Focused Ultrasound-Mediated Blood-Brain Barrier Opening (FUS-BBBO) is safe, transient, and noninvasive facilitating trans-BBB drug delivery and neuroimmune modulation. It can serve as a complementary method for the treatment of Alzheimer's disease (AD), eliciting improved cognition and reduction of associated-pathology in the form of amyloid-beta plaques (Aβ) and neurofibrillary tau tangles among murine AD models and clinical patients. Establishing optimal parameters is warranted for safe and efficacious FUS-BBBO to better inform clinical adoption. Lower ultrasound frequencies are used in humans compared to rodents to account for penetration depth and attenuation of ultrasound energy through a thicker and more heterogeneous skull. It is necessary to characterize and identify differences in the mechanism of FUS-BBBO at pre-clinically and clinically used parameters.11-13-week-old female transgenic microglia-GFP expressing mice (GFP-Cx3cr1) underwent FUS using a single-element FUS transducer operated at either its fundamental (0.5 MHz) or 1.5 MHz (n=6-7/per group). In-house manufactured microbubbles were intravenously injected at 1:10 dilution. A phased array (P4-2, ATL Philips, f_c = 2.5 MHz, # of elements: 64) was used for B-mode acquisition and targeting as well as cavitation monitoring with a research ultrasound imaging system (Verasonics Vantage 256 ^{TM}). T2-weighted images were acquired to assess edema. Contrast-enhanced T1-weighted images were acquired to assess blood-brain barrier opening volume ($BBBO_v$). Mice were sacrificed at either Day 1 or post-closing. A subset of brains underwent H&E staining to evaluate safety (n=1/per group). Coronal sections corresponding to the $BBBO_V$ were stained to identify activated microglia with CD68 (abcam, ab282654). Immunofluorescence was quantified using the area of fluorescence intensity (FI) and normalized optical density (NOD) on ImageJ. The $BBBO_v$ at 0.5 MHz and 1.5 MHz was respectively 82.42 ± 21.49 mm^3 and 35.02 ± 20.12 mm^3 (P = 0.0017). Stable harmonic cavitation dose was significantly greater at 0.5 MHz compared to 1.5 MHz (P = 0.015). Red blood cell extravasation was observed at 0.5 MHz on Day 1 post-treatment. Microglial activation increased at 0.5 MHz and was quantified through area of FI and NOD (P = 0.0053, P = 0.0058). Closing occurred 6.25 ± 1.7 days and 3.83 ± 0.93 days for 0.5 MHz and 1.5 MHz. Initial $BBBO_v$ at 0.5 MHz was 2.4x larger than 1.5 MHz. Increased SCD_H indicates greater stable oscillation at the lower frequency. FUS-BBBO promoted significant activation of microglia post-closing that was enhanced at the clinically relevant frequencies. Overall, the study highlights the importance of clinical FUS-BBBO parameters and differences compared to pre-clinical applications that may be beneficial in the clinical applications and otherwise not obtained in the small animal studies.