

## Pilot Plant Production of a P2Y<sub>12</sub>-Antagonist Containing (*R*)-3-Phosphonoalanine

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**ACT-246475** is a P2Y<sub>12</sub> antagonist for inhibition of platelet aggregation that was selected for clinical development at Actelion Pharmaceuticals Ltd. It features several challenges for scale-up, like two chiral centres, the lack of solid intermediates, 18 chemical steps, and, specifically, the large scale production of enantiomerically pure non-natural amino acid (*R*)-3-phosphono alanine that was lacking a scalable access. The production of a pro-drug of **ACT-246475**, namely **ACT-281959** posed formidable challenges for the isolation and purification as it is a highly viscous oil (glassy). The evolution of the routes from Medicinal Chemistry to GMP manufacturing of **ACT-246475** is described, thereby highlighting the solutions to safely and reproducibly scale up the process. 2<sup>nd</sup> Generation processes to cut the Cost of Goods and to raise robustness and throughput are presented.

