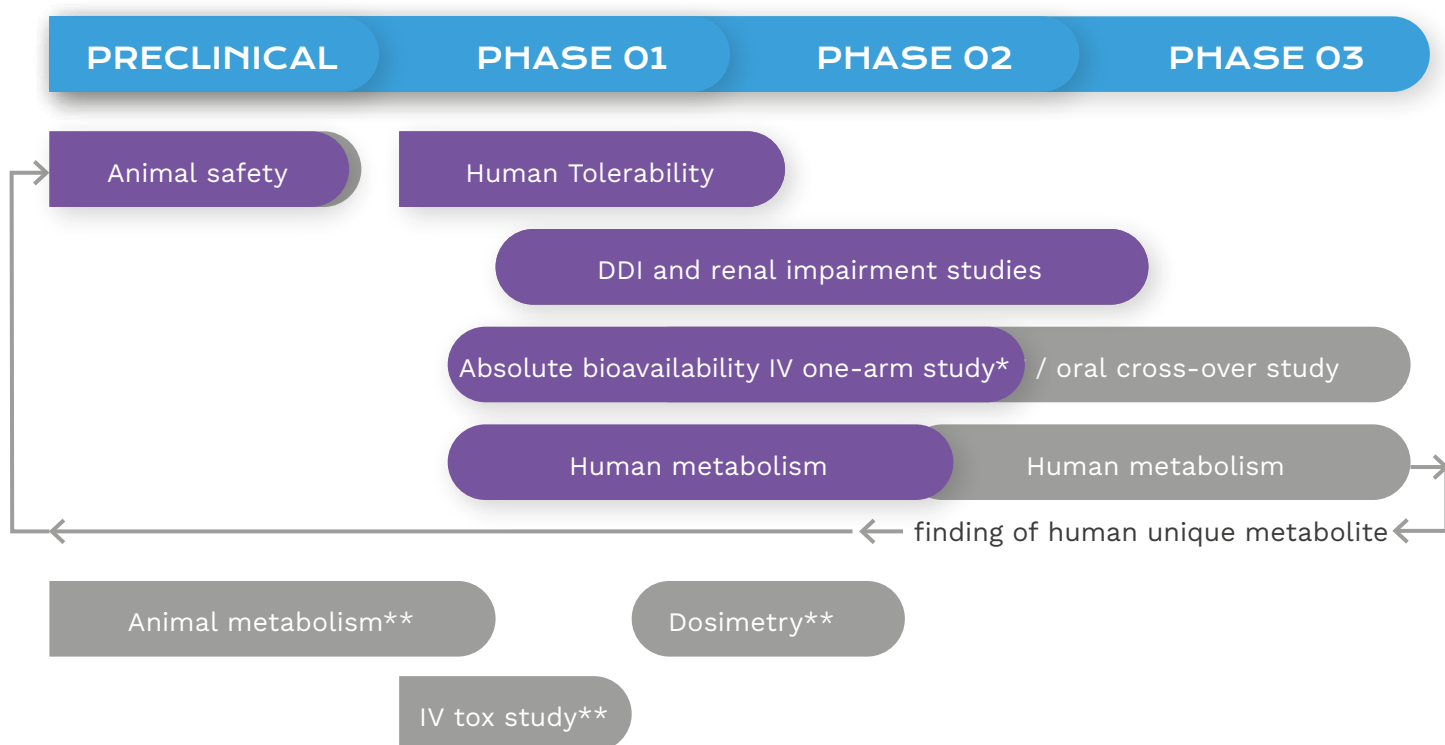




EFFICIENT ENRICHMENT OF HUMAN DATA IN EARLY-STAGE CLINICAL DEVELOPMENT

● MICROTRACER STUDIES versus ● CONVENTIONAL METHODS



* With an absolute bioavailability IV one-arm study, there is no need for a second study.

** Animal metabolism and IV tox study can be waived in this workflow, and dosimetry can be pushed back.

ACCELERATE. DE-RISK. REDUCE COSTS.

MICROTRACER STUDIES AS THE NEW STANDARD FOR HUMAN ADME

CONVENTIONAL	MICROTRACER STUDIES
- Human unique metabolites are generally found in Phase 2b/3 placing the human ADME trial on the critical path - Dosimetry/QWBA is required due to Ethical Class 2 of the ICRP - DDI and impairment studies based on <i>in vitro</i> and <i>in vivo</i> animal data - Lack of LSC sensitivity for PK and/or metabolites in plasma of candidates with long half-life (> 100 hr) - Regular dose is 100 µCi while the LSC sensitivity is ~ 0.5 Bq/LC fraction - Human ADME data and AbsBA data are collected in separate studies at oral therapeutic dose - AbsBA is a two arm cross-over design of two-periods requiring IV toxicity data - IV toxicity study is required - Separate studies do not allow determination of fraction absorbed (Fa) - Conducted with full GMP material, also for 14C material - Animal MB/MP studies are conducted to de-risk drug development - Therapeutic dose IV formulations are complex for BCS class II and class IV with low aqueous solubility - Should always be conducted in dedicated facilities	- Human metabolite safety concerns are caught from Phase 1 - Dosimetry not required before human microtracer study - Early hADME data optimizes design of DDI and hepatic/renal studies - AMS has the required sensitivity for candidates with long half-life - Microtracer dose is between 0.1 and 1 µCi (100-fold ↓) - AMS sensitivity is ~ 10 µBq/LC fraction (500-fold higher sensitivity) - Human ADME and AbsBA can be combined in a single cohort study due to low IV dose of ≤ 100 µg - One arm study design is sufficient for determination of AbsBA - No IV toxicity data is required - Fraction absorbed can be determined in a two-period study - Qualified 14C material often tolerated - Early human metabolism data enables early MIST assessment - Microtracer dose IV formulations are generally below solubility limits - Possibilities for piggy-backing the microtracer on existing clinical trials - Complies with ALARA principle for radiation burden of participants



FDA recommendation: “Usually, sponsors have conducted human *in vivo* metabolism studies relatively later in drug development, but we **strongly recommend** that sponsors conduct **in vivo metabolic evaluation in humans as early as feasible.**”
(FDA Safety Testing of Drug Metabolites Guidance for Industry)



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