



BIA 10-2474 Accident

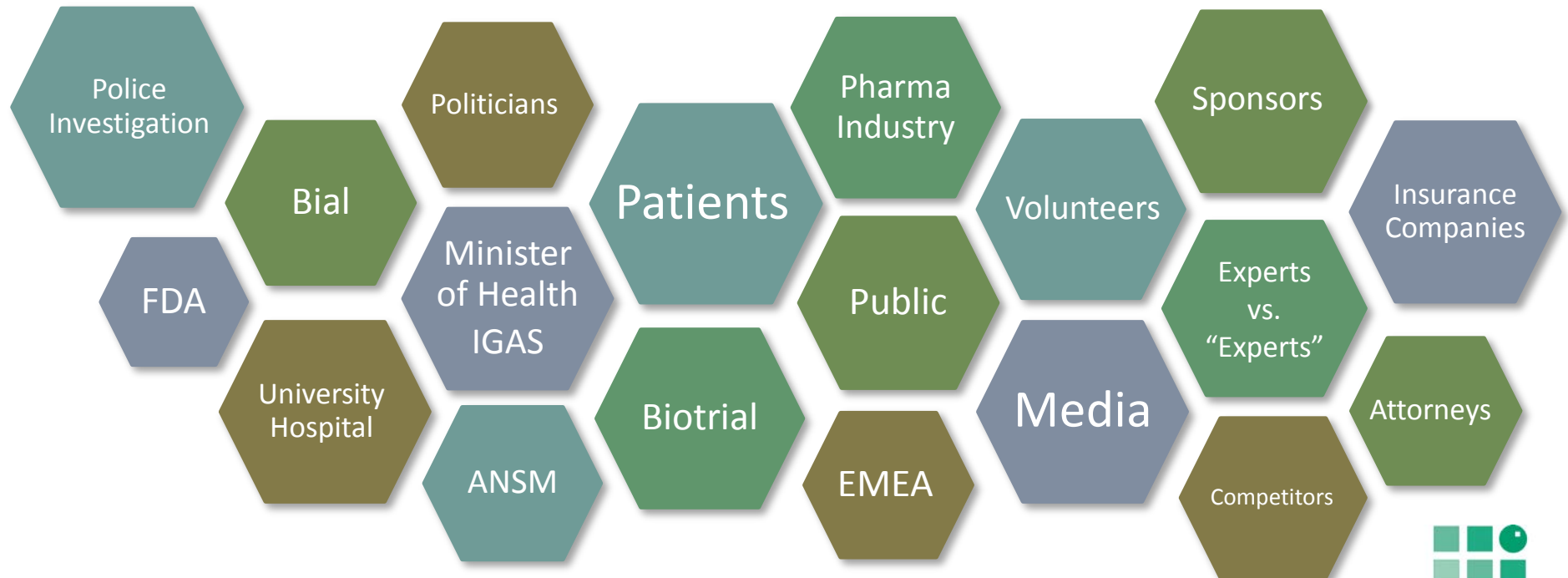
Biotrial Crisis Management: Facts, Impact & Lessons

Jean-Marc Gandon, PharmD
President & CEO
Biotrial

*Presented at the ASCPT Annual Meeting,
Washington D.C., March 18th, 2017*

Focus of this Discussion

- Give an overview of the facts of the event as a basis for the discussion
- Provide insight into our experience in the midst of the entire community following the accident, including:



Background of the Molecule & MOA

- Previous studies performed for Bial (good, long-term relationship)
- Routine study with the 10th FAAH inhibitor of its class positioned for neuropathic pain, 3rd at Biotrial
- Mechanism of Action (MOA) considered safe
- Small molecule not considered “high risk” by competent authorities
- As with any CRO, no assessment of Pharmaceutical Chemistry nor of Structure-Activity relationships was conducted (not the role of the CRO)
- Submitted and approved by IRB and ANSM (French Competent Authority)

→ All the lights were green

Background of the Molecule & MOA

- Investigational Drug Brochure content **at or above standard** especially in toxicology: 4 species in GLP studies for 3-6 months
- 98 safety-binding experiments done at 10 μ M
- Several possible therapeutic indications, although Phase I not specific except in additional arms (not executed) testing antitussive, analgesic and antiemetic properties
- Reviewed by Medical Officer and Principal Investigator as per SOP

→ **All the lights were green**

Principles of the Protocol

- SAD study with maximum human dose calculated on NOAEL of the most sensitive species (rat) **starting dose 1/400th** of predicted Human Equivalent Dose (conservative). **Top dose planned: 100 mg**
- Sentinel group in first cohort
- Predefined progression with a big jump from 1st cohort (5 fold) and then **geometric progression of 2-2.5 fold**
- MAD: 10 days multiple dosing once daily dosing regimen based on exposure reached in Single Dose
- 6 active and 2 placebo per parallel group
- ⚠ **Many studies conducted with the same design;** aiming at MTD definition at exposure \leq NOAEL.
- ⚠ Biomarkers of heterogeneous quality (marijuana scale from NIDA, circulating anandamide and enzyme activity monocytes ex-vivo) to be analyzed at the end of study.

JUL AUG SEP OCT NOV DEC JAN FEB

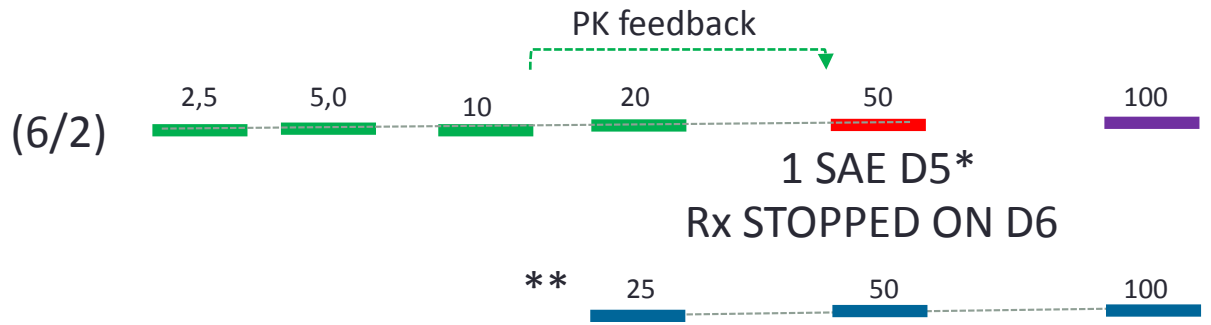
Single Ascending Dose



Food



Multiple Ascending Dose



**moderate intensity on D5, becoming severe on D6, **alternative standard design*



Facts & Events: Overview

- During the FTIM study of BIA-102474 the single ascending dose was uneventful up to its completion (100 mg 8th cohort) and drug well tolerated
- The multiple dose was also uneventful up to 20 mg for 10 days.
- During the 5th cohort (50 mg) on Day 5, a subject presented moderate headache, dysarthria, cerebellar syndrome and diplopia. **The transfer to the emergency room was decided not due to life-threatening or severe condition but to refer for neurologist advice and imaging explorations to exclude other reasons.** The CT and angio scan **done and considered as normal.** A MRI was planned for the next morning and subject expected to come back after.
- He then degraded clinically the morning after (when MRI was performed) and progressed to death over 7 days.

Facts & Events: Overview

- In the absence of any further warning from the hospital, the moderate AE status before hospitalization and the lack of similar clinical AEs in all the other subjects of the cohort, dosing was done according to protocol.
- All subjects hospitalized in the same ward were witnesses of the transfer, and information was provided to them as soon as Biotrial received it.
- Study was suspended as soon as the MRI was interpreted.
- Hemorrhagic and vasogenic/cytotoxic lesions of the brain were seen on the MRI. **He had a pre-existing vascular disease which was identified during the autopsy.**
- 4 other subjects of this group then developed neurological symptoms after dosing discontinuation (2-4 days later) and/or comparable MRI abnormalities, treated with corticosteroids, and they improved slowly and were discharged.

TSSC: Conclusions & Hypotheses

Temporary Specialized Scientific Committee (TSSC) created by the ANSM

- Low potency (micromolar) inhibitory effect on FAAH of BIA-102474*
- Irreversibility of the covalent bound with hydrolase serine 241 although some slow reversibility was seen with the PF compound
- Relative lack of selectivity
- Toxic effects with a very steep curve in humans [absent 20 mg, present 50 mg] (symmetrical lesions of the pons and hippocampi with bleeding and vasogenic/cytotoxic lesions) [NEJM 2016]
- Several mechanisms of toxicity were hypothesized:
 - **Inhibition of other hydrolases**
 - **Toxicity of the imidazole-pyridine “leaving group” interacting with many brain proteins**
 - More potency in humans than in rats*
 - Little comprehension of the 20 mg to 50 mg progression, but no consensus on escalation methods*,**

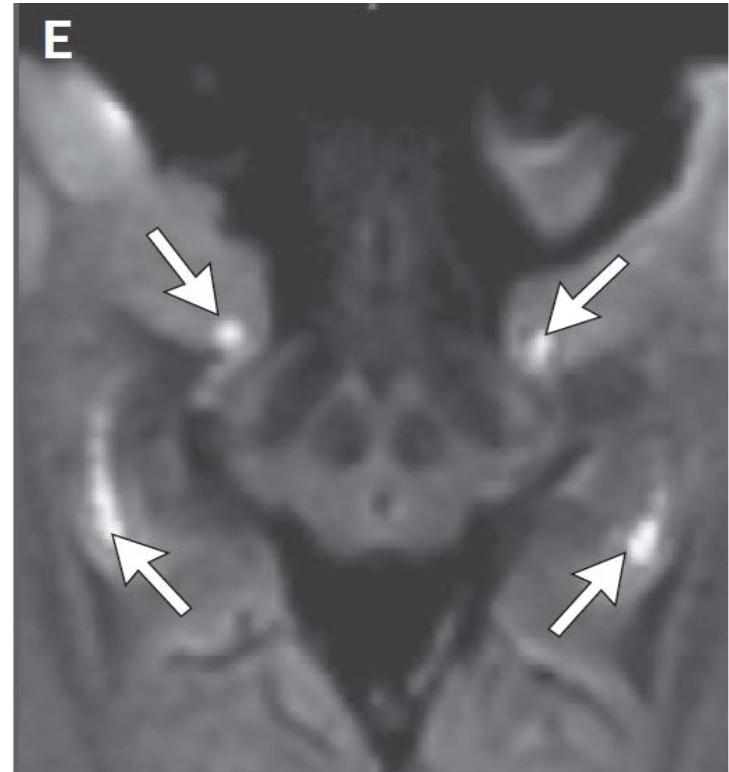
strong counter-arguments exist ,standard multiple dose design is with 3 doses*

Type of Lesions in NEJM, Nov 2016

PONS



HIPPOCAMPUS & AMYGDALA



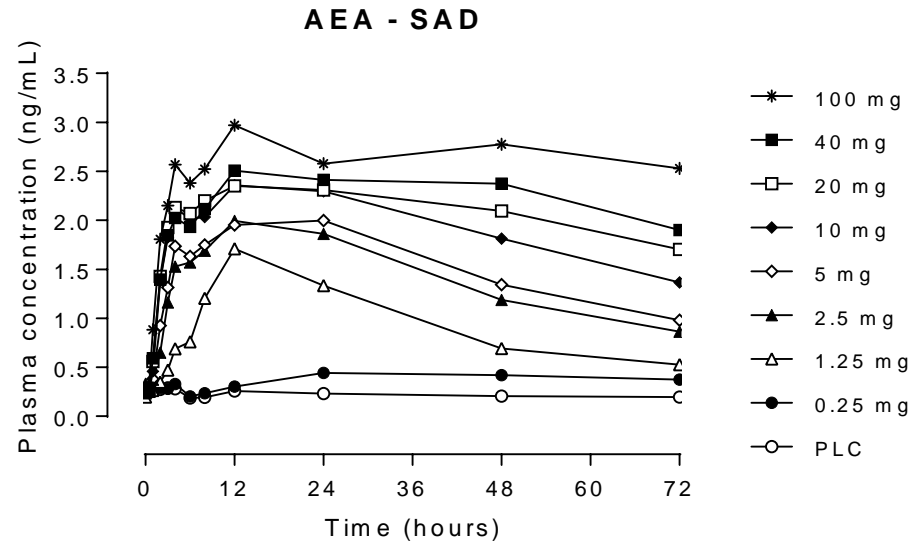
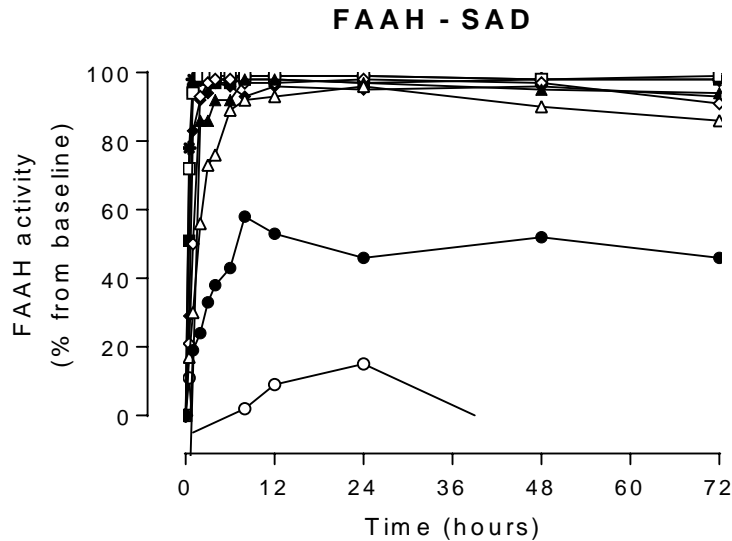
Lesions very specific, not resembling anything known, no vascular topography

Counterarguments to TSSC Conclusions

- **“Complete FAAH inhibition should have been achieved by a dose of 1.25 mg”, “100 mg appears unjustified.”**
 - Complete discrepancies between a circulating cells ex-vivo enzymatic assay ‘de-qualified by the provider’ during the study and a validated plasma anandamide assay.
 - Impossible to reconcile both
 - Looking at anandamide levels, there is progression from 40-100 mg.
 - PF 04457845 showed 100% inhibition at 0.3 mg with a top dose of 40 mg (Li et al. BJCP 2011)
 - Comments in opposition with exploration of the supratherapeutic exposure

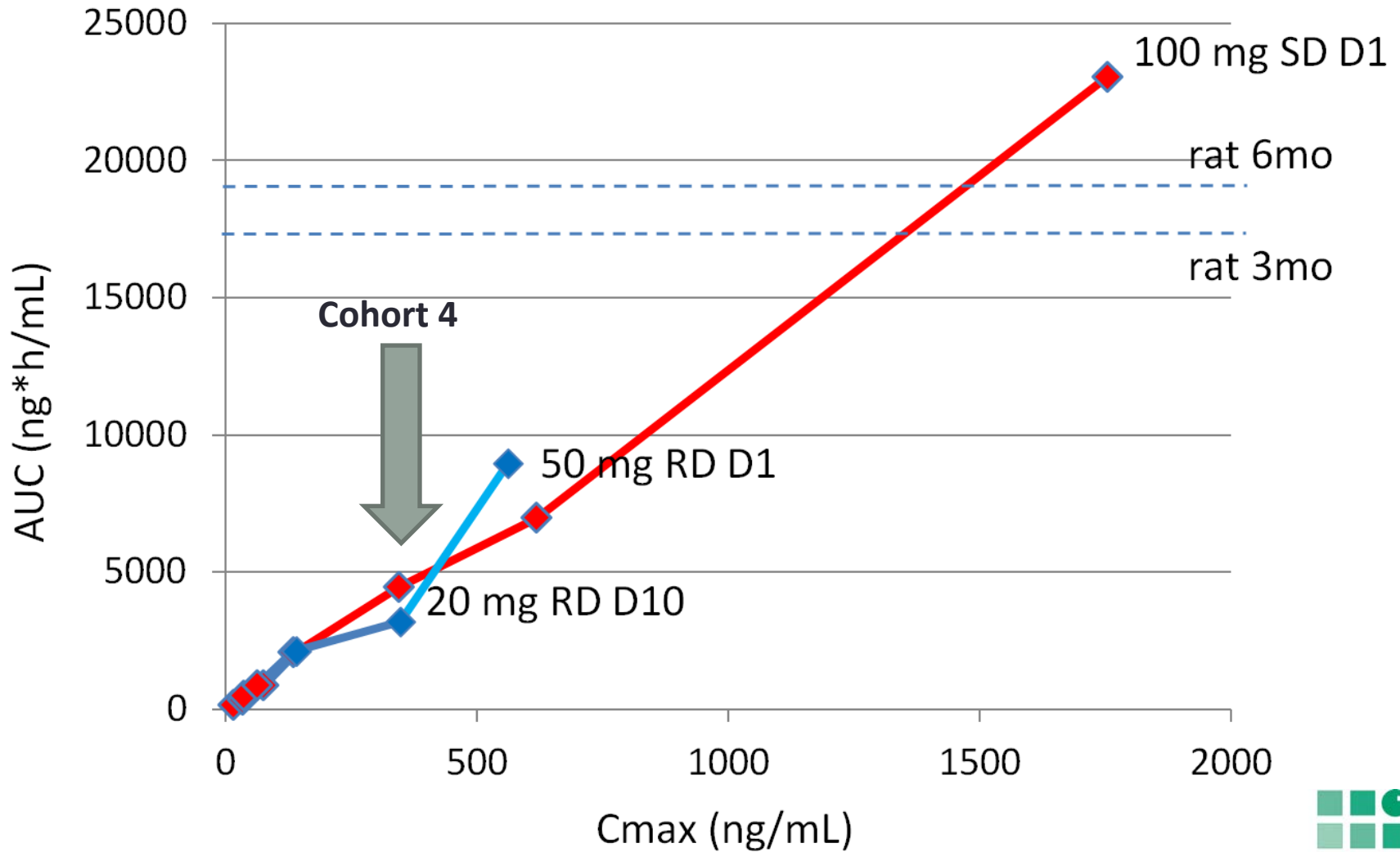
Comparison of Ex-vivo Enzyme Inhibition Versus Anandamide Levels (Active Moiety)

Mean FAAH activity (% baseline) and plasma levels of AEA following single-doses of Placebo and up to 100 mg BIA 10-2474

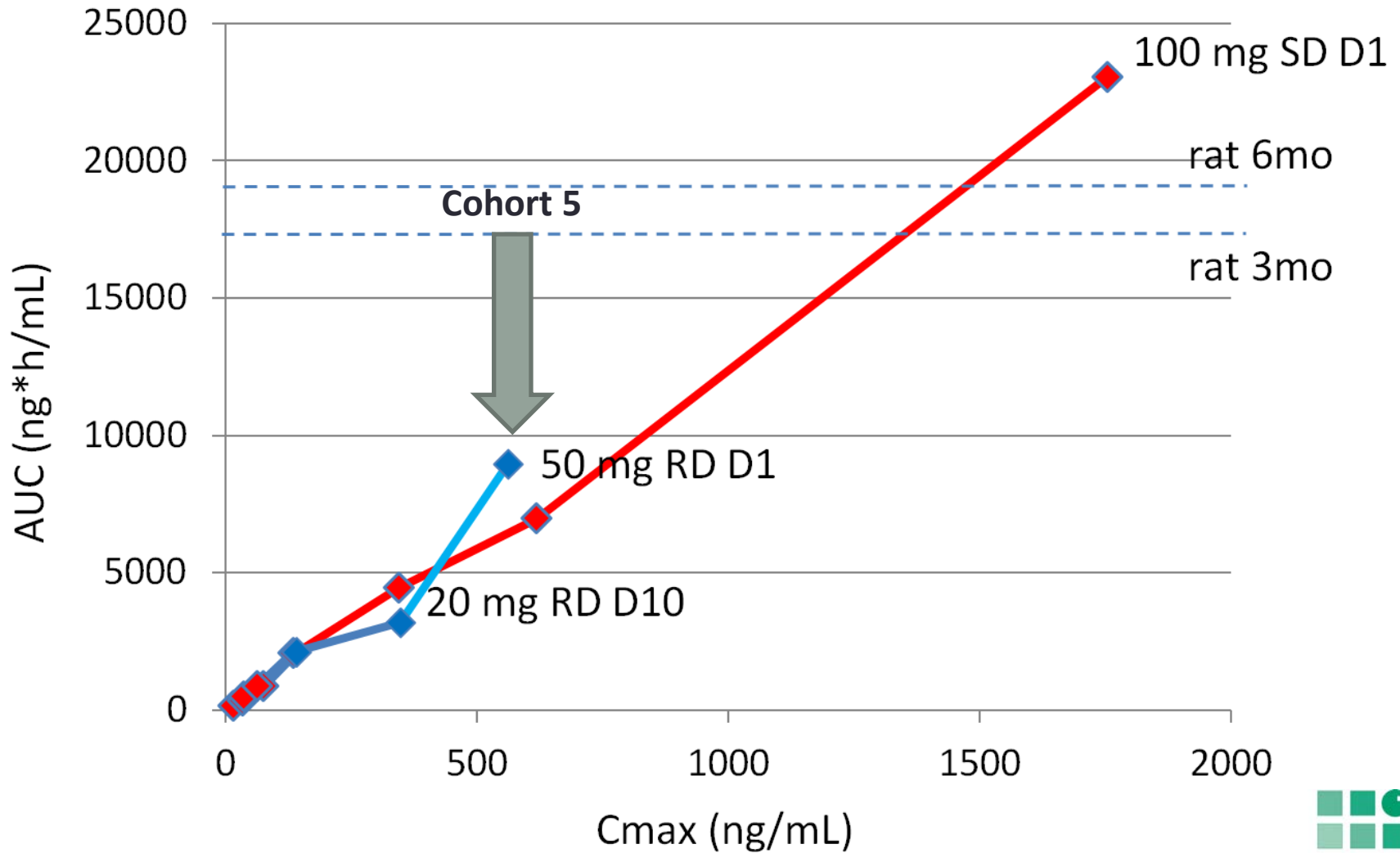


Rocha et al. BPS 13-15 Dec 2016

PK Exposure Per Cohort



PK Exposure Per Cohort



Scrutiny of All Other Subjects' MRIs by TSSC (2nd Round, Oct. 2016)

- Dual-reader examination of 79 MRI scans from all cohorts
- 53% of random findings similar to reference surveys:
 - **One 1 to 3 month-old posterior cerebellar artery stroke with no similarity with the stereotyped toxicity associated with BIA 10-2474**
 - One benign tumor
 - Other (Several white matter hyperintensities (35), cerebellar atrophy (1), mega cisterna magna (3), various venous abnormalities (3))
- **No resemblance with the very specific and peculiar abnormalities seen in Cohort 5 and similar to the prevalence in the literature**

Clear Statement by the Public Prosecutor

June 14th, 2016

“

- The product administered to healthy volunteers was not altered
- Endogenous factors, unique to each volunteer, could explain the variability
- **The deceased victim, well before his participation in the trial, had an occult intracranial vascular pathology, which could explain his fatal outcome, unlike the other volunteers within the cohort**
- Tests carried out on animals, exposed to very high doses over long periods of time, **did not appear to predict** the unwanted effects which occurred in the human tests, where subjects were exposed to much lower doses and over a shorter period of time
- **The test molecule appears to be the cause however the pathophysiological mechanism that was triggered remains unknown to this day**

”

Media Impact

- **Over 1000 articles on the event**
- **724** articles with Biotrial's name in the title
- Over **30 major media outlets** requested interviews at the height of the crisis (The New York Times, CNN, NBC News, Sky News, The Guardian, The Independent, Die Zeit...)
- French Government Virality Scale **rated event as Major Crisis with 10,000 tweets over the course of one day**
- Systematic use of Biotrial's name and logo instead of the sponsor's, Bial, partially due to the similar names. A shift in comparison to the Tegenero accident.
- Ongoing issue that the Bial/BIA 10-2474 is called the Rennes Accident, or worse, the Biotrial Accident

Impact on the Inspections

- More than 130 depositions taken during the judicial investigation
- 25 full days of on site inspections by Competent Authority (over 4 different periods)
- Rennes Biotrial site accreditation continuously maintained by the French Ministry of Health throughout the event, accreditation has recently been renewed as is routinely done every three years
- **Conclusion: No critical findings, nothing was found that could explain the accident**

Impact on the Public

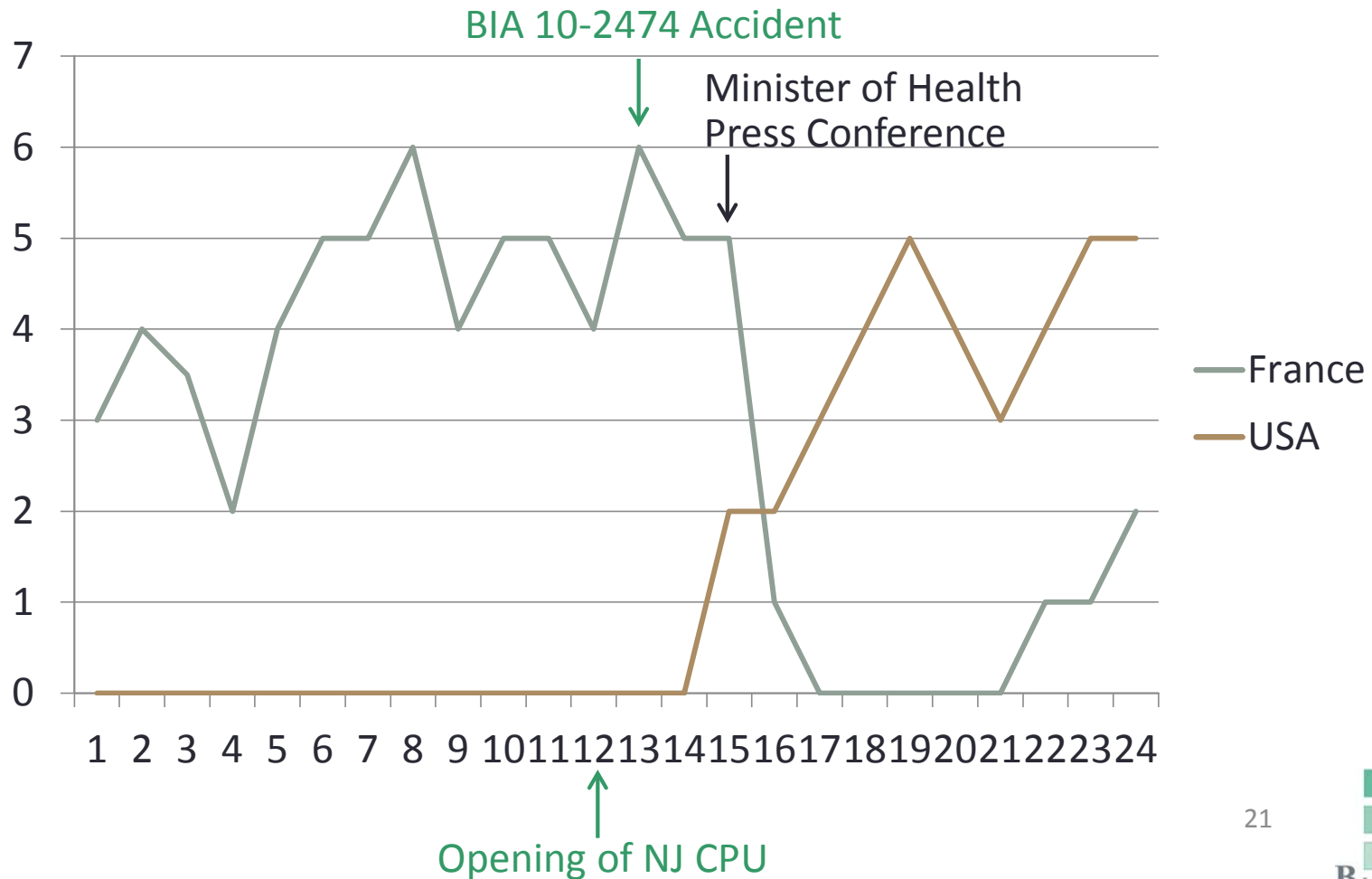
- Event dramatized by the Minister of Health through a press conference where event was labeled as “Unprecedented Catastrophe”.
- Significant amount of pressure from two newspapers relaying **totally distorted information** “dogs had died” or “the study drug had expired”, etc.
- **Paradoxical effect** on subjects: calls to the volunteer hotline to participate in studies tripled in volume
- **Heterogeneous impact on volunteers having previously participated in studies:** some reiterating their will to continue, some expressing that they would not do it again

Impact on Staff

- Very high level of stress because of the event and the media, especially for the Rennes staff (180 out of 300 employees)
- Threatening phone calls (due to information regarding dog toxicology studies, which were not performed at Biotrial, etc.)
- PTSD prevention put into place
- A few people resigned
- No layoffs

Impact on Business

- Number of studies initiated per month over 24 months



Impact on Regulators

- All hospitalizations of healthy volunteers (not of patient volunteers) in Phase I are a “New Medical Event” and require immediate notification to the French Ministry of Health
- EMA is circulating a draft guidance on how to better identify and mitigate risks in Phase I
- FDA stated that based on available information, BIA 10-2474 exhibits a unique toxicity that does not extend to the other drugs in the class

Lessons

- All ongoing thoughts suggest that an off-target activity was missed during usual process of drug development. No red light in toxicology either. Final understanding of cause not found.
- Technological issue with off target not resolved (in silico? Giving up MTD definition in Phase I?, high quality online biomarkers?)
- Strong reaction of the Minister of Health indicating that “things will change” (in France)
- This has operated as a deterrent for studies in France with a shift of business to the USA

Lessons: Crisis Management

What Was Anticipated

- Safety aspects (medical surveillance, decision-making chain, global relationship with the hospital's neurology department)
- The strong relationship with the sponsor, Bial
- Communication with the regulatory authorities, the inspectors and the insurance partners
- Financial strength

What Was Not Anticipated

- The level and intensity of media coverage and the pressure on the politicians and agencies (exacerbated by social media day and night)
- If “no fault is identified” it is not the private insurance that pays but rather a national public fund to assist the victims (same process as in the event of a terrorist attack), which complicates the relationship with the volunteers
- Internal communication to non-medical staff during the crisis
- Overall client communication

Lessons: Collective Support

- It was normal, to us, to be present to assist the sponsor in the communication, but would have expected that there be more presence from different entities, who have an important role in the process to collectively explain the objectives, regulations and the importance of drug development
- We found ourselves alone to explain the entire process as well as respond to a vast amount of misinformation published in the media, e.g.:
 - age & number of volunteers participating in Phase I trials
 - use of a placebo
 - who was responsible for writing and approving the protocol
 - role of Non-Clinical studies in the drug development process
 - etc.
- Different entities and agencies involved in the development process were not scrambling to put themselves on the front line
- “Where did it happen?”, others were relieved to say “At Biotrial”, protecting and preserving their image
- Could happen anywhere, to anyone

Conclusions

- Very harmful impact of media putting pressure on politicians and on the scientific committee who should have been allowed to work in complete serenity, not under media harassment.
- Clinical Research on new and innovative medicine should be encouraged and promoted in all countries in order to cure illnesses and to improve the patients' quality of life:
 - “Bial ‘has the confidence and the support of the Portuguese government’, the Ministry of Economy stated in a press release, calling on the laboratory to ‘continue research and development of projects that help the Portuguese economy as well as the well-being of citizens and patients’.”

Statement by the Portuguese Government, May 2016

Conclusions

- None of the measures requested by the Ministry of Health would have modified the real time decisions made, none of their new directives would have saved the volunteer.
- Residual risk remains – linked to the fact that the unique toxic mechanism of action is still unknown. This represents a challenge for the scientific community for the safety of the volunteers and the development of innovative therapeutic treatments.

Message from the ECNP President



Friday, January 29th, 2016

Regulation could be further tightened on the testing of new drugs: more forms, more approvals required from bodies for whom managing risk means avoiding risk. **In fact, we have no guarantee that rare fatal events of this kind can ever be avoided completely, except by stopping drug development in its entirety.** The truth is that, as a Principal Investigator, we have to run the risk that something horrible will happen. Translational research involves giving drugs to people to find out what will happen. It's the human condition.

A handwritten signature in black ink, appearing to read 'Guy Goodwin', written in a cursive style.

Guy Goodwin
ECNP President



Additional Slides

BIA 10-2474 Accident Biotrial Crisis Management: Facts, Impact & Lessons

Jean-Marc Gandon, PharmD
President & CEO
Biotrial

*Presented at the ASCPT Annual Meeting,
Washington D.C., March 18th, 2017*

Counterarguments to TSSC Conclusions

- Surprising for a molecule acting via the CNS, volunteer selection, inclusion and follow-up did not include a neuropsychological assessment with clinical interview and cognitive tests.
 - **Agree that cognitive testing to eliminate potential behavioral toxicity is useful (planned in the PD part of the study), and specific CNS assessment necessary only when there is a rationale leading to exclusion criteria. No impact on covalent binding or off-target effects.**
- Dose escalation in study appeared to be too abrupt toward end of escalation: Dose escalation MAD cohorts 1 to 2 (2.5 to 5 mg) was 2-fold, whereas the dose escalation cohorts 4 to 5 (20 to 50 mg) was 2.5-fold.
 - **A 2-3 fold increase is common practice as far as safety is not alerting and PK linear**

Facts: Cohort 5, 50 mg

Day 5 - Sunday night

- Benign AE in (S2508): mild transient **blurred vision** and **mild headache** at 3:30 pm (reported at 6:30 pm)
- Worsening at 6:30 pm with occurrence of **moderate headache, slurred speech (dysarthria), drunken feeling (cerebellar syndrome), floating specks and diplopia**. Relationship to study drug considered as possible (26 marketed compounds can produce this pattern, a stroke as well).
- **The transfer to emergency was decided** not due to life-threatening or severe condition but for obtaining a neurologist advice and Brain Imaging. Admitted at 8:50 pm. Emergency physician proposed to send the subject back, after evaluation was completed even if the clinical status remained stable Biotrial physician **declined** after evaluation was completed even if the clinical status remained stable .
- Resident neurologist considered an emergency MRI not necessary and therefore **CT and angio scan done and considered as normal**. Treatment with low doses of aspirin and acetylleucine ware initiated. A MRI was planned for the next morning and subject expected to come back to Biotrial CPU after.

Facts: Cohort 5, 50 mg - Continued -

- **Biotrial expected to be informed by the hospital if subject clinical status aggravated or abnormalities found in imaging (current legal rules when a physician sends a patient to the hospital)**
 - At 8 am morning dosing done in the other subjects.
 - At 9 am Biotrial called the Hospital emergency and it was indicated that there was no news and that subject was undergoing the MRI
 - At 10 am **the Hospital emergency called Biotrial to inform that MRI showed a massive stroke of the pons (in this 49 year-old subject).**
- Code was open, study halted and sponsor notified
- He evolved to coma during the day
- *A posteriori* (months after) we were informed that subject had degraded 15 minutes before 8 am, becoming agitated and confused.
- **One day after, 1 subject developed amnesia and MRI abnormalities in hippocampi**
- **Two days later, 2 additional subjects became symptomatic:** S2507 (slurred speech, cerebellar syndrome, headache, blurred vision) and S2505 (headache and weakness of right hemibody) abnormal MRI on Day 8, MRI done for all active subjects of the cohort: 4 subjects with and 2 subjects without MRI abnormalities
- **On day later, 1 asymptomatic subject (S2503 had in fact microbleeding in MRI done systematically on Day 8) was admitted and became symptomatic later when in hospital**