

MODELING CATEGORICAL TRIAL OUTCOMES

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TALK STRUCTURE

- **Categorical outcome data:**
 - ◆ definitions
 - ◆ models
- **Categorical outcome simulation example - Naratriptan**

OUTCOME DATA TYPES

- **Continuous:**
 - ◆ measurements of continuous processes
 - ◆ time-to-event (survival) data
- **Categorical:**
 - ◆ nominal (not ordered)
 - ◆ **ordinal**
 - ❖ counts
 - ❖ scale-derived
 - ◆ **binary**

COMPOSITE OUTCOME EXAMPLE: ACR20% in Rheumathoid Arthritis

- (Semi-) Continuous components:

- ◆ Swollen joints count
- ◆ Tender joints count
- ◆ Patient pain assessment
- ◆ Patient global assessment
- ◆ Physician global assessment
- ◆ Patient self-assessed disability
- ◆ Acute phase reactant

- ACR Success Definition:

- ◆ $\geq 20\%$
- ◆ $\geq 20\%$

} $\geq 20\%$ in
three of
the five

POINT TO REMEMBER!!!

DISCRETIZATION LEADS TO LOSS OF INFORMATION

**INFORMATION
CONTENTS**



CONTINUOUS VARIABLES

CATEGORICAL VARIABLES

BINARY VARIABLES

BINARY OUTCOME MODEL: LOGISTIC FUNCTION

$$\Pr\{Y = 1\} = \frac{e^x}{1 + e^x}$$

- X is (combination of) explanatory variable(s):
 - ◆ independent variables
 - ◆ covariates
- Y=1 is “success”

NARATRIPTAN CTS&D

- Naratriptan - second-in-line anti-migraine drug
- Success = headache relief
- AIM - To design a phase II oral dose ranging trial, which has the highest probability of showing the dose - response relationship

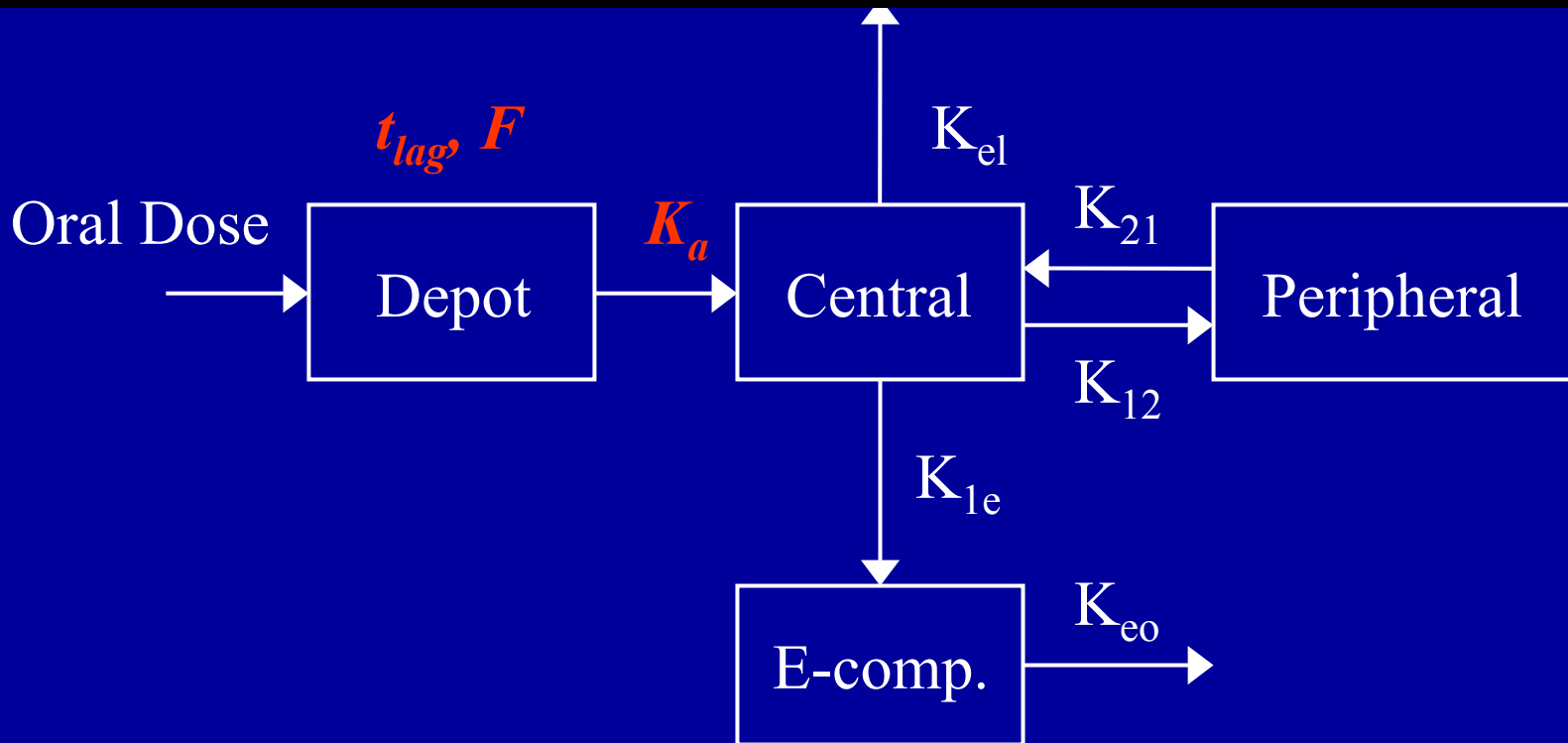
CLINICAL TRIAL DESIGN

- The system (“biology”) - PK/PD model and modeling assumptions.
- The trial:
 - ◆ the power of the design;
 - ◆ controllable factors:
 - ❖ number of arms, sample sizes;
 - ❖ dosing and sampling schedules, sites and modes;
 - ◆ uncontrollable factors:
 - ❖ model uncertainties (parameters, structures, assumptions);
 - ◆ optimality and logistics (incl. the cost).

DATA AVAILABLE

- Phase I PK data - **healthy male volunteers** (n=26) with various routes of administration (SC, IV, PO - **solution**);
- General information - changes in PK during **migraine attacks**;
- Sumatriptan data - Phase II pharmacodynamic model after nasal administration - **logistic function**;
- Preclinical information - **relative potency** of naratriptan *wrt* sumatriptan;

NARATRIPTAN PK/PD MODEL

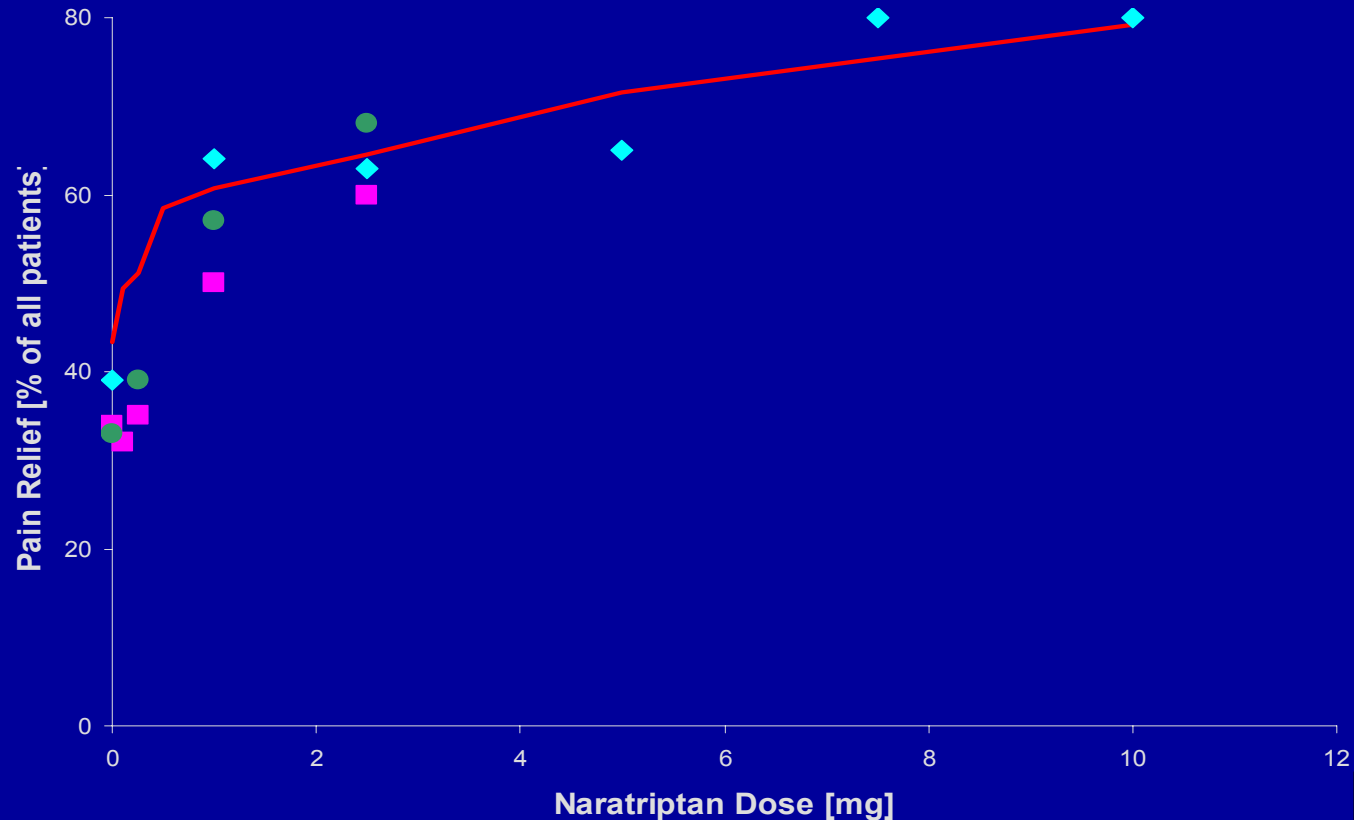


$$E(t) = Pr(t) = \frac{e^{\text{logit}}}{1 + e^{\text{logit}}}$$

$$\text{logit} = b_1 + b_2 \cdot \log(t) + \frac{b_3 C_e(t)}{b_4 + C_e(t)} + \eta$$

SIMULATIONS

- Extensive clinical trial with 8 arms: 0, 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 2.5 mg, 5 mg, 10 mg and 1000 patients per arm;



USING TABLES FOR SAMPLE SIZE AT 80% POWER

Dose Comparisons	Effect Sampling Times [h]			
	1	2	4	6
<i>0.5 mg vs 0 mg</i>	1600	490	396	564
<i>2.5 mg vs 0 mg</i>	164	73	71	90
<i>10 mg vs 0 mg</i>	46	26	27	32
<i>2.5 mg vs 0.5 mg</i>	351	194	220	248
<i>10 mg vs 0.5 mg</i>	67	43	49	55
<i>10 mg vs 2.5 mg</i>	204	152	171	192

RELATIVE EFFICIENCY OF ALTERNATIVE TRIAL DESIGNS*

Doses [mg]	Effect Sampling Times [h]	Replicates	Relative efficiency [%]
0, 0, 4.73, 20	0.6, 0.6, 3.68, 9.23	1	100
0, 0.5, 2.5, 10	2, 4	2	55.1
0, 0.75, 2.5, 10	2, 4	2	55.9
0, 1, 2.5, 10	2, 4	2	56.8
0, 0.1, 0.25, 1, 2.5, 5, 7.5, 10	2, 4	1	52.5

*D Optimal Design with Baseline Pain Severity Score 3

RECOMMENDED TRIAL DESIGN

(based on the integrated model)

- 4 arms: 0, 0.5, 2.5, 10 mg;
- Minimum effective dose is around 0.5 mg;
- Maximum non-effective dose is < 0.5 mg;
- at least 250 patients per arm (depending on acceptable level of trial failure);
- sample PD response at 0, 2 & 4 h;

CONCLUSIONS

- CTS&D critically depends on the PK/PD models used;
- Naratriptan PK/PD model developed by integration of information from:
 - ◆ Phase I naratriptan clinical trial;
 - ◆ In vitro relative potency data;
 - ◆ First-in-line (sumatriptan) data;
 - ◆ General knowledge about migraine.
- Integration of information fares better than using Phase IIa s.c. trial naratriptan data.