BIOAGE

BGE-102, a Novel NLRP3 Inhibitor, Demonstrated Robust Anti-Inflammatory Activity in a Phase 1 Study in Healthy Volunteers and Participants with Obesity

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Abstract

Introduction and Objective:
NLRP3-driven inflammation contributes to metabolic dysfunction, insulin resistance, and cardiovascular risk in obesity and type 2 diabetes. BGE-102 is a potent, structurally novel, orally bioavailable, brain-penetrant small molecule inhibitor of NLRP3 inflammasome. We evaluated safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of BGE-102 in healthy volunteers and participants with obesity.

Methods:
This randomized, double-blind, placebo-controlled Phase 1 study included single ascending dose (SAD) cohorts in healthy volunteers and participants with obesity (10–120 mg; N=45); multiple ascending dose (MAD) cohorts in healthy volunteers (60 & 120 mg QD, 14 d; N=18); and a MAD cohort in participants with obesity and high-sensitivity C-reactive protein (hsCRP) ≥ 3 mg/L at baseline (120 mg QD, 14 d; N=18). A MAD cohort in participants with obesity and elevated hsCRP is pending. A single-dose food effect cohort was included for patients with obesity. Primary endpoints were safety and tolerability. Secondary endpoints included PK. Exploratory endpoints included ex vivo IL-1β inhibition and hsCRP.

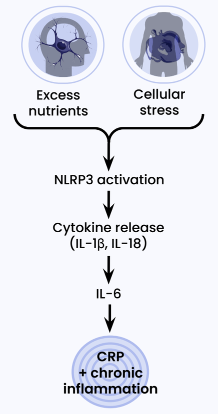
Results:
BGE-102 was well tolerated with all adverse events mild to moderate and self-resolving; no dose-limiting toxicities occurred. PK showed dose-proportional exposure supporting once-daily dosing. Food had no clinically relevant effect on oral bioavailability. At Day 14, trough plasma concentrations exceeded IL-1β IC90 by ~2× at 60 mg and ~5× at 120 mg. Ex vivo IL-1β suppression at trough was 90% at 60 mg and 98% at 120 mg. In the 120 mg MAD cohort with obese participants, hsCRP was reduced 86% at Day 14 vs 43% with placebo; 93% of treated participants achieved normal hsCRP (<2 mg/L).

Conclusion:
BGE-102 was well tolerated and showed sustained IL-1β suppression in treated participants and significant hsCRP reduction in participants with obesity. These results support advancing BGE-102 into proof-of-concept studies for metabolic and inflammatory conditions.

Chronic NLRP3 activity drives disease & predicts poor longevity

NLRP3 overview

- **Normal NLRP3 function:** innate immune response to danger signals
- **In pathology:** cellular stress & nutrient excess stimulates chronic activation (NLRP3 → IL-1β → IL-6 → CRP)
- **Resulting chronic inflammation** drives a range of diseases



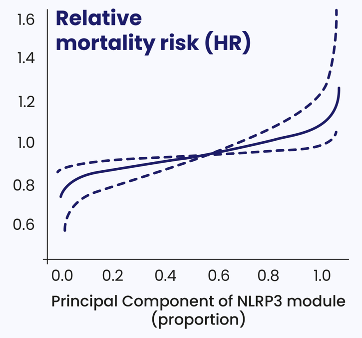
NLRP3 in human longevity & disease

Reduced NLRP3 activity is associated with longevity

Strong human genetic evidence for NLRP3 in cardiometabolic disease

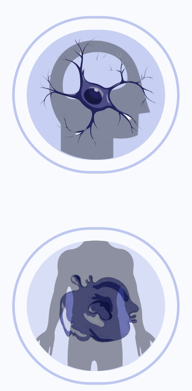
Mendelian randomization: NLRP3 levels strongly predictive of heart failure (↑ 1 SD expression = up to ↑ 70% risk)

GoF mutations ↓ lean mass & body composition ↑ atherosclerosis



BGE-102: A potent, oral NLRP3 inhibitor

Well positioned to address diseases driven by inflammation in both the CNS and the periphery



Potential best-in-class potency based on Phase 1 trial results
1.8 nM IC_{90} by human ex-vivo whole blood stimulation

24h IC_{90} coverage at 60 mg QD provided 24 hour IL-1β suppression ≥90%

86% hsCRP reduction; 87–93% of subjects achieved normalized CRP (<2 mg/L)* in line with injectable anti-IL-6 drugs

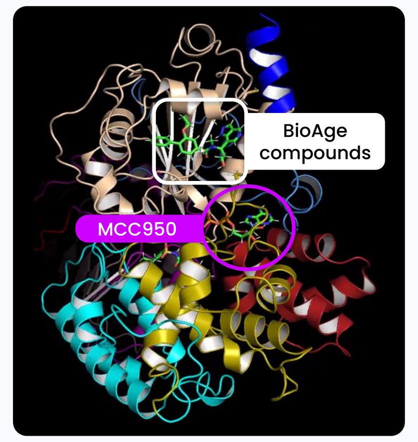
CNS penetrant
~0.7 Kp,uu_{CSF}
(120 mg MAD, day 14)

Attractive safety & tolerability
All AEs to date mild / moderate, self-limited, with no dose dependency

50–97x safety margin for 60 mg dose**
based on 3-month GLP tox

Strong IP position
2045 composition of matter & claims for novel NLRP3 binding site

Unique binding site



Phase 1 trial design

	Single Ascending Dose HVs & obese	Multiple Ascending Dose HVs - 14 days of dosing	Multiple Ascending Dose Obese - 14-21 days of dosing
	Safety & tolerability, pharmacokinetics, pharmacodynamics (IL-1β, hsCRP)		
Subjects	HVs (N=36) & obese subjects (N=9)	HVs (N=18)	Obese subjects with hsCRP > 3 mg/L (N=41)
Design	5 cohorts x; HVs: 10 mg | 30 mg | 60 mg | 120 mg; Obese: 60 mg (fed / fasted)	2 cohorts x; 60 mg | 120 mg	60 mg 21 days; 120 mg 14 days

BGE-102 was safe and well tolerated across all doses tested

All cohorts

TEAEs	All BGE-102 (N=82)	All placebo (N=22)
Subjects with at least 1 AE	50 (61.0%)	13 (59.1%)
Subjects with mild TEAEs	49 (59.8%)	12 (54.5%)
Subjects with moderate TEAEs	8 (9.8%)	3 (13.6%)

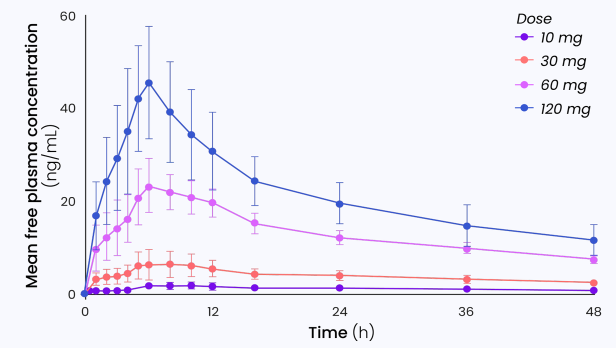
- Only mild / moderate treatment-emergent AEs (TEAEs); all self-limited with no dose dependency
- No serious AEs or TEAEs leading to discontinuation
- No clinically meaningful adverse changes in vital signs, laboratory values, or ECGs

Obese MAD cohorts

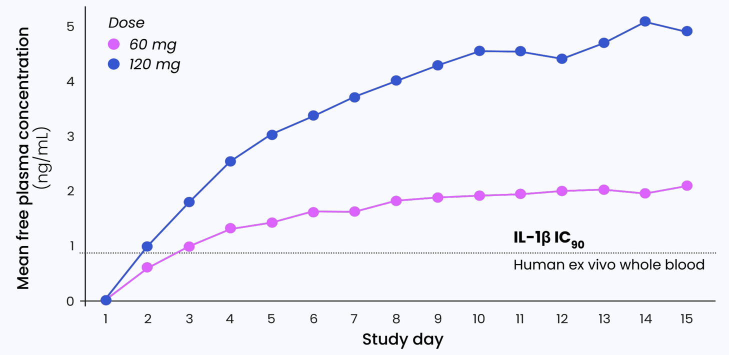
TEAEs	60 mg obese MAD (N=19)	120 mg obese MAD (N=14)	Obese placebo (N=8)
Subjects with any related TEAE, n (%)	5 (26.3%)	2 (14.3%)	1 (12.5%)
Subjects with TEAE leading to discontinuation, n	0	0	0
Subjects with SAE or severe TEAE, n	0	0	0
TEAE: neutropenia, thrombocytopenia, or infections and infestations, n	0	0	0

Dose-proportional PK; trough plasma and CSF exposures above IL-1β IC90

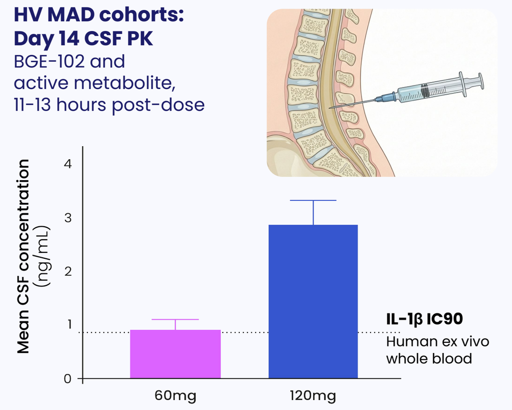
Healthy volunteer SAD cohorts: mean plasma PK
BGE-102 and active metabolite* free concentration



HV MAD cohorts: mean plasma PK at trough (pre-dose)
BGE-102 and active metabolite free concentration

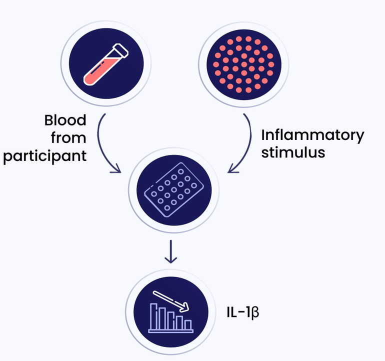


HV MAD cohorts: Day 14 CSF PK
BGE-102 and active metabolite, 11-13 hours post-dose

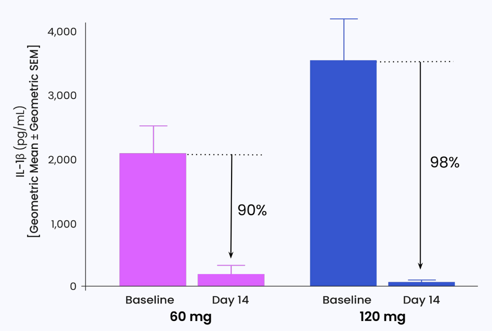


Robust target engagement: >90% 24h ex vivo IL-1β suppression

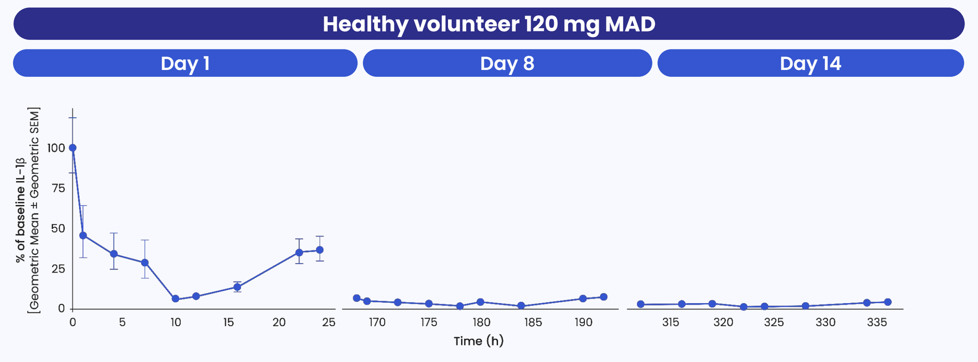
Ex vivo whole blood stimulation



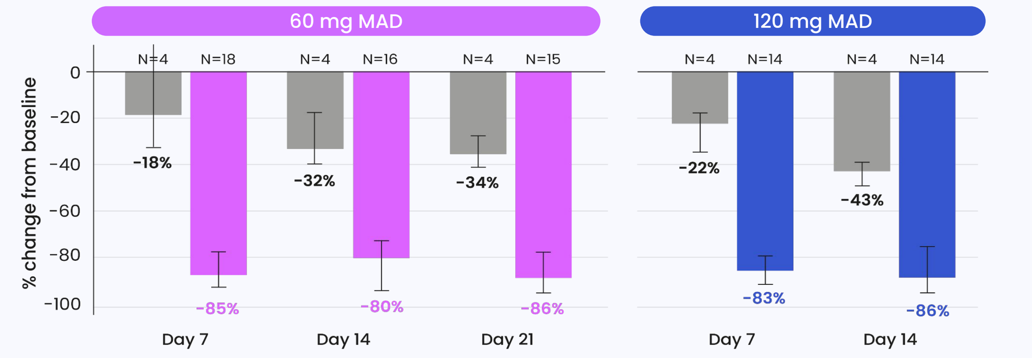
Healthy volunteer MAD cohorts: Mean IL-1β with ex vivo stimulation at trough
baseline vs Day 14

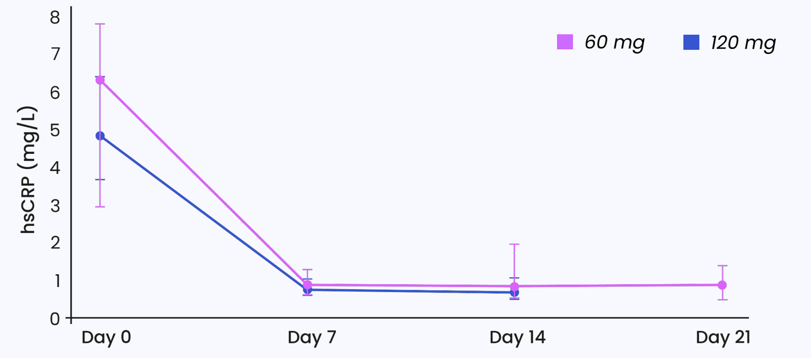


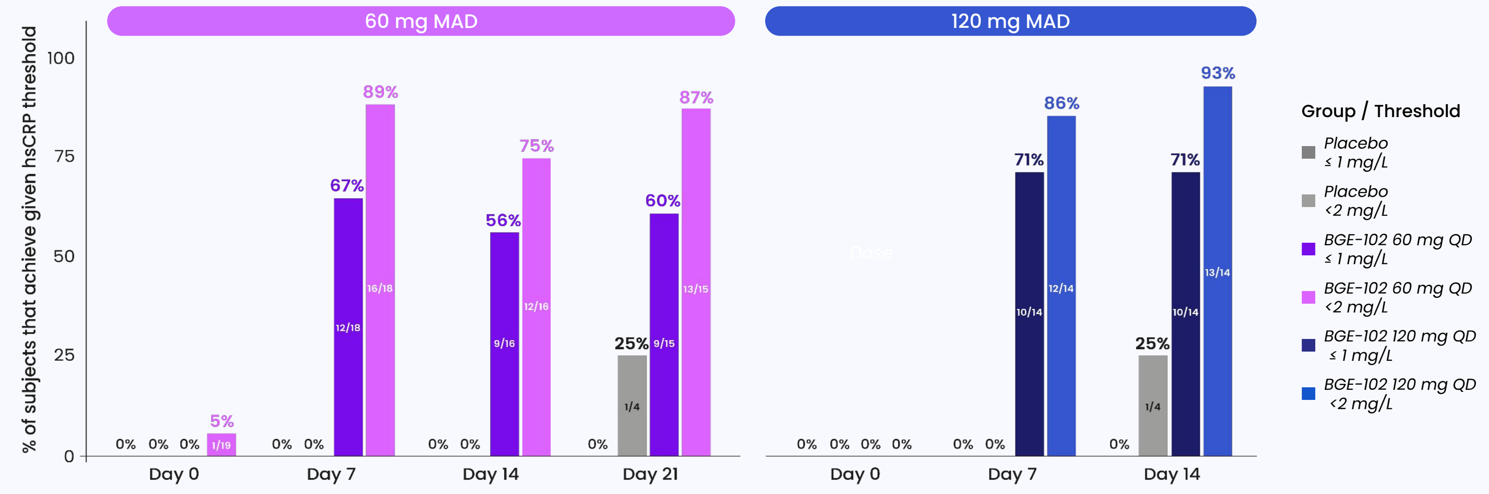
Healthy volunteer 120 mg MAD



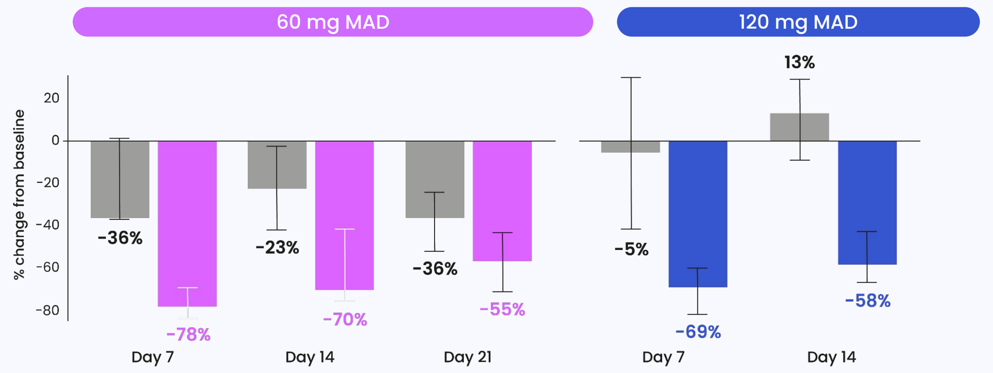
Rapid, profound, sustained hsCRP reductions in obese MAD cohorts

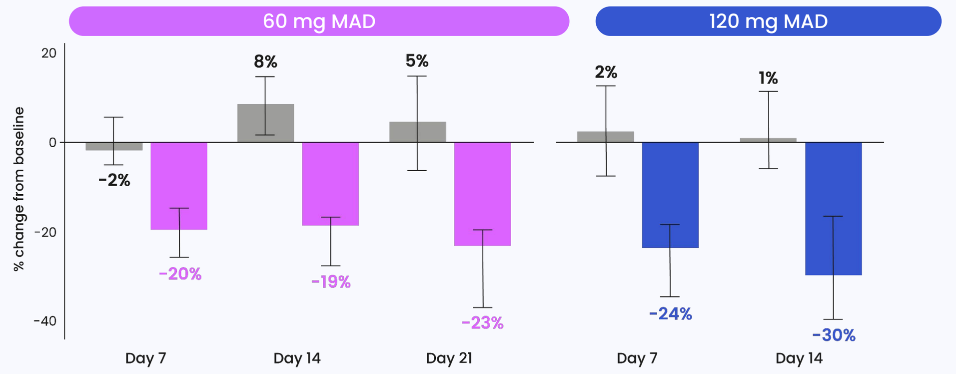






Concordant reductions in IL-6 and fibrinogen in obese MAD cohorts





Planned Phase 2 CV proof-of-concept

Key eligibility criteria
- Age 18+
- BMI 32-42
- hsCRP > 3 mg/L
- ≥1 additional CV risk factor

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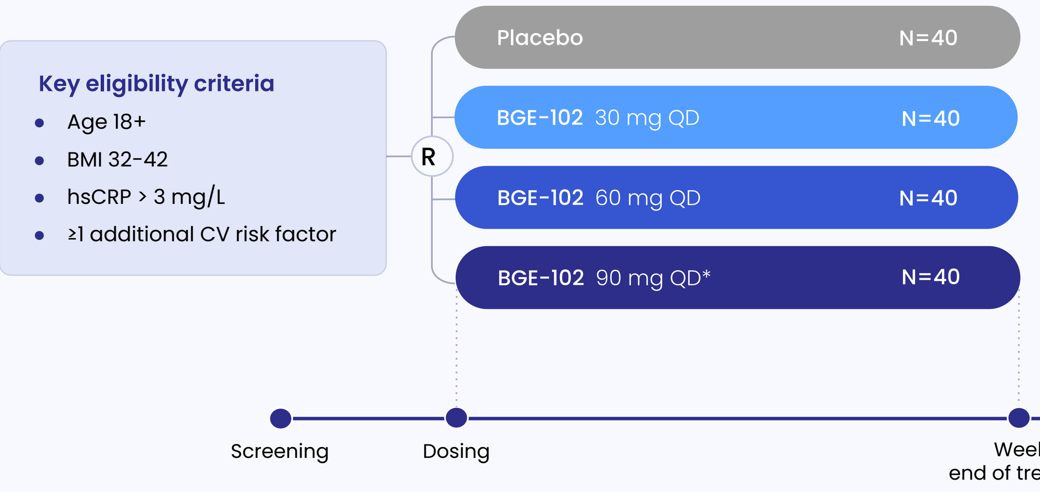

Primary endpoint
- % change in hsCRP

Key secondary endpoints
- % normalization of hsCRP (<2 mg/L and ≤1 mg/L)

Exploratory endpoints
- Additional CV risk factors (e.g., Lp(a), fibrinogen, IL-6)
- MRI imaging
- Metabolic parameters(e.g., fasting glucose, HbA1c)
- Body weight

Disclosures: All authors are employees and/or shareholders of BioAge Labs.