CLINICAL STUDY PROTOCOL

Open Label Ib/IIa Trial of a Combination of IPH2201 and Ibrutinib in Patients with Relapsed, Refractory or Previously Untreated Chronic Lymphocytic Leukemia

Protocol No. IPH2201-202
IND No.: 123958 **- NCT No 02557516**

Test Product:	IPH2201
Indication:	Relapsed, refractory or previously untreated CLL
Study Phase:	Ib/IIa
Sponsor:	Innate Pharma SA 117 avenue de Luminy BP 30191 13276 Marseille Cedex 09, France Tel: 33 (0)4 30 30 30 30 Fax: 33 (0)4 30 30 30 00 e-mail: info@innate-pharma.fr Web site: www.innate-pharma.fr
Responsible Contract Research Organization (CRO):	[redacted]
Principal Coordinating Investigator:	
Date of Protocol:	12 August 2016

The study will be conducted according the regulations of each state in which investigators are engaged. The study will be conducting according the declaration of Helsinki and the Good Clinical Practices.

Document history

Document	Date of Issue	Summary of change
[redacted]		

Open Label Ib/IIa Trial of a Combination of IPH2201 and Ibrutinib in Patients with Relapsed, Refractory or Previously Untreated Chronic Lymphocytic Leukemia Protocol No. IPH-2201-202

Signature Page

Approved by the following:

[redacted]

Dr Renaud BUFFET
Medical and Translational Research
Senior Director
Innate Pharma

Date: August 12th, 2016

Signature: [signature]

Investigator Signature Page

Investigator:

I have read the protocol of the following study:

Open Label Ib/IIa Trial of a Combination of IPH2201 and Ibrutinib in Patients with Relapsed, Refractory or Previously Untreated Chronic Lymphocytic Leukemia

I agree:

- To conduct the study as outlined in the protocol and in compliance with Good Clinical Practice (GCP) and with applicable regulatory requirements;
- To provide the protocol and all drug information relating to pre-clinical and prior clinical experience, supplied to me by the sponsor, to all physicians under my responsibility and who participate in this study. I will discuss the material with them to ensure that they are fully informed regarding the drug and the conduct of the study;
- To appropriately direct and assist the staff under my control who will be involved in the study;
- To use the study material including drug supplies only according to the instructions of the protocol;
- To permit monitoring, auditing and inspection;
- To retain the study-related essential documents until the Sponsor (Innate Pharma) informs that these documents are no longer required.

I have been informed that some Regulatory Authorities require the Sponsor to obtain and supply details about the investigator's ownership interest in the Sponsor or the study drug, and more generally about his/her financial ties with the Sponsor. Innate Pharma will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply Innate Pharma with any information regarding ownership interest and financial ties (including those of my spouse and dependent children);
- Agree to promptly update this information if any relevant changes occur during the cycle of the study and for 1 year following completion of the study;
- Agree that Innate Pharma may disclose this information about such ownership interests and financial ties to regulatory authorities.

[redacted]

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List of abbreviations

ADCC	Antibody-dependent cell cytotoxicity
AE	Adverse event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine amino transferase (serum glutamic pyruvic transaminase)
AML	Acute Myeloid Leukemia
APTT	Activated partial thromboplastin time
AR	Adverse reaction
AST (SGOT)	Aspartate amino transferase (serum glutamic oxalo-acetic transaminase)
ATM	Ataxia-telengiectasia mutated
BCR	B cell receptor
BM	Bone Marrow
BP	Blood pressure
BR	Bendamustine plus rituximab
BTK	Bruton's Tyrosine Kinase
CA	Competent Authorities
CAR	Chimeric antigen receptor
CD	Cluster of Differentiation
GGT	Gamma Glutamyl-Transferase
CHO	Chinese Hamster Ovary cells
Cinf end	Concentration at the end of the administration
CL	Clearance
CLB	Chlorambucil
CLL	Chronic Lymphocytic Leukemia
Cmax	Maximum plasma concentration
CR	Complete response
CRi	CR with incomplete blood count recovery
CTL	Cytotoxic T Lymphocytes
eCRF	Electronic case report form
CRO	Contract research organization
CRP	C-reactive protein
CTCAE	Common terminology criteria for adverse events (National Cancer Institute; Version 4.03 to be used for this study)
DBP	Diastolic Blood Pressure
DILI	Drug-Induced Liver Injury
DLT	Dose limiting toxicity
DSMB	Data Safety Monitoring Board
DUN	Dispensing Unique Number
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group performance status scale
EDC	Electronic Data Capture
EFS	Event-free survival
	End of Study

EOS	End of treatment
EOT	Erythropoietin
EPO	Fludarabine, cyclophosphamide and rituximab
FRC	Fluorescence in situ
FISH	First Patient First Visit
FPFV	Follow-Up
FU	Good Clinical Practices
GCP	Granulocyte colony stimulating factor
G-CSF	Gamma Glutamyl Transferase
GGT	Granular Mononuclear – Colony Stimulating Factor
GM-CSF	Graft versus Leukemia
GvL	Human Anti-Human antibody
HAHA	Hepatitis B Virus
HBV	Hepatitis B Surface Antigens
HBS	Hematopoietic Cell Transplantation
HCT	Hepatitis C Virus
HCV	Human leukocyte antigen
HLA	Human Immuno-deficiency virus
HIV	High Group Level Term
HGLT	High Level term
HLT	Investigational medicinal product
IMP	Intravenous(ly)
IV	International Conference on Harmonization
ICH	Interferon
IFN	Immunoglobulin G
IgG	Immunoglobulin Heavy Chain
IGHV	Interleukin-2 (Aldesleukin)
IL-2	Investigational Medical Product
IMP	Innate Pharma
IPH	Institutional Review Board
IRB	International Workshop on Chronic Lymphocytic Leukemia
IWCLL	Inducible Tyrosine Kinase
ITK	Interactive Web Response System
IWRS	Killer Immunoglobulin like Receptors
KIR	Lactate Dehydrogenase
LDH	Leukemia-free survival
LFS	Lower Level Term
LLT	Lymph Node
LN	Leukemia-specific survival
LSS	Last Patient Last Visit
LPLV	Monoclonal antibody
mAb	Monoclonal B Lymphocytosis
MBL	Medical dictionary for regulatory activities
MedDRA	Modification of Diet in Renal Disease
MDRD	Myelodysplastic Syndrome

MDS	Major Histocompatibility Complex
MHC	Macrophage Inflammatory Protein-1β
MIP-1β	Minimal Residual Disease
MRD	Maximum tolerated dose
MTD	Mean Corpuscular Volume
MCV	National Cancer Institute (of the United States of America)
NCI	Non-Hodgkin Lymphoma
NHL	Natural Killer cells (immune system)
NK	NOD-scid gamma
NSG	Obinutuzumab
OBI	Ofatumumab
OFA	Overall Response Rate
ORR	Overall Survival
OS	Peripheral Blood
PB	Peripheral Blood Mononuclear Cell
PBMC	Pharmacodynamic
PD	Principal investigator
PI	Phosphatidyl inositol 3 kinase
PI3K	Progression-free survival
PFS	Pharmacokinetics
PK	Per os
PO	Time elapsed between P and R spike during ECG
PR	Prothrombin time
PT	Time for rapid depolarization of the right and left ventricles measured by ECG
QRS	Time elapsed from beginning of the QRS complex to the end of the T wave during ECG
QT	Corrected “QT” interval
QTc	Rheumatoid Arthritis
RA	Receptor Saturation Assay
RSA	Red blood cell(s)
RBC	Serious adverse event
SAE	Statistical Analysis Plan
SAP	Systolic Blood Pressure
SBP	Subcutaneous(ly)
SC	Surveillance, Epidemiology and End Results
SEER	Small Lymphocytic Lymphoma
SLL	System Organ Class
SOC	Suspected unexpected serious adverse reaction
SUSAR	Spleen Tyrosine Kinase
SYK	Time prior drug administration = Pre dose
H0	Terminal half-life
T1/2	T Cell Receptor
TCR	Tumor Lysis Syndrome
TLS	Trial Material Manual
TMM	Tumor Necrosis Factor

TNF	Time to Relapse
TTR	Time to treatment
TTT	UL16 Binding Proteins
ULBP	Upper limit of normal
ULN	White blood cell(s)
WBC	Water For Injection
WFI	

STUDY SYNOPSIS

Name of company: Innate Pharma	
Name of finished product: IPH2201	
Name of active substance: IPH2201 (formerly known as NNC0141-0100), a humanized anti-NKG2A monoclonal antibody (CHO production), INN: monalizumab	
Study code: IPH2201-202	Development phase: Ib/IIa
Study title: Open label Ib/IIa trial of a combination of IPH2201 and ibrutinib in patients with relapsed, refractory or previously untreated chronic lymphocytic leukemia	
Version: [redacted]	Release Date: 12 August 2016
Principal coordinating investigator: [redacted]	
Study centers: Phase Ib: 4 sites (US sites) Phase IIa: up to 10 sites (US sites)	
Study period (planned calendar): FPFV: 9 November 2015 LPLV: 1Q 2019	
Rationale: [redacted]	

[redacted]

[redacted]

Study objectives:

Phase Ib

- The primary objective of the phase Ib is to assess the safety of IPH2201 given IV as a single agent and in combination with ibrutinib in patients with relapsed, refractory or previously untreated chronic lymphocytic leukemia.
- The secondary objectives of the phase Ib are:
  1) To determine the PK and PD of IPH2201 given concomitantly with ibrutinib, and to confirm the PK/PD relationship of IPH2201
  [redacted]
  3) To document the anti-leukemic activity of the combination of IPH2201 and ibrutinib
  [redacted].

Phase IIa

- The primary objective of the phase IIa is to evaluate the anti-leukemic activity of the combination of IPH2201 and ibrutinib in patients with relapsed, refractory or previously untreated chronic lymphocytic leukemia.
- The secondary objectives are:
  1) To assess the safety of the combination of IPH2201 and ibrutinib
  2) To determine the PK and PD of IPH2201 given concomitantly with ibrutinib, and to confirm the PK/PD relationship of IPH2201
  [redacted]

Trial design:

Multicenter, open label Phase Ib/IIa study consisting of 2 parts:

- A part 1 dose escalation phase Ib to confirm the safety of IPH2201 as a single agent during 4 weeks and thereafter combined with ibrutinib during 52 weeks
- A part 2 single-arm phase IIa assessment of IPH2201 combined with ibrutinib during 52 weeks

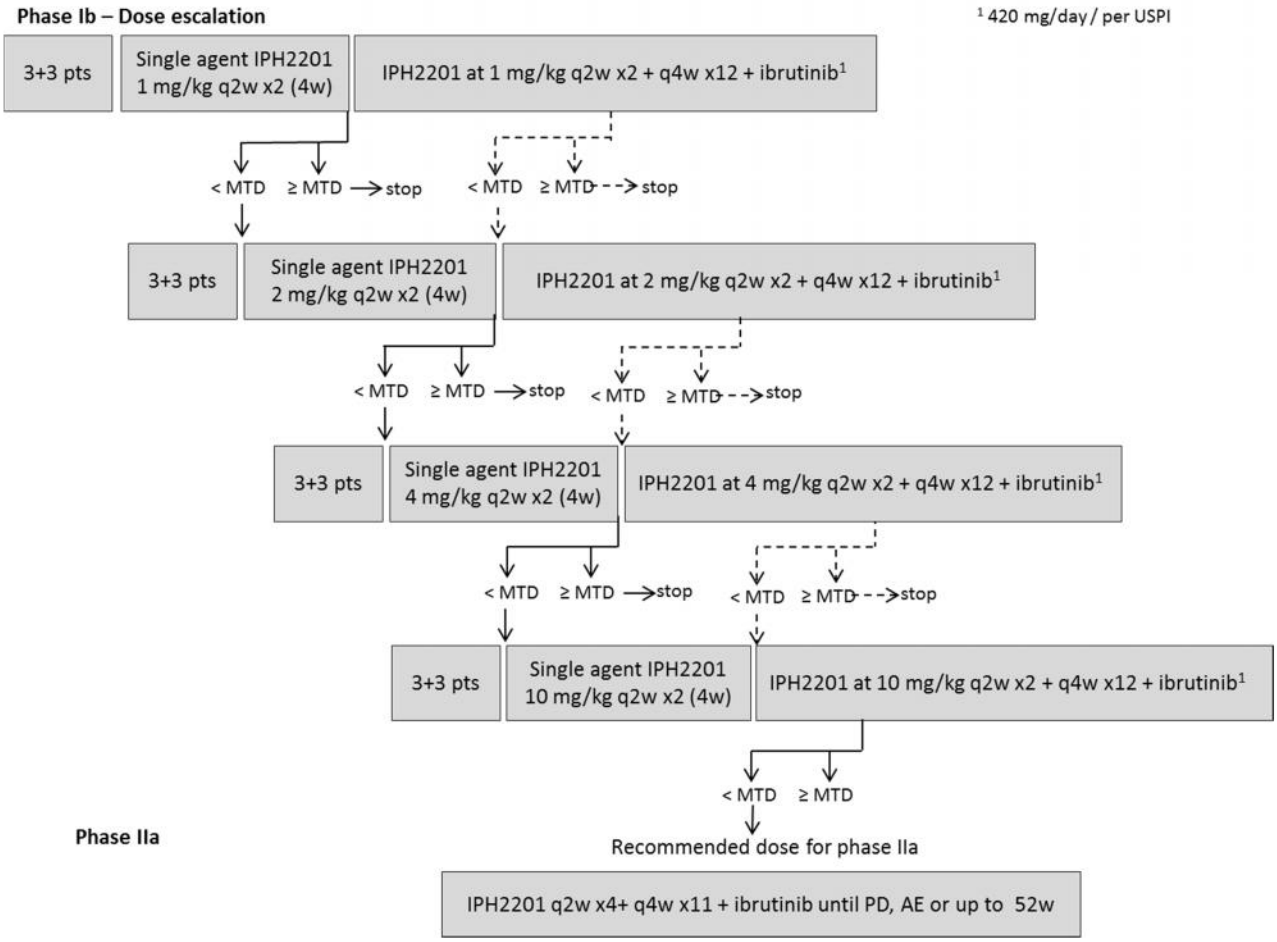
During the phase Ib, a 3+3 design will be employed. Four doses are planned to be assessed if MTD is not previously reached:

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.

Overall Study Scheme



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 IPH2201.

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 IPH2201 in combination with ibrutinib.

During the phase IIa, patients will receive IPH2201 in combination with ibrutinib from the first day of the phase IIa.

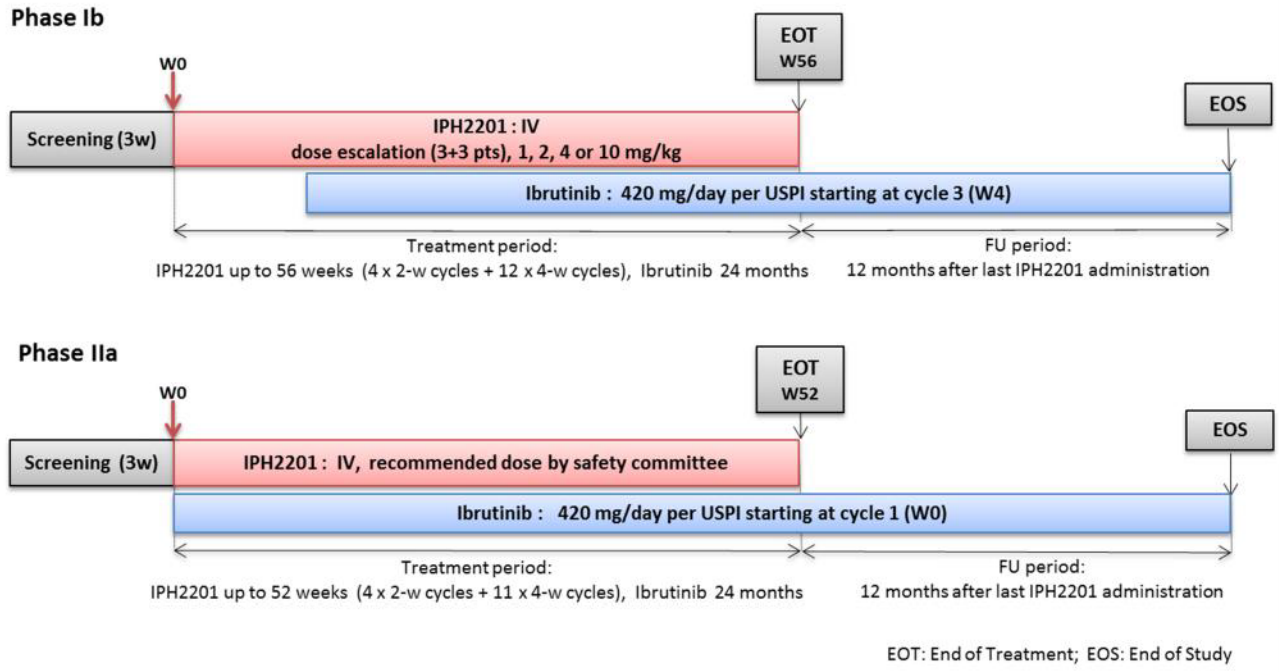
Follow-up period:

Treatment by IPH2201 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 IPH2201 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.

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.

Patient Calendar



EOT: End of Treatment; EOS: End of Study

Sample size:

36 to 45 patients will be enrolled in this clinical study:

- 12 to 24 patients (3 to 6 patients at each dose level) will be enrolled in the dose-escalation phase Ib
- Up to 24 patients in the phase IIa.

The 3 to 6 patients treated during the phase Ib at the recommended dose for the phase IIa will be included in the efficacy analysis set of the phase IIa part.

If 6 patients (3+3 for safety reasons) are treated during the phase Ib with the recommended dose for the phase IIa, a maximum of 21 patients will be included in the phase IIa; otherwise 24 patients will be included in the phase IIa study.

If 24 patients were enrolled in the phase Ib of the trial, including 6 at the recommended dose for the phase IIa, no more than 21 patients would need to be enrolled in the phase IIa. This means than the total number of patients will never exceed 45 (24+21).

The recruitment of the patients is expected to approximately cover an 18-month period.

Part 1: phase Ib

Primary endpoint:

The primary endpoint will be the safety of 2 repeated administrations of IPH2201 given as a single agent during 4 weeks, and thereafter, given in combination with ibrutinib during 52 weeks:

- 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

Safety will be assessed using the CTCAE version 4.03, apart from neutropenia and thrombocytopenia for which severity will be graded by using the IWCLL grading scale reported in appendix IV. It will include a descriptive analysis of the frequency and severity of AEs; related AEs followed to resolution (grade ≤ 1) unless deemed irreversible and clinical laboratory tests collected to assess lab abnormalities, as well as results of vital sign measurements, electrocardiograms (ECGs), physical examinations and imaging studies.

Secondary endpoints:

- Rate of overall and complete or partial response (PR) defined according to the IWCLL guidelines with an additional category of "PR with lymphocytosis", achieved with IPH2201 given as a single agent during the first 2 cycles, and thereafter, achieved with the combination of IPH2201 and ibrutinib, and assessed 52 weeks after the initiation of the combined treatment and during the in-study follow-up period.
- [redacted]
- Duration of response, progression-free survival (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.
- [redacted].
- Pharmacokinetic endpoints.
  - Concentration at the end (Cinf end) of the 1st to 4th administrations of IPH2201 (every 2 weeks) and thereafter, at the end of every other administration (every 8 weeks)
  - Accumulation index in terms of Cmax ratio, between 1st administration and selected later administrations
  - Area under the curve from 0 time to 14 days at the 1st (IPH2201 administered alone) and 3rd (IPH2201 and ibrutinib) administrations for patients in the dose escalation phase
  - Terminal half-life (T1/2) and clearance (CL) for patients who will complete the study.
- [redacted]
  - [redacted]
- [redacted]

Part 2: phase IIa

Primary endpoint:

The primary endpoint will be the rate of complete response, achieved with a combination of IPH2201 and ibrutinib, assessed 52 weeks after the beginning of the treatment, defined according to the guidelines of the IWCLL (Hallek, Cheson et al. 2008) and confirmed by a bone marrow biopsy.

Secondary endpoints:

- Rate of CR defined according to the IWCLL guidelines and documented during the in-study follow-up period of the study.
- Rate of overall and PR defined according to the IWCLL guidelines with an additional category of "PR with lymphocytosis"
- [redacted]
- Duration of response, progression-free survival (PFS) and OS. Disease Progression is defined according to the IWCLL guidelines with the exception that lymphocytosis cannot be used as the sole criterion for disease progression.
- [redacted]
- Safety will be assessed using the CTCAE version 4.03, apart from neutropenia and thrombocytopenia which severity will be graded by using the IWCLL grading scale reported in appendix IV.
- Pharmacokinetic endpoints
  - Concentration at the end (Cinf end) of the 1st, 2nd and 4th administrations and thereafter–at the end of every other administration (every 8 weeks).
  - Accumulation index in terms of Cmax ratio, between 1st administration and selected later administrations.
- [redacted]

Diagnosis and main selection criteria:

Inclusion criteria:

Patients must meet all of the following criteria for inclusion into the study:

1. Confirmed diagnosis of chronic lymphocytic leukemia (CLL) according to the IWCLL classification
2. Relapsed,refractory or previously untreated CLL
3. CLL requiring treatment according to the IWCLL criteria; patients must be eligible for ibrutinib therapy

4. Age ≥ 18 years
5. Eastern Cooperative Oncology Group performance status of 0-2
6. Life expectancy of ≥ 3 months
7. Adequate liver and renal function (total bilirubin ≤ 1.5 X institutional UNL, AST and ALT ≤ 2.5 X institutional UNL, serum creatinine ≤1.5 X institutional UNL or actual creatinine clearance ≥50 mL/min)
8. Negative serum pregnancy test within 72 hours before starting study treatment in women of childbearing potential. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation, including a minimum of 5 months after last IPH2201 treatment administration
9. Ability to understand a written informed consent document
10. Signed informed consent prior to any protocol-specific procedures

Exclusion criteria:

Patients will not be eligible for the study if they fulfil one or more of the following exclusion criteria:

1. Patients who have previously received ibrutinib or another inhibitor of BTK
2. History of allergic reactions attributed to compounds of similar chemical or biologic composition to ibrutinib
3. Central nervous system involvement by CLL
4. Abnormal hematological function which is not due to the bone marrow failure related to the CLL (hemoglobin <9.0 g/dL, absolute neutrophil count <1,000/mm^3 and/or platelets <100,000/mm^3)
5. Patients requiring a treatment by oral vitamin K antagonists
6. Serious concurrent uncontrolled medical disorder
7. Medical condition or organ system dysfunction which, in the investigator opinion could interfere with absorption or metabolism of ibrutinib
8. Moderate or severe hepatic impairment (Child-Pugh classes B and C)
9. Active auto-immune disease, which currently or previously required systemic immuno-suppressive or immunomodulatory therapy (including corticosteroids administered by systemic route) and/or has a substantial probability to cause an irreversible injury to any tissue and/or is recent or unstable or has a substantial risk to progress and cause severe complications
10. Abnormal cardiac status with any of the following:
    - Unstable angina
    - Myocardial infarction within the last 6 months
    - Arrhythmia requiring treatment and which is not stabilized by the treatment
    - QTc > 500ms (Bazett)
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
11. Pregnant women are excluded from this study; breastfeeding should be discontinued
12. Current active infectious disease, or positive serology for HIV, and/or positive PCR for HCV, or chronic HBV infection (positive Hbs Ag, and in patients treated by IVIG, a positive HBV PCR)
13. History of another malignancy within 3 years, except a malignancy, which in the opinion of the investigator is inactive and would not limit survival to less than 5 years
14. History of allogeneic stem cell or solid organ transplantation
15. Intermittent or continuous renal replacement therapy

16. Concomitant treatment with other investigational agents
17. Systemic treatment with steroids or other immunosuppressive agents within 30 days prior to entry, but physiological replacement with hydrocortisone or equivalent is acceptable
18. Patients who are on chronic treatment with strong or moderate CYP3A4 inhibitors (e.g., nefazodone, aprepitant, ciprofloxacin, diltiazem, erythromycin, fluconazole, grapefruit juice, imatinib, verapamil) or inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort) should be excluded from study entry (see Appendix V)
19. Patients should not have psychological, familial, sociological, or geographical conditions that do not permit medical follow-up and compliance with study protocol

Treatment:

In the part 1 (dose escalation phase Ib) corresponding to the first 12 to 24 patients, IPH2201 is given as a single agent during the first 2 administrations, at week 0 and week 2; ibrutinib is introduced as a combination therapy from 3rd administration at week 4.

In the part 2 (phase IIa), both drugs start from the beginning of the study, at week 0. On the days scheduled for both IPH2201 and ibrutinib therapy, IPH2201 is administered first, followed by ibrutinib, after end of IPH2201 perfusion.

In both parts of the trial, the first 4 administrations of IPH2201 (from week 0 to week 6) occur every 2 weeks. From the 5th administration IPH2201 is administered every 4 weeks.

- IPH2201

IPH2201 is administered as a 60-minute intravenous (IV) infusion starting on week 0, day 1 visit. No pre-medication is to be given at 1st administration to avoid masking the potential risk of infusion reactions. However, from the 2nd administration, pre-medication with acetaminophen or anti-histamines may be prescribed, at the investigator's discretion, if the patient experienced any grade 1 to 3 infusion-related AE in the previous cycle.

In the part 1, dose escalation phase Ib of the trial, 4 doses are planned to be assessed:

Dose level 1: 1 mg/kg

Dose level 2: 2 mg/kg

Dose level 3: 4 mg/kg

Dose level 4: 10 mg/kg

At each of the explored dose levels, a period of at least 7 days must be respected between the first IPH2201 administration to the first treated patient and the first IPH2201 administration to the following patients.

In the part 2, phase IIa of the clinical trial, the dose of IPH2201 will be selected by the safety committee.

Intra-patient dose escalation is not allowed.

- Ibrutinib

Ibrutinib is administered according to the FDA-approved label, i.e., at the dose of 420 mg (three 140 mg capsules) orally once daily.

In the part 1, phase Ib of the clinical trial, ibrutinib will be administered starting at 3rd administration of IPH2201-at week 4, in the absence of unacceptable toxicity.

In the part 2, phase IIa of the clinical trial, both drugs will be administered on the same day, from the 1st administration and from the beginning of the phase IIa.

- Prevention of the Tumor Lysis Syndrome (TLS)

In order to prevent the Tumor Lysis Syndrome (TLS), several preventative measures should be followed in phase Ib, including hydration, administration of allopurinol and Biochemistry monitoring.

Patients may be initially hospitalized in outpatient facilities. Evidences of the TLS may lead to hospitalize systematically overnight the patients.

Treatment modifications:

- IPH2201

Intra-patient dose escalation is not allowed.

In case of IPH2201 treatment discontinuation, the continuation of ibrutinib treatment is left to investigator's discretion.

- Ibrutinib

Adverse events (AEs):

Interrupt ibrutinib therapy for any grade ≥ 3 non hematological AEs, grade ≥ 3 neutropenia with infection or fever or grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to grade 1 or baseline (recovery), ibrutinib may be reinitiated at the starting dose. If the toxicity reoccurs and persists or after discontinuation of IPH2201, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following 2 dose reductions, discontinue ibrutinib.

Concomitant medications: strong CYP3A inhibitors (see appendix V) are contra-indicated if they should be given more than 7 days. If a strong CYP3A inhibitor should be given 7 days or less consider interrupting ibrutinib until the CYP3A inhibitor is no longer needed. If a moderate inhibitor (see Appendix V) should be given for any time period, reduce ibrutinib dose to 140 mg.

Elective procedures: stop ibrutinib 3 days before and after a minor procedure (e.g. invasive exploration such as a colonoscopy) and 7 days before and after a major procedure (e.g. surgery).

In case of ibrutinib treatment discontinuation, the continuation of IPH2201 treatment is left to investigator's discretion, at the same dosage and schedule as before ibrutinib discontinuation.

IPH2201 re-dosing criteria:

- Absence of progression or clinical deterioration
- Absence of grade 4 treatment-related non-hematologic AE following the previous administration
- Resolution of grade 3 or higher adverse event to grade 2 or lower

IPH2201 treatment delay:

- A delay of up to 2 weeks during phase Ib and 4 weeks during phase IIa in the treatment schedule is authorized in the absence of resolution to a grade 2 or lower of any grade ≥ 3 adverse events.

IPH2201 treatment withdrawal:

- Disease progression (IWCLL 2008 criteria)
- Adverse events: a patient may be removed from the study following a severe (grade 3) or life-threatening (grade 4) adverse event at the discretion of the treating physician
- Withdrawal of consent by the patient
- Major protocol deviations (i.e., non-compliance with treatment procedures)
- Investigator's decision
- Sponsor's decision if an inacceptable toxicity observed in another patient led the Safety Committee to recommend a transient or permanent discontinuation of the study

Patient replacement

- In any case, if patient does not receive at least 1 administration of IPH2201
- In the two phases of the trial (Ib and IIa), in case of treatment discontinuation of IPH2201 due to disease progression before the end of 8 weeks of treatment

Statistical methods

Up to 24 patients will be enrolled in the dose escalation phase Ib of the study (3 to 6 patients at each of the 4 dose levels).

After the completion of the part 1, dose escalation phase Ib, up to 27 evaluable patients will be treated with IPH2201, as part of the phase IIa of the study, at the dosage recommended at the end of the first dose level. The 3 to 6 patients enrolled during the part 1 of the study, at the dosage recommended for the phase 2 part, may be included in the group of patients used for the assessment of efficacy, thereby reducing the sample size in part 2 from 24 to 21 patients.

Primary efficacy endpoint: complete response rate based on IWCLL criteria.

The significance level (alpha risk) is set at 0.05 and power at 80%. The one-sided null hypothesis is specified as H_0: p =0.05 and the alternative H_1: p= 0.20, p the probability to achieve a CR.

Further investigation is deemed warranted if ≥ 4 patients achieve a CR by the end of the study (≥ 4/27).

The study could be technically stopped as soon as 4 CRs are documented, but, in that case, accrual of a minimum of 12 patients is recommended to further document safety, pharmacologic endpoints and biomarkers.

Safety Committee

The safety committee will consist of:

- The principal investigators of the study
- A medical and pharmacologist representatives of the sponsor
- The sub-investigators, including, the Director of the division of Hematology at OSU, as hematologist with high experience in CLL, as optional members
- A physician with relevant expertise related to the reviewed safety issues can join the safety committee as optional member

The safety committee will review the data for progression and safety with data collected as follows:

- During the dose escalation phase Ib of the trial, at each dose level after the completion of the first 2 cycles of IPH2201 by the *last* patient of the cohort
- During phase Ib, at each dose level the safety committee will also review patients data after the completion of the first 2 cycles of IPH2201 in combination with ibrutinib by the *last* patient of the cohort
- Furthermore, at any time during the phase Ib, considering any additional safety information, the safety committee may decide to decrease the dose of IPH2201 to a lower dose level
- During the phase IIa of the trial, every six months
- The Safety Committee could also be involved at any time should a major safety issue occur.

The functions of the safety committee are multiple:

- To analyse the causality of the AEs in the phase Ib
- At each dose level, to allow dose escalation as above described
- To select the dose of IPH2201 which will be assessed during the phase IIa, taking into account all the safety, pharmacology and anti-leukemia activity data gathered at each dose level. The recommended dose for phase IIa may correspond to the MTD, to the highest tested dose level or to a lower dose level, chosen during or at the end of the dose escalation. The safety committee may, therefore,

decide to stop prematurely the dose escalation, even if the MTD was not reached. The report of the safety committee will be forwarded to the FDA.

- To recommend the discontinuation of the study, transiently or permanently, or a decrease in the dose, after the occurrence of 2 unacceptable reactions in patients treated by the combination of IPH2201 and ibrutinib during the first or second phase of the study .

Dose limiting toxicities(DLTs) and unacceptable reactions are defined as:

- Any grade 3 or grade 4 non hematologic toxicity
- Grade 4 neutropenia (ANC <500/µl) lasting ≥7 days after discontinuation of therapy in patients with pre-treatment ANC ≥ 1,000/µl
- Grade 4 thrombocytopenia (platelet count <20,000/ µl and/or ≥75% decrease from pre-treatment value)
- Grade 3 or 4 thrombocytopenia associated with bleeding
- Any dose delay due to AE for > 14 consecutive days

Such events will be considered as DLTs whenever they occurred during the first 4 cycles (8 weeks) of treatment in phase Ib (including 2 administrations of treatment with IPH2201 alone and 2 administrations of treatment with IPH2201 + ibrutinib).

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														
[redacted]															
[redacted]															
[redacted]															
[redacted]		X	X												
Pharmacokinetics[17]		X	X	X	X		X	X	X	X		W12, W20, W28, W36, W44, W52	X	X	X
[redacted]															
[redacted]															
[redacted]															
[redacted]															

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 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 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 and 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 by 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 [redacted]

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 [redacted].

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

20 [redacted]

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 event of disease progression.

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[28]	X										
Molecular Testing and cytogenetics [19]	X										
[redacted]											

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 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, and thereafter at W16 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 [redacted]
17 For patients in Phase 2a part, PK assessments at W0 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 [redacted]
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.

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

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 CLINICAL BACKGROUND: CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

1.1.1 Definition and epidemiology

Chronic Lymphocytic Leukemia (CLL) results from progressive accumulation of morphologically mature CD5+ and CD23+ B lymphocytes in the blood, bone marrow and lymphatic tissues. According to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria, a diagnosis of CLL requires the presence of > 5 x 10^9 /l clonal B lymphocytes with a typical immuno-phenotype in the peripheral blood (Hallek, Cheson et al. 2008).

In Western countries, CLL is the most common form of leukemia, accounting for about 25% of all of leukemias. Incidence increases with age: CLL is extremely rare before the age of 30 years; the incidence is < 1/100,000 in individuals younger than 45 years but increases to 20/100,000 in individuals older than 85 years. An estimated around 15,500 new cases will occur in 2014 in the US, causing 4600 deaths (Siegel, Ma et al. 2014). According to data of the Surveillance, Epidemiology and End results (SEER), the median age for diagnosis of CLL is 70 years for males and 74 years for females (http://seer.cancer.gov/statfacts). CLL is almost twice as frequent in males as compared to females; and predominantly diagnosed in Caucasians while it is rare in Hispanics and Asians.

Pathogenesis

The B cell malignant clone is quiescent in circulating blood but replicates actively in bone marrow (BM) and lymphoid tissues (Messmer, Messmer et al. 2005).

Like other malignant cells, CLL cells accumulate numerous genetic abnormalities, affecting oncogenes. However, none of these aberrations is CLL-specific. Their accumulation is even not sufficient to support the growth of the malignant B cells which remains dependent on their micro-environment.

The malignant B cell clone develop in unique niches, the “proliferation centers” (or “pseudo follicles”) of lymphoid tissues where they interact with accessory cells, in particular macrophages, stromal follicular dendritic cells, and activated CD4+ T cells, as do antigen-specific normal B cells within germinal centers of lymph nodes during an immune response (Burger and Gribben 2014). One mechanism plays an essential role for the proliferation and survival of CLL cells in pseudo follicles: B-cell receptor (BCR) signaling (for review (Stevenson, Krysov et al. 2011; Woyach, Johnson et al. 2012; Burger and Chiorazzi 2013). Three kinases are pivotal for BCR signaling pathway: the phosphatidyl inositol 3 kinase (PI3K), the spleen tyrosine kinase (SYK) and, more downstream, amplifying the signal, the Bruton agammaglobulinemia tyrosine kinase (BTK). These 3 kinases are not only essential for the activation of multiple pathways of proliferation or survival of CLL cells but they are also involved in signaling mediated by the chemokine receptors which drive the adhesion and migration of the B cells in the microenvironment.

Initially, proliferation is almost counterbalanced by apoptosis. As a result, in some patients, CLL is a slowly evolving disease over years. In many patients however, the malignant clone eventually escape the surveillance of the immune system. Multiple immune defects have been described in CLL patients, impacting both T and NK cell compartments:

- T cells defects: increase in CD8 T cell count; fall in CD4:CD8 T cell ratio; chronic activation with up-regulation of CD69, HLA-DR and CD57; Th2 polarization; exhaustion with expression of inhibitory receptors PD1, CD160, CD244; increase in CD4, high CD25 and regulatory T cells (Mackus, Frakking et al. 2003); (Porakishvili, Roschupkina et al. 2001); (Riches, Davies et al. 2013); (Ramsay, Clear et al. 2012); (Beyer, Kochanek et al. 2005).

- NK cells defects: defective cytotoxic function; impaired formation of the immunological synapse; low expression of activating receptors NK30 and NKG2D (Ziegler, Kay et al. 1981; Kay and Zarling 1984); (Veuillen, Aurran-Schleinitz et al. 2012); (Huergo-Zapico, Acebes-Huerta et al. 2014).
- The CLL cells are poorly immunogenic. CLL cells develop several mechanisms of immune-resistance: low expression of ligands of activating receptors such as NKG2D ligands (MICA-B, ULBP1-3), DNAM1 ligands, CD2 ligands (CD58/LFA3) and LFA1 ligands (CD54/ICAM1); high expression of ligands of inhibitory receptors (PDL1, HVEM, CD200, B7H3); release of soluble factors by NK cells; expression of non-conventional class I MHC (HLA-G, HLA-E) (Veuillen, Aurran-Schleinitz et al. 2012); (Ramsay, Clear et al. 2012); (Burton, Weitz et al. 1989); (Katrinakis, Kyriakou et al. 1996);(Reiners, Topolar et al. 2013); (Maki, Hayes et al. 2008); (Gorgun, Holderried et al. 2005); (Jewell, Worman et al. 1992); (Spitz, Zucker-Franklin et al. 1988; Boissel, Betancur et al. 2009).
- Many treatment modalities used in CLL patients may induce a long lasting immunosuppression (Riches, Ramsay et al. 2012)

Interestingly, the functional defects of NK cells can be restored by IL-2*ex vivo,* and the resistance of CLL cells can be overcome by the IL-2 and/or IL-15, as shown *ex vivo*, but also *in vivo* in a xenogeneic model: NOD-scid gamma (NSG) mice inoculated by patient CLL cells and treated by an adoptive transfer of cytokine-activated NK cells (Veuillen, Aurran-Schleinitz et al. 2012).

Finally, several other lines of evidence suggest the importance of the immune system, and immune intervention, in the control of CLL:

- The role of Graft versus Leukemia effect, after allogeneic HCT, or of chimeric antigen receptor-T cells (CAR-T cells) as mentioned in section 1.14
- With respect to NK cells, not only experimental data, but also indirect clinical evidences: the higher cytotoxicity of NK cells in early stage of B cell malignancies, the so called monoclonal B lymphocytosis (MBL) as compared to overt CLL (Kimby, Mellstedt et al. 1989), and the correlation, shown at various stages of the disease, between the ratio of NK to CLL cell and time to treatment (TTT) (Palmer, Hanson et al. 2008)

1.1.2 Clinical manifestations

There are multiple clinical manifestations of CLL (Chiorazzi, Rai et al. 2005):

- Progressive lymphocytosis, lymphadenopathy, splenomegaly, and, more rarely, hepatomegaly. Extra-nodal involvement is not uncommon and can be observed in virtually any organ.
- Pancytopenia (anemia, thrombocytopenia, neutropenia) most often due to bone marrow involvement is responsible for fatigue, hemorrhage, and infections. Infections may also be related to the immune dysfunction, including hypo-gammaglobulinemia and a limited response to some antigens and vaccines (Morrison 2010). Infection remains the first cause of death in CLL patients. Finally, cytopenia, in some patients, may be caused by auto-immune mechanisms.

The clinical course of CLL is markedly variable. Only one third of CLL remains indolent (limited to a lymphocytosis often combined with asymptomatic lymphadenopathies) and does not impact overall survival (OS). Two thirds of the patients, however, need to be treated: half of them at or rapidly after the diagnosis and the other half after several months to years of slow progression. Finally, around 10% of CLL transform to an aggressive high grade, large B cell lymphoma (or sometimes to a Hodgkin lymphoma), the so called Richter syndrome.

1.1.3 Prognosis

Two staging systems have been used for decades to estimate long-term outcome in this heterogeneous disease. Both are based on simple clinical and biological information. The Rai classification, commonly used in the US, distinguishes 4 stages and 3 levels of risk (Wierda, O'Brien et al. 2007). The weakness of the Rai classification is a relative inability to assess the prognosis of early stage; it is not uncommon that patients categorized as low or intermediate risk do progress rapidly. More recently, molecular and genetic markers have been investigated as prognostic factors and appear to be very valuable in untreated early-stage patients. When present, these markers correlate with poor prognosis and more rapid progression of CLL (Jones and Byrd 2014). The 2 markers most often cited in the literature are:

- Unmutated variable regions of immunoglobulin heavy chain (IGHV) genes, which remain homologous to the germline sequence. They are present in about 50% of CLL patients. Mutated IGHV CLL has a median survival $\geq$ 20 years and may never require treatment. In contrast, unmutated IGHV CLL typically requires treatment within a few years from diagnosis and is associated with a shorter survival of 8 to 10 years (Hamblin, Davis et al. 1999)
- Expression of the tyrosine kinase ZAP 70, involved in signaling of T and NK cells, as well as CLL B cells. High expression of ZAP-70 is linked, although inconsistently, to the presence of unmutated IGHV genes (Wiestner, Rosenwald et al. 2003).

In addition, cytogenetic abnormalities are identified by fluorescence in situ (FISH) in approximately 80% of CLL. Two of them are associated to a worse outcome: the deletion of the chromosome 17p and 11q, affecting the p53 gene and the ataxia-telangiectasia mutated (ATM) gene, present at diagnosis in less than 20% and 10% of the cases, respectively. Median survival in patients with 17p and 11q mutated CLL has been reported to be around 32 and 79 months, respectively. In contrast, trisomy 12 typically correlates to an excellent prognosis (Dohner, Stilgenbauer et al. 2000). 17p deletion, although relatively infrequent in newly diagnosed patients, becomes more common in relapsed diseases and correlates with poor treatment response to conventional chemotherapies (Grever, Lucas et al. 2007).

1.1.4 Standards of care: classical treatments

Treatment guidelines have been developed by the IWCLL (Hallek, Cheson et al. 2008) for various clinical situations (rapidly progressive lymphocytosis; constitutional symptoms due to CLL; symptomatic massive lymphadenopathy or splenomegaly; progressive marrow failure with worsening anemia and/or thrombocytopenia; autoimmune cytopenia poorly responsive to corticosteroid treatment).

Several drugs have been approved for the treatment of CLL (for review: (Hallek 2013)):

- Cytotoxic drugs such as chlorambucil (CLB), fludarabine and bendamustine.
- Cytotoxic monoclonal antibodies (mAbs). In particular, rituximab, an anti-CD20 mAb, has activity mediated by antibody-dependent cell cytotoxicity (ADCC). Ofatumumab (OFA) has a marked complement-dependent cytotoxicity. Obinutuzumab (GA 101, OBI) has an engineered Fc fragment that enhances ADCC.

Used as single agents, these drugs have a limited efficacy. They rarely induce objective response and their impact on survival is not consistent. Chemo-immunotherapy has been a major advance in CLL. The combined use of different treatment modalities improved treatment efficacy markedly by increasing the frequency and quality of the responses, and, above all, by improving OS (Hallek 2013).

One of these regimens, the so called "FCR" combinations (6 monthly cycles of fludarabine, cyclophosphamide and rituximab), is currently considered the golden standard frontline therapy for CLL based on large prospective, randomized, phase 3 studies (Tam, O'Brien et al. 2008; Hallek, Fischer et al. 2010). FCR induces an overall response rate exceeding 90% and a complete response (CR) rate around 45%. After a median follow-up of 5.9 years, Progression Free Survival (PFS) reached 38% and OS, 69%. The FCR combination, however, has poor efficacy in CLL with 17p deletion/ p53 mutations as compared to patients without these deletions (Hallek, Fischer et al. 2010).

In addition, the FCR combination is associated with significant toxicity, particularly in elderly or unfit patients. Considering that the median age of CLL is 70 years, FCR is, in practice, very difficult to use in a majority of CLL patients (Hallek 2013).

In light of these shortcomings, alternative treatments have been tested as frontline therapy or for the treatment of relapses:

- The combination of CLB with OBI as first line treatment in unfit patients with CLL (Goede, Fischer et al. 2014). Positive results led to the approval of OBI as first line treatment of CLL.
- The combination of bendamustine with rituximab ("BR") in patients with relapsed CLL, as well as in the frontline setting (Fischer, Cramer et al. 2012). The data suggest that BR is both less active and less toxic than FCR; a randomized trial comparing BR with FCR confirmed that FCR should remain the standard therapy in fit patients but bendamustine + rituximab was associated with less toxic effects (Eichhorst, Fink et al. 2016).

Allogeneic hematopoietic cell transplantation (HCT) is potentially curative in part because of a potent graft-versus-leukemia effect. Reduced intensity conditioning regimens are preferred because they have less toxicity and are tolerable in elderly patients. Most studies, however, report a transplant related mortality of 10-20% at 1 year (Gribben 2009). As a consequence, allogeneic HCT remains largely confined to fit patients with adverse disease features such as 17p deletion or refractoriness to a purine based treatment (Dreger, Corradini et al. 2007; Zenz, Gribben et al. 2012).

The development of adoptive cell therapy using modified autologous T cells was initially hampered by safety issues (Brentjens, Yeh et al. 2010). In the majority of studies, recombinant chimeric antigen receptors (CARs) autologous T cells are used. The chimeric protein transduced in the cells combines the recognition domain of an antibody, most often directed against CD19, with intracellular signaling domains. Future studies will help clarify the role of CAR T cells therapy in the treatment of CLL (Gribben and Riches 2013).

With the availability of very active treatment options, "deep, high quality" responses became more frequent and the importance of such responses became better appreciated. The "minimal residual disease" status (MRD) corresponds to a situation where malignant CLL cells continue to persist in peripheral blood (PB) or BM of patients in CR. These malignant cells can be detected and quantified by standardized techniques of molecular biology or flow cytometry, with a sensitivity of 10^{-4} cells. These methods have been used in large multicenter studies. Flow cytometry has been used in large multicenter studies and standardized by an international group of experts (Bottcher, Hallek et al. 2013); (Rawstron, Villamor et al. 2007).

MRD was detected in 44% of the patients treated by FCR, and in 80% of patients treated by CLB + OBI (Bottcher, Ritgen et al. 2012; Goede, Fischer et al. 2014). While these numbers cannot be compared due to different techniques of detection of MRD, both studies showed that MRD detection was an independent negative predictor of PFS and OS, irrespective of other pre-treatment prognostic factors. Two other recent studies confirmed the prognostic value of MRD analysis (Strati, Keating et al. 2014); (Santacruz, Villamor et al. 2014).

1.1.5 Standards of care: B cell receptor targeted therapies

Several BCR kinase antagonists have been developed to inhibit a variety of kinases of the BCR

pathway. Inhibition of these kinases promotes apoptosis of CLL cells. They also induce a so-called "redistribution lymphocytosis" which is now well recognized and should not be confused with progressive disease (PD) (Jones and Byrd 2014). Two orally bioavailable agents have been recently approved: ibrutinib, an inhibitor of BTK, and idelalisib, an inhibitor of the p110δ PI3 kinase (PI3K) isoform.

1.1.5.1 BTK inhibitors and ibrutinib

Ibrutinib binds covalently and inhibits irreversibly BTK (as well as other tyrosine kinases).

In relapsed CLL, ibrutinib showed impressive anti-leukemia activity, although complete responses were very rare:

- In 85 patients with refractory CLL (or small lymphocytic lymphoma, SLL) treated at 420 or 840 mg daily, response rate was 71%; all responses, apart from two, were partial (Byrd, Furman et al. 2013). In an additional group of 34 patients treated at 820 mg daily, the overall response rate was quite similar (71%), and all responses were partial. An additional 15-20% of the patients had a partial response (PR) with peripheral lymphocytosis at either dose levels. A subsequent report suggested that persistent lymphocytosis does not adversely impact patient outcome, as compared with achievement of a true PR (Woyach, Awan et al. 2014). The response rate was not impacted by cytogenetic abnormalities, such as the 17p13.1 deletion. At 26 months, the estimated progression-free survival in the 85 treated patients was 75% and the rate of OS was 83% (Byrd, Furman et al. 2013).

- The "RESONATE" randomized phase III trial compared ibrutinib with the anti CD20 mAb OFA in relapsed and refractory CLL. The study enrolled 391 patients, including 127 patients with 17p deletion or resistance to chemo-immunotherapy and was stopped after a pre-planned interim analysis showed a significant reduction of the progression or death in ibrutinib treated patients. Furthermore, similar ORR, PFS and OS were observed in ibrutinib treated patients (Byrd, Brown et al. 2014).

- Ibrutinib showed also impressive anti-leukemia activity and superiority to chlorambucil in previously untreated CLL patients. The "RESONATE-2" randomized phase III trial evaluated the use of Ibrutinib versus chlorambucil in 269 treatment-naïve patients with CLL or small lymphocytic lymphoma (SLL) aged 65 years or older. Median PFS was significantly longer in the ibrutinib arm as compared to chlorambucil treated patients (median not reached vs 18.9 months); 86% of the patients responded to ibrutinib (35% to chlorambucil, $p< 0.001$). However CR remained rare, even in the ibrutinib arm, reaching 4% after a median follow-up of 18 months (Burger, Tedeschi et al. 2015).

- A smaller study but a longer (three years) follow-up, conducted in naïve and previously treated patients enrolled in RESONATE trials, provides additional information: CR rate improved, albeit very slowly, with longer follow-up and duration of the treatment. In previously untreated patients, the median time to CR was 21 months (range 4.6-42.5 months). While the CR rate at 12 months was 6%, it increased to 23% 42 months after the initiation of ibrutinib. The cumulative incidence of relapses remains far lower in previously treated patients: 3% at 12 months and 7% at 42 months (Byrd, Furman et al. 2015).

- In all above presented trials, ibrutinib was well tolerated. The most common adverse events, constitutional symptoms, fatigue, and non-specific gastro-intestinal disorders, were mild to moderate. Grade ≥ 3 infections occurred frequently. Sub-arachnoidal hemorrhages were reported in a few patients receiving anti vitamin K antagonists.

Ibrutinib was first approved in the US in February 2014 at the dose of 420 mg orally given until progression for patients with CLL who have received at least one prior therapy, as well as for first line treatment for for patients with 17p deletion CLL irrespectively of the line of therapy (July 2014). In

March 2016, ibrutinib was granted approval in the US as a first-line treatment for patients with chronic lymphocytic leukemia (CLL).

1.1.5.2 PI3K inhibitors and idelalisib

In contrast with ibrutinib, idelalisib inhibits reversibly, and specifically, its target, the PI3Kδ.

- After an initial phase I trial of single agent idelalisib in patients with relapsed CLL (Brown, Byrd et al. 2014), idelalisib was developed in combination with anti-CD20 mAbs and/or chemotherapies.
- In a randomized phase III study in 220 patients unfit for chemo-immunotherapy (Furman, Cheng et al. 2014), the combination of idelalisib and rituximab significantly improved the overall response rate (ORR), PFS, and OS as compared to placebo and rituximab (Furman, Sharman et al. 2014). However, there were no CRs and toxicity was substantial in both groups, with grade ≥ 3 adverse events being more common with the idelalisib group.

Idelalisib has been approved by the US FDA in combination with rituximab for patients with relapsed CLL for whom rituximab alone would be considered as appropriate therapy due to other comorbidities.

1.1.6 Current treatment recommendations and unmet medical need

Front line treatment

- For patients in good physical condition, purine-based immunotherapy, usually the FCR combination, remains the recommended first line treatment and typically results in PFS ≥ 5 years.
- For patients with impaired physical condition, less toxic front line treatment should be offered, such as the combination of CLB and OBI (Hallek 2013; Byrd, Jones et al. 2014). Ibrutinib as a standalone is another attractive option in this setting, since its approval by FDA in March 2016 as initial therapy of CLL. Results achieved with ibrutinib alone in untreated CLL remains less favorable than those achieved with the FCR chemo-immunotherapy, with markedly less CR, and likely shorter PFS (Brown, Hallek et al. 2016).
- In CLL with 17p deletion, ibrutinib should be preferred to FCR, even in patients in good conditions (Byrd, Jones et al. 2014).

In patients with relapsed CLL

- In patients in whom the first line therapy was well tolerated and remission exceeded 24 months, the usual recommendation is to reinstitute the same treatment.
- In all the other cases (including the patients with the 17p mutation), ibrutinib as a single agent is recommended (Byrd, Jones et al. 2014). The combination of idelalisib and rituximab is an option for patients for whom rituximab alone would not be considered as appropriate therapy due to other comorbidities. Patients may also be considered for clinical trials.

Despite these advances, major challenges persist:

- The available treatments do not eradicate CLL. This issue is especially critical in in patients with poor prognostic factors such as unmutated IGHV and in young patients.
- In the first line setting, the FCR regimen is difficult to use in many patients due to toxicity, so there is a need to identify alternative treatments that are as effective but less toxic.
- Ibrutinib has definite activity but CR is rare. The probability that ibrutinib will eradicate the disease is low, and selection of resistant mutants may result in an escape to ibrutinib therapy.

There is a need to identify more active agents and combinations. One avenue of great interest is to restore immuno-surveillance, and NKG2A blockade by IPH2201 could be one way to achieve this goal.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.2.4 Benefits and risks

1.2.4.1 Benefits

Based on the above considerations, the present study aims at inducing MRD negative CR (Byrd, Jones et al. 2014). Achieving such deep responses could provide substantial benefit to patients:

- A delay in the time to occurrence of acquired BTK and PLCγ2 mutations
- A lower rate of disease-related complications (e.g. infections and auto-immune complications)
- A prolongation of PFS and OS

1.2.4.2 Risks

Both drugs, IPH2201 and ibrutinib, are individually well tolerated, and their respective mechanisms of action indicate no particular theoretical safety risk when administered in combination. Several precautionary measures will further limit the risks for participating patients:

- Trial design

The initial tested dose (1 mg/kg) is 10 times lower than the highest dose (10 mg/kg) tested and proven to be safe in the phase I trial of IPH2201.

During the dose escalation part of the study, IPH2201 will be given as a single drug for 2 cycles over a total of 28 days. 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 2 cycles of single agent IPH2201. Introduction of ibrutinib at a new dose level will be allowed by the safety committee after review of the data from all patients of the *previous* cohort, after they have completed 2 cycles of IPH2201 in combination with ibrutinib.

- Prevention of the lysis syndrome

No tumor lysis syndrome (TLS) has been reported in patient treated by ibrutinib alone (Byrd, Furman et al. 2013). A very limited risk of TLS is expected with IPH2201 administered as single agent given the dysfunction of NK cells and the low immunogenicity of CLL cells. However, literature data suggest that CLL is associated with an intermediate risk of TLS in patients with CLL treated with targeted and / or biological therapies (Cairo, Coiffier et al. 2010). Therefore, adequate prevention and monitoring of TLS will be adopted for the 2 first administrations of IPH2201 as well as for the 2 first administrations of the combination of IPH2201 + ibrutinib in every patient in the dose-escalation phase, including hydration, administration of allopurinol, and clinical and biochemical monitoring.

- Patient selection

All provisions of the ibrutinib FDA label will be applied for the selection of patients for the present study (for instance, patients treated with anti-vitamin K will be excluded) (Byrd, Jones et al. 2014). In addition, patients will be excluded if they have a history of auto-immune diseases, including immunologic cytopenia. Patients with CLL in relapse after allogeneic HCT will be excluded.

- Safety Committee

Dose escalation will be overseen by a safety committee. The safety committee will also review all available data (safety, pharmacology and anti-leukemic activity) to select the dose of IPH2201 for the phase IIa part. The safety committee may decide to prematurely stop the dose escalation, even if the MTD was not reached. The safety committee may also recommend a dosage decrease after the occurrence of 2 unacceptable reactions to the combination of IPH2201 and ibrutinib. Finally, the committee will review the safety data or at any time if a major safety issue occurred during the progression of the trial.

2 STUDY / TRIAL OBJECTIVES AND PURPOSE

2.1 PRIMARY OBJECTIVES

- Phase Ib

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

- Phase IIa

The primary objective of the phase IIa is to evaluate the anti-leukemic activity of the combination of IPH2201 and ibrutinib in patients with relapsed, efractory or previously untreated chronic lymphocytic leukemia.

2.2 SECONDARY OBJECTIVES

The secondary objectives are:

- Phase Ib
  1. To determine the PK and PD of IPH2201 given concomitantly with ibrutinib, and to confirm the PK/PD relationship of IPH2201

     [redacted]
  3. To document the anti-leukemic activity of the combination of IPH2201 and ibrutinib

     [redacted]
- Phase IIa
  1. To assess the safety of the combination of IPH2201 and ibrutinib
  2. To determine the PK and PD of IPH2201 given concomitantly with ibrutinib, and to confirm the PK/PD relationship of IPH2201

     [redacted]

3 STUDY DESIGN

3.1 STUDY ENDPOINTS

3.1.1 Primary Endpoints

Part 1: phase Ib

The primary endpoint will be the safety of 2 repeated administrations of IPH2201 given as a single agent during 4 weeks and, thereafter, given in combination with ibrutinib during 52 weeks:

- 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

Safety will be assessed using the CTCAE version 4.03, apart from neutropenia and thrombocytopenia which severity will be graded by using the IWCLL grading scale reported in appendix IV. It will include a descriptive analysis of the frequency and severity of AEs, as well as clinical laboratory tests collected to assess lab abnormalities, results of vital sign measurements, electrocardiograms (ECGs), physical examinations and imaging studies. Related AEs will be followed to resolution (≤ grade 1) unless deemed irreversible.

Part 2: phase IIa

The primary endpoint will be the rate of complete response, achieved with a combination of IPH2201 and ibrutinib, assessed 52 weeks after the beginning of the treatment, defined according to the guidelines of IWCLL (Hallek, Cheson et al. 2008), and confirmed by a bone marrow biopsy.

3.1.2 Secondary endpoints

Part 1: phase Ib

Secondary endpoints are:

- Rate of overall and complete or partial response defined according to the IWCLL guidelines with an additional category of "PR with lymphocytosis" achieved with IPH2201 given as a single agent during 2 cycles, and, thereafter, with the combination of IPH2201 and ibrutinib, and assessed 52 weeks after the initiation of the combined treatment and during the in-study follow-up period.
- [redacted]
- 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
- [redacted]
- Pharmacokinetic endpoints
  - Concentration at the end (Cinf end) of the 1st to 4th administrations of IPH2201 (every 2 weeks) and thereafter, every at the end of every other administration (every 8 weeks)
  - Accumulation index in terms of Cmax ratio, between 1st administration and selected later administrations
  - Area under the curve from 0 time to 14 days at the 1st (IPH2201 administered alone) and 3rd (IPH2201 and ibrutinib) administrations for patients in the dose escalation phase

- Terminal half-life (T1/2) and clearance (CL) for patients who will complete the study

[redacted]

Part 2: phase IIa

Secondary endpoints are:

- 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"
- [redacted]
- Duration of response, progression-free survival (PFS) and overall survival (OS); progression is defined according to the IWCLL guidelines with the exception that lymphocytosis cannot be used as the sole criterion for disease progression
- [redacted]
- Safety of IPH2201: will be assessed using the CTCAE version 4.03 (descriptive analysis of frequency and severity of adverse events); related adverse events followed to resolution (grade ≤ 1) unless deemed irreversible. Safety evaluation will also be based on clinical laboratory tests collected to assess lab abnormalities, as well as results of vital sign measurements, electrocardiograms (ECGs), physical examinations and imaging studies.

The following endpoints are optional in the phase IIa part of the study

- Pharmacokinetic endpoints
  - Concentration at the end (Cinf end) of the 1st, 2nd and 4th administrations and thereafter-at the end of every other administration (every 8 weeks).
  - Accumulation index in terms of Cmax ratio, between 1st administration and selected later administrations.

[redacted]

3.2 OVERALL DESIGN

This is a multicenter, open label, single arm Phase Ib/IIa study, consisting of 2 parts:

- A part 1 dose escalation phase Ib to confirm the safety of IPH2201 as a single agent during 4 weeks and thereafter combined with ibrutinib during 52 weeks
- A part 2 single-arm phase IIa assessment of IPH2201 combined with ibrutinib during 52 weeks

36 to 45 patients will be enrolled in this clinical study:

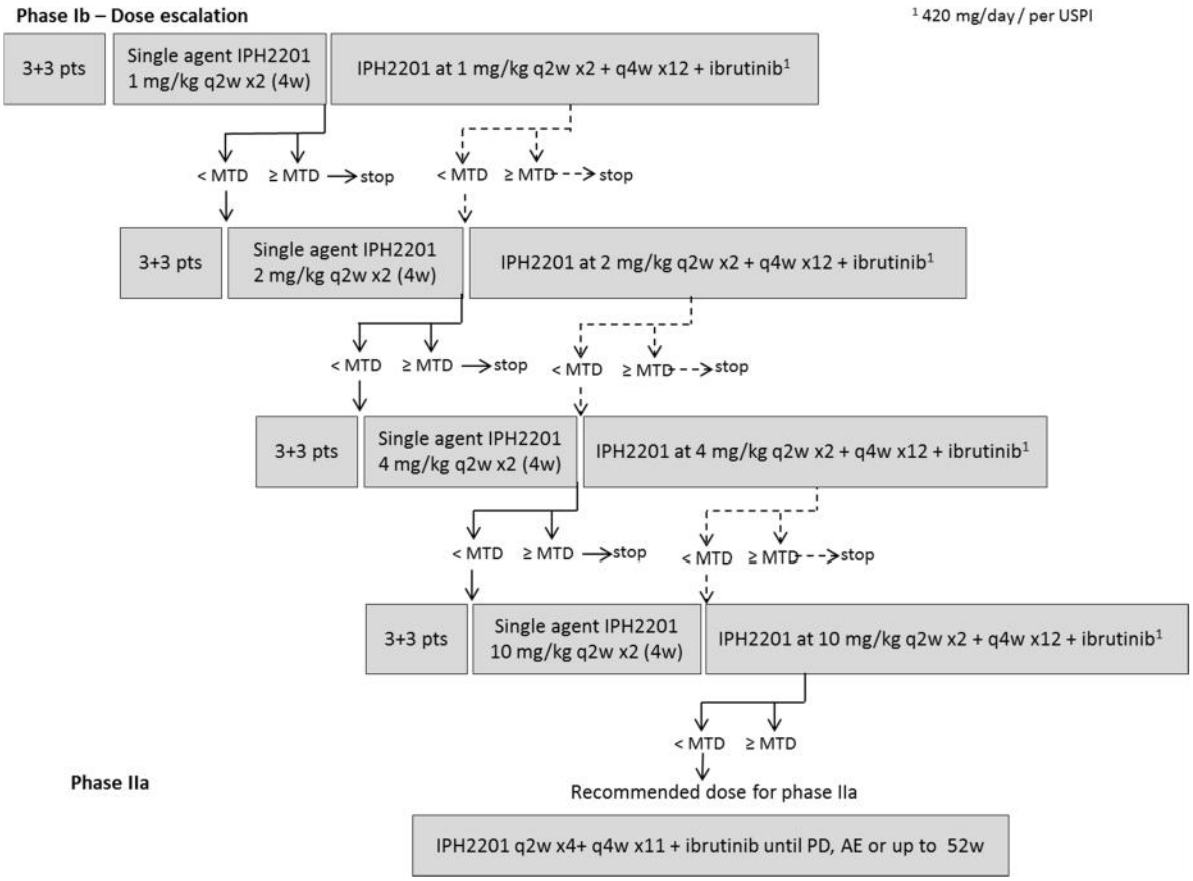
- 12 to 24 patients (3 to 6 patients at each dose level) will be enrolled in the dose-escalation phase Ib
- Up to 24 patients in the phase IIa

The last 3 to 6 patients treated during the phase Ib with the IPH2201 recommended dose level for the phase IIa (in principle 10 mg/kg) will be included in the efficacy analysis set of the phase IIa part.

If 6 patients (3+3 for safety reasons) are treated during the phase Ib with the IPH2201 recommended dose level for the phase IIa, a maximum of 21 patients will be included in the phase IIa.

If 24 patients were enrolled in the phase Ib of the trial (including 6 at the IPH2201 recommended dose level for the phase IIa), no more than 21 patients would need to be enrolled in the phase IIa. Therefore, the total number of patients will never exceed 45 (24+21).

Overall Study Scheme



3.3 ADMINISTRATION / DOSAGE

- In the part 1 (dose escalation phase Ib) corresponding to the first 12 to 24 patients, IPH2201 is administered as a single agent during the first 2 administrations, at week 0 and week 2; ibrutinib is introduced as a combination therapy from 3rd administration, at week 4.
- In the part 2 (phase IIa) corresponding to the patients treated at the dose selected by the safety committee, both drugs are administered on the same day from the beginning of the phase IIa, at week 0. On the days scheduled for both IPH2201 and ibrutinib therapy, IPH2201 is administered first, followed by ibrutinib, after end of IPH2201 perfusion.
- In both parts of the trial, the first 4 administrations of IPH2201 (from week 0 to week 6) occur every 2 weeks. From the 5th administration IPH2201 is administered every 4 weeks.
- Both IPH2201 and ibrutinib may be administered on an outpatient basis
- Treatment by IPH2201 is limited to 56 weeks, or less in the event of a CR with undetectable minimal residual disease documented for 2 months
- Treatment by ibrutinib at least is administered until the end of the follow-up period unless a disease progression (IWCLL), untoward toxicity, or consent withdrawal leads to the premature interruption of the treatment. Patients will be followed 12 months after interruption of IPH2201 treatment

3.3.1 IPH2201

IPH2201 is administered as a 60-minute intravenous (IV) infusion starting on week 0, day 1 visit. No pre-medication is to be given at 1st administration to avoid masking the potential risk of infusion reactions. However, from the 2nd administration, pre-medication with acetaminophen or anti-histamines may be prescribed at the investigator's discretion if the patient experienced any Grade 1 - 3 infusion-related AE during the previous cycle.

Part 1: phase Ib

In the part 1, dose escalation phase Ib of the trial, 4 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: 10mg/kg

At each of the explored dose levels, a period of at least 7 days must be respected between the first IPH2201 administration of the first treated patient and the first IPH2201 administration of the following patients.

In the part 2, phase IIa of the clinical trial, the doses of IPH2201 will be selected by the safety committee.

Intra-patient dose escalation is not allowed.

In case of any grade ≥3 adverse event:

- Treatment will be temporarily suspended for one week
- Treatment will be resumed at the same dosage in case of resolution to a grade 2 or lower
- In the absence of resolution to a grade 2 or lower, the treatment suspension will be prolonged by 1 more week
- In the absence of resolution to a grade 2 or lower after a 2-week suspension, the patient will be taken off study
- In case of recurrence of a grade 3 related reaction after a temporary suspension, the same suspension will apply, but after resolution to a grade 2 or lower, treatment will be resumed at the lower dose level

Part 2: phase IIa

In the part 2, phase IIa of the clinical trial, the doses of IPH2201 will be selected by the safety committee.

In case of any grade ≥3 adverse event:

- Treatment will be temporarily suspended for 2 weeks
- Treatment will be resumed at the same dosage in case of resolution to a grade 2 or lower
- In the absence of resolution to a grade 2 or lower, the treatment suspension will be prolonged by 2 more weeks
- In the absence of resolution to a grade 2 or lower after a 4-week suspension, the patient will be taken off study
- In case of recurrence of a grade 3 related reaction after a temporary suspension, the same suspension will apply, but after resolution to a grade 2 or lower, treatment will be resumed at the lower dose level

In case of IPH2201 treatment discontinuation, the continuation of ibrutinib treatment is left to investigator's discretion.

3.3.2 Ibrutinib

Ibrutinib will be administered according to the FDA-approved label, i.e., at the dose of 420 mg (three 140 mg capsules) orally once daily. Ibrutinib will be supplied commercially.

In the part 1, phase Ib of the clinical trial, ibrutinib will be administered starting at 3rd administration of IPH2201 at week 4, in the absence of unacceptable toxicity.

In the part 2, phase IIa of the clinical trial, both drugs will be administered on the same day, from the 1st administration and from the beginning of the phase IIa at week 0.

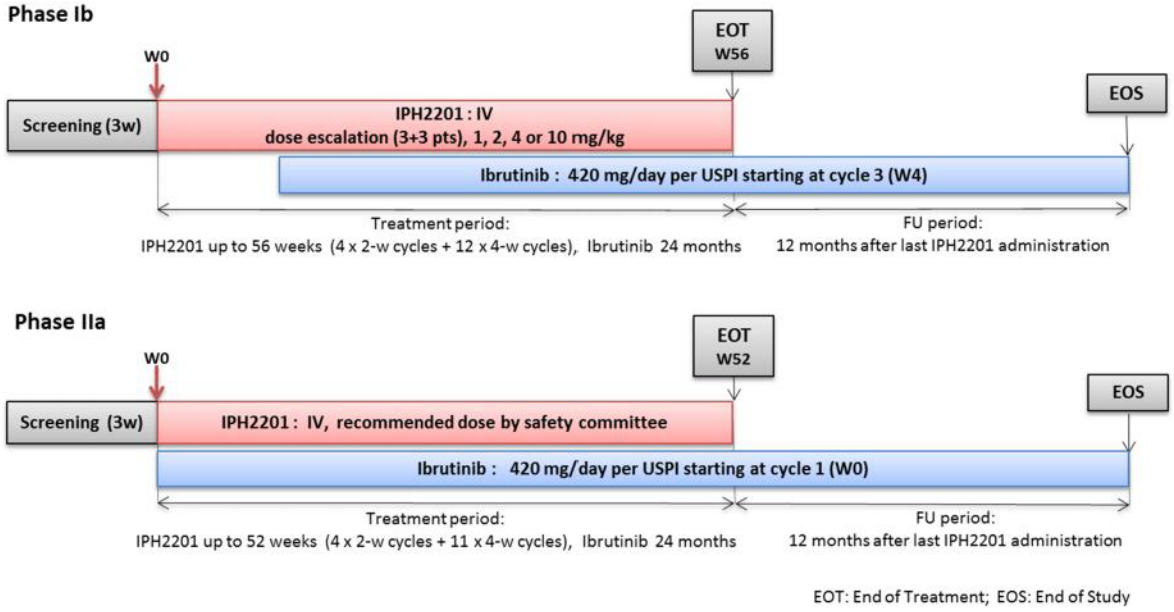
Adverse events (AEs): interrupt ibrutinib therapy for any grade ≥ 3 or greater non hematological AEs, grade ≥ 3 neutropenia with infection or fever or grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to grade 1 or baseline (recovery), ibrutinib may be reinitiated at the starting dose. If the toxicity reoccurs and persists or after discontinuation of IPH2201, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following 2 dose reductions, discontinue ibrutinib. For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 140 mg daily (one capsule).

Concomitant medications: strong CYP3A inhibitors (see appendix V) are contra-indicated if they should be given more than 7 days. If a strong CYP3A inhibitor should be given 7 days or less consider interrupting ibrutinib until the CYP3A inhibitor is no longer needed.–If a moderate inhibitor (see appendix V) should be given for any time period, reduce ibrutinib dose to 140 mg. Strong CYP3A inducers (see appendix V) should be avoided with ibrutinib.

Elective procedures: stop ibrutinib 3 days before and after a minor procedure (e.g. invasive exploration such as a colonoscopy) and 7 days before and after a major procedure (e.g. surgery).

In case of ibrutinib treatment discontinuation, the continuation of IPH2201 treatment is left to investigator's discretion at the same dosage and schedule as before ibrutinib discontinuation.

Patient Calendar:



EOT: End of Treatment; EOS: End of Study

3.3.3 Retreatment Criteria

Patients may be retreated if all the following criteria are fulfilled:

- Absence of progression or clinical deterioration
- Absence of grade 4 treatment-related non-hematologic AE following the previous administration
- Resolution of grade 3 or higher adverse event to grade 2 or lower

3.3.4 Prevention of Tumor Lysis Syndrome

In order to prevent TLS, several preventative measures should be followed in patients participating in the phase Ib part of the study.

- Hydration: patients should begin *per os* hydration 3 days before each of the first 4 infusions of IPH2201 (at least 8 full glasses of water -approximately 2 liters daily). On the day of IPH2201 administration, patients should receive IV fluids (at least 1.5 liter of normal saline) during at least 6 hours, from the first to the fourth administration during the phase Ib. Thereafter, in the absence of TLS, the patient should receive IV fluids (at least 1 liter) during 4 hours on the day of each IPH2201 administration
- Daily administration of allopurinol (200-300 mg/ day) should be given 3 days before and 4 days after the first 4 infusions of IPH220 at week 0 and Week 2 visits (IPH2201 alone) and at Week 4 and Week 6 visits (combined therapy)
- Biology should be frequently monitored from the first to the fourth administration of IPH2201, as described in the flow chart foot notes, in synopsis and in section 6 (complete blood count with differential and comprehensive metabolic panel 4 hours after the beginning of IPH2201 infusion)

Patients may be initially hospitalized in outpatient facilities. Evidences of TLS should lead in any case to keep the patient hospitalized overnight to infuse at least 4 liters of IV fluids /24hr, or perform an EKG, and, if needed, to begin a continuous cardiac monitoring until the improvement of TLS.

Evidence of TLS may lead the investigator to hospitalize the patient overnight during subsequent administrations, and to monitor closely the biochemistry.

In the absence of clinical and biological sign of TLS during the first 4 IPH2201 infusions, these preventative measures will not be necessary for subsequent IPH2201 infusions.

3.4 DURATION OF STUDY

The recruitment of up to 45 patients is expected to approximately cover an 18-month period.

Patients in part 1 may be treated up to 56 weeks: 4 cycles of 2 weeks each followed by 12 cycles of 4 weeks each.

Patients in part 2 may be treated up to 52 weeks: 4 cycles of 2 weeks each followed by 11 cycles of 4 weeks each.

Treatment by ibrutinib will be at least administered until the end of the study follow-up unless a disease progression (IWCLL), untoward toxicity or consent withdrawal leads to the premature interruption of the treatment.

Patients will be followed for 12 months after interruption of IPH2201 treatment (End of Study visit). Furthermore, patients will be enrolled in a post study follow-up enabling the documentation of disease progression (IWCLL) or death for 3 additional years after the completion of their study follow-up.

3.5 DISCONTINUATION

3.5.1 Discontinuation of the individual treatment

If a patient is progressing at any time during the study, treatment administration will be discontinued and the patient will be withdrawn from the study. For patient withdrawal, see section 5.3.

If a patient discontinues the study for safety reason, disease progression and survival information will be collected.

3.5.2 Discontinuation of the study

The sponsor may discontinue the study at any time if an unacceptable toxicity is observed in a patient that leads the safety committee to recommend a transient or permanent discontinuation of the study. If the study is prematurely discontinued, all study data must be returned to Innate Pharma. In addition, the site must conduct final disposition of all unused study drug in accordance with Innate Pharma procedures for the study.

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

Patients must meet all of the following criteria for inclusion into the study:

1. Confirmed diagnosis of CLL according to the IWCLL classification
2. Relapsed, refractory or previously untreated CLL
3. CLL requiring treatment according to the IWCLL criteria; patients must be eligible for ibrutinib therapy
4. Age ≥ 18 years
5. Eastern Cooperative Oncology Group performance status of 0-2
6. Life expectancy of ≥ 3 months
7. Adequate liver and renal function (total bilirubin ≤ 1.5 X institutional ULN, AST and ALT ≤ 2.5 X institutional ULN, serum creatinine ≤1.5 X institutional ULN or actual creatinine clearance ≥50 mL/min)
8. Negative serum pregnancy test within 72 hours before starting study treatment in women with childbearing potential. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation, including a minimum of 5 months after last IPH2201 treatment administration
9. Ability to understand a written informed consent document
10. Signed informed consent prior to any protocol-specific procedures

4.2 EXCLUSION CRITERIA

Patients will not be eligible for the study if they fulfil one or more of the following exclusion criteria:

1. Patients who have previously received ibrutinib or another inhibitor of BTK
2. History of allergic reactions attributed to compounds of similar chemical or biologic composition to ibrutinib
3. Central nervous system involvement by CLL
4. Abnormal hematological function which is not due to the bone marrow failure related to the CLL (hemoglobin < 9.0 g/dL, absolute neutrophil count <1,000/mm^3 and/or platelets <100,000/mm^3)
5. Patients requiring a treatment by oral vitamin K antagonists
6. Serious concurrent uncontrolled medical disorder
7. Medical condition or organ system dysfunction which, in the investigator opinion could interfere with absorption or metabolism of ibrutinib
8. Moderate or severe hepatic impairment (Child-Pugh classes B and C)
9. Active auto-immune disease, which currently or previously required systemic immunosuppressive or immunomodulatory therapy (including corticosteroids administered by systemic route) and/or has a substantial probability to cause an irreversible injury to any tissue and/or is recent or unstable or has a substantial risk to progress and cause severe complication

10. Abnormal cardiac status with any of the following:
    - Unstable angina
    - Myocardial infarction within the last 6 months
    - Arrhythmia requiring treatment and which is not stabilized by the treatment
    - QTc > 500ms (Bazett)
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
11. Pregnant women are excluded from this study; breastfeeding should be discontinued
12. Current active infectious disease or positive serology for HIV and/or positive PCR for HCV, or chronic HBV infection (positive Hbs Ag, and in patients treated by IVIG, a positive HBV PCR)
13. History of another malignancy within 3 years, except a malignancy, which in the opinion of the investigator is inactive and would not limit survival to less than 5 years
14. History of allogeneic stem cell or solid organ transplantation
15. Intermittent or continuous renal replacement therapy
16. Concomitant treatment with other investigational agents
17. Systemic treatment with steroids or other immunosuppressive agents within 30 days prior to entry, but physiological replacement with hydrocortisone or equivalent is acceptable
18. Patients who are on chronic treatment with strong or moderate CYP3A4 inhibitors (e.g., nefazodone, aprepitant, ciprofloxacin, diltiazem, erythromycin, fluconazole, grapefruit juice, imatinib, verapamil) or inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort) should be excluded from study entry (see Appendix V)
19. Patients should not have psychological, familial, sociological, or geographical conditions that do not permit medical follow-up and compliance with study protocol

4.3 WITHDRAWAL CRITERIA

Patients will be withdrawn from the study in the following situations:

- Disease progression (IWCLL 2008 criteria)
- Adverse events: a patient may be removed from the study following a severe (grade 3) or life-threatening (grade 4) adverse event at the discretion of the treating physician
- Withdrawal of consent by the patient
- Major protocol deviations (i.e., non-compliance with treatment procedures)
- Investigator's decision
- Sponsor's decision if an inacceptable toxicity observed in another patient led the Safety Committee to recommend a transient or permanent discontinuation of the study

After treatment withdrawal, patients will be followed for at least 4 weeks after last study drug administration or until recovery from all related adverse events to grade 1 or less, or until the toxicity level is stable for at least 6 weeks (except in case of consent withdrawal – see below). The patient will then complete the End of Study (EOS) visit.

After the EOS visit, information on the survival of the patients will be collected periodically by the sponsor through contact with the investigator. In addition, appropriate alternative treatment will be proposed by the investigator to the withdrawn patient.

4.3.1 Data Collection for withdrawal patient

In case of premature discontinuation from the study for any reason (except in case of withdrawal of consent), the investigator must make every effort to perform the end of study assessments. These data should be recorded in the medical record and eCRF, as they consist of an essential evaluation that should be done prior to withdrawing any patient from the study.

The primary reason for withdrawal will be clearly documented in the patient's medical record and recorded in the eCRF.

If a patient has a premature treatment discontinuation, the treating physician will contact the patient every 3 months for 3 years as part of the post-study follow-up. Patients will be followed until they die or withdraw consent for contact in which case the date of death will be determined from public records (e.g. the Social Security database or publications).

4.3.2 Patient Replacement Policy

In any case, if patients do not receive at least 1 administration of IPH2201.

In the two phases of the trial (Ib and IIa), in case of treatment discontinuation of IPH2201 due to disease progression before the end of 8 weeks of treatment.

5 STUDY TREATMENT(S)

5.1 INVESTIGATIONAL MEDICINAL PRODUCT (IMP): IPH2201

[redacted]

5.1.1 Packaging and labelling of trial product

IPH2201 is provided by Innate Pharma in boxes of 4 vials.

This study is open labelled.

Labelling is in accordance with local law and trial requirements. Besides, each vial is identified by a specific and single Dispensing Unique Number (DUN) number.

5.1.2 Doses of Investigational Medicinal Product

IPH2201 will be administered by intravenous route, over 1 hour infusion at 1, 2, 4 or 10 mg/kg.

5.1.3 Drug preparation and administration instructions

The Investigational Medicinal Product preparation is performed as follow:

[redacted]

DETAILED DRUG INSTRUCTIONS REGARDING RECONSTITUTION AND ADMINISTRATION ARE GIVEN IN THE CURRENT VERSION OF THE TMM.

The TMM is a guideline on how to handle all trial materials supplied by INNATE PHARMA for the trial. It is prepared in order to ensure correct ordering, handling, distribution and storage of the trial materials. All staff involved in the handling of trial materials must follow this guideline.

5.1.4 Storage

The storage and shipping conditions for IPH2201 are +5°C +/-3°C.

The investigator and/or the pharmacist must ensure the availability of proper storage conditions, including proper temperature monitoring. Calibration of the temperature monitoring unit must be done at least once a year. Preferably, the temperature must be recorded by continuous, automatic, stationary equipment. If the equipment does not record the temperature continuously, the temperature must be logged at least once every working-day. The equipment must have a "memory function" of temperatures (e.g. min/max temperatures are recorded), and the temperature must be logged the next working day after holidays.

No trial IMP should be dispensed to any person not enrolled in the trial.

Unused IMP must be stored separately from used IMP.

The pharmacist must keep an accurate record of all IMP received and the IMP used for each patient in a Drug Accountability Record. Used and partly used IMP will be retained at the investigators site pending review of drug accountability by the monitor.

An IMP may only be destroyed upon instruction from the monitor and will be documented in the Investigator's file.

5.1.5 Recall of Investigational Products

In case of recall of investigational medicinal products (decided by the Competent Authorities [CA] or the sponsor), the investigator and the pharmacist will be immediately informed by Innate Pharma.

The investigator and the pharmacist, in collaboration with the study monitor, must urgently:

- Put the concerned products in quarantine
- Recall the products dispensed in care units
- Stop the delivery of the concerned investigational medicinal products to the patients

The monitor will organize the return of the recalled product to the sponsor drug supply unit, according to the sponsor procedures.

5.1.6 Supply of Other Study Materials

Please refer to the Innate Pharma TMM for further information regarding the auxiliaries for preparation and administration of IPH2201.

5.2 IBRUTINIB

Ibrutinib will be supplied commercially.

5.3 CONCOMITANT TREATMENTS

5.3.1 Permitted

No pre-medication is to be given at 1st administration to avoid masking the potential risk of infusion reactions. However, from the 2nd administration a pre-medication by acetaminophen or anti-histamine drug might be prescribed, at the investigator discretion, if the patient experienced any grade 1 to 3 infusion-related AE at the previous cycle.

Patients should receive all necessary supportive care in the form of treatment or prophylaxis as clinically indicated e.g. transfusion of blood products, antibiotics, anti-histaminics, analgesics.

Corticosteroids by systemic route are prohibited, as mentioned below in section 5.3.2.

Any blood product and/or concomitant medication administered should be recorded in the medical record and eCRF, including dose, start and stop dates.

5.3.2 Not Permitted

The following concomitant treatments are not permitted until the end of the treatment period (End of Treatment) and must be stopped before the start of treatment accordingly with their pharmacological effects:

- Any chemotherapy or other systemic anti-tumor therapy (including other monoclonal antibody)
- Any irradiation
- Corticosteroids IV or *per os* (PO) (except for the treatment of grade ≥ 3 infusion reaction)
- Other Investigational drugs
- Cytokines and/or growth factors
- Immunosuppressive agents
- Antivitamin K anticoagulants

Strong CYP3A inhibitors (see appendix V) are contra-indicated if they must be given more than 7 days. If a strong CYP3A inhibitor must be given for 7 days or less consider interrupting ibrutinib until the CYP3A inhibitor is no longer needed.–If a moderate inhibitor (see appendix V) must be given for any time period, the dose of ibrutinib should be reduced to 140 mg. Strong CYP3A inducers (see appendix V) should be avoided with ibrutinib.

5.4 ELECTIVE PROCEDURE

Ibrutinib should be discontinued 3 days before and 3 days after a minor procedure (e.g. invasive exploration such as a colonoscopy) and 7 days before and 7 days after a major procedure (e.g. surgery). It is not required to discontinue IPH2201 under those circumstances.

5.5 COMPLIANCE

Study treatments must be administered in the investigational center and supervised by a physician or a nurse of the department.

6 STUDY VISITS AND PROCEDURES

6.1 INFORMED CONSENT AND SCREENING VISIT

Written informed consent will be obtained from the patient before any study specific procedure is undertaken.

Patients will be informed about the study verbally and by reviewing the patient information sheet and consent form. An additional information sheet and consent form will be given to patients for exploratory examinations (i.e., lymph node punch biopsies and bone marrow examination 4 weeks after the first administration of IPH2201, both of which remain optional). The patient must be given the opportunity to ask questions and time to consider his or her participation. The investigator and the patient will both sign and personally date the consent form as confirmation of consent at the screening visit.

Patients screened for the study must be registered in the IWRS system to receive a screening number.

The start of the screening period should be performed within 3 weeks prior to the planned first study drug administration (Week 0).

The following assessments will be performed at the Screening Visit or during the screening period:

- Inclusion/Exclusion criteria
- Demography data: gender, date of birth
- Medical history (including CLL)
- Concomitant illness, Concomitant medication
- Tumor assessment
- Safety assessments
  - A full physical examination including height and weight is required at baseline visit
  - Vital signs (heart rate, body temperature, diastolic and systolic blood pressure) (see detailed vital signs in Section 9.2 Safety Assessments)
  - ECOG status
  - 12-Lead ECG
- Laboratory assessments
  - Hematology: red blood cell(s) (RBC), WBC with differential count, platelets, hemoglobin; Mean Corpuscular Volume (MCV), hematocrit
  - 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
  - Urinalysis: PH, glucose, leucocytes, proteins, blood and hemoglobin
  - Coagulation factors: activated partial thromboplastin time (APTT), prothrombin time (PT)
  - HIV/Hepatitis screen (HBV and HCV)
  - Thyroid gland: TSH, Free T3 and Free T4
- Are required at the end of the screening period and when eligibility criteria have been confirmed:
  - A Bone Marrow aspirate, if not performed within 1 month before the screening visit
  - [redacted]
  - Molecular testing and cytogenetics, including detection of genetic abnormalities usually associated to CLL and IgVh mutational status

- [redacted]
- Testing for IgG, IgM, IgA and total immunoglobulin levels
- Testing of β2 microglobulin level
- [redacted]

6.2 DESCRIPTION OF STUDY CYCLES

The treatment administration visits will be performed every 2 weeks +/- 3 days during 4 cycles (8 weeks), then every 4 weeks +/- 7 days during a maximum of 12 cycles (48 weeks).

Week0 (W0) defines the first dosing visit

H0 is the start time of the 1-hour infusion and also defines the pre-dose assessments.

6.2.1 Patients in part 1 - Phase Ib

6.2.1.1 Cycle 1

Cycle 1 is a 2-week cycle and consists of 3 visits, the dosing visit (W0), a visit 24 hours after dosing (W0D2) and a visit 1 week after dosing (W0D8).

Week 0 visit (W0)

At week 0 visit, IPH2201 only will be administered.

The following pre-dose assessments must be done prior to IPH2201 administration:

- Inclusion/Exclusion criteria
- Concomitant illness/Concomitant medication
- Safety assessments
  - Vital signs (including weight)
  - Physical examination, focused on symptoms and new findings (from screening visit)
  - ECOG status
  - Adverse events
  - 12-lead ECG
- Pre-dose Safety laboratory (H0)
  - Hematology: red blood cell(s) (RBC), white blood cells (WBC) with differential count, platelets, hemoglobin, Mean Corpuscular Volume (MCV), hematocrit
  - 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
  - Pregnancy test
- Pre-dose PK/PD assessments (H0)
  - [redacted]
  - Pharmacokinetics
  - [redacted]
  - [redacted]

- [redacted]

IPH2201 will be administered as a 1-hour intravenous (IV) infusion, at one of the following dose levels:

Dose level 1: 1 mg/kg

Dose level 2: 2 mg/kg

Dose level 3: 4 mg/kg

Dose level 4: 10 mg/kg

No pre-medication is to be given to avoid masking the potential risk of infusion reactions.

The following post-dose assessments are required at cycle Week 0:

- 12-lead ECG at H0+3 (± 1 hour)
- Biochemistry at H0+4 (3 hours after *end* of infusion) sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, total proteins, and albumin, urea, uric acid, creatinine, ALP, total bilirubin, LDH, AST (SGOT), ALT (SGPT), gamma glutamyl transferase (GGT), amylase, lipase, glucose, C-reactive protein (CRP) and fibrinogen
- Hematology at H0+4 (3 hours after *end* of infusion): RBC, WBC with differential count, platelets, hemoglobin; MCV, hematocrit
- [redacted]
- PK assessments at H0+1 (at end of IPH2201 infusion) and H0+3 (2 hours after end of IPH2201 infusion)
- [redacted]

<u>Week 0 day 2 (W0D2)</u>

To be performed 24 hours ±6 hours after the administration visit at W0. The following evaluations and sampling are to be performed.

- Concomitant illness/Concomitant medication
- Vital signs
- Adverse events
- Hematology: RBC, WBC with differential count, platelets, hemoglobin; MCV, hematocrit
- 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
- [redacted]
- PK
- [redacted]

Week 0 day 8 (W0D8)

W0D8 visit will be performed 7 days ±3 days after IPH2201 administration. The following assessments should be performed:

- Concomitant illness/Concomitant medication
- Vital signs
- Adverse events
- Hematology
- Biochemistry
- PK

6.2.1.2 Cycle 2

Cycle 2 is a 2-week cycle and consists of 2 visits, the dosing visit (W2) and a visit 24 hours after dosing (W2D2).

Week 2 day 1 (W2)

As for cycle 1, IPH2201 only will be administered at week 2 day 1 (W2) visit.

The following pre-dose assessments must be done prior to IPH2201 administration:

- Concomitant illness/Concomitant medication
- Safety assessments
  - Vital signs (including weight)
  - Physical examination, focused on symptoms and new findings (from screening visit)
  - ECOG status
  - Adverse events
- Pre-dose Safety laboratory (H0)
  - 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
  - Hematology: RBC, WBC with differential count, platelets, hemoglobin; MCV, hematocrit
- PK assessment at H0

IPH2201 administration should be performed 14 days +/- 3 days after the previous administration.

Redosing criteria include the resolution of any grade 3 or higher adverse event to grade 2 or lower, the absence of disease progression and the absence of grade 4 treatment-related non-hematologic AE following the previous administration.

- The following post-dose assessments are required at W2 visit:
  - Biochemistry at H0+4: 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
  - Hematology at H0+4 : RBC, WBC with differential count, platelets, hemoglobin; MCV, hematocrit
  - PK assessments at H0+1 (end of IPH2201 infusion) and H0+3 (2 hours after end of IPH2201 infusion)

Week 2 day 2 (W2D2)

To be performed 24 hours +/- 6 hours after the administration visit at W2. All the following evaluations and sampling are to be performed.

- Concomitant illness/Concomitant medication
- Vital signs
- Adverse events
- Hematology
- Biochemistry

6.2.1.3 Cycle 3

Cycle 3 is a 2-week cycle and consists of 3 visits, the dosing visit (W4), a visit 24 hours after dosing (W4D2) and a visit 1 week after dosing (W4D8).

Week 4 day 1 (W4)

During phase 1b part patients will receive both IPH2201 and ibrutinib at Week 4 (W4) as the first cycle of combined therapy.

The following pre-dose assessments must be done prior to IPH2201 and ibrutinib administrations:

- Concomitant illness/Concomitant medication
- Safety assessments
  - Vital signs (including weight)
  - Physical examination, focused on symptoms and new findings (from screening visit)
  - ECOG status
  - Adverse events
- Pre-dose Safety laboratory (H0)
  - Hematology
  - Biochemistry
  - Coagulation factors
  - Urinalysis
- Pre-dose PK/PD assessments (H0)
  - PK
  - [redacted]
- Other specific assessments at cycle 3 are required, after completion of the treatment period by IPH2201 alone:
  - Tumor assessment: A tumor assessment by physical examination and a new CT-scan are required at W4 visit
  - A bone marrow examination: optional at cycle 3, and requiring specific consent from the patient
  - [redacted]

IPH2201 administration should be performed 14 days ± 3 days after previous administration. Re-dosing criteria include the resolution of any grade 3 or higher adverse event to grade 2 or lower, the absence of disease progression and the absence of grade 4 treatment-related non-hematologic AE following the previous administration.

For patients in dose escalation phase Ib, ibrutinib will be administered at the dose of 420 mg (three 140 mg capsules) orally once daily, from cycle 3 day 1.

IP2201 will be administered first, followed by ibrutinib, to be taken after the end of IPH2201 perfusion.

The following post-dose assessments are required at C3D1:

- Biochemistry at H0+4
- Hematology at H0+4
- PK assessments at H0+1 (end of IPH2201 infusion) and H0+3 (2 hours after end of IPH2201 infusion)
- [redacted]

Week 4 day 2 (W4D2)

To be performed 24 hours +/- 6 hours after the administration visit at W4. All the following evaluations and sampling are to be performed.

- Concomitant illness/Concomitant medication
- Vital signs
- Adverse events
- Hematology
- Biochemistry
- PK
- [redacted]
- [redacted]
- [redacted]

Week 4 day 8 (W4D8)

W4D8 visit will be performed 7 days ± 3 days after IPH2201 administration. The following assessments should be performed:

- Concomitant illness/Concomitant medication
- Vital signs Adverse events
- Hematology
- Biochemistry
- PK

6.2.1.4 Cycle 4

Cycle 4 is a 2-week cycle and consists of 2 visits, a dosing visit (W6) and a visit 24 hours after dosing (W6D2).

Week 6 day 1 (W6)

The following pre-dose assessments must be done prior to IPH2201 and ibrutinib administrations:

- Concomitant illness / Concomitant medication
- Safety assessments as following:
  - Vital signs (including weight)

- Physical examination, focused on symptoms and new findings (from screening visit)
- ECOG status
- Adverse events

- Pre-dose Safety laboratory (H0)
  - Biochemistry
  - Hematology
  - A 12-lead ECG
- Pre-dose PK/PD assessments (H0)
  - PK
  - [redacted]
  - [redacted]

IPH2201 administration should be performed 14 days +/- 3 days after the previous administration.

- The following post-dose assessments are required at W6 visit:
  - Biochemistry at H0+4
  - Hematology at H0+4 PK assessments at H0+1 (at end of the 1-hour infusion of IPH2201)

<u>Week 6 day 2 (W6D2)</u>

To be performed 24 hours +/- 6 hours after the administration visit at W6. The following evaluations and sampling are to be performed:

- Concomitant illness/Concomitant medication
- Vital signs
- Adverse events
- Hematology
- Biochemistry

6.2.1.5 Cycle 5 to cycle 16

From cycle 5 (W8) cycles last for 4 weeks and consist of 1 dosing visit only.

Patients who were enrolled according to a previous version of the protocol [redacted] will switch to a 4-week cycle schedule of visits after they have completed and signed an amended informed and consent form. The switch to the new schedule of visits will occur in place of the nearest *odd visit*.

[redacted]

The following pre-dose assessments must be done prior to IPH2201 and ibrutinib administrations:

- Concomitant illness/Concomitant medication
- Tumor assessment:
  - a tumor assessment by physical examination is required at all dosing visits starting from W8 visit (monthly assessments);
  - a CT-scan should be performed at W16 and at any other visit to confirm a CR or progression, whenever one of these events is suspected
- Safety assessments
  - Vital signs (including weight)
  - Physical examination, focused on symptoms and new findings (from screening visit)

- ECOG status
- Adverse events
- A 12-lead ECG is required at W16 and W32

- Pre-dose Safety laboratory (H0)
  - Hematology
  - Biochemistry, required at W8, W12, W16, then every 2 months, at W24, W32, W40 and W48
  - Coagulation factors to be performed at W8
  - Urinalysis at W32 only
- Pre-dose PK/PD assessments (H0)
  - Pharmacokinetics at W12, W20, W28, W36, W44, W52
  - [redacted]
  - Testing for IgG, IgM, IgA and total immunoglobulin levels in predose of W16 and W32
  - [redacted]

IPH2201 administration should be performed 28 days +/- 7 days after previous administration.

IP2201 will be administered first, followed by ibrutinib taken after the end of IPH2201 perfusion.

The following post-dose assessments are required:

- PK assessments at H0+1 (end of IPH2201 infusion) at W12, W20, W28, W36, W44, W52

6.2.2 Patients in part 2 – Phase IIa

6.2.2.1 Cycle 1

Cycle 1 is a 2-week cycle and consists of 2 visits, the dosing visit (W0) and a visit 24 hours after dosing (W0D2).

Week 0 day 1 (W0)

For the first patients included in the phase IIa part, IPH2201 and ibrutinib will be administered as combined therapy from W0 visit.

The following pre-dose assessments must be done prior to IPH2201 administration:

- Inclusion/Exclusion criteria
- Concomitant illness/Concomitant medication
- Safety assessments
  - Vital signs (including weight)
  - Physical examination, focused on symptoms and new findings (from screening visit)
  - ECOG status
  - Adverse events
  - 12-lead ECG
- Pre-dose Safety laboratory (H0)

- Hematology: red blood cell(s) (RBC), WBC with differential count, platelets, hemoglobin; Mean Corpuscular Volume (MCV), hematocrit
- 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), GGT, amylase, lipase, glucose, CRP and fibrinogen
- Pregnancy test

- Pre-dose PK/PD assessments (H0)
  - [redacted]
  - PK
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

IPH2201 will be administered as a 1-hour intravenous (IV) infusion. Patients will be treated at the recommended dose by the Safety Committee.

H0 is the start time of the 1-hour infusion.

For patients in the phase IIa part, ibrutinib will be administered at the dose of 420 mg (three 140 mg capsules) orally once daily, from W0.

IP2201 will be administered first, immediately followed by ibrutinib.

The following post-dose assessments are required at W0:

- 12-lead ECG at H0+3 +/- 1 hour
- Biochemistry at H0+4: 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
- Hematology at H0+4 : RBC, WBC with differential count, platelets, hemoglobin; MCV, hematocrit
- PK assessments at H0+1 (end of IPH2201 infusion)

<u>Week 0 day 2 (W0D2)</u>

To be performed 24 hours +/- 6 hours after the administration visit at W0. The evaluations and sampling quoted at this visit are to be performed.

- Concomitant illness/Concomitant medication
- Vital signs
- Adverse events
- Hematology
- Biochemistry
- RSA
- NK & T cells markers and Immunophenotyping
- Functional assay (PBMC)

6.2.2.2 Cycle 2

Cycle 2 is a 2-week cycle and consists of 2 visits, the dosing visit (W2) and a visit 24 hours after dosing (W2D2).

Week 2 day 1 (W2)

The following pre-dose assessments must be done prior to IPH2201 and ibrutinib administration:

- Concomitant illness/Concomitant medication
- Safety assessments
  - Vital signs (including weight)
  - Physical examination, focused on symptoms and new findings (from screening visit)
  - ECOG status
  - Adverse events
- Pre-dose Safety laboratory (H0)
  - Hematology
  - Biochemistry
  - Urinalysis
- Pre-dose PK/PD assessments (H0)
  - PK
  - [redacted]

IPH2201 administration should be performed 14 days ± 3 days after previous administration. Re-dosing criteria include the resolution of any grade 3 or higher adverse event to grade 2 or lower, the absence of disease progression and the absence of grade 4 treatment-related non-hematologic AE following the previous administration.

The following post-dose assessments are required at W2 visit:

- PK assessments at H0+1 (end of IPH2201 infusion)
  - Biochemistry at H0+4: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, total proteins, and albumin, urea, uric acid, creatinine, ALP, total bilirubin, LDH, AST (SGOT), ALT (SGPT), gamma glutamyl transferase (GGT), amylase, lipase, glucose, C-reactive protein (CRP) and fibrinogen
  - Hematology at H0+4 : RBC, WBC with differential count, platelets, hemoglobin; MCV, hematocrit

Week 2 day 2 (W2D2)

To be performed 24 hours ± 6 hours after the administration visit at W2. The following evaluations should be performed at the visit:

- Concomitant illness/Concomitant medication
- Vital signs
- Adverse events
- Hematology
- Biochemistry

6.2.2.3 Cycle 3

Cycle 3 is a 2-week cycle and consists of 1 dosing visit (W4) only.

Week 4 day 1 (W4)

The following pre-dose assessments must be done prior to IPH2201 and ibrutinib administrations:

- Concomitant illness/Concomitant medication
- Safety assessments
  - Vital signs (including weight)
  - Physical examination, focused on symptoms and new findings (from screening visit)
  - ECOG status
  - Adverse events
- Pre-dose Safety laboratory (H0)
  - Hematology
  - Biochemistry
  - Coagulation factors
- Other specific assessments are required at W4 visit
  - Tumor assessment: A tumor assessment by physical examination and a new CT-scan are required at W4 visit
  - [redacted]

IPH2201 administration should be performed 14 days ± 3 days after previous administration
IP2201 will be administered first, followed by ibrutinib, to be taken after the end of IPH2201 perfusion.

There are no required post-dose assessments at W4

6.2.2.4 Cycle 4

Cycle 4 is a 2-week cycle and consists of 1 dosing visit (W6) only.

Week 6 day 1 (W6)

The following pre-dose assessments must be done prior to IPH2201 and ibrutinib administrations:

- Concomitant illness / Concomitant medication
- Safety assessments as following:
  - Vital signs (including weight)
  - Physical examination, focused on symptoms and new findings (from screening visit)
  - ECOG status
  - Adverse events
- Pre-dose Safety laboratory (H0)
  - Biochemistry
  - Hematology
  - A 12-lead ECG
- Pre-dose PK/PD assessments (H0)
  - PK
  - [redacted]

IPH2201 administration should be performed 14 days +/- 3 days after the previous administration.

IP2201 will be administered first, followed by ibrutinib, to be taken after the end of IPH2201 perfusion.

- The following post-dose assessments are required at W6 visit:
  - PK assessments at H0+1 (at end of the 1-hour infusion of IPH2201)

6.2.2.5 Cycle 5 to cycle 15

From cycle 5 (W8) cycles last for 4 weeks and consist of 1 dosing visit only.

The following pre-dose assessments should be done prior to IPH2201 and ibrutinib administrations:

- Concomitant illness/Concomitant medication
- Tumor assessment:
  - a tumor assessment by physical examination is required at all dosing visits starting from W8 visit (monthly assessments);
  - a CT-scan should be performed at W16 and at any other visit to confirm a CR or progression, whenever one of these events is suspected
- Safety assessments
  - Vital signs (including weight)
  - Physical examination, focused on symptoms and new findings (from screening visit)
  - ECOG status
  - Adverse events
  - A 12-lead ECG is required at W16 and W32
- Pre-dose Safety laboratory (H0)
  - Hematology: RBC, WBC with differential count, platelets, hemoglobin; MCV and hematocrit
  - 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), GGT, amylase, lipase, glucose, CRP and fibrinogen, required at W16, W24, W32, W40 and W48
  - Urinalysis at predose of W32
- Pre-dose PK/PD assessments (H0)
  - Pharmacokinetics at W12, W20, W28, W36 and W44
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
  - Testing for IgG, IgM, IgA and total immunoglobulin levels in predose of W16 and W32
- Other specific assessments (H0)
  - [redacted]
  - [redacted]

IPH2201 administration should be performed 28 days +/- 7 days after the previous administration.

IP2201 will be administered first, followed by ibrutinib, to be taken after the end of IPH2201 perfusion.

The following post-dose assessments are required:

- PK assessments at H0+1 (end of IPH2201 infusion) at W12, W20, W28, W36 and W44

6.3 END OF TREATMENT VISIT

The end of Treatment (EOT) visit takes place in case of premature discontinuation or 14 ± 5 days after last treatment cycle.

The following assessments are required:

- Concomitant illness/Concomitant medication
- Tumor assessment:
  - a tumor assessment by physical examination
  - a CT-scan should be performed to confirm a CR or progression, whenever one of these events is suspected
- [redacted]
- Safety assessments:
  - Vital signs (including weight)
  - Physical examination, focused on symptoms and new findings (from screening visit)
  - ECOG status
  - Adverse events
- Safety laboratory
  - Hematology
  - Biochemistry
  - Coagulation factors
  - Urinalysis
- PK/PD assessments
  - [redacted]
  - [redacted]
  - Pharmacokinetics
  - [redacted]
  - [redacted]
  - [redacted]
  - Serum Ig: Testing for IgG, IgM, IgA and total Immunoglobulin levels are required at EOT visit
  - [redacted]

6.4 FOLLOW-UP VISITS

Phase Ib:

For the patients included in phase Ib, follow-up visits are performed after the End of Treatment visit and during a 12-month period. The follow-up visits FU1 to FU4 will be done monthly, follow-up visit FU5 will take place 2 months after FU4, and follow-up visits FU6 and FU7 will be performed every 3 months

Phase IIa:

For the patients included in the phase IIa part of the study, follow-up visits are performed after the End of Treatment visit every 3 months for a 12-month period.

At follow-up visits the following assessments are required:

- Concomitant illness/Concomitant medication
- Tumor assessment:
  - a tumor assessment by physical examination is required at all follow-up visits

- a CT-scan should be performed to confirm a CR or progression, whenever one of these events is suspected

- Safety assessments:
  - Vital signs (including weight)
  - Physical examination, focused on symptoms and new findings (from screening visit)
  - ECOG status
  - Adverse events
- Safety laboratory
  - Hematology
  - Biochemistry: at FU3, FU5, FU6, FU7 in phase Ib, and at FU1, FU2, FU3 and FU4 in phase II (assessments every 3 months)
- PK/PD assessments
  - [redacted]
  - Pharmacokinetics
  - [redacted]
  - [redacted]

6.5 END OF STUDY VISIT

The End of Study (EOS) Visit is performed in case of premature discontinuation or at the end of the follow-up period.

The following assessments are required:

- Concomitant illness/Concomitant medication
- Tumor assessment:
  - a tumor assessment by physical examination is required
  - a CT-scan should be performed to confirm a CR or progression, whenever one of these events is suspected
- Safety assessments:
  - Vital signs (including weight)
  - Physical examination, focused on symptoms and new findings (from screening visit)
  - ECOG status
  - Adverse events
  - 12-lead ECG at EOS
- Safety laboratory
  - Hematology
  - Biochemistry
  - Thyroid gland
  - Pregnancy test : urinary test
- PK/PD assessments
  - [redacted]
  - PK
  - [redacted]
  - [redacted]

[redacted]

7 Efficacy Parameters

The primary objective of the phase IIa is to evaluate the anti-leukemic activity of the combination of IPH2201 and ibrutinib in patients with relapsed or refractory CLL previously treated with at least one line of treatment.

7.1 COMPLETE REMISSION, DEFINITION

A CR is defined in the IWCLL guidelines (Hallek, Cheson et al. 2008). CR requires all the following criteria assessed at least 2 months after the discontinuation of IPH2201:

- Peripheral blood lymphocytes $<4x10^9$/l (4 000 /µl)
- Absence of significant lymphadenopathy by physical examination, with lymph nodes ≤ 1.5 cm in diameter
- Absence of constitutional symptoms
- Blood counts above the following values
  - Neutrophils $>1.5x10^9$/l without need for exogenous growth factors
  - Platelet $>100x10^9$/l (100 000/µl) without need for exogenous growth factor
  - Hemoglobin >11g/dl without red blood cell transfusion or ned for exogenous erythropoietin

Several examinations should be performed in this clinical trial to confirm the CR

- CT scans of abdomen, pelvis and thorax should be performed to confirm the absence of significant lymphadenopathy, hepatomegaly and splenomegaly.
- Bone marrow examination (with aspiration and biopsy) performed at least 2 months after the achievement of CR criteria, clinically and in peripheral blood. To define a CR, the marrow sample must be at least normocellular for age with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. In some cases, lymphoid nodules can be found; the nodules should be recorded as “nodular PR”. Immunohistochemistry should be performed to define whenever these nodules are composed primarily of T cells or lymphocytes other than CLL cells or of CLL cells, reflecting residual disease

7.2 OTHER EFFICACY PARAMETERS DEFINED IN THE IWCLL GUIDELINES

The following parameters will be assessed according to the IWCLL guidelines (Hallek, Cheson et al. 2008) by repeated tumor assessments by clinical examination performed within 3 weeks before the first dosing, at week 4, week 8, afterwards at all visits until EOS and CT scans planned at baseline, week 4, week 16, and whenever a progression or a CR are suspected.

7.2.1 Partial response (with the addition of PR with lymphocytosis)

PR is defined as:

- A decrease in the number of blood lymphocytes by 50% or more from the values before start of IPH2201 treatment
- Reduction in lymphadenopathy *(by CT scans in clinical trials or by palpation in general practice)* as defined by:
  - A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes or in the largest diameter of the enlarged lymph node detected prior to treatment

- No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (< 2cm), an increase of less than 25% is not considered to be significant

- A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected by CT scan or palpation
- The blood count should show one of the following results:
  - Neutrophils more than $1.5x10^9$/L (1,500 µL) without need for exogenous growth factors
  - Platelets count greater than 100 x109/L (100,000/µL) or 50% improvement over baseline without need for exogenous growth factors
  - Hemoglobin greater than 110 g/L (11.0 g/dL) or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin

7.2.2 Progressive disease

Progressive disease during or after treatment is characterized by at least one of the following:

- Lymphadenopathy. Progression of lymphadenopathy is often discovered by physical examination and should be recorded. In CLL, the use of CT scans usually does not add much information for the detection of progression or relapse. Therefore, the use of imaging methods to follow CLL progression is at the discretion of the investigator. Disease progression occurs if one of the following events is observed:
  - Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, or other organ infiltrates
  - An increase by 50% or more in greatest determined diameter of any previous site.
- An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly
- An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter
- Transformation to a more aggressive histology (e.g., Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy
- Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL
  - <u>During treatment.</u> Cytopenias may occur as a side effect of many therapies and should be assessed according to the Grading scale for hematologic toxicity in CLL studies (see appendix IV). During treatment, cytopenias cannot be used to define disease progression
  - <u>After treatment.</u> The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of hemoglobin levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than 100 $x10^9$/L (100,000/µL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells

7.2.3 Progression free survival (PFS)

PFS is defined as the time from study entry until objective disease progression or death.

7.2.4 Overall survival (OS)

OS is defined as the time from study entry until death from any cause, and is measured in the intent-to-treat population.

[redacted]

8 EXPLORATORY PHARMACOKINETIC / PHARMACODYNAMIC ASSESSMENTS

[redacted]

8.3 PHARMACOKINETICS

Analyses of IPH2201 concentration in human serum will be performed (ELISA).

[redacted]

[redacted]

[redacted]

8.10 SPECIAL PROCEDURES

[redacted]

8.10.2 Bone Marrow Examination

The following tests will remain exploratory and performed at baseline and whenever a BM examination is indicated during the treatment or the follow-up period.

- [redacted]
- For BM biopsy, an immunological study of the tissue by immunohistochemistry and quantitative PCR analysis:
  - For tumor cells, the expression of HLA-E and ligands for activating or inhibitory receptors
  - For immune effectors cells, the expression of CD94/NKG2A and other activating or inhibitory receptors

Specimens will be split. One part will be frozen, while the other one will be fixed in formalin and embedded paraffin.

The possibility to assess the function of infiltrated immune effectors extracted from the tumor will be explored if there is enough material.

9 SAFETY ASSESSMENT

The methods for collecting safety data are described below.

9.1 ADVERSE EVENT

9.1.1 Definitions

The definitions of Adverse Events (AEs) and Serious Adverse Events (SAEs) are given below. It is the responsibility of the PI to ensure that all staff involved in the study are familiar with the content of this section.

The occurrences of AEs and SAEs are recorded from the time of signed informed consent until the end of the study. All AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) of the NCI, version 4.03 (June 14, 2010).

9.1.1.1 Adverse Event

An AE is any untoward medical occurrence or worsening of pre-existing medical condition in a patient or clinical investigation patient administered an investigational product (study drug), and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

An AE related to the IMP is defined as an Adverse Reaction (AR) and includes all unintended responses to an investigational product related to any dose (see section 9.1.1.4). Symptoms and lab abnormalities not related to the IMP should not be reported as AEs but every effort has to be made to establish a cause and a diagnosis which has to be then reported as AE. In addition any procedure (e.g. surgery, stent, etc.) should not be reported as AE but the event which led to the procedure (e.g. appendicitis, myocardial infarction, etc.).

Disease (CLL) relapse/progression is not considered as an Adverse Event in this study.

9.1.1.2 Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused it if it was more severe)
- Requires patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (The disability is a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly or birth defect
- Is an important medical event which is defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention (i.e., specific measures or corrective treatment) to prevent one of the other outcomes listed above and which should also usually be considered serious

Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasia (e.g., agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc.) or convulsions (seizures, epilepsy, epileptic fit, absence, etc.); ALT > 3 x ULN + total bilirubin > 2 x ULN or asymptomatic ALT increase < 10 x ULN; relapse of a previous malignancy or second primary malignancy.

Suspected transmission of an infectious agent (e.g. pathogenic or non-pathogenic) via the study drug is considered a SAE.

Although pregnancy, overdose or cancer, are not always serious by regulatory definition, these events must be handled as SAEs.

Any event or hospitalization that is unequivocally due to relapse of disease must not be reported as a SAE.

NOTE:

The following hospitalizations are not considered SAEs in Innate Pharma clinical studies:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery or procedure (e.g. stent), planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than remedying ill health state and planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

Disease relapse/progression is not considered as a SAE in this study.

9.1.1.3 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined (as per ICH Topic E2A) as an adverse reaction which nature or severity is not consistent with the relevant source document (Investigator's Brochure for IPH2201). When reported as serious, the unexpected adverse reaction is defined as Suspected Unexpected Serious Adverse Reaction (SUSAR).

9.1.1.4 Determination of relatedness

The Investigator will use medical consideration to determine the relatedness of an AE with the study drug based on the following definitions:

- Not Related

This category applies to AEs that are due to extraneous causes (disease, concomitant medication, environment, etc.) and are not related to the administration of study drug.

- Probably Not Related (must have first two criteria below)

This category applies to AEs that are unlikely related to the administration of the study drug. The relationship of an AE to the study drug can be considered probably not related if:

- The AE does not follow a reasonable temporal sequence from administration of the drug
- The AE could readily have been a result of the patient's clinical state or other underlying medical condition, environmental or toxic factors, or other modes of therapy administered to the patient
- The AE does not follow a known response pattern to the suspected drug
- The AE does not reappear or worsen when the Study Drug is re-administered

- Possibly Related (must have first two criteria below)

This category applies to AEs that are unlikely to be related to the administration of the study drug, but the possibility cannot be ruled-out with certainty. The relationship of an AE to the study drug can be considered possibly related if:

- The AE follows a reasonable temporal sequence from administration of the study drug
- The AE could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The AE follows a known response pattern to the suspected Study Drug

- Probably Related (must have first three criteria below)

This category applies to AEs that are considered with a high degree of certainty to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered probably related if:

- The AE follows a reasonable temporal sequence from administration of the study drug
- The AE could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The AE disappears or decreases upon cessation of study drug or reduction in dose
- The AE follows a known response pattern to the suspected study drug

- Definitely Related (must have first three criteria below)

This category applies to AEs that are determined with certainty to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered definitely related if:

- The AE follows a reasonable temporal sequence from administration of the study drug or study drug levels have been established in body fluids or tissues
- The AE could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient;
- The AE disappears or decreases upon cessation of study drug or reduction in dose and, if applicable, appears upon rechallenge
- The AE follows a known response pattern to the suspected Study Drug
- There are exceptions when an AE does not disappear upon discontinuation of the study drug, yet study drug relatedness clearly exists; e.g., 1) tardive dyskinesia, 2) fixed drug eruptions

9.1.1.5 Death

All deaths that occur during the study period must be reported.

Death as a result of disease progression is not considered as AE/SAEs. Death as a result of other disease is not considered as (S)AE but the disease which led to the death must be considered as a (S)AE. However, death must be collected on the appropriate eCRF form. The site should continue to follow all subjects for survival and collect information around the death on the appropriate eCRF form until the end of the trial.

9.1.2 Adverse Events Collection and Reporting

All AEs and SAEs, whether related or not related to study drug, including those thought to be associated with protocol-specified procedures, must be collected throughout the study from the time of patient signing the consent form until the end of study visit, or until the patient's last study visit. All reported AEs and SAEs will be followed until resolution. The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.

All AEs will be recorded on the eCRFs. The records will describe the nature (diagnosis or single syndrome as much as possible, alternatively signs and symptoms) severity, using the NCI CTCAE term (version 4.3 of June 14, 2010), date/time of onset, date/time of end, actions taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and causality (relationship to study treatment according to the investigator's assessment).

It will be specified whether the event is serious or not according to the definition of SAE (See section 9.1.1).

A sponsor safety representative will determine the causal relationship when it is not clearly provided by the investigator.

Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:

- Symptomatic and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion

9.1.2.1 Follow-up and Handling of unresolved AE/SAEs at completion/withdrawal

Ongoing adverse events should be reviewed at each subsequent assessment. If resolved, the details should be recorded in the eCRF. If any AE changes for the worse in frequency of attacks/symptoms or in severity, a new record of the event must be started (i.e. distinct reports are required for differing frequencies and/or severity of the same event to enable comprehensive safety reports and later analysis).

All non-serious AEs must be followed until the outcome of the event is "recovering" (for chronic conditions) or recovered, or until the patient's last study visit and until all queries related to these AEs have been resolved.

If the patient dies from another event, these cases can be closed with an outcome "not recovered".

All AEs and SAEs must be followed until resolution or stabilization.

9.1.3 Serious Adverse Events Reporting

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

Investigators and other site personnel must report all SAEs within 24 hours of becoming aware of a SAE to Medpace (see as below).

SAEs must be reported within 24 hours (immediately but no later than the end of the next business day), regardless of the time that may have elapsed since the time the event occurred, and regardless of the causal relationship of the investigational medicinal product to the event.

All SAEs should be reported on an SAE form (initial report), which should be completed by the investigator/other relevant site staff, signed by the investigator and faxed to Medpace (see as below). In addition, SAEs should be reported on the adverse event eCRF page.

The investigator will be requested to supply as much detailed information regarding the event as is available at the time of the initial contact.

ANY SERIOUS ADVERSE EVENTS, WHETHER OR NOT RELATED TO THE STUDY DRUG, MUST BE REPORTED IMMEDIATELY TO:

[redacted]

The investigator must immediately or as soon as possible send (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to Pharmacovigilance.

In addition, care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, the investigator must include the laboratory normal ranges.

A back-up plan (using a paper CRF process) is available and should be used when the e CRF system does not work.

9.1.3.1 Follow-up of Serious Adverse Events

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

A follow-up report to an SAE should be prepared if any relevant change in the condition of the patient occurs after the initial report, or any new relevant information becomes available.

The follow-up report should be supplied on an SAE report form and clearly labeled as 'follow-up'. Follow-up forms should contain only essential patient and event identifying data and all new data; there should be no repetition of any data given in the initial report.

All SAEs will be followed up until the outcome of this event is recovered, recovered with sequelae or fatal and until all queries have been resolved.

For cases of chronic conditions or if the patient dies from another event, these cases can be close with an outcome of "recovering" or "not recovered".

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s).

Any SAE brought to the attention and assessed to and by the Investigator, occurring at any time after the end of the study visit and that may be related with a reasonable possibility to the study treatment, as assessed by the investigator, should also be notified to the monitoring team.

9.1.4 Abnormal laboratory values/vital signs

The reporting of laboratory / vital signs / ECG abnormalities as laboratory findings / vital signs / ECG and as AEs should be avoided. They should not be reported as AEs (using the NCI CTCAE version 4.3 of June 14, 2010 terminology) unless any one of the following are met:

- Any criterion for a SAE is fulfilled
- The laboratory / vital signs / ECG abnormality causes the subject to discontinue from the study treatment

- The laboratory / vital signs / ECG abnormality causes the subject to interrupt the study treatment
- The laboratory / vital signs / ECG abnormality requires intervention as corrective treatment or consultation and/or
- Symptomatic and/or
- The Investigator believes that the abnormality should be reported as an AE

All laboratory tests for which abnormal results are collected after the initiation of study treatment should be repeated until the values return to normal or to a stable status. Abnormal results are defined as those falling out of the normal laboratory range and that are clinically significant. The frequency with which such checks should be made will be defined by the investigator's opinion depending on the degree of abnormality.

9.1.5 Overdose

An overdose is defined as the accidental or intentional ingestion or infusion of any dose of a product that is considered both excessive and medically significant.

All symptoms associated with the overdose should be reported as SAEs.

9.1.6 Pregnancy Reporting

If the subject or partner of a subject participating in the study becomes pregnant during the study or within 5 months of discontinuing study medication, the investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure In Utero form to the investigator for completion.

A patient becoming pregnant while on IMP will immediately be withdrawn from the study and early termination study procedures will be performed

The subject or partner should be followed by the investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets criteria for immediate classification as a SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting as SAE.

9.1.7 Drug Induced Liver Injury (DILI)

Potential drug induced liver injury (DILI) is considered an important medical event. Although they are not always serious by regulatory definition, these events must be handled as SAEs.

Wherever possible, timely confirmation within 48-72 hours of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3. No cholestatic or other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

9.1.8 Reporting to Competent Authorities and Ethics Committees

Investigator Brochure will be the reference document for safety assessment.

Innate Pharma is responsible for notifying SUSARs to health authorities in accordance with local regulations.

The investigator is responsible for informing the Institutional Review Board (IRB) in a timely manner and in accordance with local procedures.

9.2 SAFETY ASSESSMENTS

Subjects will be considered evaluable for safety if they have received any dose of the study drug. Toxicity assessments will be continuous during the Treatment period and the Clinical Follow-up periods.

9.2.1 Clinical Safety

The following assessments will allow the safety evaluation of the treatment according to the study flow chart:

- Full physical examination,
- Vital signs (Systolic and Diastolic Blood Pressure, Orthostatic Response, Heart Rate, Height, Weight)
  - Determination of the reference arm for blood pressure (BP) measurements: At first visit after the patient has rested comfortably for at least 10 minutes, BP is measured on both of the patient´s arms while the patient is in sitting position and then again after two minutes on both arms. The arm with the higher diastolic BP will be determined at this visit, identifying the reference arm for future measurement throughout the study. The highest value will be recorded in the e-CRF (all BP values are to be recorded in the source data) as the BP to determine the reference arm. An additional measurement may be made to determine the screening BP
  - BP at all subsequent visits should be measured when the patient is quiet and seated and with their determined reference arm outstretched in line with mid-sternum and supported. Measurement at all subsequent visit should be taken under standardized conditions, approximately at the same time of the day, on the reference arm, with the same device (after the patient has rested comfortably for at least five minutes) and the values are to be recorded in the e-CRF. Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) should be recorded
  - Heart rate will be measured at the time of the BP measurement
  - Height will be measured at screening visit when the patient's shoes are off, feet together and arms by the sides. Heels, buttocks and upper back should also be in contact with the wall when the measurement is made

- Body weight should be obtained at screening visit and at end of treatment, with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The floor surface on which the scale rests must be hard and should not be carpeted or covered with other soft material. The same scale should be used throughout the study, and calibrated on a regular basis as recommended by the manufacturer. The weight is read and recorded in the e-CRF and Source Data. Self-reported weights are not acceptable and patients must not read the scales themselves

- Collection of AEs
- 12 lead ECG standard. The ECG machine should compute the heart rate, PR, QT and QTC (calculated using Bazett's formula), QRS duration. The investigator or a cardiologist will evaluate the ECG. ECGs which are assessed by them as "abnormal, clinically significant", should be reported as AEs. A standard copy of each anonymized ECG should be archived by the sponsor of the study

9.2.2 Laboratory Investigations

The primary endpoint will be The safety of 2 repeated administrations of IPH2201 given as a single agent during 4 weeks during 2 cycles of 14 days, and thereafter, given in combination with ibrutinib during 26 14 cycles 52 weeks is the primary endpoint during the dose escalation part of the trial.

- 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

Safety will be assessed using the CTCAE version 4.03; it will include a descriptive analysis of the frequency and severity of AEs; related AEs followed to resolution (≤ grade 1) unless deemed irreversible and clinical laboratory tests collected to assess lab abnormalities, as well as results of vital sign measurements, electrocardiograms (ECGs), physical examinations and imaging studies.

The following laboratory blood tests will be performed at study site according to the study flow chart:

- Hematology: RBC, WBC with differential count, platelets, hemoglobin, MCV hematocrit

  Serum Biochemistry: sodium, potassium, calcium, magnesium, total proteins, and albumin, urea, uric acid, creatinine, calculated creatinine clearance, ALP, total bilirubin, LDH, lipase, amylase, AST (SGOT), ALT (SGPT), GGT, glucose, CRP and fibrinogen
- Coagulation factors: APTT
- prothrombin time (PT)
- Serology HIV HCV HPV

Other tests will also be performed: urinary pregnancy test, and urinalysis (PH, glucose, leucocytes, proteins, blood and hemoglobin).

Abnormal laboratory values considered to be clinically relevant by the investigator must be repeated to rule out laboratory error and followed up until they have returned to normal except if an adequate explanation is found.

9.3 SAFETY COMMITTEE

A safety committee will be constituted to monitor data and overall safety in this study in order to determine the dose to be administered to the patients after phase Ib.

The safety committee will consist of:

- The principal investigators of the study
- A sponsor medical and pharmacologist representative
- The sub-investigators as optional members, including the Director of the division of Hematology at OSU as hematologist with high experience in CLL
- A methodologist or physicians with relevant expertise related to the reviewed safety issues can join the safety committee as optional member

The Safety Committee will review the data for progression and safety with data collected as following:

- During the dose escalation phase Ib of the trial, at each dose level after the completion of the 2 cycles of IPH2201 by the *last* patient of the cohort
- During phase Ib, at each dose level the safety committee will also review patients data after completion of 2 cycles of IPH2201 in combination with ibrutinib by the *last* patient of the cohort
- Furthermore, at any time during the phase Ib, considering any additional safety information, the safety committee may decide to decrease the dose of IPH2201 to a lower dose level
- During the phase IIa of the trial, every six months
- The Safety Committee could also be involved at any time should a major safety issue occur.

The functions of the safety committee are multiple:

- To analyze the causality of the AEs in phase Ib
- At each dose level, to allow dose escalation as above described
- To select the dose of IPH2201 which will be assessed during the phase IIa, taking into account all the safety, pharmacology and anti-leukemia activity data gathered at each dose level, with a minimum of follow-up of 4 weeks after the introduction of ibrutinib, in the last patient enrolled in the dose escalation study. Such a dose may correspond to the MTD, to the highest tested dose level or to a lower dose level, chosen during or at the end of the dose escalation. The safety committee may therefore decide to stop prematurely the dose escalation, even if the MTD was not reached. The report of the safety committee will be forwarded to the FDA
- To recommend the discontinuation of the study, transiently or permanently, or a decrease in the dose, after the occurrence of 2 unacceptable reactions in patients treated by the combination of IPH2201 and ibrutinib during the first or second phase of the study

DLTs and unacceptable reactions are defined as:

- Any grade 3 or grade 4 non hematologic toxicity
- Grade 4 neutropenia (ANC < 500/µl) lasting ≥7 days after discontinuation of therapy in patients with pre-treatment ANC ≥ 1,000/µl
- Grade 4 thrombocytopenia (platelet count <20,000/µl and/or ≥75% decrease from pre-treatment value)
- Grade 3 or 4 thrombocytopenia associated with bleeding
- Any dose delay due to AE for > 14 consecutive days

Such events will be considered as DLTs whenever they occurred during the first 4 cycles (8 weeks) of treatment in phase Ib (including 2 administrations of treatment with IPH2201 alone and 2 administrations of treatment with IPH2201 + ibrutinib).

10 STATISTICS

10.1 METHODS AND PLANNING

Only descriptive analyses will be performed.

All analyses will be performed on all treated patients, and will be presented by dose (1 mg/kg, 2 mg/kg, 4 mg/kg and 10 mg/kg). Analyses will be performed using SAS 9.3 or a later version.

A statistical analysis plan (SAP) will be prepared as a separate document and will include a more technical and detailed description of the planned statistical analyses. The SAP will be finalized before database lock.

10.2 SAMPLE SIZE

36 to 48 patients will be enrolled in this clinical study:

Up to 24 patients (3 to 6 patients at each dose level) will be enrolled in the dose-escalation phase Ib

Up to 24 patients in the phase IIa

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.

If 6 patients (3+3 for safety reasons) are treated during the phase Ib with the phase IIa recommended dose, a maximum of 21 patients will be included in the phase IIa

If 24 patients were enrolled in the phase Ib of the trial (including 6 at the recommended dose of the phase IIa, no more than 21 patients would need to be enrolled in the phase IIa; Which means than the total number of patients will never exceed 45 (24+21)

Primary efficacy endpoint: CR rate based on IWCLL criteria

The significance level (alpha risk) is set at 0.05 and power of at least 80%. The one-sided null hypothesis is specified as H0: p =0.05 and the alternative H1: p= 0.20, p the probability to achieve a CR.

Further investigation is deemed warranted if ≥ 4 patients achieve a CR by the end of the study (≥ 4/27).

10.3 TERMINATION CRITERIA

The study could be technically stopped as soon as 4 CRs are documented, but, in that case, accrual of a minimum of 12 patients is recommended to further document safety, pharmacologic endpoints and biomarkers.

10.4 DEVIATIONS

Any deviation from the initial analysis plan will be described in the Clinical Study Report.

10.5 Selection of Subjects

Evaluable patients: all patients who received at least 1 administration of IPH2201 will be evaluable for efficacy and safety. Patients who do not receive at least 1 administration of IPH2201 will be documented in the study report. These patients will be replaced to reach a total of 27 evaluable patients. In addition, in the two phases of the trial (Ib and IIa), patients will be replaced in case of treatment discontinuation of IPH2201 due to disease progression before the end of 8 weeks of treatment.

10.6 Access to Data

The investigator will make all study-related source data and documents available to the Monitor or a quality assurance auditor mandated by the sponsor, or to domestic or foreign regulatory inspectors, after appropriate notification.

10.7 Source Data and Documents

Source data are defined as all information available in the original source documents or certified copies of the source document of any clinical findings, observations, or other activities that are necessary for the reconstruction and evaluation of the study.

For each patient included, the investigator will indicate in the source documents that the patient participates in this study, and will record the appropriate information. This will include (non-exhaustive list): patient name, date of birth, sex, medical history, information that the patient is included in the study, visit dates, product administration, primary evaluation criteria, nature of AEs with date of start and related treatment.

Source documents will be preserved for the maximum period of time requested by local recommendation or ICH, whichever occurs last.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 SOURCE DATA AND DOCUMENTS

In addition to the initial visit for site-initiation, the monitor will contact and visit the investigator periodically to evaluate the study progress and the compliance of the study site with GCP, regulations and the study protocol as well as to verify and collect data reported in the EDC System. The investigator as well as any study staff member will cooperate with the monitor to ensure that any problem that may be identified is resolved.

For this study, the average frequency of the monitoring visits is intended to be approximately 6 weeks when patients are not yet in the follow-up period, with the first visit occurring as soon as possible after the first patient inclusion. Intervals may be adjusted according to patient enrolment, protocol changes or site performance.

11.2 PERIODIC MONITORING

Innate Pharma will provide an EDC system to allow data entry by site users (Investigator and Investigator's authorized staff). EDC system development will be delegated to [redacted] Each member of the site will be assigned a username, a personal login and a password to enter into the EDC system. Each login uniquely identifies the user. Appropriate permissions for system access will be set-up according to the user's role. The access to the system will be granted once the user's training has been completed and documented.

The eCRF will be set-up in a way that facilitates navigation and data entry by the site personnel.

All study documentation will be securely stored and maintained in an electronic trial master file (eTMF).

11.3 DATA MANAGEMENT

Data will be entered into the EDC system on an ongoing basis, ensuring all relevant items are completed, there is no missing data and that all data entered are consistent with the source documentation.

Data will be entered according to the data entry instructions provided.

The investigator will confirm that the information is complete and accurate by signing the electronic forms.

11.3.1 Data Entry

The data will be electronically verified through use of automatic checks during data entry, SAS programmed edit checks to check complex conditions (if any) and data monitoring.

Data correction will be made by site users.

An audit trail will identify the person entering/correcting the data, date and time of data entry and reason for correction.

11.3.2 Data Review

Real-time online reports will be available in the EDC system.

Sponsor, Monitors and Data managers will have the possibility to generate manual queries in the EDC system.

Monitors are responsible for source data verification. As soon as the data have been reviewed by the monitor, they should be signed by the monitor in order to allow the investigator to sign the data.

The investigator signature is equal to a legal signature. As soon as the data have been signed by the investigator, the data are frozen. The data can no longer be changed unless a request of unfreeze is sent to the data manager.

11.3.3 Data Coding

AEs will be reported and graded according to the NCI-CTCAE version 4.03 of 14th June 2010 by the investigator. AEs will be coded according to the MedDRA dictionary.

11.3.4 Study

Database will be recorded on CD-ROM.

At the end of the trial, Patient eCRF data will be provided on CD to the Investigator site in an electronic readable format for archiving.

[redacted]

11.3.6 SAE data reconciliation

The CRO in charge of data management and CRO in charge of Pharmacovigilance will collaborate in the performance of the safety data reconciliation.

11.3.7 Data Freezing

Before database lock, all queries must be resolved and coding must be validated by the Sponsor. Reconciliation of SAEs between the clinical database and the Pharmacovigilance database also has to be completed. The data will be extracted from the database into the data files for statistical analysis.

11.4 AUDIT AND INSPECTION

The main purposes of an audit or inspection are to confirm that the rights and well-being of the patients have been adequately protected, and that all data relevant for the evaluation of the study drug have been processed and reported in compliance with ICH GCP and applicable regulatory requirements.

12 ETHICS

12.1 ETHICAL CONDITIONS

This study will be performed in accordance with the principles stated in the Declaration of Helsinki and subsequent amendments and in accordance with the Guidance on GCP (CPMP/ICH/135/95).

12.2 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD (IEC/IRB) APPROVAL

The investigator is responsible for ensuring that this protocol and the consent form have been reviewed and approved by a relevant IEC/IRB prior to the start of the study. The IEC/IRB shall be appropriately constituted and perform its functions in accordance with the Food and Drug Administration, ICH/GCP and local requirements as applicable.

In addition, the IEC/IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, patient recruitment procedures (e.g. advertisements), written information to be provided to patients, the Investigator's Brochure, available safety information, information about payment and compensation available to patients, the Investigator's *curriculum vitae* and/or other evidence of qualifications and any other documents requested by the IEC/IRB and Regulatory CA as applicable.

The investigator is responsible for keeping the IEC/IRB informed of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case at least once a year. The investigator must also keep the IEC/IRB informed of any serious and significant AEs.

12.3 PATIENT INFORMATION AND CONSENT

Information providing the common features of the research must be given to patients themselves. Restraints and risks must be explained, as well as the right to refuse or discontinue their participation in the study at any stage, without further affecting the relationship with the investigator and/or their future care.

This written information and consent form will be given to the patient with an oral explanation before the patient enters the study and it will be agreed and signed by the patient. The investigator is responsible for ensuring that written informed consent is obtained for all patients.

For a patient who is legally incompetent, or physically or mentally incapable of giving consent, the investigator must obtain informed consent from the patient's legally authorized representative in accordance with applicable laws.

Two original copies of the information and consent document will be produced; one copy will be kept by the investigator and the other copy will be given to the patient.

If any information becomes available during the study that may be relevant to the patient's willingness to keep on participating in the study, an updated informed consent must be submitted to the patient to confirm his/her agreement to continue participating.

12.4 CONFIDENTIALITY

In compliance with United States federal regulations, Innate Pharma requires the Investigator(s) to permit Innate Pharma's representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

The present materials (protocol, CRF, investigator's brochure) contain confidential information. The investigator agrees to hold such information in confidence, and not to disclose it to others (except where required by applicable law) except as may otherwise be agreed to in writing with the sponsor.

12.5 DATA HANDLING AND RECORD KEEPING

The investigator will be kept informed of the methods used for the relevant ratings and completion of CRFs, and of important information that relates to the safe use of the study drug(s) as the study proceeds.

The site's staff, e.g. residents, nurses, laboratory technicians and any other personnel providing care to the study patients or handling biological specimen will be informed of the characteristics of the study drug and receive safety instructions.

12.6 INVESTIGATORS INFORMATION

The investigator will be kept informed of the methods used for the relevant ratings and completion of CRFs, and of important information that relates to the safe use of the study drug(s) as the study proceeds.

The site's staff, e.g. residents, nurses, laboratory technicians and any other personnel providing care to the study patients or handling biological specimen will be informed of the characteristics of the study drug and receive safety instructions.

12.7 CASE REPORT FORMS

For each patient included, an eCRF must be completed, in English, by the investigator or designee and signed by the investigator. Investigators will be provided with detailed eCRF Completion Guidelines that will identify the required data points to be collected, how to document them and when the data should be documented. This document will also show how to manage any change to initial data recorded in eCRF. Appropriate training in electronic data capture and support will be provided. If a patient is withdrawn from the study, the reason must be noted in the eCRF. If a patient is withdrawn from the study because of an AE, thorough efforts will be made to clearly document the outcome.

A reduced set of information on patients not included after the screening period will be entered in screening log file; especially patients screening number and reason for non-inclusion.

12.8 PROVISION OF ADDITIONAL INFORMATION

On request, the investigator will provide the sponsor or its representative with additional data relating to the study, or copies of relevant source documents, duly anonymized.

In case of particular issues or governmental queries, it may be necessary to have access to the complete source documents, provided that the patients' confidentiality is protected in accordance with applicable requirements.

12.9 ARCHIVING

12.9.1 Investigator Site File

The investigator is responsible for maintaining all records that enable the conduct of the study at the site to be fully documented, in accordance with the ICH GCP standard and applicable legal requirements.

This documentation will be kept by the investigator for at least 2 years following the date of the last marketing application approval for the study drug(s) for the indication for which it is being investigated in this study, or if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued. If a longer archiving period is required, the local law/regulation must be followed. The sponsor will inform the investigator when documents may be destroyed. No study site document may be destroyed without prior written agreement between the investigator and the sponsor.

Patient files and other source data shall be kept for the maximum period of time permitted by the hospital, institution or private practice.

Should the investigator elect to assign the study documentation to another party, or move it to another location, the sponsor must be notified. If the investigator cannot guarantee this archiving requirement on site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in a sealed container away from the site so it can be returned sealed to the investigator in case of an audit/inspection.

12.9.2 Study Master File

The sponsor will archive the study master file in accordance with GCP and applicable regulatory requirements.

13 INSURANCE

In accordance with the provisions of the law and ICH GCP, Innate Pharma acting as sponsor, has affected sufficient insurance to cover the relevant liability of the sponsor and the investigators for any damage suffered by the patients as a result of their participation in the Study.

However, sponsor shall not be held responsible for any claim for the payment of damages made by investigators or the site for:

- Injuries or damages incurred if they are the result of or are alleged to be the result of negligence or willful misconduct on the part of the investigators, or the site, its employees or agents
- Activities contrary to the Protocol
- Unauthorized warranties made by the investigators, the site or its employees concerning the Study Drug; or
- Any case in which written informed consent of the patient was not obtained

14 PUBLICATION POLICY

14.1 CLINICAL STUDY REPORT(S)

Data analysis, statistical reporting and clinical research reports preparation will be the responsibility of the sponsor and the CRO in charge of data management.

The report will include a review of the objectives and methods, a presentation and discussion of the results will be drawn up according to ICH Guidelines (Structure and Content of Clinical Study Reports, ICH-E3, CPMP/ICH/137/95). The report will be signed by the sponsor representative(s) and the coordinating investigator(s).

The report may be used for regulatory purposes as considered necessary by the sponsor.

14.2 CONFIDENTIALITY OF STUDY DATA

Any information relating to the study drug(s) or the study, including any data and results from the study is the exclusive property of the sponsor and is considered as confidential information. Documents and information are supplied to the investigators under conditions of strict confidentiality. Neither the investigator nor any person working on his/her behalf may disclose any of the information therein, or use any of the information for any purpose other than the Study described in the Protocol, without having obtained prior written consent from the sponsor.

14.3 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings by investigators in compliance with the following provisions.

At least sixty (60) days prior to making any submission for publication or other public disclosure in which any direct or indirect reference is made to information related to this Study, the investigators shall submit to Sponsor all drafts and content of manuscripts, presentations or abstracts to the sponsor prior to scientific meeting or journal submission for review and comment.

Sponsor shall have the right to require removal of any of its confidential information and to provide comments based on information from other studies that may not yet be available to the investigator.

The Sponsor shall further be entitled to postpone the intended publication or other disclosure for up to ninety (90) days if in its opinion, publication or other disclosure is believed to interfere with Sponsor's patent work or involves know-how, results or other confidential information developed by Sponsor and relating to this Study.

In accordance with consistent editorial practice, the Sponsor supports publication of multi-center studies in their entirety and not as individual center data unless ancillary study/data.

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16 APPENDICES

APPENDIX I: LIST OF KEY STAFF AND RELEVANT DEPARTMENTS

Sponsor

Sponsor Company

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APPENDIX II: ECOG PERFORMANCE STATUS SCALE

Grade	ECOG Performance Status
0	Fully active, able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work
2	Ambulatory and capable of all self-care but unable to carry out any work. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

APPENDIX III: RESPONSE DEFINITION AFTER TREATMENT FOR PATIENTS WITH CLL

According to the IWCLL guidelines (Hallek M, Blood 2008).

Parameter	CR*	PR*	PD*
Group A			
Lymphadenopathy†	None > 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/µL	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi (5.1.6).	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B			
Platelet count	> 100 000//µL	> 100 000/ µL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils‡	> 1500/µL	> 1500/ µL or ≥ 50% improvement over baseline	

Group A criteria define the tumor load, group B criteria define the function of the hematopoietic system (or marrow).

*CR (complete remission): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR (partial remission): at least two of the criteria of group A plus one of the criteria of group B have to be met; SD is absence of progressive disease (PD) and failure to achieve at least a PR; PD: at least one of the above criteria of group A or group B has to be met.

†Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials or by physical examination in general practice).
‡These parameters are irrelevant for some response categories.

APPENDIX IV: GRADING SCALE FOR HEMATOLOGIC TOXICITY IN CLL STUDIES

According to the IWCLL guidelines (Hallek M, Blood 2008).

Grade*	Decrease in platelets† or Hb‡ (nadir) from pretreatment value, %	Absolute neutrophil count/µL§ (nadir)
0	No change to 10%	≥ 2000
1	11%-24%	≥ 1500 and < 2000
2	25%-49%	≥ 1000 and < 1500
3	50%-74%	≥ 500 and < 1000
4	≥ 75%	< 500

*Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.

†Platelet counts must be below normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is < 20 x 109/L (20 000/ µL), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (e.g., 20 < 109/L [20 000/ µL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

‡Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.

§If the absolute neutrophil count (ANC) reaches < 1 x 109/L (1000/ µL), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was < 1 x 10^9/L (1000/ µL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity, but should be documented.

APPENDIX V – LIST OF CYP3A4 INHIBITORS AND INDUCERS

According to FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers

Strong CYP3A4 inhibitors 5-fold increase in AUC or > 80% decrease in CL	Moderate CYP3A4 inhibitors 2 but < 5-fold increase in AUC or 50-80% decrease in CL
boceprevir, clarithromycin, conivaptan, grapefruit juice (1), indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice (1), imatinib, verapamil

Strong Inducers 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC
carbamazepine, phenytoin, rifampin, St. John's wort(2)	bosentan, efavirenz, etravirine, modafinil, nafcillin

(1) The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

(2) The effect of St. John's wort varies widely and is preparation-dependent.