Signature Page for IPH2201-202_SAP
Study IPH2201-202 v2.0
ClinicalTrials.gov Identifier: NCT02557516

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Statistical Analysis Plan

Sponsor:	Innate Pharma
Protocol Title:	Open label Ib/IIa trial of a combination of IPH2201 and ibrutinib in patients with relapsed, refractory or previously untreated chronic lymphocytic leukemia.
Study Code:	IPH2201-202

ClinicalTrials.gov Identifier: NCT02557516

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For Innate Pharma:

Reviewers:

- Franceline Calmels, Clinical Trial Manager
- Agnès Boyer Chammard, Medical Director
- Federico Rotolo, Statistician

TPL N°: eTPL SA-02-01
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TPL Effective Date: 31 Mar 2016

TPL Version: 02

Approved in Vault: 3/8/2019

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1. List of Abbreviations and Definition of Terms

Abbreviation	Term
AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANC	Absolute Neutrophils Count
AST (SGOT)	Aspartate Transaminase
BOR	Best Overall Response
cCR	confirmed Complete Remission
CR	Complete Remission
CRF	Case report form
CRP	C-reactive protein
CTC	Common Toxicity Criteria
CLL	Chronic Lymphocytic Leukemia
DLT	Dose Limiting Toxicity
DOCR	Duration Of Complete Remission
DOR	Duration of Remission
ECG	Electrocardiogram
DLT	Dose Limiting Toxicity
HAHA	Human anti-human antibody response
IPH2201	Monalizumab
Ig	Immunoglobulin
ITT	Intent-To-Treat
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal Residual Disease
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not Evaluable
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive disease or PharmacoDynamic
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Remission
RBC	Red Blood Cells

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RP2D	Recommended phase II dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable Disease
TE	Treatment emergent
uCR	unconfirmed Complete Remission
WHO	World Health Organization
WBC	White Blood Cells

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2. Introduction

This Statistical Analysis Plan was written for the clinical trial IPH2201-202 conducted in the US. The ICH guideline E3 "Structure and Content of Clinical Study Reports" was used as a guide to the writing of the plan. This Statistical Analysis Plan is based on the version 5.0 of the clinical study protocol. This SAP applies both to the Phase Ib and Phase IIa part of the study.

3. Study Design and Objectives

3.1 Study Objectives

3.1.1 Phase Ib

3.1.1.1 Primary Objective

The primary objective of the phase Ib is to assess the safety of monalizumab (IPH2201) given IV as a single agent and in combination with ibrutinib in patients with relapsed, refractory or previously untreated chronic lymphocytic leukemia. The two primary endpoints of the phase Ib are:

- Occurrence of DLT and identification, if any, of the MTD, during the administration of IPH2201 as a single agent and given in combination with ibrutinib
- Occurrence of AEs and SAEs

3.1.1.2 Secondary Objectives

The secondary objectives are

- To document the anti-leukemic activity of the combination of monalizumab and ibrutinib. This corresponds to the analysis of the following endpoints:
  - Rate of overall and complete or partial response defined according to the IWCLL guidelines with an additional category of "PR with lymphocytosis" achieved with monalizumab given as a single agent during 2 cycles, and, thereafter, with the combination of monalizumab and ibrutinib, and assessed 52 weeks after the initiation of the combined treatment and during the in-study follow-up period
  - Quantitative changes of the CLL clone in the peripheral blood and the rate of response with undetectable MRD in peripheral blood and bone marrow of patients in CR (immune-phenotype by flow cytometry)
  - Duration of response, PFS and OS. Progression is defined according to the IWCLL guidelines with the exception that lymphocytosis cannot be used as the sole criterion for disease progression

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3.1.2 Phase IIa

3.1.2.1 Primary Objective

The primary objective of the phase IIa is to evaluate the anti-leukemic activity of the combination of monalizumab (IPH2201) and ibrutinib in patients with relapsed, refractory or previously untreated chronic lymphocytic leukemia. The primary endpoint will be the rate of complete response, achieved with a combination of monalizumab and ibrutinib, assessed 52 weeks after the beginning of the treatment, defined according to the guidelines of IWCLL (Hallek, Cheson et al. 2008 [1]), and confirmed by a bone marrow biopsy.

3.1.2.2 Secondary Objectives

The secondary objectives are

- To document the anti-leukemic activity of the combination of monalizumab and ibrutinib. This corresponds to the analysis of the following endpoints:
  - Rate of complete response defined according to the IWCLL guidelines, documented during the in-study follow-up period of the study
  - Rate of overall and partial response defined according to the IWCLL guidelines with an additional category of "partial response with lymphocytosis"
  - Quantitative changes of the CLL clone in the peripheral blood and the rate of response with undetectable MRD in peripheral blood and bone marrow of patients in CR (immune-phenotype by flow cytometry)
  - Duration of response, PFS and OS. Progression is defined according to the IWCLL guidelines with the exception that lymphocytosis cannot be used as the sole criterion for disease progression
- To assess the safety of the combination of monalizumab and ibrutinib. This corresponds to the analysis of adverse events, laboratory abnormalities, as well as results of vital sign measurements, electrocardiograms (ECGs), physical examinations and imaging studies.

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3.2 Study Design

The trial will consist of 2 parts:

- A phase Ib dose escalation to confirm the safety of monalizumab as a single agent during 4 weeks and thereafter combined with ibrutinib during 52 weeks.
- A phase IIa single-arm assessment of monalizumab combined with ibrutinib during 52 weeks

3.2.1 Phase Ib

Monalizumab is administered as an intravenous infusion as a single agent during the first 2 administrations, at week 0 and week 2; ibrutinib is introduced as a combination therapy at week 4. Monalizumab is administered at week 4 and 6 and then every 4 weeks. Ibrutinib is administered orally once daily.

During the phase Ib, a 3+3 design will be employed. Four doses are planned to be assessed if MTD is not previously reached:

- Dose level 1: 1 mg/kg
- Dose level 2: 2 mg/kg
- Dose level 3: 4 mg/kg
- Dose level 4: 10 mg/kg

Three patients will be entered at each dose level. If a Dose Limiting Toxicity (DLT) is encountered in the initial cohort at a given dose level, that cohort will be expanded to a total of 6 patients. MTD will be considered to have been exceeded if >1/6 patients experience a DLT at that same dose level. MTD will be sought at the previous dose level by enrolling 3 additional patients, unless this cohort has been previously expanded to 6. If less than 2 out of 6 patients develop a DLT at that level, it will be defined as the MTD.

Dose-escalation will be based on a review by the safety committee of the data from all patients of the current cohort, after they have completed first 2 cycles of single agent monalizumab. Introduction of ibrutinib at a new dose level will be allowed by the safety committee after review of the data of all patients of the previous cohort, after they have completed 2 cycles of monalizumab in combination with ibrutinib.

3.2.2 Phase IIa

During the phase IIa, patients will receive monalizumab in combination with ibrutinib from the first day of the phase IIa. Monalizumab is administered as an intravenous infusion at week 0, 2, 4 and 6 and then every 4 weeks. Ibrutinib is administered orally once daily.

3.2.3 Both phases

In both phases, treatment by monalizumab will be limited to 56 weeks, or less, in the event that a complete response with undetectable MRD is documented for 2 months. Treatment by ibrutinib will be at least administered until the end of the study follow-up period (up to 12 months after end of monalizumab treatment), unless disease progression (International Workshop on Chronic Lymphocytic Leukemia (IWCLL)), untoward toxicity, or consent withdrawal leads to the premature interruption of the ibrutinib treatment.

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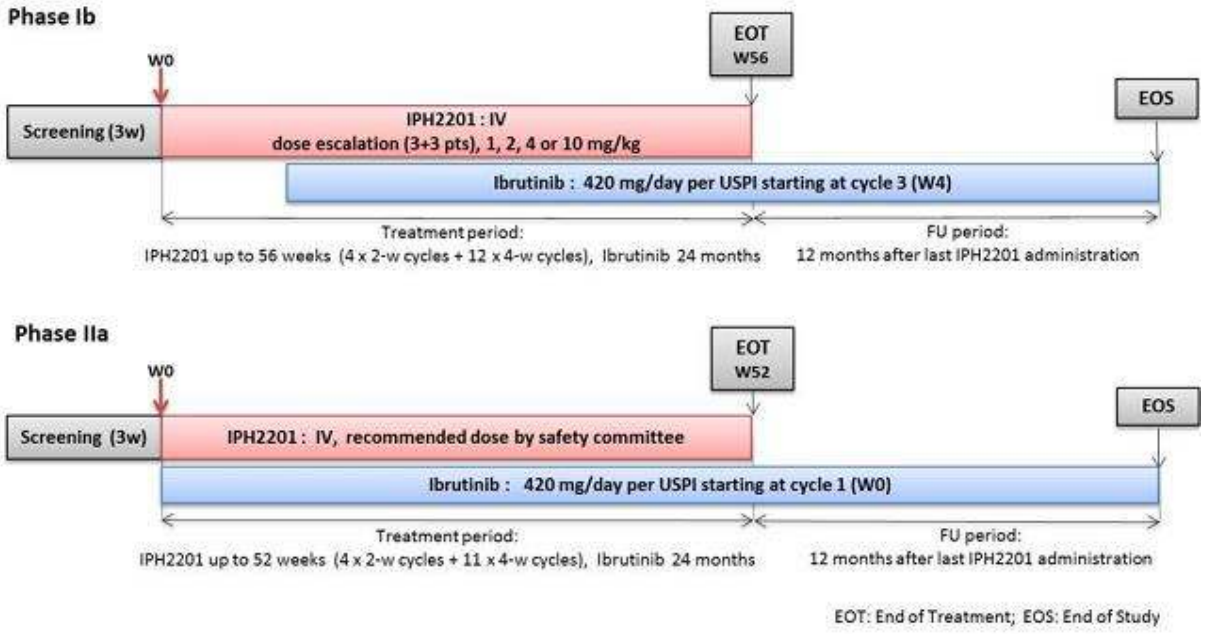
Patients will be enrolled for a post study follow-up enabling the investigator to document disease progression (IWCLL) or death, for 3 additional years after the completion of their in study follow-up.

The following figure illustrates the treatment schedule in both phases:



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The schedule of assessments is shown in Table 1 and Table 2.

Table 1

PHASE I Flow-chart	Screening[3]	W0 C1	W0D2 C1	W0D8 C1	W2 C2	W2D2 C2	W4 C3	W4D2 C3	W4D8 C3	W6 C4	W6D2 C4	W8 to W52 C5 to C16	EOT[9] W56	FU1 to FU7[15]	EOS[12]
Informed consent	X														
Inclusion / Exclusion criteria	X	X													
Demography, Medical history	X														
Concomitant illness	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tumor assessment[14]	X						X					X	X	X	X
IPH2201 administration[1]		**X**			**X**		**X**			**X**		**X**			
Ibrutinib administration[2]							**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Safety assessments															
Weight	X	X			X		X			X		X	X	X	X
Height	X														
Physical examination[4]	X	X			X		X			X		X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG status	X	X			X		X			X		X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[11]	X	X								X		W16, W32			X
Laboratory assessments															
Hematology[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry[6]	X	X	X	X	X	X	X	X	X	X	X	W8, W16, W24, W32 W40,W48	X	FU3, FU5, FU6, FU7	X
Coagulation factors[8]	X						X					W8	X		
Thyroid gland[7]	X														X
Urinalysis[10]	X						X					W32	X		
Pregnancy test		X													X
HIV / HBV / HCV screen	X														
Beta 2 microglobulin	X														
Serum Ig[13]	X											W16, W32	X		

C1 to C4 = 14-day cycles / C5 to 16 = 28-day cycles

PHASE I Flow-chart	Screening[3]	W0 C1	W0D2 C1	W0D8 C1	W2 C2	W2D2 C2	W4 C3	W4D2 C3	W4D8 C3	W6 C4	W6D2 C4	W8 to W52 C5 toC16	EOT[9] W56	FU1 to FU7[15]	EOS[12]
Immuno-pharmacological assessments															
Bone Marrow Examination	X						X[27]								
Molecular testing and cytogenetics[19]	X														
BTK mutations[20]	X						X						X		X
CLL clone monitoring[25]	X						X					W16, W28, W40, W52	X	FU3, FU5, FU6, FU7	X
Lymph Nodes biopsy[26]	X						X					W8			
MHC (HLA-E) typing	X														
RSA[16]	X	X	X										X	X	X
Pharmacokinetics[17]		X	X	X	X		X	X	X	X		W12, W20, W28, W36, W44, W52	X	X	X
HAHA & neutralizing assay[21]		X					X			X		W12, W20, W28, W36, W44, W52	X	FU2, FU4,FU5, FU6, FU7	X
NK & T Cell markers and Immunophenotyping[18]		X	X				X	X				W28	X		X
Functional assay PBMC[22]		X	X				X	X				W28	X		X
Cytokines Release[23]		X	X				X	X							
Soluble ligands[24]		X					X			X		W12, W28	X		

C1 to C4 = 14-day cycles / C5 to C16 = 28-day cycles

PHASE I flow chart foot notes:

1) IPH2201 administration should be performed 14 days + 3 days after previous administration from W0 to W6. Starting from W8, IPH2201 administration should be performed 28 days +/ -7 days after previous administration.

2) Ibrutinib will be administered at the dose of 420 mg (three 140 mg capsules) orally once daily.

3) Screening visit must be performed 3 weeks maximum prior to W0 visit;

4) Full physical exam at baseline; focused on symptoms and any new findings at all subsequent visits

5) Hematology: red blood cell(s) (RBC), WBC with differential count, platelets, hemoglobin; mean Corpuscular Volume (MCV), hematocrit. All visits, pre-dose. Additional samplings at W0 H0+4, W2 H0+4, W4 H0+4 and W6 H0+4.

6) Biochemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, total proteins, and albumin, urea, uric acid, creatinine, calculated creatinin e clearance, ALP, total bilirubin, LDH, AST (SGOT), ALT (SGPT), gamma glutamyl transferase (GGT), amylase, lipase, glucose, C -reactive protein (CRP), and fibrinogen. At every visit from screening until W12, then every 2 months, at W24, at W32, W40, W48; at EOT, FU3, FU5, FU6, FU7 and EOS. At W0 H0+4, W2 H0+4, W4 H0+4 an d W6 H0+4 additional samplings are required.

7) Thyroid: TSH, free T3 and free T4

8) Coagulation factors: activated partial thromboplastin time (APTT), prothrombin time (PT). at Screening, at predose of W4 and W8, and at EOT

9) EOT visit to be performed in case of premature discontinuation - or 14 days +3 days after W52 visit.

10) Urinalysis: PH, Glucose, Leucocytes, proteins, blood and hemoglobin, to be performed at screening, in predose of W4 and W32 visits and at EOT

11) 12-lead ECG should be performed at screening, W0 predose, W0 H0+3 +/ - 1 hour, in predose of W6, W16, W32 visits and at EOS

12) End of study visit to be performed in case of premature discontinuation, or at the end of the follow up, +/ - 7 days after previous visit

13) Testing for IgG, IgM, IgA and total immunoglobulin levels at screening, in predose of W16 and W32 visits and at EOT.

14) Tumor Assessment: pretreatment tumor assessment should be performed within 3 weeks before the first dose. Tumor assessments b y physical examination should be performed at W4, W8; afterwards at all visits until EOS. A CT scan (with contrast unless contraindicated) of the chest, abdomen, and pelvis is required for the pretreatment tumor assessment. New CT-scan should be performed at W4 visit, at W16 visit, at EOS, and to confirm any CR or progression.

15) Follow up visits, after EOT and during 12 months: follow-up visits FU1 to FU4 to be performed monthly and hereafter follow-up visits FU5 2 months after FU4, FU6 and FU7 to be performed every 3 months.

16) Receptor Saturation Assay: to be performed at Screening visit for baseline value; for patients in phase 1b part, at W0 H0 (predose), and H0+3 (2 hours after end of IPH2201 infusion);W0D2; EOT; FU1 to FU7 and at EOS

17) For patients in phase 1b part, PK assessments at W0 H0 (pre-dose), H0+1 (end of IPH2201 infusion) and H0+3 (2 hours after end of IPH2201 infusion); W0D2 (24 hours after end of IPH2201 infusion, +/- 6 hours); W0D8 W2 at H0 (pre-dose), H0+1 and H0+3; W4 at H0 (pre-dose), H0+1 and H0+3; W4D2; W4D8; W6, W12, W20, W28, W36, W14 and W52 visits, at H0 and H0+1; at EOT, FU1 to FU7 and EOS

18) NK & T cell markers and immunophenotyping sampling is to be performed at predose of W0, W0D2, W4, W4D2, W28 visits; at EOT a nd at EOS.

19) Include detection of genetic abnormalities usually associated to CLL, IgVh mutational status and ZAP 70 methylation profile

20) BTK mutations are detected at least at screening visit, W4 visit predose, EOT and EOS, and upon sponsor request if a quantitative change in the CLL cells clone occurred

21) HAHA predose assessments to be done at W0, W4, W6, W12, W20, W28, W36, W44, and W52, EOT, FU2, FU4, FU 5, FU6 and FU7 visits and at EOS

22 Functional assay sampling is to be performed at W0 predose, W0D2, W4 predose, W4D2, W28 predose, EOT and at EOS.

23) For patients in phase 1b part, cytokines release assessments will be performed at W0 and W5 at predose, H0+1, H0+3, H0+6 and at W0D2 and W4D2

24) Soluble ligands sampling to be performed at W0, W4, W6, W12 and W28 visits (predose) and at EOT

25) CLL-cells clone monitoring in peripheral blood to be performed at screening, at W4 visit and thereafter every 3 months at W16, W28, W40, W52, EOT, FU3, FU5, FU6, FU7, EOS; and in bone marrow aspirate sample when a bone marrow examination is required (in case of PD or CR).

26) Lymph nodes biopsy is optional and requires specific consent. To be done at screening, W4, W8 visits (if technically possible) and thereafter in case of disease progression

27) A bone marrow examination is required at screening visit if not performed within 1 month; at C3D1 it is optional and requires a specific consent from the patient; at least 2 months after the achievement of complete response (CR) criteria clinically and in peripheral blood, in order to confirm the CR; and in the eve nt of disease progression

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Table 2

PHASE II Flow-chart	Screening[3]	W0 C1	W0D2[8] C1	W2 C2	W2D2 C2	W4 C3	W6 C4	W8 to W48 C5 to C15	EOT[9] W52	FU1 to FU4[15]	EOS[12]
Informed consent	X										
Inclusion / Exclusion criteria	X	X									
Demography, Medical history	X										
Concomitant illness.	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Tumor assessment[14]	X					X		X	X	X	X
IPH2201 administration[1]		**X**		**X**		**X**	**X**	**X**			
Ibrutinib administration[2]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Safety assessments											
Weight	X	X		X		X	X	X	X	X	X
Height	X										
Physical examination[4]	X	X		X		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
ECOG status	X	X		X		X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X
12-lead ECG[11]	X	X					X	W16, W32			X
Laboratory assessments											
Hematology[5]	X	X	X	X	X	X	X	X	X	X	X
Biochemistry[6]	X	X	X	X	X	X	X	W16, W24, W32, W40, W48	X	X	X
Coagulation Factors[8]	X					X			X		
Thyroid gland[7]	X										X
Urinalysis[10]	X			X				W32	X		
Pregnancy test		X									X
HIV / HBV and HCV screen	X										
Beta 2 microglobulin	X										
Serum Ig[13]	X							W16, W32	X		
Immuno-pharmacological assessments											
Bone Marrow Examination[26]	X										
Molecular Testing and cytogenetics[19]	X										
BTK mutations[20]	X					X			X		X
CLL clone monitoring[24]	X					X		W16, W28, W40	X	X	X
Lymph Nodes core needle biopsy[25]	X					X		W8			
MHC (HLA-E) typing	X										
RSA[16]	X	X	X						X	X	X
NK & T Cell markers and Immunophenotyping[18]		X	X					W28	X		X
Pharmacokinetics[17]		X		X			X	W12, W20, W28, W36, W44	X	X	X
HAHA & neutralizing assay[21]		X		X			X	W12, W20, W28, W36, W44	X	X	X
Functional assay PBMC[22]		X	X					W28	X		X
Soluble ligands[23]		X		X				W12, W28	X		

PHASE II flow chart foot notes:

1) IPH2201 administration should be performed 14 days +/- 3 days after previous administration from W2 to W6. Starting from W8, IPH2201 administration should be performed 28 days +/ -3 days after previous administration.

2) Ibrutinib will be administered at the dose of 420 mg (three 140 mg capsules) orally once daily.

3) Screening visit must be performed 3 weeks maximum prior to W0;

4) Full physical exam at baseline; focused on symptoms and any new findings at all subsequent visits

5) Hematology: red blood cell(s) (RBC), WBC with differential count, platelets, hemoglobin; mean Corpuscular Volume (MCV), hematocrit. At W0 H0+4 and W2 H0+4, additional samplings are required

6) Biochemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, total proteins, and albumin, urea, uric acid, creatinine, calculated creatinine clearance, ALP, total bilirubin, LDH, AST (SGOT), ALT (SGPT), gamma glutamyl transferase (GGT), amylase, lipase, glucose, C -reactive protein (CRP) and fibrinogen. At every visit from screening until W6 visit, then every 2 months, at W16, W24, W32, W40, W48 visits; at EOT, FU1 to FU4 and EOS. At W0 H0+4 and W2 H0+4, additional samplings are required

7) Thyroid: TSH, Free T3 and Free T4

8) Coagulation factors: activated partial thromboplastin time (APTT), prothrombin time (PT). at Screening, at predose of W4 visit and at EOT

9) EOT visit To be performed in case of premature discontinuation - or 28 days +/-3 days after W48 visit

10) Urinalysis: PH, Glucose, Leucocytes, proteins, blood and hemoglobin, to be performed at screening, in predose of W2 and W32 and at EOT

11) 12-lead ECG should be performed at screening, W0 predose, W0 H0+3 +/ - 1 hour, in predose of W6, W16, W32 visits and at EOS

12) End of study visit to be performed in case of premature discontinuation, or at the end of the follow up, +/ - 7 days after previous visit

13) Testing for IgG, IgM, IgA and total immunoglobulin levels at screening, in predose of W16, W32 visits and at EOT

14) Tumor Assessment: pretreatment tumor assessment should be performed within 3 weeks before the first dose. Tumor assessments by p hysical examination should be performed at W4, W8; afterwards at all visits until EOS. A CT scan (with contrast unless contraindicated) of the chest, abdomen, and pelvis is required for the

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pretreatment tumor assessment. New CT-scan should be performed at W4, and thereafter at W 16 and at EOS, and to confirm any CR or progression.

15) Follow up visits: to be performed every 3 months after EOT and during 12 months

16) Receptor Saturation Assay: to be performed at Screening visit for baseline value; For patients in Phase 2a part, RSA to be performed at W0 H0 (pre-dose); W0D2; EOT; FU1 to FU4; EOS

17) For patients in Phase 2a part, PK assessments at W 0 H0 (pre-dose) and H0+1 (end of IPH2201 infusion); W0D1, W6, W12, W20, W28, W36, W44, W52 at H0 and H0+1; EOT, FU1 to FU4 (every 3 months); EOS

18) NK & T cell marker and Immunophenotyping sampling is to be performed at predose of W0, W0D2,W28 visits, at EOT and EOS

19) Molecular testing and cytogenetics: at screening, include detection of genetic abnormalities usually associated to CLL, IgVh mutational status and ZAP 70 methylation profile.

20) BTK mutations are detected at least at screening visit, W4 predose, EOT and EOS , and upon sponsor request in case of disease progression and / or if a quantitative change in the CLL cells clone occurred

21) HAHA predose assessments at W0; W0D1; W6D1; W12, W20, W28, W36, W44, EOT, FU1 to FU4 visits (every 3 months) and EOS

22) Functional assay sampling is to be performed at W0 predose, W0D2, W28 predose and EOT

23) Soluble ligands sampling to be performed at W0, W0D1, W12 and W28 (predose) and at EOT

24) CLL-cells clone monitoring in peripheral blood to be performed at screening, at W4 visit and thereafter every 3 months at W16, W28, W40 visits; at EOT, FU1, FU2, FU3, FU4, EOS; and in bone marrow aspirate sample when a bone marrow examination is required (in case of PD or CR).

25) Lymph nodes biopsy is optional and requires specific consent. To be done at screening, W4, W6 visits and thereafter in case of disease progression

26) A bone marrow examination is required at screening if not performed within 1 month; at least 2 months after the achievement of complete response (CR) criteria clinically and in peripheral blood, in order to confirm the CR; and in the event of disease progression

Here are also the correlation tables of visit names between Protocol V4.0 and Protocol V5.0 for patients enrolled according to previous versions of protocol.

In Phase 1 part

Calendar	-3W	W0	W0	W1	W2	W2	W4	W4	W5	W6	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	W28
Protocol V4.0	SCR	C1D1	C1D2	C1D8	C2D1	C2D2	C3D1	C3D2	C3D8	C4D1	C4D2	C5D1	C6D1	C7D1	C8D1	C9D1	C10D1	C11D1	C12D1	C13D1	C14D1	C15D1
Protocol V5.0	SCR	W0	W0D2	W0D8	W2	W2D2	W4	W4D2	W4D8	W6	W6D2	W8	-	W12	-	W16	-	W20	-	W24	-	W28

Calendar	W30	W32	W34	W36	W38	W40	W42	W44	W46	W48	W50	W52	W54	W56	Mo1	Mo2	Mo3	Mo4	Mo6	Mo9	Mo12	Mo12 +1w
Protocol V4.0	C16D1	C17D1	C18D1	C19D1	C20D1	C21D1	C22D1	C23D1	C24D1	C25D1	C26D1	C27D1	C28D1	EOT	FU1	FU2	FU3	FU4	FU5	FU6	FU7	EOS
Protocol V5.0	-	W32	-	W36	-	W40	-	W44	-	W48	-	W52	-	EOT	FU1	FU2	FU3	FU4	FU5	FU6	FU7	EOS

In Phase II part

Calendar	-3W	W0	W0	W2	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	W28
Protocol V4.0	SCR	C1D1	C1D2	C2D1	C2D2	C3D1	C4D1	C5D1	C6D1	C7D1	C8D1	C9D1	C10D1	C11D1	C12D1	C13D1	C14D1	C15D1
Protocol V5.0 Hyp.1	SCR	W0	W0D2	W2	W2D2	W4	W6	W8	-	W12	-	W16	-	W20	-	W24	-	W28

Calendar	W30	W32	W34	W36	W38	W40	W42	W44	W46	W48	W50	W52	Mo3	Mo6	Mo9	Mo12	Mo12+1w
Protocol V4.0	C16D1	C17D1	C18D1	C19D1	C20D1	C21D1	C22D1	C23D1	C24D1	C25D1	C26D1	EOT	FU1	FU2	FU3	FU4	EOS
Protocol V5.0 Hyp.1	-	W32	-	W36	-	W40	-	W44	-	W48	-	EOT	FU1	FU2	FU3	FU4	EOS

[redacted]

3.3 Sample Size Justification

3.3.1 Phase Ib

3 to 24 patients will be included.

3.3.2 Phase IIa

The design chosen for the calculation of the sample size is the one-stage Fleming design [2]. The hypotheses are α =0.05 one sided, power of 0.80. The one-sided null hypothesis is specified as H0: p =0.05 and the alternative H1: p= 0.20, p is the probability to achieve a CR. The sample size needed is 27 patients and the trial will be considered as positive if at least 4 CR are observed. The trial will be considered as negative if 3 CR or fewer are observed.
As the 3 to 6 patients treated during the phase Ib with the phase IIa recommended dose will be included in the efficacy analysis set of the phase IIa part, this means that 21 to 24 new patients will be enrolled in the phase IIa. This also means than the total number of patients will never exceed 45 (24+21).

4. General Analysis Definitions

4.1 General comments

Data will be analyzed using SAS (Version 9.3 or higher). Graphs will be produced in SAS or R.

No tests of significance will be carried out to compare treatment arms on baseline data. Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages. By default, those percentages will be calculated on the number of patients in the analysis population.

- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, first and third quartiles, minimum and maximum values.

For phase Ib results, all tables will be presented by dose level and overall. For Phase II, there will be only 1 column. Listings with individual values will be provided for all data presented in the tables.

The patients treated during the phase Ib with the phase IIa recommended dose will be analyzed in all the outputs of both phases of the trial.

4.2 Definition of Populations

4.2.1 Intent-to-treat (ITT) / safety population

The safety population will be equivalent to the ITT population and will include all patients who have received at least one dose of monalizumab. All patients will be analyzed according to the first dose of monalizumab they received.

4.2.2 Main endpoint population

The main endpoint population will include all patients:

- who have received at least one dose of monalizumab.

- who have received their first dose (W0D1) at least 52 weeks before the data cut-off date.

Patients who discontinued from monalizumab treatment due to disease progression before the end of 8 weeks of treatment will not be part of this population.

4.3 Subgroup Definitions

No subgroup is defined.

4.4 Calculated Variables

- **Baseline** is defined as the last non-missing value done before the first dose of any study treatment, i.e. date ≤ first dose. Assessments done on the date of study treatment administration are assumed to take place before the administration, unless specified otherwise.
- **Treatment-emergent** (TE) data are defined as values after the first dose of any study treatment, i.e. date ≥ first dose, and before or on 28 days after the last dose of any study treatment, i.e. date ≤ last dose +28 days

4.5 Partial Dates

As a general rule, no imputation of partial dates will be done.

However, in order to evaluate if an adverse event is treatment emergent or not and to evaluate if a medication is concomitant or not, the following rules will be applied.

For the adverse events:

- If only the day of the start date of the AE is missing, the missing day will be considered as the last day of the month. If this "imputed" date is after the date of last study treatment administration, "imputed" date will be equal to the date of last study treatment administration. However, the original variable will not be imputed and only a temporary variable will be created in order to perform the evaluation.
- If the day and the month of the start date of the AE are missing, the missing day and month will be considered as the last day of the year (i.e. 31DEC). If this "imputed" date is after the date of last study treatment administration, "imputed" date will be equal to the date of last study treatment administration. Again, the original variable will not be imputed and only a temporary variable will be created in order to perform the evaluation.
- If the date is completely missing the adverse event will be considered as treatment emergent.

For the concomitant medications:

- If only the day of the start date or end date of the concomitant medication is missing, the missing day will be considered as the last day of the month. However, the start date cannot be after the end date; in this situation, the start date will be the same as the end date. However, the original variable will not be imputed and only a temporary variable will be created in order to perform the evaluation.

[redacted]

- If the day and the month of the start date or end date of the concomitant medication are missing, the missing day and month will be considered as the last day of the year (i.e. 31DEC). However, the start date cannot be after the end date; in this situation, the start date will be the same as the end date. Again, the original variable will not be imputed and only a temporary variable will be created in order to perform the evaluation.
- If the date is completely missing the medication will be considered as concomitant.

In patient data listings, the documented date as given in the CRF, i.e. without imputation, will be reported (e.g. XXMAR2014 in case of day missing, but month and year available).

4.6 Methods To Be Used For Handling Missing Data

Missing data will not be imputed

5. Study Patients

5.1 Disposition of Patients

The number of patients in the ITT population will be presented by phase, dose level and overall.

The number of screened patients and the number of screen failure patients with their reason(s) of screening failure will be displayed.

The frequency of discontinuation from monalizumab treatment, of discontinuation from ibrutinib treatment and from study will be given for each phase, dose level and overall. The primary reason for discontinuation will be summarized. The details of the 'other reason' will be included in a listing.

5.2 Protocol Deviations

Major protocol deviations will be summarized for the ITT/safety population. Deviations to the protocol will be classified as major or minor by Innate pharma in a list sent to [redacted] before database lock.

5.3 In- and Exclusion Criteria

Listing of all in- and exclusion criteria not met will be provided.

6. Demographic and other Baseline Characteristics

Descriptive statistics with respect to patient characteristics at baseline will be displayed for the ITT/safety population.

The variables to be summarized are:

- Sex, age, race and ethnicity
- Height, weight and BMI
- Cancer history
  - Time between initial diagnosis of CLL and date of first administration of study drug (in Months)

  - Number of previous line(s) of systemic CLL Treatment
  - Presence of CLL abnormalities (yes, no or unknown) and type of genetic abnormalities of CLL at the time of diagnosis of CLL
  - IGHV gene mutation (mutated, un-mutated or unknown) and ZAP 70 expression (positive, negative or uncertain/unknown) at the time of diagnosis of CLL
- Last line of previous systemic CLL treatment
  - The reasons for this treatment line will be displayed by the categories specified in the CRF
  - The IWCLL status before this CLL treatment and the progression status before CLL treatment will be displayed
  - The number of cycles as well as the type of treatment will be displayed
  - The IWCLL best response to the induction will be summarized. If any maintenance/consolidation/intensification treatment was given, the IWCLL best response to this treatment will be displayed. And if any autologous transplant was performed, the IWCLL best response to this treatment will be displayed.
- CLL status at screening
  - Rai stage (0, I, II, III or IV)
  - Disease status (Relapse CLL, Refractory CLL or previously untreated CLL)
  - Time between the date of diagnosis of the current CLL progression and the date of first administration of study drug (in Months)
  - For patients with relapse CLL: IWCLL status and progression status before CLL treatment
  - For patients with relapse CLL or previously untreated CLL: the reasons for giving the study drug treatment will be displayed by the categories specified in the CRF
  - Presence of CLL abnormalities (yes, no or unknown) and type of genetic abnormalities of CLL at screening
  - IGHV gene mutation (mutated, un-mutated or unknown) and ZAP 70 expression (positive, negative or uncertain/unknown) at screening
- Bone marrow examination
  - Bone marrow aspirate: the quality of this sampling, the normocellular status for age, the cellularity status and the percentage of nucleated cells for lymphocytes will be summarized
  - Bone marrow biopsy: the quality of this sampling, the normocellular status for age, the cellularity status, the percentage of nucleated cells for lymphocytes (by the categories specified in the CRF), the presence of nodules and the main composition of these nodules will be summarized
- Medical history will be tabulated by system organ class and preferred term with four separate tables for 'ongoing' and 'not ongoing'and for related and not related to CLL.
- ECOG performance status
- Baseline laboratory serology results: HIV, HCV, Hbs antigen and Hbs antibody
- Child-bearing potential (yes or no, and reason for non-child-bearing potential), contraception practice and pregnancy test result.

7. Prior and Concomitant Treatment and procedures

The number and percentage of participants receiving a prior or concomitant medication will be displayed by ATC level 4 and first Anatomical Therapeutic Chemical class (ATC 1) for the ITT/safety population. Prior medications are the medications that

started and stopped before the date of first administration of the study drug. The concomitant medications will be grouped in two categories. The first group of concomitant medications corresponds to the medications which started before the date of first administration of study drug and which stopped on or after this date. The second group of concomitant medications corresponds to the medications which started on or after the date of first administration of study treatment and which stopped on or after this date. The medications with missing start and end dates will be classified in this last category. The prior medications and the two groups of concomitant medications will be displayed in three separate tables.

Concomitant procedures and surgeries will also be tabulated by system organ class and preferred term for the ITT/safety population.

8. Efficacy Evaluation

All the efficacy analyses are performed on both phases of the trial. The rates of remission (§ 8.1-8.4) will be assessed using the main endpoint population. The survival endpoints (§ 8.5) will be assessed in the ITT/safety population.

8.1 Rate of complete remission

In both phases, the rate of complete remission is assessed 52 weeks after the initiation of combined treatment

The rate of complete remission (CR) will be calculated in the main endpoint population (see §4.2.2). Within this population, the CR rate will be computed as the number of patients with a confirmed complete remission at W52 divided by the total number of patients in the main endpoint population.

The rate of complete remission with 95% confidence interval will be summarized overall and in the subgroup treated at the RP2D.

In order to claim a CR, the CR must be confirmed. In order to have a confirmed CR (cCR), the CR must be confirmed by a scan and a bone marrow assessment assessed at least 2 months after the first occurrence of CR.

8.2 Rate of overall and partial remission

The rate of overall and partial remission is assessed 52 weeks after the initiation of combined treatment and during the in-study follow-up.

The rates of overall (i.e cCR, uCR or PR) and partial remission (PR) will be calculated in the main endpoint population (see §4.2.2). Within this population, the overall/partial remission rates will be computed as the number of patients with a any/partial remission at W52 divided by the total number of patients in the main endpoint population.

The rate of overall (and partial) remission will be summarized overall and by dose level and the 95% confidence interval for this rate will be calculated only overall and in the subgroup treated at the RP2D.

The Best Overall Response (BOR) of each patient will be displayed in a summary table. The BOR is the best response (i.e cCR, uCR, PR, SD, PD or NE) taking into account all assessment results until the last disease assessment. The PR does not need to be confirmed and there is no minimum duration for SD. However, a listing with all the derived BOR will be sent to the Sponsor for medical review before the database lock.

The evolution of tumor response over time will be displayed, separately by patient, via a Swimmer plot (an example of swimmer plot can be found on page 2 of the following document: https://www.pharmasug.org/proceedings/2014/DG/PharmaSUG-2014-DG07.pdf).

8.3 Quantitative changes of the CLL clone in the peripheral blood

The median change from baseline value of the percentage of CLL cells of all lymphocytes and of the percentage of CLL cells of all Leukocytes will be displayed graphically for all patients.

8.4 Remission with undetectable MRD

Undetectable MRD is defined as the percentage of CLL cells of all lymphocytes below 0.01%. The rate of patients in cCR at W52 with undetectable MRD in peripheral blood and bone marrow will be summarized overall and by dose level, and the 95% confidence interval for this rate will be calculated only overall for the patients in the phase Ib and for the patients in the phase IIa. Remission with undetectable MRD needs to be confirmed, i.e. CR and undetectable MRD should be met jointly and confirmed jointly. The rate of remission with undetectable MRD in peripheral blood and in bone marrow will be displayed separately.

8.5 Duration of Remission (DOR), Duration of Complete Remission (DOCR), Progression free Survival (PFS) and Overall Survival (OS)

The duration of Remission (DOR) and duration of complete Remission (DOCR) will be assessed in the main endpoint population, whereas the Progression Free Survival (PFS) and Overall Survival (OS) will be assessed in the ITT/safety population.

The DOR, for the remission assessed at 52 weeks, is defined as the time from the date of first evaluation of the remission (CR or PR) to the first documentation of progressive disease, relapsed disease or death. In case an assessment of a progressive disease, relapsed disease or death record does not exist, the duration of remission is censored at the time of the last disease assessment date. The duration of remission is only calculated for the patients with a cCR, an uCR or a PR assessed at 52 weeks.

The DOCR is calculated similarly for the patients with a cCR assessed at 52 weeks.

The PFS is defined as the time from first dose administration until the occurrence of progressive disease, relapsed disease or death from any cause. Patients without an event at the time of the analysis will be censored at his or her last disease assessment date; patient with no post-baseline assessments will be censored at the day of first dose administration.

The OS is defined as the time from first dose administration until death from any cause. Alive Patients are censored at the most recent date they are known to be alive. Subjects with no assessment post-baseline will be censored at the day of first dose administration.

The Kaplan-Meier method will be used to display graphically the DOR, PFS and OS for all patients. The number of patients and the number of DOR, PFS and OS events will also be displayed on the graph. The median (with its 95% confidence interval) DOR and DCOR will be displayed. Listing with individual values will also be displayed.

[redacted]

9. Safety Evaluation

All safety analyses will be done for the ITT/safety population.

9.1 Dose Limiting Toxicity

For the patients enrolled in the phase Ib trial, the occurrence of dose limiting toxicity (DLT) and the type of DLT will be tabulated by dose level, and overall.

[redacted]

9.2 Extent of Exposure

The following outcomes will be summarized descriptively:

- Number of doses received per patient, both as categorical and continuous variable, for monalizumab and ibrutinib
- Duration of treatment for monalizumab and ibrutinib.
    - For monalizumab: if a patient discontinued prematurely from treatment, the duration of treatment is defined as the time between the date of first administration of study drug and the day before the next planned dose administration of study drug (in Months). The way of calculating the next planned dose administration is the same as for patients who did not discontinue from treatment. If a patient did not discontinue prematurely from treatment, the duration of treatment is defined as the time between the date of first administration of study drug and the date of last administration of study drug + 27 days (in Months) if the next administration is planned after Week 8; for the patients who remained under protocol version 4.0 until end of study and for patients under protocol version 5.0 with a next planned administration on or before Week 8, the duration of treatment is defined as the time between the date of first administration of study drug and the date of last administration of study drug + 13 days (in Months)
    - For ibrutinib: the duration of treatment is defined as the time between the date of first administration of study drug and the date of last administration of study drug (in Months).
- Number of patients experiencing a monalizumab dose reduction at the lower dose level
- Number of patients experiencing at least one dose administration delayed for monalizumab
- Number of patients experiencing at least one interruption during drug administration for monalizumab

- Number of patients experiencing at least one interruption of ibrutinib
- Number of patients who had an ibrutinib dose reduction from 3 capsules (420 mg) to 2 capsules (280 mg) and number of patients who had an ibrutinib dose reduction to 1 capsule (140 mg)

9.3 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities and will be graded according to the National Center Institute Common Terminology Criteria for AEs (NCI-CTCAE criteria [v4.0] [3]). Adverse events will be analyzed in terms of their type, incidence, severity and relationship to the study treatment. Related AEs are defined as events with a relationship to study treatment equal to 'possibly related', 'probably related', or 'definitively related' or with missing relationship.

Adverse events in this section will be tabulated if they are treatment-emergent (TE), see definition in Section 4.4. Partial dates will be handled according Section 4.5.

A summary table will present the frequency of patients with at least one:

- TEAE
- TEAE related to monalizumab or ibrutinib
- TEAE related to monalizumab
- TEAE related to ibrutinib
- TEAE causing monalizumab or ibrutinib discontinuation
- TEAE causing monalizumab discontinuation
- TEAE causing ibrutinib discontinuation
- TEAE causing dose delayed of monalizumab
- TEAE causing monalizumab infusion interrupted
- TEAE causing dose reduction of monalizumab at the lower dose level
- TEAE causing dose reduction of ibrutinib
- TEAE causing dose interruption of ibrutinib
- Grade 3 or worse TEAE
- Serious TEAE
- Monalizumab or ibrutinib related serious TEAE
- Monalizumab related serious TEAE
- Ibrutinib related serious TEAE
- Fatal TEAE
- Fatal TEAE related to monalizumab or ibrutinib

In addition, tabulations of the number of patients who experienced TEAEs as well as severity of the events will be presented by SOC and PT, by grade, by dose and overall. Patients will only be counted once for each preferred term. In case a patient experienced the same event more than once, the worst severity will be presented.

The following tabulations will be presented:

- All TEAEs
- Monalizumab or ibrutinib related TEAEs
- Monalizumab related TEAEs
- Ibrutinib related TEAEs
- TEAE causing monalizumab or ibrutinib discontinuation
- TEAE causing monalizumab discontinuation
- TEAE causing ibrutinib discontinuation
- TEAE causing dose reduction of monalizumab at the lower dose level
- TEAE causing dose reduction of ibrutinib
- Grade 3 or worse TEAE
- Serious TEAEs
- Monalizumab or ibrutinib related Serious TEAEs
- Monalizumab related Serious TEAEs
- Ibrutinib related Serious TEAEs
- Fatal TEAE

Listings of serious adverse events will be provided, flagging the ones that are TE, including the patient identifier, verbatim, preferred term, duration of the event, severity, action taken, outcome, causality, and date of onset.

9.4 Deaths

The number of deaths will be tabulated together with the cause of death.

A listing with the cause of death will be provided.

[redacted]

[redacted]

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[redacted]

9.6 Vital Signs, Physical Findings and Other Observations Related to Safety

Descriptive statistics of ECOG results will be presented by a shift table, comparing the worst value over the study versus baseline.

Descriptive statistics of ECGs results (normal, abnormal not clinically significant, abnormal clinically significant), heart rate, PR interval, QT interval, Bazzett's QTc and QRS duration will be presented by visit. For the continuous parameters, both absolute values and change from baseline will be presented. Unscheduled visits will not be taken into account.

Data from vital signs and physical examination will only be listed.

10. References

[1] Hallek M, Cheson BD, Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines; Blood. 2008;111(12):5446-56.

[2] Fleming T. One sample multiple testing procedure for phase II clinical trials. Biometrics 1982;38:143-151.

[3] Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, dd. June 14, 2010 - National Cancer Institute

[redacted]

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[redacted]

11.2 Efficacy outputs

[redacted]

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[redacted]

[redacted]

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[redacted]