Exploratory Clinical Trials: The AstraZeneca Perspective 2006-2009

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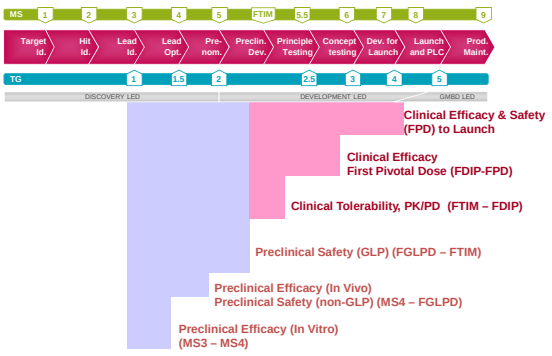
AstraZeneca
RESEARCH & DEVELOPMENT
GLOBAL SAFETY ASSESSMENT

"The dogmas of the quiet past
are inadequate to the stormy present…
As our case is new, so we must think anew.
We must disenthrall ourselves."

Abraham Lincoln
Annual Message to Congress
01 December 1862

Traditional Drug Development



Exploratory Clinical Trials

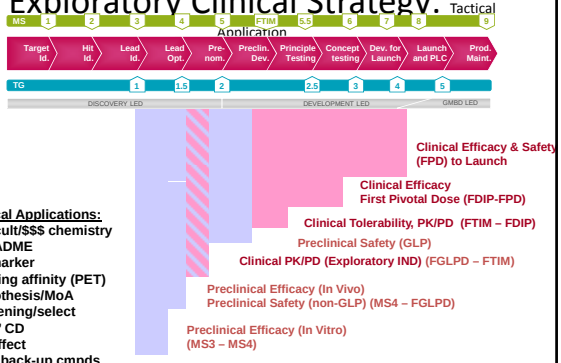
Tactical Application

- Candidate Drug (CD, or later)
- De-risk a compound or compound selection
- GMP chemistry
- Investigational drug is possible launch candidate
- Clinical endpoints:
  - PK, ADME
  - PD
  - Efficacy biomarker
  - Select Phase I CD
  - Confirm back-up CD

Strategic Application

- Lead compounds
- De-risk basic biology (e.g. therapy target)
- Pre-GMP chemistry
- Investigational drug (probably) not a launch candidate
- Clinical endpoints
  - Proof of Principle (PD, biomarker)
  - Select chemistry platform (PK, ADME)

Exploratory Clinical Strategy: Tactical Application



Tactical Applications:
- **Difficult/$$$ chemistry**
- **PK, ADME**
- **Biomarker**
- **Binding affinity (PET)**
- **Hypothesis/MoA**
- **Screening/select 'best' CD**
- **PD effect**
- **Park back-up cmpds**

AZ Candidate A – 'First in Class' Antibacterial

- Available non-clinical data:
  - Novel mechanism of action, 1st clinical candidate
  - Pharmacology, toxicology, safety pharmacology and pharmacokinetic studies
  - Support single oral dose FTiH study to evaluate safety, tolerability and PK profile.
- Target plasma AUC for efficacy known:
  - Highly variable PK between preclinical species – impact upon human PK prediction
  - Candidate A was viewed 'at risk' not to meet its Therapeutic Product Profile
- Critical clinical hypothesis:
  - Does Candidate A's PK profile in man support a therapeutic plasma AUC with a commercially viable dosage regimen?

Non-clinical Data Package for Candidate A

- Mouse - 14-day (MTD)
  - 10/sex/dose
  - Identify target organ toxicity
  - Determine NOAEL: 632 mg/m2/day
- Dog - 7-day (MTD)
  - 3/males/dose
  - Identify target organ toxicity
  - Determine NOAEL
- Genotoxicity:
  - Ames, mouse lymphoma, rat micronucleus
- Safety Pharmacology
  - Core battery (CV, CNS, Respiratory)
- First Human Dose
  - 1/50th of mouse NOAEL dose (mg/m2) agreed with MHRA
  - Starting dose: 24mg (12.6 mg/m2)

Candidate A

- Regulatory strategy:
  - Submitted 'exploratory IMPD' to the MHRA based on the recent FDA Exploratory IND guidance
  - Two MHRA meetings held to discuss toxicology data and specific starting and maximum doses for the study
- Non-clinical metrics:
  - ~ 650 g Compound A (of which ~400g for nonclinical package)
  - ~ 7 months from FGLPD to FTiH
- Clinical metrics:
  - Rational for clinical start dose:
  - First subject received 24 mg; the final cohort received 300 mg.
- Outcome:
  - The exploratory strategy allowed efficient and expeditious data generation supporting a GO/NO GO decision
- Retrospective:
  - Project Team felt that a traditional non-clinical program might have provided useful information to guide future research efforts

'Candidate B' is the 3rd CD in a series:

- 1st CD is currently in Phase II
  Promising phase II data but has less than optimal PK profile
- 2nd CD is about to start conventional Fitch
  Has an improved non-clinical PK profile, compared to 1st CD
- 3rd CD (Compound B)
  Somewhat behind, but has further preclinical improvements vs. 2nd CD

An exploratory clinical approach provides opportunity to gain critical data on Candidate B, for a rapid PK comparison across the 3 CDs to select optimum candidate moving forward.

Non-clinical Data Package for Candidate B

- Rat - 7-day (MTD)
  - 10/sex/dose
  - Identify target organ toxicity
  - Determine NOEL: 50 mg/kg/d
- Dog - 7-day (capped dosing)
  - 3/sex/dose
  - Explore safety and tolerability in the dog
  - At least 30-fold margin to planned maximum exposure in clinical study
  - Determine NOAEL: 50 mg/kg/d
- Genotoxicity:
  - Ames, mouse lymphoma, rat micronucleus
- Safety Pharmacology
  - Core battery (CV, CNS, Respiratory)
- Clinical safety data generated for previous CDs would provide additional supporting data
  - No target-related effects identified in healthy volunteers

Candidate B: Single Ascending Dose Pharmacokinetic Study

- Study design:
  - Single center, single dose, placebo-controlled study
  - Up to 4 ascending single dose cohorts, up to 6 healthy male volunteers per cohort
  - Each subject will only receive a single dose
  - PK parameters will be assessed at each dose level before escalating the dose.
  - Standard safety monitoring
- Study objectives:
  - To define the pharmacokinetics of Candidate B in humans
  - Allows for appropriate comparison with other AstraZeneca compounds in development

- Exploration of PK at an exposure predicted to approach those to be explored in patients is required to allow accurate PK comparison
  - To assess Candidate B it was important to start at a dose no greater than 1/50 of the NOAEL from the toxicology study in the most sensitive species on a mg/m2 basis
- The maximum dose was set using the most conservative of the following criteria:
  - ¼ of the 7-day rodent NOAEL on a mg/m2 basis
  - Up to ½ of the AUC at the NOAEL in the rodent study, or the AUC in the dog at the rat NOAEL, whichever is lower
  - Observation of an adverse clinical response
  - ½ of the predicted therapeutic dose of 80 mg (i.e. 40 mg) will be the maximum target dose for the PK study
  - PK at a maximum target concentration of 2400nmol/L
- The dose was escalated following an adaptive design in response to the exposure achieved by the previous administration

Candidate B: Exploratory CTA

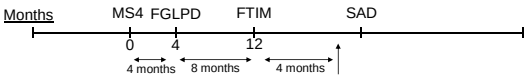
- Exploratory CTA submitted to MHRA in October 2008
- Discussed at MHRA multidisciplinary CTU assessors' meeting in late October
- Approval received by UK MC by end October 08 with minimal comments:
  - Safety from previous cohorts to be assessed before next cohort was dosed
  - Shelf-life of products must start from manufacture of drug substance
- Overall MHRA review timing from CTA resubmission = 18 days
- EC approval obtained without questions
- FTiH to Clinical decision: <3 months

Candidate B: Standard vs. Exploratory CTA Timings

Standard

Data available for decision making (24 mo)

Exploratory



Data available for decision making (16 mo)

Candidate B: Benefits and Challenges

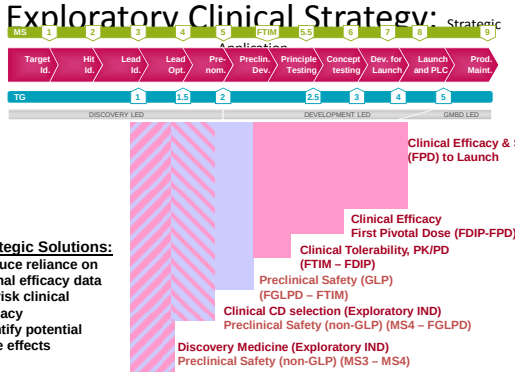
Benefits

- Rapid transition from candidate drug selection to FTiH
- Successful CTA submission and approval with agency input
- Provide earlier readout than conventional SAD to allow for review of data and comparison with more advanced programs.
- Less pre-clinical investment to get to this point.

Challenges

- Projects not set up for exploratory clinical trial consideration. This, and limited experience, led to protracted discussions.
- By the time that Projects consider the exploratory CTA for a CD1, it may not be worth doing – easier for CD2s onwards.
- If Candidate B is selected over 2nd CD:
  - Need to carry out a conventional SAD/MAD program which may prolong overall time to FTiP.
  - Need to conduct pivotal 1m tox to enable MAD. Because the dog was a capped dose, additional DRF work required before these, potentially leading to a delay between eSAD and full SAD / MAD

Exploratory Clinical Strategy:



Strategic Solutions:

- Reduce reliance on animal efficacy data
- De-risk clinical efficacy
- Identify potential side effects

AZ Candidate C

- Very attractive target; time to market important
- Competitors may be leading on this target
- Lack of human target validation / translation
- Rapid 'Proof of Mechanism' read-out possible in humans (single dose ranging study), with an appropriate investigational compound
- Positive Proof of Mechanism from exploratory clinical trial would justify front-loading investments needed for rapid start of Phase IIb for 'Launch' of a subsequent CD

Candidate C: Family Strategy

- CD1:
  - Exploratory compound to progress only to SAD study to achieve PoM / PoP vs. biological target
- CD2
  - A 'candidate drug' addressing known deficiencies of CD1 - to be nominated prior to CD1 SAD studies.
  - Positive PoM from CD1 (along with acceptable toxicology in 7 day rat & dog DRF studies) would trigger acceleration of chemical synthesis and nonclinical program to support most rapid progression to Phase III
- CD3
  - Backup compound to CD2 (same profile, structurally diverse, addressing remaining perceived risks of CD2)

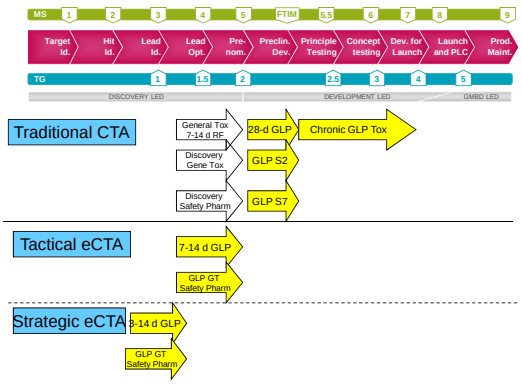
Non-clinical Data Package for Candidate C

- Rat – single dose w/extended observations
  - 10+5/sex/dose
  - Identify target organ toxicity
  - Determine NOAEL
- Dog – single-dose w/extended observations
  - 3+2/sex/dose
  - Identify target organ toxicity
  - Determine NOAEL
- Genotoxicity:
  - Ames, mouse lymphoma, rat micronucleus
- Safety Pharmacology
  - Core battery (CV, CNS, Respiratory)

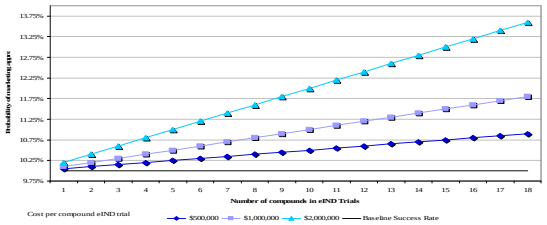
Summary: Non-Clinical Packages for Exploratory CTA

- The primary objectives of AZ's nonclinical study packages are to protect the safety of participating volunteers and patients, to enable the clinical trial to proceed (e.g. gain regulatory approval), and to minimize the use of research animals
- In minimizing animal use, AZ considers not only the immediate exploratory trial, but also the probability that additional nonclinical studies will be commissioned if the test article is subsequently advanced for Phase 1 clinical trials
  - If the test article is CD quality, the nonclinical program is designed to allow the studies enabling exploratory trial to:
    - Support later Phase 1 entry, or
    - Provide necessary range finding for pivotal nonclinical Phase 1 enabling studies.
- In any event, anticipatable repetition of a nonclinical animal study (e.g. for MTD or reversibility) should be avoided, even if to do so requires expenditure of additional resource (e.g. compound, etc.), and/or lengthens timelines.

AZ Preclinical Strategies



Exploratory CTAs & Probability of Product Launch



AZ Conclusions

- Exploratory clinical strategies are first & foremost a investigational tool, requiring collaboration between clinicians, bio-scientists, chemists, toxicologists, and regulatory scientists
- Exploratory strategies should be considered for those projects where the risks for failure are greatest; however, to be successful exploratory studies must deliver critical human data for a decision-making hypothesis
- The decision to use an exploratory strategies must be made early, ideally at (or before) lead optimization
- Exploratory studies are most effective when applied strategically, leading to subsequent selection of a CD for clinical development based upon critical human data.
- Exploratory studies are NOT for every project. A project with one CD and no prospect for additional chemical support can not take advantage of an exploratory strategy, except to make a 'Quick Kill'.

Acknowledgements

- AZ Exploratory IND Support Group