GSK experience of application of AMS to clinical studies...the last 5 years & GBC (LC+AMS) Team update

Graeme Young, GSK
(& the GBC AMS harmonisation team)

26th March 2015
GSK Clinical study support by AMS – the last 5 years
And into the future........
Innovative approaches to Clinical PK & metabolism data;
GSK examples – iv & po, $^{14}$C & cold, small & large [MWt.], early & late...

**FTIH mAb-dAb**
- Validated the platform
- F = ~13%

**FTIH IV PK**
- Acceptable for progression
- Highly Information rich; definitive PK & routes of metabolism at early stage; limited cost/effort
- To model therapeutic IV doses and investigate human metabolism

**DDI study**
- DDI confirmed at µdose; No Go
- To provide input to formulation dev. & establish metabolism in humans incl. biliary

**FTIH IV/PO**
- Acceptable for progression
- Abs. bio. for Reg submissions; reduced variability, study size (only n=4 patients) & study duration

**Trametinib**
- Concentration in human plasma following IV (5µg) and oral (2mg) doses

**Dabrafenib**
- Concentration in human plasma following IV (5µg) and oral (2mg) doses

Discovery Phase | Phase 0 | Phase I | Phase II | Phase III | Phase IV/Launch
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Graeme Young, PTS DMPK
Phase 0 (PK) 2010*

Background
- IV clearance data sought to model oral FIH
- Scaling from rat/dog PK (very different clearance)
- ‘Phase 0’ approach proposed

Key Question
- Does the molecule have acceptable clinical PK?

Results & Impact
- Acceptable plasma clearance in humans
- ~20% drug in urine

Lessons learned/Value added
- Optimize FIH design/doses/regimen
- Allow early planning of PoM via FIH extension

Early Phase 2: IV microtracer (2010)

Background

- Switch from oral to IV administration as therapeutic route
- Better info. for IV starting dose/escalation for next study
- Collect info. on route & rates of elimination

Key Questions

- Absolute bioavailability and characterising IV PK?
- What IV doses are needed for progression?

Lessons learned/value added

- Data used to model therapeutic IV doses
- Data used to build picture of human metabolism – particularly biliary elimination
Late Phase 2: IV microtracer (2011)*

Background

• Drug Y has variable PK following oral dosing to humans
• Selection of appropriate formulation for Phase 3 will be assisted by understanding of absolute bioavailability & optimal regional absorption in humans

Key Questions

• Window of absorption; guide phase 3 formulation development
• Test promising formulations for optimal delivery
• Maximise info. on bioavailability & metabolism for phase 3

Lessons learned/value added

• F was low at <30% (all formulations)
• Data used to provide input to formulation development effort
• Data used to further establish picture of human metabolism – particularly biliary elimination

Background

- Regulatory requirement for definition of absolute bioavailability

Key Questions

- Define absolute bioavailability in target population; cancer patients

Lessons learned/value added

- Absolute bioavailability measured in only 4 patients (F=72%); precedent set by study on dabrafenib
- Value of microtracer approach to reduce variability and hence study size and clinical study duration – allowing release of patients to rollover therapy study

* Concomitant oral and microdose intravenous pharmacokinetics of trametinib, a MEK inhibitor, in subjects with solid tumours, Leonowens C et al., 2014 Sep, 78(3), 524-532.
Global Bioanalysis Consortium: New Frontiers - AMS harmonisation team

• Representatives from the pharmaceutical industry and biomedical AMS CROs; Graeme Young (GSK) – chair; Mark Seymour & Paul Steinberg (Vitalea Science), Julie Zalikowski (Accium BioSciences), Mike Butler (Xceleron), Philip Timmerman (Janssen), Kohei Nozawa (Sekisui Medical), Wouter Vaes (TNO), Steve Dueker (Sivvon)

• Output to date; focussed on LC+AMS assays for isolated individual analytes (rather than total radioactivity)
  – Publication


  Included aspects related to -
  ❖ Instrument performance: linearity, accuracy and precision
  ❖ Assay qualification/validation: Accuracy and precision – details of the procedures yet to be harmonised
  ❖ Analyte recovery
  ❖ Use of QC samples; Preparation of standards and QCs
  ❖ Analyte stability; including reliance on existing data from eg. LC/MS assay support
  ❖ Assay robustness

• Further harmonisation is underway including;
  ❖ adoption of the acceptance criteria routinely applied to LC/MS assays
  ❖ generation of calibrants & confirmation by LSC
Future of AMS development...

• Gas analysis
  – Increased throughput...from days to minutes!
  – Improved sensitivity (carry over may be the main challenge)

• Simpler instruments??
  – ETH Zurich – smaller footprint; BIOMICADAS and pre-prototype \( \mu \text{CADAS} \)
Additional GSK AMS study related references


- Absorption, distribution, metabolism, and elimination (ADME) of umeclidinium (UMEC) in healthy adults, Kelleher D. Poster at European Respiratory Society (ERS), Vienna, Austria Sep 2012


The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents.