BITTERROOTBIO

DEVELOPMENT OF BRB-002, A NOVEL NEXT-GENERATION ANTI-CD47 MOLECULE, FOR ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

B. ALEX YI [1], ALICIA CLAWSON [1], SWAPAN CHOWDHURY [1], PIERRE SIGNORE [2], KEVIN PAAVOLA [2], ANN M. MARSEILLES [1], SHARLINE CHEN [2], RUI YUN [2], ANDREW MORRISON [1], LILI ADAMS [2], BRITTANY WINNER, NICHOLAS LEEPER [2,3], VIJAY BHARGAVA, SHARON CRUGNALE [1], PAVAN CHERUVU [2], CRAIG T. BASSON [1]

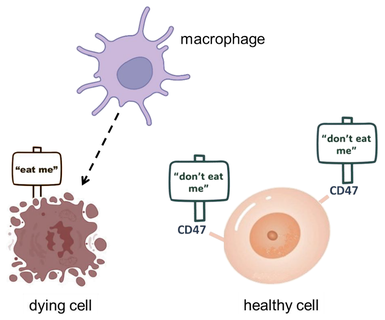
1. Bitterroot Bio, Needham, MA, USA; **2.** Bitterroot Bio, Palo Alto, CA, USA; **3.** Divisions of Vascular Surgery and Cardiovascular Medicine, Stanford University, Stanford, CA, USA

BACKGROUND

Atherosclerosis is characterized by the deposition of lipoproteins in the vessel wall leading to inflammatory changes and the accumulation of cellular debris as discrete atherosclerotic lesions. The cell surface marker CD47 has been shown to be upregulated in atherosclerotic lesions. CD47 acts as a *'don't eat me'* signal that prevents the efficient clearance of cellular debris by binding to its cognate receptor, SIRPα, on macrophages. Dysregulated CD47 may contribute to the expansion of atherosclerotic lesions by inhibiting efferocytosis.

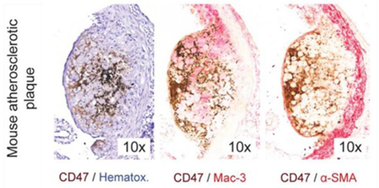
CD47 IS A *'DON'T EAT ME'* SIGNAL FOR MACROPHAGES

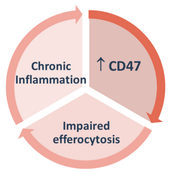
- ~200 billion cells die and turnover every day in the human body as part of normal tissue homeostasis
- Yet few apoptotic cells are found in healthy tissues because cell debris is rapidly and efficiently cleared
- Programmed cell removal (also known as efferocytosis) is carried out by macrophages in a highly regulated fashion
- CD47 is the predominant *'don't eat me'* signal expressed by healthy cells



IMPAIRED EFFEROCYTOSIS CONTRIBUTES TO ATHEROGENESIS

CD47 is highly expressed in advanced atherosclerotic plaque.





Hypothesis:
Antagonizing CD47 can stimulate efferocytosis and can lead to clinical benefit in atherosclerotic cardiovascular disease.

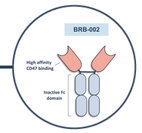
Kojima Y et al (2016) "CD47-blocking antibodies restore phagocytosis and prevent atherosclerosis" Nature. 536:86.

BRB-002

BRB-002 is a next-generation CD47 inhibitor without hematologic adverse effects for atherosclerotic cardiovascular disease.

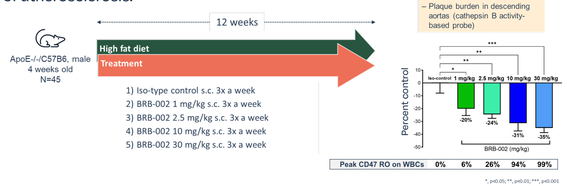
Formulation and Dosing

- ✓ Formulated as a **SC route of administration** to minimize C_{max}-mediated hematologic adverse effects
- ✓ **Large safety margin** for dosing BRB-002 based on GLP toxicology studies conducted in non-human primates



- **High affinity CD47 binding**
- **Does not induce hemagglutination of red blood cells**
- **Promotes phagocytosis**
- **No ADCC or CDC properties**

BRB-002 demonstrated dose-dependent efficacy in the apoE mouse model of atherosclerosis.



PHASE 1 SINGLE ASCENDING DOSE STUDY

Figure. Single ascending dose study

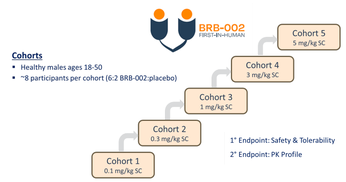


Table 1. Baseline Characteristics

		BRB-002 0.1 mg/kg N=4	BRB-002 0.3 mg/kg N=6	BRB-002 1 mg/kg N=6	BRB-002 3 mg/kg N=6	BRB-002 5 mg/kg N=4	Overall BRB-002 N=26	Pooled Placebo N=10
Age (years)	Mean	27	31	34	29.3	27.3	30.1	31.2
	Median	23	30	38.5	29	26.5	28.5	31
	Range	19 – 43	24 – 41	20 – 42	24 – 35	25 - 31	19 – 43	20 - 49
Sex	Male	4 (100%)	6 (100%)	6 (100%)	6 (100%)	4 (100%)	26 (100%)	10 (100%)
Race	American Indian or Alaska Native	0	1	1	1	1	4	3
	Asian	1	0	2	2	1	6	2
	Black or African American	0	0	0	0	0	0	0
	Native Hawaiian or Other Pacific Islander	0	0	0	1	0	1	0
	White	3	5	3	2	2	15	5
	Other	0	0	0	0	0	0	0
Weight (kg)	Mean	83.2	77.8	82.1	79.1	70.7	78.8	78.8
	Median	82.1	80.1	82.9	86.3	70.6	78.5	76.6
	Range	58.3 – 110.3	61.8 – 91.1	66.9 – 102.4	54.9 – 92.2	63.3 – 78.5	54.9 – 110.3	68 – 89.6
BMI (kg/m2)	Mean	25.2	24.7	25.9	24.7	25.8	25.2	25.6
	Median	25.3	25.1	25.4	25.1	26.4	25.1	25.2
	Range	18.2 – 31.9	19.5 – 29.7	20.9 – 30.4	20.4 – 29.1	20 – 30.3	18.2 – 31.9	23.1 – 29.3

SAFETY OF BRB-002

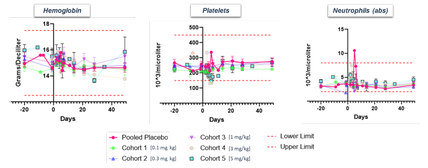
- No Serious Adverse Events (no deaths)
- Most common treatment-emergent adverse events (TEAE) were injection site reactions (ISRs) and headaches
- Similar rates of ISRs in BRB-002 treated (23.1%) vs placebo-treated (20%) participants

Table 2. Summary of safety

	BRB-002 0.1 mg/kg N=4 n (%)	BRB-002 0.3 mg/kg N=6 n (%)	BRB-002 1 mg/kg N=6 n (%)	BRB-002 3 mg/kg N=6 n (%)	BRB-002 5 mg/kg N=4 n (%)	Overall BRB-002 N=26 n (%)	Pooled Placebo N=10 n (%)
Number of Participants Reporting at least one:							
TEAE	2 (50.0%)	4 (66.7%)	3 (50.0%)	6 (100.0%)	4 (100.0%)	19 (73.1%)	8 (80.0%)
Serious TEAE	0	0	0	0	0	0	0
TEAE administration site reactions	1 (25.0%)	0	0	3 (50.0%)	2 (50.0%)	6 (23.1%)	2 (20.0%)
TEAE Grade 3 (no Grade 4 or 5 TEAEs)	0	0	0	2 (33.3%)	4 (100.0%)	6 (23.1%)	1 (10.0%)
TEAE Related to Study Drug	1 (25.0%)	3 (50.0%)	2 (33.3%)	6 (100.0%)	4 (100.0%)	16 (61.5%)	4 (40.0%)
TEAE leading to Study Discontinuation	0	0	0	0	0	0	0
TEAE leading to Death	0	0	0	0	0	0	0

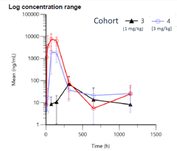
n = Number of Participants with Events

Figure. BRB-002 does not produce significant effects on key hematologic parameters



PHARMACOKINETICS

Figure.
Dose dependent increases in BRB-002 PK exposures

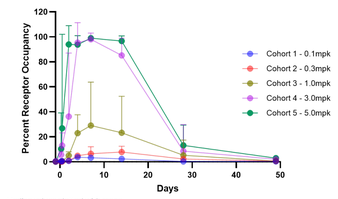


Exposures in Cohorts 1 and 2 subjects were below the limits of quantitation

DOSE-DEPENDENT INCREASE IN CD47 RECEPTOR OCCUPANCY WITH BRB-002

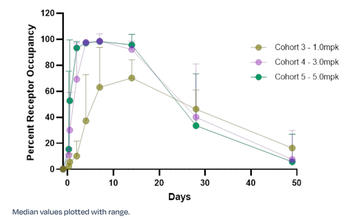
- CD47 receptor occupancy (RO) increases in a dose-dependent manner to 100% receptor occupancy
- CD47 RO is sustained for at least two weeks after BRB-002 administration

Figure. CD47 RO increased in a dose-dependent fashion to 100% in white blood cells (CD45+ cells)



Median values plotted with range.

Figure. CD47 RO increased in a dose-dependent fashion in dose-dependent fashion to 100% in red blood cells (CD45- cells)



Median values plotted with range.

CONCLUSION

BRB-002 was safe at all doses tested with no serious adverse events. BRB-002 target engagement was demonstrated by CD47 RO on RBCs and WBCs. CD47 RO was sustained for greater than 2 weeks post dose. Starting at the 1 mg/kg dose, a dose-dependent rise in BRB-002 plasma PK exposure was measured as BRB-002 dosing exceeds target mediated drug disposition clearance.

These results suggest that CD47 blockade has potential as a novel therapy for atherosclerosis.

A Phase 2 proof-of-concept trial of BRB-002 in patients with established atherosclerosis is expected to initiate in the first half of 2025.

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