ISB[M]

Pain killers: to evaluate possible project risks

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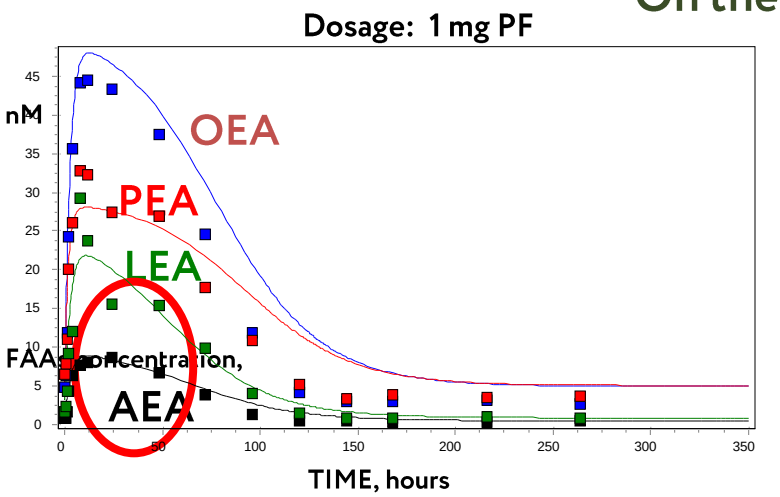
Anandamide (AEA) is natural agonist of CB1 receptor which activation results in **analgesic and anti-convulsant effect.**

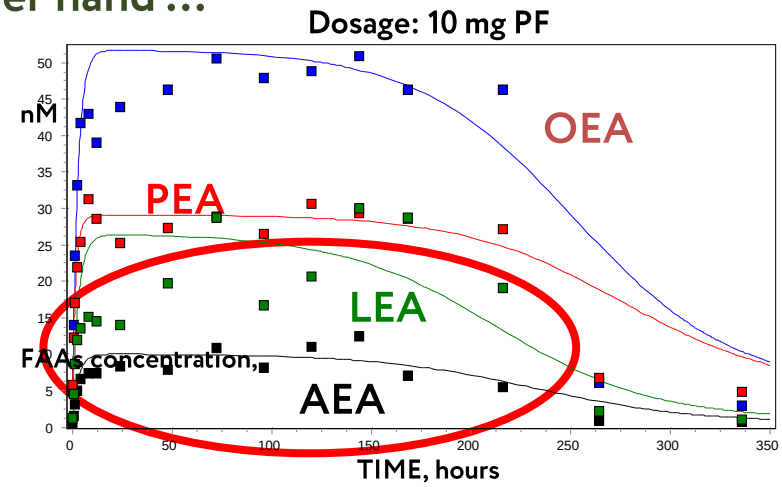
Fatty acid amide hydrolase (FAAH) is one of the main contributor to **the degradation of anandamide.**

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

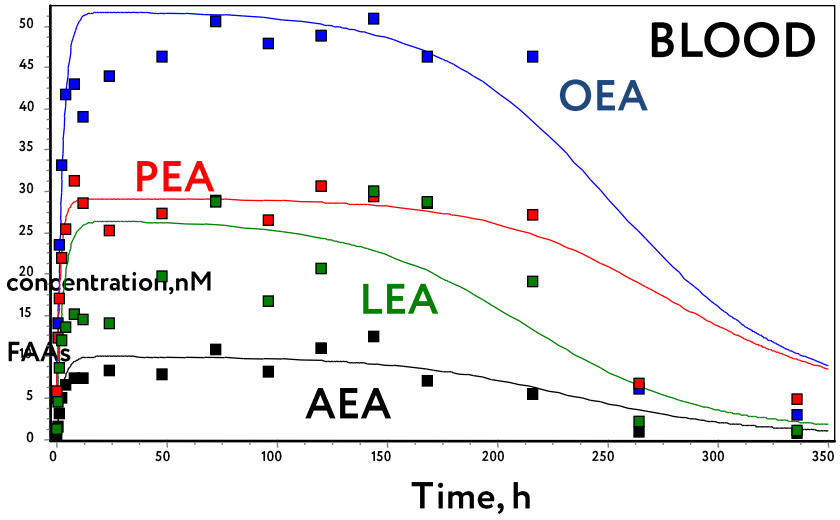
(2) Increase in *PF-* dose changes duration of the peak plateau

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?

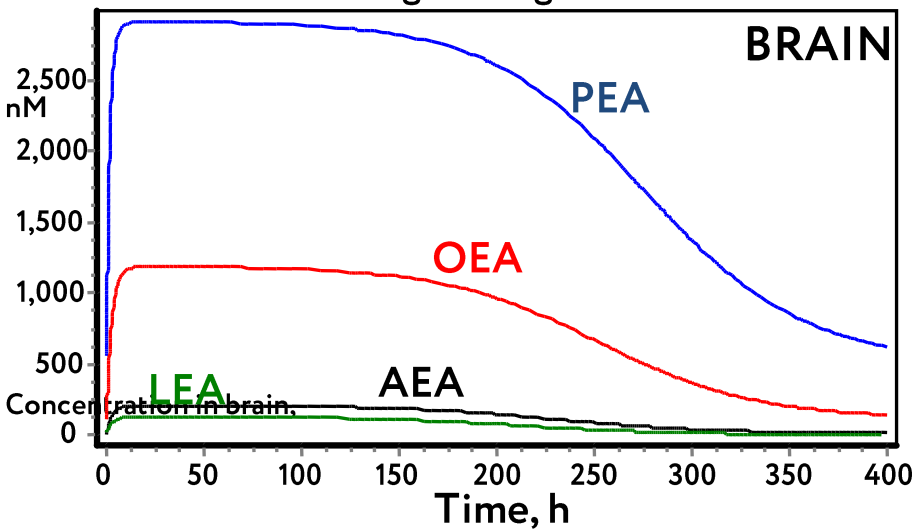
Examples of model verifications and simulations

Dosage: 10 mg PF

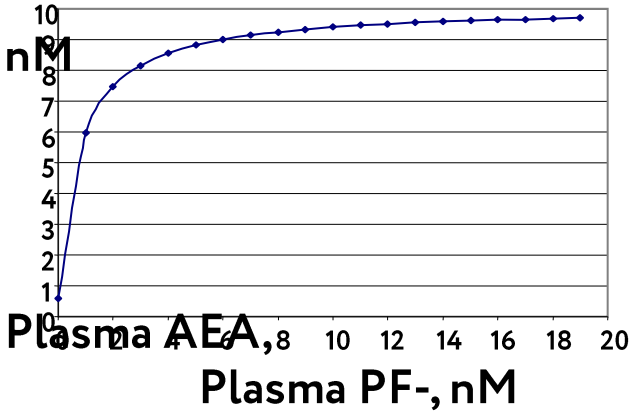


Time dependence of ethanolamides at 10 mg single dose of PF-04457845: clinical trial data VS simulations

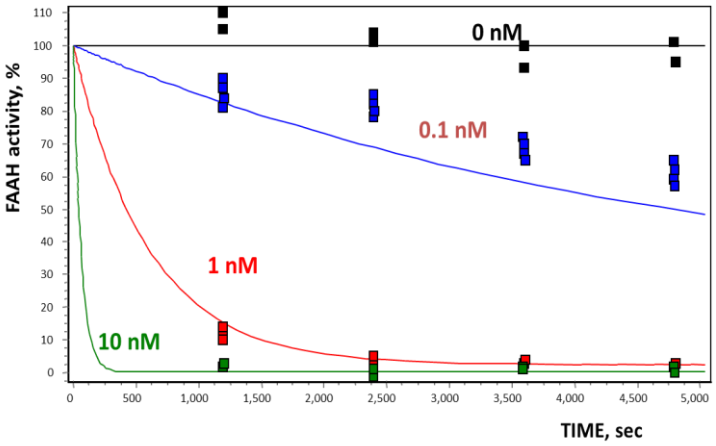
Dosage: 10 mg PF



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-acylethanolamine 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.

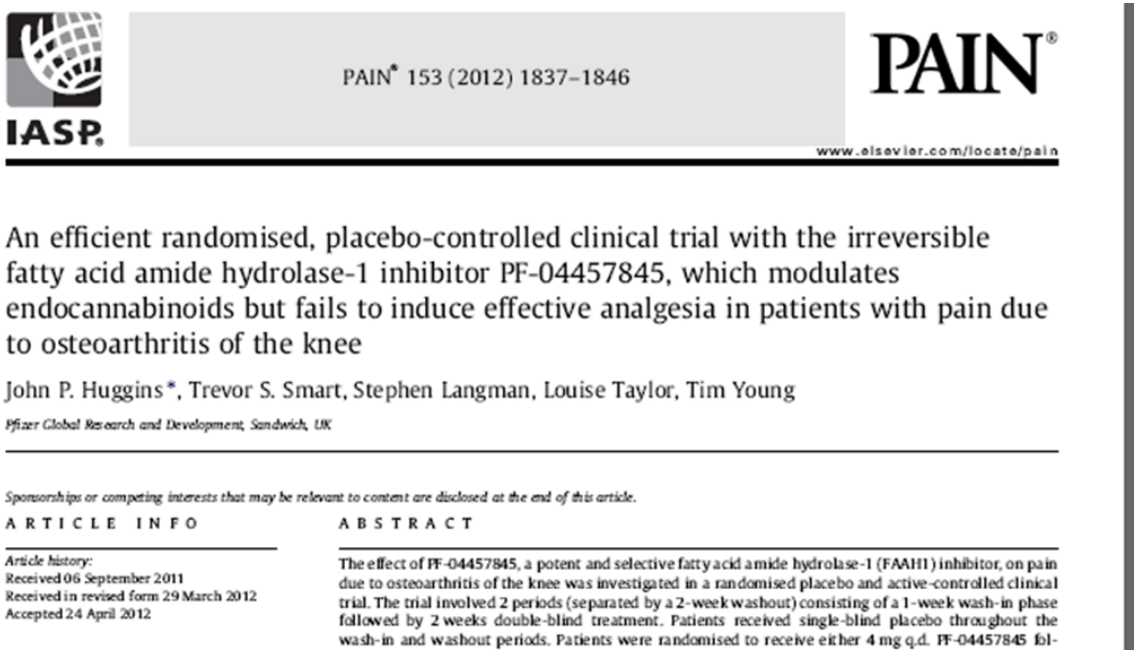
- Is concentration of AEA after PF-04457845 administration enough to distinguish therapeutic effect?

  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 inhibitio

Development of PF-04457845 has been terminated



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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 (FAAH1) 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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