Superior Efficacy and Selectivity of Novel Small-Molecule Kinase Inhibitors of T790M-Mutant EGFR in Preclinical Models of Non- Small Cell Lung Cancer (NSCLC)

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Abstract:

The clinical utility of approved EGFR small-molecule kinaseinhibitors is plagued both by toxicity against wild-type EGFRand by metastatic progression in the central nervous system, a disease sanctuary site. Here, we report the discovery and

preclinical efficacy of GNS-1480, GNS-1481 and GNS-1486 , three small-molecule EGFR kinase inhibitors that are selective for T790M-mutant isoforms of EGFR. GNS agents were effective in multiple mouse xenograft models of human lung adenocarcinoma(T790M-positive or -negative), exhibiting less activity against wild-type EGFR than existing approved EGFR kinase inhibitors (including osimertinib). In addition, GNS-1480 showed superior potency against intracranial metastasis of EGFR-mutant lung adenocarcinoma. Our results offer a preclinical

proof of concept for new EGFR kinase inhibitors with the potential to improve therapeutic index and efficacy against brain metastases in patients.