SYNOPSIS

Name of Sponsor: Innate Pharma	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of finished product: IPH2101	**Volume:**	
Name of active ingredient: Fully human anti-KIR monoclonal antibody (anti-KIR 1-7F9, hybridoma production)	**Page:**	

Title of Study: Open randomised phase II study evaluating the anti-tumour activity, safety and pharmacology of two different dose regimen of IPH2101, a human monoclonal anti-KIR antibody, in patients with multiple myeloma in stable partial response after a first-line therapy.

Investigators:

Principal coordinating investigator: Prof Michel Attal (Purpan's Hospital, Toulouse - France).

Study centers: C.H.U. de Dijon, DIJON-France; C.H.R.U. de Lille, LILLE- France; Hôpital Dupuytren, LIMOGES- France; Institut Paoli Calmettes, MARSEILLE- France; C.H.R.U. de Nantes, NANTES- France; Hôpital Saint Antoine, PARIS- France; Hôpital Saint-Louis, PARIS- France; Hôpital de Purpan, TOULOUSE- France; C.H.R.U. de Tours, TOURS- France; C.H.U. de Nancy, VANDOEUVRE LES NANCY- France.**;** CH.R.U. de Caen, CAEN- France.

Publication (reference): Not applicable.

Study period: The first patient visit was on 16 Nov 2009, and the last patient visit on 5 Jun 2012	**Phase of development:** Phase II

Objectives:

Primary objective: To evaluate the clinical activity, measured by serum M-protein or free light-chain (FLCS) levels, of two different dose regimens (0.2 mg/kg, leading to an intermittent saturation of NK receptors, and 2 mg/kg, leading to a sustained saturation of NK receptors) of IPH2101 administered as a single agent in patients with multiple myeloma (MM) who achieved a partial or very good partial response (PR or VGPR), lasting for at least 2 months, after the completion of any first-line treatment, including conventional or high-dose chemotherapies.

Secondary objectives: 1. To confirm the safety profile of the dose and administration schedules of IPH2101 in this population; 2. To assess the pharmacokinetics (PK) of two different dose regimens of IPH2101; 3. To evaluate the biological activity of IPH2101 on KIR occupancy, NK cell phenotype, NK cell function, and cytokine release; 4. To confirm the absence of immunogenicity of IPH2101; 5. To document on study and post-study efficacy parameters until 2 years after the end of study (overall survival [OS], duration of response [DOR], progression-free survival [PFS], and time to progression [TTP]).

Methodology:

Two-arm, open-label, randomized, multicentre phase II study with a Gehan's one-stage design evaluating response as per M-protein levels in serum to two different dose regimens of a human monoclonal anti-KIR antibody, IPH2101. Patients were randomly allocated to receive four injections of IPH2101, at the dose of either 0.2 mg/kg or 2 mg/kg administered as a 1-hour infusion every 4 weeks. Patients responding at 4 months (i.e., any decrease in serum M-protein, or FLCS levels for patients with serum M- protein <3 g/l at study entry) were allowed to receive 4 additional monthly administrations. Patients were to be followed until a

KIR occupancy level below 30%, for up to approximately 4 months after the completion of the treatment. A post-study follow-up was organized for a maximum of 2 years after the end of the trial (up to the completion of the study in September 2012) to collect the date of disease progression (DP) and/or death.

Number of patients:

The number of patients was based on Gehan's one-stage phase II design. Up to 14 patients were to be treated in each arm, for a total of 28 patients to be included in the trial. Actually, a total of 27 patients were included, 14 at the 0.2 mg/kg dose level, and 13 at the 2 mg/kg dose level.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

- MM previously treated with systemic first-line therapy conventional doses of chemotherapy or high-dose chemotherapy and an autologous hematopoietic-cell transplantation, followed or not by a consolidation treatment;
- Residual disease considered as evaluable with:
    - Quantifiable serum M-protein: ≥3 g/l, except for spike in the beta globulin area (in this particular case serum M-protein is considered quantifiable if ≥10 g/l); if serum M-protein is <3 g/l, measurability involved FLCS ≥ 100 mg/l and an abnormal free-light-chain ratio (<0.26 or > 1.65);
- Responses (PR or VGPR) in plateau for at least 2 months since last administration of any anticancer therapy:
    - PR should meet the International Myeloma Working Group (IMWG) criteria: a ≥50% reduction in serum M-protein levels compared with levels before the first-line chemotherapy and a reduction in 24-h urinary M-protein by ≥90% or to <200 mg / 24 h;
    - VGPR should meet the IMWG criteria: ≥90% reduction in serum M-protein levels plus urine M-protein level <100 mg/24 h;
    - Plateau phase is defined by:
        - For patients with serum M-protein ≥3 g/l: stable levels of M-protein in serum during at least 2 months measured on at least three consecutive samples, with the third evaluation performed within 4 weeks before study entry. Fluctuations of ± 25% and ± 2 g/l in serum M-protein levels are allowed;
        - For patients with serum M-protein <3 g/l: stable levels of FLCS during at least 2 months measured on at least three consecutive samples, with the third evaluation performed within 4 weeks before study entry. Fluctuations of ± 25% of involved FLCS are allowed;
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2;
- Clinical laboratory values at screening:
    - Calculated creatinine clearance (according to MDRD) >50 ml/min;
    - Platelets >50 x 10^9/l;
    - Absolute neutrophil count >1 x 10^9/l;
    - Bilirubin levels <1.5 times the upper limit of normal;
    - Alanine transaminase and aspartate transaminase <2.5 times the upper limit of normal;
- Male or female patients who accept and are able to use recognized effective contraception (oral contraceptives, intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal jelly) throughout the study;
- Signed inform consent obtained before any trial-related activities.

Exclusion criteria:

- Age <18 years or >75 years;
- Previous consolidation/maintenance therapy with thalidomide, lenalidomide, or bortezomib within the last 2 months;
- Treatment with chemotherapy or a systemic corticosteroid within the previous 2 months;
- Treatment with hematopoietic growth factors within the previous 1 month;
- Radiotherapy for bone or visceral lesion within the last 3 months;
- Use of any investigational agent within the last 2 months;
- Primary or associated amyloidosis;
- Peripheral neuropathy of grade ≥3 according to the National Cancer Institute Common Terminology Criteria for Adverse Events;
- Abnormal cardiac status with any of the following:
    - New York Heart Association stage III or IV congestive heart failure;
    - Myocardial infarction within the previous 6 months;
    - Symptomatic cardiac arrhythmia despite treatment;
- Current active infectious disease or positive serology for HIV, HCV or positive HBs antigen;
- History of or current autoimmune disease;
- Serious concurrent uncontrolled medical disorder;
- History of other active malignancy within the last 5 years (except basal cell carcinoma of the skin, or *in situ* cervix carcinoma);
- History of allogeneic hematopoietic-cell or solid-organ transplantation;
- Pregnant or lactating women;
- Any medical condition which is regarded by the investigator as incompatible with the study participation;
- Any psychological, family, social or geographic condition potentially hampering compliance with the study protocol and follow-up schedule.

Test product, dose and mode of administration, batch number:

IPH2101 is a fully human IgG_4 monoclonal antibody that facilitates NK-cell–mediated killing of cancer cells by blocking the interaction of inhibitory KIR receptors on NK cells with their ligands on target cells. Before administration of the lower dose (0.2 mg/kg), the trial product was diluted with a sterile diluent and administered by intravenous infusion over 1 hour. The higher dose (2 mg/kg) was administered intravenously without dilution over 1 hour.

IPH2101 was provided as 5 mL fill in 10 mL vial of the liquid with formulation strength of 10 mg/mL for intravenous injection/infusion supplied by Innate Pharma. Batch numbers of IPH2101 were TLDS001 (10 mg/mL) and IPH210101b-03 (10 mg/mL). Batch numbers of diluent were TLDP016 and IPH2101-DIL01b; they were used for the lower dose (0.2 mg/kg).

Duration of treatment:

Patients received four monthly injections of IPH2101. Those with any response at 4 months (as defined in the protocol on the basis of a decrease in serum M-protein or FLCS) were allowed to receive an additional four monthly administrations following the same procedures. Patients would be followed for approximately 7 months (i.e., 4 months after the completion of the treatment) during the study, and for 11 months in case of additional treatment.

Reference therapy, dose and mode of administration, batch number: Not applicable.

Criteria for evaluation:

Efficacy: The primary efficacy variables were (1) the level of M-protein, and (2) FLCS levels, the latter for patients with baseline M-protein levels <3 g/l. Secondary efficacy variables were (1) 24-hour urinary protein electrophoresis; (2) PFS; (3) OS; (4) the skeletal survey; (5) pharmacodynamic variables (KIR occupancy, the expression levels of various immune-cell regulation markers and NK/T receptors, immunophenotyping, cytokine levels, macrophage inflammatory protein-1 β [MIP-1β] levels, and NK-cell function); and (6) additional immunological assessments (detection of human antibodies against IPH2101, and HLA-C and KIR typing).

Safety: Safety was assessed by the frequency and severity of adverse events (AEs) and serious AEs (SAEs), as well as by monitoring of vital signs and electrocardiogram.

Statistical methods:

A statistical analysis plan (SAP) was provided as a separate document signed prior to database lock and analysis. All analyses of efficacy were performed on the intention-to-treat (ITT) population, which consisted of all randomized patients, regardless of the treatment actually received. The safety population was used for the safety analyses and consisted of all patients who received at least one injection of IPH2101. Summary statistics were calculated for quantitative variables, and frequency counts with a 95% confidence interval (CI) were computed for qualitative variables as appropriate.

Up to 14 patients were to be treated in each arm, and a dose regimen was to be rejected if no response was seen. Activity was estimated by the rate of patients achieving a response, measured by M-protein serum levels. According to the SAP, a response would be a reduction of serum M-protein levels of at least 25% from baseline, confirmed on two consecutive determinations at 4 week intervals, in patients with a serum M-protein >5 g/L, or a negative electrophoresis, in patients with a serum M-protein ≤5 g/L. If at least one response was seen, the dose regimen would be deemed to have activity. If either dose was rejected for lack of activity, there is 95% confidence that that dose had a true response rate below 20%. Furthermore, if both doses of the experimental treatment were rejected for lack of activity, there is 95% confidence that the treatment (at either dose) had a true response rate below 10%. If both doses showed activity and similar toxicity profiles, a 'selection-design' principle was to be used to choose the dose with the largest number of responses for further testing, with 80%power to choose the correct dose under the assumption that the less active dose had a response rate around 5%, and the more active dose a response rate around 15%.

RESULTS AND CONCLUSION

EFFICACY RESULTS:

Twenty-seven patients were included in the study, all of whom received at least one dose of IPH2101 (14 patients received 0.2 mg/kg of IPH2101, and 13 received 2 mg/kg of IPH2101). There was no screen failure, and 10 patients were discontinued prematurely, five in each treatment arm, most often because of DP. Eight of the 27 patients received additional cycles of therapy: seven had 4 more cycles and one had 2 more cycles.

Eighteen patients were male, and 9 were female. Their age ranged between 34 and 68 years, with a mean of 57.3 years. Fourteen patients had International Staging System stage I disease at diagnosis, and 10 had stage II disease. Nineteen patients had Durie-Salmon stage IIIA disease. The mean time between initial diagnosis of MM and the date of first treatment administration was 26.9 months in the 0.2 mg/kg arm and 23 months in the 2 mg/kg arm. Regarding prior induction regimens, six (22%) patients received treatments that did not include either thalidomide/lenalidomide or bortezomib; the others received treatment that included at least one of these agents, with the most commonly used regimen being the combination of bortezomib plus dexamethasone. All 27 patients underwent at least one autologous stem-cell transplant. The mean time between the last transplantation and the first day of IPH2101 administration was 21.3 months in the 0.2 mg/kg arm *vs*. 17.5 months in the 2 mg/kg arm. The median serum M-protein level after first-line therapy was 9.6 g/L, with a range of 2.9 g/L to 24.4 g/L

Using a definition of response to therapy that required a reduction of the serum M-protein value of at least 25% from baseline, confirmed on two consecutive determinations at 4 week intervals in patients with a serum

M-protein value >5 g/L at baseline, only one patient in the 2 mg/kg arm had a response.

No patient in the study had a complete response. Overall, 81% (95% CI, 62% to 94%) of patients had stable disease at the end of treatment (EOT), and 59% (95% CI, 39% to 78%) at the end of study (EOS). These proportions were similar in both treatment groups. The serum M-protein levels during treatment remained relatively constant across the first four cycles: across both arms, the median value at baseline was 8.9 g/L, and it was 8.8 g/L at cycle 1, 9.1 g/L at cycle 2, 9.0 g/L at cycle 3, and 9.6 g/L at cycle 4. DP occurred in 19% of the patients before the EOT and it was documented in 37% of the patients by the EOS. There was no case of serum or urine M-protein undetectable on electrophoresis, so no serum immunofixation was performed, and no Kappa light chains, Lambda light chains or free-light-chain ratios were available.

Among the 7 patients who received 4 additional cycles, 6 patients had serum M-protein measurements available during these 4 additional cycles, and these levels also remained quite constant. Limited information was available regarding the urinary M-protein. A response, corresponding to the definition given in the protocol, was observed in a single patient, who was enrolled in the 2 mg/kg arm. The value of his serum M-protein reached respectively 11.4 g/L at baseline, 8.1 g/L at week 9 and 8.4 g/L at week 13, i.e., at the next determination 4 weeks later. These week 9 and week 13 consecutive values of M-protein represented respectively a reduction of 29% and 26% from baseline levels.

The overall median PFS time was 11.9 months (95% CI, 7.9 months to 23.0 months), with no difference between treatment arms. TTP results, when measured from the start of study treatment, were identical to the PFS results, as there were no deaths recorded. In an exploratory analysis, the median TTP from the start date of induction therapy was 38.3 months (95% CI, 28.4 months to 48.8 months), again with comparable results between treatment arms.

Peak KIR occupancy was observed 1 h or 6 h after IPH2101 administrations and was above 97% with a single exception. KIR occupancy was above 90% for 7 days following the first administration of IPH2101 in the majority of patients in the 0.2 mg/kg arm, whereas in the 2 mg/kg arm, sustained KIR saturation was above 90% at all time points but one (89% in one patient in one visit). The time taken for KIR occupancy to decrease <30% on two successive measurements tended to correlate with dose.

In a majority of patients in both arms, a decrease of peripheral NK-cell numbers was observed 24 h after IPH2101 administration, but at 7 days post-dose the numbers were close to baseline. In some patients, the first dose of IPH2101 induced a transient increase in CD69 expression in the IPH2101-positive NK-cell subset. However, IPH2101 treatment did not impair NK cell phenotype. Monitoring of NK-cell function by comparing patient pre-dose samples with samples from an age- and sex-matched cohort of healthy donors showed similar responses in terms of CD107 exposure at the cell surface and intracellular IFN-γ production in response to various stimuli. The impact of IPH2101 treatment on NK-cell function was also assessed *in vitro* and this assessment suggested a benefit for the anti-KIR treatment in terms of HLA+ tumor cell rejection.

There was no significant release of IL-1β in either arm. Plasma IL-6 was detected in the majority of the patients in both arms, with peaks being reached 3 to 6 hours following the first administration of IPH2101. IL-6 concentrations were below or close to the lower limit of quantification (LLOQ) within 24 h following IPH2101 administration. Release of IFN-γ following the first administration of IPH2101 was detected in 5/14 (36%) patients in the 0.2 mg/kg arm and in 7/13 (54%) patients in the 2 mg/kg arm. Maximal IFN-γ concentrations were reached 1 to 3 hours after administration, but were below LLOQ within 24 h in the majority of patients in both arms. Increase in TNF-α concentration following the first administration of IPH2101 was detected in all but two patients in the 0.2 mg/kg arm. Maximal TNF-α concentrations were reached 1 to 3 hours following the first administration, decreasing within 24 h and reaching values similar to baseline within 7 days. In most patients in both arms, further administration of IPH2101 did not induce notable production of TNF-α.

Plasma MIP-1β was detected in the majority of samples from all patients and at all time points. Maximal MIP-1β concentrations were reached 3 hours after administration (with one exception), but concentrations were close to baseline values within 24 h. Much lower increases in MIP-1β concentrations were detected after subsequent administrations of IPH2101.

No firm conclusion concerning the absence of immunogenicity could be drawn, the detection of anti IPH2101 antibody being impaired by residual levels of circulating IPH2101 in sera.

SAFETY RESULTS:

The median number of cycles was four in both treatment arms; of the seven patients who received four additional cycles, three were in the 0.2 mg/kg arm, and four were in the 2 mg/kg arm.

At least 1 AE was reported in 25 of the 27 patients. None of these AEs led to premature discontinuation or death. In two patients in the 0.2 mg/kg arm, AEs led to dose delays. However, only 52% of AEs were considered to be related to study treatment. None of the AEs considered to be related to study treatment led to dose delays or premature discontinuation. There was one SAE consisting of an episode of bronchitis in the 0,2 mg/kg arm. That episode was not considered to be drug-related. One patient in the 0.2 mg/kg arm was hospitalized for DP. There were no deaths on study.

None of the AEs reported in the study appeared to be of particular concern with regard to their nature or incidence, and most of the reported AEs are common among patients with MM. The most frequent AEs were general disorders, such as asthenia, fatigue, pain (headache, back pain, chest pain, and muscle spasms) and upper respiratory tract infections. The analysis of the numbers of patients with AEs in both treatment groups suggests no pattern regarding the dose of IPH2101. All AEs considered related to study treatment were of grade 1 or 2 severity. The most frequent related AEs were again general disorders.

Most laboratory assessments during the study showed no abnormalities. The most frequent laboratory changes were grade 1 and 2 hematologic abnormalities such as leukopenia and neutropenia, and there were only two instances of grade 3 hematologic abnormalities. Treatment with IPH2101 did not seem associated with unexpected metabolic, renal or hepatic laboratory abnormalities.

Twelve patients had at least one systolic blood pressure reading ≤100 mm Hg (nine in the 2 mg/kg arm and three in the 0.2 mg/kg arm), but only two patients in the 2 mg/kg arm had a single systolic blood pressure reading <90 mm Hg. All patients had at least grade 1 hypertension during the study, but 14 already had hypertension at baseline. Fever (≥37.8ºC) was noted in a single instance in 3 patients, all in the 2 mg/kg arm.

Four patients had corrected QT interval prolongation during the study, always of grade 1 or 2. No patient experienced ECG alterations during the study that were regarded by the investigators as clinically significant.

CONCLUSION:

The current study suggests that IPH2101 may have antitumor activity in MM. Although only one patient in the 2 mg/kg arm had a response, the vast majority of patients (81%) had stable disease at treatment termination. Other efficacy endpoints, such as PFS and TTP from start of induction therapy, were also encouraging for this patient population. However, lack of a control group with no active treatment precludes differentiating the effect of IPH2101 from the natural history of MM.

The trial was not designed to compare the 2 dose regimens. Still, it is noteworthy that no pattern emerged to suggest a dose-response relationship in terms of antitumor activity or safety. The pharmacodynamic results show that (1) IPH2101 can induce IL-6, IFN-γ, TNF-α and MIP-1β production upon first administration; (2) further administrations of IPH2101 induce no or very low production of these molecules; (3) cytokines and MIP-1β productions tend to be higher at the highest dose tested in this study (albeit with no statistically different results).

The current study confirms the safety experience accumulated to date with IPH2101. The drug is generally well tolerated, with a low frequency of AEs that are mostly mild to moderate.

In summary, IPH2101 may have antineoplastic activity in MM. Further studies are needed to clarify the role of this agent alone or in combination with other agents or treatment modalities. Finally, no new safety signals have emerged from this study and none of the AEs or laboratory abnormalities reported here appears to be of particular concern with regard to its nature or its incidence.