# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761149Orig1s000

# NON-CLINICAL REVIEW(S)

# MEMORANDUM

**DEPARTMENT OF HEALTH & HUMAN SERVICES**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**

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Date: August 3, 2020

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist
Acting Director, Division of Pharmacology/Toxicology-Neuroscience
Office of Neuroscience

Subject: BLA 761149 (satralizumab)

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Satralizumab (Enspryng) is a humanized IgG2 monoclonal antibody targeting soluble and membrane-bound human interleukin 6 (IL-6) receptors. A BLA for satralizumab for the treatment of patients (b) (4) diagnosed with neuromyelitis optica spectrum disorder was submitted by Genentech, Inc. on August 15, 2019. Clinical development was conducted under IND 118183.

The pivotal nonclinical studies submitted in the BLA consist of pharmacology, PK, and toxicity (including 4- and 26-week) studies, and an enhanced pre- and postnatal development (ePPND) study. The pivotal studies were conducted in cynomolgus monkey, the only pharmacologically relevant species. Carcinogenicity studies were not conducted, as agreed to by the Division (email communication, June 14, 2016).

These data were reviewed by Dr. Hawver (Pharmacology/Toxicology BLA Review and Evaluation, BLA 761149, May 15, 2020), who concluded the nonclinical studies are adequate to support approval of satralizumab for the proposed indication.

The pharmacology studies demonstrate similar binding of satralizumab to membrane-bound ($EC_{50}$ of 0.019 µg/mL) and soluble ($K_D$ of 2.0-1.5 nM) IL-6 receptors in monkey and human.

In general toxicity studies in monkey, weekly subcutaneous doses of up to 50 mg/kg for 4 or 26 weeks resulted in no notable toxicity or effects on male (sperm analysis) and female (menstrual cycle) reproductive parameters and organs. In the 26-week study, plasma exposures ($AUC_{(0\text{-}7d)}$) at the high dose were 23000 and 20000 µg*d/mL in males and females, respectively.



Reference ID: 4651120

In the ePPND study in monkey, satralizumab (0, 2, and 50 mg/kg) was administered weekly to dams by subcutaneous injection from gestation day (GD) 20 to delivery. Offspring were followed to postnatal day 293. No adverse effects were observed on developmental parameters; however, impaired immune function (TDAR using KLH) was observed in offspring at both doses.

Plasma exposures ($AUC_{(0\text{-}7d)}$) in dams were 117 and 3610 µg*d/mL on GD 20 and 565 and 18000 µg*d/mL on GD 146 at the low and high dose, respectively. Excretion of satralizumab into milk was documented ($AUC_{(14\text{-}175d)}$ of 0.448 and 41.2 µg*d/mL at the low and high dose, respectively). In offspring, satralizumab was detectable through PND 63 at the low dose and PND 203 at the high dose; plasma exposures ($AUC_{(14\text{-}293d)}$) during the postnatal period were 1200 and 69100 µg*hr/mL at the low and high dose, respectively.

In humans, satralizumab is to be administered by subcutaneous injection at a dose of 120 mg at Weeks 0, 2, and 4 and then every 4 weeks thereafter. At steady state (Week 8), plasma exposure ($AUC_{(0\text{-}t)}$) was 737 ± 386 µg*d/mL.

The highest dose tested in the pivotal nonclinical studies, although not associated with dose-limiting toxicity, did provide an adequate safety margin (>10-fold), based on comparison of plasma exposures in monkey and human.

Recommendation

The nonclinical studies are adequate to support approval of satralizumab for the intended use.

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/s/

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

# PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

| | |
|---|---|
| Application number: | 761149 |
| Supporting document: | 1 |
| Applicant's letter date: | August 15, 2019 |
| CDER stamp date: | August 15, 2019 |
| Product: | ENSPRYNG (Satralizumab) |
| Indication: | Treatment of neuromyelitis optica spectrum disorders |
| Applicant: | Genentech, Inc. |
| Review Division: | Neurology 2 |
| Reviewer: | David B. Hawver, Ph.D. |
| Supervisor: | Lois M. Freed, Ph.D. |
| Acting Division Director: | Nicholas Kozauer, M.D. |
| Project Manager: | Candido Alicea |

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Reference ID: 4609287

# 1 Executive Summary

## 1.1 Introduction

Satralizumab is a recombinant humanized IgG2 monoclonal antibody that binds to soluble and membrane-bound human interleukin 6 receptors (IL-6R) and prevents signaling through these receptors. IL-6 is a cytokine involved in inflammatory processes such as activation and differentiation of B cells and T cells, production of antibodies, and changes in blood-brain-barrier permeability. The proposed indication is the treatment of adult (b) (4) with neuromyelitis optica spectrum disorder (NMOSD). NMOSD is a severe demyelinating inflammatory autoimmune disorder associated with axonal damage primarily in the spinal cord and optic nerve, increased IL-6 in CSF and serum during periods of disease activity, and (often) the presence of autoantibodies to aquaporin-4 (AQP4), a membrane protein involved in the maintenance of water homeostasis in the brain. The inhibition of IL-6R signaling by satralizumab is thought provide clinical benefit, at least in part, by reducing the survival and function of the plasmablasts that produce anti-AQP4 autoantibodies. The proposed dosing regimen is loading doses of 120 mg satralizumab by subcutaneous (SC) injection at Weeks 0, 2, and 4, followed by maintenance doses of 120 mg SC once every 4 weeks thereafter.

## 1.2 Brief Discussion of Nonclinical Findings

Pharmacology studies demonstrated that satralizumab specifically binds to, and inhibits the activation of, IL-6 receptors in human and cynomolgus monkey. The toxicology of satralizumab was adequately assessed in general toxicity studies and an enhanced pre- and postnatal development (ePPND) study in cynomolgus monkey. In the general toxicity studies, no adverse effects were observed in monkeys administered satralizumab (0, 2, 10, or 50 mg/kg/week SC) for 4 or 26 weeks.

In the ePPND study, administration of satralizumab (0, 2, and 50 mg/kg/week SC) to pregnant females resulted in a dose-dependent reduction in the antibody responses to antigenic challenge in infants. Median maximum titers of IgM and IgG were reduced 15% and 16%, respectively, in low-dose infants, and 30% and 50%, respectively, in high-dose infants. A no-effect level was not established. This immunosuppressive effect was not unexpected in view of the intended pharmacological effects of satralizumab to inhibit the survival and function of plasmablasts. However, infants of women treated with satralizumab during pregnancy may be at increased risk of adverse effects such as infection or impaired response to vaccinations.

Other than the immunosuppression described above, no adverse effects were observed in the pivotal 26-week toxicity or ePPND studies of satralizumab in cynomolgus monkey assessing plasma exposures up to 26-fold or greater than those expected at steady-state in patients receiving the proposed clinical dose.

## 1.3 Recommendations

### 1.3.1 Approvability

The nonclinical data submitted adequately support the approval of satralizumab for the treatment of NMOSD patients (b) (4)

### 1.3.2 Additional Nonclinical Recommendations

The impaired antibody responses observed in the ePPND study in monkey should be described in labeling.

### 1.3.3 Labeling

The sponsor's proposed labeling for the nonclinical sections should be revised as specified below:

### 8.1 Pregnancy

Risk Summary

There are no (b) (4) In an animal reproduction study, ~~no adverse effects on maternal animals or fetal development were observed in pregnant monkeys and their~~ immunosuppression was observed in offspring~~, with administration~~ of pregnant monkeys administered satralizumab at doses ~~up to~~ of 2 and 50 mg/kg/week (see Data). (b) (4)

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(b) (4).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2 – 4% and 15 – 20%, respectively.

Clinical Considerations

Fetal/neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to ENSPRYNG in utero [see *Warnings and Precautions* (5.2)]

Data

Animal Data

(b) (4) administration of satralizumab (0, 2, or 50 mg/kg/week SC) to (b) (4) monkeys (b) (4).

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responses to antigenic challenge in infants. A no-effect level was not established. (b) (4).

### 8.2 Lactation

Risk Summary

No information is available on the presence of satralizumab in human milk, the effects of the drug on the breastfed infant, or the effects of the (b) (4) on milk production. (b) (4) the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENSPRYNG and any potential adverse effects on the breastfed (b) (4) from (b) (4) or from the underlying maternal condition.

(b) (4)

### 8.4 Pediatric Use

(b) (4)

Safety and effectiveness in pediatric patients (b) (4) have not been established.

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## 12 Clinical Pharmacology

### 12.1 Mechanism of Action

(b) (4) to both soluble and membrane-bound human IL-6 receptors (b) (4)

(b) (4)

(b) (4)

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13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

(b) (4)

Mutagenesis

(b) (4)

Impairment of Fertility

(b) (4)

# 2 Drug Information

## 2.1 Drug

Nonproprietary Name
Satralizumab

Proprietary Name
ENSPRYNG

Code Names
RO5333787; SA237; CH5333787

Molecular Weight
143, (b) (4) Da (peptide sequences only)

Biochemical Description
Satralizumab is a recombinant humanized monoclonal antibody based on a human IgG2 framework containing 2 heavy chains ($V_H$; 443 amino acids each) and 2 kappa light chains $V_K$ (214 amino acids each). (b) (4) ). The amino acid sequences of the component light and heavy chains are shown in the figures below:

**Figure S.1.2-1 Amino Acid Sequence of Satralizumab Light Chain**

```
          10         20         30         40         50
DIQMTQSPSS LSASVGDSVT ITCQASTDIS SHLNWYQQKP GKAPELLIYY
          60         70         80         90        100
GSHLLSGVPS RFSGSGSGTD FTFTISSLEA EDAATYYCGQ GNRLPYTFGQ
         110        120        130        140        150
GTKVEIERTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
         160        170        180        190        200
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
         210
LSSPVTKSFN RGEC
```

Note 1: The calculated molecular mass of the light chain is 23,185 Da (cysteine residues are in the reduced form).
Note 2: Complementarity-determining regions according to Kabat are shown in **bold** (Kabat E.A. 1991)
*(page 5, section 2.2, Introduction)*

**Figure S.1.2-2 Amino Acid Sequence of Satralizumab Heavy Chain**

```
          10                  20                  30                  40                  50
QVQLQESGPG LVKPSETLSL TCAVSGHSIS HDHAWSWVRQ PPGEGLEWIG

          60                  70                  80                  90                 100
FISYSGITNY NPSLQGRVTI SRDNSKNTLY LQMNSLRAED TAVYYCARSL

         110                 120                 130                 140                 150
ARTTAMDYWG EGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD

         160                 170                 180                 190                 200
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSNFGTQTY

         210                 220                 230                 240                 250
TCNVDHKPSN TKVDKTVERK SCVECPPCPA PPVAGPSVFL FPPKPKDTLM

         260                 270                 280                 290                 300
ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV

         310                 320                 330                 340                 350
VSVLTVVHQD WLNGKEYKCK VSNKGLPAPI EKTISKTKGQ PREPQVYTLP

         360                 370                 380                 390                 400
PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPMLDSDG

         410                 420                 430                 440
SFFLYSKLTV DKSRWQEGNV FSCSVMHEAL HAHYTQKSLS LSP
```

Note 1: The calculated molecular mass of heavy chain with carbohydrate is 49,966 Da (assumed that one G0F oligosaccharide is attached, and with pyroglutamate formation at the N-terminus of the heavy chain).
Note 2: The glycosylation site at Asn295 is shown as N (position 297 according to generic Eu numbering system [Edelman et al. 1969]).
Note 3: Complementarity-determining regions according to Kabat are shown in **bold** (Kabat E.A. 1991).

*(page 5, section 2.2, Introduction)*

Pharmacologic Class
Satralizumab is an IL-6R antagonist.

## 2.2 Relevant INDs, NDAs, BLAs, and DMFs

IND 118183 satralizumab for the treatment of neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorders (NMOSD)

## 2.3 Drug Formulation

Satralizumab is formulated as a sterile solution for SC injection, containing 120 mg drug substance in a pre-filled 1 mL syringe. The quantities of satralizumab and other components of the solution are listed in Table P.1-1 below:

**Table P.1-1 Composition of Satralizumab Drug Product**

| Ingredients | Nominal Amount per Syringe | Concentration | Function | Specification |
|---|---|---|---|---|
| Satralizumab | 120 mg | 120 mg/mL | Active ingredient | Section S.4.1 *Specification* |
| L-Histidine | 3.1 mg | 20 mmol/L[a] | (b) (4) | USP-NF/ Ph. Eur/JP |
| L-Aspartic Acid | q.s. to pH 6.0 | q.s.to pH 6.0 | pH-adjusting agent | USP-NF/ Ph. Eur/JP |
| L-Arginine | 26.1 mg | 150 mmol/L | (b) (4) | USP-NF/ Ph. Eur/JP |
| Poloxamer 188[b] | 0.5 mg | 0.5 mg/mL | | USP-NF/ Ph. Eur/JPE |
| Water for Injection | q.s. to 1 mL | NA | | USP-NF/ Ph. Eur/JP |

Abbreviations: NA = not applicable; q.s. = quantum satis (as much as may suffice).

[a] (b) (4)

[b] Poloxamer 188 = polyoxyethylene (160) polyoxypropylene (30) glycol.

*(page 1, section 3.2.P.1, Description and Composition of the Drug Product)*

## 2.4 Comments on Novel Excipients

No novel excipients are present in the drug product.

## 2.5 Comments on Impurities/Degradants of Concern

No impurities or degradants of concern were identified.

## 2.6 Proposed Clinical Population and Dosing Regimen

Satralizumab is to be administered (b) (4) to adult (b) (4) with NMOSD. The proposed dosing regimen is 120 mg SC loading doses at Weeks 0, 2, and 4, followed by 120 mg SC maintenance doses once every 4 weeks.

## 2.7 Regulatory Background

Satralizumab was (b) (4)

(b) (4) and that an ePPND study of satralizumab in a non-human primate (NHP) would need to be conducted. The Division agreed to provide comments on an ePPND study protocol and stated that the need for that study to support approval could be discussed further at a pre-BLA meeting (Pre-IND 118183 Meeting Minutes, August 8, 2013).

The Division provided comments (December 12, 2013) on the ePPND study of satralizumab in monkey, including recommendations to provide additional justification of the high dose and to assess learning and memory using the Wisconsin Test Apparatus.

Following a communication (February 11, 2015) of the Division's continuing concern regarding possible disruption by satralizumab of IL-6/IL-6R signaling in the CNS of the developing monkey and recommendation to include "cognitive testing of offspring (using the Wisconsin General Test Apparatus) in the ePPND study," the study protocol was amended to include that assessment.

The Division and the Executive Carcinogenicity Assessment Committee agreed (June 14, 2016) with the sponsor's justification for not conducting carcinogenicity studies of satralizumab.

# 3 Studies Submitted

## 3.1 Studies Reviewed

**Pharmacology**
Examination of cross reactivity of SAQRA to mouse IL-6 receptor
(Chugai Study PHM08-0069S)

Examination of the cross reactivity of SAQRA to rat IL-6 receptor
(Chugai Study PHM08-0095S)

Measurement of CH5333787 dissociation constant by SPR
(Chugai Study PHM09-0192)

Evaluation of pH dependency of the affinity of SA237 and tocilizumab to human IL-6 receptor
(Chugai Study PCA17116)

Assessment of the binding activity of CH5333787 to membrane-bound interleukin-6 receptor (IL-6R)
(Chugai Study PHM10-0045)

Binding activity of CH5333787 to Fc receptors by SPR
(Chugai Study PHM09-0194)

Assessment of ADCC and CDC activities of CH5333787 in vitro
(Chugai Study PHM09-0217)

Evaluation of the neutralizing activity of CH5333787 against human and cynomolgus IL-6Rs
(Chugai Study PHM10-0048)

Examination of neutralizing activity of CH5333787 against human gp130 family cytokine receptors
(Chugai Study PHM09-0228)

Effect of CH5333787 on PHA-L- and IL-6-induced proliferation in human peripheral blood T cells
(Chugai Study PHM10-0076S)

Effect of CH5333787 on IL-6- and soluble IL-6R-induced MCP-1 and VEGF production by human synovial cells
(Chugai Study PHM10-0079)

Inhibitory effect of SA237 on IL-6-induced IgG1 production in human plasmablasts
(Chugai Study PHM15-0118)

Effect of CH5333787 on IL-6-induced CRP production in the cynomolgus monkey (Chugai Study PHM09-0181)

Determination of CH5333787 concentration, anti-CH5333787 antibody titer, tocilizumab concentration, anti-tocilizumab antibody concentration, total sIL-6R concentration and free sIL-6R concentration in plasma from the study "Effect of CH5333787* on cynomolgus IL-6-induced CRP production in cynomolgus monkey" (Chugai Study PHM10-0002; (b) (4) Study B091387)

Effect of CH5333787 on collagen-induced arthritis in cynomolgus monkey (Chugai Study PHM09-0124; (b) (4) Study SBL036-083)

**Pharmacokinetics**

Method Validation Studies

Method validation for the determination of CH5333787 in cynomolgus monkey plasma by ELISA (Chugai Study TOX09-0185; (b) (4) Study PRD09-221)

Method validation for detection of the anti-CH5333787 antibody in cynomolgus monkey plasma by immunoassay (Chugai Study TOX09-0186; (b) (4) Study PRD09-222)

Validation study of the analytical method for determination of sIL-6R (total) in cynomolgus monkey plasma (Chugai Study ADM09-0176; (b) (4) Study B091109)

Validation study of the analytical method for determination of sIL-6R (free) in cynomolgus monkey plasma (Chugai Study ADM10-0004; (b) (4) Study B091430)

Validation study of the analytical method for determination of IL-6 in cynomolgus monkey plasma (Chugai Study ADM09-0188; (b) (4) Study B091207)

Method validation for the determination of CH5333787 in cynomolgus monkey milk by ELISA (Chugai Study TOX13-0097; (b) (4) Study PRD13-397)

**Single-Dose Toxicity**

Plasma concentration and toxicity evaluation of CH5333787 after single intravenous administration of CH5333787 in cynomolgus monkeys (Chugai Study ADM09-0208; (b) (4) Study B091169)

Plasma concentration and toxicity evaluation of CH5333787 after single subcutaneous administration of CH5333787 in cynomolgus monkeys

(Chugai Study ADM09-0209; (b) (4) Study B091170)

**Repeat-Dose Toxicity**
A 4-week intermittent dose (once every week, total 5 doses) intravenous toxicity study of CH5333787 in cynomolgus monkeys (dose range-finding study)
(Chugai Study TOX09-0010S; (b) (4) Study 0741-011)

A 4-week intermittent dose (once weekly, 4 doses) subcutaneous administration toxicity study of CH5333787 in cynomolgus monkeys
(Chugai Study TOX10-0001; (b) (4) Study 8220145)

A 26-week intermittent dose (once weekly, 26 doses) subcutaneous administration toxicity study of CH5333787 with a 13-week recovery phase in mature cynomolgus monkeys
(Chugai Study TOX10-0034; (b) (4) Study 8224665)

**Carcinogenicity**
Carcinogenicity Assessment Document
(Roche Report 1094639)

**Reproductive and Developmental Toxicology**
Intermittent subcutaneous dose (once weekly) enhanced study for effects on pre- and postnatal development of CH5333787 in cynomolgus monkeys
(Chugai Study TOX13-0108; (b) (4) Study 8290717)

**Other**
Satralizumab: Toxicological assessment report on the excipients histidine, arginine, aspartic acid, and poloxamer 188 in a SC drug formulation for use in adolescent patients
(Roche Report 1093380)

A tissue cross-reactivity study of fluorescein-conjugated CH5333787 with normal human and cynomolgus monkey tissues
(Chugai Study TOX09-0132; (b) (4) Study 0050001131)

Blood compatibility study with human blood in CH5333787
(Chugai Study TOX10-5017)

Whole blood cytokine assay for in vitro cytokine release from human whole blood after treatment with CH5333787
(Chugai Study TOX10-0005S)

## 3.2 Studies Not Reviewed

None

### 3.3 Previous Reviews Referenced

None

# 4 Pharmacology

## 4.1 Primary Pharmacology

**Examination of cross reactivity of SAQRA to mouse IL-6 receptor**

(Chugai Study PHM08-0069S; (b) (4)
Final Report dated August 28, 2013; non-GLP; non-QA)

Satralizumab showed no cross-reactivity to the mouse IL-6 receptor in an in vitro cell growth assay. Tocilizumab showed a similar lack of effect. In contrast, a rat anti-mouse IL-6R homolog mAb dose-dependently inhibited IL-6-induced cell growth.

**Examination of the cross reactivity of SAQRA to rat IL-6 receptor**

(Chugai Study PHM08-0095S; (b) (4)
Final Report dated July 13, 2009; non-GLP; non-QA)

Satralizumab showed very little cross-reactivity to the rat IL-6 receptor in an in vitro T cell growth assay. In contrast, an anti-human IL-6 mAb markedly suppressed T cell growth stimulated by IL-6 and phytohemagglutinin-L (PHA-L).

**Measurement of CH5333787 dissociation constant by SPR**

(Chugai Study PHM09-0192; (b) (4)
Final Report dated March 11, 2010; amended June 16 and 30, 2010; non-GLP; non-QA)

The $K_D$ values for binding to hsIL-6R were determined by surface plasmon resonance (SPR) to be 1.5 ± 0.1 nM for satralizumab and 5.8 ± 0.3 nM for tocilizumab; $K_D$ values for binding to cynomolgus monkey soluble IL-6R (cyno.sIL-6R) were 2.0 ± 0.1 nM and 8.6 ± 0.2 nM, respectively. The rates of dissociation from hsIL-6R were similar for satralizumab and tocilizumab at pH 7.4 but were higher for satralizumab at pH 5.8. Finally, satralizumab competitively displaced binding of tocilizumab to hsIL-6R and cyno.sIL-6R, suggesting the epitopes for these two antibodies overlap.

**Evaluation of pH dependency of the affinity of SA237 and tocilizumab to human IL-6 receptor**

(Chugai Study PCA17116; (b) (4) Final Study Report dated December 15, 2017; non-GLP; QA)

In vitro evaluations of binding to hIL-R using SPR demonstrated greater pH dependence for satralizumab than for tocilizumab.

**Table 1 Results of pH dependency of binding kinetics of tocilizumab and SA237 to hIL-6R**

| | | $k_a$ value ($\times 10^4$ L/mol·s) | $k_d$ value ($\times 10^{-4}$/s) | $K_D$ value ($\times 10^{-9}$ mol/L) |
|---|---|---|---|---|
| pH 7.4 | tocilizumab | 21.3 | 11.6 | 5.44 |
| | SA237 | 46.8 | 8.85 | 1.89 |
| pH 7.0 | tocilizumab | 21.1 | 12.4 | 5.89 |
| | SA237 | 47.0 | 12.4 | 2.64 |
| pH 6.5 | tocilizumab | 18.9 | 15.1 | 8.10 |
| | SA237 | 43.8 | 29.9 | 6.87 |
| pH 6.0 | tocilizumab | 19.4 | 18.7 | 9.66 |
| | SA237 | 32.7 | 110 | 33.6 |

*(page 5 of Study Report)*

**Assessment of the binding activity of CH5333787 to membrane-bound interleukin-6 receptor (IL-6R)**

(Chugai Study PHM10-0045; (b) (4) Final Report dated June 28, 2010; amended July 21 and August 6, 2010; non-GLP; non-QA)

Satralizumab showed specific binding to membrane-bound IL-6R from human ($EC_{50}$ = 0.0192 µg/mL) and cynomolgus monkey ($EC_{50}$ = 0.0194 µg/mL) when assessed using flow cytometry with CHO cells expressing the recombinant membrane receptors. Tocilizumab also showed specific binding ($EC_{50}$ = 0.0170 and 0.0179 µg/mL for human and monkey, respectively).

**Binding activity of CH5333787 to Fc receptors by SPR**

(Chugai Study PHM09-0194; (b) (4) Final Report dated June 22, 2010; amended January 21, 2011; non-GLP; non-QA)

The specific binding of satralizumab (a modified human IgG2 mAb) to human neonatal Fc receptor (hFcRn), cynomolgus neonatal Fc receptor (cyno.FcRn), 8 types of human Fcγ (hFcγR) and 7 types of cynomolgus Fcγ receptor (cyno.FcγR) was evaluated using

SPR, and compared to that of tocilizumab (a non-modified human IgG1 mAb) and panitumumab (a non-modified human IgG2 mAb).
The results demonstrated that satralizumab bound with higher affinity than tocilizumab or panitumumab to human and monkey FcRn, consistent with its longer residence time in the blood. In addition, binding of satralizumab to hFcγR was weaker than that of tocilizumab and panitumumab, suggesting that adverse effects related to FcγR binding are less likely to occur.

**Assessment of ADCC and CDC activities of CH5333787 in vitro**

(Chugai Study PHM09-0217; (b) (4)
Final Report dated April 22, 2010; amended July 28, 2010; non-GLP; non-QA)

Satralizumab showed no antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) against U266 cells expressing hIL-6R when assessed in standard in vitro assays in human donor PBMCs or baby rabbit complement sera, respectively. In contrast, the positive control anti-CD20 mAb (rituximab) showed dose-dependent ADCC and CDC activity against BALL-1 cells expressing CD20, as expected.

**Evaluation of the neutralizing activity of CH5333787 against human and cynomolgus IL-6Rs**

(Chugai Study PHM10-0048; (b) (4)
Final Report dated July 15, 2010; amended August 30, 2010; non-GLP; non-QA)

Satralizumab showed concentration-dependent inhibition of 1) hIL-6-induced growth of BaF cells expressing hmIL-6R and gp130, the protein that transduces the signal following binding of IL-6 to its membrane-bound ligand, mIL-6R ($IC_{50}$ = 11 µg/mL; classic signalling); 2) cyno.IL-6-induced growth of BaF cells expressing cyno.mIL-6R and gp130 ($IC_{50}$ = 3.9 µg/mL); 3) growth of BaF cells expressing gp130 stimulated by addition of hIL-6 and the soluble ligand, hsIL-6R ($IC_{50}$ = 0.038 µg/mL; trans-signalling); and 4) growth of BaF cells expressing gp130 stimulated by addition of cyno.IL-6 and cyno.sIL-6R ($IC_{50}$ = 0.046 µg/mL). Similar concentration-dependent inhibition was observed for tocilizumab ($IC_{50}$ = 5.1, 2.1, 0.078, and 0.067 µg/mL, respectively).

**Examination of neutralizing activity of CH5333787 against human gp130 family cytokine receptors**

(Chugai Study PHM09-0228; (b) (4)
Final Report dated April 22, 2010; amended July 23, 2010; non-GLP; non-QA)

Satralizumab concentration-dependently inhibited hIL-6-dependent growth of BaF cells expressing hIL-6R but did not interfere with hIL-11-dependent growth of BaF cells expressing hIL-11R, human oncostatin M-dependent growth of BaF cells expressing hOSMR, human leukemia inhibitory factor-dependent growth of BaF cells expressing

hLIFR, or human ciliary neurotrophic factor-dependent growth of BaF cells expressing hCNTFR.

**Effect of CH5333787 on PHA-L- and IL-6-induced proliferation in human peripheral blood T cells**

(Chugai Study PHM10-0076S; (b) (4)
Final Report dated July 15, 2010; non-GLP; non-QA)

Satralizumab and tocilizumab concentration-dependently inhibited hIL-6-dependent proliferation of PHA-L-activated human peripheral blood T cells when analyzed in the $^{3}$H-thymidine uptake assay ($IC_{50}$ = 4.4 and 2.9 µg/mL, respectively).

**Effect of CH5333787 on IL-6- and soluble IL-6R-induced MCP-1 and VEGF production by human synovial cells**

(Chugai Study PHM10-0079; (b) (4)
Final Report dated July 15, 2010; non-GLP; non-QA)

Satralizumab and tocilizumab concentration-dependently inhibited the increases in monocyte chemoattractant protein-1 (MCP-1) and vascular endothelial growth factor (VEGF) in the medium of cultured human fibroblast-like synoviocytes-rheumatoid arthritis (HFLS-RA) stimulated by the addition of hIL-6 + hsIL-6R ($IC_{50}$ = 0.17 and 0.26 µg/mL, respectively, for MCP-1; and 0.44 and 0.32 µg/mL, respectively, for VEGF).

**Inhibitory effect of SA237 on IL-6-induced IgG1 production in human plasmablasts**

(Chugai Study PHM15-0118; (b) (4)
Final Report dated June 28, 2018; non-GLP; non-QA)

Satralizumab (1 µg/mL) inhibited hIL-6-dependent production of IgG1 in human plasmablasts purified from the peripheral blood of 12 human donors and cultured for 6 days ($P<0.05$ compared to PBS controls).

**Effect of CH5333787 on IL-6-induced CRP production in the cynomolgus monkey**

(Chugai Study PHM09-0181; (b) (4)
Final Report dated October 21, 2019; amended March 8 and May 23, 2019; non-GLP; non-QA)

Cynomolgus monkeys (4-5 M/group) were administered a single SC injection of vehicle (20 mM histidine, 150 mM arginine-aspartic acid, 0.5 mg/mL poloxamer 188, pH 6.0), satralizumab (0.5, 1, or 2 mg/kg), or tocilizumab (1 or 2 mg/kg in 22 mM phosphate, 0.048% polysorbate, pH 6.4) on Day 0. Blood was collected prior to dosing and daily from Days 3-11 (Protocol 1) or every other day from Days 4-28 (Protocol 2) for analysis of plasma CRP, total sIL-6R, free sIL-6R, satralizumab, tocilizumab, and anti-

tocilizumab concentrations; and anti-satralizumab titers. Cyno.IL-6 (5 µg/kg SC) was administered on Days 3-11 after blood collection (Protocol 1) or every other day from Day 5-27 (Protocol 2).

Results of Protocol 1:

As shown in Figure 1 below, the peak plasma concentration of satralizumab (0.5 mg/kg) was like that of tocilizumab (1 mg/kg); satralizumab concentrations declined more slowly over time, remaining detectable on Day 11.

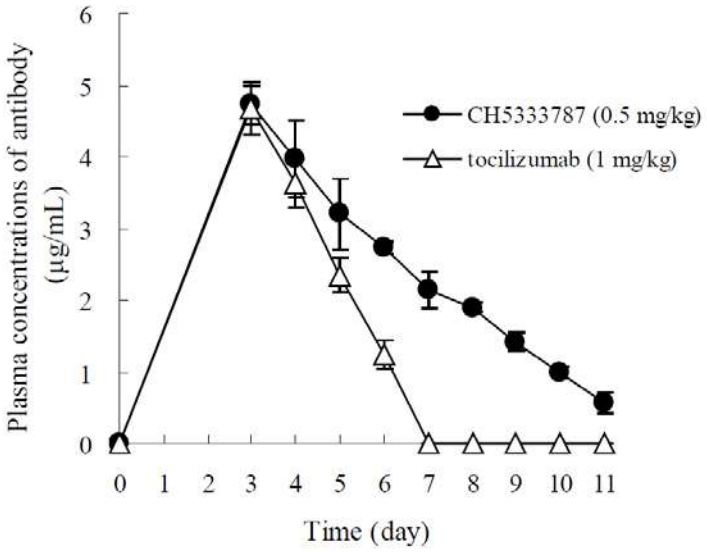


**Figure 1 Plasma concentrations of CH5333787 and tocilizumab in cynomolgus monkey (Study protocol 1).**

Each point on the curve represents mean ± SE.

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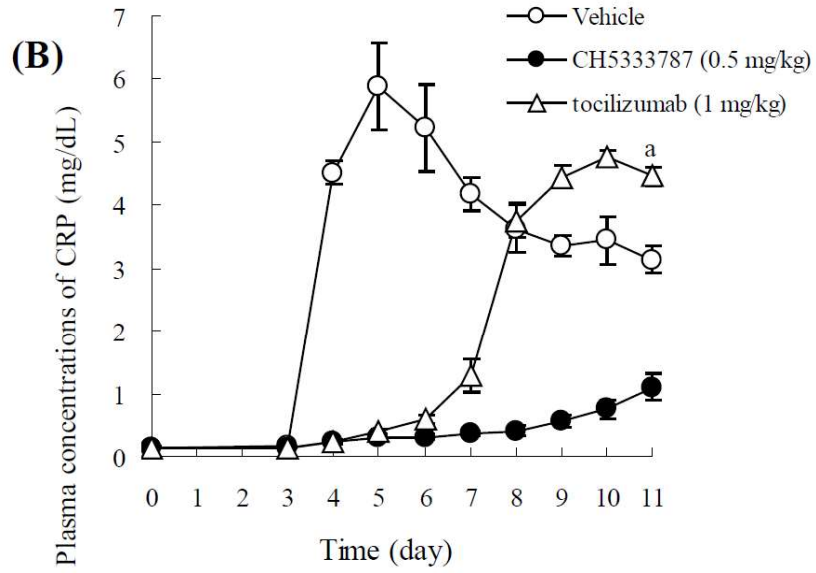
Positive anti-drug antibody (ADA) titers were observed in 2/4 animals from Day 9-10 onward after 0.5 mg/kg satralizumab and in 2/4 animals from Day 11. Day 11 tocilizumab concentrations were below the level of quantification in the two animals positive for ADA; therefore, these animals were excluded from further analyses.

As shown in the figure below, the inhibition of cyno.IL-6-induced increases in CRP by satralizumab was sustained through Day 11, whereas the inhibition mediated by tocilizumab was sustained only through Day 8.

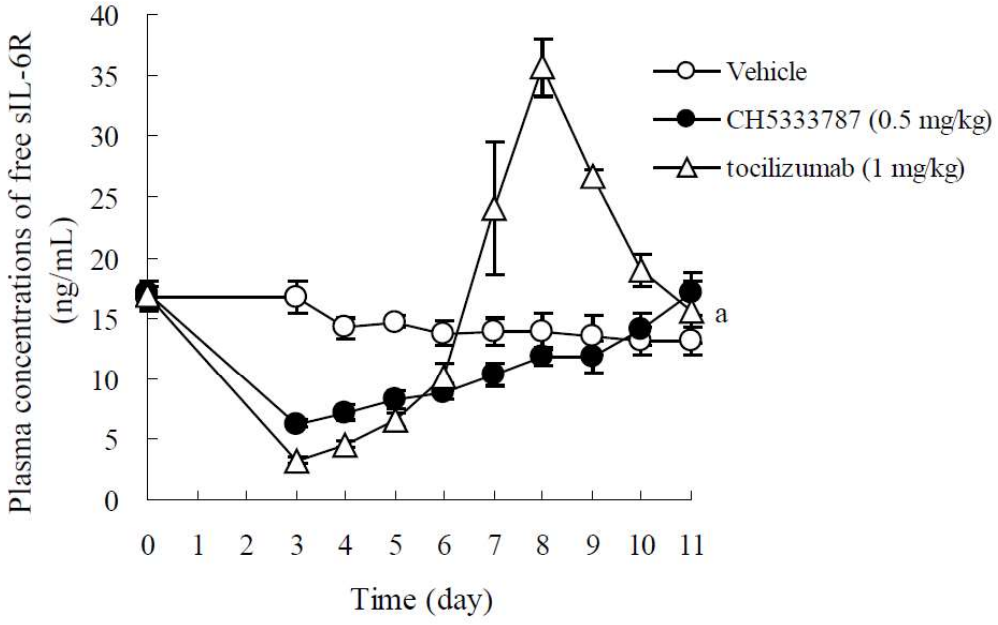


Reference ID: 4609287



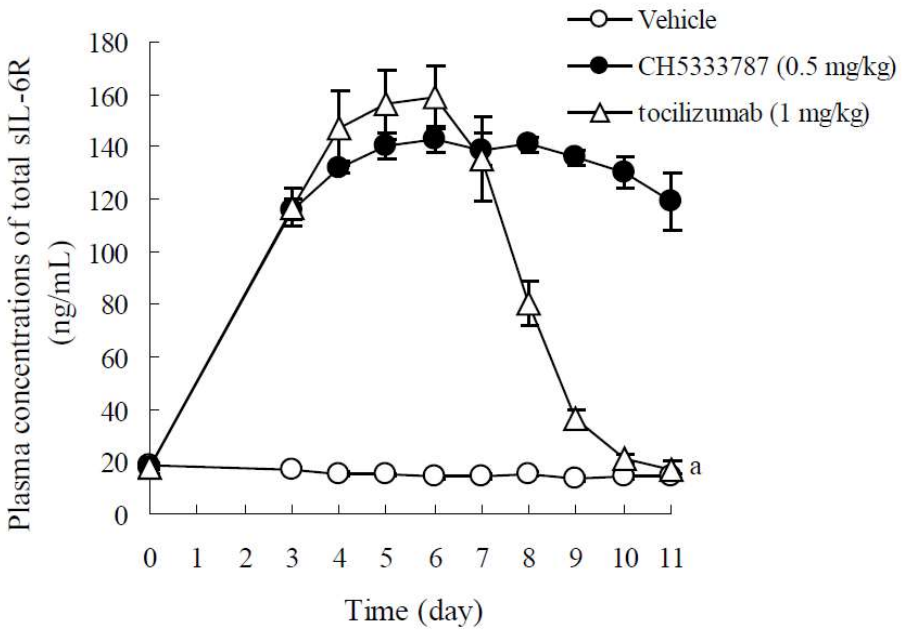

*(page 29 of Study Report)*

As shown in the figure below, the reduction in free plasma sIL-6R observed after SC injection of satralizumab was sustained through Day 9, whereas that observed after SC injection of tocilizumab was sustained only through Day 6 and was followed by an overshoot to ~2x baseline levels by Day 8.




*(page 30 of Study Report)*

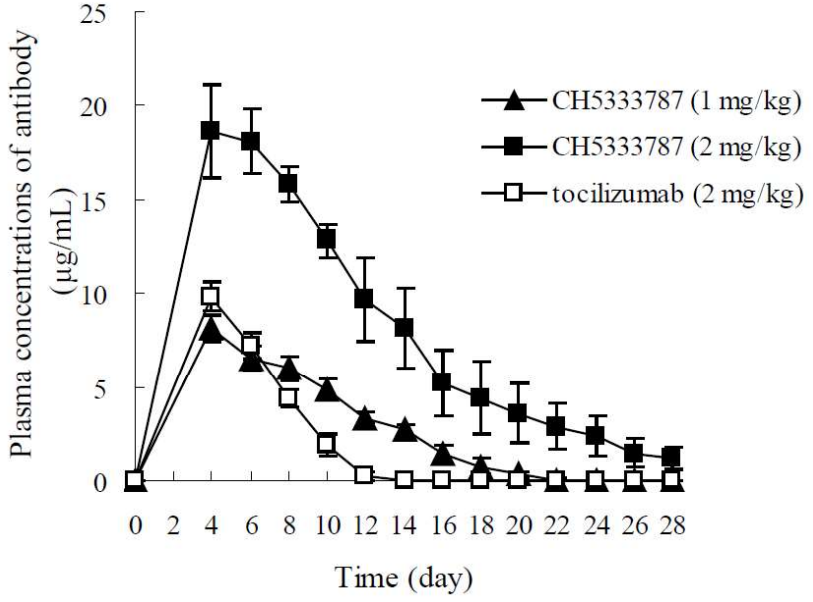
As shown in the figure below, the increase in total plasma sIL-6R observed after SC injection of satralizumab was sustained through Day 11, whereas that observed after SC injection of tocilizumab was sustained only through Day 8.




*(page 31 of Study Report)*

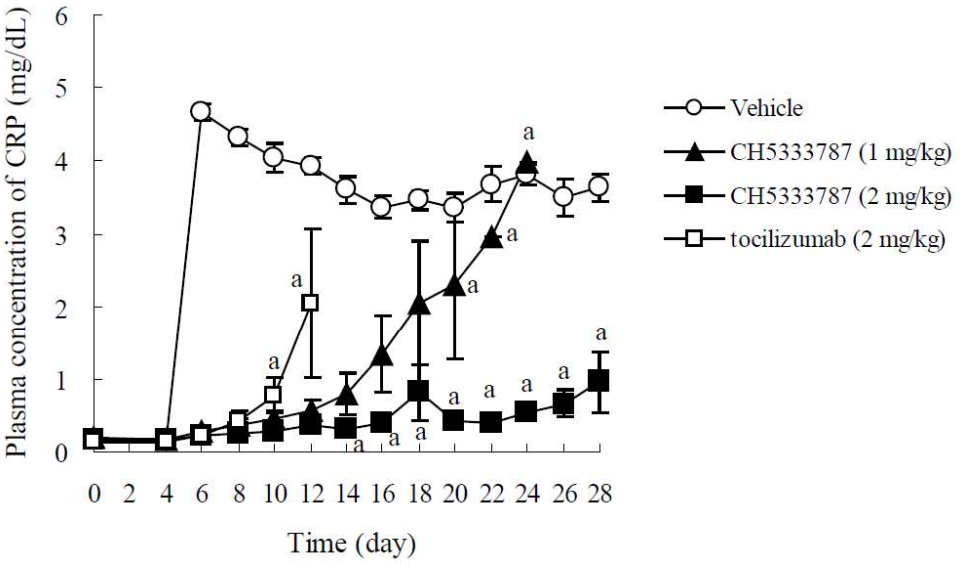
Results of Protocol 2:

Plasma concentrations of antibody following SC administration of tocilizumab (2 mg/kg SC) or satralizumab (1 or 2 mg/kg SC) to male cynomolgus monkeys are shown in the figure below.



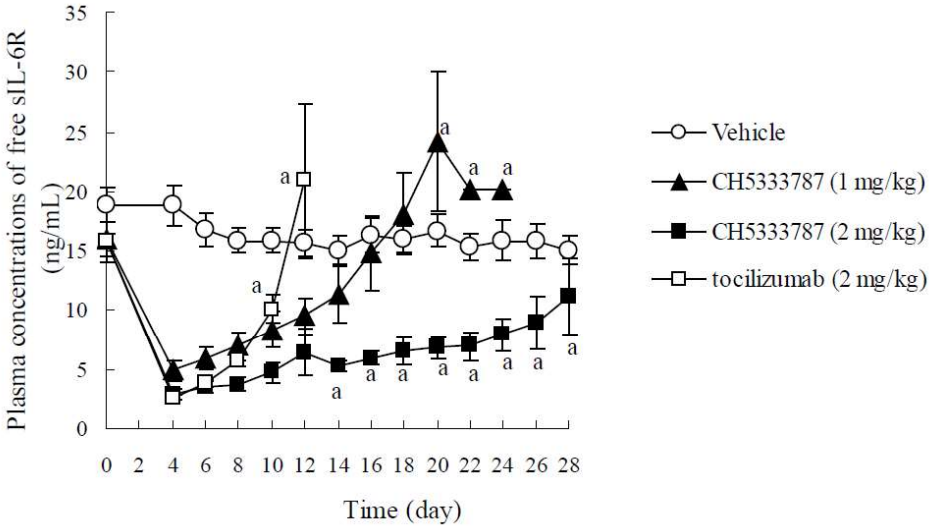

*(page 32 of Study Report)*

As shown in the figure below, the inhibition of the cyno.IL-6-induced increase in plasma CRP was sustained longer after administration of 2 mg/kg compared to 1 mg/kg satralizumab or 2 mg/kg tocilizumab.



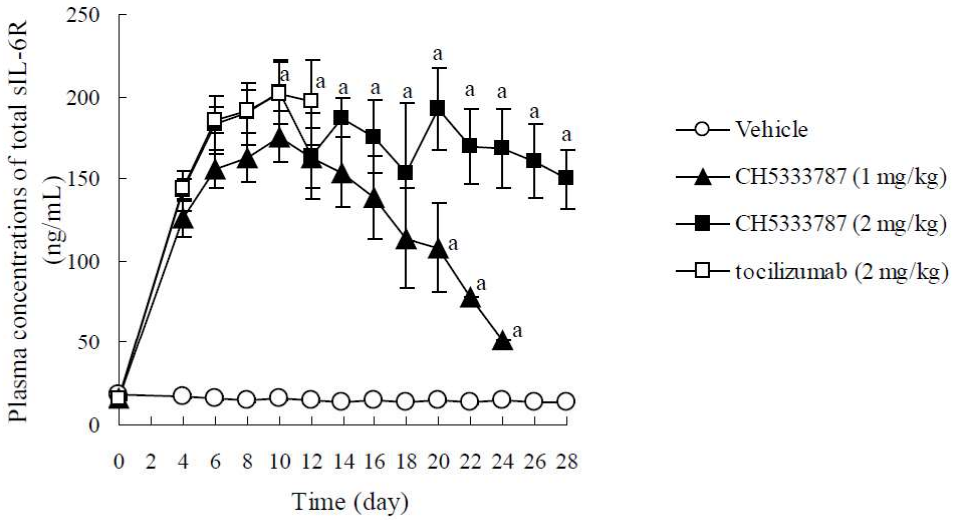

*(page 33 of Study Report)*

As shown in the figure below, the reduction in free plasma sIL-6R was sustained longer after administration of 2 mg/kg satralizumab compared to 1 mg/kg satralizumab or 2 mg/kg tocilizumab.




*(page 34 of Study Report)*

As shown in the figure below, the increase in total plasma sIL-6R was sustained longer after administration of 2 mg/kg compared to 1 mg/kg satralizumab.




*(page 34 of Study Report)*

Correlations between plasma antibody concentration and plasma CRP or plasma CRP normalized to $CRP_{max}$ were similar for satralizumab and tocilizumab.

Conclusion

These data demonstrate that the changes made to tocilizumab to create satralizumab succeeded in increasing the blood residence time and the duration of activity of the antibody—satralizumab inhibited both classical IL-6→mIL-6R and IL-6 + sIL-6R trans-signalling pathways for 28 days following a single administration of 2 mg/kg SC.

**Determination of CH5333787 concentration, anti-CH5333787 antibody titer, tocilizumab concentration, anti-tocilizumab antibody concentration, total sIL-6R concentration and free sIL-6R concentration in plasma from the study "Effect of CH5333787* on cynomolgus IL-6-induced CRP production in cynomolgus monkey"**

(Chugai Study PHM10-0002; (b) (4) Study B091387; (b) (4) Final Report dated July 12, 2010; non-GLP; QA)

Key data from this study were included in the review of Study PHM09-0181 above. Relative errors, coefficients of determination of standard curves, and accuracy of quality control samples were within acceptable limits for a valid study.

**Effect of CH5333787 on collagen-induced arthritis in cynomolgus monkey**

(Chugai Study PHM09-0124; (b) (4) Study (b) (4) 036-083; (b) (4) Final Report dated August 6, 2010; non-GLP; QA)

Female cynomolgus monkeys that had been previously immunized with bovine type 2 collagen in Freund's adjuvant to induce arthritis were administered 3 doses of vehicle (20 mM histidine, 150 mM arginine-aspartic acid, 0.5 mg/mL poloxamer 188, pH 6.0;

N=8) or satralizumab (30 mg/kg; N=12) by SC injection at 2-week intervals. The mean percentage change in arthritis score (a measure of swelling/rigidity of 64 joints/animal) from Day 1 to Day 36 was significantly (P<0.05) different in the satralizumab group (-49.5%) compared to controls (+11.7%), after exclusion of animals that were euthanized early because of arthritis-related debility or those that had ADA and no detectable satralizumab in plasma. A significant negative correlation was observed between the change in arthritis score on Day 36 and plasma satralizumab concentrations. Histological analyses showed reductions in degeneration of joint cartilage (29%), granulation tissue morphogenesis (20%), osteoclasia (19%), and osteogenesis (29%) in the satralizumab group. However, X-ray analyses of joint space narrowing and bone atrophy showed no marked differences between groups. Mean plasma IL-6 and sIL-6R concentrations were increased after administration of satralizumab. Satralizumab-related changes also included increases in albumin and decreases in leukocytes, neutrophils, platelets, and CRP. No satralizumab-related effects were observed on clinical signs, body weight, food consumption, or necropsy.

### 4.2 Secondary Pharmacology

No secondary pharmacology studies of satralizumab were submitted.

### 4.3 Safety Pharmacology

No stand-alone safety pharmacology studies of satralizumab were submitted. Safety pharmacology assessments were incorporated into the pivotal toxicology studies of satralizumab in monkey.

## 5 Pharmacokinetics/ADME/Toxicokinetics

### 5.1 PK/ADME

No separate PK/ADME studies for satralizumab were submitted.

### 5.2 Toxicokinetics

Toxicokinetic data for satralizumab were reviewed with the toxicity studies in monkey.

### 5.3 Methods of Analysis

The analytical method validation studies (listed in Section 3.1) for the determination of satralizumab, ADA, IL-6, and sIL-6R (total and free) in plasma, and satralizumab in milk, were reviewed and found to adequately support the conclusions of the pivotal toxicity studies of satralizumab in cynomolgus monkey.



Reference ID: 4609287

# 6 General Toxicology

## 6.1 Single-Dose Toxicity

**Plasma concentration and toxicity evaluation of CH5333787 after single intravenous administration of CH5333787 in cynomolgus monkeys**

(Chugai Study ADM09-0208; (b) (4) Study B091169; (b) (4) initiated December 18, 2009; non-GLP; QA)

Cynomolgus monkeys (3 M/group) were administered a single dose of satralizumab (0.4, 2.0, 10, or 50 mg/kg) in vehicle (150 mM arginine-aspartic acid (b) (4) with 20 mM histidine and 0.5 mg/mL poloxamer 188, pH 6.(b) (4) 0.32 mL/kg) via IV injection. There was no control group.

As shown in the table below, satralizumab exposures ($C_0$ and AUC) increased approximately dose-proportionally.

| Test substance Dose | | $C_0$ (µg/mL) | $t_{1/2}$ (h) | $AUC_{0\text{-}168h}$ (µg·h/mL) | $AUC_{0\text{-}t}$ (µg·h/mL) | $AUC_{all}$ (µg·h/mL) | $AUC_{0\text{-}inf}$ (µg·h/mL) | $CL_{total}$ (mL/h/kg) | $Vd_{ss}$ (mL/kg) | $MRT_{0\text{-}inf}$ (h) |
|---|---|---|---|---|---|---|---|---|---|---|
| CH5333787 | Mean | 10.3 | 45.8 | 675 | 774 | 780 | 794 | 0.514 | 44.9 | 88.1 |
| 0.4 mg/kg | S.D. | 0.3 | 17.9 | 93 | 148 | 142 | 130 | 0.093 | 5.1 | 7.1 |
| CH5333787 | Mean | 51.5 | 153.4 | 3920 | 6300 | 6300 | N.C. | N.C. | N.C. | N.C. |
| 2.0 mg/kg | S.D. | 4.9 | 156.2 | 360 | 2590 | 2590 | | | | |
| CH5333787 | Mean | 258 | 620.2 | 25000 | 86900 | 86900 | 107000 | 0.0998 | 68.2 | 770.2 |
| 10 mg/kg | S.D. | 36 | 448.6 | 1000 | 11800 | 11800 | 34000 | 0.0298 | 19.4 | 467.6 |
| CH5333787 | Mean | 1320 | 541.7 | 127000 | 476000 | 476000 | 585000 | 0.0955 | 70.8 | 762.6 |
| 50 mg/kg | S.D. | 150 | 52.3 | 29000 | 170000 | 170000 | 230000 | 0.0392 | 21.9 | 81.3 |

*(page 75 of Study Report)*

ADAs were detected in 1/3 and 3/3 animals administered 1.0 and 2.0 mg/kg satralizumab, respectively, starting on Day 14, 21, or 31. ADAs had no clear effect on satralizumab exposures with one possible exception: one animal given 2.0 mg/kg developed ADA by Day 14 and showed satralizumab decreasing to BLQ by Day 21, 10 days earlier than the other animals in this group. Mean plasma IL-6 concentrations increased from ≤4 pg/mL before dosing to peak levels of 40 to 64 pg/mL 7 hours postdose, returned to baseline by Day 11 and 28 in the 0.4 and 2.0 mg/kg groups, respectively, and remained elevated through the end of the 56-day observation period in the 2 higher dose groups. Similarly, mean plasma sIL-6R (total) concentrations peaked at 7 to 14 days postdose, returned to baseline by Day 21 and 35 in the 0.4 and 2.0 mg/kg groups, respectively, and remained elevated in the two higher dose groups. Mean plasma free sIL-6R was markedly reduced in all dose groups, returned to baseline by Day 9 and 28 in the 0.4 and 2.0 mg/kg groups, respectively, and remained reduced in the two higher dose groups.

No satralizumab-related effects were observed on mortality, clinical signs, body weight, food consumption, hematology, or clinical chemistry; post-mortem analyses were not conducted.



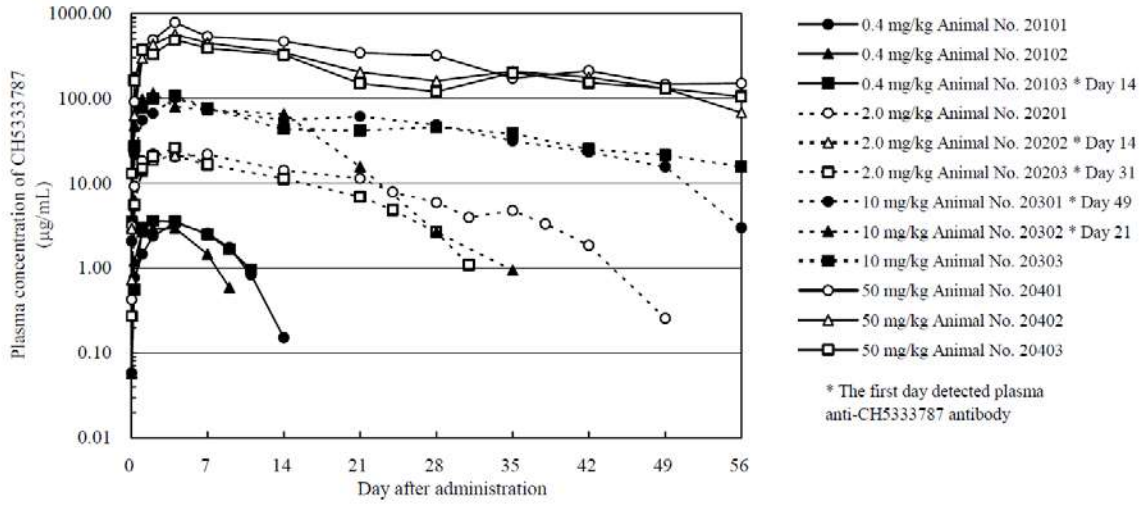
Reference ID: 4609287

**Plasma concentration and toxicity evaluation of CH5333787 after single subcutaneous administration of CH5333787 in cynomolgus monkeys**

(Chugai Study ADM09-0209; (b) (4) Study B091170; (b) (4) initiated December 18, 2009; non-GLP; QA)

Cynomolgus monkeys (3 M/group) were administered a single dose of satralizumab (0.4, 2.0, 10, or 50 mg/kg) in vehicle (150 mM arginine-aspartic acid (b) (4) with 20 mM 0.5 mg/mL poloxamer 188, pH 6.(b) (4) 0.32 mL/kg) via SC injection. There was no control group.

As shown in Figure 2 and the summary table below, satralizumab exposures ($C_{max}$ and AUC) generally increased greater than dose-proportionally.




Lower limit of quantification: 0.05 μg/mL
Plasma anti-CH5333787 antibody was detected from Day 14 in animal Nos. 20103 and 20202, and from Days 21, 31 and 49 in animal Nos. 20302, 20203 and 20301, respectively.

**Figure 2** **Individual plasma concentrations of CH5333787 after a single subcutaneous administration of CH5333787 to male cynomolgus monkeys at 0.4, 2.0, 10 and 50 mg/kg**

*(page 133 of Study Report)*

| Test substance Dose | | $C_{max}$ (μg/mL) | $t_{max}$ (h) | $t_{1/2}$ (h) | $AUC_{0\text{-}168h}$ (μg·h/mL) | $AUC_{0\text{-}t}$ (μg·h/mL) | $AUC_{all}$ (μg·h/mL) | $AUC_{0\text{-}inf}$ (μg·h/mL) | $MRT_{0\text{-}inf}$ (h) | BA[a)] (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| CH5333787 | Mean | 3.33 | 80.0 | 52.5 | 438 | 570 | 579 | 621 | 133.4 | 78.2 |
| 0.4 mg/kg | S.D. | 0.35 | 27.7 | 18.7 | 52 | 113 | 107 | 134 | 19.7 | 16.9 |
| CH5333787 | Mean | 23.2 | 80.0 | 95.5* | 3150 | 7310 | 7310 | 9750* | 315.4* | N.C. |
| 2.0 mg/kg | S.D. | 2.6 | 27.7 | | 230 | 4180 | 4180 | | | |
| CH5333787 | Mean | 108 | 80.0 | 544.8 | 13800 | 45900 | 45900 | 66700* | 664.6* | 62.3* |
| 10 mg/kg | S.D. | 7 | 27.7 | 272.1 | 1100 | 17600 | 17600 | | | |
| CH5333787 | Mean | 616 | 96.0 | 442.3 | 76600 | 344000 | 344000 | 418000 | 772.7 | 71.4 |
| 50 mg/kg | S.D. | 152 | 0.0 | 172.0 | 14300 | 74000 | 74000 | 108000 | 161.6 | 18.4 |

*(page 74 of Study Report)*

ADAs were detected in 1/3, 2/3, 2/3, and 0/3 animals at 0.4, 2.0, 10, and 50 mg/kg, respectively. ADAs had no clear effect on satralizumab exposures with one exception: animal 20302 in the 10 mg/kg group developed ADA on Day 21 and showed reduced exposures starting on Day 21 (see Figure 2).

Mean plasma IL-6 concentrations increased from ~1 to 5 pg/mL before dosing to peak levels of ~20 to 70 pg/mL 7 hours to 4 days postdose, returned to baseline by Day 11 in the 0.4 mg/kg group, and remained elevated in other groups at 56 days postdose. Similarly, mean plasma sIL-6R (total) concentrations peaked at 7 to 14 days postdose, returned to baseline by Day 21 in the 0.4 mg/kg group, and remained elevated throughout the study in the 2 higher dose groups. Mean plasma free sIL-6R was markedly reduced and remained reduced throughout the study.

No satralizumab-related effects were observed on mortality, clinical signs, body weight, food consumption, hematology, or clinical chemistry; post-mortem analyses were not conducted.

## 6.2 Repeat-Dose Toxicity

**A 4-week intermittent dose (once every week, total 5 doses) intravenous toxicity study of CH5333787 in cynomolgus monkeys (dose range-finding study)**

(Chugai Study TOX09-0010S; (b) (4) Study 0741-011; (b) (4) initiated February 23, 2009; GLP; non-QA)

Cynomolgus monkeys (1/sex/group) were administered vehicle ((b) (4) mM arginine (b) (4) with 20 mM histidine, pH 6.0) or satralizumab (8, 40, or 200 mg/kg) via SC injection weekly for 4 weeks (5 doses). No satralizumab-related effects were observed on mortality, clinical signs, body weight, food consumption, ECG, hematology, clinical chemistry, immunophenotyping, IL-6 levels, organ weight, macroscopic evaluations, or histopathology. ADA was detected in the LDM on Days 57 through 141, correlated with much lower plasma satralizumab concentrations compared to the LDF.

**A 4-week intermittent dose (once weekly, 4 doses) subcutaneous administration toxicity study of CH5333787 in cynomolgus monkeys**

(Chugai Study TOX10-0001; (b) (4) Study 8220145; (b) (4) initiated January 13, 2010; GLP; QA)

Cynomolgus monkeys (4/sex/group) were administered vehicle ((b) (4) mM arginine (b) (4) with 20 mM histidine, pH 6.0) or satralizumab (2, 10, or 50 mg/kg) via SC injection weekly for 4 weeks (4 doses). Animals were sacrificed one week after the final dose. No drug-related effects were observed on mortality, clinical signs, body weight, food consumption, ECG, BP, ophthalmology, hematology, clinical chemistry, urinalysis, immunophenotyping, organ weight, macroscopic evaluations, or histopathology. Mean serum IL-6 concentrations were increased at all doses compared to controls and baseline. The erythroid:myeloid ratio in bone marrow was slightly

increased in M at all doses and in HDF. ADA was detected in 6/8 LD and 2/8 MD monkeys, correlated with neutralizing activity and lower satralizumab exposures in 2 LD and 1 MD animals.



Reference ID: 4609287

**A 26-Week intermittent dose (once weekly, 26 doses) subcutaneous administration toxicity study of CH5333787 with a 13-week recovery phase in mature cynomolgus monkeys**

| | |
|---|---|
| Study no.: | Chugai Study Tox10-0034 (b) (4) Study 8224665 |
| Study report location: | edr |
| Conducting laboratory and location: | (b) (4) Laboratories (b) (4) (b) (4) |
| Date of study initiation: | March 10, 2010 |
| GLP compliance: | Yes, except for the absolute white blood cell count in bone marrow |
| QA statement: | Yes |
| Drug, lot #, and % purity: | CH5333787 Lot CB01A-bulk, 99.9% pure |

**Key Study Findings**

- The NOAEL was the high dose of 50 mg/kg/week.

Methods

| | |
|---|---|
| Doses: | 0, 2, 10, and 50 mg/kg/week CH5333787 (satralizumab) |
| Frequency of dosing: | Weekly |
| Route of administration: | SC injection, alternating among 4 sites: left and right shoulders and flanks |
| Dose volume: | 0.42 mL/kg |
| Formulation/Vehicle: | 150 mmol/L arginine (b) (4) containing 20 mmol/L histidine and 0.5 mg/mL poloxamer 188, pH 6.0 |
| Species/Strain: | Cynomolgus monkeys from China |
| Number/Sex/Group: | 3/s/grp main study; 2/s/grp 13-week recovery period |
| Age: | 4-6 years old at initiation of dosing |
| Weight: | 5.0-8.3 kg M; 2.8-4.6 kg F |
| Satellite groups: | None |
| Unique study design: | Blood pressure, respiratory rate, WBC immunophenotyping, ADA, serum IL-6 level, and M and F fertility parameters were evaluated |
| Deviation from study protocol: | No deviations were reported that affected study validity or interpretation |

**Observations and Results**

**Dosing Solution Analysis**

Dosing solutions used in Weeks 1, 4, 13, and 26 were analyzed and found to be within acceptable ranges of nominal concentrations (actual range: 98.7%-103.8%). No CH5333787 was detected in the placebo control samples.

**Mortality**

Mortality was assessed twice daily. No satralizumab-related effects were observed.

**Clinical Signs**

Behavior, appearance, and feces were evaluated twice daily. No satralizumab-related effects were observed.

**Body Weights**

Body weight was assessed weekly. No satralizumab-related effects were observed.

**Food Consumption**

Food consumption was assessed twice daily. No satralizumab-related effects were observed.

**Semen Evaluation**

Semen samples were evaluated 3 times predose, in Weeks 5, 11, and 24 of the dosing phase and in Week 12 of the recovery phase for ejaculate weight and sperm count, motility, and morphology. No satralizumab-related effects were observed.

**Testicular Size**

Testicular size was evaluated by ultrasound once predose, in Weeks 5, 11, and 24 of the dosing phase and in Week 12 of the recovery phase. No satralizumab-related effects were observed.

**Vaginal Evaluation**

Menstrual cycle was evaluated by daily assessment of vaginal bleeding. No satralizumab-related effects were observed.

**Ophthalmoscopy**

Ophthalmoscopic examinations were conducted once predose, in Weeks 4, 12, and 25 of the dosing phase and in Week 13 of the recovery phase. No satralizumab-related effects were observed.



Reference ID: 4609287

**Electrocardiogram, Blood Pressure, and Respiratory Rate**
Electrocardiogram, blood pressure, and respiratory rate evaluations were conducted twice predose, in Weeks 1, 4, 13, and 26 of the dosing phase (3 days after dosing) and in Week 13 of the recovery phase. No satralizumab-related effects were observed.

**Hematology, Coagulation, Clinical Chemistry, and Immunophenotyping**
Blood was collected twice predose, on Days 22, 85, and 176 of the dosing phase, at necropsy, and in Week 13 of the recovery phase for hematology, coagulation, clinical chemistry, and immunophenotyping; and on Days 2, 23, 86, and 177 of the dosing phase for CRP concentration. In addition to standard parameters, evaluations included serum CRP, IgG, IgM, CD3+ T cells, CD3+CD8+ cytotoxic T cells, CD3+CD4+ T helper cells, CD20+ B cells, and CD3-CD16+ NK cells. No satralizumab-related effects were observed.

**Urinalysis**
Urine was collected predose and in Weeks 4, 12, and 25 of the dosing phase. No satralizumab-related effects were observed.

**Serum IL-6**
Serum IL-6 was analyzed in samples collected prior to the dosing phase, predose and 8 hours postdose on Day 1 and in Weeks 4, 13, and 26 of the dosing phase, on the day of necropsy, and in Week 13 of the recovery phase. As expected, based on the satralizumab-mediated inhibition of binding of IL-6 to the IL-6 receptor, serum IL-6 increased slightly at all doses, decreasing toward baseline in those animals with neutralizing anti-drug antibodies during the dosing phase and in all animals during the recovery phase.

**Gross Pathology**
All animals surviving to scheduled termination were necropsied at the terminal sacrifice (Day 183/184 of the dosing phase) or at the end of the recovery period (Day 92 of the recovery phase). Necropsies were conducted using standard procedures. No satralizumab-related effects were observed.

**Organ Weights**
Organs were isolated and weighed using standard procedures. No satralizumab-related effects were observed.

**Histopathology**
Histopathology was conducted on all main-study and recovery animals using standard procedures. The battery of tissues examined was adequate. Peer Review was not conducted. A signed pathology report was provided. Absolute white blood cell count was evaluated in bone marrow.

<u>Histological Findings</u>
No satralizumab-related effects were observed.



Reference ID: 4609287

**Toxicokinetics**
Blood samples were collected from all animals predose (at least 7 days before dosing initiation); on Day 1 and in Weeks 4, 13, and 26 of the dosing phase (at 0, 8, 24, 48, 96, and 168 hours postdose); in Weeks 3, 9, and 20 of the dosing phase (at Time 0); and in Weeks 2, 4, 6, 8, 10, 12, and 14 of the recovery phase.

No CH5333787 was detected in control samples. CH5333787 exposures ($C_{max}$ and $AUC_{0\text{-}168\ hr}$) increased roughly dose-proportionally, were generally similar in males and females, and increased ~3- to 10-fold from Day 1 to Week 26.



Reference ID: 4609287

**Table 9 $C_{max}$ of CH5333787 in Cynomolgus monkeys**

Male

| Dose level (mg/kg/week) | Animal No. | | Day 1 (μg/mL) | Week 4 (μg/mL) | Week 13 (μg/mL) | Week 26 (μg/mL) |
|---|---|---|---|---|---|---|
| 0 | 14939 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 14942 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 16035 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 16040 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 16045 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | Mean | | N.C. | N.C. | N.C. | N.C. |
| | SD | | N.C. | N.C. | N.C. | N.C. |
| 2 | 16167 | | 13.3 | 144 | 102 | 122 |
| | 16169 | | 9.12 | 68.5 | 119 | 104 |
| | **16179** | * | 13.7 | 76.2 | 0.167 | 0.139 |
| | 16182 | | 12.3 | 67.4 | 109 | 56.8 |
| | 16189 | | 10.2 | 68.9 | 181 | 144 |
| | Mean | | 11.7 | 85.0 | 102 | 85.4 |
| | | ** | 11.2 | 87.2 | 128 | 107 |
| | SD | | 2.0 | 33.2 | 65 | 57.5 |
| | | ** | 1.9 | 37.9 | 36 | 37 |
| 10 | 16171 | | 90.1 | 338 | 394 | 505 |
| | 16172 | | 161 | 365 | 586 | 402 |
| | 16175 | | 107 | 396 | 579 | 631 |
| | 16176 | | 95.1 | 385 | 575 | 509 |
| | 16180 | | 119 | 404 | 489 | 658 |
| | Mean | | 114 | 378 | 525 | 541 |
| | SD | | 28 | 27 | 83 | 104 |
| 50 | 16030 | | 488 | 1890 | 2270 | 4180 |
| | 16047 | | 365 | 1760 | 3110 | 3790 |
| | 16048 | | 344 | 1650 | 2900 | 5170 |
| | 16185 | | 324 | 1420 | 2620 | 3220 |
| | 16186 | | 315 | 1520 | 1390 | 2670 |
| | Mean | | 367 | 1650 | 2460 | 3810 |
| | SD | | 70 | 190 | 680 | 950 |

* Neutralizing activity to CH5333787 was confirmed in animal which was ADA-positive.

** Calculated by excluding the ADA-positive animal in which the neutralizing activity to CH5333787 was confirmed

N.C.: Because 3 or more of the measured values showed B.L.Q., the mean and SD were not calculated.

*(page 1557 of Study Report)*



Reference ID: 4609287

**Table 9 $C_{max}$ of CH5333787 in Cynomolgus monkeys (Cont.)**

Female

| Dose level (mg/kg/week) | Animal No. | | Day 1 (μg/mL) | Week 4 (μg/mL) | Week 13 (μg/mL) | Week 26 (μg/mL) |
|---|---|---|---|---|---|---|
| 0 | 15258 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 15298 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 15305 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 15313 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 16013 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | Mean | | N.C. | N.C. | N.C. | N.C. |
| | SD | | N.C. | N.C. | N.C. | N.C. |
| 2 | 15271 | | 12.8 | 29.2 | 40.9 | 66.4 |
| | **15292** | * | 18.7 | 0.144 | 2.71 | 24.7 |
| | **16023** | * | 20.8 | 64.6 | 0.290 | 0.00 |
| | 16026 | | 21.2 | 74.6 | 124 | 124 |
| | **16069** | * | 21.2 | 63.4 | 0.166 | 0.00 |
| | Mean | | 18.9 | 46.4 | 33.6 | 43.0 |
| | | ** | 17.0 | 51.9 | 82.5 | 95.2 |
| | SD | | 3.6 | 31.0 | 53.4 | 52.8 |
| | | ** | 5.9 | 32.1 | 58.8 | 40.7 |
| 10 | 15241 | | 89.8 | 321 | 279 | 344 |
| | 15286 | | 233 | 264 | 543 | 609 |
| | 15306 | | 195 | 184 | 527 | 490 |
| | 15994 | | 305 | 161 | 294 | 722 |
| | 16009 | | 112 | 227 | 351 | 487 |
| | Mean | | 187 | 231 | 399 | 530 |
| | SD | | 88 | 64 | 127 | 142 |
| 50 | 15101 | | 1170 | 1440 | 1750 | 3570 |
| | 15996 | | 1440 | 1400 | 2110 | 2850 |
| | 15998 | | 1190 | 1070 | 1810 | 3120 |
| | 16008 | | 1200 | 1270 | 2240 | 3270 |
| | 16011 | | 670 | 1620 | 2640 | 3700 |
| | Mean | | 1130 | 1360 | 2110 | 3300 |
| | SD | | 280 | 200 | 360 | 340 |

* Neutralizing activity to CH5333787 was confirmed in animal which was ADA-positive.

** Calculated by excluding ADA-positive animal in which the neutralizing activity to CH5333787 was confirmed

N.C.: Because 3 or more of the measured values showed B.L.Q., the mean and SD were not calculated.

*(page 1558 of Study Report)*



Reference ID: 4609287

## Table 11 $AUC_{0-168}$ of CH5333787 in Cynomolgus monkeys

Male

| Dose level (mg/kg/week) | Animal No. | | Day 1 (μg•hr/mL) | Week 4 (μg•hr/mL) | Week 13 (μg•hr/mL) | Week 26 (μg•hr/mL) |
|---|---|---|---|---|---|---|
| 0 | 14939 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 14942 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 16035 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 16040 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 16045 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | Mean | | N.C. | N.C. | N.C. | N.C. |
| | SD | | N.C. | N.C. | N.C. | N.C. |
| 2 | 16167 | | 1640 | 18200 | 11900 | 18200 |
| | 16169 | | 1020 | 9750 | 18800 | 14900 |
| | **16179** | * | 1860 | 10100 | 16.6 | 7.76 |
| | 16182 | | 1500 | 9320 | 16200 | 9040 |
| | 16189 | | 1420 | 9340 | 23600 | 22900 |
| | Mean | | 1490 | 11300 | 14100 | 13000 |
| | | ** | 1400 | 11700 | 17600 | 16300 |
| | SD | | 310 | 3800 | 8900 | 8800 |
| | | ** | 270 | 4400 | 4900 | 5800 |
| 10 | 16171 | | 11900 | 47600 | 61000 | 64700 |
| | 16172 | | 19600 | 45700 | 85200 | 58400 |
| | 16175 | | 14900 | 40500 | 83700 | 74100 |
| | 16176 | | 12800 | 56300 | 89100 | 67500 |
| | 16180 | | 13800 | 57500 | 77900 | 98000 |
| | Mean | | 14600 | 49500 | 79400 | 72500 |
| | SD | | 3000 | 7200 | 11000 | 15300 |
| 50 | 16030 | | 70900 | 284000 | 361000 | 594000 |
| | 16047 | | 50400 | 251000 | 470000 | 566000 |
| | 16048 | | 47300 | 257000 | 437000 | 788000 |
| | 16185 | | 44100 | 219000 | 410000 | 438000 |
| | 16186 | | 45800 | 234000 | 217000 | 369000 |
| | Mean | | 51700 | 249000 | 379000 | 551000 |
| | SD | | 11000 | 25000 | 99000 | 161000 |

* Neutralizing activity to CH5333787 was confirmed in animal which was ADA-positive.

** Calculated by excluding the ADA-positive animal in which the neutralizing activity to CH5333787 was confirmed

N.C.: Because 3 or more of the measured values showed B.L.Q., the mean and SD were not calculated.

*(page 1560 of Study Report)*



Reference ID: 4609287

## Table 11 $AUC_{0-168}$ of CH5333787 in Cynomolgus monkeys (Cont.)

Female

| Dose level (mg/kg/week) | Animal No. | | Day 1 (μg•hr/mL) | Week 4 (μg•hr/mL) | Week 13 (μg•hr/mL) | Week 26 (μg•hr/mL) |
|---|---|---|---|---|---|---|
| 0 | 15258 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 15298 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 15305 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 15313 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | 16013 | | 0.00 | 0.00 | 0.00 | 0.00 |
| | Mean | | N.C. | N.C. | N.C. | N.C. |
| | SD | | N.C. | N.C. | N.C. | N.C. |
| 2 | 15271 | | 1500 | 4090 | 5400 | 10300 |
| | **15292** | * | 2030 | 11.4 | 295 | 3370 |
| | **16023** | * | 2580 | 7250 | 13.7 | 0.00 |
| | 16026 | | 2800 | 11100 | 19200 | 14300 |
| | **16069** | * | 2500 | 6730 | 5.98 | 0.00 |
| | Mean | | 2280 | 5840 | 4980 | 5590 |
| | | ** | 2150 | 7600 | 12300 | 12300 |
| | SD | | 520 | 4110 | 8270 | 6430 |
| | | ** | 920 | 4960 | 9800 | 2800 |
| 10 | 15241 | | 12000 | 41500 | 40100 | 51900 |
| | 15286 | | 33300 | 40400 | 82000 | 66700 |
| | 15306 | | 21800 | 26500 | 81300 | 51600 |
| | 15994 | | 34400 | 14300 | 45100 | 86900 |
| | 16009 | | 11600 | 30500 | 55000 | 51900 |
| | Mean | | 22600 | 30600 | 60700 | 61800 |
| | SD | | 11000 | 11200 | 19900 | 15400 |
| 50 | 15101 | | 106000 | 206000 | 264000 | 512000 |
| | 15996 | | 171000 | 181000 | 328000 | 435000 |
| | 15998 | | 148000 | 149000 | 279000 | 460000 |
| | 16008 | | 102000 | 185000 | 343000 | 465000 |
| | 16011 | | 76500 | 226000 | 392000 | 526000 |
| | Mean | | 121000 | 189000 | 321000 | 480000 |
| | SD | | 38000 | 29000 | 51000 | 38000 |

* Neutralizing activity to CH5333787 was confirmed in animal which was ADA-positive.

** Calculated by excluding ADA-positive animal in which the neutralizing activity to CH5333787 was confirmed

N.C.: Because 3 or more of the measured values showed B.L.Q., the mean and SD were not calculated.

*(page 1561 of Study Report)*



Reference ID: 4609287

**Table 8 Plasma concentrations of CH5333787 in Cynomolgus monkeys (Recovery phase)**

Male

| Dose level | Animal | CH5333787 concentration (μg/mL) Sample time (recovery phase) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (mg/kg/week) | No. | Week 2 | Week 4 | Week 6 | Week 8 | Week 10 | Week 12 | Week 14 |
| 0 | 14939 | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. |
| | 14942 | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. |
| 2 | 16182 | 41.4 | 15.7 | 3.38 | 0.140 | B.L.Q. | B.L.Q. | B.L.Q. |
| | 16189 | 111 | 71.0 | 47.7 | 27.9 | 15.6 | 8.10 | 5.23 |
| 10 | 16175 | 416 | 278 | 257 | 169 | 97.2 | 56.4 | 39.0 |
| | 16176 | 417 | 258 | 184 | 109 | 81.5 | 49.5 | 41.4 |
| 50 | 16185 | 1750 | 1230 | 1430 | 759 | 755 | 377 | 185 |
| | 16186 | 613 | 322 | 121 | 103 | 87.4 | 26.5 | 10.5 |

B.L.Q.: Below lower limit of quantification (< 0.05 μg/mL)

Female

| Dose level | Animal | CH5333787 concentration (μg/mL) Sample time (recovery phase) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (mg/kg/week) | No. | Week 2 | Week 4 | Week 6 | Week 8 | Week 10 | Week 12 | Week 14 |
| 0 | 15258 | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. |
| | 16013 | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. |
| 2 | 15292 | 3.56 | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. |
| | 16069 | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. | B.L.Q. |
| 10 | 15994 | 492 | 106 | 118 | 78.3 | 47.4 | 17.5 | 4.30 |
| | 16009 | 270 | 63.8 | 90.0 | 48.9 | 20.6 | 7.15 | 1.67 |
| 50 | 15996 | 1090 | 801 | 582 | 429 | 287 | 137 | 42.2 |
| | 15998 | 1060 | 563 | 381 | 278 | 178 | 49.7 | 25.7 |

B.L.Q.: Below lower limit of quantification (< 0.05 μg/mL)

*(page 1556 of Study Report)*

**Anti-satralizumab Antibody Analysis**

Blood was collected from all animals prior to the dosing phase, predose in Weeks 3, 4, 9, 13, 20, and 26 of the dosing phase, on Day 183, and in Weeks 2, 4, 6, 8, 10, 12, and 14 of the recovery phase.

ADA was observed in 2/5 LDM (titer = x1) and 3/5 HDF (titer = x1, x1, and x10) in the predose phase; none of these showed neutralizing activity. ADA was observed in 1/5 Con M (x1), 1/5 Con F (x1), 2/5 LDM (x10 and x100), 4/5 LDF (x1, x100, $x10^3$, $x10^4$), and 2/5 MDF (x100) during the dosing phase; of these, 1 LDM (M16179) and 3 LDF (F15292, F16023, and F16069) showed neutralizing activity. ADA was observed in 2/5 LDF (F15292 [x100] and F16069 [$x10^4$]), 1/5 MDF (x1), and 1/5 HDF (x1) during the recovery phase; of these, the 2 LDF showed neutralizing activity—the MDF and HDF could not be assessed for neutralizing activity.

# 7 Genetic Toxicology

No genotoxicity studies of satralizumab were conducted because antibodies are generally unable to interact with genetic material.

# 8 Carcinogenicity

Carcinogenicity studies of satralizumab were not conducted because satralizumab does not bind to rat or mouse IL-6R, and the use of a mouse homolog antibody was determined not to be feasible because of immunogenicity. The Division informed the sponsor that carcinogenicity studies of satralizumab would not be required to support a BLA (see email of June 14, 2016). The effect of satralizumab administration on the risk of malignancy in humans is unknown.

# 9 Reproductive and Developmental Toxicology

## 9.1 Fertility and Early Embryonic Development

No effects of satralizumab on histopathology of reproductive organs, menstrual cycle, or sperm (count, motility, or morphology) were observed following SC administration for 26 weeks in the chronic toxicity study in cynomolgus monkey.

## 9.2 Embryofetal Development

The potential effects of satralizumab on embryofetal development were assessed in the enhanced pre- and postnatal development study in monkey.



Reference ID: 4609287

## 9.3 Prenatal and Postnatal Development

**Intermittent subcutaneous dose (once weekly) enhanced study for effects on pre- and postnatal development of CH5333787 in cynomolgus monkeys**

| | |
|---|---|
| Study number: | Chugai Study TOX13-0108 (b) (4) Study 8290717 |
| Study report location: | edr |
| Conducting laboratory and location: | (b) (4) Laboratories (b) (4) |
| Date of study initiation: | March 18, 2014 |
| GLP compliance: | Yes, except for X-ray evaluation and CRP determination |
| QA statement: | Yes |
| Drug, lot #, and % purity: | CH5333787, Lot CB11A, 99.8% pure |

**Key Study Findings**

- Administration of satralizumab (2 or 50 mg/kg/week SC) to pregnant monkeys resulted in dose-dependent reductions in T-cell dependent antibody responses to antigenic challenge. Median maximum titers of IgM and IgG were reduced 15% and 16%, respectively, in LD infants, and 30% and 50%, respectively, in HD infants.
- Other than reduced TDAR in infants, no adverse effects on maternal, reproductive, or developmental parameters were observed.
- Satralizumab was detected in milk from 5/16 LDF (0.0536-0.488 µg/mL) and 12/12 HDF (0.435 to 1.84 µg/mL) on PP D14.
- Mean PP D14 plasma satralizumab concentration was 45.6 µg/mL for LD and 1840 µg/mL for HD infants.
- Mean maternal GD 146 plasma $C_{max}$ was 78.4 µg/mL for LDF and 2760 µg/mL for HDF.

**3.1.7 Study Design**

| Group Number | Group Description | Color Code | Number of Pregnant Females* | Dose Level (mg/kg) | Number of Life Infants on Day 7 p.p. |
|---|---|---|---|---|---|
| 1 | Control | White | 17** | 0 | 9 |
| 2 | Low | Blue | 17** | 2 | 16*** |
| 3 | High | Red | 16 | 50 | 11 |

* Based upon ICH S6 (R1) guideline - Note 5 - the selected number of pregnant females/group should provide for 6-8 live infants per group on Day 7 p.p. Dose volume was 0.41 mL/kg for all groups.

** Starting group sizes were 16 pregnant animals in each group. On GD 20, animal nos. 18165, 0 mg/kg/week, and 18068, 2 mg/kg/week, were inadvertently dosed with test item at the concentration for Group 3. Therefore, one female was added to each of Groups 1 and 2 respectively, yielding 17 per group, to ensure maintaining the required number of infants. The misdosed animals were retained on study and data used where considered appropriate

*** Excluding the infant from animal no. 18068, that was inadvertently dosed with test item at the concentration for Group 3.

*(page 23 of Study Report)*



Reference ID: 4609287

Methods

| | |
|---|---|
| Route of administration: | SC injection to the upper left back; 0.41 mL/kg |
| Formulation/Vehicle: | vehicle: 150 mM arginine (b) (4) with 20 mM histidine and 0.5 mg/mL poloxamer 188, pH 6.0 |
| Species/Strain: | cynomolgus monkey, of Asian origin |
| Study design: | Females aged ≥4 years and ≥ . were mated with non-dosed males, confirmed pregnant by ultrasound, and dosed weekly at 0, 2, or 50 mg/kg satralizumab from GD 20 through delivery (or abortion); maternal animals and infants were fasted overnight prior to necropsy on postpartum Day 293 ± 1 |
| Deviation from study protocol: | One control and one LD animal received the HD on the first day of dosing, and were replaced; these and other minor deviations reported did not affect study validity or interpretations |

**Observations and Results**

**Dosing Solution Analysis**

Dosing formulations were analyzed weekly; mean values were within 7% (range: 93.9% to 103.7%) of the nominal concentrations.

**Toxicokinetic and Anti-Drug Antibody Analysis**

Blood samples were collected from maternal animals on GD 20, 83, and 146 (at 0, 8, 24, 48, and 168 hours after dosing) and on GD 51 and 114 (just prior to dosing); and from maternal and infant animals on PP Days 14, 28, 63, 91, 119, 147, 175, 203, 231, 259, and 293; for analysis of satralizumab and ADA concentrations in plasma, and of ADA neutralizing activity.

Satralizumab was not detectable in maternal control samples (except for the animal inadvertently given the HD on GD 20). As shown in the summary tables below, maternal plasma satralizumab exposures increased slightly greater than dose-proportionally (~30x with a 25x increase in dose) on GD 20 and GD 83. Exposures on GD 83 and GD 140 were ~4- to 5-fold those on GD 20.



Reference ID: 4609287

| Dose level (mg/kg/week) | | Time points | | | | | |
|---|---|---|---|---|---|---|---|
| | | GD 20 | | | GD 83 | | |
| | | $C_{max}$ (µg/mL) | $T_{max}$ (day) | $AUC_{0-7d}$ (µg•day/mL) | $C_{max}$ (µg/mL) | $T_{max}$ (day) | $AUC_{0-7d}$ (µg•day/mL) |
| 2 | Mean | 20.4 | 5.75 | 116 | 75.6 | 1.80 | 475 |
| | (number of females) | (16) | (16) | (16) | (16) | (15) | (16) |
| 50 | Mean | 618 | 4.50 | 3560 | 2460 | 1.13 | 15300 |
| | (number of females) | (16) | (16) | (16) | (13) | (13) | (13) |

Means were calculated by excluding:

- the animals which were given the highest dosage on GD 20 by mistake
- where there was "no sample"
- "not available"

*(page 1710 of Study Report)*

| Dose level (mg/kg/week) | | Time points | | | | |
|---|---|---|---|---|---|---|
| | | GD 146 | | | | |
| | | $C_{max}$ (µg/mL) | $T_{max}$ (day) | | $AUC_{0-7d}$ (µg•day/mL) | $T_{1/2}$ (day) |
| 2 | Mean | 78.4 | 1.56 | | 498 | 12.3 |
| | (number of females) | (14) | (13) | | (14) | (12) |
| 50 | Mean | 2760 | 1.67 | 1.76 | 17600 | 15.0 |
| | (number of females) | (11) | (11) | (11) | (11) | (8) |

$T_{1/2}$: Using the data of from GD 146 to Day 293 ±1 p.p.

Since $T_{max}$ of Animal No.18230 was two parameters (24 hours and 48 hours after dosing), the mean was calculated using each $T_{max}$.

- the animals which were given the highest dosage on GD 20 by mistake
- where there was "no sample"
- "not available"

*(page 1711 of Study Report)*

Satralizumab was not detectable in infant control samples. Satralizumab was measurable in samples from all infants from LD and HD mothers, except for one LD animal whose mother developed neutralizing ADA. As shown in the summary table below, satralizumab exposures in infants increased greater than dose-proportionally

(~40x for $C_{max}$ and ~60x for AUC, with a 25x increase in dose). The $C_{max}$ in infants was 0.6-0.7x that in maternal plasma on GD 146.

| Dose level (mg/kg/week) | | Time points: From Day 14 p.p. to Day 293 ±1 p.p. | | | |
|---|---|---|---|---|---|
| | | $C_{max}$ (µg/mL) | $T_{max}$ (day) | $AUC_{14\text{-}293d}$ (µg•day/mL) | $T_{1/2}$ (day) |
| 2 | Mean (number of infants) | 45.6 (16) | 14.0 (15) | 1210 (16) | NC |
| 50 | Mean (number of infants) | 1840 (10) | 14.0 (10) | 69100 (10) | 11.6 (10) |

NC: Not calculated

Means were calculated by excluding:

- the animals which were given the highest dosage on GD 20 by mistake
- where there was "no sample"
-"not available"

*(page 1713 of Study Report)*

ADA was detected in samples from 16 maternal animals (4 Con, 9 LD, 5 HD) and 10 infants (3 Con, 4 LD, 3 HD). Of these, neutralizing activity was observed in 7 maternal animals (6 LD, 1 HD) and 3 infants (1 Con, 2 LD). One of these infants had a high ADA titer ($x10^4$ on Day 14 PP, like that of its mother [$x10^3$ or $x10^4$ from GD 51 onward]) that diminished to x1 by Day 259 PP, suggesting placental transfer of the ADA likely occurred in this case. Satralizumab concentrations were BLQ by GD 51 in this maternal animal and were undetectable in this infant. In the 5 other LD and 1 HD maternal animals with neutralizing ADA, satralizumab levels were still detectable.

**Milk Analysis**

Maternal milk samples were collected on Days 14, 28, 63, 91, 119, 147, and 175 postpartum (PP) for analysis of satralizumab concentrations.

Satralizumab levels were below the lower limit of quantification in all control samples. Satralizumab was detected in 5/16 LDF on Day 14 PP (range: 0.0536 to 0.488 µg/mL) and in 2 of these on Day 28 PP (0.183 and 0.102 µg/mL). At the HD, satralizumab was detected in 12/12 on Day 14 PP (mean: 0.982 µg/mL; range: 0.435 to 1.84 µg/mL); in 12/12 on Day 28 PP (mean: 0.568 µg/mL; range: 0.229 to 1.06 µg/mL); in 11/12 on Day 63 PP (mean: 0.328 µg/mL; range: 0.0572 to 0.851 µg/mL); in 7/12 on Day 91 PP (mean: 0.0749 µg/mL; range: BLQ to 0.186 µg/mL); and in 3/12 on Day 119 PP (range: BLQ to 0.113 µg/mL).



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**Pregnant Females ($F_0$)**

**Mortality**

All animals were observed for signs of ill health or overt toxicity twice daily throughout the study.

No satralizumab-related effects on mortality were observed during gestation, delivery, or lactation. One LD animal was found dead after delivery of a live infant; necropsy showed discolored mucosa in multiple areas of the intestine. One HD animal was found prostrate in poor physical condition on GD 161, with hypothermia, and subsequently gave birth to a live infant; despite supportive treatment, this animal died. Necropsy showed abnormal content in uterus, discolored mucosa of cecum, and abnormal appearance of skin/subcutis. These two deaths were within the background range of spontaneous deaths during parturition in monkeys and likely unrelated to satralizumab.

**Clinical Observations**

All animals were observed twice daily for behavior and appearance, and weekly at 1, 3, and 6 hours postdose. Detailed clinical examinations were conducted weekly.

No satralizumab-related effects on clinical signs were observed.

**Body Weight**

Body weights were recorded weekly.

No satralizumab-related effects on body weight were observed.

**Food Consumption**

Food consumption (per cage) was estimated twice daily.

No satralizumab-related effects on food consumption were observed.

**Clinical Pathology**

Blood samples were collected on GD 19 and 146 for analyses of standard hematology, coagulation, and clinical chemistry parameters, as well as serum IL-6 concentrations.

No satralizumab-related effects on hematology, coagulation, or clinical chemistry parameters were observed. Mean serum IL-6 increased from 3.29 and 10.48 pg/mL at baseline to 37.95 and 39.68 pg/mL after 18 weeks of dosing at 2 and 50 mg/kg/week, respectively. Mean control levels were 4.83 pg/mL on PP D19 and 2.92 pg/mL on PP D146.

**$F_1$ Generation**

**Fetal Examination**

Ultrasound examinations were conducted every two weeks for heart rate (GD 30-156), head circumference (GD 44-156), femur length (GD 72-156), and crown-rump length (GD 30-44).

No satralizumab-related effects were observed on fetal growth parameters.



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**Neonatal/Infant Examination**
Infants were examined for sex and external abnormalities on PP D1.

No satralizumab-related effects were observed on fetal/infant survival, sex ratio, or external abnormalities.

**Clinical Observations**
Infants were observed twice daily for behavior and appearance; detailed inspections were conducted weekly and the day before necropsy.

No satralizumab-related effects were observed on clinical signs.

**Body Weight**
Infant body weights were recorded on PP D1, 7, 14, 21, and 28, then weekly.

Individual infant body weights were slightly lower than controls in the 2 and 50 mg/kg/week groups, although no adverse clinical signs or effects on development were observed in these individuals. Body weights had normalized by the end of the maturation phase.

**Morphological Measurements**
Standard morphological measurements were conducted on PP D1, 21, 84, 168, and the day before necropsy.

No satralizumab-related effects on morphological measurements were observed.

**Neurobehavioral Assessment**
Standard neurobehavioral parameters were assessed 10-15 minutes following separation from the mother on PP D1 and PP D7.

No satralizumab-related effects on neurobehavioral parameters were observed.

**Grip Strength**
Grip strength was evaluated on PP D28.

No satralizumab-related effects on grip strength were observed.

**Skeletal Development**
Skeletal development was assessed by x-ray evaluation conducted on PP D35.

No satralizumab-related effects on skeletal development parameters were observed.

**Ophthalmic Examinations**
Standard ophthalmic examinations were conducted on PP D168.

No satralizumab-related effects on ophthalmic parameters were observed.



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**ECG**
Standard ECG parameters were evaluated on PP D168 and PP D175 on non-anesthetized animals.

No satralizumab-related effects on ECG parameters were observed.

**Clinical Pathology**
Blood samples were collected on PP 28 (hematology), 35 (coagulation), 42 (clinical chemistry) and 178 and 287 (all three).

No satralizumab-related effects on hematology, coagulation, or clinical chemistry parameters were observed.

**Immunophenotyping**
Blood samples were collected on PP D28 and 178 for immunophenotyping.

No satralizumab-related effects on immunophenotyping parameters were observed.

**Cytokine Analysis**
Blood samples were collected on PP D21, 91, 140, 178, and 287 for analysis of serum IL-6 concentrations.

Mean serum IL-6 concentrations were increased in HDM infants from PP D91 to 140 (86-128 pg/mL), and in HDF infants from PP D21 to 140 (38-142 pg/mL), followed by return to control levels (1.30-24.24 pg/mL) by PP D287, correlating with the decreases in plasma satralizumab.

**T-Cell Dependent Antibody Response**
Infants were injected SC on PP D147 with an antigenic challenge (0.1 mL of 10 mg/mL Keyhole Limpet Hemocyanin [KLH]). Blood samples were collected on PP D147 (pre-challenge), and PP Days 154, 161, 168, and 180, for analysis of anti-KLH IgG and IgM antibody titers in serum.

T-cell dependent antibody responses to antigen challenge were dose-dependently reduced. Median maximum titers of IgM and IgG were reduced 15% and 16%, respectively, in LD infants, and 30% and 50%, respectively, in HD infants. Maximum titers of IgM were reduced compared to median control values in 9/14 LD and 9/10 HD animals. Maximum titers of IgG were reduced compared to median control values in 10/14 LD and 8/10 HD animals. Median values were compared because the means were skewed by very high titers observed in a few animals.

**Learning Ability Test**
Infants were trained on the Wisconsin General Testing Apparatus starting at age 6 months and evaluated for memory one week following a successful learning test.

No satralizumab-related effects on learning or memory parameters were observed.



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**Necropsy**
Necropsy examinations were performed on mother-infant pairs on PP D293 ± 1, following overnight fasting.

No satralizumab-related effects on macroscopic findings were observed.

**Organ Weights**
Organs weighed included adrenals, brain, heart, kidneys, liver, lungs, ovaries, spleen, testes, thymus, thyroids/parathyroids, and uterus/cervix.

No satralizumab-related effects on organ weights were observed.

**Histopathology**
A standard list of organs and tissues from infant animals was evaluated by the study pathologist, with contemporaneous peer review by the sponsor's pathologist. Only thyroid glands were examined from maternal animals.

No satralizumab-related effects on microscopic findings were observed.



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# 10 Special Toxicology Studies

**Satralizumab: Toxicological assessment report on the excipients histidine, arginine, aspartic acid, and poloxamer 188 in a SC drug formulation for use in adolescent patients**

(Roche Report 1093380; February 15, 2019)

**L-histidine**

L-histidine is a non-essential amino acid used as a flavoring agent, nutrient, dietary supplement, and medicine. The satralizumab formulation includes 20 mM histidine (3.1 mg per 1 mL dose), to be administered by SC injection biweekly for 4 weeks and monthly thereafter. The safety of this level of exposure to L-histidine has been adequately assessed based on the following:

- The FDA Inactive Ingredients Database listed a maximum potency of 0.39% for L-histidine administered via SC injection, which is greater than the proposed concentration in the proposed satralizumab formulation (3.1 mg/mL = 0.31%).

- No adverse effects were observed in monkeys receiving weekly doses of SC histidine exceeding 3.1 mg/dose for 26 weeks in the chronic toxicity study or from GD 20 through delivery in the ePPND study of satralizumab.

- The 3.1 mg/dose L-histidine for satralizumab is approximately equal to or exceeded by the maximum doses in the following FDA-approved agents: ILARIS® (up to 5.6 mg/dose SC), XOLAIR® (up to 4.5 mg/dose SC), an HEMLIBRA® (up to 0.06 mg/kg/dose * 50 kg adolescent = ~3 mg/dose).

- IV solutions of amino acids are indicated for use in Europe for nutritional support of pediatric patients at doses containing up to 1150 mg/day (Aminoplasmal Paediatric 10% solution®) or 790 mg/day (Aminosyn®-PF 7%) histidine for a 10 kg infant.

**L-Arginine**

L-arginine is a non-essential amino acid and a normal metabolite in animals and humans. The satralizumab formulation includes 150 mM arginine (26.1 mg per 1 mL dose), to be administered by SC injection biweekly for 4 weeks and monthly thereafter. The safety of this level of exposure to L-arginine has been adequately assessed based on the following:

- The FDA Inactive Ingredients Database listed a maximum potency of 0.35% (w/v) for L-arginine administered via SC injection, which is lower than the proposed concentration in the proposed satralizumab formulation (26.1 mg/mL = 2.61%). The maximum potency for IV injection was 880 mg/dose.



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- No adverse effects were observed in monkeys receiving weekly doses of SC arginine exceeding 26.1 mg/dose for 26 weeks in the chronic toxicity study or from GD 20 through delivery in the ePPND study of satralizumab.
- The approved SC dose of 3 mg/kg/week HEMLIBRA® includes L-arginine at ~25 mg/dose for a 50 kg adolescent patient.

- IV formulations include L-arginine at up to 2470 mg/dose (R-Gene 10®, for a 60 kg patient; FDA approved in 1973), 2275 mg/dose (Aminoplasmal Paediatric 10% solution®, for a 10 kg infant), and 3100 mg/dose (Aminosyn®-PF 7%, for a 10 kg infant).

**L-Aspartic Acid**

L-arginine is a non-essential amino acid produced by plants and animals and ubiquitous in the diet of humans. The satralizumab formulation includes (b) (4) mM aspartic acid ((b) (4) mg per 1 mL dose), to be administered by SC injection biweekly for 4 weeks and monthly thereafter. The safety of this level of exposure to L-aspartic acid has been adequately assessed based on the following:

- No adverse effects were observed in monkeys receiving weekly doses of SC aspartic acid exceeding (b) (4) mg/dose for 26 weeks in the chronic toxicity study or from GD 20 through delivery in the ePPND study of satralizumab.

- The approved SC dose of 3 mg/kg/week HEMLIBRA® includes L-aspartic acid at ~21.5 mg/dose for a 50 kg adolescent patient.

- IV formulations include L-arginine at up to 1650 mg/dose (Aminoplasmal Paediatric 10% solution®, for a 10 kg infant) and 1330 mg/dose (Aminosyn®-PF 7%, for a 10 kg infant).

**Poloxamer 188**

Poloxamer 188 (aka Pluronic F-68 or Poloxalene) is a polyethylene-polypropylene glycol. The satralizumab formulation includes 0.5 mg Poloxamer 188 per 1 mL dose, to be administered by SC injection biweekly for 4 weeks and monthly thereafter. The safety of this level of exposure to L-aspartic acid has been adequately assessed based on the following:

- The FDA Inactive Ingredients Database listed a maximum potency of 0.3% (w/v) for Poloxamer 188 administered via SC injection, which is greater than the proposed concentration in the proposed satralizumab formulation (0.5 mg/mL = 0.05%).

- Toxicity studies of multiple species by multiple routes (including SC administration) “suggest that exposure to Poloxamer 188 does not cause a high degree of toxicity” *(page 11 of sponsor’s assessment report on excipients)*. No adverse effects were observed in a pre- and postnatal toxicity study of Poloxamer 188 in rat at 10 mg/kg/day (route not specified).

- No adverse effects were observed in monkeys receiving weekly doses of SC Poloxamer 188 exceeding 0.5 mg/dose for 26 weeks in the chronic toxicity study or from GD 20 through delivery in the ePPND study of satralizumab.
- FDA-approved SC formulations include Poloxamer 188 at up to 0.6 mg/day (Norditropin®, for a 10 kg patient) and 0.5 mg/dose (HEMLIBRA®, for a 50 kg patient).

**A tissue cross-reactivity study of fluorescein-conjugated CH5333787 with normal human and cynomolgus monkey tissues**

(Chugai Study TOX09-0132; (b) (4) Study 0050001131; (b) (4) initiated March 24, 2010; GLP; QA)

The potential cross-reactivity of fluorescein-conjugated satralizumab was evaluated in cryosections of normal human and cynomolgus monkey tissues (3 donors per tissue) at 1 and 10 µg/mL.

Consistent specific membrane and cytoplasmic immunostaining was observed in mononuclear cells within T-cell rich areas of lymphoid tissues in both species (bone marrow, lymph node, spleen, thymus, tonsil, peripheral blood, and GALT in esophagus and stomach) and in monkey alone (GALT in colon and small intestine, bronchial-associated lymphoid tissue in lung). Resident and/or migrating/trafficking mononuclear cells were stained in human and monkey salivary gland, in human stomach and urinary bladder, and in monkey fallopian tube, liver, pancreas, pituitary, ureter, and uterus. Epithelial cells were stained (small brown cytoplasmic granules) in human and monkey mammary gland, fallopian tube, small intestine, pancreas, pituitary, urethra, salivary gland, skin, ureter, urinary bladder, and uterus, in monkey prostate ducts and cervix, and in human rete testis and sinusoidal lining of liver. Specific staining was also observed in human and monkey hematopoietic cells of bone marrow, glomerular cells of kidney, and Hofbauer cells of placenta and in human spermatogenic cells of testis.

The control FITC-conjugated human IgG2 antibody and positive, negative, and ancillary control tissues stained as expected, demonstrating that the assay was sensitive, specific, and reproducible.

In conclusion, only a few tissues showed specific staining in human but not in monkey: resident/migrating/trafficking mononuclear cells in stomach and urinary bladder; epithelial cells in rete testis and sinusoidal lining of liver; and spermatogenic cells of testis.

**Blood compatibility study with human blood in CH5333787**

(Chugai Study TOX10-5017; (b) (4) initiated July 9, 2010; GLP 2008 (b) (4) QA)

A 101-fold dilution of satralizumab (1.182 mg/mL; 1.0 mL) was evaluated for hemolytic potential by incubation with an equal volume of whole blood from five male human donors for 30 minutes at 37 °C, compared to negative control (saline) and positive control (water for injection). The supernatant was obtained by centrifugation and evaluated by visual observation and a hematology analyzer. No hemolysis was observed in any of the samples incubated with satralizumab or negative control. All five blood samples incubated with positive control showed moderate hemolysis (5.6 ± 1.0 g/dL hemoglobin).

A 101-fold dilution of satralizumab (1.182 mg/mL; 0.5 mL) was evaluated for precipitation potential by mixing with an equal volume of plasma from five male human donors, compared to negative control (saline) and positive control (7% w/v nitric acid). Mixtures were evaluated by visual inspection for flocculation, precipitation, and coagulation. No flocculation, precipitation, or coagulation was observed in samples mixed with satralizumab or negative control. All five plasma samples mixed with positive control showed flocculation and precipitation.

In conclusion, a 1.182 mg/mL solution of satralizumab showed no hemolytic potential in human whole blood or precipitation potential in human plasma.

**Whole blood cytokine assay for in vitro cytokine release from human whole blood after treatment with CH5333787**

(Chugai Study TOX10-0005S; (b) (4) initiated March 26, 2010; non-GLP; non-QA)

Satralizumab, high-risk reference products (alemtuzumab and TGN1412a), a low-risk reference product (panitumumab), an anti-IL-6R mAb comparator (tocilizumab), and a negative control (PBS) were evaluated for release of cytokines (IL-8, IL-6, and TNF) after incubation with 193 µL/well blood from each of 12 human donors at 0.1, 1, 10, and 100 µg/mL final concentrations for 24 hours at 37 °C. The Stimulation Index (SI) was calculated as the mean of the experimental wells divided by the mean of the concurrent negative control wells.

Satralizumab induced positive responses in Donor 5 (IL-8 SI = 8.9 at 100 µg/mL; IL-6 SI = 3.9 at 100 µg/mL), Donor 6 (IL-6 SI = 3.2, 5.1, and 3.0 at 1, 10, and 100 µg/mL, respectively), Donor 9 (IL-6 SI = 3.1 at 100 µg/mL), and Donor 10 (IL-6 SI = 3.2 at 100 µg/mL).

High-risk comparators showed positive responses in more donor samples and with higher peak SIs. Alemtuzumab showed positive responses in 11/12 donors for IL-8 (peak SI 4.4-93.4), 9/12 for IL-6 (SI 1.0-195.6), and 10/12 for TNF (SI 0.7-65.4).

TGN1412a showed positive responses in 9/12 for IL-8 (SI 3.1-211.5), 5/12 for IL-6 (SI 0.9-72.4), and 0/12 for TNF.

The low-risk comparator, panitumumab, showed positive responses in 2/12 for IL-8 (SI 5.5-18.8), 1/12 for IL-6 (SI 3.1), and 0/12 for TNF. Tocilizumab showed positive responses in 2/12 for IL-8 (SI 5.3-5.8), 4/12 for IL-6 (SI 3.1-5.4), and 0/12 for TNF.

In conclusion, the results of this in vitro assay suggest the risk of cytokine release with administration of satralizumab is relatively low.



Reference ID: 4609287

# 11 Integrated Summary and Safety Evaluation

Satralizumab is a recombinant humanized IgG2 monoclonal antibody designed to bind and block the human IL-6R, thereby reducing inflammatory processes and the number and function of anti-AQP4-antibody-producing plasmablasts that may cause axonal damage in the spinal cord and optic nerve of patients with NMOSD. The drug product is a sterile solution containing 120 mg satralizumab and non-novel excipients in a pre-filled 1 mL syringe. The proposed dosing regimen is 120 mg SC loading doses once every 2 weeks (Weeks 0, 2, and 4), followed by maintenance doses of 120 mg SC once every 4 weeks. The proposed indication is for administration to adult (b) (4) (b) (4) with NMOSD.

Pharmacological studies of satralizumab evaluated species specificity, target selectivity, binding to Fc receptors, and pharmacodynamic activity. In in vitro assays, satralizumab demonstrated concentration-dependent inhibition of IL-6-induced growth of cells expressing human or cynomolgus monkey IL-6R; no inhibition was observed in cells expressing rat or mouse IL-6R or in cells expressing hIL-11R, hOSMR, hLIFR, or hCNTFR, when growth was induced with hIL-11, hOSM, or hLIF, respectively. In vitro binding studies also showed specific nanomolar binding of satralizumab to human and monkey IL-6R (both soluble and membrane-bound) and pH-dependence of its binding to hIL-6R ($K_D$ increased as pH decreased from 7.4 to 6.0). Satralizumab demonstrated higher affinity binding to human and monkey FcRn compared to tocilizumab, consistent with its longer residence time in blood. Binding to hFcγR showed lower affinity than tocilizumab, consistent with the lack of ADCC and CDC activity demonstrated by satralizumab in separate in vitro assays.

In in vitro activity assays, satralizumab inhibited hIL-6-dependent proliferation of PHA-L-activated human peripheral blood T cells, hIL-6 + hsIL-6R-stimulated increases in MCP-1 and VEGF in the medium of cultured HFLS-RA cells, and hIL-6-dependent production of IgG1 in plasmablasts isolated from human donors. In vivo, a single dose of 0.5-2 mg/kg SC satralizumab resulted in sustained inhibition of IL-6-induced increases in plasma CRP, increases in total sIL-6R, and decreases in free sIL-6R.

Administration of single doses of satralizumab (0.4, 2.0, 10, or 50 mg/kg IV or SC) to male cynomolgus monkeys resulted in plasma exposures that were approximately dose-proportional after IV injections and were generally greater than dose-proportional after SC injections. In both studies, there were dose-dependent increases in plasma IL-6 and total sIL-6R and dose-dependent reductions in free IL-6R. No adverse effects were observed on mortality, clinical signs, body weight, food consumption, hematology, or clinical chemistry.

Repeat-dose toxicity studies were conducted only in cynomolgus monkey because satralizumab was not pharmacologically active in rodent. No adverse effects were observed in a dose-ranging study of satralizumab (0, 8, 40, or 200 mg/kg IV weekly for 5 doses; N=1/sex/group), a GLP 4-week study (0, 2, 10, or 50 mg/kg SC weekly for 4 doses; N=4/sex/group), or a GLP 26-week study (0, 2, 10, or 50 mg/kg SC weekly for 26

doses; N=3/sex/group main study, 2/sex/group 13-week recovery). As expected, the binding of satralizumab to IL-6R resulted in slight dose-related increases in serum IL-6. Some animals, primarily in the low- and mid-dose groups, developed ADA in all three studies; a few of these also showed neutralizing activity correlated with reduced satralizumab plasma exposure. However, exposures were sufficient in the mid- and high-dose groups to allow a valid assessment of the toxicity of satralizumab.

Carcinogenicity studies of satralizumab were not conducted or required based on the absence of pharmacological activity at rodent IL-6R. The effects of satralizumab treatment on the risk of malignancy in humans is unknown.

The lack of effects on reproductive organs, menstrual cycle, and sperm parameters in the 26-week toxicity study in monkey suggests satralizumab is not likely to adversely affect fertility. Potential effects of satralizumab on reproduction and development were assessed in an enhanced pre- and postnatal development study in monkey. Administration of 2 or 50 mg/kg/week SC satralizumab to pregnant monkeys resulted in dose-dependent reductions in T-cell dependent antibody responses to antigenic stimulation in infants. Median maximum titers of IgM and IgG were reduced 15% and 16%, respectively, in LD infants, and 30% and 50%, respectively, in HD infants. These results are consistent with the expected inhibitory effects of satralizumab on the survival and function of plasmablasts and suggest that infants exposed to satralizumab in utero may have increased risk of infections and/or impaired responses to vaccinations. On post-partum day 14, satralizumab was present in milk from LDF and HDF at levels up to 0.5 and 1.8 µg/mL, respectively, much lower than the mean levels in infant plasma (45.6 and 1840 µg/mL, respectively) or maternal plasma ($C_{max}$ = 78.4 and 2760 µg/mL in LDF and HDF, respectively, after dosing on GD 146).

Tissue cross-reactivity studies in normal human and monkey tissues demonstrated specific binding in human (but not monkey) mononuclear cells in stomach and urinary bladder, epithelial cells in rete testis and sinusoidal lining of liver, and in spermatogenic cells of testis.

In vitro studies suggested that satralizumab has little or no potential for hemolysis or cytokine release in human whole blood, or for precipitation in human plasma.

In summary, no safety margin was established for the reductions in TDAR observed in infants in the ePPND study. With this exception, no satralizumab-related adverse effects were observed in animals up to the highest doses evaluated. As illustrated in Table 2 below, predicted satralizumab plasma exposures (AUC) in humans at steady-state during treatment with the proposed clinical dose were ≥26-fold lower than those observed at the maternal NOAEL in the ePPND study and at the HD (NOAEL) in the pivotal 26-week study. The safety margins were even greater considering that 7-day exposures in animals dosed weekly were compared to 28-day exposures in humans dosed once every 4 weeks.



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**Table 2 Animal Exposure and Exposure Margins (Without ADA in Monkeys and Humans)**

| Species | Study type | Dose (mg/kg) | $C_{trough}$ (μg/mL)[b] / Exposure Margin[c] | $C_{max}$ (μg/mL)[b] / Exposure Margin[c] | $AUC_{0-7d}$ (μg • d/mL) / Exposure Margin[c] |
|---|---|---|---|---|---|
| **Cynomolgus Monkey** | 4-Week SC Repeat-Dose | 50[a] | M: 1050<br>F: 1270<br>/ 57-69 | M: 1400<br>F: 1440<br>/ 48-49 | M: 8330<br>F: 8250<br>/ 12 |
| | 26-Week SC Repeat-Dose | 50[a] | M: 3010<br>F: 3040<br>/ 164-166 | M: 3810<br>F: 3300<br>/ 112-130 | M: 23,000<br>F: 20,000<br>/ 28-33 |
| | ePPND | 50[a] | 2410[d]<br>/ 132 | 2810[d]<br>/ 96 | 18,000[d]<br>/ 26 |

$C_{trough}$ = concentration prior to dosing; ePPND = enhanced pre- and postnatal development; F = female; M = male; SC = subcutaneous.

[a] NOAEL of the study.

[b] At 4th dose, 26th dose and gestation Day 146 in 4-week SC, 26-week SC repeat-dose and ePPND study, respectively.

[c] Calculated based on mean satralizumab plasma $C_{trough}$ (18.3 μg/mL), simulated $C_{max}$ (29.4 μg/mL) or simulated $AUC_{0-28d}$ (705 μg • d/mL) values in human (study number BN40898 and BN40900, at 10th cycle).

[d] One animal shows anti-drug antibody production with neutralization activity and was excluded from the calculation.

*(page 16 of sponsor's Toxicology Written Summary; see Appendix for human PK data)*

## Recommendations

The nonclinical data submitted adequately support the approval of satralizumab for the treatment of adult [redacted] (b) (4) with NMSOD. Pregnancy labeling should be revised to include a description of the impaired T-cell dependent antibody responses observed in the ePPND study in monkey.

# 12 Appendix

**Table 10 Median [Q05–Q95] Predicted Steady-State Exposures by Body Weight in NMO/NMOSD Patients (Studies BN40898 and BN40900), Conditional Simulation for Final Model following 120 mg SC Q4W Dosing**

| Covariate | Level | N | $C_{trough}$ (mcg/mL) | $C_{max}$ (mcg/mL) | $AUC_{0-28d}$ (µg/mL day) | Weight (kg) |
|---|---|---|---|---|---|---|
| All NMO/NMOSD Patients | | 154 | 18.3 [2.79–41.2] | 29.4 [10–57.3] | 705 [199–1410] | 63.2 [47.3–111] |
| Body Weight Tertile | 39.3–57.3 kg | 52 | 29.5 [12.5–46.8] | 44 [28.4–61.8] | 1070 [585–1550] | 51 [43.9–57] |
| | 57.3 75.0 kg | 52 | 20.1 [7.84–34.4] | 31 [19.1–48.2] | 739 [376–1190] | 63.4 [58.2–74.4] |
| | 75.0–151.0 kg | 50 | 8.98 [0.226–19.9] | 17 [5.43–29.1] | 379 [69.4–721] | 89.8 [76.3–139] |

*(page 64, Summary of Clinical Pharmacology Studies))*

**Table 11 Predicted Steady-State Exposures and Receptor Occupancy by Study, Conditional Simulation in Children and Adults**

| Parameter | Age <18 NMO/NMOSD Patients Study BN40898 | | Age ≥18 NMO/NMOSD Patients Studies BN40898 and BN40900 | |
|---|---|---|---|---|
| | Mean (SD) | Median [Q05 - Q95] | Mean (SD) | Median [Q05 - Q95] |
| $C_{trough}$ (µg/mL) | 19.9 (16.1) | 13.7 [3.29–44.5] | 19.7 (12) | 18.8 [2.88–40.2] |
| $C_{max}$ (µg/mL) | 31.9 (20.9) | 23.4 [9.49–62.5] | 31.5 (14.6) | 29.5 [10.4–56.9] |
| $AUC_{0-28, ss}$ (µg/mL day) | 746 (529) | 527 [195–1540] | 736 (379) | 710 [202–1400] |
| RO (%) at $C_{trough}$ | 86.8 (29.5) | 96.7 [42.5–99] | 94.4 (11.8) | 97.6 [86.2–98.9] |
| Fraction of dose eliminated by linear pathway | 0.487 (0.198) | 0.475 [0.201–0.694] | 0.469 (0.153) | 0.508 [0.191–0.668] |

*(page 66, Summary of Clinical Pharmacology Studies))*

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