### Safety Pharmacology

Safety pharmacology assessments were included in the repeated dose toxicity study as recommended by International Conference on Harmonisation (ICH) S6 (R1): Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals and ICH S9: Nonclinical Evaluation of Anticancer Therapeutics. In the 4-week (5-dose) repeat-dose toxicity study in cynomolgus monkeys (Study PROJECT 12-026), cardiovascular (electrocardiograms, blood pressure), respiratory and central nervous system function were evaluated. No abnormal findings were noted in any safety pharmacology parameter ≤ 200 mg/kg.

### Pharmacodynamic Drug Interactions

No pharmacodynamic drug interaction studies of PROJECT 12 have been conducted to date.

## Toxicology

Safety of PROJECT 12 has been evaluated in 2 pivotal repeat-dose toxicity studies (Studies PROJECT 12-025 and PROJECT 12-026), 1 tissue cross-reactivity study (Study PROJECT 12-024) and 1 cytokine-release and proliferation assay (Study PROJECT 12-027). PROJECT 12 showed comparable binding affinity to mouse, rat, cynomolgus monkey and human NRP1 (Study PROJECT 12-002). Since PROJECT 12 demonstrated comparable binding affinity to all species evaluated, rat and cynomolgus monkey were selected as the relevant species for safety evaluation of PROJECT 12.

### Single-dose Toxicity

Single dose tolerability of PROJECT 12 was evaluated in non-GLP studies of rats and cynomolgus monkeys (Studies PROJECT 12-034 [PROJECT 12-008] and PROJECT 12-035

[PROJECT 12-009], respectively). No treatment-related effects were noted on mortality, clinical observations or body weights [Section[s 4.1.1.3](#_bookmark30) and [4.1.1.4](#_bookmark35)]. The single dose toxicity of PROJECT 12 was evaluated after the first dose in the repeat-dose toxicity studies in rats and cynomolgus monkeys, respectively (Studies PROJECT 12-025 and PROJECT 12-026). In these studies, there were no toxicity findings after a single dose of PROJECT 12 at ≤ 500 mg/kg and

≤ 200 mg/kg in rats and cynomolgus monkeys, respectively.

### Repeat-dose Toxicity

One 4-week (5-dose) definitive intravenous toxicity study in rats and one 4-week (5-dose) definitive intravenous toxicity study in cynomolgus monkeys were conducted. A tabulated summary of the 2 pivotal repeat-dose toxicity studies can be found in [End-of-Text

Table 3.2].

### A 4-Week (5-Dose) Study of PROJECT 12 by Intravenous Infusion in Cynomolgus Rats with a 4-Week Recovery Period

Crl:CD(SD) rats (10 males and 10 females per group) were administered PROJECT 12 by intravenously (60-minute infusion) at doses of 0, 50, 150 and 500 mg/kg once weekly for

4 weeks (Study PROJECT 12-025). The main study animals were dosed on days 1, 8, 15, 22 and 29 and sacrificed on day 30. To assess the reversibility of toxicity findings during a subsequent 4-week recovery period, 5 additional animals/sex received control or PROJECT 12 at a dose level of 500 mg/kg. An additional 3 animals/sex in the control group, and

9 animals/sex in all dose groups, were assigned to toxicokinetic satellite groups and dosed in the same manner. Further, 6 males and 6 females per group were treated in the same manner to perform immunophenotyping analysis.

Intravenous administration of PROJECT 12 was well-tolerated and did not result in any mortality or toxicologically relevant findings at 500 mg/kg. In the clinical pathology, increased total protein, increased globulin and decreases in albumin/globulin (A/G) ratio were noted in males and/or females at 500 mg/kg. In addition, decreased triglyceride at ≥ 150mg/kg in females, with no recovery by the end of recovery period, was observed. These changes were considered to be non-adverse, since there were no associated findings and changes were minimal and within historical control ranges. There were test article-related higher absolute and relative liver weights in males and females and an increase in thymic weights in females at 500 mg/kg. These organ weight changes were considered non-adverse since they were not accompanied by microscopic and/or clinical pathology findings. Based on these results, the no-observed-adverse-effect level (NOAEL) under the conditions of this study was considered to be 500 mg/kg, which correlated to a serum AUC168h (sex combined) value of

1178400 µg·h/mL and a Cmax value of 13500 μg/mL [End-of Text Table 3.2.1].

### 4-Week (5-Dose) Study of PROJECT 12 by Intravenous Infusion in Cynomolgus Monkeys with a 4-Week Recovery Period

Cynomolgus monkeys (3 males and 3 females per group) were administered PROJECT 12 by intravenous infusion (60 minutes) at doses of 0 (vehicle control), 20, 60 and 200 mg/kg for

4 weeks (Study PROJECT 12-026). The animals were dosed on days 1, 8, 15, 22 and 29 and sacrificed on day 30. In addition, 2 animals/sex were added to the control and 200 mg/kg dose groups to assess the reversibility of toxicity findings following a 4-week recovery period.

There were no changes in any of the parameters evaluated that were considered toxicologically relevant. PROJECT 12-related clinical pathology changes included non-adverse, decreases in triglycerides at ≥ 20 mg/kg, with no recovery by the end of the recovery period.

In addition, non-adverse, minimally increased globulins and decreased A/G ratio were noted at 200 mg/kg, with complete or partial recovery. Based on these results, the NOAEL under the conditions of the study was considered to be 200 mg/kg, which correlated to a serum AUC168h (sex combined) value of 809000 µg·h/mL and Cmax of 7320 μg/mL [End-of Text Table 3.2.2].

### Genotoxicity

Genotoxicity studies of PROJECT 12 were not conducted and are not scheduled, since the studies routinely conducted are not considered relevant for a monoclonal antibody product

[ICH S6(R1)].

### Carcinogenicity

Carcinogenicity studies of PROJECT 12 were not conducted and are not scheduled, since the studies are not considered necessary for anti-cancer agents intended for treatment of advanced systemic disease [ICH S1A and S9].

### Reproductive and Developmental Toxicity

No reproductive and developmental toxicity studies with PROJECT 12 have been conducted as of the preparation of this IB.

### Local Tolerance

Local irritation was evaluated as part of the repeat intravenous dose toxicity study (Studies PROJECT 12-025 and PROJECT 12-026). There were no apparent differences between the PROJECT 12 and vehicle control dosing group in the histopathologic examination.

### Other Toxicity Studies

* + - 1. **Tissue Cross-reactivity**

PROJECT 12 was applied to cryosections of 36 different normal cynomolgus monkey tissues (2 donors per tissue) and human tissues (3 donors per tissue) at concentrations of 5 and

0.5 µg/mL (Study PROJECT 12-024). In addition, monoclonal human IgG4 with hinge stabilizing mutation was used as an isotype control.

Similar reactivity with PROJECT 12 was observed in endothelium, spindle cells and mononuclear cells in the human and cynomolgus monkey tissue panels. Neuropil, adrenal cortical epithelium and ovarian theca cells were stained only in cynomolgus monkey tissues, while Kupffer cells, pituicytes and bone marrow hematopoietic cells were stained only in human tissues.

The staining observed with PROJECT 12 in the monkey and human tissues in the tissue cross- reactivity study was cytoplasmic in nature, with the exception of the neuropil staining observed in a single monkey brain sample.

### 4.3.7.2 Cytokine-release and Proliferation Assay

The in vitro effects of PROJECT 12 on cytokine-release from human PBMCs and proliferation of human PBMCs were assessed in both wet coated and soluble assays (Study PROJECT 12-027).

Samples provided from 10 healthy human donors were incubated with PROJECT 12 in 2 formats; a soluble assay format (0.3, 3.0, 30 and 300 µg/mL) and a wet-coated immobilized assay format (0.06, 0.6, 6.0 and 60 µg/well). For the wet-coated format, PROJECT 12 was immobilized to an assay plate, while in the soluble format, PBMCs were incubated with PROJECT 12 in solution. For each assay, a negative control, an isotype control and positive controls (anti-human CD3 antibody and/or phytohemagglutinin [PHA]) were included.

In vitro incubation of human PBMCs with PROJECT 12 in the soluble format did not induce the secretion of IL-2, IL-10, IL-12(p70) and IFNγ at any PROJECT 12 concentration.

In vitro incubation of human PBMCs with PROJECT 12 in the soluble format resulted in 5.5-fold increase of IL-6 at 30 µg/mL when compared to the isotype control, and increases in IL-1β, IL-6, IL-8, TNFα and G-CSF were noted at 300 µg/mL when compared to the isotype control (9.6-, 28.0-, 6.1-, 5.2- and 5.9-fold, respectively). In the positive controls, the degree of induced IL-1β, IL-6, IL-8, TNFα and G-CSF was 32-, 55-, 4-, 9- and 13-fold (anti-CD3 antibody) or 297-, 1285-, 11-, 83- and 1207-fold (PHA), respectively. Additionally, increases were observed in IL-8 at 30 µg/mL in 3 out of 10 donors, however, the overall group median fold change was minimal compared to that of isotype control.

In the wet-coated immobilized format, no PROJECT 12-related increases in any cytokines were observed when compared to the isotype control.

In vitro incubation of human PBMCs for 3 days with PROJECT 12 in the soluble or wet-coated format did not induce PBMC proliferation at any PROJECT 12 concentration in any donor.

## Integrated Nonclinical Overview and Conclusion: Potential Clinical Relevance

### Summary of Nonclinical Data Package

PROJECT 12 is a high affinity, fully human, anti-NRP1 immunoglobulin IgG4 antibody with S228P hinge stabilization mutation, which binds to NRP1 to block ligand interactions on the surface of Tregs to reverse the suppressive activity of these cells. PROJECT 12 has a high affinity for mouse, rat, cynomolgus monkey and human recombinant NRP1. Therefore, the binding affinity of PROJECT 12 for rat and cynomolgus monkey NRP1 supported both as appropriate species for safety studies.

The pharmacological properties of PROJECT 12 to modulate the immunosuppressive phenotype of Tregs and promote immune mediated reduction of tumor burden was shown in 2 mouse syngeneic tumor models. Using the CT26 colon model, the antitumor efficacy of PROJECT 12 as a single agent was demonstrated using mPROJECT 12, a chimeric version of PROJECT 12 consisting of a mouse IgG2a scaffold, with the N297A mutation to reduce ADCC and CDC effector functions. mPROJECT 12 displayed antitumor efficacy greater than that of an anti-PD-1 antibody. The combination of mPROJECT 12 with the anti-PD-1 antibody resulted in increased antitumor efficacy over that of either treatment alone. Antitumor efficacy correlated with full RO of NRP1, which was achieved in the mPROJECT 12 and mPROJECT 12/anti-PD-1 antibody treated groups. mPROJECT 12 as a single agent or in combination with anti-PD-1 antibody resulted in significant decreases in the expression levels of NRP1 and the transcription factor Helios on splenic Tregs, as well as decreases in Treg proliferation. Re-stimulation of CD8+ T cells isolated from tumors treated in vivo with the combination of mPROJECT 12 and anti-PD-1 antibody had a significantly higher frequency of cells producing IFNγ and TNF, as well as a significantly higher frequency of CD8+ T cells producing both cytokines simultaneously. A pharmacologic dose-response study of mPROJECT 12 was conducted in the MC38 syngeneic colon tumor model in mice. Again, single agent activity was observed in this model, and efficacy occurred with maximum RO when circulating levels of mPROJECT 12 were maintained above approximately 100 μg/mL. Dose-dependent changes were observed in peripheral immune cell phenotypes such as a decrease of Helios and FoxP3 expression in Tregs, as well as a decrease in their proliferation.

The pharmacokinetics and toxicokinetics of PROJECT 12 were characterized in rats and cynomolgus monkeys in single- and repeat-dose studies. The pharmacokinetics and toxicokinetics of PROJECT 12 are characterized by TMDD, with nonlinear behavior at a single dose (3 to 30 mg/kg) in both rats and cynomolgus monkeys and approximately linear behavior during repeated dosing (50 to 500 mg/kg in rats and 20 to 200 mg/kg in cynomolgus monkeys). No apparent sex differences were observed in exposure in either rats or cynomolgus monkeys. After repeated weekly administration, an increase in exposure (Cmax and AUCtau) was generally observed.

ADAs were observed at 3 to 30 mg/kg in rats and at 3 to 10 mg/kg in cynomolgus monkeys in pharmacokinetic studies. No animals were found positive for ADAs after PROJECT 12 administration (50 to 500 mg/kg in rats and 20 to 200 mg/kg in cynomolgus monkeys) in the GLP toxicity studies.

The safety of PROJECT 12 was assessed in 4 nonclinical studies: (1) 4-week (5-dose) repeated intravenous dose toxicity study with 4-week recovery in rats (Study PROJECT 12-025), (2) 4-week (5-dose) repeated intravenous dose toxicity study with 4-week recovery in cynomolgus monkeys (Study PROJECT 12-026), (3) human and cynomolgus monkey tissue cross-reactivity study (Study PROJECT 12-024) and (4) cytokine-release and proliferation assessment study in human PBMCs (Study PROJECT 12-027).

Intravenous administration of PROJECT 12 resulted in an approximately dose-proportional increase in Cmax and AUC. Exposure ratios based on the animal exposure and the predicted human exposure of PROJECT 12 are shown in [[Table 11](#_bookmark71)].

### Table 11 Exposure Ratios Based on Animal Exposure and Predicted Human Exposure of PROJECT 12

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Type (Study No.)** | **Sex** | **Dose† (mg/kg)** | **Cmax (µg/mL)** | | **Cmax Exposure Ratios‡** | | | | **AUC168h (µg•h/mL)** | | **AUC168h**  **Exposure Ratios‡** | |
| **Day 1** | **Day 22 or 29§** | **Day 1** | | **Day 22 or 29§** | | **Day 1** | **Day 22 or 29§** | **Day 1** | **Day 22 or 29§** |
| Rat/4-week, iv (PROJECT 12-025) | M | 50 | 1230 | 2390 | 1.4 | | 2.8 | | 69120 | 179280 | 0.7 | 1.8 |
| F | 50 | 1170 | 1310 | 1.4 | | 1.5 | | 65760 | 121920 | 0.7 | 1.3 |
| M | 150 | 2110 | 5780 | 2.5 | | 6.8 | | 225120 | 535200 | 2.3 | 5.5 |
| F | 150 | 3430 | 6610 | 4.0 | | 7.8 | | 219840 | 547200 | 2.3 | 5.6 |
| M | 500 | 9620 | 14100 | 11.3 | | 16.6 | | 835200 | 1178400 | 8.6 | 12.1 |
|  |  |  |  |
| F | 500 | 6220 | 12800 | 7.3 |  | 15.1 |  | 643200 | 1180800 | 6.6 | 12.1 |
|  | |  | |
| Monkey/4-week, iv  (PROJECT 12-026) | M | 20 | 690 | 967 | 0.8 | | 1.1 | | 48100 | 97900 | 0.5 | 1.0 |
| F | 20 | 821 | 827 | 1.0 | | 1.0 | | 49400 | 60800 | 0.5 | 0.6 |
| M | 60 | 1980 | 4430 | 2.3 | | 5.2 | | 148000 | 390000 | 1.5 | 4.0 |
| F | 60 | 1990 | 3630 | 2.3 | | 4.3 | | 141000 | 317000 | 1.5 | 3.3 |
| M | 200 | 5730 | 7050 | 6.7 | | 8.3 | | 424000 | 828000 | 4.4 | 8.5 |
| F | 200 | 6230 | 7590 | 7.3 | | 8.9 | | 431000 | 790000 | 4.4 | 8.1 |

F: female; M: male; NOAEL: no-observed-adverse-effect level;

† The underlined dose represents the NOAEL.

‡ The exposure ratios were calculated as (AUC168h × 2 [or Cmax]) / (estimated human systemic exposure level at the efficacious dose). The estimated human systemic exposure level of Cmax or AUC336h was 850 µg/mL or 8100 µg·day/mL (194400 µg·h/mL), respectively, at the estimated efficacious dose of 1200 mg/2 weeks.

§ Day 29 for rats, day 22 for monkey. Source: Studies PROJECT 12-025 and PROJECT 12-026

No mortalities were seen following weekly administration of PROJECT 12 for 4 weeks (5 doses) in either rats or cynomolgus monkeys at doses ≤ 500 mg/kg and ≤ 200 mg/kg, respectively. In addition, no target organs of toxicity were identified in either species at exposure ratios 8.1- to 12.1-fold higher than the predicted human systemic exposure at the estimated clinical efficacious dose [[Table 11](#_bookmark71)]. Decreases in triglyceride levels were noted in both rats and cynomolgus monkeys. Similar findings have been reported in these same species following administration of the anti-NRP1 monoclonal antibody, MNRP1685A [Zafra et al, 2010]. The mechanism of the decrease in triglyceride is unknown, however, these changes were not considered adverse or toxicologically significant as there were no gross or histopathological changes associated with this finding. In addition, the absence of a similar finding in the clinical trial of MNRP168A suggests that the decrease in triglyceride levels seen in the nonclinical studies may not be relevant to humans [Weekes et al, 2014; Patnaik et al, 2014].

In vitro, PROJECT 12 bound to cytoplasmic elements in normal cynomolgus monkey and human tissues. The one difference was that PROJECT 12 bound to a dense feltwork of interwoven cytoplasmic processes of nerve cells (dendrites and axons) and neuroglial cells, termed neuropil in the cynomolgus monkey but not in the human brain. Monoclonal antibody binding to cytoplasmic sites generally is considered of little to no toxicologic significance,

due to the inability of antibody therapeutics to access the cytoplasmic compartment in vivo [Leach et al, 2010; Hall et al, 2008].

In the cytokine-release and proliferation assessment study, PROJECT 12 induced proinflammatory cytokine-release from normal human PBMCs at concentrations ≥ 30 µg/mL in the soluble format assay only. No increase in any cytokine was observed at any PROJECT 12 concentration in the wet-coated format assay. The increased IL-6 observed at 30 µg/mL in the soluble assay was approximately 5.5-fold when compared to that of the isotype control, the level was much lower than IL-6 concentration induced by the positive control (anti-CD3 antibody; 55-fold). PROJECT 12 did not induce PBMC proliferation in either format. In the repeat-dose cynomolgus monkey study, administration of PROJECT 12 was not associated with indications of proinflammatory mediator release nor were there indications of immunostimulation. While these animal results provide a certain level of confidence regarding the immune associated risk, the animal results may not accurately predict the human response. Since the in vitro cytokine-release assay is considered a tool for a hazard identification rather than for a quantitative risk assessment, the impact of the cytokine findings with PROJECT 12 on human safety is unclear [Finco et al. 2014; Vidal et al., 2010]. In the clinical trials, careful monitoring of appropriate parameters should be considered.

### Starting Dose Rationale

PROJECT 12 has been shown to stimulate the immune system in nonclinical pharmacology models [Section [4.1](#_bookmark5)]. The FDA recommends that a minimally anticipated biologic effect level (MABEL) be considered for selection of a starting dose for biopharmaceuticals with immune agonistic properties [FDA Guidance for Industry, International Conference on Harmonisation [ICH] S9 Nonclinical Evaluation for Anticancer Pharmaceuticals, 2010]. The starting dose of PROJECT 12 FIH study is chosen as 70 mg based on the systemic receptor occupancy using a MABEL approach, with the following considerations:

* A 70 mg dose of PROJECT 12 is predicted to be within the TMDD range in human, with a transient saturation of systemic RO (< 1 day) and rapid loss of exposure to drug [Section [4.2.6.1](#_bookmark56)]. In addition, the predicted maximum concentration (Cmax) of 70 mg PROJECT 12 is

3.5 to 6.6 μg/mL, about 5- to 9-fold less than the lowest observed effect level (LOEL) of 30 μg/mL observed in the in vitro cytokine release and proliferation assay.

* In the non-GLP pharmacokinetic and pharmacodynamic studies and the GLP toxicity studies in rat and monkey, no significant safety findings were identified at PROJECT 12 doses that saturated systemic target occupancy.
* PROJECT 12 is not the first anti-NRP1 antibody moving into the clinic. Another anti-NRP1 antibody, MNRP1685A, has been tested up to 40 mg/kg (2 mg/kg starting dose) in a phase 1 clinical trial without reaching a maximum tolerated dose [Weekes et al, 2014]. MNRP1685A displayed similar TMDD behaviors as PROJECT 12 across a wide range of doses in nonclinical species and human. In humans, a significant number of infusion- related reactions (IRRs) were observed at high doses (> 10 mg/kg) of MNRP1685A, which was successfully mitigated with dexamethasone pretreatment.

Considering the overall favorable safety profile of PROJECT 12 in toxicity studies and the clinical experience with the existing anti-NRP1 antibody (MNRP1685A), a starting dose of 70 mg PROJECT 12 is deemed safe in humans.

The clinical efficacious dose is estimated to be ~ 1200 mg Q2W based on results from the mouse MC38 syngeneic tumor model [Section [4.1.1.2](#_bookmark13)]. The dose escalation portion of the FIH study will evaluate 5 PROJECT 12 dose levels: 70, 200, 700, 1200 and 2000 mg. Dose escalation will take half-log (~ 3-fold) steps initially, with smaller steps once approaching the predicted efficacious dose levels. The NOAEL in the repeat-dose toxicity studies was

500 mg/kg in rat and 200 mg/kg in cynomolgus monkey (the highest dose tested for each species in each study), which achieved a Cmax of 13500 µg/mL and 7320 µg/mL (sex combined), respectively. These concentrations are more than 1100-fold higher than the projected steady state Cmax at the FIH starting dose of 70 mg (3.5 to 6.6 μg/mL) and greater than 5-fold higher than the top dose of 2000 mg (810 to 1600 μg/mL).

## Conclusion

Based on the currently available safety data, it was concluded that there were no identified toxicological findings that would preclude initiation of clinical development of PROJECT 12. Cytokine-release was noted in vitro, the clinical impact of which is unknown. Monitoring of appropriate parameters in clinical studies should be considered [[Section 6.2.5](#_bookmark82)].

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