Metabolite profiling in early clinical Drug Development: 
Current status and future prospects

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Conflict of interest

- Full-time employee of Idorsia Pharmaceuticals Ltd.
Presentation outline

- Relevance of metabolite profiling for drug development
- Regulatory framework
- Human ADME study vs. novel approaches (e.g. micro-tracer studies)
- Future of metabolite profiling
Relevance of metabolite profiling

Questions to be addressed in context of drug development

• Which metabolites are formed in animals and humans?
• How are the metabolites formed?
• How abundant are the metabolites identified?
• Are there any human-specific metabolites?
• Are there any active and/or potentially toxic metabolites?
• What are the main routes of elimination?

• Which Clin Pharm studies need to be performed (e.g. PK-DDI)?
• Is there a need for concomitant drug use restrictions and/or dose adjustment?

➢ Selection of best drug candidate for further clinical development
➢ Elaboration of an optimal clinical development plan
➢ Mitigation of drug development risks
Reasons for failure in drug development
Disproportionate, toxic metabolites may be a contributing factor

Pre-clinical: Toxicology

Phase-I: Clinical safety

Phase-II/III: Clinical efficacy

Five-dimensional framework to enhance R&D productivity

PK/PD & metabolite profiling information vital for decision-making

- Greater focus on biological understanding for target selection led to a change in pipeline target class composition (Kinases ↑; GCRs ↓)
- New drug discovery platforms, e.g. stem cell biology, phenotypic screening, precise genome editing and genomics (CRISPR)
- Early, good understanding of PK, PK/PD and ADME properties for any molecule is crucial for improving quality in lead and drug candidate selection
- Model-based PK/PD predictions incorporating ADME data early-on (76% vs. 58% of projects with matching predicted/observed PK)
- Creating the ‘right culture’, i.e. a priori setting of quantitative decision-making criteria; encouragement for asking ‘killer’ questions
- Success rates from candidate drug nomination to phase III completion improved from 4% in 2005–2010 to 19% in 2012–2016

Metabolite profiling
Regulatory landscape

FDA guidance: Safety testing of drug metabolites («MIST» guidance»)

Guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (ICH M3(R2)) and related Q&A document

Note for guidance on toxicokinetics: the assessment of systemic exposure in toxicity studies (ICH S3A) and related Q&A document

FDA guidance: In-vitro DDI studies

FDA guidance: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMA FiH guidance)

S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

S7A Safety Pharmacology Studies for Human Pharmaceuticals

FDA guidance: Clinical DDI studies

FDA guidance: In-vitro DDI studies
Safety Testing of Drug Metabolites

FDA guidance - Nov 2016

“We encourage the identification of any differences in drug metabolism between animals used in nonclinical safety assessments and humans as early as possible during the drug development process.

The discovery of disproportionate drug metabolites late in drug development can potentially cause development and marketing delays.

Generally, metabolites identified only in human plasma or metabolites present at disproportionately higher levels in humans than in any of the animal test species should be considered for safety assessment.”
In-vitro & Clinical DDI studies

FDA guidance - Oct 2017

In-vitro DDI guidance

• “Sponsors should evaluate the DDI potential of an investigational drug’s metabolites for their impact on the drug’s safety and efficacy using a risk-based assessment that considers safety margins, likely concomitant medications, and therapeutic indications. “

• “A metabolite with significant plasma exposure or pharmacological activities may need to be evaluated for its DDI potential as a substrate or as an inhibitor of metabolizing enzymes.”

Clinical DDI guidance

• “Sponsors should evaluate DDIs before the product is administered to patients who are likely to take concomitant medications that could interact with the investigational drug. Furthermore, sponsors should collect enough DDI information to prevent patients from being unnecessarily excluded from any clinical study because of their concomitant medication use.”

• “The sponsor should determine metabolite concentrations if the results provide information about the effect of a DDI on the investigational drug’s safety or efficacy, or if the data inform the mechanism of the drug interaction.”

→ Evaluate DDI potential as early as possible in drug development
Human ADME study
Conventional approach towards metabolite profiling

• Single-dose study in n=6 healthy adults
• Sampling of blood, urine, feces (occasionally expired air)
• Requires synthesis of radio-labeled compound and calculation of radioactive burden
  – Need for dosimetry studies and whole-body auto-radiography data
• Purpose:
  ➢ Assessment of mass balance based on cumulative excretion of radioactivity
  ➢ Identification/quantification of metabolites by NMR and mass spectrometry

Cumulative excretion

Conc. over time («cold vs. hot»)
Identification/quantification of metabolites
Technologies applied in context of hADME trials: NMR & MS

Can we do any better?
Available options to allow for earlier metabolite profiling


Figure 1. Different approaches of metabolite profiling in clinical development.
## Accelerated mass spectrometry (AMS) vs. liquid scintillation counting (LSC)

<table>
<thead>
<tr>
<th></th>
<th>AMS</th>
<th>LSC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technology</strong></td>
<td>Isotope-ratio mass spectrometry</td>
<td>Energy from atomic decay is converted to photons of light $\rightarrow$ Photodetection</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>Ratio of $^{14}$C to total carbon (C)</td>
<td>Photon emission count</td>
</tr>
<tr>
<td><strong>LLOQ</strong></td>
<td>App. 0.1 dpm/mL</td>
<td>App. 10-50 dpm/mL</td>
</tr>
<tr>
<td><strong>Radioactive dose</strong></td>
<td>$\leq$ 1 $\mu$Ci</td>
<td>$\leq$ 100 $\mu$Ci</td>
</tr>
<tr>
<td><strong>Study approach</strong></td>
<td>Micro-tracer/Micro-dose study</td>
<td>Conventional hADME study</td>
</tr>
</tbody>
</table>

Micro-dose studies generally provide adequate metabolite profiling data

A comparison with regular dose studies

**TABLE 1** Recovery data of $^{14}$C-labeled drug material in excreta and evaluation of metabolite profiling results in the total sample of studies versus regular- and low-dose studies

<table>
<thead>
<tr>
<th>Study type</th>
<th>No. studies</th>
<th>Dose of $^{14}$C-labeled drug material</th>
<th>Recovery of $^{14}$C-labeled drug material (range)</th>
<th>Recovery &gt;90%$^a$</th>
<th>Metabolite profiling reported and successful</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>40</td>
<td>0.0074–7.4 MBq$^b$</td>
<td>92% ± 7% (72%–103%)</td>
<td>27 of 40 studies (67.5%)</td>
<td>18 of 18 studies</td>
</tr>
<tr>
<td>Regular dose</td>
<td>28</td>
<td>1.8–7.4 MBq$^b$</td>
<td>93% ± 5% (83%–103%)</td>
<td>21 of 28 studies (75%)</td>
<td>13 of 13 studies</td>
</tr>
<tr>
<td>Low dose</td>
<td>12</td>
<td>0.0074–0.074 MBq$^b$</td>
<td>89% ± 9% (72%–98%)</td>
<td>6 of 12 studies (50%)</td>
<td>5 of 5 studies</td>
</tr>
</tbody>
</table>

Unless the IP shows…

- Non-linear PK
- Solubility limitations
- Saturable drug transport/metabolism

Accelerated development of the dual orexin receptor antagonist ACT-541 468
Integration of a micro-tracer in the first-in-human study

- Single-ascending dose study in healthy, male adults
- N=6/2 subjects on ACT-541468/placebo per dose level (5, 25, 50, 100, 200 mg p.o.)
- Objectives:
  - **Safety/tolerability**: AEs and other safety data (ECG, laboratory, vital sign)
  - **PK**: Cmax, AUC, Tmax, T1/2…
  - **PD**: CNS-related effects (based on saccadic peak velocity, adaptive tracking, body sway)
  
  - **Mass balance and metabolite identification/profiling**:
    - ACT-541468 (50 mg p.o.) + 14C-labeled microtracer by oral administration
    - Collection of blood, urine, and feces up to 168h post dosing
    - Quantification by accelerated mass spectrometry
  
  - **Absolute bioavailability**:
    - ACT-541468 (100 mg p.o.) + 14C-labeled microtracer by i.v. administration over 15 min

Accelerated development of the dual orexin receptor antagonist ACT-541 468 (cont.)

Integration of a microtracer in the first-in-human study

Mass balance

![Graph showing mass balance with average recovery of 84.5%]

- Excretion via feces (57%) and urine (28%)
- N=77 metabolites identified

Conc. over time («i.v. vs. oral»)

![Graph showing concentration over time for i.v. and oral administration]

- Abs. bioavailability: 62 % (95 % CI: 52-75)

→ Data will be used to seek for study waivers (abs. BA & hADME study)

A comparison between conventional vs. novel approach of metabolite profiling

<table>
<thead>
<tr>
<th></th>
<th>&quot;Conventional approach&quot; (= hADME study)</th>
<th>&quot;Novel approach&quot; (= micro-tracer or micro-dose study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethics/safety aspects</td>
<td>Radiation burden needs to be calculated based on QWBA data</td>
<td>No radiation burden determination required Micro-dosing can be useful in case of “high-uncertainty” drugs</td>
</tr>
<tr>
<td>CMC aspects</td>
<td>Use of non-GMP material may not be acceptable</td>
<td>Non-GMP material can be used</td>
</tr>
<tr>
<td>Regulatory aspects</td>
<td>Well-established approach proven to be adequate for regulatory submissions Comprehensive toxicology data required</td>
<td>Innovative approach, i.e. need for regulatory buy-in Limited toxicology data sufficient</td>
</tr>
<tr>
<td>Costs</td>
<td>App. 1.5-3.0 Mio. USD</td>
<td>App. 0.3 -0.5 Mio. USD</td>
</tr>
<tr>
<td>Data availability</td>
<td>Phase II</td>
<td>Phase I</td>
</tr>
<tr>
<td>Pharmacological aspects</td>
<td>Pharmacologically active dose</td>
<td>Uncertainty about tentative therapeutic dose Lack of PD and safety data in case of micro-dosing approach</td>
</tr>
</tbody>
</table>

CMC - Chemical Manufacturing Control; GMP - Good Manufacturing Practice; hADME - human absorption, distribution, metabolism, and elimination; PD - Pharmacodynamics; QWBA - Quantitative whole-body autoradiography

The future of metabolite profiling

A paradigm shift on the horizon?

• Traditionally, hADME studies have been conducted rather late in the drug development process (i.e. during phase-II/III)

• Integration of metabolite profiling in FiH trials is expected to become more common due to several advantages

• Additional up-front investments are required, but may pay off provided the drug candidate is pushed further through the development life cycle

• The scope of metabolite profiling may expand in the coming years
  – Currently, it refers to the identification and quantification of *exogenous* metabolites originating from an investigational drug.
  – The potential value of assessing the *endogenous* metabolite profile in response to drug treatment and/or in relation to diseases remains to be further evaluated (i.e. metabolomics).
Metabolite profiling ≠ Metabolomics

Human metabolome project
http://www.hmdb.ca/
Conclusions

• Early identification of reactive and/or disproportionate metabolites is encouraged by regulatory bodies
• In recent years, the feasibility of integrating metabolite profiling in early clinical drug development has markedly increased
• Metabolite profiling by means of micro-dose or micro-tracer approaches may be more commonly applied in the near future and replace the need for conventional hADME studies at late-stage development
• Integration of metabolite profiling in early clinical development is in line with efforts to maximize the informative value of FiH trials by complementary objectives, e.g. related to abs. BA, food effect, proof-of-mechanism, etc.
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Thanks for your attention!

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