



Continuing Education AM3: Translational Medicine

Case studies for the application of
safety pharmacology to clinical
development



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Basic Tenet

Humans are animals but animals are not human...

- Important to recognize differences and limitations
- In the absence of one-to-one correlation, must take a body-of-evidence approach



First Principles

In drug development,

- Primary objective: Safety
- Secondary objective: Safety

- Does the drug have a benefit?
Risk (aka safety)-benefit



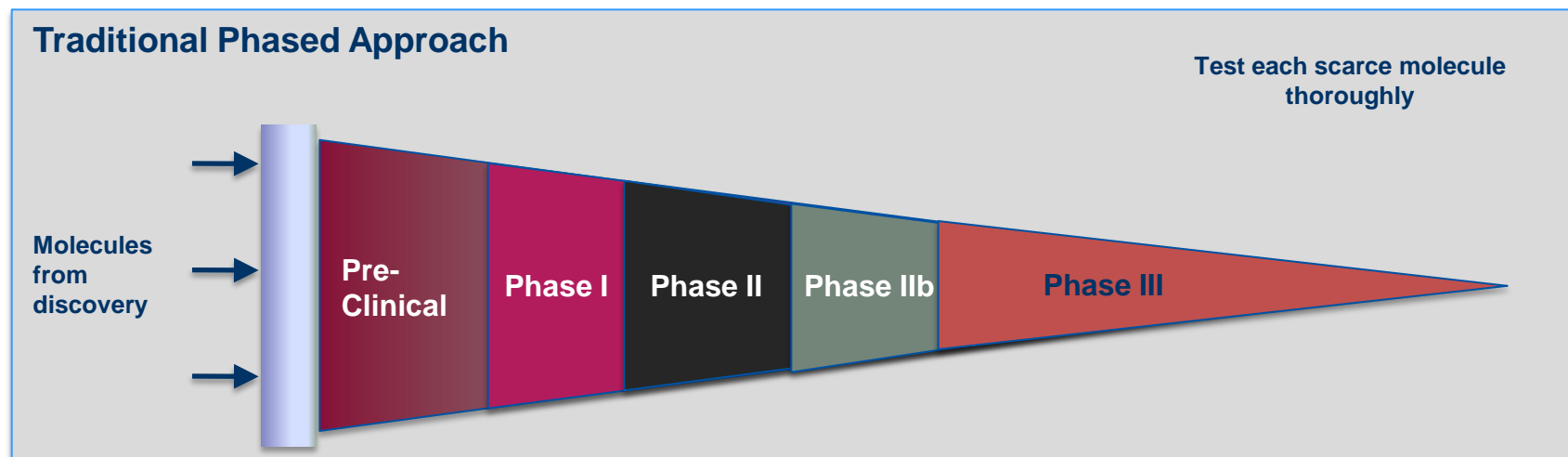
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Elements of a Phase 1 Study



Phases of Clinical Development



Source: William Blair & Company, (Bain and Company) Covance Investors Overview June 16, 2010



Objectives of Phase 1

- Evaluate safety
- Explore pharmacokinetics
- Hint (?) of pharmacology
(receptor engagement, proof-of-mechanism)
- Answer questions to help design the next study or Phase of clinical development



Critical Documents

Clinical Protocol

- Who will be studied?
Inclusion/exclusion criteria
- What will be done?
Assessments like vital signs, ECGs, blood collection
- When?
Timing of assessments, schedule of events
- How will the data be collected and analyzed?
Statistical plan
- Ethics and study oversight



Additional critical documents

Investigator's brochure (IB)

- Summary of pharmacological rationale, nonclinical safety data, description of product



Informed Consent Form (ICF)

- Description of the risk associated with participation in the study
- Written in everyday language
- Risks derived from IB and protocol





Additional critical documents

Investigational New Drug (IND) Application

- Animal pharmacology & toxicology, Chemistry & Manufacturing, Clinical protocols, Investigator Brochure

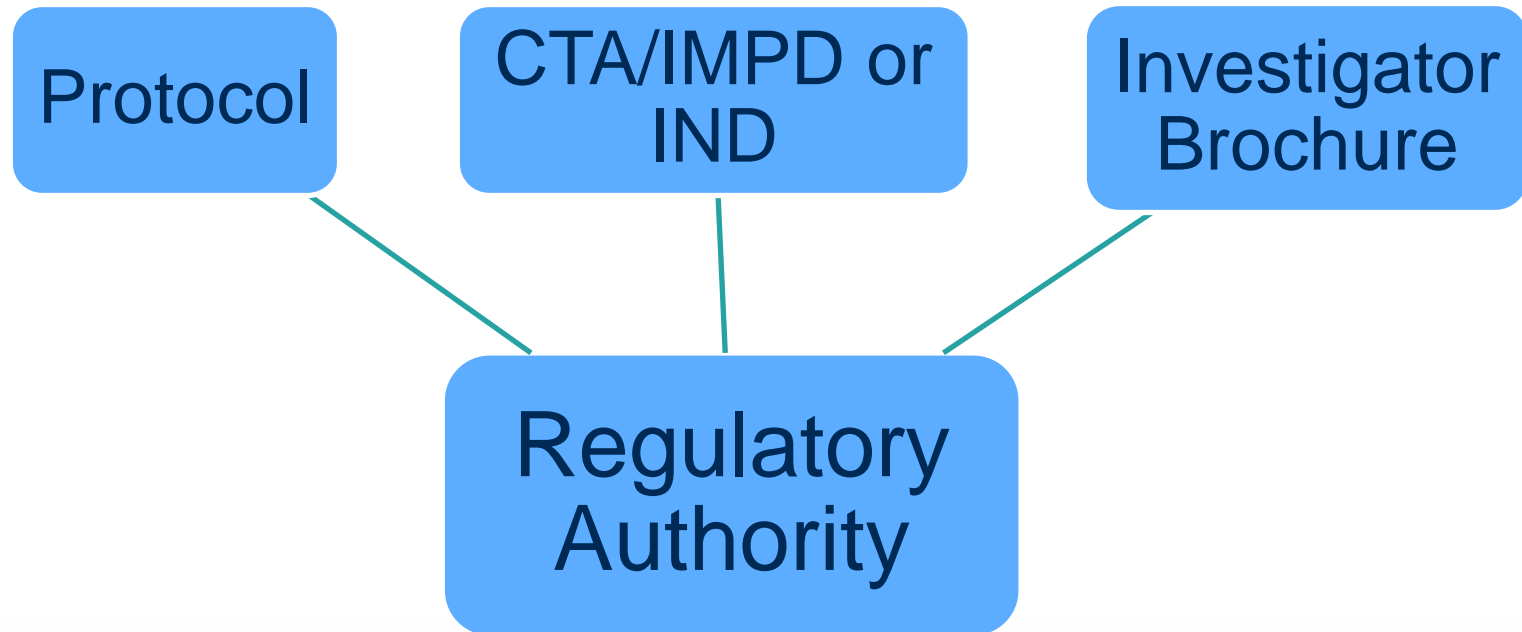
Clinical Trial Application (CTA)

Investigational Medicinal Product Dossier (IMPD)

- Information related to quality, manufacture and control, nonclinical & clinical use

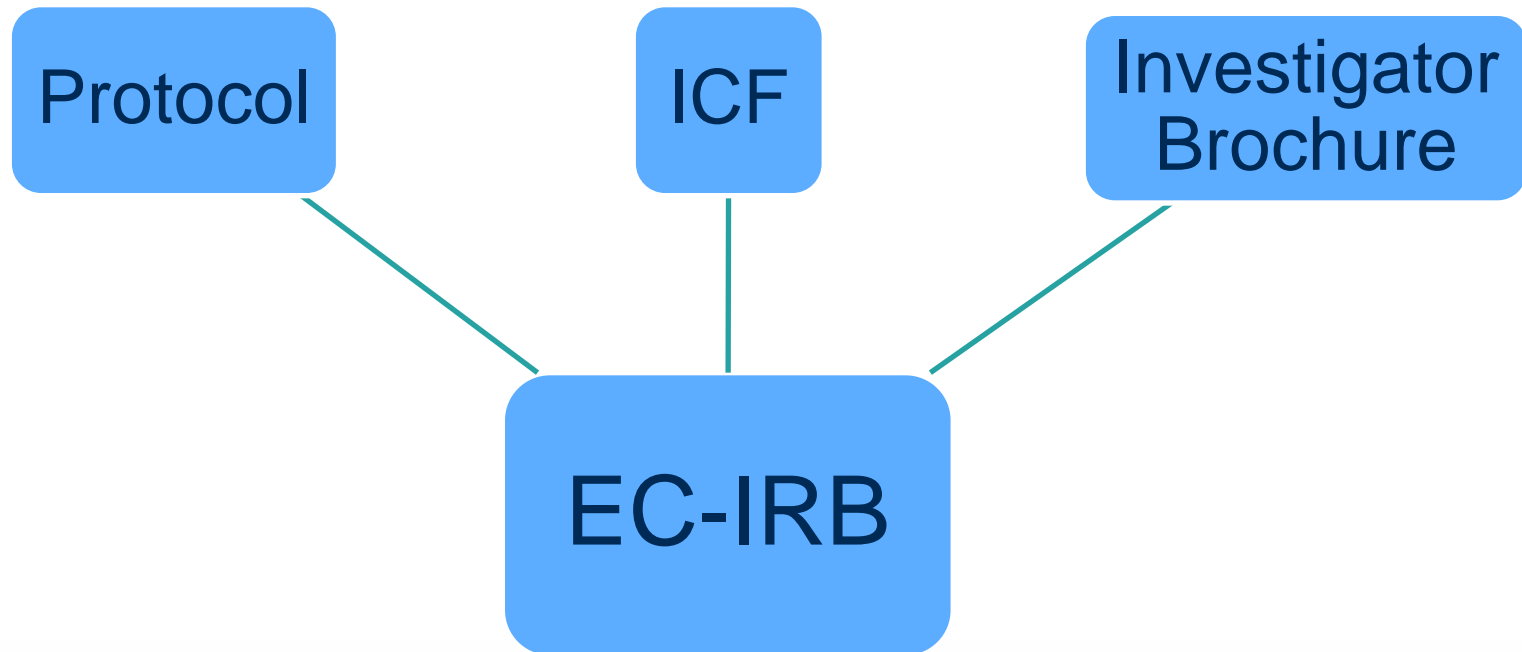


The Process: Regulatory approval





The Process: Ethics approval





Regulatory approval AND Ethics approval

Necessary prior to start of the clinical trial



First-in-Human

- First transition from animal to human
- Use animal pharmacology and toxicology observations to predict what the human response would be
- How do we chose the first dose to give humans?



Guidance for Industry

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

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**July 2005
Pharmacology and Toxicology**



Maximum Recommended Starting Dose (MRSD)

1. Review and evaluate animal data to assess the No Observed Adverse Effect Level (NOAEL)
2. Calculate Human Equivalent Dose (HED)
 - a. Body Surface Area
 - b. Dose (mg/kg)
 - c. Other scaling factors
3. Select most appropriate species
4. Application of a safety factor
5. Consider pharmacologically active dose



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Step 1

Determine NOAELs (mg/kg) in toxicity studies

Is there justification for extrapolating animal NOAELs to human equivalent dose (HED) based on mg/kg (or other appropriate normalization)?

Yes

HED (mg/kg) = NOAEL (mg/kg) (or other appropriate normalization)

No

Convert each animal NOAEL to HED (based on body surface area; see Table 1)

Step 2

Select HED from most appropriate species

Step 3

Step 4

Choose safety factor and divide HED by that factor

Maximum Recommended Starting Dose (MRSD)

Step 5

Consider lowering dose based on a variety of factors, e.g., PAD



Conversion table

Table 3: Conversion of Animal Doses to Human Equivalent Doses Based on Body Surface Area

Species	Reference Body Weight (kg)	Working Weight Range ^a (kg)	Body Surface Area (m ²)	To Convert Dose in mg/kg to Dose in mg/m ² Multiply by k _m	To Convert Animal Dose in mg/kg to HED ^b in mg/kg, Either	
					Divide Animal Dose By	Multiply Animal Dose By
Human	60	---	1.62	37	---	---
Child ^c	20	---	0.80	25	---	---
Mouse	0.020	0.011-0.034	0.007	3	12.3	0.081
Hamster	0.080	0.047-0.157	0.016	5	7.4	0.135
Rat	0.150	0.080-0.270	0.025	6	6.2	0.162
Ferret	0.300	0.160-0.540	0.043	7	5.3	0.189
Guinea pig	0.400	0.208-0.700	0.05	8	4.6	0.216
Rabbit	1.8	0.9-3.0	0.15	12	3.1	0.324
Dog	10	5-17	0.50	20	1.8	0.541



Example

NOAEL (rat FOB)	100 mg/kg
Human equivalent dose	16.2 mg/kg (100 mg/kg x 0.162) 600 mg/m ² (100 mg/kg x 6)
Proposed human starting dose	10 mg (0.17 mg/kg or 6.2 mg/m ²)
Safety factor	~97 (600 mg/m ² ÷ 6.2 mg/m ² or 16.2 mg/kg ÷ 0.17 mg/kg)



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GOING FROM FIRST DOSE TO THE NEXT...



Dose escalation

Reminder: Objective in Phase 1 to determine safety of the compound. May need to cover a large range of doses to find the maximum tolerated dose

- Half-log (1, 3, 10, 30, 100) ← aggressive increase
- Fibonacci sequence (1, 2, 3, 5, 8, 13, 21, 34)
 - Ratio of successive numbers approaches a constant of ~ 1.61 .
Modified Fibonacci have incremental ratios of 2, 1.67, 1.5, 1.33



Example of Dose Escalation Rules

A decision to proceed to the next higher dose administration will be made jointly by the Sponsor and the PI following the review of all pertinent blinded safety/tolerability data (e.g., physical examinations, electrocardiograms (ECGs), vital signs, clinical laboratory tests, and adverse events [AEs]) through 5 days following dosing for at least 6 out of 8 subjects of the current dose level cohort and those from all previous cohorts. Together they will make one of the following determinations:

1. To continue with the study as planned.
2. To continue with the study and add additional safety evaluations.
3. To continue with the study by repeating the dose, adjusting to a dose between the current dose and the next planned dose, or adjusting to a dose between the current dose and the previous lower dose, or agree to continue the dose escalation



Example of Stopping Rules

- To stop dose escalation of the study. The study will be terminated if ≥ 2 subjects in a cohort meet any of the following criteria and the subjects were determined to have received active drug after unblinding:
 - a. Have a drug related SAE (see Section 11.1.8.3).
 - b. Experience a drug related grade ≥ 3 toxicity (see Section 11.1.8.2).
- A period of at least xx days will take place between the dosing of each cohort in order for the PI and the Sponsor to adequately review of safety data from the prior cohort.
- PK data from a cohort may be used for a dose-escalation decision.



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Types of Phase 1 Studies



First-in-human (FIH)

Single Ascending Dose (SAD)

- 5 to 8 cohorts
- Healthy volunteers (18-45 years old)
- 6 to 8 subjects per cohort
- Most often, placebo controlled (1:3)
- Evaluate safety & pharmacokinetics



Multiple Ascending Dose (MAD)

- 3-6 cohorts
- Healthy volunteers or “healthy” patients
- 6 to 8 subjects per cohort
- Placebo controlled (1:3)
- Dose to steady state



Food-effect?

For oral route of administration, will food effect drug absorption/PK?

- Cross-over, fed versus fasted
- Often added as an arm of the SAD or MAD study



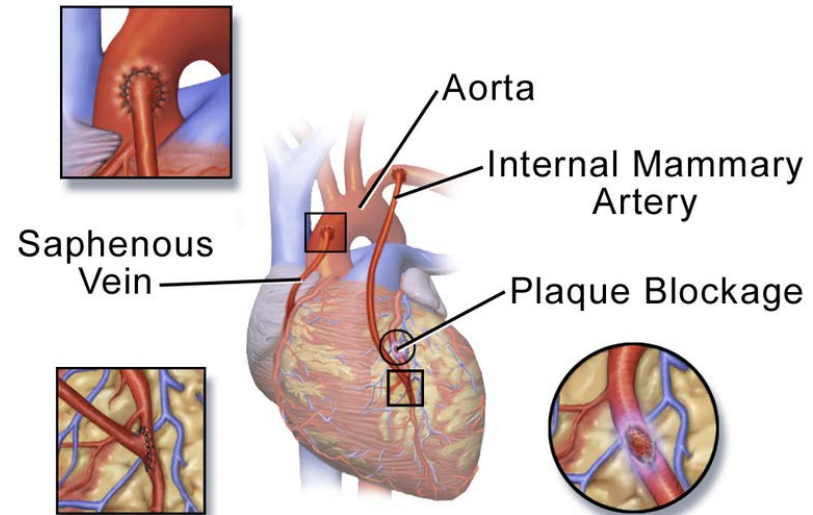
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Case Study #1: Safety evaluation in patients



Coronary Artery By-Pass Graft

- Surgical procedure to relieve angina (heart attack) due to blockage of the coronary artery (or arteries)
- Usually performed when the heart is stopped: On-pump Cardiopulmonary bypass (CPB) using a heart-lung machine
- Cognitive-impairment observed, especially in older individuals
- Hypothesis: when blood is shunted from/to heart during CPB, micro-emboli (bubbles) cause mini-strokes in the brain





Case study #1: Safety in patients

- Intravenous product (single dose) with preclinical data suggesting cognitive protection (rodent stroke models)
- Well-tolerated in healthy participants (Phase I SAD) at doses up to 300 mg
- Diabetes a major (30%) co-morbidity in CABG patients
- Phase II risk-management
 - What will be the product safety profile in CABG patients?
 - Compromised patient population
 - Can information be obtained in Phase I to address this?



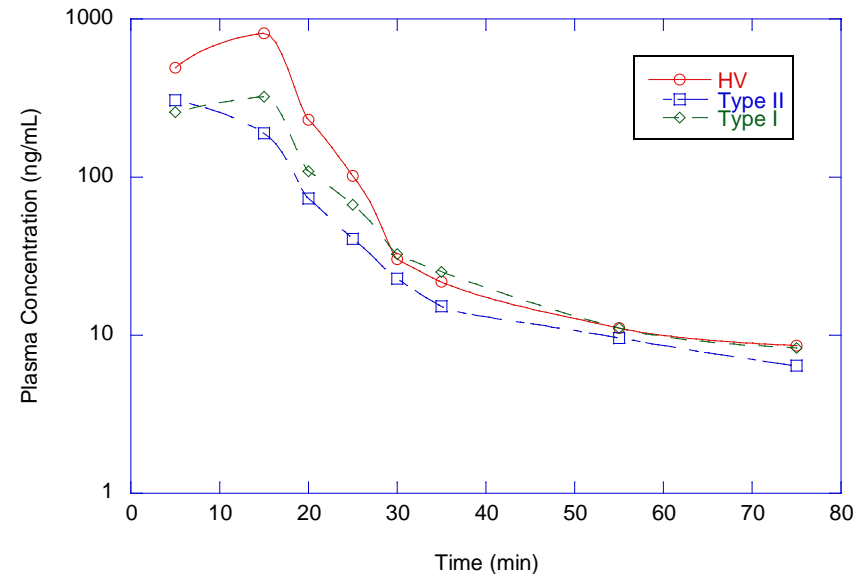
Phase Ib: Multiple Ascending Dose study

- Three groups with 6 active and 2 placebo
 - Group 1: Healthy participants
 - Group 2: Type 2 diabetics
(C-peptide > 1.5 ng/mL, HbA1c between 6.3 and 10.4)
 - Group 3: Type 1 diabetics
(C-peptide < 0.8 ng/mL, stable insulin)
- Dose:
 - 100 mg BID on day 1
 - 200 mg BID for three days (days 2 to 4)
- Endpoint: Safety and pharmacokinetics



Case study #1: Results

- Adverse event profile similar in HV and diabetics
 - No change in glucose or insulin required during study
- No difference in PK between HV and diabetics



Good to go to Phase II



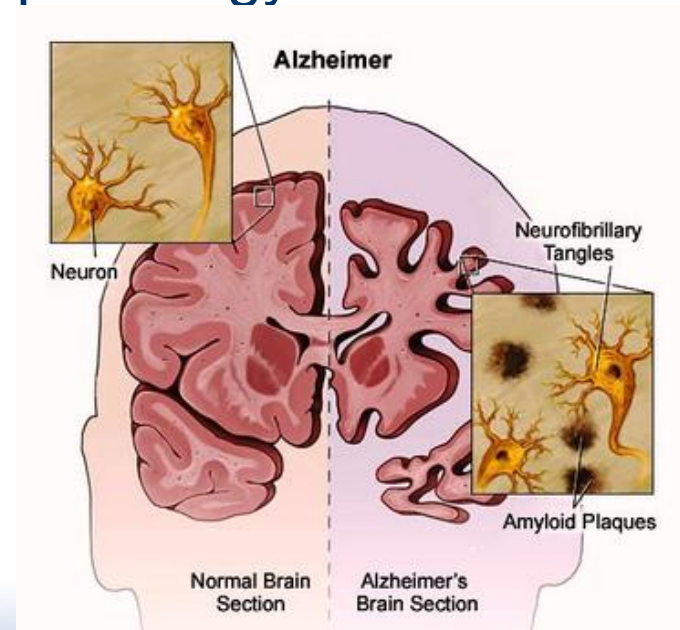
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CASE STUDY #2: PK DIFFERENCES IN PATIENTS?



Intranasal product for Alzheimer's disease

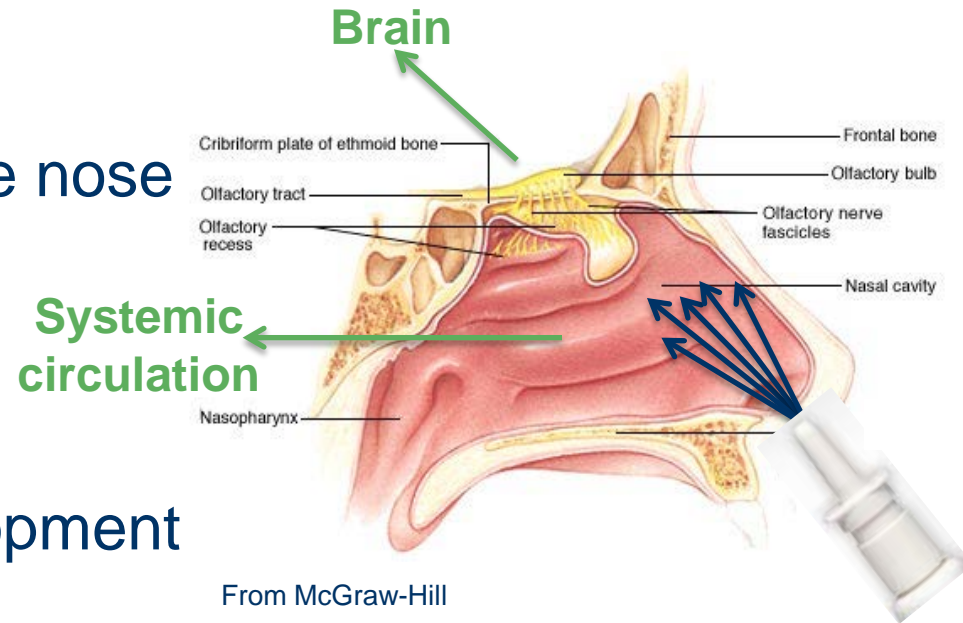
- Neuroprotective compound prevented neurofibrillary tangles (NFT) in animal models of tau pathology
 - CNS: Pharmacodynamic compartment
 - Literature suggests the blood-brain-barrier altered in AD
 - Need to understand drug distribution into the PD compartment
 - Will there be a difference in exposure in AD patients?





Mechanism by which drug gets to the brain

- Additional question:
How does drug go from the nose to the brain?
- Implications in drug development
- Drug exposure and safety





Difference in PK between HV and AD?

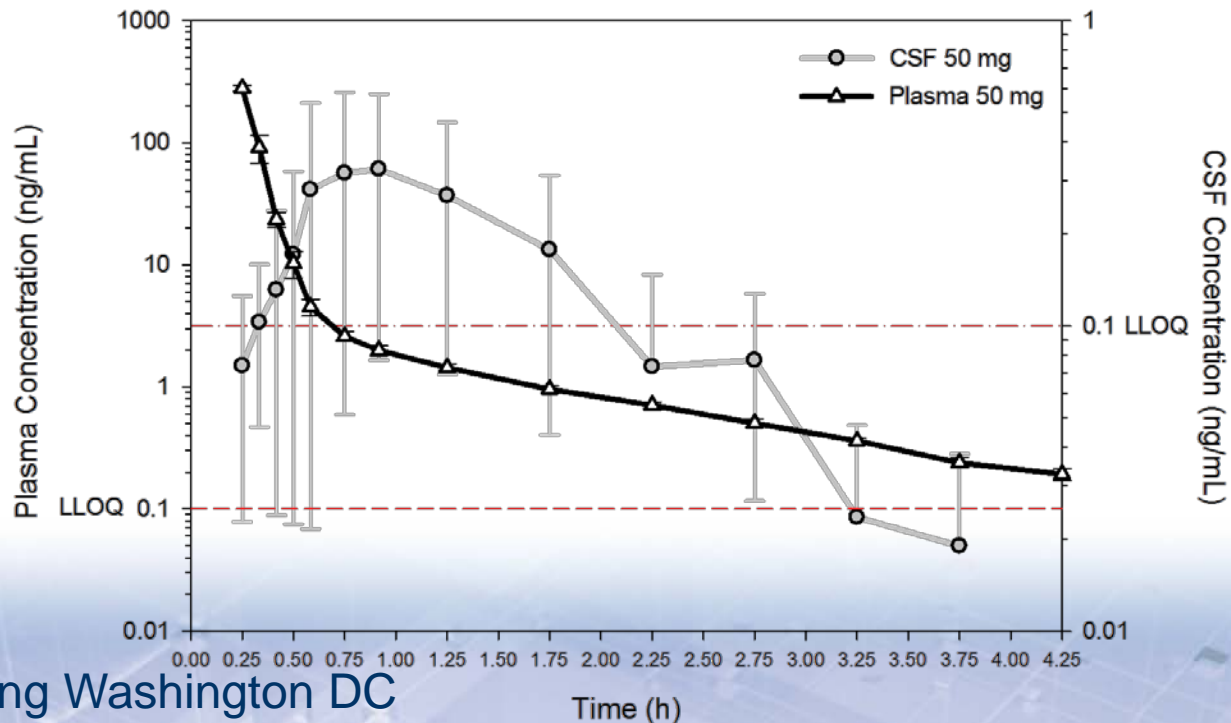
- Open-label, single dose, plasma & continuous CSF collection
 - Lumbar (L3-L4) catheterization
 - CSF collected at 0.2 mL/min for 4 hours, 1 mL fractions
 - 6 participants per group
 - Measured drug levels as well as various AD biomarkers
- Healthy Adult (18-45 years)
 - 50 mg intravenous
 - 300 mg intravenous
 - 15 mg intranasal
- Mild-to-Moderate AD patients
 - 15 mg intranasal





Plasma & CSF Profile: 50 mg IV

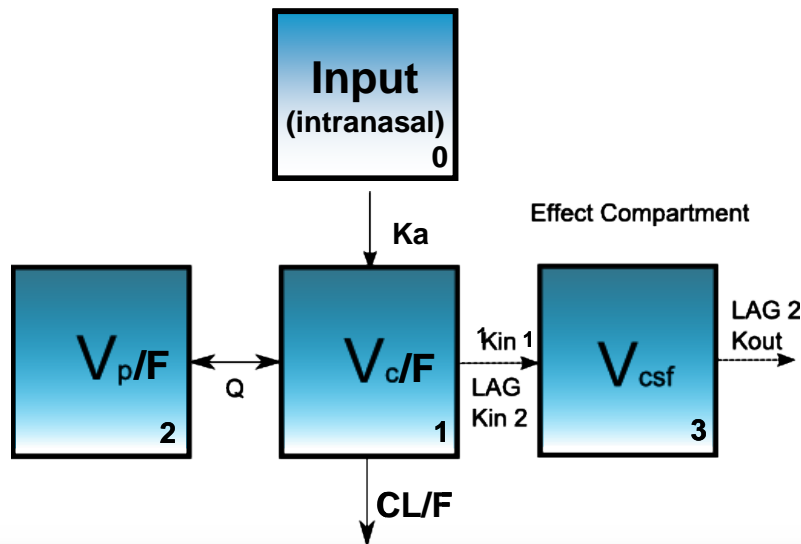
- Continuously collect CSF and plasma
- Healthy participants (n=6)
- Measure drug levels with validated LC-MS/MS assay





2-Compartment PK Model

- Explored various compartmental PK models
- Best fit: two-compartment model



Plasma (Central Volume of Distribution):

For IN administration

$$\frac{dA_0}{dt} = \text{Dose} - Ka \times A_0$$

$$\frac{dA_1}{dt} = Ka \times A_0 + \frac{Q \times A_2}{V_p} - \frac{Q \times A_1}{V_c} - \frac{CL \times A_1}{V_c}$$

Peripheral Volume of Distribution (for IV and IN)

$$\frac{dA_2}{dt} = \frac{Q \times A_1}{V_c} - \frac{Q \times A_2}{V_p}$$

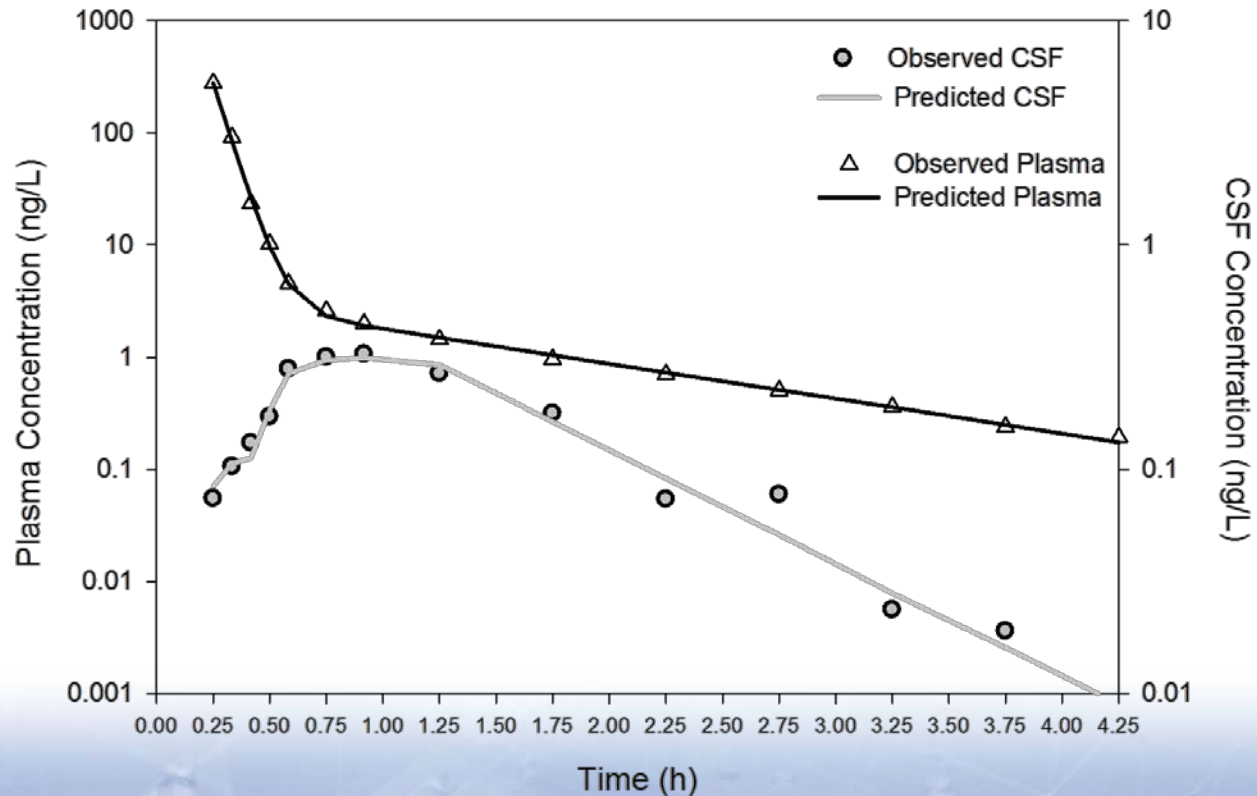
CSF:

$$\frac{dA_3}{dt} = + \left[(Kin1_{0\ to\ LAG1} + Kin2_{LAG1\ to\ LAG2}) \times A_1 \right] - \left[Kout_{LAG2\ to\ \infty} \times A_3 \right]$$



PK Model: Applied

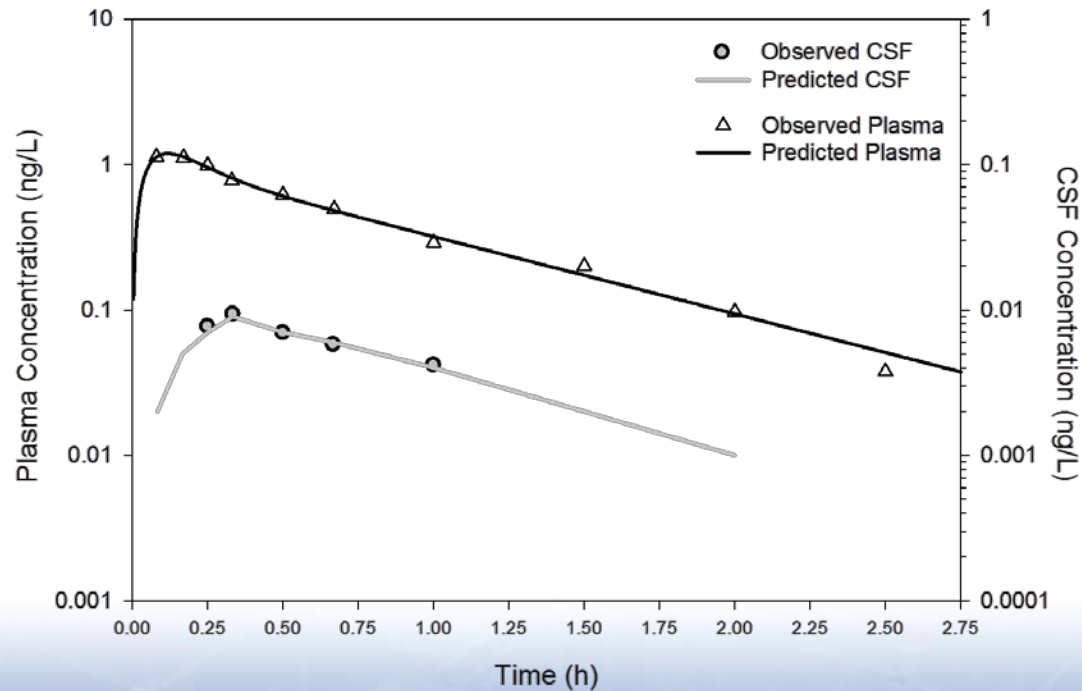
- Computational model predicts experimental data





Intranasal Pharmacokinetics

- Model derived from intravenous data maps to intranasal experimental data





Case study #2: Conclusions

- Plasma and CSF exposure was no different in HV and AD patients
- Intranasal drug administration results in systemic distribution (not direct nose-to-brain)
- PK model allowed for sparse blood sampling in Phase II/III



Case study #2: Conclusions (cont)

- Able to develop a robust PK model to conduct PK simulations for Phase II/III
 - Looked at dose and dose paradigms (QD, BID, TD)
 - Optimize for steady state CSF concentrations

