Osimertinib

**Cat. No.:** HY-15772

**CAS No.:** 1421373-65-0

**Molecular Formula:** C₂₈H₃₃N₇O₂

**Molecular Weight:** 499.61

**Target:** EGFR

**Pathway:** JAK/STAT Signaling; Protein Tyrosine Kinase/RTK

**Storage:**
- Powder: -20°C, 3 years; 4°C, 2 years
- In solvent: -80°C, 6 months; -20°C, 1 month

**SOLVENT & SOLUBILITY**

**In Vitro**

DMSO : 100 mg/mL (200.16 mM; Need ultrasonic)

H₂O : < 0.1 mg/mL (insoluble)

<table>
<thead>
<tr>
<th>Concentration</th>
<th>1 mg</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM</td>
<td>2.0016 mL</td>
<td>10.0078 mL</td>
<td>20.0156 mL</td>
</tr>
<tr>
<td>5 mM</td>
<td>0.4003 mL</td>
<td>2.0016 mL</td>
<td>4.0031 mL</td>
</tr>
<tr>
<td>10 mM</td>
<td>0.2002 mL</td>
<td>1.0008 mL</td>
<td>2.0016 mL</td>
</tr>
</tbody>
</table>

Please refer to the solubility information to select the appropriate solvent.

**In Vivo**

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.00 mM); Clear solution

2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.00 mM); Clear solution

**BIOLOGICAL ACTIVITY**

**Description**

Osimertinib (AZD-9291) is an irreversible and mutant selective EGFR inhibitor with IC₅₀s of 12 and 1 nM against EGFR L858R and EGFR L858R/T790M, respectively.

**IC₅₀ & Target**

<table>
<thead>
<tr>
<th>IC₅₀ &amp; Target</th>
<th>EGFR L858R</th>
<th>EGFR L858R/T790M</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 nM (IC₅₀, Enzyme assays)</td>
<td>1 nM (IC₅₀, Enzyme assays)</td>
<td></td>
</tr>
</tbody>
</table>

**In Vitro**

Osimertinib (AZD-9291) shows similar potency to early generation tyrosine kinase inhibitor (TKIs) in inhibiting EGFR...
phosphorylation in EGFR cells harboring sensitising EGFR mutants including PC-9 (ex19del), H3255 (L858R) and H1650 (ex19del), with mean IC₅₀ values ranging from 13 to 54 nM for AZD-9291. Osimertinib (AZD-9291) also potently inhibits phosphorylation of EGFR in T790M mutant cell lines (H1975 (L858R/T790M), PC-9VanR (ex19del/T790M), with mean IC₅₀ potency less than 15 nM[1].

In Vivo

The tumor-bearing mice are treated with Osimertinib (AZD-9291) (5 mg/kg/day) for one to two weeks. Within days of treatment, 5 of 5 C/L858R mice displays nearly 80% reduction in tumor volume by magnetic resonance imaging MRI after therapy with Osimertinib (AZD-9291), while 5 of 5 mice treated with vehicle shows tumor growth[1]. Osimertinib (AZD-9291) demonstrates improved rat PK, reduced hERG affinity, and improved IGF1R margins relative to the previously described compounds, and so this compound is selected for further investigation. Osimertinib (AZD-9291) also offers an additional degree of broader chemical and profile diversity when compared to the previously described lead compounds. Upon dosing Osimertinib (AZD-9291) in three efficacy models, The comparable efficacy is observed at relatively low doses (10 mg/kg per day). The excellent efficacy is also observed when Osimertinib (AZD-9291) is dosed at 5 mg/kg per day[2].

PROTOCOL

Cell Assay[1]

PC-9 cells are seeded into T75 flasks (5×10⁵ cells/flask) in RPMI growth media and incubated at 37°C, 5% CO₂. The following day the media is replaced with media supplemented with a concentration of EGFR inhibitor equal to the EC₅₀ concentration predetermined in PC-9 cells. Media changes are carried out every 2-3 days and resistant clones allowed to grow to 80% confluency prior to the cells being trypsinised and reseeded at the original seeding density in media containing twice the concentration of EGFR inhibitor. Dose escalations are continued until a final concentration of 1.5 μM ZD1839, 1.5 μM BIBW 2992, 1.5 μM WZ4002 or 160 nM Osimertinib (AZD-9291) are achieved[1].

Animal Administration[1][2]

Mice[1]
The EGFRL858R and EGFRL858R+T790M mice (male and female) are used. Osimertinib (AZD-9291) is suspended in 1% Polysorbate 80 and administered via oral gavage once daily at the doses of 7.5 mg/kg and 5 mg/kg, respectively. Mice are imaged weekly at the Vanderbilt University Institute of Imaging Science. For immunoblot analysis, mice are treated for eight hours with drug as described before dissection and flash freezing of the lungs. Lungs are pulverized in liquid nitrogen before lysis.

Rats[2]
The male RccHan:WIST rats (10-week-old) are received a single oral dose of Osimertinib (AZD-9291) (200 mg/kg). Blood glucose levels are measured using an Accuchek Active meter.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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REFERENCES
