

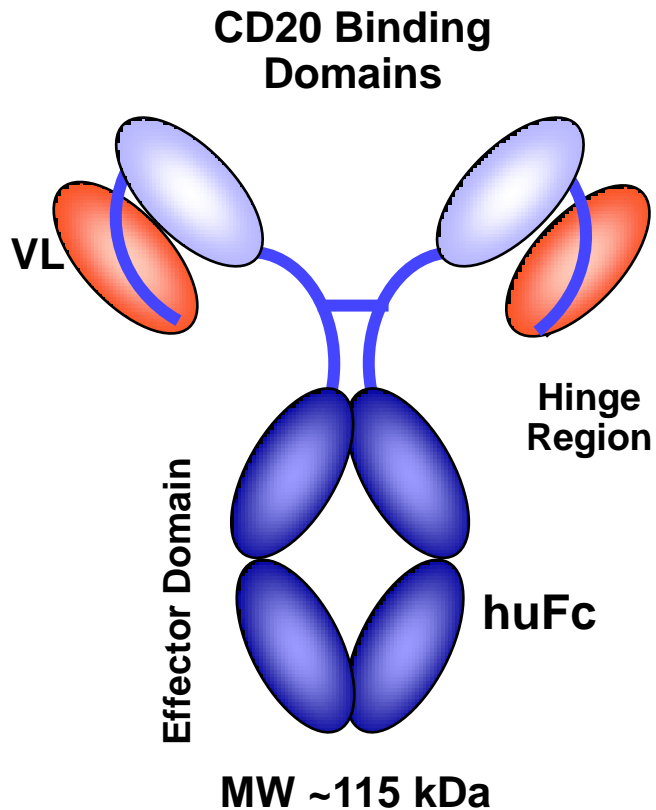
Subcutaneous Administration of SBI-087 Provides Potent B Cell Depletion in Subjects With Controlled RA

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SMIP™ SBI-087: CD20 Directed Therapy for Inflammation and Autoimmunity

SMIP SBI-087 Molecule



- **SMIP™:**
 - Small Modular ImmunoPharmaceutical
- **Novel protein scaffold**
- **Anti -human CD20**
 - Two identical disulfide bonded polypeptide chains
- **Potential advantages**
 - Better tolerability
 - More convenient dosing
 - Reduce the potential for immunogenicity through a humanized scFv region
- **High affinity binding to human B cells**
- **High potency in activation of Fc-mediated cellular cytotoxicity and complement fixation**

Summary of Effector Functions of SBI-087

Biologics	CDC	FcDCC
SBI-087	+++	+++(+)
SBI-087 P331S*	-	+++
rituximab	++	+++

- Versus SBI-087 P331S and RTX in a non-human primate study, SBI-087 demonstrates:
 - More sustained peripheral B cell depletion activity
 - More potent and sustained activity in the lymph nodes and bone marrow
- Increased CDC of SBI-087 vs RTX may offer the advantage of better peripheral and tissue B cell depletion.

*SBI-087 P331S is a mutated version of SBI-087 with no *in vitro* CDC activity.

SBI-087 RA Phase 1 Studies: Protocol Design

- **First in human study in patients with mild RA**
 - Phase 1, multicenter, sequential-group study of single ascending intravenous (IV) and subcutaneous (SC) doses
 - 1°endpoint: Safety and tolerability of ascending single IV and SC doses of SBI-087 in subjects with controlled RA
 - 2°endpoint: Describe PK and PD profiles (CD19+ B cell profile)
 - Ongoing open-label study
- **Single doses**
 - IV infusions
 - ◆ 0.015, 0.05, 0.15, 0.5, 1.5 and 2 mg/kg
 - SC doses
 - ◆ 50, 100*, 200*, and 300 mg*
 - *Pre-treatment regimen of 40 mg oral steroids, 500 mg acetaminophen, and an antihistamine
 - *Post-treatment regimen of 20 mg oral steroids at hr 4 and acetaminophen at hr 4 and hr 10

Demography

	IV Cohorts (mg/kg)						SC Cohorts (mg)			
	0.015	0.05	0.15	0.5*	1.5	2	50	100	200	300
N	4	4	4	4	6	6	6	14	6	6
Female, n (%)	3 (75)	3 (75)	1 (25)	4 (100)	5 (83)	5 (83)	6 (100)	12 (85)	6 (100)	6 (100)
Age, y (SD)	64 (6.8)	52.5 (13.4)	61.5 (7.0)	58.8 (10.5)	60.7 (7.3)	47.8 (12.4)	55 (7.5)	55.6 (10.0)	50.3 (6.9)	50.2 (10.0)
Duration RA, y (SD)	14.7 (12.4)	17.1 (6.2)	13.4 (8.7)	17.5 (17.1)	7.6 (5.7)	10.3 (7.6)	11.0 (8.8)	10.2 (9.0)	4.8 (3.5)	8.4 (8.5)
Baseline B cell count (SD)	202 (254)	201 (95)	119 (102)	211 (101)*	188 (116)	159 (99)	206 (96)	145 (140)	245 (161)	248 (177)

RF and anti-CCP were positive at baseline in 66 to 100% of subjects in individual cohorts

*One subject in this cohort was excluded due to abnormally high baseline B cell counts.

AEs After SC Injection and IV Infusion

- **SC Injection**

- **Fever, chills, malaise (8 of 14)**
 - ◆ Grade 1 or 2
 - ◆ Usually 2-10 hrs after injection
 - ◆ Resolved with acetaminophen or ibuprofen
- **Not seen after initiation of oral steroid premedication regimen**
 - ◆ 40 mg prednisone 2 hours pre-injection, 20 mg 4 hours post-injection

- **SC Injection Site Reactions (ISRs)**

- **3 of 32: mild or moderate ISRs (itching and redness) lasting one to four days**

- **IV Infusion Reactions (IR)**

- **5 of 28 had IR (grades 1-2)**
 - ◆ Occurred at 0.5 mg/kg and 1.5 mg/kg IV doses
 - ◆ Similar to first dose rituximab infusion reactions

- **Immunoglobulins:**

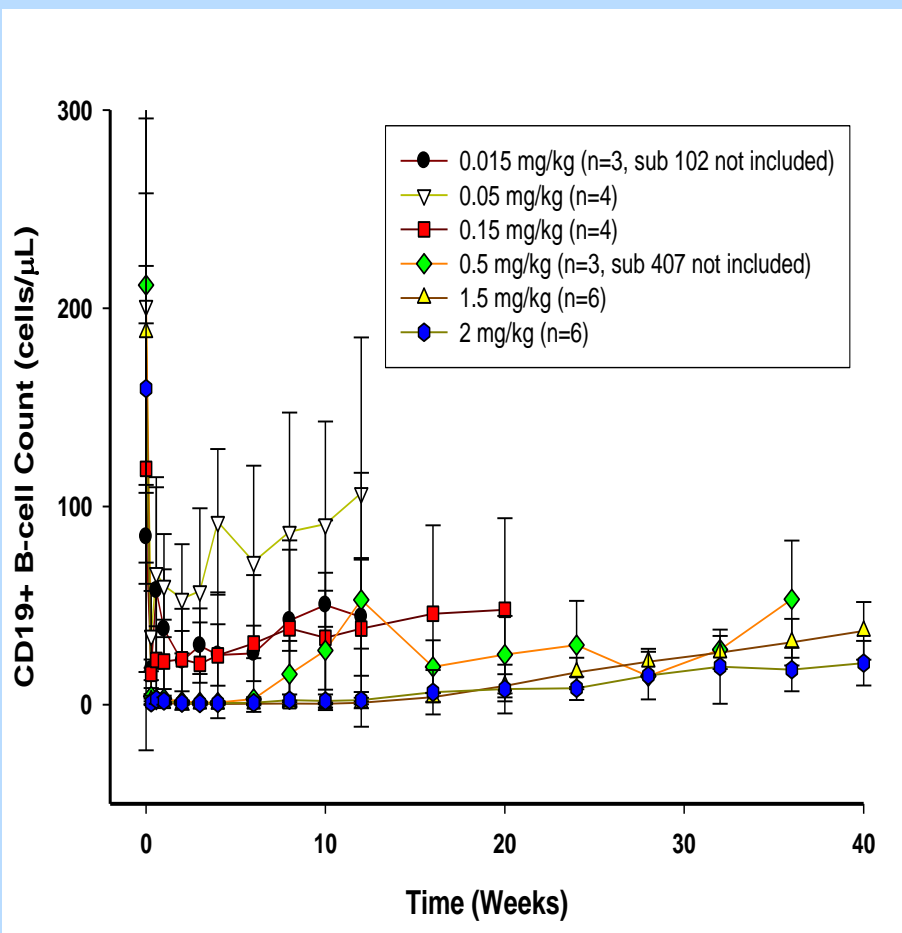
- **No clinically significant sustained decreases in IgG or IgM levels observed**

Overall Safety Summary

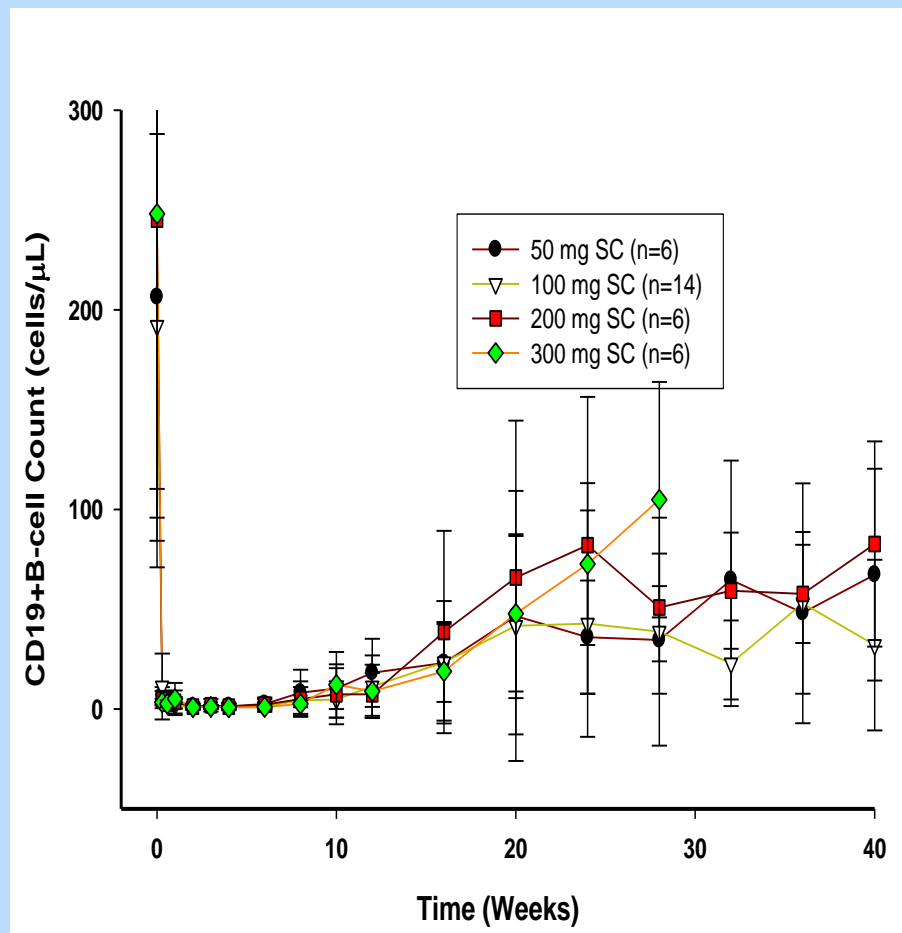
- **Most common TEAEs (>10%):**
 - URI (18%), HA (18%), Chills (13%), Diarrhea (13%), Fever (12%), Vessel puncture hematoma (12%), Fatigue (10%)
- **SAEs:**
 - 0.015 mg/kg IV: (1) exacerbation of COPD
 - 0.5 mg/kg IV: (1) Breast cancer; (1) elevated LFTs
 - 1.5 mg/kg IV: (1) herniated bowel correction surgery
 - 100 mg SC: (1) worsening of DJD; (1) bladder neoplasm
 - 300 mg SC: (1) Total hip replacement; (1) numbness and weakness in extremities
 - **Serious Infections:**
 - ♦ 0.015 mg/kg IV: (1) Bronchitis
 - ♦ 1.5 mg/kg IV: (1) Pneumonia; (1) Post-operative wound infection

Mean \pm SD B Cell Depletion Following Single SBI-087 Doses in Subjects with RA

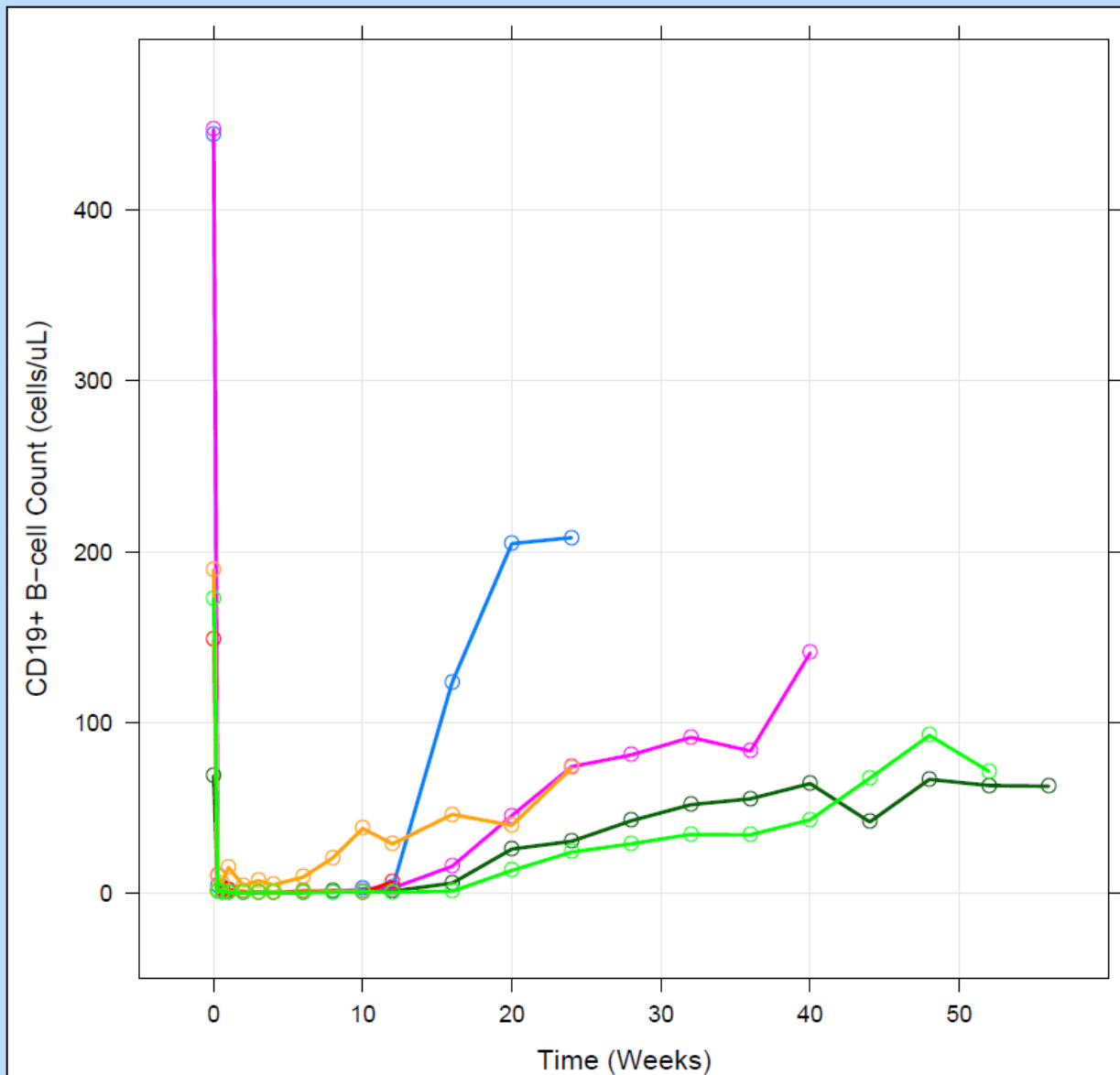
IV Cohorts



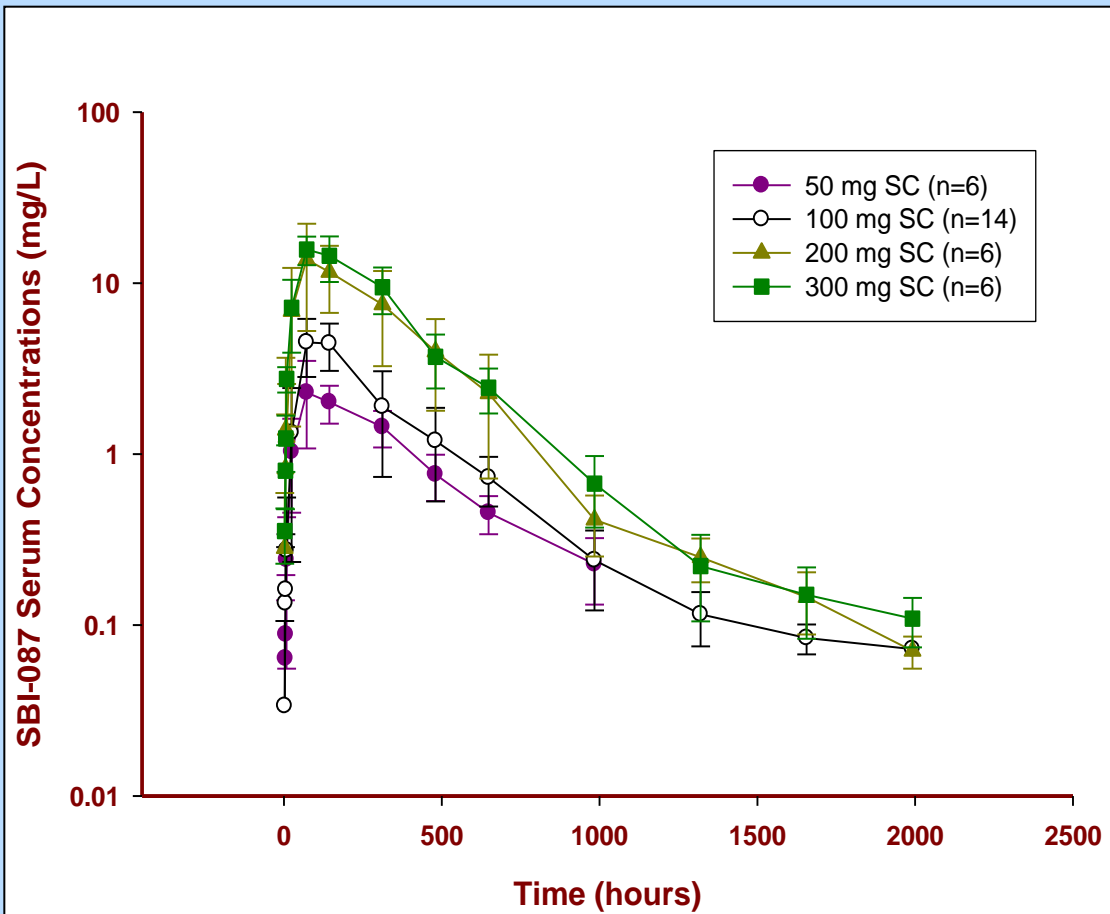
SC Cohorts



B Cell Depletion Following A Single 200 mg SC Dose of SBI-087 in Subjects with RA



SBI-087 Serum Concentrations After Single SC Doses in Subjects with RA



• Absorption

- Bioavailability of 200 mg SC: ~56%
- Delayed T_{max}: 96 – 123 hr (mean)
- 200 mg SC C_{max}: 14.04 ± 8.38

• Distribution

- Small volume of distribution
- V_{ss} (IV): 3.67 – 8.3 L

• Elimination

- Low clearance (IV): 0.023 – 0.112 L/h
- Long t_{1/2}: 230 – 340 hr (mean, SC)

Conclusions

- **SBI-087: humanized CD20-directed SMIP biologic that differs from RTX in structure and has enhanced B cell depleting activity**
 - Demonstrated sustained B cell depletion in blood, bone marrow, and lymph nodes (preclinical data)
- **SC and IV formulation provides similar B cell depletion**
 - SC delivery: no need for IV infusion; more convenient for patients
- **Single SC doses of SBI-087 with a day-of-treatment oral steroid regimen were generally well tolerated; potent B cell depletion**
- **SBI-087 PK profile similar to monoclonal antibodies**
- **SC doses of 100 mg and above provide depletion to <5 cells/uL; maintained for at least 12 weeks**
- **The 200 mg SC dose is being investigated in a Phase 2 study in subjects with active RA**

Acknowledgements

This study was supported by Pfizer Inc.

**SBI-087 is being developed in collaboration with
Trubion Pharmaceuticals.**