

# ISB<sup>M</sup>

## Pain killers: to evaluate possible project risks

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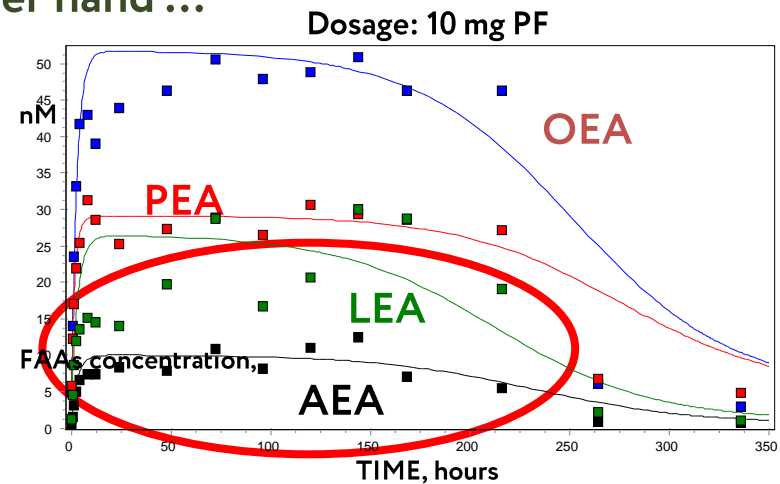
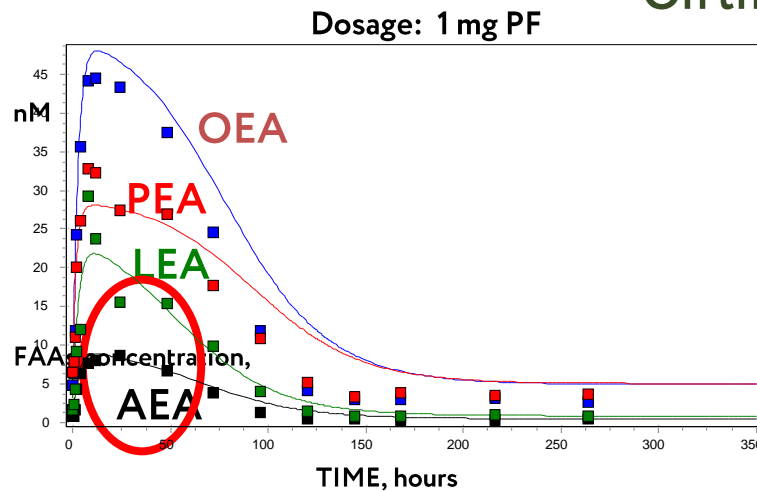
Anandamide (AEA) is natural agonist of CB1 receptor which activation results in analgesic and anti-convulsant effect.

Fatty acid amide hydrolase (FAAH) is one of the main contributor to the degradation of anandamide.

Blockage of FAAH cause the increase in concentration of AEA in blood confirming potency of target.

PF-04457845 is one of the inhibitors investigated in Pfizer in preclinical and phase I studies.

On the other hand ...



Observations :

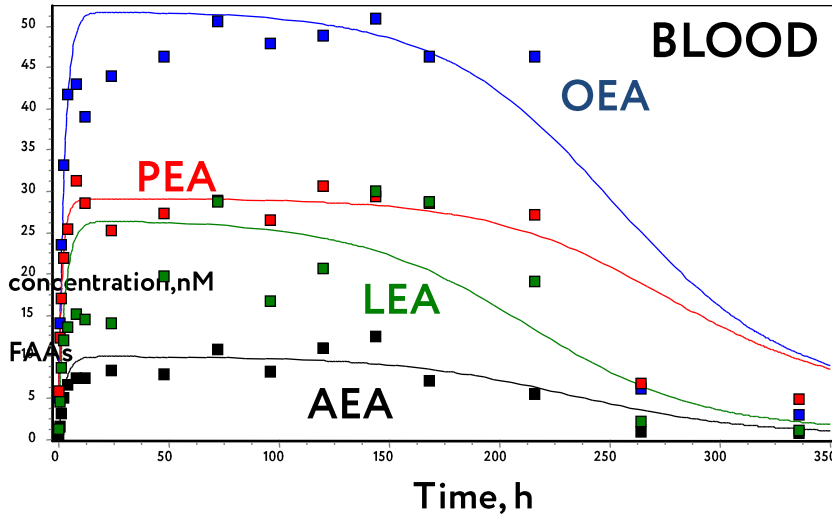
- (1) Increase in *PF*- dose does not change maximal level of biomarker concentration
- (2) Increase in *PF*- dose changes duration of the peak plateau

## Questions to address:

- Why does increase in *PF-04457845* dose changes duration of the peak plateau only and **does not** change maximal level of biomarker (AEA, OEA, ...) concentration?
- Is concentration of AEA after *PF-04457845* administration enough to distinguish therapeutic effect?
- If not how to achieve the higher level of AEA in CNS?

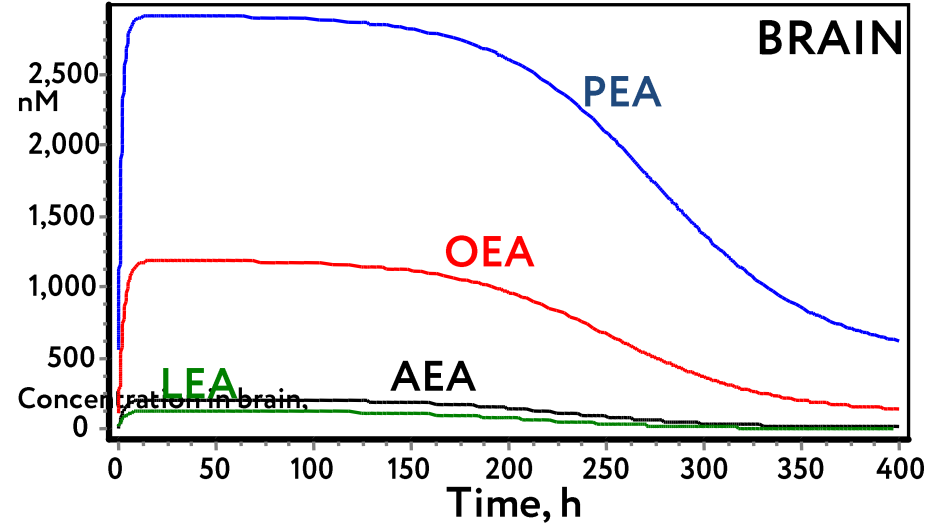
# Examples of model verifications and simulations

Dosage: 10 mg PF

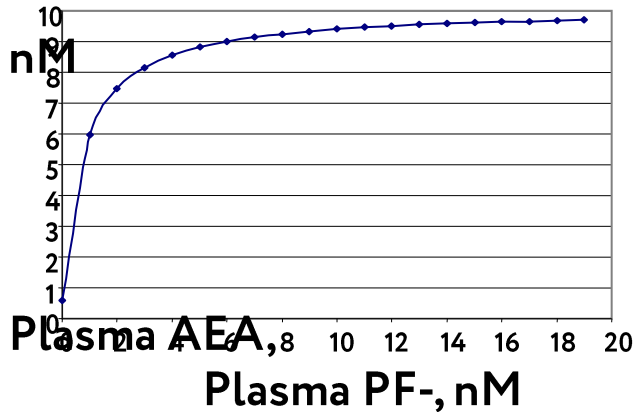


Time dependence of ethanolamides at 10 mg single dose of PF-04457845: clinical trial data VS simulations

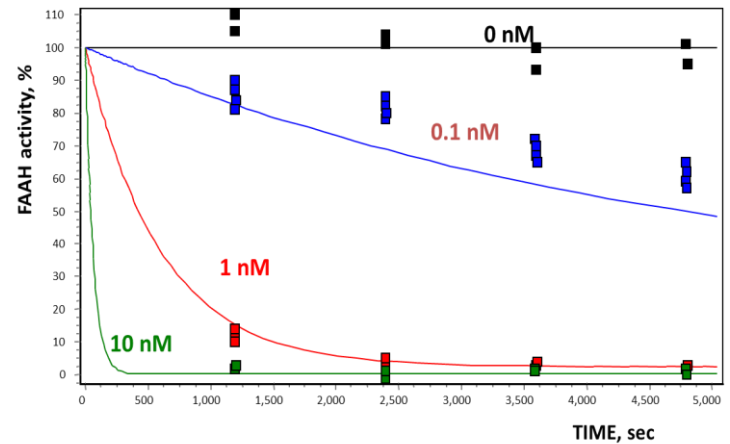
Dosage: 10 mg PF



Predicted concentration of ethanolamides in human brain on time at 10 mg single dose of PF-04457845



Predicted concentration-effect relationships of PF-04457845



Ex vivo data measured in experiments with human blood vs modeling curves

**Objective of the study** is to develop QSP model integrating both “in-house” preclinical and clinical results and published data on endocannabinoids metabolism...

**CONCLUSION:** The developed systems pharmacology model satisfactory reproduces preclinical and clinical data on PF-04457845. The model simulates different treatment regimes and effectiveness of FAAH inhibitors on the basis its PK and binding properties.

**...to answer the questions:**

- Why does increase in *PF-04457845* dose changes duration of the peak plateau only and **does not** change maximal level of biomarker (AEA,OEA,...) concentration?

**CONCLUSION:** AEA is subject to an **alternative clearance process that limits the AEA increase** following FAAH inhibition. On the basis of our data and the available literature we speculate that this process is due to the enzyme N-acyl ethanolamine hydrolysing acid amidase (**NAAA**).

- How to estimate the concentration of anandamide in human CNS and tissues on the basis of biomarkers levels in blood?

**CONCLUSION:** QSP model allows to predict AEA concentration in CNS and tissues on the basis of biomarker levels in blood and drug PK.

- Is concentration of AEA after PF-04457845 administration enough to distinguish therapeutic effect?

**CONCLUSION:** The predicted occupancy of CB1 receptor changes from 3% to 26% after drug (PF-) administration with high doses that possibly not enough for therapeutic purposes.

- If not how to achieve the higher level of AEA in CNS?

**CONCLUSION:** Inhibition of alternative clearance processes (NAAA??) allows to increase AEA level in CNS. A set of experiments was proposed to check the high NAAA activity after FAAH inhibition

## Development of PF-04457845 has been terminated



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[www.elsevier.com/locate/pain](http://www.elsevier.com/locate/pain)

An efficient randomised, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee

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### ABSTRACT

The effect of PF-04457845, a potent and selective fatty acid amide hydrolase-1 (FAAH) inhibitor, on pain due to osteoarthritis of the knee was investigated in a randomised placebo and active-controlled clinical trial. The trial involved 2 periods (separated by a 2-week washout) consisting of a 1-week wash-in phase followed by 2 weeks double-blind treatment. Patients received single-blind placebo throughout the wash-in and washout periods. Patients were randomised to receive either 4 mg q.d. PF-04457845 fol-

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