The BIAL 10-2474 Accident : facts of public knowledge

Phase I Club, 22 March 2016, Paris

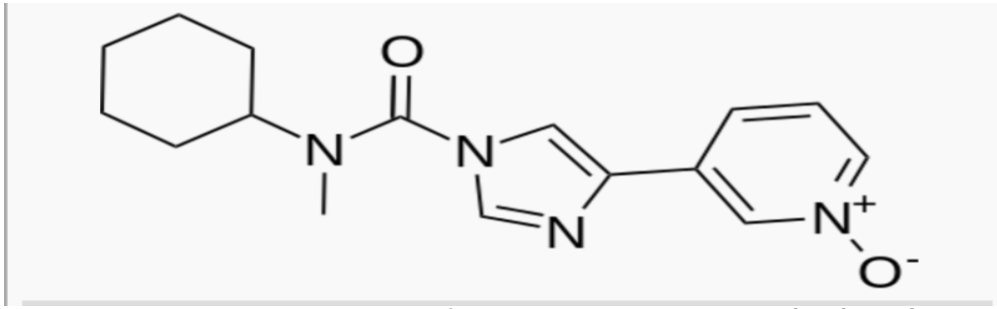
The Biotrial Team

Overall Status of Study and Drug

- First in Man with sequential arms: Single Ascending Dose, food effect, Multiple Ascending Dose, Pharmacodynamic arm
- ANSM authorization: June 26,2015
- CPP (Ouest VI) approval: July 3,2015
- Me-too drug enzyme inhibitor , 7th of the same class
- Small molecule , no safety issue with any drugs of the same class, some discontinued for lack of efficacy (e.g. PF-04457845)
- Not in the definition of EMA 2007 Guidance for « high risk compounds » following Tegenero

The Compound

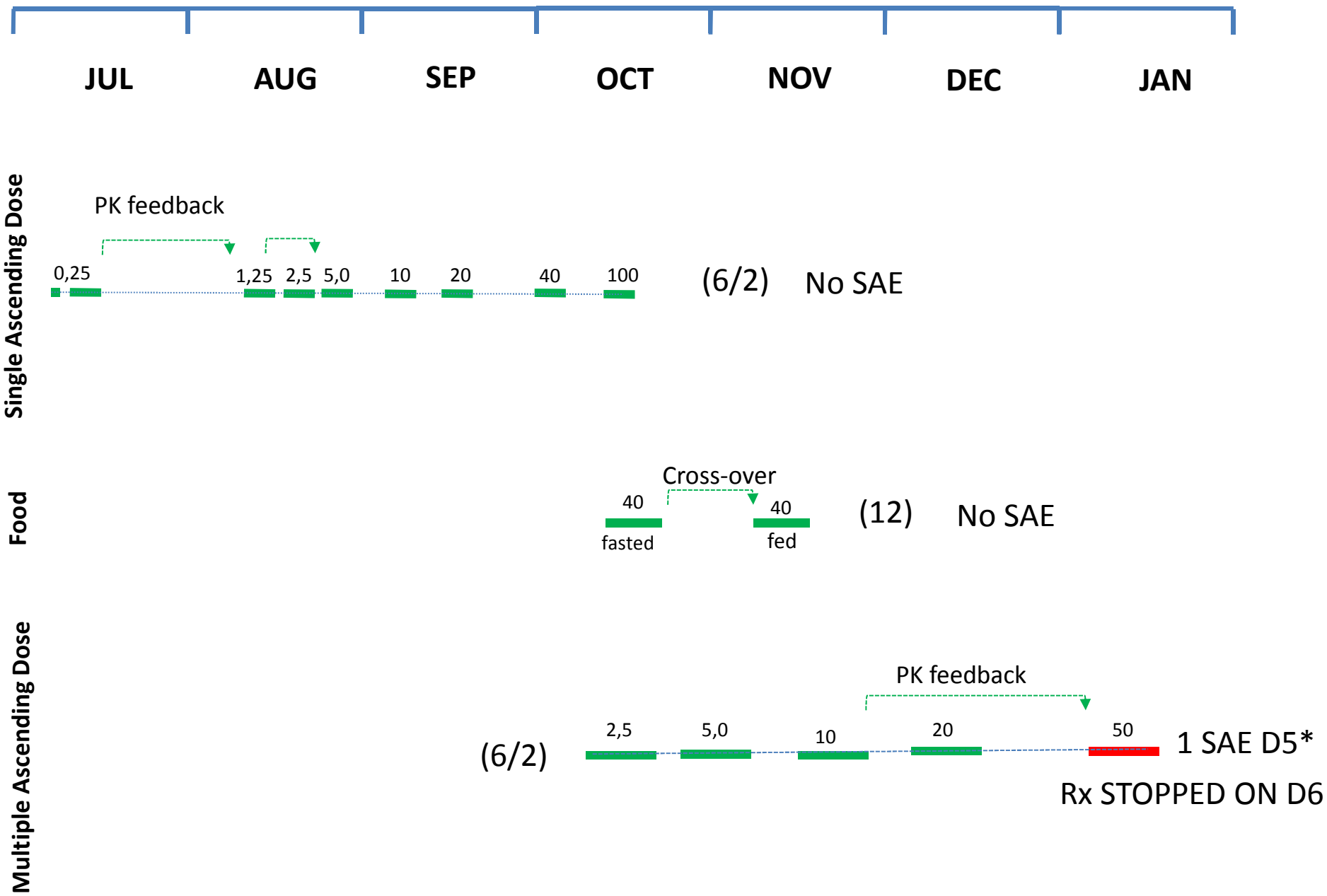
- BIA 10-2474 a Fatty Acid Amide Hydrolase inhibitor (BJCP)



- Broad patent covering many diseases; FIM only looking at safety, tolerability and PK with a supplementary pharmacodynamic arm at the end;
- Low potency drug **micromolar** inhibition in rats (1-1,7µM) and human recombinant enzyme;
- Inhibition **presented as reversible**; chemical structure advocates irreversible inhibition of enzyme (ANSM-CSST);
- 4 species in GLP toxicology studies(including cynomolgus) with 3 or 6 months dosing and **no target organ** identified (ANSM-CSST);
- Comforting screen on multiple targets (high throughput at 10µM) part of ANSM questions.

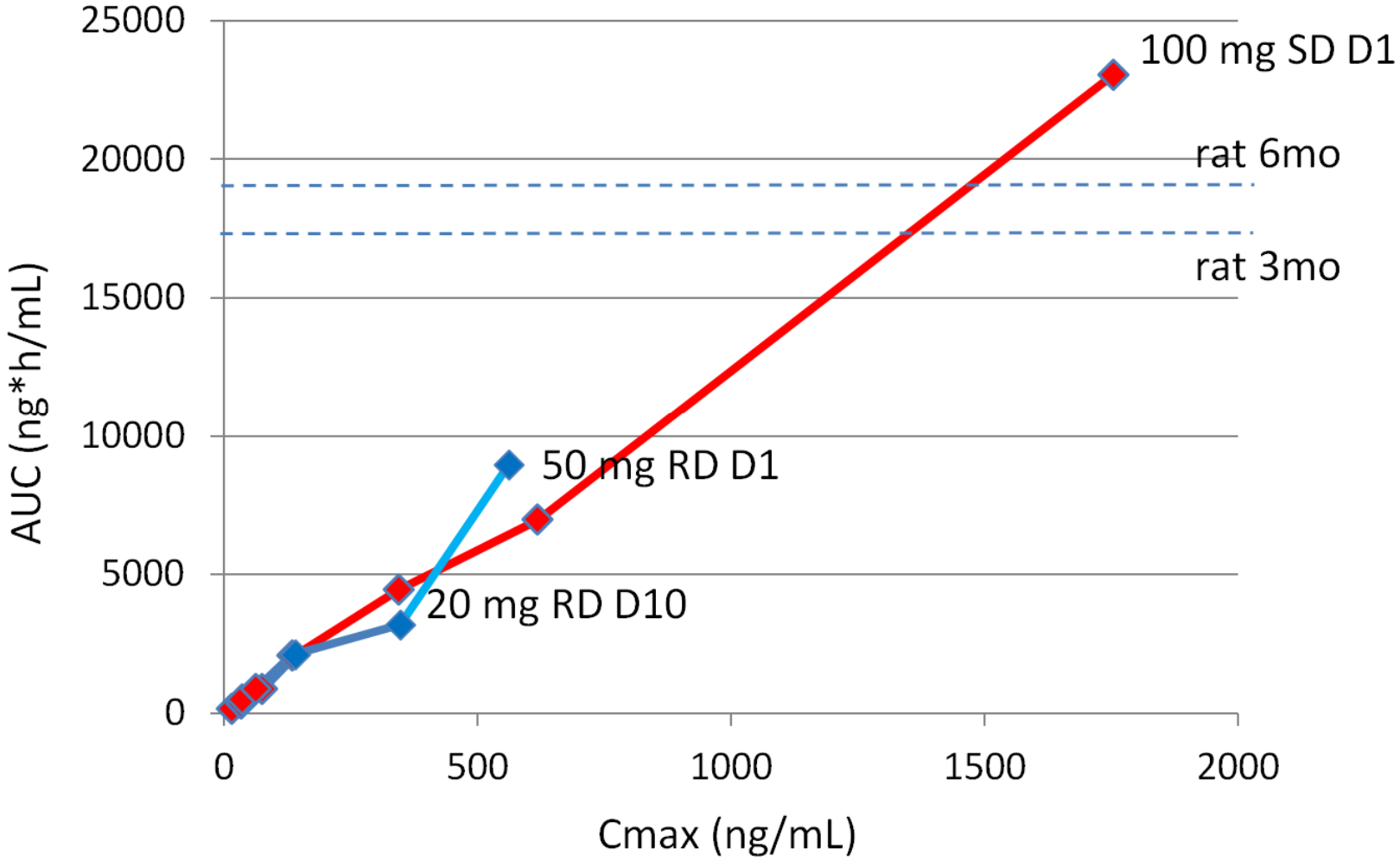
Principles of the protocol

- Conventional SAD study with maximum human dose calculated on NOAEL of the most sensitive species (rat) **starting dose 1/400th** of predicted Human Equivalent Dose. **Top dose planned 100mg**;
- First dose cohort with a sentinel group in order to rule out wrong estimates or unexpected massive response;
- Predefined progression with a big jump form 1st cohort (5 fold) and then **geometric progression of 2-2,5 fold;**
- Interaction with food with a built-in safety ratio of 2,5 (in case of increased absortion);
- MAD: 10 days mutiple dosing once daily dosing regimen (morning);
- Pharmacodynamic challenges at the end in an additional cohort to assess **antiemetic** and **antitussive** effects and a hint of **pain processing;**
- **Wet biomarkers** in plasma (ethanolamides) or monocytes ex-vivo FAAH inhibition assayed after SAD and MAD.



**: moderate intensity on D5 becoming severe on D6*

PK exposure per cohort



Before the 50 mg multiple dose cohort

- 84 subjects exposed to BIA 10-2474
- No SAE
- benign CNS symptoms at 10 mg (headache[1], transient blurred vision) but none of these at 20 mg
- Excellent safety and tolerability
- PK within the expected exposure, slightly supraproportional exposure between 40 and 100 mg

1: most frequent AE in Phase I (18% of all AEs) according to a pooled analysis BMS ASCPT 2015

Sunday to Monday night

- **Sunday 10 January** : mild AEs (blurred vision, floating specks) in one subject with a worsening in the evening (headache, dysarthria and diploplia) leading to **refer him for specialist advice and paraclinic explorations (admitted at 20:50)**;
- Hospital emergency Physician judjed the **subject status not requiring him to stay if CT scan was OK** and proposed to send him back to the Unit. Option declined by Biotrial Physician until subject is fully explored (MRI was operating for confirmed emergencies only, on Sunday night). Subject return was expected after it on Monday morning.

- **On Monday morning** no initial feedback from hospital, return of subject still expected;
- All other subjects dosed a 8 AM on this basis;
- At **9 AM Biotrial called the Hospital** and it is indicated that subject is undergoing the MRI;
- At **10 AM a call from the Hospital** was received indicated a **massive stroke of the pons (**49 years) on MRI.
- Dosing on-hold on Monday for all subjects during the day and code broken for one
- Further worsening of subject's symptoms during the day;

Within the 50 mg dose cohort

- From **Day 5** gradual neurological symptoms in one subject resulting in his hospitalization (first SAE);
- Then followed **on Day 8 by 3 additional subjects becoming symptomatic** with a variable severity of neurological symptoms hopitalized
- **Day 9 one asymptomatic subject (with microbleeding in MRI) was admitted and became symptomatic later when in hospital**
- **Day 10 one asymptomatic subject** was admitted and remained asymptomatic.
- Rapid progression of symptoms severity to death 7 days later for the first subject affected;
- Relative improvement of symptoms in the 4 other subjects;
- Very **unusual MRI patterns with lesions of the hippocampi and pons** of variable severity in the 5 subjects with symptoms;
- **Explosive and delayed toxicity** not simply related to exposure levels.
- PK exposure of parent or circulating metabolites as expected.

Working hypotheses of the expert group created by ANSM (as of March 7)

- **Off target activity** due to the lack of demonstrated selectivity vs other targets amongst which hydrolases -*BIAL to address the selectivity issue*;
- Overaccumulation of anandamide leading to $TRPV_1$, ion chanels,PPAR, NMDA or $MAPK_{38}$ activation or by and leading to the production other mediators like eicosanoids. As class is safe, low probability hypothesis under investigation.
- **Local metabolism in brain** leading to a reactive isocyanate interacting with many proteins in brain- *Brain microscopy of Monkey study could contribute to conclusions if available*;

- *Some suggestions of protocol improvements to be discussed but not directly related to the causative factor (e.g. cognitive testing at screening, altered dose progression etc).*