Lessons Learned When Integrating Studies for the Development of a Biopharmaceutical

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Overview

• Regulatory Guidance allows for alternatives to a dedicated study for assessing cardiovascular endpoints.

• There are business and scientific drivers that favor this strategy.

• The design and execution of these studies imposes certain restrictions and presents several challenges to the collection of such endpoints.

• Biological agents typically have a long half-life compared to small molecules, and route of administration will impact Tmax.

• As biological agents are often exquisitely targeted, off target effects are not anticipated, but may emerge as a consequence of extended exposure and secondary responses.

• Monitoring Safety Pharmacology endpoints in a repeat-dose toxicology study does provide the opportunity to evaluate potential impact of extended exposure.

• Goal: recognize the limits imposed by the study design and collect best quality data possible.
Regulatory Drivers: ICH S6 (R1)

• 4.1 Safety Pharmacology
• It is important to investigate the potential for undesirable pharmacological activity in appropriate animal models and, where necessary, to incorporate particular monitoring for these activities in the toxicity studies and/or clinical studies. Safety pharmacology studies measure functional indices of potential toxicity. These functional indices may be investigated in separate studies or incorporated in the design of toxicity studies. The aim of the safety pharmacology studies should be to reveal any functional effects on the major physiological systems (e.g., cardiovascular, respiratory, renal, and central nervous systems)... All of these studies may allow for a mechanistically-based explanation of specific organ toxicities, which should be considered carefully with respect to human use and indication(s).
Regulatory Drivers: ICH S9 (oncology)

- **2.2 Safety Pharmacology**
- An assessment of the pharmaceutical’s effect on vital organ functions (including cardiovascular, respiratory and central nervous systems) should be available before the initiation of clinical studies; such parameters could be included in general toxicology studies. Detailed clinical observations following dosing and appropriate electrocardiographic measurements in non-rodents are generally considered sufficient. Conducting stand-alone safety pharmacology studies to support studies in patients with advanced cancer is not called for. In cases where specific concerns have been identified that could put patients at significant additional risks in clinical trials, appropriate safety pharmacology studies described in ICH S7A and/or S7B should be considered. In the absence of a specific risk, such studies will not be called for to support clinical trials or for marketing.
Business Drivers

- Efficiency
  - Combining study objectives provides cost savings
  - Reduce the amount of compound needed for program
- Reduces the number of animals used (3Rs)
Scientific Drivers

- Biologics often have dramatically different pharmacokinetics than small molecules
  - Toxicity may be more related to AUC than Cmax
  - Depending on route of administration, Tmax may be many hours or even days after administration
- Testing for cardiovascular changes over a much longer time-frame may be more relevant
- Detecting functional changes that emerge as exposure matures may be more relevant to patient safety
- Correlating functional changes with other Toxicology endpoints can be very informative
Unfortunate Realities

• What you start out with may not be what you end up with
  • Regulatory studies may have limited pre-existing data to inform as to long term toleration
    • The one month study in NHP is sometimes the first toxicology study beyond dose ranging
    • May have doses higher than those previously tested if no treatment related toxicity noted earlier
  • Treatment related toxicity (not necessarily related to the cardiovascular system) may compromise animal health or even eliminate dose groups
    • This may complicate the interpretation of data
Unfortunate Realities II

- Oncology treatments often involve cytotoxic drugs
- The emergence of toxicity over time may confound the interpretation of the data
  - Loss of animals in a group or an entire dose group is possible
- Distressed or moribund animals may not provide quality data
- Biologics targeting other therapeutic areas may immune-related responses
  - Anti-Drug Antibodies may decrease exposure over time
CNS & Respiratory endpoints

- Cage side observations and chairing for evaluations of responses and reflexes are possible
  - Consider logistics of how long each assessment takes and the total time required to get through the entire cohort.
  - May want to stagger doses to allow assessment of males and females on separate days
  - May want multiple teams to expedite process

- As assessments will be typically be in the room, the behavior of all the animals will be influenced.

- Respiratory assessment will be observational. Respiratory rate may be influenced by observation.
Cardiovascular endpoints

• Reliable, relevant measures of blood pressure require instrumentation.

• Telemetry implantation is expensive, but may be justified for specific concerns
  • Hypotension, hypertension, contractility changes, sudden death

• Surgical implantation may complicate subsequent pathology

• Economies
  • Fewer groups (vehicle and high dose only)
  • Single sex

• Dedicated SP-CV study may be simpler.
Jacketed External Telemetry with BP

- Less invasive surgery
- Retain Jacket liabilities (acclimation)
- Amenable to standard toxicology study design
- Limited to arterial blood pressure
- No restraint artifacts, undisturbed in home cage
- Quality of data depends on training of staff and adherence to SP study processes
Jacketed External Telemetry - ECG

• Probably the default paradigm considered for inclusion of SP endpoints into a toxicology study
• Amenable to study design
• Bluetooth technology
• Group housing possible
• ECG data will inform as to some cardiovascular endpoints, but not all
  • For precisely targeted biological agent with low likelihood of off-target interactions, may be the ideal solution
Jacketing Non-Human Primates

- One size may not fit all
- Acclimation to the jacket is required
  - Regimens vary
    - Ours: 3 sessions of increasing duration up to 36 hours
  - Duration of acclimation isn’t forever
    - 2 weeks likely
    - 3 weeks maybe
    - Circadian pattern of HR and BP changes is a good indicator
    - May have to accept ‘new baseline’ vs. ‘normal’
- Fitting and adjusting the jackets will require restraint
  - Repeated chemical restraint carries some risk
Jacketing II

- Jackets must be secured
  - Dogs roll and bounce around
  - NHPs will attempt to remove the jackets
    - Zip ties are handy
- Electrode placement may require several attempts to optimize
  - Requires review of signals during jacketing
    - Take the time to get it right.
  - Skilled technical staff required
  - Repeated reviews to verify consistency
Acclimation to Jackets is Critical

PCT-derived mean arterial pressure data from NHP

Elapsed Time (relative to dosing, hours)

Mean Arterial Pressure (mmHg)

Light Cycle

Night Cycle

Light Cycle

K Derakhchan et al., SPS 2009
Study Design Tradeoffs

- Parallel Design vs. Latin Square Crossover
- Male and Female data
  - Combine or analyze separately?
- Getting data from lots of animals vs. analyzing data from lots of animals
  - 40 NHP: HR ~150: 24 hrs collection:
    - $40 \times 150 \times 60 \times 24 = 8,640,000$ beats
The Parallel Dose Group Design Generates a LOT of Data

- Standard 8 animal Latin Square Crossover with 4 doses
  - 8 x 4 = 32 animal-data days
  - If add in 8 days of baseline data: total = 40
- JET: n=5, 3, 5, 3/sex (32 total)
  - Beginning and end of study = 64
  - Adding in baseline data = 96 animal-data days!
  - Recovery animals (2 veh, 2 MD/sex) = 8 more
- Prompt turnaround of data will require aggressive resourcing
Super Intervals for Statistical Analysis

• Day one taken up by toxicology endpoints
• With a biologic, dynamic events unlikely
• Averaging bigger blocks of time into larger intervals will improve the sensitivity to detect changes
  • Obvious blocks would be related to light/dark cycles
  • Exclude timeframes with external events
    • Feeding, husbandry, light/dark transitions
# Study Design Impact on Statistical Power

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<th>Values</th>
<th>PR (msec)</th>
<th>QRS (msec)</th>
<th>QT (msec)</th>
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Statistical Significance vs. Treatment Related Effect

• Not everything that counts can be counted and not everything that can be counted, counts. (Einstein)

• Lack of statistical significance does not remove the possibility of treatment related effects.
  • Conversely, a change that is statistically significant may not be biologically relevant.
  • An examination of individual animal responses is always warranted.
Maximizing the Chances for Success

- Understand what you are trying to measure
- Recognize logistical constraints
- Take advantage of local expertise and experience
  - Skilled and engaged technical staff are a must
- If at all possible, do a dry run
  - If you think education is expensive, try ignorance.
  - Trust, but verify
Beware the network!

- Network driven events may disrupt data collection
  - Software updates
  - Virus library updates
  - Virus scans
- Validated Systems should not have software updates unless it can be proven that the update will not affect performance.
  - Your study should not be the test
Best Strategy

• Early planning essential to success

• Obtain the best data possible to support the relevant risk assessment
  • Will the most relevant endpoint be covered?
  • Do you understand the impact of the study design?
  • Will the study satisfy the required level of sensitivity?
  • Do you have confidence in the study execution?

• Be open to novel options
  • Experience is a good teacher
Summary - Integrating SP Endpoints into a General Toxicology Study

• Can it be done?
  • Yes, absolutely.

• Is it always a substitute for a dedicated Safety Pharmacology Study?
  • No.

• Will it satisfy regulatory requirements?
  • Biopharmaceuticals: Yes.
  • Oncology: Yes.
  • Small molecules: ???
  • Will it satisfy the Scientific requirements? Perhaps.