HB2198: A Tetravalent Bispecific anti-CD19/CD20 Antibody with Dual Fc Domains for Enhanced Immune Effector Functions and Deep B Cell Depletion in SLE

Brendon Frank[1], Brian Law[1], Larisa A Troitskaya[1], Marina E Fomin[1], Nelson LS Chan[1], Ursula Edman[1], Keith T Akama[1], Rob Hershberg[1], Jennifer Cooper[1], Alpana Naresh[1], Paul Brunetta[1], Emir Redzepagic[2], Stephen Hall[2], Gavin Lewis[1], Steven J Chapin[1], Juha Punnonen[1]

[1]Hinge Bio, Inc., Redwood City, CA, USA, [2]Veritus Research, Melbourne, Australia

Abstract #2447369

Abstract

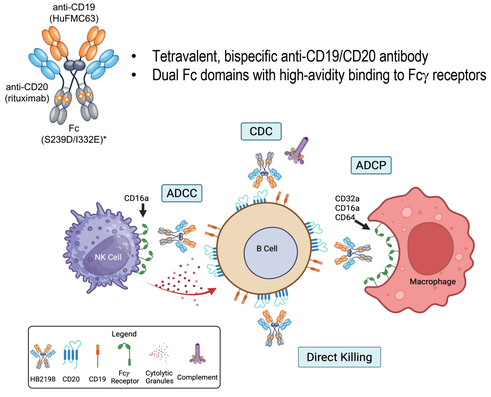
Background: Systemic lupus erythematosus (SLE) remains a disease of high unmet need, where conventional monoclonal antibodies often fail to achieve consistent B cell depletion and clinical benefit. Elevated IgG immune complexes, engagement of Fcγ receptors (FcγR), and impaired immune effector cell functions likely contribute to the variable benefits of B cell depleting antibodies. While CAR-T cells and T cell engagers have shown encouraging early clinical results, their use is limited by complexity and safety considerations. HB2198 is a bispecific anti-CD19/CD20 antibody with dual Fc domains, designed to enable potent B cell depletion with the off-the-shelf convenience and safety of antibody therapies.

Methods: HB2198 was generated using GEM-DIMER™ platform to bivalently target CD19 and CD20. It incorporates two Fc domains with S239D/I332E mutations, which enhance FcγR binding and downstream immune effector functions. We analyzed FcγR binding on immune cells and lipid raft association using flow cytometry. Antibody-dependent cellular phagocytosis (ADCP) by primary macrophages was quantified via both flow cytometry and kinetic, image-based analysis. ADCP assays were performed under varying physiological conditions, including cultures containing SLE patient serum, increasing concentrations of competing human IgG, or effector cells pre-armed with antibodies. For FcγR-independent pathways, direct apoptosis of purified B cells isolated from SLE patients was measured. *In vivo* efficacy was evaluated by monitoring the depletion of peripheral and tissue-resident B cells as a pharmacodynamic readout.

Results: Compared to conventional antibodies, HB2198 demonstrated superior binding to FcγR -bearing cells in human whole blood. This enhanced profile was accompanied by partial redistribution into Triton X-100-insoluble lipid rafts, robust complement-dependent cytotoxicity (CDC), and potent FcγR-independent direct killing of primary human B cells. In IgG-rich environments and SLE patient serum, HB2198 mediated greater ADCP activity and enabled superior FcγR pre-arming compared to conventional Fc-enhanced monoclonal antibodies, such as tafasitamab or obinutuzumab. HB2198 supported memory B cell depletion in the absence of FcγR-bearing effector cells *in vitro*. *In vivo*, HB2198 achieved robust B cell depletion in peripheral blood and lymphoid tissues, resulting in durable memory B cell depletion in cynomolgus monkeys.

Conclusions: HB2198 represents a new differentiated class of B cell-depleting antibody with a multimodal mechanism of action. The dual Fc domains drive increased binding to FcγR-bearing cells and potent ADCP, ADCC, and CDC. Additionally, independent of the Fc domains, HB2198 resulted in potent direct cell killing and partial redistribution into insoluble lipid rafts. This multimodal mechanism is designed to overcome immune complex–mediated resistance and impaired effector function in SLE without inducing T cell activation or associated cytokine release.

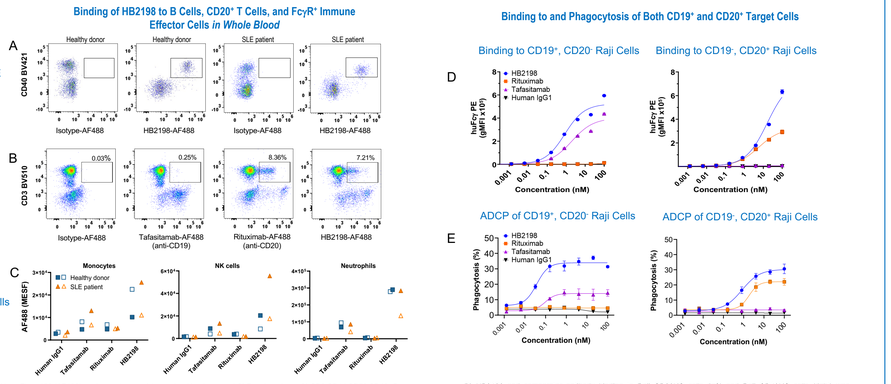
HB2198: Four Mechanisms of Killing CD19⁺ and CD20⁺ Target Cells



- Tetravalent, bispecific anti-CD19/CD20 antibody
- Dual Fc domains with high-avidity binding to FcγR receptors

Data source: Lewis et al., Sci Rep. 15:31563, 2025
** Lazar et al, PNAS, 103: 4005, 2006*
Image support: BioRender

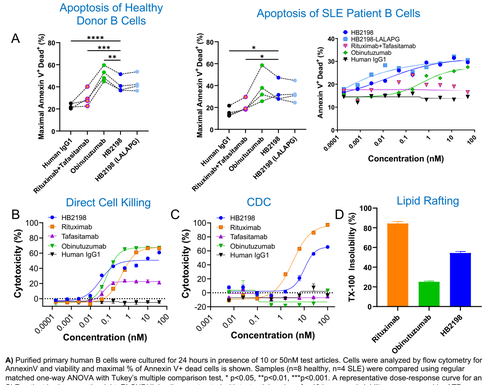
HB2198 Demonstrates a Unique Combination of Binding and Functional Properties on CD19⁺, CD20⁺ Target Cells and Immune Effector Cells



Binding of Alexa Fluor 488 (AF488)-conjugated test articles on healthy donor and SLE patient donor **A)** CD3⁻CD14⁻CD56⁻CD40⁺ B cells, **B)** CD3⁺ T cells, and **C)** CD3⁻CD56⁻CD14⁺ monocytes, CD3⁻CD14⁻CD56⁺ NK cells, and CD3⁻CD56⁻CD14⁻CD66b⁺ neutrophils was evaluated by flow cytometry in whole blood. Representative dot plots of isotype and HB2198 lymphocyte staining at 400 nM are shown in A and B. **C)** Conjugated test article geometric mean fluorescence intensity (gMFI) at 400 nM quantitated by Quantum Alexa Fluor® 488 Molecules of Soluble Fluorochrome (MESF) are shown.

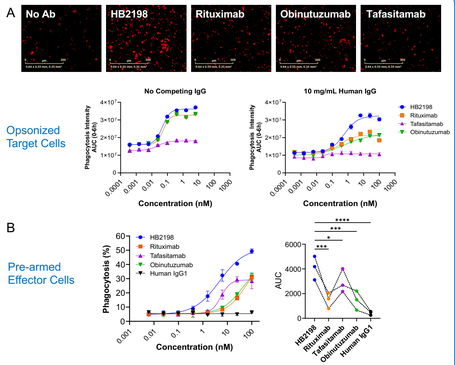
D) HB2198 and comparator antibody binding to Raji CD20KO cells (left) and Raji CD19KO cells (right) was evaluated by flow cytometry. Triplicate mean ± SD of gMFI are shown. **E)** Raji CD20 KO cells (left) and Raji CD20 KO cells (right) were incubated with human M2 macrophages for 2 hours in 1:2 ratio with HB2198 and comparator antibodies as indicated in the presence of 10 mg/mL human IgG1. Triplicate mean ± SD of percent of macrophages positive for target cells by flow cytometry is shown.

Potent FcγR-independent Direct Killing, CDC, and Partial Redistribution into Lipid Rafts



A) Purified primary human B cells were cultured for 24 hours in presence of 10 or 50nM test articles. Cells were analyzed by flow cytometry for AnnexinV and viability and maximal % of Annexin V+ dead cells is shown. Samples (n=8 healthy, n=4 SLE) were compared using regular matched one-way ANOVA with Tukey's multiple comparison test, * p<0.05, **p<0.01, ***p<0.001. A representative dose-response curve for an SLE patient is shown on the right. **B)** SUDHL4 cells were treated with test articles alone for 48 hours, and viability was assessed by ATP content (CellTiter-Glo) to calculate percent cytotoxicity relative to the no-antibody control. **C)** SUDHL4 cells were cultured with test articles and 20% human serum for 2 hours to evaluate complement-dependent cytotoxicity. **D)** Raji cells were incubated with AF-488-labeled test articles for 30 minutes, and percent Triton X-100 insolubility was determined by comparing MFI of lysed (0.5% Triton X-100) versus unlysed samples.

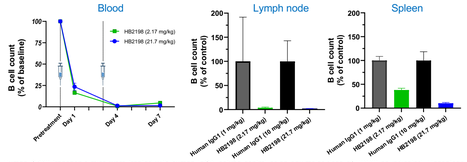
HB2198 Directs Potent ADCP of Human B Cells, Including via Pre-armed Primary Macrophages



A) pHrodo-labeled Ramos cells were opsonized with test article and co-cultured with M0 macrophages ± competing human IgG (10 mg/mL). Live-cell imaging (IncuCyte) tracked phagocytosis over 6 hours, quantified by area under the curve (AUC_{0-6h}). Representative images highlight pHrodo⁺ phagocytic cells at 6 hours ± 1.6 nM test article. **B)** Macrophages were pre-incubated in duplicate with titrated test articles and 2 mg/mL competing human IgG for 1.5 hours, washed, and cultured with Ramos target cells for 3 hours. Results show a representative dose-titration curve (left) and a summary AUC data across three independent experiments using different CD14⁺ cell donors (right). Values are compared by regular matched One-way ANOVA with Holm-Šídák's multiple comparisons test. * p< 0.05, ** p<0.01, *** p<0.001, **** p<0.0001

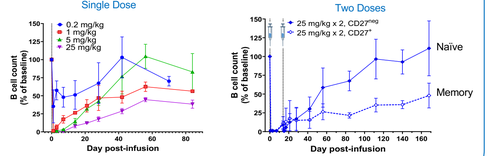
Deep and Durable Impact on B Cell Compartment *in vivo*

HB2198 Depletes B Cells in Lymphoid Tissue in HuCD20TG mice



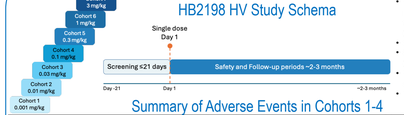
Human CD20 transgenic mice were treated with human IgG1 isotype control or an equimolar dose of H2198 as indicated. Mesenteric lymph nodes and spleens were harvested on Day 7. Percent of baseline (blood) or percent of control (lymph node, spleen) B cell count is shown after two infusions on days 0 and 3.

HB2198 Mediates Potent and Durable Memory B Cell Depletion in Monkeys



Cynomolgus monkeys were treated with HB2198 as indicated. Percent of baseline B cell number is shown for 3 months after single infusion of 0.2, 1, 5, or 25 mg/kg and up to 6 months post infusion for CD27⁺ and CD27⁻ B cells after two infusions of 25 mg/kg (Day 0, Day 14).

Phase 1 Clinical Trial in Healthy Volunteers (HV): Study Schema and Safety



- Randomized, double-blind, placebo-controlled ongoing trial in healthy volunteers (NCT07439263)
- Single Ascending Dose
- 8 participants per cohort (6 HB2198, 2 placebo)
- First in human – extensive safety, PK & PD evaluations
- Melbourne, Australia

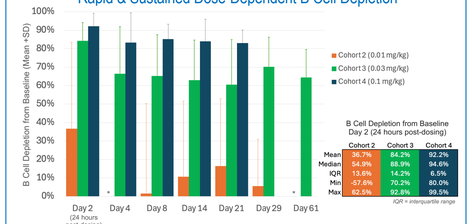
Summary of Adverse Events in Cohorts 1-4

System organ class	Preferred term	Cohort 1 Subjects N = 8	Cohort 1 AEs (13 Total)	Cohort 2 Subjects N = 8	Cohort 2 AEs (15 Total)	Cohort 3 Subjects N = 8	Cohort 3 AEs (20 Total)	Cohort 4 Subjects N = 8	Cohort 4 AEs (15 Total)
Eye disorders	*Ocular discomfort*					1 (12.5%)	1		
	Ocular hyperaemia					1 (12.5%)	1		
	Photophobia					1 (12.5%)	1		
Gastrointestinal disorders	*Abdominal pain*			1 (12.5%)	1				
	Constipation			1 (12.5%)	1				
	Diarrhoea							1 (12.5%)	1
	Dyspepsia					1 (12.5%)	1		
	Gastrooesophageal reflux disease					1 (12.5%)	1		
	Nausea			2 (25%)	3	1 (12.5%)	1		
General disorders and administration site conditions	*Asthenia*	1 (12.5%)	1						
	Fatigue	2 (25%)	3	3 (37.5%)	3			2 (25%)	2
	Infusion site pain	1 (12.5%)	1						
	Myodesopsia							1 (12.5%)	1
Infections and infestations	*Lower respiratory tract infection*			1 (12.5%)	1				
	Nasopharyngitis					1 (12.5%)	1		
	Oral herpes							1 (12.5%)	1
	Upper respiratory tract infection	1 (12.5%)	1			1 (12.5%)	1		
Injury, poisoning and procedural complications	*Contusion*					1 (12.5%)	1		
	Thermal burn	1 (12.5%)	1						
Metabolism and nutrition disorders	*Increased appetite*					1 (12.5%)	1		
	Polydipsia							1 (12.5%)	1
Musculoskeletal and connective tissue disorders	*Myalgia*							1 (12.5%)	1
	Pain in extremity	1 (12.5%)	1						
Nervous system disorders	*Dizziness*	2 (25%)	2	1 (12.5%)	1	1 (12.5%)	1		
	Dysgeusia					1 (12.5%)	1		
	Headache	2 (25%)	3	1 (12.5%)	1	3 (37.5%)	4	4 (50%)	4
	Paraesthesia					1 (12.5%)	1		
	Presyncope			1 (12.5%)	1				
	Somnolence					2 (25%)	2		
Psychiatric disorders	*Depressed mood*							1 (12.5%)	1
	Poor quality sleep			1 (12.5%)	1				
Reproductive system and breast disorders	*Menstruation irregular*					1 (12.5%)	1		
Respiratory, thoracic and mediastinal disorders	*Cough*			2 (25%)	2				
	Dysphonia							1 (12.5%)	1
	Oropharyngeal pain							1 (12.5%)	1
Skin and subcutaneous tissue disorders	*Skin reaction*							1 (12.5%)	1

Subjects = number (%) of eligible subjects with at least one AE of the preferred term; AEs = number of AE records. Denominator is the number of eligible subjects in the cohort (both placebo and HB2198-dosed subjects). Generated 13Oct2026 14:38.

All AEs were Grade 1 or 2 as of October 13, 2026.

Initial Phase 1 Healthy Volunteer Data: B Cell Depletion Following a Single Low Dose



B Cell Depletion from Baseline Day 2 (24 hours post-dosing)

	Cohort 2	Cohort 3	Cohort 4
Mean	36.7%	84.2%	92.2%
Median	54.9%	88.9%	94.6%
IQR	13.6%	14.2%	6.5%
Min	-57.6%	70.2%	80.0%
Max	62.5%	92.6%	99.5%

IQR = interquartile range

B cells were measured as CD45+, CD40+, CD3-, CD14-, CD56- B lymphocytes. Cohorts in this analysis exclude placebo subjects who were analyzed as a separate group. All placebo and cohort 1 (0.001 mg/kg) participants had <10% B cell depletion at all timepoints. Cohort 2 had no B cell depletion (*) on Days 4 and 61. Data pending for cohort 4 on Days 29 and 61 as of the data cutoff date of October 13, 2026.

- As of October 13, 2026, there have been no dose-limiting toxicities, serious adverse events or infusion-related adverse events limiting the 2 hour infusion.
- There are no major vital sign or lab abnormalities of significance, or any unexpected safety findings. All AEs were Grade 1 or 2.
- There is rapid and significant peripheral blood B cell depletion that is sustained over time at the low and single doses of 0.03 mg/kg and 0.1 mg/kg.
- The normal healthy volunteer study is ongoing and additional data will be communicated at study conclusion.

A separate HB2198 open-label basket trial is underway for SLE, RA and SSc (NCT07491900).

Summary & Conclusions

- A single HB2198 infusion resulted in rapid and potent B cell depletion in healthy volunteers at low doses with no meaningful safety signals in an ongoing Phase 1 clinical trial.
- Preclinical studies demonstrate unique binding and functional characteristics of HB2198:
  - Targets both CD19⁺ and CD20⁺ cells, including CD20⁺ T cells, with high-avidity binding to Fcγ receptors in human whole blood
  - ADCC, ADCP, Fc-independent direct killing, and CDC, associated with partial redistribution into lipid rafts
  - Enables pre-arming of effector cells for potent phagocytosis of target cells
  - Deep depletion of lymph node and splenic B cells in HuCD20 transgenic mice in the absence of human CD19
  - Even with weak crossreactivity with monkey CD19, a durable shift in memory vs naïve B cells in cynomolgus monkeys, consistent with the goal of immune reset
- Enrollment in a Phase 1 basket trial in SLE, rheumatoid arthritis, and systemic sclerosis patients is ongoing (NCT07491900).

These studies were sponsored by Hinge Bio, Inc.

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from the author of this poster.