Addressing Evolving CHMP Guidance of Phase I Study Designs

**BIA 10-2474 background**

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*Roche Innovation Center Basel*
Context: Modern Ph I Studies Are Generally Safe with Isolated High Impact Cases of Morbidity & Mortality

<table>
<thead>
<tr>
<th>Therapeutic areas</th>
<th>Neuropsych, CV, Pulmonary, GI, Gyn, Rheum, ID (note: no oncology)</th>
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<tbody>
<tr>
<td>Total # of studies</td>
<td>394 total (~4.6k total unique individuals, ~11k participants)</td>
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<td>IMP type</td>
<td>Small molecules &gt;&gt; biologics</td>
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<td>Safety of starting dose (in HVs)</td>
<td>• Not described</td>
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<td>Overall safety</td>
<td>• No deaths. No life-threatening AE. No persistent disabilities.</td>
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<td>• 34 total SAEs (0.31% of dosed participants), 11/34 SARs</td>
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<td>• 4 SAEs in placebo, 1 in biologics, 6 in small molecules</td>
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<td>• 85% of AEs mild, 4.4% moderate, 1.0% severe</td>
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Analysis of Roche (pRED) small molecule FIH studies

Meta-Analysis, non-Roche HV phase I studies (BMJ 2015)

- U.Penn Gene Therapy Death
- IRB oversight
- Stronger SOPs
  - Scrutiny of high-risk P1 studies

- Tegenero (TGN 1412)
  - 2007 EMA FIH Guidance

- Bial (BIA 10-2474)
  - 2017 EMA FIH Guidance
Summary of BIA 10-2474 Incident

- **Bial**: pharma company developing pain medications (CNS)
- **BIA 10-2474**: Orally dosed small molecule inhibitor of FAAH, likely by covalent inactivation
  - Not potent: IC50 in rats 1.1-1.7 uM
  - No safety issues identified with competitor molecules through phase II
  - Apparently, BIA 10-2474 animal studies (4 species) did not show acute-onset cerebral toxicity
- **Phase I** SAD/MAD in France conducted by CRO Biotrial
  - SAD: well-tolerated 0.25 → 100 mg (1:1 sentinel in each cohort)
  - MAD: 2.5, 5, 10, 20, 50, 100 mg/d x 10d planned
    - serious rapid-onset neuro AEs occurred midway through the 50 mg/d cohort
    - 1 death + others w/neuro injuries with a similar pattern seen on MRI
    - 1 subject receiving active drug was unaffected
- Widespread coverage in media
- HA response: investigations, re-evaluation of phase I practices
BIA 10-2474 Phase I Plan and Dosing Strategy

• Phase I: Single-site, blinded, placebo-controlled study in HVs
  1. SAD (8 cohorts of 8:2): 0.25 → 100 mg
  2. MAD (6 cohorts of 6:2, 10 d): 2.5 → 100 mg/d x 10d
  3. Food effects cohort
  4. Pharmacodynamic study (never conducted)

• Dosing strategy
  – SAD: 0.25, 1.25, 2.5, 5, 10, 20, 40, 100
    • Sentinels at each SAD level (1:1), then dose others 24h later
  – MAD: 2.5, 5, 10, 20, 50, 100 mg/d x 10d planned
    • Neuro SAEs day 5&6 in 50 mg/d MAD cohort
    • Based on accumulation, exposure at 50 mg/d MAD likely exceeds exposure of 100 mg SAD

• Dosing range not inappropriate (acc to TSSC)
  – Starting dose: 0.25 mg is ~1/400th the NOAEL
  – Unclear relationship to NOEL
  – Per TSSC calculations, reasonable to test up to 96-100 mg/d
BIA 10-2474 Syndrome of Cerebral Toxicity

- Single doses (0.25 to 100 mg) well tolerated, no severe AEs
- Multiple doses (2.5 to 20 mg for 10 d) well tolerated, no severe AEs

- In 50 mg/d cohort (6 active: 2 placebo):
  - Acute rapidly progressive syndrome in 5 of 6 subjects receiving 50 mg/d
    - Day 5: acute and rapid onset headache, cerebellar syndrome, memory impairment, altered consciousness
    - MRI: bilateral, symmetric lesions in pons & hippocampus (hemorrhagic)
      - 1 died
      - 1 residual memory impairment
      - 1 residual cerebellar syndrome
      - 2 eventually improved
      - 1 subject was unaffected, no AEs

  NEJM 2016

- No exposure data reported
### BIA 10-2474 - Minimal Clinical Assessments During the MAD

#### Flow chart 3: MAD part

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<th>PROCEDURES</th>
<th>Screening (D-28 to D-3)</th>
<th>Admission (Day-2 even)</th>
<th>D-1</th>
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**Days 3-9:**
- No vitals
- No ECGs
- No Phys exam
- No Neuro exam
- 1 set of labs on day 5

This differs from our more intensive in-patient FIH monitoring practices
BIA 10-2474 Human CNS toxicity mechanism is unknown and likely an Off-Target Effect

- Data package NOT released...we can only speculate
  - Nonclinical data not available
  - Available data: trial supported by tox studies in 4 species, no findings of similar pattern to human CNS lesions
  - Full clinical data not available*, including PK
  - MRIs: similar symmetric pattern of CNS lesions & hemorrhage suggests a unifying mechanism

- No neurotoxicity with other FAAH inhibitors (Pfizer, J&J)

- Not likely a reversible FAAH inhibitor
  - Structurally similar to Pfizer and Janssen compounds
  - More likely to be irreversible inhibitor → covalent binding

- Potential for off-target effects
  - Not potent: IC50 in rats 1.1-1.7 uM is ~200X > PF-04457845
  - Post-hoc in-silico screen predicts off-target binding (factor VII & thrombin inhibition***)

- TSSC hypothesis: Reactive metabolite in CNS?
  - 4 metabolites were identified (<3% parent)
  - May produce an isocyanate, which could bind brain proteins
  - Potential intracerebral metabolism?

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** Open letter on access to the BIA 10-2474 clinical trial data **

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* NEJM Nov 2016
** Lancet Dec 2016
*** Molinksy BBRC 2016
Lessons Learned from BIA 10-2474

• **Mechanism of human toxicity is unknown**
  - Incomplete available data (nonclinical & clinical)
  - Demonstrates the importance of thorough PK-PD characterization, but human-specific toxicities may still occur
  - Extremely steep dose-response relationship
  - Likely an off-target effect, but we *can only speculate*

• **Study design could have been better**
  - Increments between cohorts
  - PK
  - Safety monitoring: frequency & intensity of assessments
  - *Consider what might have reduced harm…*

• **Serious adverse events can occur at unexpected times**
  - Lack of safety signals should not necessarily provide reassurance (i.e., new off-target effects with new molecules & human specific effects are possible)
Doing now what patients need next