may diminish life expectancy, including known cancers
15. Participation in another investigational product, biologic or medical device study within 30 days prior to screening
16. Mental instability and lack of capability of giving consent.
17. History of known or suspected clinically significant hypersensitivity to azathioprine or bone marrow disease
18. History of the use of infliximab
19. Liver failure (INR  $> 1,5$ , Bilirubine  $> 3\text{x ULN}$ )
20. Body weight  $< 40\text{kg}$  or above  $90\text{kg}$ , BMI  $< 18\text{kg/m}^2$  or  $> 30\text{kg/m}^2$
21. Not willing or not being able to comply with the study procedures
22. Transaminase elevation  $> 1000\text{ U/l}$

23. Application of life vaccines 4 weeks prior to treatment or planned application of life vaccines during the treatment

#### 10.3.2.1 Reproductive Potential

The study population includes female of child-bearing potential (FOCP). FOCP have to agree to comply with the applicable contraceptive requirements of the protocol as named below for the duration of the study or having post-menopausal status or be permanently sterilised (at least 6 weeks post-sterilisation).

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Highly effective contraception is defined as a contraceptive method with failure rate of less than 1 % per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- Combined hormonal contraceptives (with inhibition of ovulation); oral or intravaginal or transdermal
- progesterone-only hormonal contraception (with inhibition of ovulation); oral or injectable or implantable,
- intrauterine device or intrauterine system,
- intrauterine hormone-releasing system system,
- male partner sterilisation at least 6 months prior to the female patient's entry into the study, and a monogamous relationship

#### 10.3.3 Removal of Patients from Therapy or Assessment

The study in its entirety may be discontinued prematurely by the Coordinating Investigator or Sponsor at any time (see below), and/or individual patients may terminate their participation prematurely, or have their participation be terminated by an Investigator.

##### 10.3.3.1 Treatment Discontinuation

Severe infection will lead to treatment discontinuation

##### 10.3.3.2 Premature Treatment Discontinuation

Patients must stop the IMP if the patient experiences any kind of serious hypersensitivity reaction. The patient may remain in the study and continue to attend study visits but must not receive any further administrations of IMP.

Patients should be withdrawn from IMP treatment if they:

- Experience a severe adverse event probably related to study medication, severe infection will always result in discontinuation of study medication.
- Experience an elevation of transaminases >20% over baseline during the first 4 weeks of treatment
- Show a less than 50% decrease of transaminases compared to baseline after 8 weeks of treatment with infliximab.

All patients with premature treatment discontinuation will be offered standard treatment with steroids according to the guidelines

If the study treatment was premature discontinued due to safety reasons, the study site must inform the Sponsor immediately but at latest within 24h regardless if the event fulfils the SAE definition.

##### 10.3.3.3 Withdrawal of Patients from the Study

The following circumstances may lead to discontinuation of the study by an individual patient who will then be recorded as a drop-out. They include, but are not limited to the following issues:

- Withdrawal for personal reasons

## Protocol No. AIH-MAB

- Circumstances in which the health of the patient would be endangered upon continued participation in the study
- An AE, which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures
- Lost-to follow-up

If a patient withdraws from the study at any time either at his or her request or at the Investigator's discretion, an unscheduled visit should be performed and the "End of Study" eCRF section should be used to collect the relevant information. The reason(s) for withdrawal must be recorded on the relevant page of the patient's eCRF and the patient's source data.

It is vital to obtain follow-up data for any patient withdrawn from the study because of an AE. Every effort must be made to undertake protocol-specific safety follow-up procedures. If a patient is discontinued due to an AE, the event should be followed up until resolution or until the event becomes chronic.

If a patient refuses to continue study procedures, the reason for refusal should be fully documented in the patient's source document and recorded in the study-specific eCRF.

It is the patient's right to withdraw from the trial without providing a reason. In this case, the source documents and the eCRF should document the reason for discontinuation as "withdrawal of consent".

#### **10.3.3.4 Criteria for Termination of the Study**

The AIH-MAB trial will be supervised by its Executive Committee and the Steering Committee). All final decisions, however, regarding study termination or modification will be agreed with the Steering Committee and the independent DSMB.

No formal stopping rules will be set. An independent DSMB will in addition monitor safety in the trial. Should safety concerns evolve, they should recommend stopping the study. Stopping the trial for efficacy or futility is not planned.

#### **10.3.3.5 Study Termination**

The Coordinating Investigator and Sponsor may terminate the trial at any time if serious safety concerns rise for the patients. In the case of study termination, participating sites will be informed of the procedures to be followed to ensure adequate consideration is given to the protection of the patient's safety.

The Coordinating Investigator will be responsible for informing the Sponsor within 24 hours and the regulation authorities and Ethics Committee of the trial's termination within 15 days.

### **10.4 Treatments**

#### **10.4.1 Treatments Administered**

##### **10.4.1.1 Experimental Intervention**

The approved indication for Infliximab are rheumatoid arthritis, ulcerative colitis, Crohn's colitis, ankylosing spondylarthritis and psoriasis. Therefore, treatment in this study is off label.

Infliximab should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. Each patient should be observed for adverse effects for at least 120 minutes following each infliximab infusion. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

##### **10.4.1.2 Follow-up per Patient:**

Follow-up for all patients will be according to Table 1 for 6-months after last administration of IMP in the individual patient.

Protocol No. AIH-MAB

**10.4.1.3 Duration of Intervention per Patient:**

Time of each individual treatment administration will be according to product information (SmPC) of infliximab; repetitive administrations will be continued according to the treatment schedule (see Table 1 + 2) during the entire duration of the intervention (6 months).

**10.4.2 Identity of Investigational Medicinal Product(s)**

The test product is manufactured by Pfizer, Germany.

Active ingredient: Infliximab

Strength/packaging: Inflectra 100 mg powder for concentrate for solution for infusion

Excipients: Sucrose  
Polysorbate 80  
Sodium dihydrogen phosphate monohydrate  
Disodium phosphate dihydrate

Dosage form: One vial contains 100 mg of infliximab\*. After reconstitution each mL contains 10 mg of infliximab.

\* Infliximab is a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology.

Storage: as indicated on the label

Manufacturer: PFIZER PHARMA PFE GmbH, Linkstr. 10, 10785 Berlin

Additional information can be found in the SmPC.

**10.4.2.1 Preparation**

Study personnel (at least one physician) not involved in any study assessments (efficacy or safety) will be responsible for preparing and administering the study treatment infusions.

**10.4.2.2 Labelling**

N/A, open label study, labelled by manufacturer

**10.4.2.3 Packaging**

N/A packaged by manufacturer

**10.4.2.4 Storage**

The IMP must be stored in accordance with labelled storage conditions according to the manufacturer.

**10.4.2.5 Drug Accountability**

The PI has the overall responsibility for administering the IMP. The IMP must be administered in the manner specified in the study protocol and the pharmacy manual. As the IMP will be ordered via the pharmacy, no prolonged storage is planned.

At the end of the study or as instructed by the Sponsor all unused stock and empty used boxes are destroyed at the study site under the authority of the Sponsor or sent to a nominated contractor to be destroyed on behalf of the Sponsor.

Based on the entries in the site drug accountability logs, it must be possible to reconcile IMP delivered with those used and returned. One hundred percent of the IMP must be accounted for and all discrepancies investigated and documented.

**10.4.2.6 Patient Compliance**

Compliance must be assessed by the PI, or an Investigator.

Protocol No. AIH-MAB

For IMP administration, compliance must be assessed by observation of dosing. Designated members of the study team will record details on the drug accountability log or other appropriate source documents.

#### **10.4.3 Selection of Doses in the Study**

All patients will receive the IMP in a dose at 5mg/kg bodyweight.

#### **10.4.4 Prior and Concomitant Therapy**

Prohibited therapy: allopurinol, immunosuppressive treatment not associated with the treatment of autoimmune hepatitis.

Concomitant treatment: Any concomitant treatment given for any reason during the course of the study must be recorded on the eCRF and in the patient's medical records, including dosage, start and stop dates and reason for use.

#### **10.4.5 Treatment Compliance**

##### **10.4.5.1 Admission to the Study**

A patient will only be admitted to the study if all inclusion and none of the exclusion criteria are met.

##### **10.4.5.2 Patient Identification**

The PI of each site will keep a record relating the patient numbers and the names of all patient that have given their informed consent, to allow easy checking of data in patient files, when required. This record will also include the date of patient's enrolment and completion, as well as patients who could not be included in the study for whatever reason.

### **10.5 Efficacy and Safety Variables**

#### **10.5.1 Efficacy and Safety Measurement Assessed and Flow Chart**

Details regarding scheduled assessments and procedures to be conducted in this study are provided below. For detailed assessment of schedules refer to Table1.

#### **10.5.2 Appropriateness of Measurements**

##### **10.5.2.1 Screening Procedures**

Written, signed, and dated informed consent from the patient prior to the performance of any study related procedures must be obtained by an Investigator. Patients will first have ample time to read the patient information before an Investigator will start the information and informed consent process.

An Investigator will provide the patients with information of the study and explain the nature of the study point by point. During these verbal patient information process patients have already the opportunity to ask questions. After that, the patients have the opportunity to individually ask questions in a one-to-one meeting with the Investigator. If the Investigator is convinced that the patient understands the nature and risks of the trial, and each patient had ample time for consideration and formulation of questions (which could also mean that the patients first discuss the decision with friends or family members), and if all questions are answered the patient will ask to personally sign the informed consent form. A copy or a second original of the signed informed consent form must be given to the patients for their records.

Screening procedures must be completed between 2 weeks and at the day of receiving the first dose of IMP (baseline visit / Day 1). See Table 1 for a complete list of screening procedures to be performed.

Only an authorised and trained Investigator may decide on the eligibility of the patient.

##### **10.5.2.1.1 Screening Failure**

A screening failure is defined as a patient who has given informed consent and failed to meet at least one inclusion or exclusion criteria or has not been administered IMP as defined by the protocol. Screening failures will not be entered into the clinical database.

Eligible patients who meet all inclusion/exclusion criteria but are unable to participate in the study due to scheduling conflicts/timing will not be considered screening failures. These patients will not be entered into the clinical database.

#### **10.5.2.1.2 Re-screening of Patients**

If patients fail screening, re-screening is permitted if in the opinion of the Investigator the patient may be eligible with a reanalysis of failed variables.

#### **10.5.2.2 Study Examinations**

Assessments are to be performed according to the schedule shown in Table 1 and depend on time-point of IMP administration.

Safety will be evaluated by collecting reported adverse events at regular intervals throughout the study and by the assessment of physical examination findings, vital signs, clinical laboratory parameters, and adverse events.

##### **10.5.2.2.1 Medical and Medication History**

A complete medical and medication history as well as demographic information will be assessed at the time-points indicated in Table 1.

The medical history will be reviewed and recorded, including:

- Medical and Medication History
- Recent ingestion/administration of medications (10 days prior to entering the screening period)
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, haematological, neurological, psychiatric, musculoskeletal and other diseases.
- Demographic information
- Date of Birth
- Sex

##### **10.5.2.2.2 Physical Examination**

A complete symptom-targeted physical examination will be performed at the time-points described in Table 1.

The physical examination may include a review of the following body systems:

- General appearance
- Skin
- Head, Eyes, Ears, Nose and Throat
- Spine/Neck/Thyroid
- Musculoskeletal
- Respiratory
- Cardiovascular
- Neurological
- Abdomen (including liver and kidneys).

Any abnormalities or changes in intensity from the screening visit noted during the review of body systems during follow-up visits have to be documented in the medical record. Clinically significant abnormal findings discovered during a physical examination after screening will be documented either as part of medical history (patient forgot to mention an intermittent medical condition at screening), or as an adverse event.

##### **10.5.2.2.3 Electrocardiogram**

A 12-lead ECG will be done at the time points described in Table 1. Actual ECG assessment times will be documented.

Patients must be resting for at least 5 minutes prior to collecting the ECG. At a minimum, the date and time when the event was performed, the Investigator's assessment and the heart rate, RR, PR, QT, and QRS intervals are to be collected. All clinically significant abnormalities will be recorded in the appropriate source documents.

#### **10.5.2.2.4 Vital Signs**

Measurements of vital signs (systolic and diastolic blood pressure as well as pulse rate) will be performed at the time-points specified in Table 1. All measurements of vital signs must be recorded in the appropriate source documents.

#### **10.5.2.2.5 Height and Weight**

Measurements of height and weight will be performed according to the schedule in Table 1.

Height is measured in centimetres and weight is measured in kilograms. Measurements are to be taken in light clothing and socks (without shoes) with pockets emptied. The patient's height is recorded to the nearest cm and weight is recorded to the nearest 0.1 kg.

#### **10.5.2.2.6 Clinical Laboratory Evaluations**

All laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges will be supplied by the laboratory and used to assess the laboratory data for clinical significance and out-of-range pathological changes. The Investigator must assess out-of-range laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant (NCS) or clinically significant (CS). Abnormal laboratory values that are unexpected or not explained by the patient's clinical condition may be, at the discretion of the Investigator or Sponsor, repeated until confirmed, explained, or resolved as soon as possible.

The following laboratory assessments will be performed:

##### **10.5.2.2.6.1 Bio-Chemistry**

Blood samples (4.9 mL) will be collected at the time points described in Table 1. The following parameters will be assessed:

AST, ALT, Bilirubine, Albumine, Creatinine, C-reactive protein, IgG

##### **10.5.2.2.6.2 Haematology**

A 2.7 mL sample of blood will be drawn into a tube containing potassium ethylene diamine tetra-acetic acid (EDTA) anticoagulant at the time points described in Table 1. The following parameters will be assessed:

Differential blood count

##### **10.5.2.2.6.3 Urine Pregnancy Test**

If applicable, appropriately performed using fresh midstream urine.

##### **10.5.2.2.6.4 Coagulation**

A 2.7 mL sample of blood will be drawn into a tube containing citrate at the time points described in Table 1. The following parameters will be assessed:

INR

##### **10.5.2.2.6.5 Questionnaires**

The SF-12, GAD-7 and PHQ9 questionnaires must be completed as indicated in Table 1. Questionnaires should be completed before any other procedures at each visit.

##### **10.5.2.2.6.6 Concomitant Medication**

Concomitant medication will be assessed at the time points described in Table 1.

#### 10.5.2.2.7 Translational Research

Blood samples will be taken (15 mL EDTA) at the time points described in Table 1 for further analysis in research. These samples will be examined for T-cell activation and cytokine analysis.

#### 10.5.2.2.8 Adverse and Serious Adverse Events Assessments

Patients will be questioned in a general way to ascertain if AEs have occurred (e.g. "Have you had any health problems since the last time you came to the clinic/since you were last questioned?"). This open, standardised questioning should be done discretely in order to prevent patients from influencing each other. Spontaneous reports of AEs will also be recorded as well as AEs that are observed by the Investigator or a staff member.

All AEs will be reviewed, confirmed, and classified by a qualified, designated Investigator.

##### 10.5.2.2.8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An **Adverse Event (AE)** is any untoward medical occurrence in a clinical investigation patient administered an IMP and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, disease or exacerbation of a pre-existing condition temporally associated with the use of a medicinal (test) product, whether or not considered related to the medicinal product (ICH Guidance E2A 1995).

All AEs, including those associated with the protocol, are collected from the time of the first administration of IMP, regardless of the relationship to the investigational medicinal product. All AEs are to be recorded on the appropriate source documents and subsequently will be entered into the AE module of the electronic case report form (eCRF). During the trial, an AE can also occur at times when investigational medicinal product is not taken.

Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made each symptom should be entered as a separate AE.

All AEs have to be recorded until the last trial day according to the clinical trial protocol. If the Investigator becomes aware of a serious AE considered related to the investigational medicinal product, it has to be recorded even if it occurs after finalisation of the clinical trial.

All AEs must be followed up until closure (i.e. the patient's health has returned to his/her baseline status or all variables have returned to normal), an outcome is reached, stabilisation (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained regardless of whether the patient is still participating in the clinical trial and clinical judgment indicates that further follow-up is not warranted. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

##### 10.5.2.2.8.1.1 Severity Categorisation

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of IMP, must be recorded as new AEs.

The medical assessment of severity is determined by using the following definitions:

- Mild:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research patient.
- Severe:** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

The term "severe" is here used to describe the severity/intensity of the specific event; it is not the same as "serious", which is based on patient/event outcome or action criteria.

##### 10.5.2.2.8.1.2 Relationship Categorisation

An Investigator assesses each AE for its relationship to the investigational medicinal product.

## Protocol No. AIH-MAB

The assessment of the relationship of an AE to the administration of investigational medicinal product is a clinical decision based on all available information at the time of and after the occurrence of the event. The factors which may be considered when evaluating the relationship of an AE to the investigational medicinal product include: time from exposure to investigational medicinal product until onset of the event; recovery or improvement on discontinuation of investigational medicinal product; availability of alternative explanations such as underlying or intercurrent diseases; concomitant medications or treatments; pharmacology and pharmacokinetic of the investigational medicinal products; known response pattern for this class of drug; recurrence on reintroduction of the investigational medicinal product.

If there is no valid reason for suggesting a relationship, then the AE should be classified as 'not related'. Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational medicinal product and the occurrence of the AE, then the AE should be considered 'related'. The causality must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship	Definition
Related	Yes	The temporal relationship between the event and the administration of the investigational medicinal product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the patient's medical condition, other therapies, or accident.
Not Related	No	The event can be readily explained by other factors such as the patient's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational medicinal product and the event.

#### 10.5.2.2.8.1.3 Outcome Categorisation

The outcome of AEs must be recorded during the course of the study in the eCRF. Outcomes are as follows:

- Recovered/resolved
- Recovering/resolving
- Resolved with sequel
- Ongoing/not recovered/not resolved
- Fatal
- Unknown

#### 10.5.2.2.8.1.4 Clinical Laboratory Evaluations

A change in the value of a safety laboratory investigation can represent an AE if the change is clinically relevant or if, during treatment with the IMP, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the IMP, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (e.g., concomitant disease) is found for the pathological laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a patient, whether a change in a laboratory parameter is clinically significant and therefore represents an AE.

#### 10.5.2.2.8.1.5 Pregnancy

Any report of pregnancy recorded for any female patient or for a female partner of a male patient should be reported to the Sponsor within the same timelines as an SAE, i.e., immediately (within 24 hours of awareness/ within 30 days of IMP administration), but a separate form should be used.

Protocol No. AIH-MAB

Patients with a pregnancy occurring during dosing will be discontinued from study medication and follows up till birth.

#### **10.5.2.2.8.1.6 Abuse, Misuse, Overdose, and Medication Error**

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the Sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE.

Abuse - Persistent or sporadic intentional intake of a study medication at a dose higher than prescribed per protocol (but below the dose defined for overdose) or when used for non-medical purpose (e.g. altering one's state of consciousness)

Misuse - Intentional or unintentional use of a study medication other than as directed or indicated at any dose, which is at or below the dose defined for overdose. (Note: this includes a situation where the study medication is not used as directed at the dose prescribed by the protocol.)

Overdose - Intentional or unintentional intake of a dose of study medication higher than the protocol prescribed dose for each patient.

Medication Error - A mistake made in prescribing, dispensing, administration, and/or use of the study medication. For studies, medication errors are reportable only as defined below.

Administration of an expired product should be considered as a reportable medication error when associated with an AE, or if otherwise appropriate.

Cases of patients missing doses of product are not considered reportable as medication errors.

#### **10.5.2.2.8.2 Serious Adverse Event (SAE) Procedures**

##### **10.5.2.2.8.2.1 Reporting Procedures**

All SAE which occur **from individual administration until 30 days after** must be reported by the Investigator to the Safety Management Desk within 24 hours of the first awareness of the event. All SAE follow-up reports must be reported in a timely manner. The Investigator must complete, sign, and date the electronic Serious Adverse Event Form provided in the eCRF and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: source documents are not to be sent unless requested) and send the form via the eCRF to the Sponsor's Safety Desk:

Name: CTC North Safety Management  
 Fax number: +49 40 524719 222  
 Phone number: +49 40 524719 225  
 Email: [pharmacovigilance@ctc-north.com](mailto:pharmacovigilance@ctc-north.com)

##### **10.5.2.2.8.2.2 Serious Adverse Event (SAE) Definition**

A Serious Adverse Event (SAE) is any untoward medical occurrence (whether considered to be related to IMP or not) that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an Important Medical Event, i.e., an event that may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Events of severe Infections and a relevant clinical increase of liver enzymes must be considered an "Important Medical Event" even if no other serious criteria apply.

Hospitalisations which are the result of elective or previously scheduled surgery for pre-existing conditions which have not worsened after initiation of treatment should not be classed as SAEs.

However, complication(s) resulting from a hospitalisation for an elective or previously scheduled surgery that meet serious criteria must be reported as a SAE(s).

Protocol No. AIH-MAB

**10.5.2.2.8.2.3 SAE Onset and Resolution Dates**

The onset date of the SAE is defined as the date at which the event meets serious criteria. SAE Stop Date is defined as the date at which the event no longer meets serious criteria. The resolution date is the date at which the symptoms are resolved or resolved with sequel/event is no longer present.

**10.5.2.2.8.2.4 Fatal Outcome**

Any SAE that results in the patient's death (i.e. the SAE was noted as the primary cause of death) should have fatal checked as an outcome and the resolution date of death recorded as the resolution date. For all other events ongoing at time of death that did not contribute to the patient's death, the outcome should be considered not resolved, without a stop date recorded.

For any SAEs that result in the patient's death or any ongoing events at the time of death, the action taken with the IMP should be recorded as "dose not changed" or "not applicable" (if the patient never received IMP).

**10.5.2.2.8.2.5 Serious Adverse Reaction (SAR)**

An AE (expected or unexpected) that is both serious and, in the opinion of the reporting Investigator or Sponsors, believed to be possibly, probably or definitely due to an IMP or any other study treatments, based on the information provided.

**10.5.2.2.8.2.6 Suspected Unexpected Serious Adverse Reaction (SUSAR)**

A SUSAR is a SAE that is unexpected and thought to be possibly, probably or definitely related to an IMP. An Event is unexpected, if the nature or severity is not consistent with the applicable product information (summary of product characteristics).

**10.5.2.2.8.2.7 Regulatory Agency, Independent Ethics Committee, and Investigative Site Reporting**

The Sponsor is responsible for SUSAR reporting to the relevant Regulatory Authorities, Ethics committee and Investigators within 15 days or in in case the event is fatal or life threatening within 7 days

**10.5.3 Primary efficacy variable(s)****10.5.3.1 Outcome Measures**

To generate meaningful data, complete biochemical remission at 6 months is chosen as outcome measure.

**10.5.3.2 Safety Variables**

Assessment of safety is performed for the safety collective Safety data include:

- Adverse events (including changes from baseline in physical examination findings)
- Clinical laboratory results, especially a rise in transaminases of more than 30% above baseline levels.
- Vital signs

The safety evaluation will be based upon the review of the individual values (potentially clinically important abnormalities) and descriptive statistics (summary tables, graphics).

**10.5.3.2.1 Adverse Events**

The adverse events will be listed per patient using MedDRA terminology (lower level term, preferred term and system organ class) and will be reported in tables summarising the frequency of patients with adverse events and adverse events by treatment and body system, the number of adverse events and patients with adverse events by treatments and the characteristics of adverse events.

For haematology, clinical laboratory and urine analysis parameters deviations from the reference ranges will be summarised in frequency tables in the CSR.

**10.5.3.2.2 Clinical Laboratory**

All relevant clinical laboratory variables obtained during screening, final examination or the clinical trial periods will be reported in appropriate tables together with descriptive statistics in the CSR.

Protocol No. AIH-MAB

#### **10.5.3.2.3 Vital Signs**

For blood pressure and pulse rate descriptive statistics will be listed by sampling times (screening and follow-up) according to the data captured in the eCRF.

#### **10.5.3.2.4 ECG**

The results of the 12-lead ECG will be listed by sampling times according to the data captured in the eCRF.

### **10.6 Data Quality Assurance**

#### **10.6.1 Quality Assurance System**

Protocol development, case report form and trial master file, investigator site file, content of patient information and consent, application for ethics approval, data processing, central and on-site monitoring, and evaluation will follow the Standard Operating Procedures (SOP) of the CRO, and the central data management. Standard phases of the study may be subject to audits by the QAU of the Sponsor, the Monitor or the study site. Results of these audits as well as any objections will be reported directly to the Sponsor.

#### **10.6.2 Monitoring**

The CRO or a designee will be responsible for trial monitoring. A risk-based monitoring strategy will be implemented and further described in the monitoring manual. During trial conduct, remote monitoring procedures will be combined with on-site monitoring visits in order to achieve high protocol compliance and data quality, as well as to ensure patients' safety and rights. Source data verification will be performed on 50 % of enrolled patients and 50 % of data. The frequency of the monitoring visits will depend on the trial site's recruitment rate and on whether problems have been detected with the site, either by prior on-site visits or by central monitoring.

The detailed extent of the monitoring will be defined in the monitoring plan.

#### **10.6.3 Documentation and Data Collection**

eCRF will be prepared to report at least all clinical data required by the protocol.

Site staff will transfer the study data from the source documents into the eCRF. Site staff will check eCRF entries for completeness. Completed eCRF modules will be electronically signed by an Investigator in order to ensure data entry accuracy.

Corrections to source data documents will be dated and initialled. Reasons for the corrections should be given. Corrections to eCRF entries must be electronically signed and reasons for the corrections must be provided. The date on which the correction was performed is automatically recorded by the system's audit trail.

A study monitor will review the defined eCRF data for completeness and accuracy during the monitoring visits (source data verification (SDV)). The study monitor will point out any discrepancies between source data and the data captured in the eCRF. The monitor will issue electronic queries to site staff to initiate discrepancy resolution. Discrepancies which require eCRF data corrections have to be resolved by authorised site personnel by answering these monitoring queries. Discrepancies which require data corrections have to be resolved by authorised site personnel.

#### **10.6.4 Data Management**

Data management will check predefined eCRF entries as defined in the data management plan (DMP). Quality control and data validation procedures such as programmed automatic edit and consistency checks ensure data validity and accuracy immediately at the point of entry into the clinical database. The database application which is used to capture electronic study data is fully CFR part 11 compliant. Thus, it is access restricted, demands electronic signatures, maintains an electronic audit trail and provides appropriate backup functionalities. Details of the application and eCRF configuration and all further data management procedures will be described in the DMP.

The database will be locked after all queries and discrepancies that may occur during data entry are resolved.

Protocol No. AIH-MAB

Upon request safety reports and interim analysis will be generated and provided to the respective members of the DSMB.

After database lock, the data in the study database will be exported and SAS datasets will be compiled for statistical analysis. The data will be exported in SAS transport files or other SAS-compatible format and transferred electronically to the responsible biometrician for statistical analysis. The locked SAS database will be used to generate the patient listings, tabulations, and analyses for the CSR.

### **10.6.5 Archival of documents**

The Sponsor will maintain the trial documents and take measures to prevent accidental or premature destruction of these documents. All documents related to the study will be retained until at least 15 years after the end of the study.

## **10.7 Statistical Methods Planned in the Protocol and Determination of Sample Size**

### **10.7.1 Statistical and Analytical Plan**

#### **10.7.1.1 Software to be Used**

All statistical analyses will be carried out using the software ADDPLAN Version 6.1.1

#### **10.7.1.2 Eligibility for Statistical Evaluation**

Eligibility of patients will be determined in a BRM before statistical analysis will be performed.

##### **10.7.1.2.1 Analysis Population**

###### **10.7.1.2.1.1 PP Population**

The primary endpoint in AIH-MAB will be analysed as intended-to-treat. Nevertheless, a per-protocol analysis is also planned in subsequent analyses.

###### **10.7.1.2.1.2 Safety Population**

All patients receiving at least once the IMP will be included into the safety evaluation (safety collective).

##### **10.7.1.2.2 Statistical Analyses**

All statistical analyses will be carried out under the supervision of the trial statistician Prof. Wegscheider. The primary analysis population will be intention-to-treat. All details including the definition of the analysis populations will be detailed in a statistical analysis plan, which will be finalised prior to database lock. Baseline variables will be described by treatment group using appropriate summary statistics.

###### **10.7.1.2.2.1 Primary and Secondary Endpoint**

The primary endpoint "biochemical remission" is a composite endpoint. All analyses will be adjusted for important prognostic factors.

###### **10.7.1.2.2.2 Dropouts**

In the primary analyses dropout will be dealt with as independent right censoring. In case of substantial dropout this assumption will be investigated in sensitivity analyses. Missing values in baseline variables will be dealt with by multiple imputation techniques. Time to event outcomes will be visualised by Kaplan-Meier curves stratified by treatment group.

###### **10.7.1.2.2.3 Safety Endpoints**

Adverse event data will be summarised by treatment group using standard procedures. The primary analysis population will be intention-to-treat. All details including the definition of the analysis populations will be detailed in a statistical analysis plan, which will be finalised prior to database lock and unblinding.

## 10.7.2 Determination of Sample Size

### 10.7.2.1 Proposed Sample Size

The main hypotheses of the phase IIa study state that infliximab treatment in AIH patients results in a response rate of at least 50%, whereas a much higher response rate of at least 80% seems likely. The one-sided test problem is thus formulated as

$$H_0: p \leq 0.5 \text{ versus } H_1: p > 0.8,$$

where  $p$  denotes the unknown true response rate. The above null hypothesis is tested with a one-sided Binomial-test at a local significance level of 10% which is a common boundary in the context of a phase IIa study.

All other performed analyses will be of descriptive nature. Depending on the scale level of the underlying variable means and standard deviations, medians and quartiles or absolute and relative frequencies will be reported.

Statistical analysis will be performed at the Institute of Medical Biometry and Epidemiology (Medical Biometry Unit headed by Prof. Dr. Wegscheider) at the University Medical Centre Hamburg-Eppendorf.

### 10.7.2.2 Compliance / Rate of Loss to Follow Up

As the treatment is an on-site infusion treatment, adherence is granted for the infusion therapy as soon as the study participant shows up. Adherence to additional oral standard treatment with azathioprine will be collected by self-reported patient diaries. Traditionally, patients with AIH do not belong to a risk group prone to non-adherence. It has been reported that non-adherence only occurs in about 20% of patients in a real-life setting, and general study experience from patients with autoimmune liver diseases show that adherence in clinical studies is usually >90%.

## 10.8 Changes in the conduct of the study or planned analysis

Modifications of the protocol are permitted only if they are authorised by the Sponsor and the Coordinating Investigator in writing.

Deviations and changes to the study protocol will be classified by the Sponsor and the study site as:

Note-to-File: This refers to clarifications which are not considered changes of the protocol.

Study protocol amendment: This refers to substantial changes of the protocol. If they fulfil the criteria as set out in appropriate law they need to be approved by the Ethics Committees or the Competent Authorities. Changes to the study protocol may also induce revision of the patient information sheet/informed consent form. Accordingly, patients undergoing trial assessment procedures at the time of implementation of the change have to be given the amended version and have to be asked for consent to continue on this amended trial.

## 10.9 DSMB

A Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC) will be constituted to protect the safety of study participants. A DSMB is a group of external independent experts assessing the progress, safety data, and, if needed, critical efficacy endpoints of a clinical study.

The DSMB will receive CRF data in the form of tables and listings and adjudicate on patient status changes. The DSMB should meet after the first 3 patients received the 3. dosing or in the event of an SAE.

The data should include, but is not limited to, demographics, patient enrolment, baseline characteristics, AE data, SAE data (by severity and causality), laboratory data, dose adjustments, protocol adherence, and patient withdrawals.

The DSMB will evaluate the progress of the trial; assess data quality and timeliness, participant recruitment, accrual and retention, and participant risk versus benefit. In addition, the DSMB/DMC will monitor external factors relevant to the trial, for example scientific and therapeutic developments that may affect participant safety or ethical status. Based on the observed benefits or adverse effects, the DSMB will make recommendations to the Sponsor concerning continuation, termination or modifications of the trial.

Protocol No. AIH-MAB

The Sponsor will establish a Charta document explaining the working procedures for the DSMB.

In addition, a DSMB meeting will be conducted whenever safety relevant data occur that might have an influence on the trial.

## 11 REPORTS

All reports to the Sponsor will be in English. The Sponsor will receive the original CSR. The CSR is the property of the Sponsor. Publication of the report or of part of it may only be allowed when authorised by the Sponsor in consultation with the study site.

A yearly safety report (DSUR) will be issued.

### 11.1 Clinical Study Report

All clinical, analytical and statistical results will be presented in a CSR. The outline of this report will be according to the ICH-GCP E3 document "Structure and Content of Clinical Study Reports" of July 17, 1996.

## 12 REFERENCES

1. **Hennes EM, Zeniya M, Czaja AJ, Pares A, Dalekos GN, Krawitt EL, Bittencourt PL, Porta G, Boberg KM, Hofer H, Bianchi FB, Shibata M, Schramm C, Eisenmann de Torres B, Galle PR, McFarlane I, Dienes HP, Lohse AW.** 2008. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* **48**:169-176.
2. **Kirk AP, Jain S, Pocock S, Thomas HC, Sherlock S.** 1980. Late results of the Royal Free Hospital prospective controlled trial of prednisolone therapy in hepatitis B surface antigen negative chronic active hepatitis. *Gut* **21**:78-83.
3. **Gronbaek L, Vilstrup H, Jepsen P.** 2014. Autoimmune hepatitis in Denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. *J Hepatol* **60**:612-617.





# STUDY PROTOCOL

<b>Phase IIa proof-of-principle study for the            induction treatment of autoimmune hepatitis using infliximab            AIH-MAB</b>	
EudraCT No.	2017-003311-19
Protocol No.	AIH-MAB
Version/Date	Version 3.0, 27.11.2017
Sponsor	University Medical Centre Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg Germany
Coordinating Principal Investigator	Dr. Christina Weiler-Normann, MD I.Department of Medicine, University Medical Centre Hamburg-Eppendorf  Prof. Dr. Ansgar W. Lohse, MD (Deputy-LKP) I.Department of Medicine, University Medical Centre Hamburg-Eppendorf
Executive Committee	<u>Chairs:</u> Prof. Dr. Ansgar W. Lohse (Academic PI) Dr. Christina Weiler-Normann (Academic Co-PI)  <u>Executive Committee Members:</u> Prof. Dr. Christoph Schramm Prof. Dr. Marilyn Addo  <u>Comment:</u> Members of the executive committee will also be members of the steering committee, which in addition to the members of the executive committee will include the coordinating principal investigators. The steering committee will include also Prof. Wegscheider as trial statistician.

**CONFIDENTIALITY STATEMENT**

The information provided in the following document is confidential and is only available for review to Principal Investigators, the Ethics Committee and the Competent Authorities. No disclosure should take place without the written authorisation from the Sponsor, except to the extent necessary to obtain informed consent from potential patients or to obtain approval of this protocol by an Ethics Committee or Regulatory Authorities.

Protocol No. AIH-MAB

**SIGNATURES**

This protocol has been approved by the Sponsor:

**Sponsor Signature**

\_\_\_\_\_  
Sponsor Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Sponsor Name

**Coordinating Principal Investigator**

I hereby confirm that I have acknowledged the protocol and agree to conduct the study in compliance with the protocol.

\_\_\_\_\_  
Coordinating Principal Investigator Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Coordinating Principal Investigator Name

\_\_\_\_\_  
Deputy-Coordinating Principal Investigator Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Deputy-Coordinating Principal Investigator Name

Protocol No. AIH-MAB

**Statistician Signature**

---

Statistician Signature

---

Date

---

Statistician Name

Protocol No. AIH-MAB

**3 SYNOPSIS**

<b>Title of Study:</b>	Phase IIa proof of principle study for the induction treatment of autoimmune hepatitis using infliximab AIH-MAB
<b>Coordinating Principal Investigators</b>	Dr. Christina Weiler-Normann Prof. Dr. Ansgar W. Lohse (Deputy-LKP)
<b>Executive Committee</b>	<p><u>Chairs:</u> Prof. Dr. Ansgar W. Lohse (Academic PI) Dr. Christina Weiler-Normann (Academic Co-PI)</p> <p><u>Executive Committee Members:</u> Prof. Dr. Christoph Schramm Prof. Dr. Marilyn Addo</p> <p><u>Comment:</u> Members of the executive committee will also be members of the steering committee. The latter will include also Prof. Wegscheider as trial statistician, and all members of the steering committee of the AIH-MAB trial</p>
<b>Study centre:</b>	I. Department of Medicine University Medical Centre Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg, Germany
<b>Protocol-No.</b>	AIH-MAB
<b>EudraCT-No.</b>	2017-003311-19
<b>Study Period</b>	First patient in to last patient out (months): 24 Duration of the entire trial (months): 24 Recruitment period (months): 12 FPFV: Q1/2018 LPLV: Q4/2019
<b>Phase of development:</b>	Phase IIa
<b>Primary Objective:</b>	The primary objective of the AIH-MAB trial is to show that infliximab induces biochemical remission in treatment-naïve patients with autoimmune hepatitis
<b>Secondary Objectives:</b>	Secondary objectives include quality of life during the trial, decreasing liver elastography as a marker for intrahepatic inflammation and the absence of weight gain
<b>Tertiary Objectives:</b>	Tertiary objectives include immunological analysis of immune activation of peripheral blood mononuclear cells
<b>Study Design:</b>	Proof-of-principle single-armed monocentric pilot study.

<p><b>Treatment:</b></p>	<p><b><u>Test product:</u></b>          Inflectra® (Infliximab)</p> <p><b><u>Experimental intervention:</u></b>          A total of 12 patients will receive a dose of 5mg/kg bodyweight infliximab at time points 0, 2 weeks, 6 weeks and every 4 weeks thereafter for a total period of 6 months. Infliximab is administered intravenously. All patients will receive standard maintenance treatment according to clinical practice guidelines starting in week 2.</p> <p><b><u>Follow-up per patient:</u></b>          Follow-up for all patients will be until the individual patient recruited has completed 6 months' follow-up.</p> <p><b><u>Duration of intervention per patient:</u></b>          Infliximab is administered as infusion over a time of 1-2 hours. Additionally, 2 hours of monitoring is warranted after the infusion. Emergency equipment as well as trained personell will be present.</p> <p><b><u>Experimental and/or control off label or in label in Germany:</u></b>          Infliximab is not approved for the induction treatment in autoimmune hepatitis, therefore, treatment is off label.</p>
<p><b>Number of patients:</b></p>	<p><u>To be assessed for eligibility</u> (n = 50)</p> <p><u>To be allocated to trial</u> (n = 12)</p> <p><u>To be analysed</u> (n = 12)</p>

**Diagnosis and main criteria for inclusion:****Key inclusion criteria:**

1. Patients with untreated autoimmune hepatitis diagnosed in accordance to the „simplified criteria for the diagnosis of autoimmune hepatitis“
2. Female patients: Female subjects must be postmenopausal, surgically sterile, or if premenopausal and not surgically sterile, be prepared to use  $\geq 1$  effective method of contraception during the study and for 6 months after the end of treatment visit\*.
3. Must provide written informed consent and agree to comply with the study protocol

\*Effective methods of contraception are considered to be double barrier method (i. e. condom or diaphragm with spermicide), intrauterine device, vasectomy (partner), hormonal (contraceptive pill, match, intramuscular implant or injection or abstinence if in line with the preferred lifestyle of the subject.

**Key exclusion criteria:**

1. Age younger than 18 years old or older than 65 years
2. Patients with known hypersensitivity to any constituent of the product
3. History of severe heart disease or heart failure. NYHA class III or IV, severe uncontrolled cardiac disease (unstable angina, arrhythmias, clinical significant electrocardiogram abnormalities) or myocardial infarction within 6 months prior to randomization
4. Patients with a recent exposure to persons with active tuberculosis, patients with a positive result in a screening test for latent TB (Quantiferon Test) as well as patients with a history of tuberculosis or active tuberculosis
5. Patients with a current or past history of chronic infection with hepatitis B, hepatitis C, or infection with human immunodeficiency virus (HIV) -1 or -2 or who has a positive result in the screening test for those infections; patients who have an acute infection requiring oral antibiotics within 2 weeks before randomization, other serious infection within 6 months before randomization or a history of recurrent herpes zoster or other chronic or recurrent infection within 6 weeks before randomization; patients with a history of tuberculosis or a current diagnosis of tuberculosis or other granulomatous infections or other severe or chronic infection (such as sepsis, abscess or opportunistic infection, or invasive fungal infection such as histoplasmosis) or a past diagnosis without sufficient documentation of complete resolution following treatment.
6. Additional liver disease other than autoimmune hepatitis (including, but not limited to alcoholic liver disease, viral hepatitis, primary sclerosing cholangitis, primary biliary cholangitis, non-alcoholic steatohepatitis), history of alcohol abuse
7. History of decompensation of cirrhosis (ascites, variceal bleeding, encephalopathy)
8. Known or suspected hepatocellular carcinoma, history of any malignancy within 5 years prior to randomization except completely excised and cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma or cutaneous squamous cell carcinoma, history of lymphoma or lymphoproliferative disease or bone marrow hyperplasia
9. Presence of transjugular intrahepatic portosystemic shunt procedure
10. Hepatorenal syndrome or creatinine  $>2\text{mg/dl}$  at screening
11. Subjects that have undergone bariatric surgery
12. Female patients who are currently pregnant, breastfeeding or planning to become pregnant or breastfeed within 6 months of the last dose of study drug

	<ol style="list-style-type: none"><li>13. Any uncontrolled clinically significant respiratory disease (in the opinion of the investigator) including but not limited to chronic obstructive pulmonary disease, asthma, bronchiectasis or pleural effusions</li><li>14. Uncontrolled hypertension (as defined by systolic blood pressure <math>\geq 160</math> mmHg or diastolic blood pressure <math>\geq 100</math> mm Hg)</li><li>15. Diabetes mellitus unless on a stable dosing regimen for at least 4 weeks prior to screening</li><li>16. Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain Barre syndrome</li><li>17. Any conditions significantly affecting the nervous system (i. e. neuropathic conditions or nervous system damage)</li><li>18. Any other serious or chronic medical or psychiatric condition that may increase the risk associated with study participation or investigational product administration or that may interfere with the interpretation of study results</li><li>19. Other medical conditions that may diminish life expectancy, including known cancers</li><li>20. Participation in another investigational product, biologic or medical device study within 30 days or 5 half-lives, whichever is longer prior to screening</li><li>21. Mental instability and lack of capability of giving consent.</li><li>22. History of known or suspected clinically significant hypersensitivity to azathioprine or bone marrow disease</li><li>23. History of the use of infliximab</li><li>24. Liver failure (INR <math>&gt; 1,5</math>)</li><li>25. Body weight <math>&lt; 40</math>kg or above 90kg, BMI <math>&lt; 18</math>kg/m<sup>2</sup> or <math>&gt; 30</math>kg/m<sup>2</sup></li><li>26. Patients not willing or able to comply with the study procedures</li><li>27. Transaminase elevation <math>&gt; 1000</math> U/l</li><li>28. Application of live vaccines 4 weeks prior to treatment or planned application of live vaccines during the treatment</li></ol>
--	--

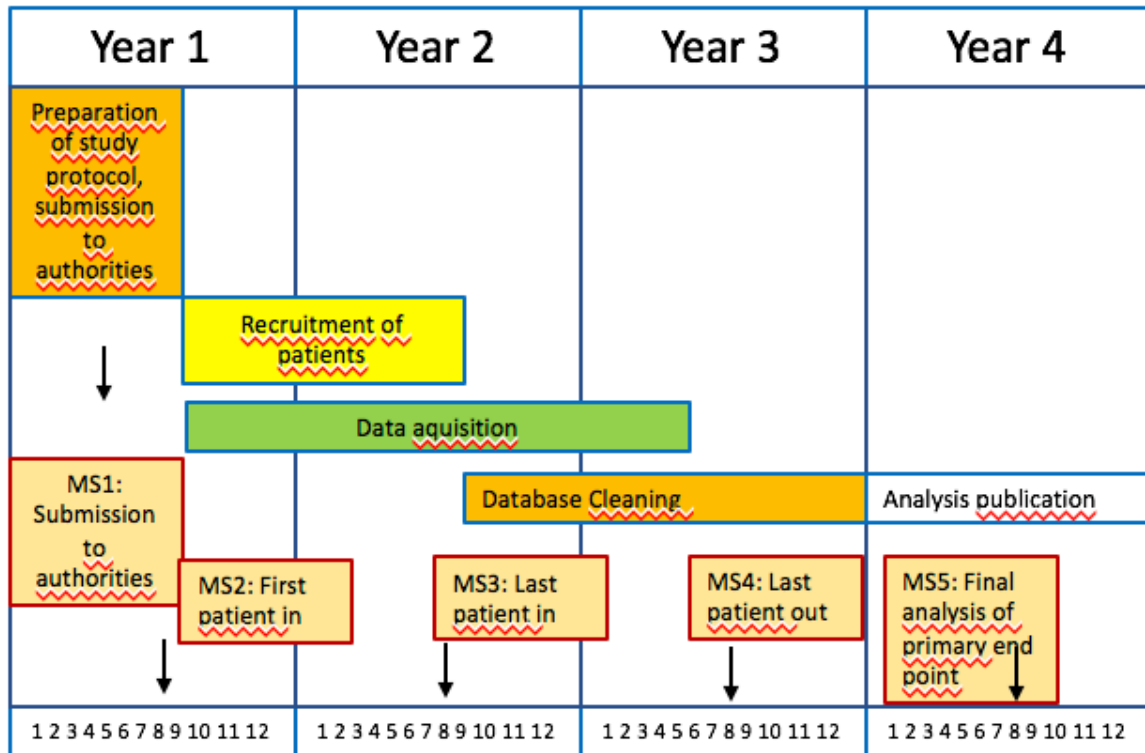
<p><b>Criteria for evaluation:</b> <b>Efficacy:</b></p>	<p><b><u>Primary Endpoints:</u></b></p> <ul style="list-style-type: none"> <li>Biochemical remission of autoimmune hepatitis defined as normalization of AST, ALT and IgG at month 6.</li> </ul> <p><b><u>Secondary Endpoints:</u></b></p> <ul style="list-style-type: none"> <li>Stable Quality of life (using standardized tools including the GAD-7, PHQ-9 and SF-12) at week 0, 4, 12, 24 and 48.</li> <li>Decrease in Elastography</li> <li>Absence of weight gain</li> </ul> <p><b><u>Tertiary Endpoints:</u></b></p> <ul style="list-style-type: none"> <li>Reduction of immune activation as shown in in-vitro experiments performed on peripheral blood mononuclear cells</li> </ul>
<p><b>Safety:</b></p>	<p>Percentage of patients meeting key safety endpoints, as well as assessment of adverse drug reactions.</p>
<p><b>Statistical methods:</b></p>	<p><b><u>Efficacy / test accuracy:</u></b></p> <p>The primary endpoint “biochemical remission” is a composite endpoint including the normalization of AST, ALT and IgG. As this is a proof-of-principle study, efficacy of at least 50%, but more likely 80% will be assumed.</p> <p><b><u>Description of the primary efficacy / test accuracy analysis and population:</u></b></p> <p>The primary analysis will be intention-to-treat. All details on the analyses, including the definition of the analysis populations, will be detailed in a statistical analysis plan, which will be finalised prior to database.</p> <p><b><u>Effect size assumed for power calculation:</u></b></p> <p>To assess the main hypotheses of the phase IIa study, the required sample size to achieve 80% power with a one-sided Binomial test at a significance level of 10% a total number of 12 patients are required (calculated with the Software ADDPLAN, Version 6.1.1). The above null hypothesis can be rejected at the level of 10% whenever at least 9 out of 12 patients show a response. In this case the estimated response rate is given by 75.0% and the one-sided 90%-confidence interval would be given as [52.5%; 100.0%] All other performed analyses will be of descriptive nature and therefore no formal sample size calculation can be made,</p> <p><b><u>Safety:</u></b></p> <p>Will be ascertained via the assessment of key safety endpoints.</p> <p><b><u>Secondary endpoints:</u></b></p> <p>Only descriptive analyses will be performed, no formal sample size can be made.</p>

**STUDY SCHEDULES:** Table 1:

Phase of study	Screening	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11 Follow-up	Visit 12/ End of Study
Point in time	- 2 wks to Day -1	- 2 wks to Day -1	Day 0	Week 1 +/- 1 day	Week 2 +/- 1 day	Week 4 +/- 3 days	Week 6 +/- 3 days	Week 8 +/- 3 days	Week 12 +/- 3 days	Week 16 +/- 3 days	Week 20 +/- 3 days	Week 24 +/- 3 days	Week 36 +/- 1 week1	Week 48 +/- 1 week1
Informed Consent	✓													
I/E Criteria	✓	✓												
Medical History & Demographics	✓													
Physical Examination <sup>a</sup>	✓	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓ <sup>a</sup>	✓
Height & Weight	✓	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>	✓ <sup>b</sup>
Vital Signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood tests as routine in AIH	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
12-lead ECG	✓					✓			✓					
Urine Pregnancy (if applicable)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Quantiferon® test	✓													
Blood test for immunological analysis	✓		✓		✓	✓		✓	✓	✓	✓	✓	✓	✓
Infusion of infliximab			✓		✓		✓	✓	✓	✓	✓	✓		
Elastography		✓							✓			✓	✓	✓
QoL Questionnaire		✓	✓	✓		✓		✓	✓	✓	✓	✓	✓	✓
Adverse Events/Severe adverse event & Hospitalisation & Concomitant medication			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

<sup>a</sup> Symptom-targeted physical examination;<sup>b</sup> Only weight

**Table 2 (detailed Trial Timeline Flow):**



**4 TABLE OF CONTENTS**

1	TITLE PAGE .....	1
3	SYNOPSIS .....	5
4	TABLE OF CONTENTS .....	13
5	LIST OF ABBREVIATIONS .....	15
6	ETHICS .....	16
6.1	Ethics Committee or Institutional Review Board .....	16
6.2	Ethical Conduct of the Study .....	16
6.3	Patient Information and Informed Consent .....	16
6.4	Confidentiality .....	16
6.5	Insurance .....	16
6.6	Publication Policy .....	16
6.7	Qualification of the Investigator .....	16
7	INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE .....	18
7.1	The Medical Problem .....	20
7.1.1	Prevalence, Incidence, Mortality .....	20
7.1.2	Burden of Disease .....	20
7.1.3	Improvement of Therapy / Impact of the Trial .....	20
7.2	Pharmacological Classification .....	20
7.3	Clinical Use .....	20
7.4	Human Pharmacodynamics .....	20
7.5	Human Pharmacokinetics .....	21
7.6	Preclinical Results .....	21
7.7	Cautions and Tolerability .....	21
7.7.1	Contraindications .....	21
7.7.2	Special Warnings and Preventive Measures for the Treatment .....	21
7.7.3	Side Effects .....	24
7.7.4	Overdose .....	27
7.8	Rationale .....	27
7.9	Risk-Benefit Considerations .....	27
8	STUDY OBJECTIVES .....	28
8.1	Primary Objective .....	28
8.2	Primary Endpoints .....	28
8.3	Secondary Objectives .....	28
8.4	Secondary Endpoints .....	28
8.5	Safety Endpoints .....	28
9	INVESTIGATIONAL PLAN .....	29
9.1	Overall Study Design and Plan-Description .....	29
9.2	Discussion of Study Design, Including the Choice of Control Groups .....	29
9.3	Selection of Study Population .....	29
9.3.1	Inclusion Criteria .....	29
9.3.2	Exclusion Criteria .....	29
9.3.3	Removal of Patients from Therapy or Assessment .....	30
9.4	Treatments .....	32
9.4.1	Treatments Administered .....	32

## Protocol No. AIH-MAB

9.4.2	Identity of Investigational Medicinal Product(s) .....	32
9.4.3	Selection of Doses in the Study .....	33
9.4.4	Prior and Concomitant Therapy .....	33
9.4.5	Treatment Compliance .....	33
9.5	Efficacy and Safety Variables .....	33
9.5.1	Efficacy and Safety Measurement Assessed and Flow Chart .....	33
9.5.2	Appropriateness of Measurements .....	34
9.5.3	Primary efficacy variable(s) .....	39
9.6	Data Quality Assurance .....	40
9.6.1	Quality Assurance System .....	40
9.6.2	Monitoring .....	40
9.6.3	Documentation and Data Collection .....	40
9.6.4	Data Management .....	41
9.6.5	Archival of documents .....	41
9.7	Statistical Methods Planned in the Protocol and Determination of Sample Size .....	41
9.7.1	Statistical and Analytical Plan .....	41
9.7.2	Determination of Sample Size .....	42
9.8	Changes in the conduct of the study or planned analysis .....	42
9.9	DSMB .....	42
10	REPORTS .....	43
10.1	Clinical Study Report .....	43
11	REFERENCES .....	43

**5 LIST OF ABBREVIATIONS**

AE	Adverese event
AIH	Autoimmune Hepatitis
ALT	Alanine-Aminotransferase
AST	Aspartate-Aminotransferase
BCG	Bacillus Calmette-Guerin
BMI	Body Mass Index
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
DMP	Data management plan
DNA	Desoxyribonuclease
ECG	Electrocardiogramme
e.g.	for example
FOCP	Females of child bearing potential
FSH	Follicle stimulating hormone
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
I/E	Inclusion/Exclusion
IgG	Immunglobulin G
IMP	Investigational Medical Product
i.e.	that is
INR	International normalized ratio
kPa	kiloPascal
PI	Prinicpal investigator
QoL	Quality of Life
SAE	Severe adverse event
SAR	Serious adverse reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TNF	Tumor necrosis factor alpha

## 6 ETHICS

### 6.1 Ethics Committee or Institutional Review Board

This study will be planned and performed in accordance with

- The Declaration of Helsinki in its version of Fortaleza, 2013 as well as AMG and GCP
- The EU Clinical Trial Directive 2001/20/EC;
- The EU Clinical Trial Directive 2001/83/EC;
- The "Note for Guidance on Good Clinical Practice" (CPMP/ICH/135/95 of January 17, 1997);

and other applicable laws.

### 6.2 Ethical Conduct of the Study

The Sponsor authorises CTC North or one of its designees to make all necessary applications.

CTC North or a designee will submit, among other documents, the study protocol, the patient information and the informed consent form to the Ethics Committee and request for approval (favourable opinion). CTC North or a designee will provide the clinical trial application to the Competent Authority. The approval of both, the Ethics Committee and the Competent Authority must be obtained prior to the start of any study related intervention.

### 6.3 Patient Information and Informed Consent

An Investigator will explain to the patients the nature, significance and implications of the study prior to the clinical examination. He will explain all methods, rules of conduct and any restrictions which may apply. Possible effects and side effects will be discussed. Patients will be informed that they are free to withdraw from the study at any time, without giving any reason for doing so. They must be able to understand the full implications of their decision.

All participants will sign an informed consent form as evidence of consent. The patient information sheet and the informed consent form of each participant will be filed in the ISF. A second original of the signed consent form and a copy of the information sheet will be handed to the patients after signature and before enrolment.

If a patient withdraws consenting to participating in the study after blood sampling and before the analysis in the laboratory has taken place, the laboratory has to be informed immediately.

### 6.4 Confidentiality

The Principal Investigator (PI) must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorised parties. Only an identification code (i.e., consists of identification number, sex and year of birth) should be recorded on any form or biological sample submitted to the laboratory, Sponsor, Competent Authorities' or Ethics Committee. The PI must keep a screening and enrolment log showing codes and names for all patients screened and for all patients enrolled in the trial.

### 6.5 Insurance

The Sponsor is responsible for the appropriate insurance coverage for the patients.

### 6.6 Publication Policy

The Sponsor has to publish the result of this study in accordance with § 42b AMG. Beside it is in the sole discretion of the Sponsor whether or not to publish the results of this study. The trial will be registered at [clinicaltrials.gov](http://clinicaltrials.gov).

### 6.7 Qualification of the Investigator

The PI and Investigators of the study site fulfil the requirements of applicable national law. Curriculum vitae of the PI and Investigators will be filed in the TMF.

## Protocol No. AIH-MAB

For conducting the study, the PI may delegate tasks to Investigators (or other qualified staff). This is to be documented properly. The PI is responsible for the adequate training and supervision of all delegates. No study related procedure must be performed by personnel which is not properly trained and delegated.

In the present document the mere term "Investigator" refers to the PI or Investigator.

## 7 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

<b>Sponsor:</b>	University Medical Centre Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg Germany
<b>Coordinating Principal Investigator:</b>	Dr. Christina Weiler-Normann I. Department of Medicine University Medical Centre Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg Germany Phone: +49 40-7410-50238 Fax: +49 40-7410-58531 Email: <a href="mailto:cweiler@uke.de">cweiler@uke.de</a>
<b>Deputy:</b>	Prof. Dr. Ansgar W. Lohse I. Department of Medicine University Medical Centre Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg Germany Phone: +49 40-7410-53910 Fax: +49 40-7410-58531 Email: <a href="mailto:alohse@uke.de">alohse@uke.de</a>
<b>Medical Monitor:</b>	PD Dr. Christof Iking-Konert III. Department of Medicine University Medical Centre Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg Germany Phone: +49 4192-902576 Fax: +49 4192-902389 Email: <a href="mailto:c.iking-konert@uke.de">c.iking-konert@uke.de</a>
	<b>Deputy:</b> Prof. Dr. Tobias B. Huber III. Department of Medicine University Medical Centre Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg Phone: +49 40-7410-53908 Fax: +49 40-7410-45186 Email: <a href="mailto:thuber@uke.de">thuber@uke.de</a>
<b>Clinical Trial Management:</b>	Project Management, Monitoring, Data Query and Safety Management CTC North GmbH & Co. KG at the University Medical Centre Hamburg-Eppendorf Martinistrasse 64

20251 Hamburg  
Germany  
Phone: +49 40-524719-200  
Fax: +49 40-524719-129

**Safety Management**

Safety Management  
CTC North GmbH & Co. KG  
at the University Medical Centre Hamburg-Eppendorf  
Phone: +49 40-524719-225  
Fax: +49 40-524719-222  
Email: [pharmacovigilance@ctc-north.com](mailto:pharmacovigilance@ctc-north.com)

**Statistician:**

Prof. Dr. Karl Wegscheider  
Institut für Biometrie  
University Medical Center Hamburg-Eppendorf  
Germany  
Phone: +49 40-7410-56110  
Fax: +49 40-7410-57485  
E-Mail: [k.wegscheider@uke.uni-hamburg.de](mailto:k.wegscheider@uke.uni-hamburg.de)

**Executive Committee**

Prof. Dr. Marylin Addo  
Department for Tropical Medicine

Prof. Dr. Christoph Schramm  
Martin Zeitz Centre for Rare Diseases  
University Medical Center Hamburg-Eppendorf  
Martinistrasse 52  
20246 Hamburg  
Germany

**Data Safety Monitoring Board**

PD. Dr. Alexander Stein  
UCCH  
University Medical Center Hamburg-Eppendorf  
Martinistrasse 52  
20246 Hamburg  
Germany

Prof. Dr. Stefan Lüth  
Klinikdirektor der Klinik für Innere Medizin II  
Klinikum Brandenburg  
Klinik für Innere Medizin II  
Hochstrasse 29  
14770 Brandenburg

## Introduction and Background

### 7.1 The Medical Problem

#### 7.1.1 Prevalence, Incidence, Mortality

Autoimmune Hepatitis (AIH) is a rare inflammatory liver disease associated with elevated transaminases, elevated Immunoglobulin G, the presence of autoantibodies and interface hepatitis in liver histology (1). If left untreated, AIH progresses to liver fibrosis and cirrhosis with its complications. Historical placebo-controlled studies could show a mortality of around 70% in the placebo-treated group(2). Today, effective immunosuppressive treatment is available and mortality is approximately twice as high as in a control population.

The prevalence of AIH is low, per definition AIH is a rare disease. Recent population-based studies have shown a rising prevalence (3).

#### 7.1.2 Burden of Disease

AIH is a rare disease with an estimated incidence rate of 1,68 per 100000 population/year (3). Clinical controlled studies are rare as AIH is a rare disease. Since incidence is rising, it is becoming an increasing health problem. Most patients are in need of medical treatment life-long.

#### 7.1.3 Improvement of Therapy / Impact of the Trial

Standard induction treatment of autoimmune hepatitis includes high doses of corticosteroids. This treatment is associated with numerous side effects that are often very bothersome for the patient and consecutively leads to reduced treatment adherence in these patients. Especially weight gain, cushingoid changes in habitus and facial appearance, hirsutism and edema are often problematic in these often young and female patients. Additionally, the potential psychological side effects as sleep disturbance, depression and development of steroid-induced psychosis can be very wearing.

In this trial, we seek to replace steroid induction treatment by treatment with the TNF-blocker infliximab.

### 7.2 Pharmacological Classification

Infliximab (Inflixtra<sup>®</sup>), is a chimeric human-murine monoclonal IgG1-antibody. It is produced with the help of recombinant DNA Technology in murine hybridoma cells. Other ingredients: Sucrose, Polysorbate 80, Sodiumdihydrogenphosphate-Monohydrate, Disodiumphosphate-Dihydrate. It will be reconstituted in *Aqua ad injectabile*.

This medication is licenced in the EU: EU/1/13/854/001, EU/1/13/854/002, EU/1/13/854/003, EU/1/13/854/004, EU/1/13/854/005. Initial licensing occurred September 10th, 2013.

### 7.3 Clinical Use

Inflixtra<sup>®</sup> is licensed for the use in ulcerative colitis, Crohn's disease, rheumatoid arthritis (in combination with Methotrexate), ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. It was first licensed as Remicade<sup>®</sup> in the United States in 1998 and in the European Union in 1999. There is broad clinical experience with the use of Infliximab

### 7.4 Human Pharmacodynamics

Elevated concentrations of TNF $\alpha$  have been found in involved tissues and fluids of patients with rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. In rheumatoid arthritis, treatment with infliximab products reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, chemoattraction [IL-8 and monocyte chemoattractant protein 1 (MCP-1)] and tissue degradation [matrix metalloproteinase 1 and 3]. In Crohn's disease, treatment with infliximab products reduced infiltration of inflammatory cells and TNF $\alpha$  production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNF $\alpha$  and interferon. After treatment with infliximab products, patients with rheumatoid arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein compared to baseline. Peripheral blood lymphocytes from infliximab product-treated

## Protocol No. AIH-MAB

patients showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients. In psoriatic arthritis, treatment with infliximab products resulted in a reduction in the number of T-cells and blood vessels in the synovium and psoriatic skin lesions as well as a reduction of macrophages in the synovium. In plaque psoriasis, infliximab products treatment may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which infliximab products exert their clinical effects is unknown.

## 7.5 Human Pharmacokinetics

In adults, single intravenous infusions of 3 mg/kg to 20 mg/kg of infliximab showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg to 10 mg/kg in rheumatoid arthritis, 5 mg/kg in Crohn's disease, and 3 mg/kg to 5 mg/kg in plaque psoriasis indicate that the median terminal half-life of infliximab is 7.7 to 9.5 days. Following an initial dose of infliximab, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8 week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8 weeks after a maintenance dose of 3 to 10 mg/kg of infliximab, median infliximab serum concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender. It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.

## 7.6 Preclinical Results

Preclinical data revealed and published in the manufacturer's information.

## 7.7 Cautions and Tolerability

### 7.7.1 Contraindications

The use of infliximab is contraindicated in

- Patients with moderate to severe heart failure
- Patients who have developed a severe hypersensitivity reaction to infliximab

### 7.7.2 Special Warnings and Preventive Measures for the Treatment

#### 7.7.2.1 Serious infections

Infliximab should not be initiated in patients with an active infection, including clinically relevant localized infections. Patients greater than 65 years of age, patients with comorbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with infliximab, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with infliximab. Treatment should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment

## Protocol No. AIH-MAB

should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

### 7.7.2.2 Malignancies

Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF blocking agents (initiation of therapy  $\leq 18$  years of age), including infliximab products. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported postmarketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports. In the controlled portions of clinical trials of all the TNF blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of infliximab clinical trials, 5 patients developed lymphomas among 5707 patients treated with infliximab (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately four-fold higher than expected in the general population. Patients with Crohn's disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blocking therapy. Cases of acute and chronic leukemia have been reported with postmarketing TNF blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia. Postmarketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including infliximab products. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males. It is uncertain whether the occurrence of hepatosplenic T-cell lymphoma is related to TNF blockers or TNF blockers in combination with these other immunosuppressants. When treating patients, consideration of whether to use infliximab alone or in combination with other immunosuppressants such as azathioprine or 6-mercaptopurine should take into account a possibility that there is a higher risk of hepatosplenic T-cell lymphoma with combination therapy versus an observed increased risk of immunogenicity and hypersensitivity reactions with infliximab product monotherapy from the clinical trial data from studies with infliximab.

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including infliximab products. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. In the controlled portions of clinical trials of some TNF blocking agents, including infliximab products, more malignancies (excluding lymphoma and nonmelanoma skin cancer) have been observed in patients receiving those TNF blockers compared with control patients. During the controlled portions of trials with infliximab, in patients with moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 14 patients were diagnosed with malignancies (excluding lymphoma and nonmelanoma skin cancer) among 4019 infliximab-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among infliximab-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for infliximab-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among infliximab-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected. In a clinical trial exploring the use of infliximab in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Psoriasis patients should be monitored for nonmelanoma skin cancers, particularly those patients who have had prior

## Protocol No. AIH-MAB

prolonged phototherapy treatment. In the maintenance portion of clinical trials for infliximab, NMSCs were more common in patients with previous phototherapy. The potential role of TNF blocking therapy in the development of malignancies is not known. Rates in clinical trials for infliximab cannot be compared to rates in clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering infliximab treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving infliximab.

### 7.7.2.3 Hepatitis B Reactivation

Use of TNF blockers, including infliximab products, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients should be tested for HBV infection before initiating TNF blocker therapy. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and anti-viral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF blocker therapy in this situation and monitor patients closely.

### 7.7.2.4 Hepatotoxicity

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis, have been reported rarely in postmarketing data in patients receiving infliximab products. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between 2 weeks to more than 1 year after initiation of infliximab; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g.,  $\geq 5$  times the upper limit of normal) develop, infliximab should be discontinued, and a thorough investigation of the abnormality should be undertaken. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving infliximab products without progression to severe hepatic injury.

### 7.7.2.5 Patients with Heart Failure

Infliximab products have been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of infliximab in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg infliximab, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking infliximab. There have also been rare postmarketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer infliximab to patients with mild or moderate heart failure, they should be closely monitored during therapy, and infliximab should be discontinued if new or worsening symptoms of heart failure appear.

### 7.7.2.6 Hematologic Reactions

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving infliximab products. The causal relationship to infliximab therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood

## Protocol No. AIH-MAB

dyscrasias or infection (e.g., persistent fever). Discontinuation should be considered in patients who develop significant hematologic abnormalities.

### 7.7.2.7 Hypersensitivity

Infliximab products have been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of infusion. However, in some cases, serum sickness-like reactions have been observed in patients after initial therapy with infliximab products (i.e., as early as after the second dose), and when therapy with infliximab products was reinstated following an extended period without treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with a marked increase in antibodies to infliximab product, loss of detectable serum concentrations of infliximab products, and possible loss of drug efficacy. Infliximab should be discontinued for severe hypersensitivity reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction. In rheumatoid arthritis, Crohn's disease and psoriasis clinical trials, readministration of infliximab after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment. In general, the benefit- risk of readministration of infliximab after a period of no-treatment, especially as a reinduction regimen given at weeks 0, 2 and 6, should be carefully considered.

### 7.7.2.8 Neurologic Reactions

Agents that inhibit TNF have been associated in rare cases with CNS manifestation of systemic vasculitis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of infliximab in patients with these neurologic disorders and should consider discontinuation of infliximab if these disorders develop.

### 7.7.2.9 Autoimmunity

Treatment with infliximab products may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with infliximab, treatment should be discontinued.

### 7.7.2.10 Live Vaccines/Therapeutic Infectious Agents

In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with infliximab is not recommended. Fatal outcome due to disseminated BCG infection has been reported in an infant who received a BCG vaccine after *in utero* exposure to infliximab products. Infliximab products are known to cross the placenta and have been detected up to 6 months following birth. At least a six month waiting period following birth is recommended before the administration of any live vaccine to infants exposed *in utero* to infliximab products. Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with infliximab. It is recommended that all patients be brought up to date with all vaccinations prior to initiating infliximab therapy. The interval between vaccination and initiation of infliximab therapy should be in accordance with current vaccination guidelines.

## 7.7.3 Side Effects

Due to long-standing clinical experience, side effects are well known and summarized in table 3 and in the summary of product characteristics.

### Table 3: Adverse drug reactions observed during clinical trials and post-marketing experience

## Protocol No. AIH-MAB

<i>Infections and infestations</i>	
Very common:	Viral infection (e.g. influenza, herpes virus infection).
Common:	Bacterial infections (e.g. sepsis, cellulitis, abscess).
Uncommon:	Tuberculosis, fungal infections (e.g. candidiasis).
Rare:	Meningitis, opportunistic infections (such as invasive fungal infections [pneumocystosis, histoplasmosis, aspergillosis, coccidioidomycosis, cryptococcosis, blastomycosis], bacterial infections [atypical mycobacterial, listeriosis, salmonellosis], and viral infections [cytomegalovirus]), parasitic infections, hepatitis B reactivation.
Not known:	Vaccine breakthrough infection (after <i>in utero</i> exposure to infliximab)*.
<i>Neoplasms benign, malignant and unspecified (including cysts and polyps)</i>	
Rare:	Lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia, melanoma, cervical cancer.
Not known:	Hepatosplenic T-cell lymphoma (primarily in adolescents and young adults with Crohn's disease and ulcerative colitis), Merkel cell carcinoma.
<i>Blood and lymphatic system disorders</i>	
Common:	Neutropenia, leucopenia, anaemia, lymphadenopathy.
Uncommon:	Thrombocytopenia, lymphopenia, lymphocytosis.
Rare:	Agranulocytosis (including infants exposed <i>in utero</i> to infliximab), thrombotic thrombocytopenic purpura, pancytopenia, haemolytic anaemia, idiopathic thrombocytopenic purpura.
<i>Immune system disorders</i>	
Common:	Allergic respiratory symptom.
Uncommon:	Anaphylactic reaction, lupus-like syndrome, serum sickness or serum sickness-like reaction.
Rare:	Anaphylactic shock, vasculitis, sarcoid-like reaction
<i>Psychiatric disorders</i>	
Common:	Depression, insomnia.
Uncommon:	Amnesia, agitation, confusion, somnolence, nervousness.
Rare:	Apathy.
<i>Nervous system disorders</i>	
Very common:	Headache.
Common:	Vertigo, dizziness, hypoaesthesia, paraesthesia.
Uncommon:	Seizure, neuropathy.
Rare:	Transverse myelitis, central nervous system demyelinating disorders (multiple sclerosis-like disease and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy).
<i>Eye disorders</i>	
Common:	Conjunctivitis
Uncommon:	Keratitis, periorbital oedema, hordeolum
Rare:	Endophthalmitis
Not known:	Transient visual loss occurring during or within 2 hours of infusion
<i>Cardiac disorders</i>	
Common:	Tachycardia, palpitation
Uncommon:	Cardiac failure (new onset or worsening), arrhythmia, syncope, bradycardia
Rare:	Cyanosis, pericardial effusion
Not known:	Myocardial ischaemia/myocardial infarction
<i>Vascular disorders</i>	
Common:	Hypotension, hypertension, ecchymosis, hot flush, flushing

## Protocol No. AIH-MAB

Uncommon	Peripheral ischaemia, thrombophlebitis, haematoma
Rare	Circulatory failure, petechia, vasospasm
<i>Respiratory, thoracic and mediastinal disorders</i>	
Very common	Upper respiratory tract infection, sinusitis
Common	Lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, epistaxis
Uncommon	Pulmonary oedema, bronchospasm, pleurisy, pleural effusion
Rare	Interstitial lung disease (including rapidly progressive disease, lung fibrosis and pneumonitis)
<i>Gastrointestinal disorders</i>	
Very common:	Abdominal pain, nausea
Common:	Gastrointestinal haemorrhage, diarrhoea, dyspepsia, gastroesophageal reflux, constipation
Uncommon	Intestinal perforation, intestinal stenosis, diverticulitis, pancreatitis, cheilitis
<i>Hepatobiliary disorders</i>	
Common:	Hepatic function abnormal, transaminases increased.
Uncommon:	Hepatitis, hepatocellular damage, cholecystitis.
Rare:	Autoimmune hepatitis, jaundice.
Not known:	Liver failure.
<i>Skin and subcutaneous tissue disorders</i>	
Common:	New onset or worsening psoriasis including pustular psoriasis (primarily palm & soles), urticaria, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia.
Uncommon:	Bullous eruption, onychomycosis, seborrhoea, rosacea, skin papilloma, hyperkeratosis, abnormal skin pigmentation.
Rare:	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, furunculosis.
Not known:	Worsening of symptoms of dermatomyositis.
<i>Musculoskeletal and connective tissue disorders</i>	
Common:	Arthralgia, myalgia, back pain.
<i>Renal and urinary disorders</i>	
Common:	Urinary tract infection.
Uncommon:	Pyelonephritis.
<i>Reproductive system and breast disorders</i>	
Uncommon:	Vaginitis.
<i>General disorders and administration site conditions</i>	
Very common:	Infusion-related reaction, pain.
Common:	Chest pain, fatigue, fever, injection site reaction, chills, oedema.
Uncommon:	Impaired healing.
Rare:	Granulomatous lesion.
<i>Investigations</i>	
Uncommon:	Autoantibody positive.
Rare:	Complement factor abnormal.

\* including bovine tuberculosis (disseminated BCG infection)

#### **7.7.4 Overdose**

No case of overdose has been reported. Single doses up to 20 mg/kg have been administered without toxic effects

#### **7.8 Rationale**

Steroid treatment is often wearing and may reduce treatment adherence due to multiple side effects. Currently, there is no alternative treatment available for induction treatment of AIH. There are small case series using cyclophosphamide or intravenous cyclosporine A as an induction treatment, but due to toxic side effects, this only serves as an emergency treatment. The rationale of this trial is to show the efficacy of infliximab in the induction treatment for AIH.

#### **7.9 Risk-Benefit Considerations**

There is substantial need to improve therapeutic options AIH. Previous data has shown treatment effect of infliximab in heavily pre-treated and difficult-to-treat AIH patients. Weighing steroid side effects and side effects by infliximab, it seems defensible to treat patients with AIH with infliximab for a period of 6 months under close monitoring. All aspects of the trial will be conducted in accordance with the Declaration of Helsinki principles, ICH-GCP rules and local laws. The study protocol will be submitted for ethical approval to the responsible ethics committee. All participants must provide written informed consent prior to any study interventions.

Therefore, it appears ethical to test infliximab in treatment-naïve AIH patients. If infliximab shows efficacy in this patient cohort, it will be a treatment alternative for patients with this condition and contraindications towards a high-dose steroid treatment.

## **8 STUDY OBJECTIVES**

The primary endpoint: “biochemical remission” is justified as:

- It has been shown in the past, that biochemical remission is associated with increased survival

The primary and secondary endpoints will be determined by primary and secondary measures:

- Laboratory values for AST, ALT and IgG
- Quality of life measured by standardized and validated tools
- Weight
- Elastography in kPa

### **8.1 Primary Objective**

The primary objective of the AIH-MAB trial is to show the efficacy of infliximab in inducing remission in treatment-naïve patients with autoimmune hepatitis.

### **8.2 Primary Endpoints**

Primary efficacy endpoint: Biochemical remission 6 months after treatment initiation.

### **8.3 Secondary Objectives**

Secondary objectives include quality of life, weight and elastography.

### **8.4 Secondary Endpoints**

- Changes in quality of life
- Weight changes
- Changes in elastography

### **8.5 Safety Endpoints**

Safety endpoints for tolerability will include all adverse events, serious adverse events and clinically relevant adverse laboratory results (including deaths and hospitalisations with date-change – all to be adjudicated), observation of episodes of anaphylactoid reactions or severe infections.

## 9 INVESTIGATIONAL PLAN

### 9.1 Overall Study Design and Plan-Description

The clinical trial is designed as monocentric single armed proof-of-principle study.

I.v. administration of infliximab will be carried out according to standard procedures, infusion will be given at a dose of 5mg/kg bodyweight every 4 weeks.

### 9.2 Discussion of Study Design, Including the Choice of Control Groups

A single-armed study design was chosen as high-dose steroid treatment leads to visible and reported side effects after 4 weeks in the vast majority of patients. Further on, good historical and own data is available from patients treated with standard treatment for comparison. All patients will receive standard treatment with azathioprine and induction treatment with infliximab will be administered instead of steroid treatment.

### 9.3 Selection of Study Population

Autoimmune hepatitis is a rare disease. As only untreated patients are eligible for this study, patients presenting with untreated autoimmune hepatitis meeting the inclusion and exclusion criteria will be offered study participation.

#### 9.3.1 Inclusion Criteria

1. Patients with untreated autoimmune hepatitis diagnosed in accordance to the „simplified criteria for the diagnosis of autoimmune hepatitis“
2. Female patients: Female subjects must be postmenopausal, surgically sterile, or if premenopausal and not surgically sterile, be prepared to use  $\geq 1$  effective method of contraception during the study and for 6 months after the end of treatment visit\*. Accepted methods of contraception are given in section 9.3.2.1.
3. Patients must provide written informed consent and agree to comply with the study protocol.

#### 9.3.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria are met at screening or on Day-1:

1. Age younger than 18 years old or older than 65 years
2. Patients with known hypersensitivity to any constituent of the product
3. History of severe heart disease or heart failure NYHA class III or IV, severe uncontrolled cardiac disease (unstable angina, arrhythmias, clinical significant electrocardiogram abnormalities or myocardial infarction within 6 months prior to randomization
4. Patients with a recent exposure to persons with active tuberculosis, patients with a positive result in a screening test for latent TB (Quantiferon Test) as well as patients with a history of tuberculosis or active tuberculosis
5. Patients with a current or past history of infection with hepatitis B, hepatitis C, or infection with human immunodeficiency virus (HIV) -1 or -2 or who has a positive result in the screening test for those infections; patients who have an acute infection requiring oral antibiotics within 2 weeks before randomization, other serious infection within 6 months before randomization or a history of recurrent herpes zoster or other chronic or recurrent infection within 6 weeks before randomization; patients with a history of tuberculosis or a current diagnosis of tuberculosis or other granulomatous infections or other severe or chronic infection (such as sepsis, abscess or opportunistic infection, or invasive fungal infection such as histoplasmosis) or a past diagnosis without sufficient documentation of complete resolution following treatment.
6. Additional liver disease other than autoimmune hepatitis (including, but not limited to alcoholic liver disease, viral hepatitis, primary sclerosing cholangitis, primary biliary cholangitis, non-alcoholic steatohepatitis), history of alcohol abuse
7. History of decompensation of cirrhosis (ascites, variceal bleeding, encephalopathy)
8. Known or suspected hepatocellular carcinoma, history of any malignancy within 5 years prior to randomization except completely excised and cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma or cutaneous squamous cell carcinoma, history of lymphoma or lymphoproliferative disease or bone marrow hyperplasia
9. Presence of transjugular intrahepatic portosystemic shunt procedure
10. Hepatorenal syndrome or creatinine  $>2\text{mg/dl}$  at screening

## Protocol No. AIH-MAB

11. Subjects that have undergone bariatric surgery
12. Female patients who are currently pregnant, breastfeeding or planning to become pregnant or breastfeed within 6 months of the last dose of study drug
13. Any uncontrolled clinically significant respiratory disease (in the opinion of the investigator) including but not limited to chronic obstructive pulmonary disease, asthma, bronchiectasis or pleural effusions
14. Uncontrolled hypertension (as defined by systolic blood pressure  $\geq 160$  mmHg or diastolic blood pressure  $\geq 100$  mm Hg)
15. Diabetes mellitus unless on a stable dosing regimen for at least 4 weeks prior to screening
16. Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain Barre syndrome
17. Any conditions significantly affecting the nervous system (i. e. neuropathic conditions or nervous system damage)
18. Any other serious or chronic medical or psychiatric condition that may increase the risk associated with study participation or investigational product administration or that may interfere with the interpretation of study results
19. Other medical conditions that may diminish life expectancy, including known cancers
20. Participation in another investigational product, biologic or medical device study within 30 days or 5 half-lives, whichever is longer prior to screening
21. Mental instability and lack of capability of giving consent.
22. History of known or suspected clinically significant hypersensitivity to azathioprine or bone marrow disease
23. History of the use of infliximab
24. Liver failure (INR  $> 1.5$ )
25. Body weight  $< 40$ kg or above 90kg, BMI  $< 18$ kg/m<sup>2</sup> or  $> 30$ kg/m<sup>2</sup>
26. Patients not willing or able to comply with the study procedures
27. Transaminase elevation  $> 1000$  U/l
28. Application of live vaccines 4 weeks prior to treatment or planned application of live vaccines during the treatment

## Reproductive Potential

The study population includes female of child-bearing potential (FOCP). FOCP have to agree to comply with the applicable contraceptive requirements of the protocol as named below for the duration of the study or having post-menopausal status or be permanently sterilised (at least 6 weeks post-sterilisation).

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Highly effective contraception is defined as a contraceptive method with failure rate of less than 1 % per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- Combined hormonal contraceptives (with inhibition of ovulation); oral or intravaginal or transdermal
- progesterone-only hormonal contraception (with inhibition of ovulation); oral or injectable or implantable,
- intrauterine device or intrauterine system,
- intrauterine hormone-releasing system system,
- male partner sterilisation at least 6 months prior to the female patient's entry into the study, and a monogamous relationship

### 9.3.3 Removal of Patients from Therapy or Assessment

The study in its entirety may be discontinued prematurely by the Coordinating Investigator or Sponsor at any time (see below), and/or individual patients may terminate their participation prematurely, or have their participation be terminated by an Investigator.

## Protocol No. AIH-MAB

**9.3.3.1 Treatment Discontinuation**

Severe infection will lead to treatment discontinuation

**9.3.3.2 Premature Treatment Discontinuation**

Patients must stop the IMP if the patient experiences any kind of serious hypersensitivity reaction. The patient may remain in the study and continue to attend study visits but must not receive any further administrations of IMP.

Patients should be withdrawn from IMP treatment if they:

- Experience a severe adverse event probably related to study medication, severe infection will always result in discontinuation of study medication.
- Experience an elevation of transaminases >20% over baseline during the first 4 weeks of treatment
- Show a less than 50% decrease of transaminases compared to baseline after 8 weeks of treatment with infliximab.

All patients with premature treatment discontinuation will be offered standard treatment with steroids according to the guidelines

If the study treatment was premature discontinued due to safety reasons, the study site must inform the Sponsor immediately but at latest within 24h regardless if the event fulfils the SAE definition.

**9.3.3.3 Withdrawal of Patients from the Study**

The following circumstances may lead to discontinuation of the study by an individual patient who will then be recorded as a drop-out. They include, but are not limited to the following issues:

- Withdrawal for personal reasons
- Circumstances in which the health of the patient would be endangered upon continued participation in the study
- An AE, which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures
- Lost-to follow-up

If a patient withdraws from the study at any time either at his or her request or at the Investigator's discretion, an unscheduled visit should be performed and the "End of Study" eCRF section should be used to collect the relevant information. The reason(s) for withdrawal must be recorded on the relevant page of the patient's eCRF and the patient's source data.

It is vital to obtain follow-up data for any patient withdrawn from the study because of an AE. Every effort must be made to undertake protocol-specific safety follow-up procedures. If a patient is discontinued due to an AE, the event should be followed up until resolution or until the event becomes chronic.

If a patient refuses to continue study procedures, the reason for refusal should be fully documented in the patient's source document and recorded in the study-specific eCRF.

It is the patient's right to withdraw from the trial without providing a reason. In this case, the source documents and the eCRF should document the reason for discontinuation as "withdrawal of consent".

**9.3.3.4 Criteria for Termination of the Study**

The AIH-MAB trial will be supervised by its Executive Committee and the Steering Committee). All final decisions, however, regarding study termination or modification will be agreed with the Steering Committee and the independent DSMB.

No formal stopping rules will be set. An independent DSMB will in addition monitor safety in the trial. Should safety concerns evolve, they should recommend stopping the study. Stopping the trial for efficacy or futility is not planned.

**9.3.3.5 Study Termination**

The Coordinating Investigator and Sponsor may terminate the trial at any time if serious safety concerns rise for the patients. In the case of study termination, participating sites will be informed of the procedures to be followed to ensure adequate consideration is given to the protection of the patient's safety.

## Protocol No. AIH-MAB

The Coordinating Investigator will be responsible for informing the Sponsor within 24 hours and the regulation authorities and Ethics Committee of the trial's termination within 15 days.

## 9.4 Treatments

### 9.4.1 Treatments Administered

#### 9.4.1.1 Experimental Intervention

The approved indication for Infliximab are rheumatoid arthritis, ulcerative colitis, Crohn's colitis, ankylosing spondylarthritis and psoriasis. Therefore, treatment in this study is off label.

Infliximab should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. Each patient should be observed for adverse effects for at least 120 minutes following each infliximab infusion. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

#### 9.4.1.2 Follow-up per Patient:

Follow-up for all patients will be according to Table 1 for 6-months after last administration of IMP in the individual patient. The end of the trial will therefore be the last study visit.

#### 9.4.1.3 Duration of Intervention per Patient:

Time of each individual treatment administration will be according to product information (SmPC) of infliximab; repetitive administrations will be continued according to the treatment schedule (see Table 1 + 2) during the entire duration of the intervention (6 months).

### 9.4.2 Identity of Investigational Medicinal Product(s)

The test product is manufactured by Pfizer, Germany.

Active ingredient:	Infliximab
Strength/packaging:	Inflectra 100 mg powder for concentrate for solution for infusion
Excipients:	Sucrose Polysorbate 80 Sodium dihydrogen phosphate monohydrate Disodium phosphate dihydrate
Dosage form:	One vial contains 100 mg of infliximab*. After reconstitution each mL contains 10 mg of infliximab. * Infliximab is a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology.
Storage:	as indicated on the label
Manufacturer:	PFIZER PHARMA PFE GmbH, Linkstr. 10, 10785 Berlin

Additional information can be found in the SmPC.

#### 9.4.2.1 Preparation

Study personnel (at least one physician) not involved in any study assessments (efficacy or safety) will be responsible for preparing and administering the study treatment infusions.

#### 9.4.2.2 Labelling

N/A, open label study, labelled by manufacturer

## Protocol No. AIH-MAB

### 9.4.2.3 Packaging

N/A packaged by manufacturer

### 9.4.2.4 Storage

The IMP must be stored in accordance with labelled storage conditions according to the manufacturer.

### 9.4.2.5 Drug Accountability

The PI has the overall responsibility for administering the IMP. The IMP must be administered in the manner specified in the study protocol and the pharmacy manual. As the IMP will be ordered via the pharmacy, no prolonged storage is planned.

At the end of the study or as instructed by the Sponsor all unused stock and empty used boxes are destroyed at the study site under the authority of the Sponsor or sent to a nominated contractor to be destroyed on behalf of the Sponsor.

Based on the entries in the site drug accountability logs, it must be possible to reconcile IMP delivered with those used and returned. One hundred percent of the IMP must be accounted for and all discrepancies investigated and documented.

### 9.4.2.6 Patient Compliance

Compliance must be assessed by the PI, or an Investigator.

For IMP administration, compliance must be assessed by observation of dosing. Designated members of the study team will record details on the drug accountability log or other appropriate source documents.

## 9.4.3 Selection of Doses in the Study

All patients will receive the IMP in a dose at 5mg/kg bodyweight.

Reason for dosing and intervals is prior experience with the drug in patients with autoimmune hepatitis(4, 5) with longer intervals between dosing or lower dosage leading to a flare of autoimmune hepatitis. Dose escalation is nowadays common in patients receiving infliximab for other diseases (6-8). We decide for rather shortening the intervals between the applications than for giving an increased dose in the first place, which is common practice in other disease treated with infliximab(9, 10).

## 9.4.4 Prior and Concomitant Therapy

Prohibited therapy: allopurinol, immunosuppressive treatment not associated with the treatment of autoimmune hepatitis.

Concomitant treatment: Any concomitant treatment given for any reason during the course of the study must be recorded on the eCRF and in the patient's medical records, including dosage, start and stop dates and reason for use.

## 9.4.5 Treatment Compliance

### 9.4.5.1 Admission to the Study

A patient will only be admitted to the study if all inclusion and none of the exclusion criteria are met.

### 9.4.5.2 Patient Identification

The PI of each site will keep a record relating the patient numbers and the names of all patient that have given their informed consent, to allow easy checking of data in patient files, when required. This record will also include the date of patient's enrolment and completion, as well as patients who could not be included in the study for whatever reason.

## 9.5 Efficacy and Safety Variables

### 9.5.1 Efficacy and Safety Measurement Assessed and Flow Chart

Details regarding scheduled assessments and procedures to be conducted in this study are provided below. For detailed assessment of schedules refer to Table1.

## 9.5.2 Appropriateness of Measurements

### 9.5.2.1 Screening Procedures

Written, signed, and dated informed consent from the patient prior to the performance of any study related procedures must be obtained by an Investigator. Patients will first have ample time to read the patient information before an Investigator will start the information and informed consent process.

An Investigator will provide the patients with information of the study and explain the nature of the study point by point. During these verbal patient information process patients have already the opportunity to ask questions. After that, the patients have the opportunity to individually ask questions in a one-to-one meeting with the Investigator. If the Investigator is convinced that the patient understands the nature and risks of the trial, and each patient had ample time for consideration and formulation of questions (which could also mean that the patients first discuss the decision with friends or family members), and if all questions are answered the patient will ask to personally sign the informed consent form. A copy or a second original of the signed informed consent form must be given to the patients for their records.

Screening procedures must be completed between 2 weeks and at the day of receiving the first dose of IMP (baseline visit / Day 1). See Table 1 for a complete list of screening procedures to be performed.

Only an authorised and trained Investigator may decide on the eligibility of the patient.

#### 9.5.2.1.1 Screening Failure

A screening failure is defined as a patient who has given informed consent and failed to meet at least one inclusion or exclusion criteria or has not been administered IMP as defined by the protocol. Screening failures will not be entered into the clinical database.

Eligible patients who meet all inclusion/exclusion criteria but are unable to participate in the study due to scheduling conflicts/timing will not be considered screening failures. These patients will not be entered into the clinical database.

#### 9.5.2.1.2 Re-screening of Patients

If patients fail screening, re-screening is permitted if in the opinion of the Investigator the patient may be eligible with a reanalysis of failed variables.

### 9.5.2.2 Study Examinations

Assessments are to be performed according to the schedule shown in Table 1 and depend on time-point of IMP administration.

Safety will be evaluated by collecting reported adverse events at regular intervals throughout the study and by the assessment of physical examination findings, vital signs, clinical laboratory parameters, and adverse events.

#### 9.5.2.2.1 Medical and Medication History

A complete medical and medication history as well as demographic information will be assessed at the time-points indicated in Table 1.

The medical history will be reviewed and recorded, including:

- Medical and Medication History
- Recent ingestion/administration of medications (10 days prior to entering the screening period)
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, haematological, neurological, psychiatric, musculoskeletal and other diseases.
- Demographic information
- Date of Birth
- Sex

#### 9.5.2.2.2 Physical Examination

A complete symptom-targeted physical examination will be performed at the time-points described in Table 1.

## Protocol No. AIH-MAB

The physical examination may include a review of the following body systems:

- General appearance
- Skin
- Head, Eyes, Ears, Nose and Throat
- Spine/Neck/Thyroid
- Musculoskeletal
- Respiratory
- Cardiovascular
- Neurological
- Abdomen (including liver and kidneys).

Any abnormalities or changes in intensity from the screening visit noted during the review of body systems during follow-up visits have to be documented in the medical record. Clinically significant abnormal findings discovered during a physical examination after screening will be documented either as part of medical history (patient forgot to mention an intermittent medical condition at screening), or as an adverse event.

### 9.5.2.2.3 Electrocardiogram

A 12-lead ECG will be done at the time points described in Table 1. Actual ECG assessment times will be documented.

Patients must be resting for at least 5 minutes prior to collecting the ECG. At a minimum, the date and time when the event was performed, the Investigator's assessment and the heart rate, RR, PR, QT, and QRS intervals are to be collected. All clinically significant abnormalities will be recorded in the appropriate source documents.

### 9.5.2.2.4 Vital Signs

Measurements of vital signs (systolic and diastolic blood pressure as well as pulse rate) will be performed at the time-points specified in Table 1. All measurements of vital signs must be recorded in the appropriate source documents.

### 9.5.2.2.5 Height and Weight

Measurements of height and weight will be performed according to the schedule in Table 1.

Height is measured in centimetres and weight is measured in kilograms. Measurements are to be taken in light clothing and socks (without shoes) with pockets emptied. The patient's height is recorded to the nearest cm and weight is recorded to the nearest 0.1 kg.

### 9.5.2.2.6 Clinical Laboratory Evaluations

All laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges will be supplied by the laboratory and used to assess the laboratory data for clinical significance and out-of-range pathological changes. The Investigator must assess out-of-range laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant (NCS) or clinically significant (CS). Abnormal laboratory values that are unexpected or not explained by the patient's clinical condition may be, at the discretion of the Investigator or Sponsor, repeated until confirmed, explained, or resolved as soon as possible.

The following laboratory assessments will be performed:

#### 9.5.2.2.6.1 Bio-Chemistry

Blood samples (4.9 mL) will be collected at the time points described in Table 1. The following parameters will be assessed:

AST, ALT, Bilirubine, Albumine, Creatinine, C-reactive protein, IgG

## Protocol No. AIH-MAB

**9.5.2.2.6.2 Haematology**

A 2.7 mL sample of blood will be drawn into a tube containing potassium ethylene diamine tetra-acetic acid (EDTA) anticoagulant at the time points described in Table 1. The following parameters will be assessed:

Differential blood count

**9.5.2.2.6.3 Urine Pregnancy Test**

If applicable, appropriately performed using fresh midstream urine.

**9.5.2.2.6.4 Coagulation**

A 2.7 mL sample of blood will be drawn into a tube containing citrate at the time points described in Table 1. The following parameters will be assessed:

INR

**9.5.2.2.6.5 Questionnaires**

The SF-12, GAD-7 and PHQ9 questionnaires must be completed as indicated in Table 1. Questionnaires should be completed before any other procedures at each visit.

**9.5.2.2.6.6 Concomitant Medication**

Concomitant medication will be assessed at the time points described in Table 1.

**9.5.2.2.7 Translational Research**

Blood samples will be taken (15 mL EDTA) at the time points described in Table 1 for further analysis in research. These samples will be examined for T-cell activation and cytokine analysis.

**9.5.2.2.8 Adverse and Serious Adverse Events Assessments**

Patients will be questioned in a general way to ascertain if AEs have occurred (e.g. "Have you had any health problems since the last time you came to the clinic/since you were last questioned?"). This open, standardised questioning should be done discretely in order to prevent patients from influencing each other. Spontaneous reports of AEs will also be recorded as well as AEs that are observed by the Investigator or a staff member.

All AEs will be reviewed, confirmed, and classified by a qualified, designated Investigator.

**9.5.2.2.8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events**

An **Adverse Event (AE)** is any untoward medical occurrence in a clinical investigation patient administered an IMP and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, disease or exacerbation of a pre-existing condition temporally associated with the use of a medicinal (test) product, whether or not considered related to the medicinal product (ICH Guidance E2A 1995).

All AEs, including those associated with the protocol, are collected from the time of the first administration of IMP, regardless of the relationship to the investigational medicinal product. All AEs are to be recorded on the appropriate source documents and subsequently will be entered into the AE module of the electronic case report form (eCRF). During the trial, an AE can also occur at times when investigational medicinal product is not taken.

Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made each symptom should be entered as a separate AE.

All AEs have to be recorded until the last trial day according to the clinical trial protocol. If the Investigator becomes aware of a serious AE considered related to the investigational medicinal product, it has to be recorded even if it occurs after finalisation of the clinical trial.

All AEs must be followed up until closure (i.e. the patient's health has returned to his/her baseline status or all variables have returned to normal), an outcome is reached, stabilisation (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained regardless of whether the patient is still participating in the clinical trial and clinical judgment indicates that further follow-up is not warranted. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

## Protocol No. AIH-MAB

**9.5.2.2.8.1.1 Severity Categorisation**

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of IMP, must be recorded as new AEs.

The medical assessment of severity is determined by using the following definitions:

- Mild:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research patient.
- Severe:** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

The term “severe” is here used to describe the severity/intensity of the specific event; it is not the same as “serious”, which is based on patient/event outcome or action criteria.

**9.5.2.2.8.1.2 Relationship Categorisation**

An Investigator assesses each AE for its relationship to the investigational medicinal product.

The assessment of the relationship of an AE to the administration of investigational medicinal product is a clinical decision based on all available information at the time of and after the occurrence of the event. The factors which may be considered when evaluating the relationship of an AE to the investigational medicinal product include: time from exposure to investigational medicinal product until onset of the event; recovery or improvement on discontinuation of investigational medicinal product; availability of alternative explanations such as underlying or intercurrent diseases; concomitant medications or treatments; pharmacology and pharmacokinetic of the investigational medicinal products; known response pattern for this class of drug; recurrence on reintroduction of the investigational medicinal product.

If there is no valid reason for suggesting a relationship, then the AE should be classified as ‘not related’. Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational medicinal product and the occurrence of the AE, then the AE should be considered ‘related’. The causality must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship	Definition
Related	Yes	The temporal relationship between the event and the administration of the investigational medicinal product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the patient's medical condition, other therapies, or accident.
Not Related	No	The event can be readily explained by other factors such as the patient's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational medicinal product and the event.

**9.5.2.2.8.1.3 Outcome Categorisation**

The outcome of AEs must be recorded during the course of the study in the eCRF. Outcomes are as follows:

- Recovered/resolved
- Recovering/resolving
- Resolved with sequel
- Ongoing/not recovered/not resolved
- Fatal
- Unknown

#### 9.5.2.2.8.1.4 Clinical Laboratory Evaluations

A change in the value of a safety laboratory investigation can represent an AE if the change is clinically relevant or if, during treatment with the IMP, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the IMP, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (e.g., concomitant disease) is found for the pathological laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a patient, whether a change in a laboratory parameter is clinically significant and therefore represents an AE.

#### 9.5.2.2.8.1.5 Pregnancy

Any report of pregnancy recorded for any female patient or for a female partner of a male patient should be reported to the Sponsor within the same timelines as an SAE, i.e., immediately (within 24 hours of awareness/ within 30 days of IMP administration), but a separate form should be used. Patients with a pregnancy occurring during dosing will be discontinued from study medication and followed up till birth.

#### 9.5.2.2.8.1.6 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the Sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE.

Abuse - Persistent or sporadic intentional intake of a study medication at a dose higher than prescribed per protocol (but below the dose defined for overdose) or when used for non-medical purpose (e.g. altering one's state of consciousness)

Misuse - Intentional or unintentional use of a study medication other than as directed or indicated at any dose, which is at or below the dose defined for overdose. (Note: this includes a situation where the study medication is not used as directed at the dose prescribed by the protocol.)

Overdose - Intentional or unintentional intake of a dose of study medication higher than the protocol prescribed dose for each patient.

Medication Error - A mistake made in prescribing, dispensing, administration, and/or use of the study medication. For studies, medication errors are reportable only as defined below.

Administration of an expired product should be considered as a reportable medication error when associated with an AE, or if otherwise appropriate.

Cases of patients missing doses of product are not considered reportable as medication errors.

### 9.5.2.2.8.2 Serious Adverse Event (SAE) Procedures

#### 9.5.2.2.8.2.1 Reporting Procedures

All SAE which occur **from individual administration until 30 days after** must be reported by the Investigator to the Safety Management Desk within 24 hours of the first awareness of the event. All SAE follow-up reports must be reported in a timely manner. The Investigator must complete, sign, and date the electronic Serious Adverse Event Form provided in the eCRF and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: source documents are not to be sent unless requested) and send the form via the eCRF to the Sponsor's Safety Desk:

Name: CTC North Safety Management  
 Fax number: +49 40 524719 222  
 Phone number: +49 40 524719 225  
 Email: [pharmacovigilance@ctc-north.com](mailto:pharmacovigilance@ctc-north.com)

#### 9.5.2.2.8.2.2 Serious Adverse Event (SAE) Definition

A Serious Adverse Event (SAE) is any untoward medical occurrence (whether considered to be related to IMP or not) that at any dose:

## Protocol No. AIH-MAB

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an Important Medical Event, i.e., an event that may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Events of severe Infections and a relevant clinical increase of liver enzymes must be considered an “Important Medical Event” even if no other serious criteria apply.

Hospitalisations which are the result of elective or previously scheduled surgery for pre-existing conditions which have not worsened after initiation of treatment should not be classed as SAEs.

However, complication(s) resulting from a hospitalisation for an elective or previously scheduled surgery that meet serious criteria must be reported as a SAE(s).

#### 9.5.2.2.8.2.3 SAE Onset and Resolution Dates

The onset date of the SAE is defined as the date at which the event meets serious criteria. SAE Stop Date is defined as the date at which the event no longer meets serious criteria. The resolution date is the date at which the symptoms are resolved or resolved with sequel/event is no longer present.

#### 9.5.2.2.8.2.4 Fatal Outcome

Any SAE that results in the patient’s death (i.e. the SAE was noted as the primary cause of death) should have fatal checked as an outcome and the resolution date of death recorded as the resolution date. For all other events ongoing at time of death that did not contribute to the patient’s death, the outcome should be considered not resolved, without a stop date recorded.

For any SAEs that result in the patient’s death or any ongoing events at the time of death, the action taken with the IMP should be recorded as “dose not changed” or “not applicable” (if the patient never received IMP).

#### 9.5.2.2.8.2.5 Serious Adverse Reaction (SAR)

An AE (expected or unexpected) that is both serious and, in the opinion of the reporting Investigator or Sponsors, believed to be possibly, probably or definitely due to an IMP or any other study treatments, based on the information provided.

#### 9.5.2.2.8.2.6 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a SAE that is unexpected and thought to be possibly, probably or definitely related to an IMP. An Event is unexpected, if the nature or severity is not consistent with the applicable product information (summary of product characteristics).

#### 9.5.2.2.8.2.7 Regulatory Agency, Independent Ethics Committee, and Investigative Site Reporting

The Sponsor is responsible for SUSAR reporting to the relevant Regulatory Authorities, Ethics committee and Investigators within 15 days or in case the event is fatal or life threatening within 7 days

### 9.5.3 Primary efficacy variable(s)

#### 9.5.3.1 Outcome Measures

To generate meaningful data, complete biochemical remission at 6 months is chosen as outcome measure.

#### 9.5.3.2 Safety Variables

Assessment of safety is performed for the safety collective Safety data include:

- Adverse events (including changes from baseline in physical examination findings)

## Protocol No. AIH-MAB

- Clinical laboratory results, especially a rise in transaminases of more than 30% above baseline levels.
- Vital signs

The safety evaluation will be based upon the review of the individual values (potentially clinically important abnormalities) and descriptive statistics (summary tables, graphics).

### 9.5.3.2.1 Adverse Events

The adverse events will be listed per patient using MedDRA terminology (lower level term, preferred term and system organ class) and will be reported in tables summarising the frequency of patients with adverse events and adverse events by treatment and body system, the number of adverse events and patients with adverse events by treatments and the characteristics of adverse events.

For haematology, clinical laboratory and urine analysis parameters deviations from the reference ranges will be summarised in frequency tables in the CSR.

### 9.5.3.2.2 Clinical Laboratory

All relevant clinical laboratory variables obtained during screening, final examination or the clinical trial periods will be reported in appropriate tables together with descriptive statistics in the CSR.

### 9.5.3.2.3 Vital Signs

For blood pressure and pulse rate descriptive statistics will be listed by sampling times (screening and follow-up) according to the data captured in the eCRF.

### 9.5.3.2.4 ECG

The results of the 12-lead ECG will be listed by sampling times according to the data captured in the eCRF.

## 9.6 Data Quality Assurance

### 9.6.1 Quality Assurance System

Protocol development, case report form and trial master file, investigator site file, content of patient information and consent, application for ethics approval, data processing, central and on-site monitoring, and evaluation will follow the Standard Operating Procedures (SOP) of the CRO, and the central data management. Standard phases of the study may be subject to audits by the QAU of the Sponsor, the Monitor or the study site. Results of these audits as well as any objections will be reported directly to the Sponsor.

### 9.6.2 Monitoring

The CRO or a designee will be responsible for trial monitoring. A risk-based monitoring strategy will be implemented and further described in the monitoring manual. During trial conduct, remote monitoring procedures will be combined with on-site monitoring visits in order to achieve high protocol compliance and data quality, as well as to ensure patients' safety and rights. Source data verification will be performed on 50 % of enrolled patients and 50 % of data. The frequency of the monitoring visits will depend on the trial site's recruitment rate and on whether problems have been detected with the site, either by prior on-site visits or by central monitoring.

The detailed extent of the monitoring will be defined in the monitoring plan.

### 9.6.3 Documentation and Data Collection

eCRF will be prepared to report at least all clinical data required by the protocol.

Site staff will transfer the study data from the source documents into the eCRF. Site staff will check eCRF entries for completeness. Completed eCRF modules will be electronically signed by an Investigator in order to ensure data entry accuracy.

Corrections to source data documents will be dated and initialled. Reasons for the corrections should be given. Corrections to eCRF entries must be electronically signed and reasons for the corrections must be provided. The date on which the correction was performed is automatically recorded by the system's audit trail.

## Protocol No. AIH-MAB

A study monitor will review the defined eCRF data for completeness and accuracy during the monitoring visits (source data verification (SDV)). The study monitor will point out any discrepancies between source data and the data captured in the eCRF. The monitor will issue electronic queries to site staff to initiate discrepancy resolution. Discrepancies which require eCRF data corrections have to be resolved by authorised site personnel by answering these monitoring queries. Discrepancies which require data corrections have to be resolved by authorised site personnel.

### 9.6.4 Data Management

Data management will check predefined eCRF entries as defined in the data management plan (DMP). Quality control and data validation procedures such as programmed automatic edit and consistency checks ensure data validity and accuracy immediately at the point of entry into the clinical database. The database application which is used to capture electronic study data is fully CFR part 11 compliant. Thus, it is access restricted, demands electronic signatures, maintains an electronic audit trail and provides appropriate backup functionalities. Details of the application and eCRF configuration and all further data management procedures will be described in the DMP.

The database will be locked after all queries and discrepancies that may occur during data entry are resolved.

Upon request safety reports and interim analysis will be generated and provided to the respective members of the DSMB.

After database lock, the data in the study database will be exported and SAS datasets will be compiled for statistical analysis. The data will be exported in SAS transport files or other SAS-compatible format and transferred electronically to the responsible biometrician for statistical analysis. The locked SAS database will be used to generate the patient listings, tabulations, and analyses for the CSR.

### 9.6.5 Archival of documents

The Sponsor will maintain the trial documents and take measures to prevent accidental or premature destruction of these documents. All documents related to the study will be retained until at least 15 years after the end of the study.

## 9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

### 9.7.1 Statistical and Analytical Plan

#### 9.7.1.1 Software to be Used

All statistical analyses will be carried out using the software ADDPLAN Version 6.1.1

#### 9.7.1.2 Eligibility for Statistical Evaluation

Eligibility of patients will be determined in a BRM before statistical analysis will be performed.

##### 9.7.1.2.1 Analysis Population

###### 9.7.1.2.1.1 PP Population

The primary endpoint in AIH-MAB will be analysed as intended-to-treat. Nevertheless, a per-protocol analysis is also planned in subsequent analyses.

###### 9.7.1.2.1.2 Safety Population

All patients receiving at least once the IMP will be included into the safety evaluation (safety collective).

##### 9.7.1.2.2 Statistical Analyses

All statistical analyses will be carried out under the supervision of the trial statistician Prof. Wegscheider. The primary analysis population will be intention-to-treat. All details including the definition of the analysis populations will be detailed in a statistical analysis plan, which will be finalised prior to database lock. Baseline variables will be described by treatment group using appropriate summary statistics.

###### 9.7.1.2.2.1 Primary and Secondary Endpoint

## Protocol No. AIH-MAB

The primary endpoint "biochemical remission" is a composite endpoint. All analyses will be adjusted for important prognostic factors.

### 9.7.1.2.2.2 Dropouts

In the primary analyses dropout will be dealt with as independent right censoring. In case of substantial dropout this assumption will be investigated in sensitivity analyses. Missing values in baseline variables will be dealt with by multiple imputation techniques. Time to event outcomes will be visualised by Kaplan-Meier curves stratified by treatment group.

### 9.7.1.2.2.3 Safety Endpoints

Adverse event data will be summarised by treatment group using standard procedures. The primary analysis population will be intention-to-treat. All details including the definition of the analysis populations will be detailed in a statistical analysis plan, which will be finalised prior to database lock and unblinding.

## 9.7.2 Determination of Sample Size

### 9.7.2.1 Proposed Sample Size

The main hypotheses of the phase IIa study state that infliximab treatment in AIH patients results in a response rate of at least 50%, whereas a much higher response rate of at least 80% seems likely. The one-sided test problem is thus formulated as

$H_0: p \leq 0.5$  versus  $H_1: p > 0.8$ ,

where  $p$  denotes the unknown true response rate. The above null hypothesis is tested with a one-sided Binomial-test at a local significance level of 10% which is a common boundary in the context of a phase IIa study.

All other performed analyses will be of descriptive nature. Depending on the scale level of the underlying variable means and standard deviations, medians and quartiles or absolute and relative frequencies will be reported.

Statistical analysis will be performed at the Institute of Medical Biometry and Epidemiology (Medical Biometry Unit headed by Prof. Dr. Wegscheider) at the University Medical Centre Hamburg-Eppendorf.

### 9.7.2.2 Compliance / Rate of Loss to Follow Up

As the treatment is an on-site infusion treatment, adherence is granted for the infusion therapy as soon as the study participant shows up. Adherence to additional oral standard treatment with azathioprine will be collected by self-reported patient diaries. Traditionally, patients with AIH do not belong to a risk group prone to non-adherence. It has been reported that non-adherence only occurs in about 20% of patients in a real-life setting, and general study experience from patients with autoimmune liver diseases show that adherence in clinical studies is usually >90%.

## 9.8 Changes in the conduct of the study or planned analysis

Modifications of the protocol are permitted only if they are authorised by the Sponsor and the Coordinating Investigator in writing.

Deviations and changes to the study protocol will be classified by the Sponsor and the study site as:

Note-to-File: This refers to clarifications which are not considered changes of the protocol.

Study protocol amendment: This refers to substantial changes of the protocol. If they fulfil the criteria as set out in appropriate law they need to be approved by the Ethics Committees or the Competent Authorities. Changes to the study protocol may also induce revision of the patient information sheet/informed consent form. Accordingly, patients undergoing trial assessment procedures at the time of implementation of the change have to be given the amended version and have to be asked for consent to continue on this amended trial.

## 9.9 DSMB

A Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC) will be constituted to protect the safety of study participants. A DSMB is a group of external independent experts assessing the progress, safety data, and, if needed, critical efficacy endpoints of a clinical study.

## Protocol No. AIH-MAB

The DSMB will receive CRF data in the form of tables and listings and adjudicate on patient status changes. The DSMB should meet after the first 3 patients received the 3. dosing or in the event of an SAE.

The data should include, but is not limited to, demographics, patient enrolment, baseline characteristics, AE data, SAE data (by severity and causality), laboratory data, dose adjustments, protocol adherence, and patient withdrawals.

The DSMB will evaluate the progress of the trial; assess data quality and timeliness, participant recruitment, accrual and retention, and participant risk versus benefit. In addition, the DSMB/DMC will monitor external factors relevant to the trial, for example scientific and therapeutic developments that may affect participant safety or ethical status. Based on the observed benefits or adverse effects, the DSMB will make recommendations to the Sponsor concerning continuation, termination or modifications of the trial.

The Sponsor will establish a Charta document explaining the working procedures for the DSMB.

In addition, a DSMB meeting will be conducted whenever safety relevant data occur that might have an influence on the trial.

## 10 REPORTS

All reports to the Sponsor will be in English. The Sponsor will receive the original CSR. The CSR is the property of the Sponsor. Publication of the report or of part of it may only be allowed when authorised by the Sponsor in consultation with the study site.

A yearly safety report (DSUR) will be issued.

### 10.1 Clinical Study Report

All clinical, analytical and statistical results will be presented in a CSR. The outline of this report will be according to the ICH-GCP E3 document "Structure and Content of Clinical Study Reports" of July 17, 1996.

## 11 REFERENCES

1. **Hennes EM, Zeniya M, Czaja AJ, Pares A, Dalekos GN, Krawitt EL, Bittencourt PL, Porta G, Boberg KM, Hofer H, Bianchi FB, Shibata M, Schramm C, Eisenmann de Torres B, Galle PR, McFarlane I, Dienes HP, Lohse AW.** 2008. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* **48**:169-176.
2. **Kirk AP, Jain S, Pocock S, Thomas HC, Sherlock S.** 1980. Late results of the Royal Free Hospital prospective controlled trial of prednisolone therapy in hepatitis B surface antigen negative chronic active hepatitis. *Gut* **21**:78-83.
3. **Gronbaek L, Vilstrup H, Jepsen P.** 2014. Autoimmune hepatitis in Denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. *J Hepatol* **60**:612-617.
4. **Weiler-Normann C, Wiegard C, Schramm C, Lohse AW.** 2009. A case of difficult-to-treat autoimmune hepatitis successfully managed by TNF-alpha blockade. *Am J Gastroenterol* **104**:2877-2878.
5. **Weiler-Normann C, Schramm C, Quaas A, Wiegard C, Glaubke C, Pannicke N, Moller S, Lohse AW.** 2013. Infliximab as a rescue treatment in difficult-to-treat autoimmune hepatitis. *J Hepatol* **58**:529-534.
6. **Nedelkopoulou N, Vadamalayan B, Vergani D, Mieli-Vergani G.** 2017. Anti-TNFalpha Treatment in Children and Adolescents With Combined Inflammatory Bowel Disease and Autoimmune Liver Disease. *J Pediatr Gastroenterol Nutr* doi:10.1097/MPG.0000000000001759.
7. **Einarson TR, Bereza BG, Ying Lee X, Lelli F.** 2017. Dose escalation of biologics in Crohn's disease: critical review of observational studies. *Curr Med Res Opin* **33**:1433-1449.
8. **Shapiro JM, Subedi S, Machan JT, Cerezo CS, Ross AM, Shalon LB, Silverstein JA, Herzlinger MI, Kasper V, LeLeiko NS.** 2016. Durability of Infliximab Is Associated With

- Disease Extent in Children With Inflammatory Bowel Disease. *J Pediatr Gastroenterol Nutr* **62**:867-872.
9. **deBruyn JC, Jacobson K, El-Matary W, Carroll M, Wine E, Wrobel I, Van Woudenberg M, Huynh HQ.** 2017. Long-term Outcomes of Infliximab use for Pediatric Crohn's disease: A Canadian Multicenter Clinical Practice Experience. *J Pediatr Gastroenterol Nutr* doi:10.1097/MPG.0000000000001672.
  10. **Fernandez-Salazar L, Barrio J, Munoz F, Munoz C, Pajares R, Rivero M, Prieto V, Legido J, Bouhmidi A, Herranz M, Gonzalez-Redondo G, Fernandez N, Santos F, Sanchez-Ocana R, Joao D, Researchers A.** 2015. Frequency, predictors, and consequences of maintenance infliximab therapy intensification in ulcerative colitis. *Rev Esp Enferm Dig* **107**:527-533.