

## Product Data Sheet

Product Name: AMG232

Cat. No.: GC15828

### Chemical Properties

Cas. No. 1352066-68-2

Chemical Name 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid

SMILES CC(S(C[C@@H](N([C@H](C1=CC=C(Cl)C=C1)[C@@H](C2=CC=CC(Cl)=C2)C[C@]3(C)CC(O)=O)C3=O)C(C)C)(=O)=O)C

Formula C<sub>28</sub>H<sub>35</sub>Cl<sub>2</sub>NO<sub>5</sub>S M.Wt 568.55

Solubility DMF: 30 mg/ml, DMSO: 30 mg/ml, Ethanol: 30 mg/ml, Ethanol: PBS (pH 7.2) (1:2): 0.33 mg/ml  
Storage Store at -20°C, unstable in solution, ready to use.

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

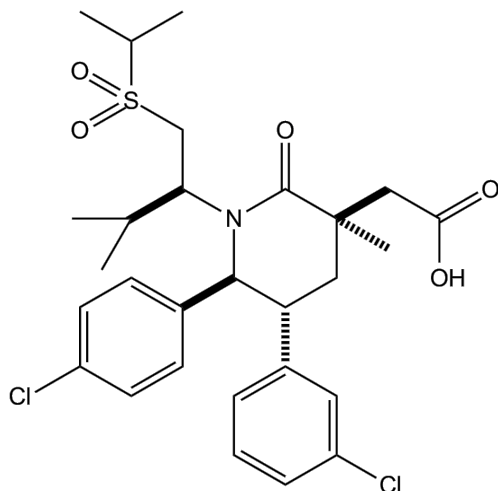
**Caution: Product has not been fully validated for medical applications. For research use only.**

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

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### Structure



### Protocol

#### Cell experiment [1,2]:

Cell lines SJSA-1, HCT116, and ACHN tumor cell lines

Soluble in DMSO. General tips for obtaining a higher concentration: Please Preparation method warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Reacting condition 0.1, 1, or 10 µmol/L, 24 hours

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**Applications** AMG 232 induced p53 signaling with an IC<sub>50</sub> of 0.6 ± 0.4 nmol/L. AMG 232 inhibits cell proliferation in p53 WT cell lines. AMG 232 treatment inhibited the growth of cells with IC<sub>50</sub> values ranging from 0.1 to 1 μmol/L. AMG 232 caused a dose-dependent accumulation of p53 and increased p21, MDM2, and PUMA proteins in both MDM2-amplified SJSA-1 cells and non-MDM2-amplified HCT116 cells. AMG 232 potentially inhibited proliferation of non-MDM2-amplified HCT116 colorectal cells.

### Animal experiment [1,2]:

**Animal models** Female athymic nude mice bearing SJSA-1 cells and HCT116 cells

**Dosage form** 10 mg/kg, 25 mg/kg, 75 mg/kg; once per day by oral gavage,

**Application** AMG 232 (10 mg/kg, 25 mg/kg, 75 mg/kg, 6 hours) treatment resulted in time- and dose-dependent induction of p21 mRNA in SJSA-1 tumor. AMG 232 treatment also caused a dose-dependent induction of p21, MDM2, and PUMA mRNA in HCT116 tumors. AMG 232 (100 mg/kg, 4 days) treatment caused cell-cycle arrest and induced apoptosis in mice bearing SJSA-1 or HCT116 tumors. AMG 232 (orally once daily) enhanced the antitumor activity of DNA-damaging cytotoxics. AMG 232 displayed robust tumor growth inhibition with an ED<sub>50</sub> of 9.1 mg/kg q.d. AMG 232 caused a dose-dependent tumor growth inhibition with an ED<sub>50</sub> of 16 mg/kg.

**Other notes** Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

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### References:

- [1]. Canon J, Osgood T, Olson S H, et al. The MDM2 inhibitor AMG 232 demonstrates robust anti-tumor efficacy and potentiates the activity of p53-inducing cytotoxic agents[J]. Molecular cancer therapeutics, 2015: molcanther. 0710.2014.
- [2]. Rew Y, Sun D. Discovery of a small molecule MDM2 inhibitor (AMG 232) for treating cancer[J]. 2014.

### Background

AMG-232 is a novel inhibitor of p53-MDM2 with IC<sub>50</sub> value of 9.2 nM [1].

Tumor protein p53 (p53) is a very unstable protein with a half-life ranging from 5 to 30 min and participates in a variety of anticancer processes, such as inducing cell apoptosis and inhibiting angiogenesis. Mouse double minute 2 homolog (MDM2), also named as E3 ubiquitin-protein ligase Mdm2, involves in mediating p53 tumor suppressor. It has been conclusively demonstrated p53 is under-expressed in tumor cells [2].

AMG-232 is a potent p53-MDM2 interaction inhibitor and is regarded as a promising drug in clinic. When tested with SJSA-1 tumor cell line, AMG-232 treatment resulted in cell-cycle arrest and inhibition of tumor cell proliferation via binding to MDM2 protein and robustly inducing p53 activity. It was shown that p53-MDM2 bond rang from a K<sub>d</sub> of 60 to 700 nM Depending on the length of p53 peptide [3].

In mouse model with SJSA-1 tumor cells subcutaneous xenograft, co-administration of AMG-232 and chemotherapies induced DNA damage and p53 activity which resulted in significantly superior antitumor efficacy and regression through arresting cell growth and inducing apoptosis [3].

### References:

- [1]. Rew, Y., et al., Discovery of AM-7209, a potent and selective 4-amidobenzoic acid inhibitor of the MDM2-p53 interaction. J Med Chem, 2014. 57(24): p. 10499-511.
- [2]. Moll, U.M. and O. Petrenko, The MDM2-p53 interaction. Mol Cancer Res, 2003. 1(14): p. 1001-8.
- [3]. Canon, J., et al., The MDM2 Inhibitor AMG 232 Demonstrates Robust Antitumor Efficacy and

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Potentiates the Activity of p53-Inducing Cytotoxic Agents. Mol Cancer Ther, 2015. 14(3): p. 649-58.

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