

A comprehensive preclinical characterization of irafamdastat (BMS-986368), a first-in-class, oral, dual inhibitor of fatty acid amide hydrolase and monoacylglycerol lipase

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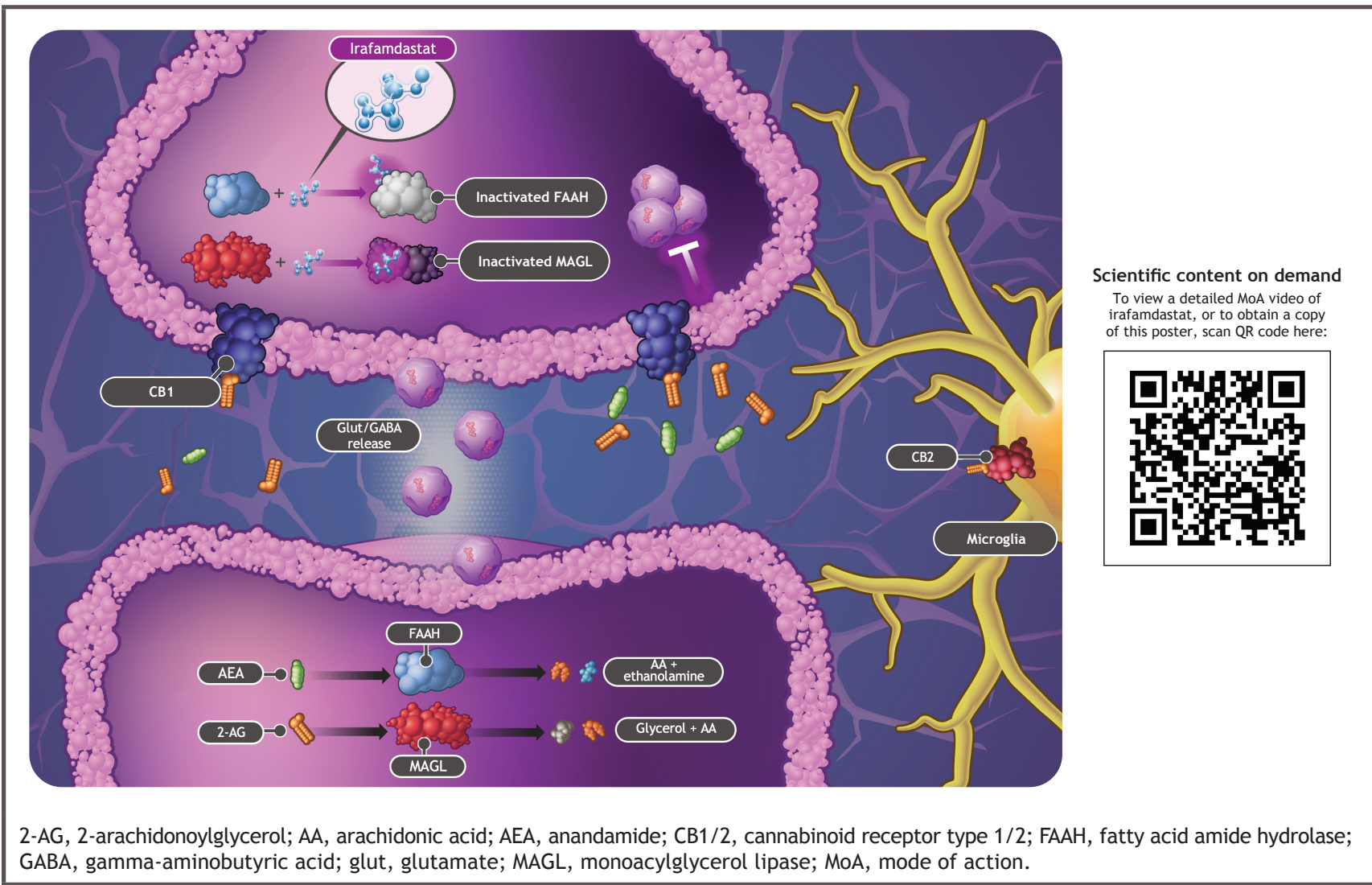
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^aAt the time of the study.

Background

- Agitation is a common and disruptive symptom of Alzheimer’s disease (AD), occurring in 45%-75% of patients¹⁻³
- Untreated agitation is associated with decline in cognition and independence,⁴ decreased quality of life,^{5,6} greater costs of care,⁷ and an increased risk of institutionalization and early death⁷
- Limited treatments are approved for AD-related agitation,^{8,9} highlighting the need for alternative options with improved side-effect profiles
- The primary endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) act as agonists of the cannabinoid type-1 and type-2 receptors (CB1 and CB2) to regulate neurotransmission and reduce neuroinflammation^{10,11}
- Low levels of endocannabinoids, such as AEA and 2-AG, can lead to neuronal hyperexcitability,¹² which is observed in many neurological conditions^{13,14} and may contribute to symptoms including AD agitation¹³
- The 2 enzymes primarily responsible for the degradation of AEA and 2-AG are fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively¹⁵
- Irafamdastat (BMS-986368) is a first-in-class, orally bioavailable, centrally penetrant, covalent, dual inhibitor of FAAH and MAGL¹⁶ (Figure 1)
- Via dual inhibition of FAAH and MAGL enzymes, irafamdastat reduces the degradation of AEA and 2-AG
- Increased levels of these primary endocannabinoids facilitate CB1 and CB2 signaling, which modulates neuronal hyperexcitability
- In preclinical models, inhibition of FAAH and MAGL significantly reduced neuronal hyperexcitability and the associated symptoms¹⁷⁻¹⁹
- Therefore, dual inhibition of FAAH and MAGL with irafamdastat may enhance endocannabinoid signaling to reduce neuronal excitability and represents a potential treatment strategy for AD agitation
- Here, we present the preclinical characterization of irafamdastat

Figure 1. Irafamdastat MoA



Methods

- In vitro and in vivo FAAH/MAGL inhibition was measured by activity-based protein profiling
- In vivo biochemical activity was evaluated in naïve female cynomolgus monkeys after single (0.01-3 mg/kg) and 5-day repeat oral dosing of irafamdastat (0.1-3 mg/kg, administered once daily), assessing plasma AEA, whole-blood 2-AG levels, and FAAH/MAGL inhibition
- Central target occupancy was assessed by positron emission tomography using [¹¹C]JMK-3168 (reversible FAAH tracer), [¹⁸F]MNI-788 (irreversible MAGL tracer), and [¹⁸F]MNI-1188 (reversible MAGL tracer) in rhesus monkeys treated with 0.001-0.5 mg/kg irafamdastat
- In vitro and in vivo studies were conducted to characterize the absorption, pharmacokinetics, distribution, metabolism, and excretion of irafamdastat
- The antiseizure and antiepileptogenic activity of irafamdastat at 2-30 mg/kg was determined using the pentylenetetrazole seizure model
- Toxicity of irafamdastat was assessed in rats for 6 months at doses of 0, 0.5, 2, or 5 mg/kg/day and cynomolgus monkeys at doses of 0, 0.5, 2.5, or 10 mg/kg/day for 9 months, respectively, both via oral gavage

Results

Molecular properties

- Irafamdastat is a small molecule with a molecular weight of 438.15 Da and a logD_{7.4} of 3.76 (Figure 2; Table 1)

Figure 2. Structure of Irafamdastat

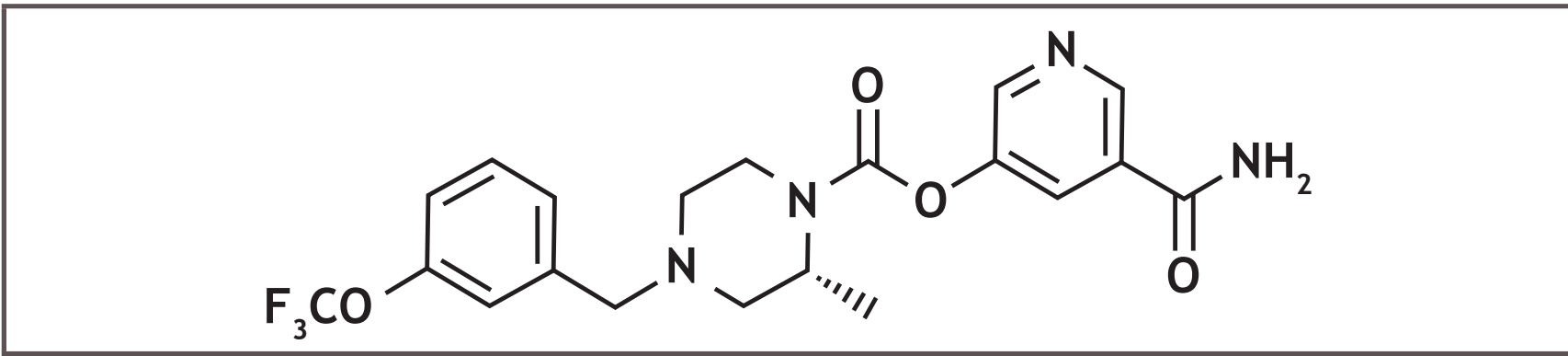


Table 1. Molecular characteristics of irafamdastat

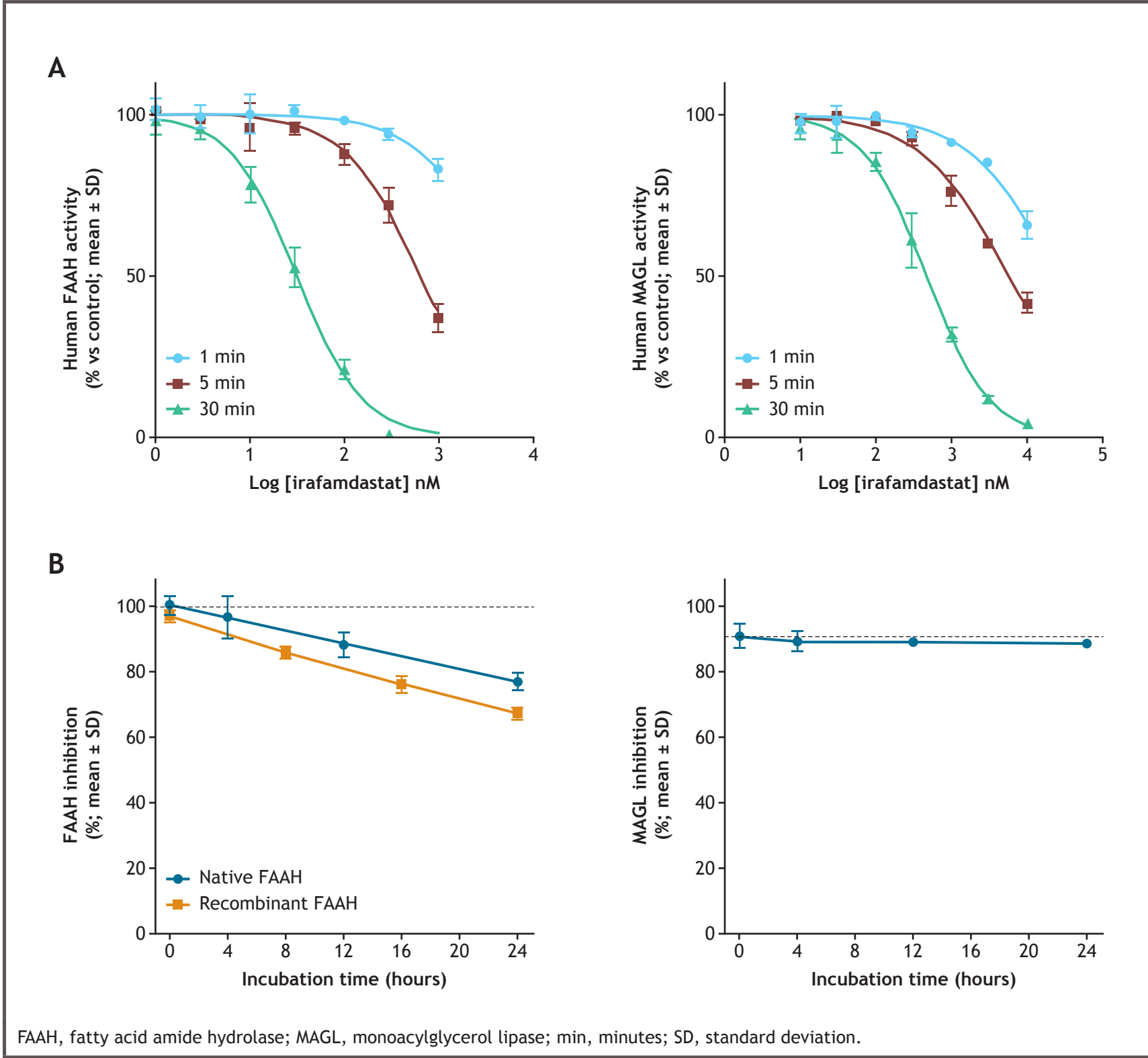
Molecular characteristic	Value
Chemical properties	
Molecular weight	438.15
pKa	6.67 (calculated); 5.79 (measured)
LogD _{7.4}	3.76 (measured)
Solubility	
pH (3, 4, 6, 7, 8)	3.3, 1.0, 0.021, 0.007, 0.007
FaSSiF V2 (mg/mL)	0.063
FeSSiF V2 (mg/mL)	1.0
Permeability	
PAMPA	P _{app} :13.2, P _{ss} :9.1 x 10 ⁻⁶ cm/s; efflux ratio = 0.69

FaSSiF, fasted state simulated intestinal fluid; PAMPA, parallel artificial membrane permeability assay; pKa, acid dissociation constant.

In vitro target inhibition

- FAAH and MAGL inhibition by irafamdastat was time-dependent and irreversible (30-minute half-maximal inhibitory concentration [IC₅₀]: FAAH, 0.032 µM; MAGL, 0.48 µM) (Figure 3A-B)
- IC₅₀ values decreased 147-fold (FAAH) and 51-fold (MAGL) with longer preincubation, indicating time-dependent covalent inhibition
- The majority of the FAAH-inhibitor adduct remained stable over 24 hours, while the MAGL-inhibitor adduct was highly stable over the same period

Figure 3. Time-dependent (A) and irreversible (B) inhibition of FAAH/MAGL activity by irafamdastat in vitro



In vivo biochemical activity

- Naïve cynomolgus monkeys (N = 4) received oral irafamdastat (0.1, 0.3, 1, or 3 mg/kg) or vehicle as a single or repeat dose for 5 days
- At 4 hours post-treatment, irafamdastat elevated plasma AEA 4.1-fold and 9-fold at doses of 0.1 mg/kg and 0.3-3.0 mg/kg, respectively, after single dosing vs vehicle; a similar pattern was observed on repeat administration (Figure 4A-B)
- Irafamdastat ≥ 0.3 mg/kg was required to increase 2-AG up to 10.4-fold after single or repeat administration vs vehicle (Figure 4C-D)
- No accumulation of AEA and 2-AG was observed over the 5-day dosing period
- A follow-on study was conducted in the same animals to determine the response to single oral administration of lower doses of irafamdastat (0.01, 0.03, 0.06, and 0.1 mg/kg) after a 7-day washout period
- Irafamdastat 0.01-mg/kg dose led to a moderate increase in plasma AEA (1.6-fold), and 0.03-0.1 mg/kg doses increased plasma AEA by 3.9- to 4.6-fold (Figure 4E), consistent with ≥ 32% inhibition of FAAH enzyme activity in peripheral blood mononuclear cells (Figure 5A and C)
- No elevation of circulating 2-AG levels (Figure 4F) or measurable inhibition of MAGL enzyme activity (Figure 5B, D-G) was observed at irafamdastat ≤ 0.1 mg/kg

Figure 4. Effects of single and repeat oral administration of irafamdastat on circulating levels of AEA and 2-AG in naïve cynomolgus monkeys

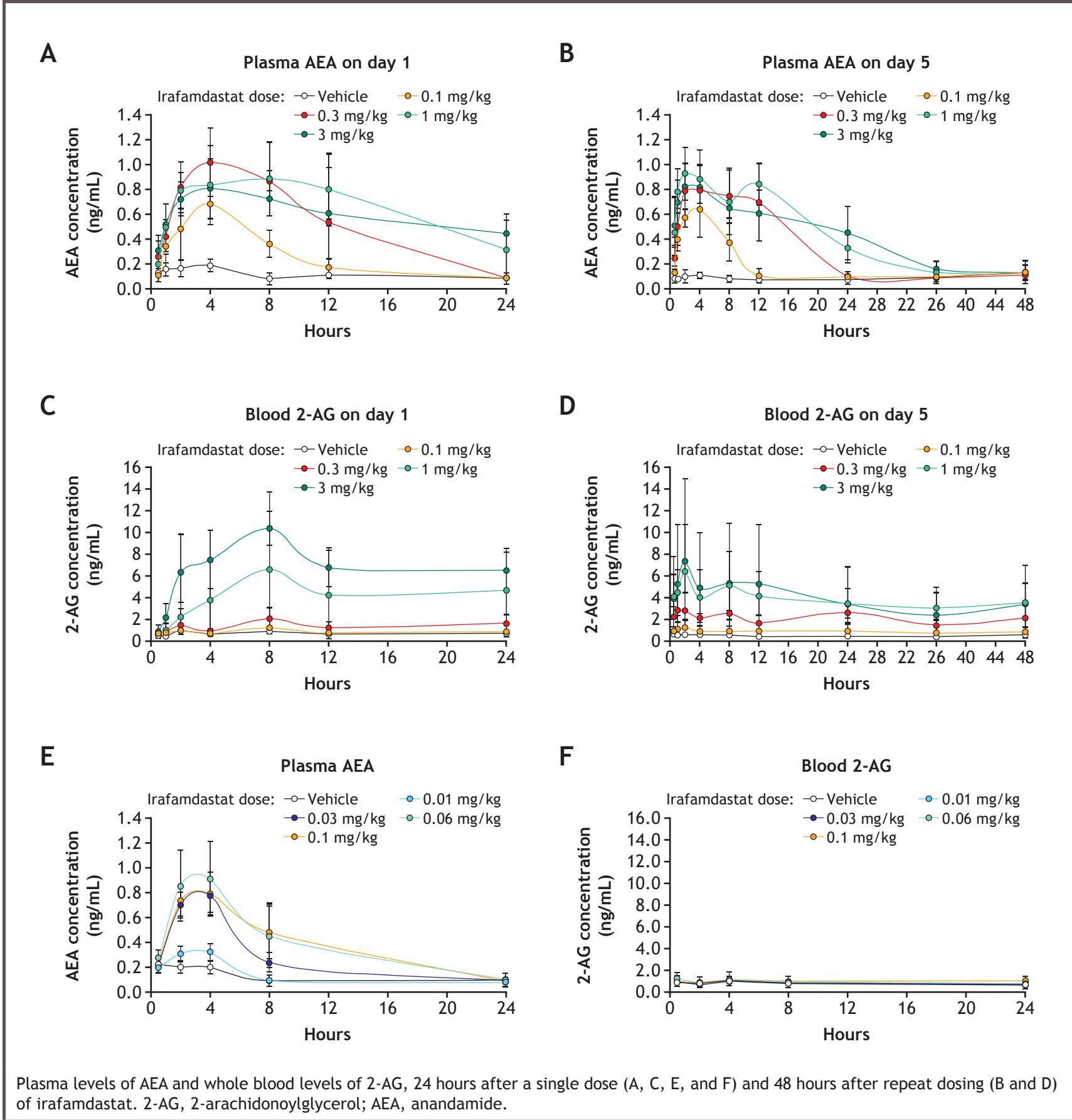
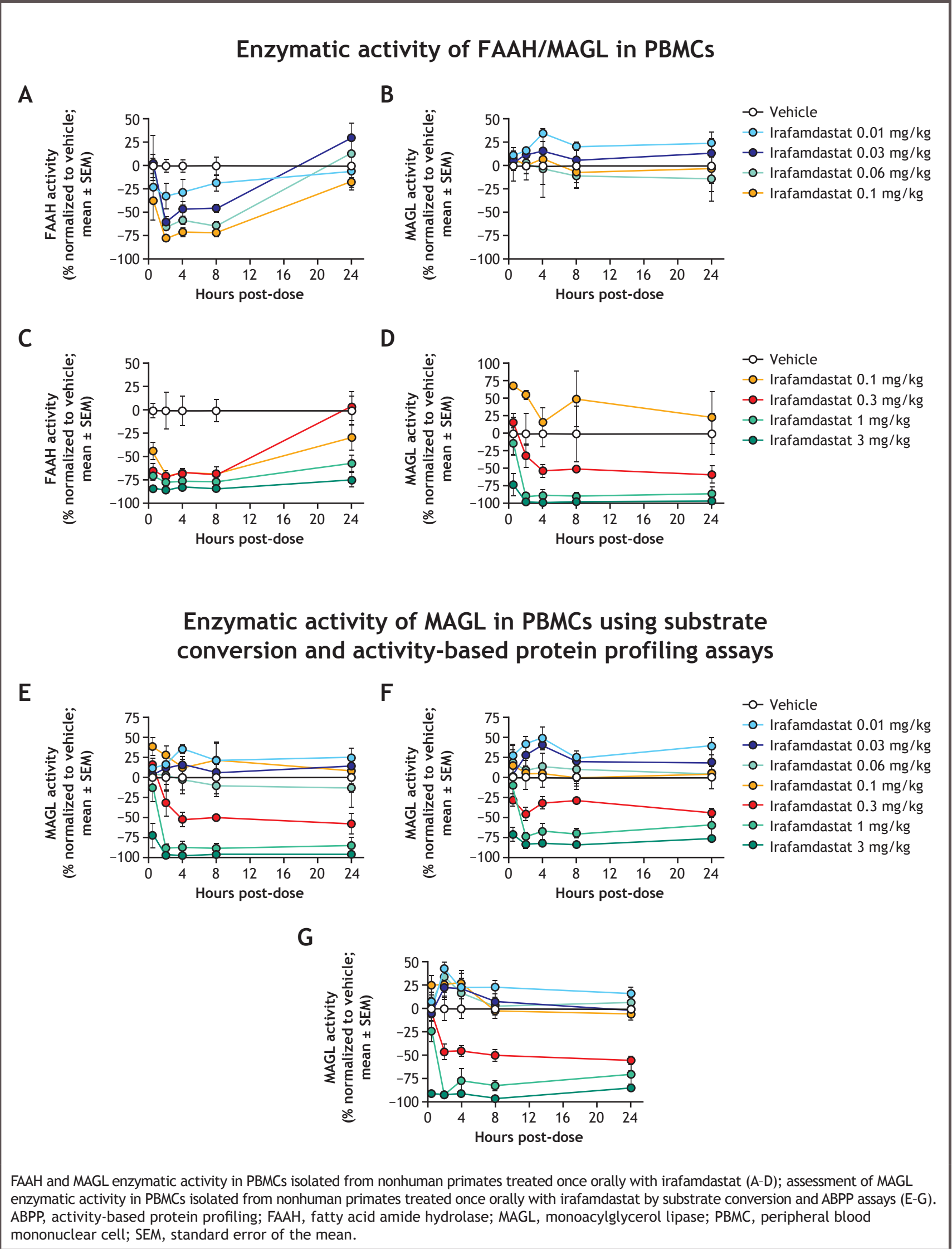


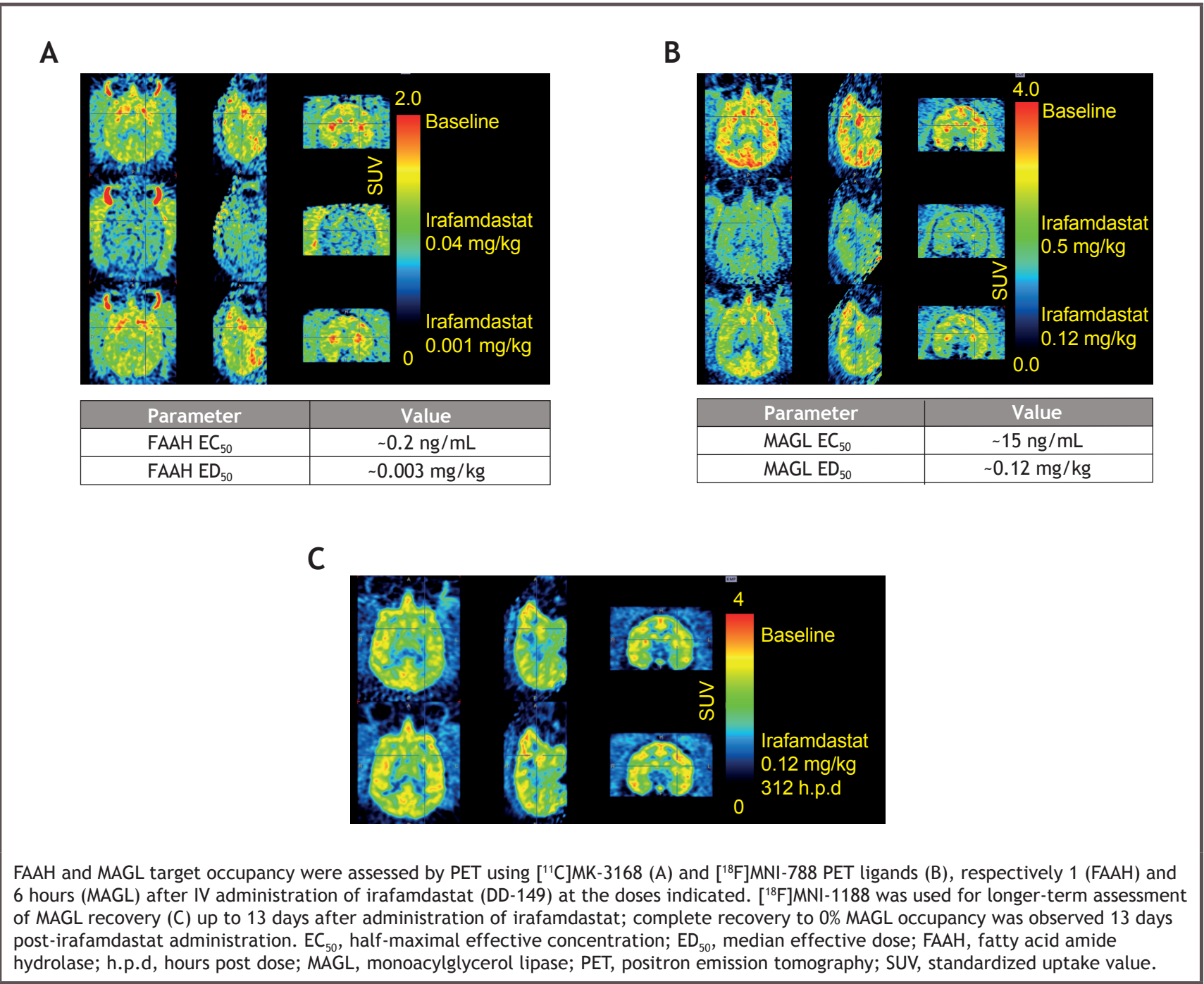
Figure 5. FAAH/MAGL activity in PBMCs from cynomolgus monkeys after a single oral dose of irafamdastat



Central target occupancy

- In rhesus monkeys, 50% central target occupancy was achieved at plasma concentrations of ~0.2 ng/mL and ~15 ng/mL, and single-dose median effective dose values of ~0.003 mg/kg and ~0.12 mg/kg for FAAH and MAGL, respectively (Figure 6A-B)
- Central MAGL target occupancy exhibited 50% recovery on day 5 and full recovery ≤ 13 days post-dose (Figure 6C)

Figure 6. Central target occupancy evaluated by PET after a single oral dose of irafamdastat in rhesus monkeys



Pharmacokinetic characteristics

- Oral bioavailability of irafamdastat was ≥ 60% at ≥ 2 mg/kg in Sprague Dawley rats and 47%-56% and 82%-88% at 2.5 mg/kg and 50 mg/kg, respectively, in cynomolgus monkeys, with no sex differences observed
- A circulating inactive metabolite, ABD-117558, was observed as a major metabolite in rats (metabolite-to-parent exposure ratio: 0.54-0.88) and a minor metabolite in monkeys (metabolite-to-parent exposure ratio: 0.03-0.08)
- In cynomolgus monkeys (1 mg/kg IV), clearance was 529-555 mL/h/kg, volume of distribution was 1.7-1.9 L/kg, and half-life was 2.2-2.9 hours

Plasma protein binding

- Plasma protein binding was > 92% with no saturation in mouse, rat, female rabbit, dog, monkey, and human plasma
- Irafamdastat partitioned into blood cells, with blood-to-plasma concentration ratios of 0.88, 0.79, and 0.67 in rat, monkey, and human blood, respectively

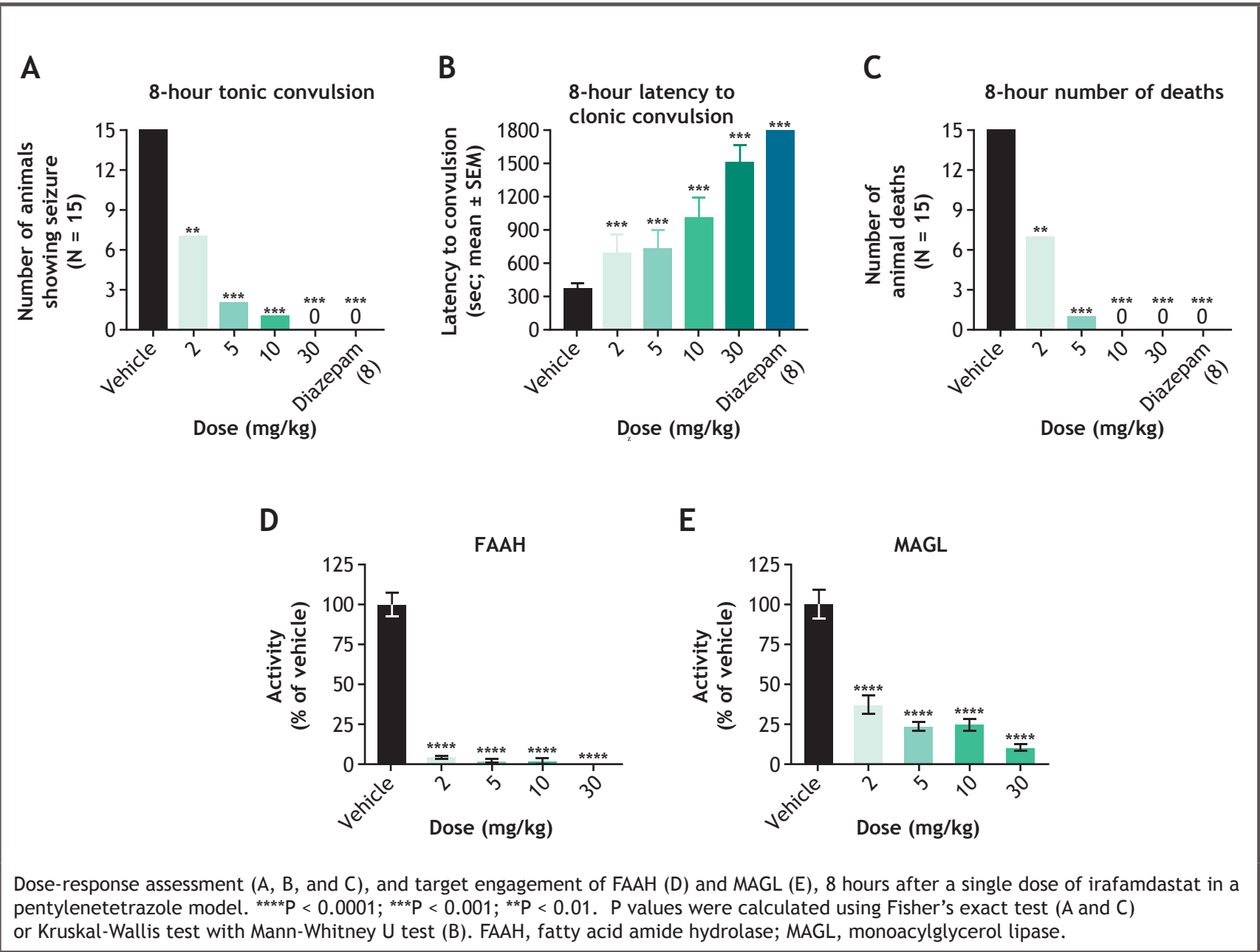
Metabolism

- The pathways involved in metabolism of irafamdastat across all species included ester and amide hydrolysis, multiple oxidations, dehydrogenation, sulfation, and glucuronidation of oxidized metabolites and a combination of these pathways
- CYP3A4 and CYP3A5 were identified as the primary isozymes involved in the metabolism of irafamdastat, with minor contributions from CYP2B6, 2C19, and 2D6
- Liquid chromatography-mass spectrometry analysis found that irafamdastat is primarily excreted in bile, while urinary excretion is a minor route

Efficacy

- Antiseizure and antiepileptogenic activity was observed in all models assessed, including electroconvulsive shock (ECS) threshold and maximal ECS tests in the pentylenetetrazole seizure model (Figure 7A-C)
- Activity was associated with ≥ 96% inhibition of FAAH and ≥ 63% inhibition of MAGL in the central compartment (Figure 7D-E)
- The same dose of irafamdastat was also effective in a 21-day rat amygdala electrical kindling model (reduced seizure activity and amygdala and cortical after-discharge activity; data not shown)

Figure 7. Antiseizure activity of irafamdastat at 8 hours post-dose in the pentylenetetrazole model



Nonclinical Safety

- Irafamdastat was well tolerated by rats for 6 months at doses ≤ 5 mg/kg/day and by cynomolgus monkeys for 9 months at doses ≤ 10 mg/kg/day, both via oral gavage
- No irafamdastat-related mortality was observed at any dose evaluated
- There were no effects on veterinary physical, ophthalmological, and electrocardiogram examinations, and no changes detected in functional observational battery parameters, body weight, food consumption, clinical pathology, urinalysis, gross observations, organ weights, or histopathology at any dose

Conclusions

- Irafamdastat is a first-in-class, orally bioavailable, centrally penetrant, covalent, irreversible dual FAAH/MAGL inhibitor
- In vitro and in vivo data demonstrate that irafamdastat potently and irreversibly inhibits FAAH and MAGL
- Irafamdastat binds to FAAH and MAGL in the central compartment in vivo, which leads to increased AEA and 2-AG
- Nonclinical pharmacokinetic studies show that irafamdastat has good oral bioavailability, is well distributed, and has a moderate-long half-life
- Irafamdastat had consistent antiseizure and antiepileptogenic activity in all models tested, suggesting potential relevance to hyperexcitability-driven symptoms including AD agitation
- Irafamdastat was well tolerated at all doses tested in long-term toxicity studies in rats and monkeys
- Irafamdastat is under phase 2 investigation for the treatment of agitation in AD (BALANCE-AAD-1; NCT06808984) and other neurologic hyperexcitability disorders

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