### AMG 232 Data Sheet

**Product Name:** AMG 232  
**Cat. No.:** HY-12296  
**CAS No.:** 1352066-68-2  
**Molecular Formula:** C28H35Cl2NO5S  
**Molecular Weight:** 568.55  
**Target:** MDM–2/p53  
**Solubility:** 10 mM in DMSO  

### BIOLOGICAL ACTIVITY:

**AMG 232** is an extremely potent inhibitor of **p53–MDM2** interaction (SPR $K_d=0.045$ nM, SJSA–1 EdU $IC_{50}=9.1$ nM).

**In Vitro:** AMG 232 (10 μM) induces p53 signaling and inhibits tumor cell proliferation in three p53 wild–type tumor cell lines (SJSA–1, HCT116, and ACHN)\(^1\). AMG 232 significantly inhibits the human MDM2–p53 interaction in the biochemical HTRF–based assay ($IC_{50}=0.6$ nM). AMG 232 potently inhibits proliferation of non–MDM2–amplified HCT116 colorectal cells in the BrdU assay ($IC_{50}=10$ nM)\(^3\).

**In Vivo:** AMG 232 (10, 25, 75 mg/kg, p.o.) activates p53 pathway activity in vivo. AMG 232 (100 mg/kg, p.o.) results in 86% TGI compared with control, and the $ED_{50}$ is 31 mg/kg in the HCT116 colorectal cancer model (KRAS mutant), and results in 97% TGI, with an $ED_{50}$ of 18 mg/kg in an A375sq2 BRAF–mutant melanoma model\(^1\). AMG 232 exhibits low clearance (<0.25 × Qh) and moderate to high oral bioavailability in mice, rats and monkeys (>42%), but high clearance (0.74 × Qh) and low oral exposure in dogs (18%)\(^2\). AMG 232 displays robust tumor growth inhibition compared to the vehicle, with an $ED_{50}$ of 9.1 mg/kg q.d. AMG 232 causes a dose–dependent tumor growth inhibition with an $ED_{50}$ of 16 mg/kg\(^3\).

### PROTOCOL (Extracted from published papers and Only for reference)

**Cell Assay:** AMG 232 is dissolved in DMSO\(^1\). Cell lines are plated in 96– or 384–well plates at optimum initial seeding densities to ensure that cells do not reach confluency by the end of the assay. The cells are treated with DMSO control or AMG 232 at various concentrations for 72 hours. CellTiter–Glo Luminescent Cell Viability or ATPlite 1step Luminescent assay kits are used to determine the numbers of viable cells. Luminescence is measured with an EnVision Multilabel Reader for each cell line at time zero (V\(_0\)) before the addition of compounds, as well as after 72 hours of compound treatment. Growth inhibition (GI) is calculated on a 200–point scale according to the following equations, where V\(_{72}\) is luminescence of DMSO control at 72 hours and TV\(_{72}\) is luminescence of the compound–treated sample: if $T_{72} > V_0$, then GI=$100 \times (1 - ((T_{72} - V_0)/V_0))$; if $T_{72} < V_0$, then GI=$100 \times (1 - ((T_{72} - V_0)/V_0))$. GI values of 0, 100, and 200 represent uninhibited cell growth (i.e., DMSO control), cell stasis, and complete cell killing, respectively. Dose–response curves are generated using XLFit software to calculate $IC_{50}$ values for AMG 232 in each cell line tested.

**Animal Administration:**\(^1\) SJSA–1 cells (5×10\(^6\) cells with Matrigel at a ratio of 2:1), NCI–H460 cells (5×10\(^6\) cells with Matrigel at a ratio of 2:1), A375sq2 (5×10\(^6\) cells with Matrigel at a ratio of 2:1), or HCT116 (2×10\(^6\) cells) are injected subcutaneously in the flank of female athymic nude mice (n=10/group). Treatment begin when tumors are established and approximately 200 mm\(^3\). AMG 232 is administered once per day by oral gavage. Cisplatin, carboplatin, doxorubicin, and CPT–11 are dosed once per week by i.p or i.v. (doxorubicin) injection. Combination treatment studies are performed in a blinded manner. Tumor dimensions are assessed twice weekly with a Pro–Max electronic digital caliper and tumor volume is calculated using the formula: length×width×height and expressed as mm\(^3\). Data are expressed as mean±SEM. Body weight is recorded twice weekly to assess tolerability. Analysis of p21 mRNA at the end of the xenograft studies is performed as described for the p21 pharmacodynamic assay.
References:


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