

RESEARCH MONOGRAPH . COMPOUND PROFILE

PF-04457845

A clinical-stage FAAH inhibitor; the most thoroughly studied FAAH inhibitor in human trials, including a tragic phase 1 fatality at Bial.

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ABSTRACT

PF-04457845 (CAS 1020315-31-4; molecular formula C₂₀H₂₁F₃N₄O₃; molecular weight 422.40) is a covalent piperidine-urea FAAH inhibitor developed at Pfizer. The compound is selective for FAAH over other serine hydrolases and produces elevated plasma and brain N-acylethanolamides (anandamide, OEA, PEA) at clinical doses. Phase 1 and 2 clinical trials in osteoarthritis pain, fibromyalgia, and (more recently) cannabis use disorder have demonstrated FAAH target engagement and modest clinical effects in some indications. The compound is most associated with the broader FAAH inhibitor scrutiny following the 2016 Bial Pharmaceuticals tragedy in Rennes, where a different FAAH inhibitor (BIA-10-2474) caused one death and severe neurological injury in a phase 1 trial; the cause was attributed to off-target effects unique to BIA-10-2474, exonerating PF-04457845 specifically. Plasma half-life is approximately 14 hours. Used as the canonical clinical-stage FAAH inhibitor for translational research.

1. Compound Identification

PF-04457845 is described as selective faah inhibitor (clinical-stage). A clinical-stage FAAH inhibitor; the most thoroughly studied FAAH inhibitor in human trials, including a tragic phase 1 fatality at Bial.

1.1 Class summary

Selective FAAH inhibitor (clinical-stage)

1.2 Subtitle

A clinical-stage FAAH inhibitor; the most thoroughly studied FAAH inhibitor in human trials, including a tragic phase 1 fatality at Bial.

2. Abstract

PF-04457845 (CAS 1020315-31-4; molecular formula $C_{20}H_{21}F_3N_4O_3$; molecular weight 422.40) is a covalent piperidine-urea FAAH inhibitor developed at Pfizer. The compound is selective for FAAH over other serine hydrolases and produces elevated plasma and brain N-acylethanolamides (anandamide, OEA, PEA) at clinical doses. Phase 1 and 2 clinical trials in osteoarthritis pain, fibromyalgia, and (more recently) cannabis use disorder have demonstrated FAAH target engagement and modest clinical effects in some indications. The compound is most associated with the broader FAAH inhibitor scrutiny following the 2016 Bial Pharmaceuticals tragedy in Rennes, where a different FAAH inhibitor (BIA-10-2474) caused one death and severe neurological injury in a phase 1 trial; the cause was attributed to off-target effects unique to BIA-10-2474, exonerating PF-04457845 specifically. Plasma half-life is approximately 14 hours. Used as the canonical clinical-stage FAAH inhibitor for translational research.

3. Mechanism of Action

Covalent FAAH inhibitor; selective for FAAH over other serine hydrolases. Elevates anandamide, OEA, and PEA in plasma and brain.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

Trial doses 1 to 4 mg per oral administration daily.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Huggins JP, et al. An efficient randomised, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845 in osteoarthritic knee pain. *Pain* 2012.
2. D'Souza DC, et al. Efficacy and safety of a fatty acid amide hydrolase inhibitor (PF-04457845) in the treatment of cannabis withdrawal and dependence. *Lancet Psychiatry* 2019.
3. Kerbrat A, et al. Acute neurologic disorder from an inhibitor of fatty acid amide hydrolase. *N Engl J Med* 2016.

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