CHDR Centre for Human Drug Research

The Investigator's Brochure
- Key Information to Support Early Clinical Trials

- what is the dose range for first-in-human administration of a CNS-active drug?

Joop van Gerven, MD, PhD

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Director of CNS Research, Centre for Human Drug Research CHDR, Leiden
Chairman, Central Committee on Research Involving Human Subjects CCMO, The Netherlands

Lecture Contents:
Rational Design of Early Human Drug Studies

- Objectives of (first-in-man) drug studies in healthy humans
  - traditional objectives
  - pharmacological objectives
- Required preclinical information
- Animal-to-human predictions
- Systemic IB summary: IB-DeRisk-tool

Van Gerven JMA, Cohen AF. Integrating data from the Investigational Medicinal Product Dossier/investigator's brochure. A new tool for translational integration of preclinical effects. Br J Clin Pharmacol. 2018 Jul;84(7):1457-1466

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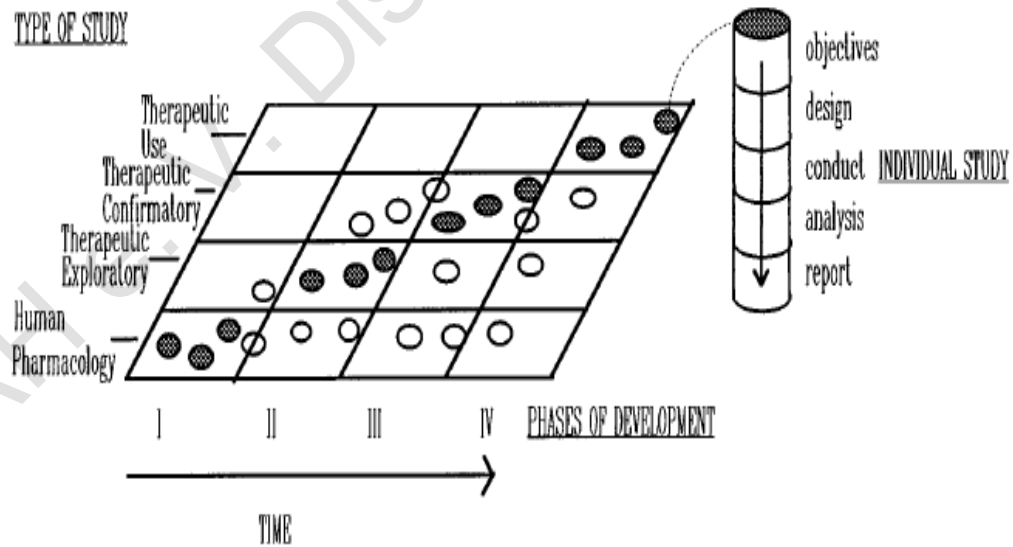
‘Traditional Objectives of Early Drug Development’

- Animals → Healthy Young Males → Females, Elderly → Patients
- ‘Determine pharmacokinetics, safety and tolerability’

Phase	Population	Numbers
Phase I	Healthy volunteers	50 - 100
Phase II	Special patients	200 - 500
Phase III	Selected patients	500 - >1000
Launch	General patient population	>10000

Figure 1.—Correlation Between Development Phases and Types of Study[1]



Federal Register / Vol. 62, No. 242 / Wednesday, December 17, 1997

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Which tolerability/safety in phase I?

- Type I and II intolerability
  - Majority of drug-related AEs
  - Based on pharmacological activity
  - Disregulation of normal physiological processes
  - Predictable and preventable if understood
- Type III and IV intolerability
  - Tissue damage caused by unknown mechanism, rare metabolite, allergy or anaphylaxis
  - Serious and infrequent (<1:1000) in predisposed subjects
  - Will be missed in Phase I
    - numbers too low for reliable detection of even 10% incidence
    - poor predictability from traditional 'safety markers'

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Sample Sizes Needed to Detect Rare Events

frequency in general population (1:n)	fold increase			
	2	3	4	5
10 000	305 625	45 510	22 695	13 455
5 000	86 205	20 865	9 885	6 720
2 500	33 645	9 480	4 935	3 363
1 250	15 465	4 740	2 472	1 680

number of person–years needed to detect significant risk increase (one-sided exact test) with significance level $\alpha=0.025$ and power $(1-\beta)=0.80$

Wu Y, Makuch RW. Sample size for post-marketing safety studies based on historical controls. Pharmacoepidemiol Drug Safety 2010; 19(8):869–875

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Even if tolerability is low..

Pharmacokinetics of RheothRx Injection in Healthy Male Volunteers

R. C. JEWELL[x], S. P. KHOR, D. F. KISOR, K. A. K. LACROIX*, AND W. A. WARGIN

Received November 29, 1996, from the *Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709.* Accepted for publication March 13, 1997[⊗]. * Present address: Quintiles Inc., 1007 Slater Road, Durham, NC 27703.

The objectives of this study were to evaluate the safety and tolerability of RheothRx Injection administered as an iv infusion in healthy male volunteers and to determine the pharmacokinetic profile of poloxamer 188.

A reversible proteinuria was observed in some subjects receiving RheothRx Injection infusions.

Eight RheothRx Injection-treated subjects had their infusions stopped prematurely because of adverse events (*e.g.*, back pain, leg pain, headache, nausea).

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…compounds are developed well into phase III

Randomized, controlled trial of RheothRx (poloxamer 188) in patients with suspected acute myocardial infarction

Charles Maynard, PhD,[a] Robert Swenson, MD,[b] Joseph A. Paris, MD,[c] Jenny S. Martin, RN,[a] Alfred P. Hallstrom, PhD,[d] Manuel D. Cerqueira, MD,[e] and W. Douglas Weaver, MD,[f] for the RheothRx in Myocardial Infarction Study Group *Seattle and Vancouver, Wash.; Buffalo, N.Y.; Washington, D.C.; and Detroit, Mich.*

The results of this and other studies of poloxamer 188 suggest that this agent has no effect in reducing infarct size and is associated with an unacceptably high incidence of transitory renal dysfunction that would possibly contribute to death in critically ill patients with AMI.

Circulation. 1997 Jul 1;96(1):192-201. **Effects of RheothRx on mortality, morbidity, left ventricular function, and infarct size in patients with acute myocardial infarction. Collaborative Organization for RheothRx Evaluation (CORE).** Three higher doses (1-hour bolus+low-dose infusion for 47 hours, 1-hour bolus+high dose, target serum concentration of 1.0 mg/ml for 24 hours, or 1-hour bolus+high dose for 48 hours) were discontinued because of high rates of renal dysfunction (8.8%). Renal dysfunction was also observed at lower doses (regimen A, 3.1%; Y, 2.7%; and B, 4.1%) compared with the control patients (1.0%). There was no significant difference in the composite outcome of death, cardiogenic shock, or reinfarction at 35 days (all RheothRx, 13.6%; control, 12.7%

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Early development cannot always predict drug efficacy

- Healthy subjects ≠ Patients
  - no disease
  - too young
- Biomarkers ≠ Clinical endpoints
- Ineffective therapies
  - poorly understood diseases
  - heterogeneous
  - multifactorial
- Confounders in patient population
  - concomitant diseases
  - co-medication
  - poor compliance
  - variable pharmacokinetics

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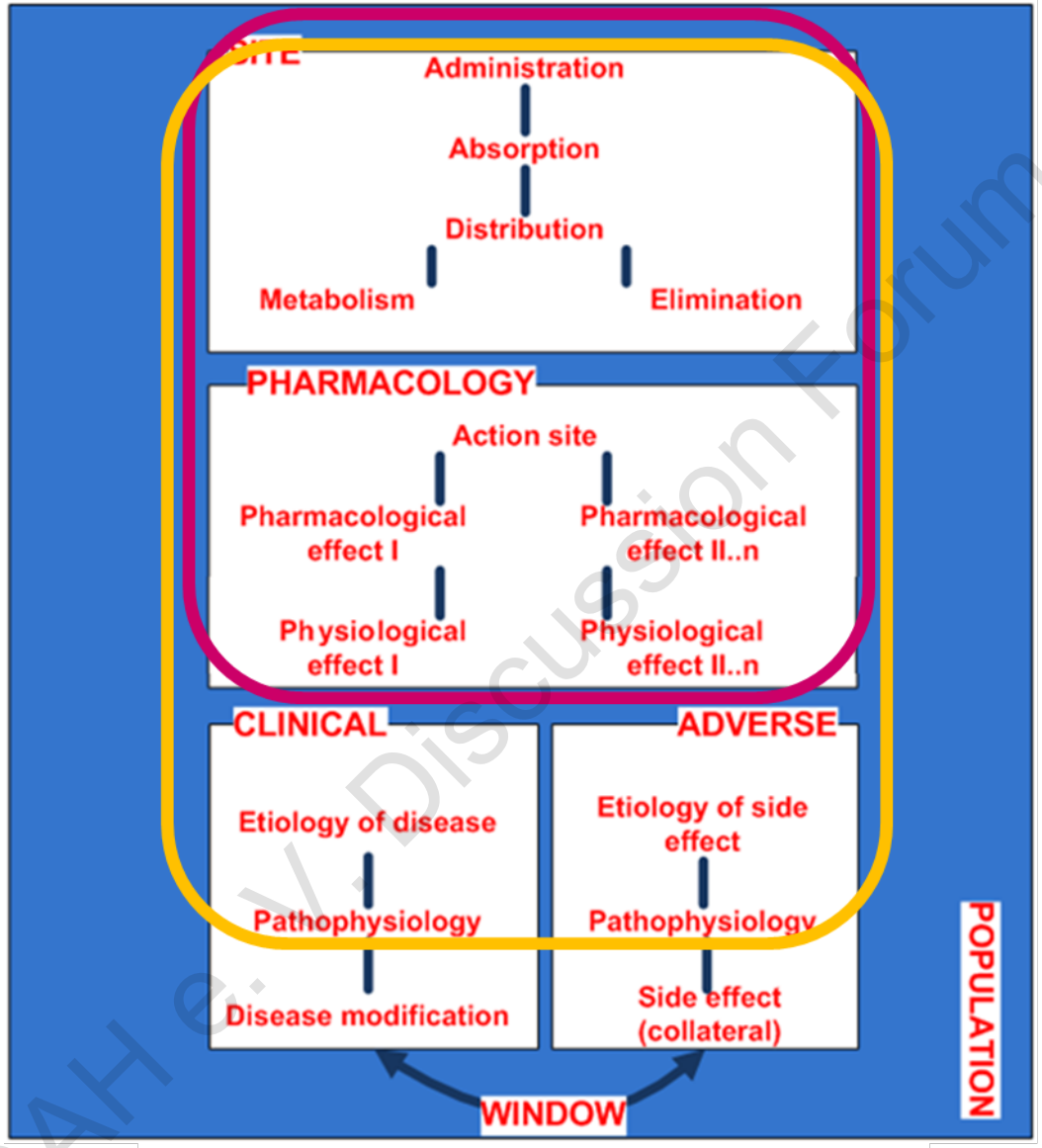
What early drug development can demonstrate:



Healthy Volunteers

Patients

Cohen AF. Developing drug prototypes: pharmacology replaces safety and tolerability? Nat Rev Drug Discov. 2010;9:856-65

Cohen AF, Burggraaf J, Gerven JM, Moerland M, Groeneveld GJ. The Use of Biomarkers in Human Pharmacology (Phase I) Studies. Annu Rev Pharmacol Toxicol. 2014 Oct 6.

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Five Main Questions for Early Phase I

- Does the biologically active compound/active metabolites get to the **site** of action?
- Does the compound cause its intended **pharmacological**/functional effect(s)?
- Does the compound have beneficial effects on **clinical** systems involved in the disease or its pathophysiology?
- Can we get an impression of the therapeutic **window**?
- Are there any major differences among the **population**?

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Required Principal Information to design early human studies

- Rationale
- Product properties
- Pharmacokinetics/route/metabolism
- Safety pharmacology
- Toxicology
- Efficacy models

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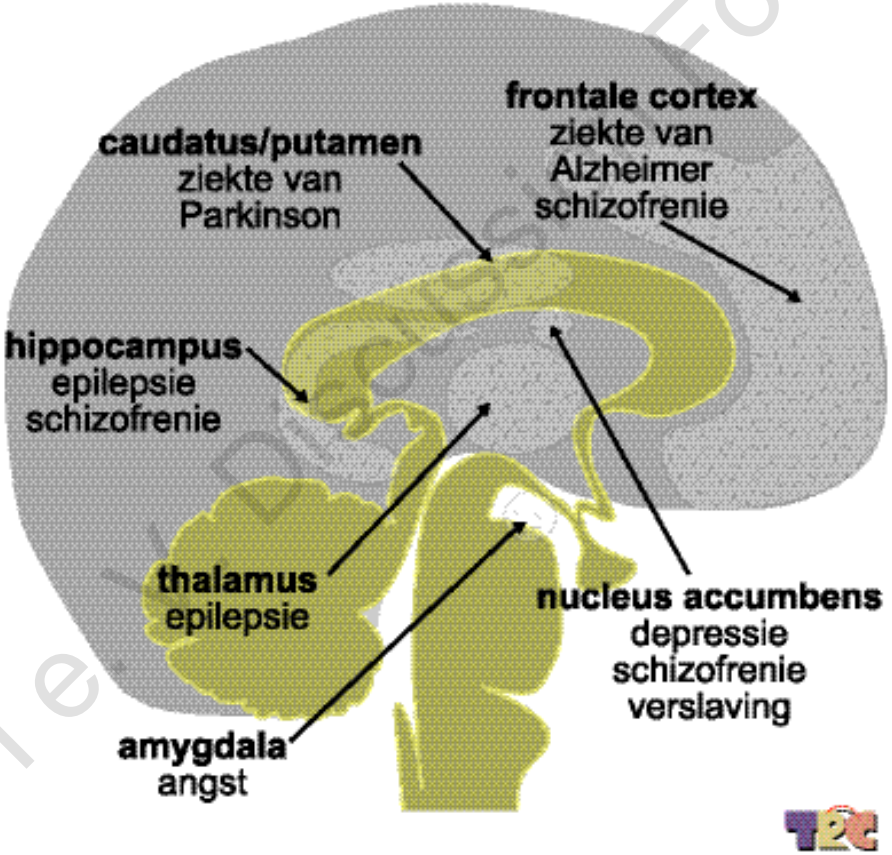
Rationale: understanding CNS-diseases



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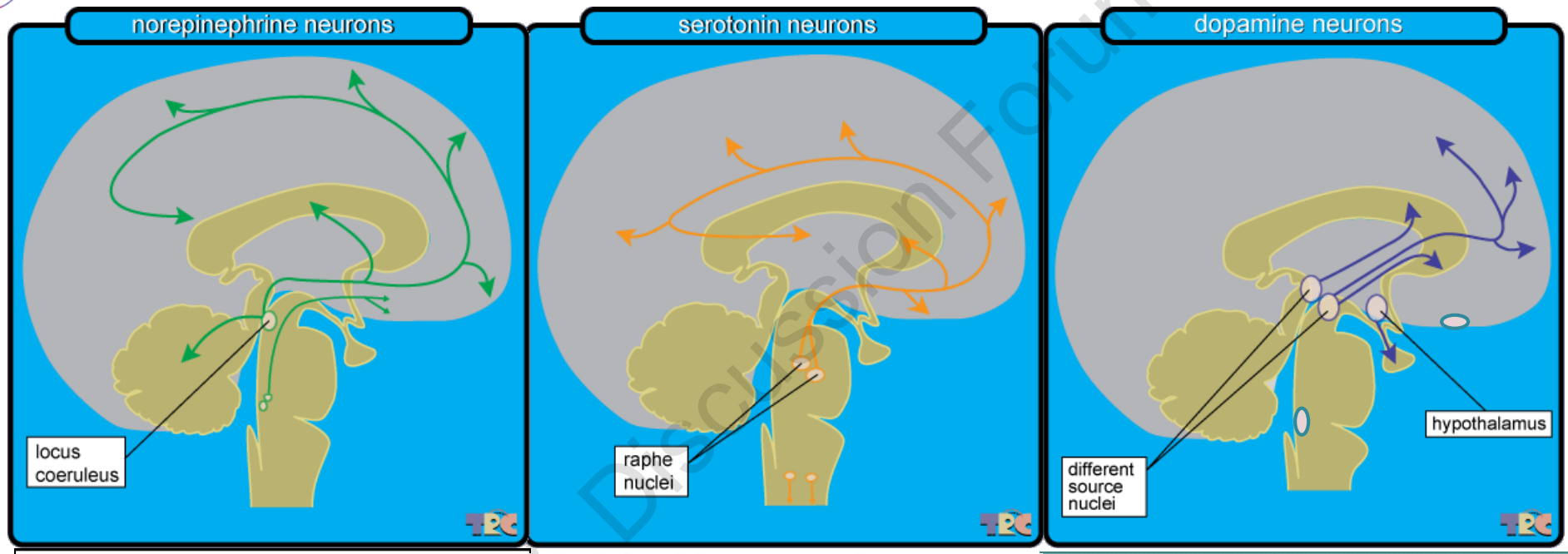
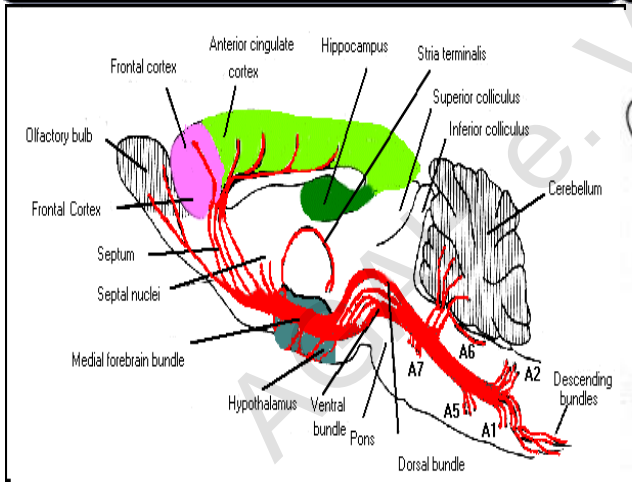
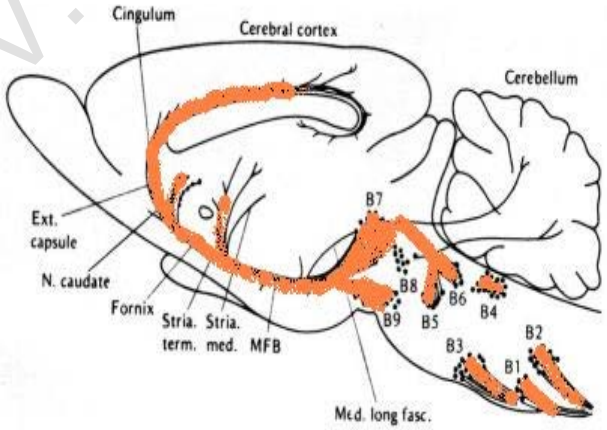
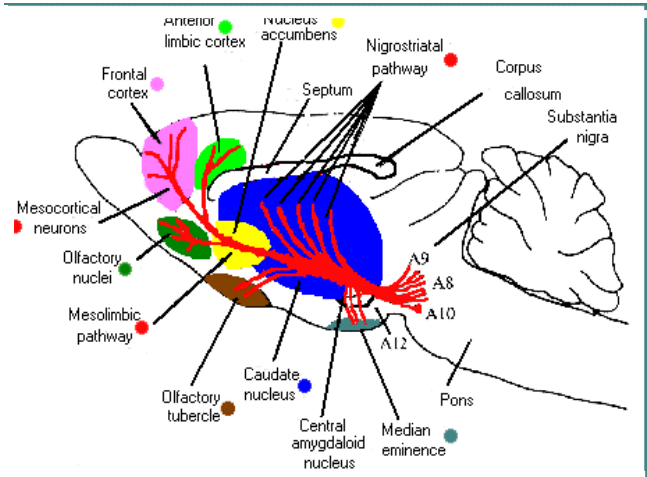
Rationale: understanding neuropharmacology









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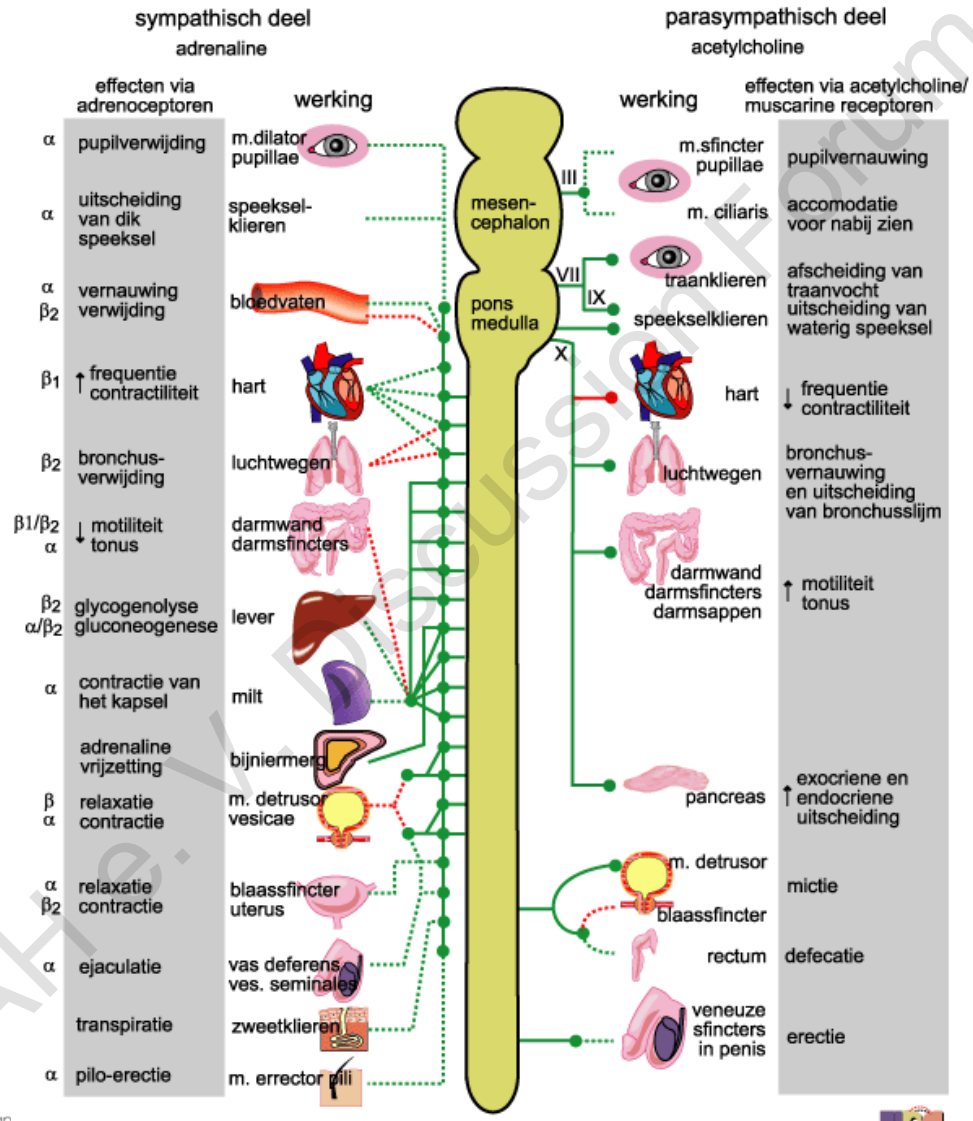
Rationale:
understanding human physiology/pharmacology



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Product Properties:
in vitro pharmacological characteristics

Compound	Human cloned muscarinic receptor (K_i)			
	m_1AChR	m_2AChR	m_3AChR	m_4AChR
Org xxxx	5.28 ± 0.05	6.11 ± 0.04	5.40 ± 0.06	5.56 ± 0.07
Org yyyy	5.34 ± 0.05	6.14 ± 0.09	5.62 ± 0.08	5.40 ± 0.01
rapacuronium	**5.92 ± 0.03***	5.71 ± 0.08	**4.55 ± 0.08***	5.79 ± 0.04
rocuronium	5.26 ± 0.04	5.75 ± 0.08	**4.64 ± 0.06***	5.41 ± 0.01
vecuronium	5.19 ± 0.04	5.61 ± 0.05	**4.56 ± 0.01***	5.25 ± 0.07
suxamethonium	**4.24 ± 0.01***	**4.26 ± 0.01***	**4.23 ± 0.00***	**4.43 ± 0.06***
scopolamine	**9.75 ± 0.06***	**9.68 ± 0.05***	**9.77 ± 0.04***	**10.07 ± 0.04***
oxotremorine	**4.94 ± 0.08***	**6.94 ± 0.26***	**4.96 ± 0.09***	5.75 ± 0.19

NovaScreen® Receptor Selectivity Report

Receptor/Selectivity	Reference Compound
Neurotransmitters:	
Adenosine	NECA
Alpha 1	Prazosin
Alpha 2	Phentolamine
Beta	Alprenolol
Dopamine 1	SCH 23390
Dopamine 2	Sulpiride
$Gaba_A$	Muscimol
$Gaba_B$	Baclofen
Seratonin 1	Serotonin
Seratononin 2	Methylsergide
Muscarinic 3	4-DAMP
Nmda	NMDA
Kainate	Kainic Acid DME
Quisqualate	Quisqualic Acid
Glycine (stry sens.)	Strychnine Nitrate
Regulatory Sites:	
Benzodiazepine (centrl)	RO-151788
Glycine (stry insens.)	Glycine
Pcp	PCP
Mk-801	MK801
Brain/Gut Peptides:	
Angiotensin Ty 2	Angiotensin II
Arg-Vasopressin V_1	arg-Vasopressin
Bombesin	GRP
CCK Central	CCK
CCK Peripheral	CCK
Substance P	substance P
Substance K	Neurokinin A
Npy	Neuropeptide Y
Neurotensin	Neurotensin
Somatostatin	Somatostatin
Vip	VIP
Growth Factors And Peptides:	
Anf1	ANP
Egf	EGF
Ngf	NGF
Ion Channels:	
Calcium (Type N)	w-Conotoxin
Calcium (Type T & L)	Nifedipine
Chloride	TBPS
Potassium (low conduct)	Apamin
Second Messengers:	
Forskolin	Forskolin
Phorbol Ester	PDBU
Inositol Triphosphate	IP3
Monoamine oxidase inhibition:	
Monoamine Oxidase A	N/A
Monoamine Oxidase B	N/A

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Product Properties:
Preclinical Pharmacokinetics *(in vitro/in vivo)*

- Plasma pharmacokinetics
- Tissue penetration
- Metabolism
- Toxicokinetics

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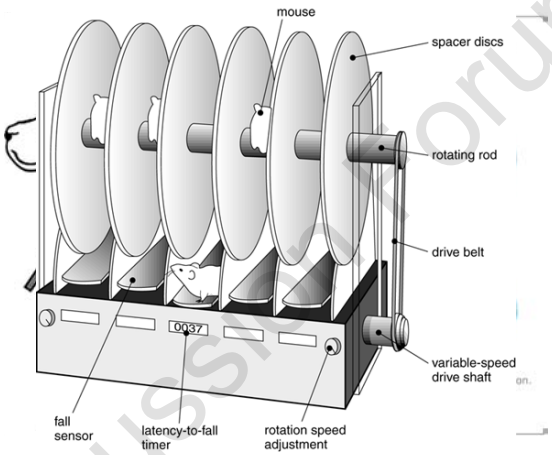
Product Properties:
Preclinical Safety (*in vitro/in vivo*)

- Genotoxicity/Carcinogenicity
  - Ames-test
  - clastogenicitiy
- Safety pharmacology
  - central nervous system
  - cardiovascular
  - respiratory
  - target systems
- Toxicology
  - acute
  - repeat-dose
  - reproduction
  - reversibility
  - measurability
- Other safety issues:
  - immunotoxicity, phototoxicity, abuse potential
  - general observation, ‘common sense’
- No-Observed-(Adverse)-Effect-Level (NOAEL)



human	rodent	non-rodent
single	2 weeks	2 weeks
<2 weeks	1 month	1 month
2-4 weeks	3 months	3 months
1-3 months	6 months	6 months
>3 months	6 months	9 months

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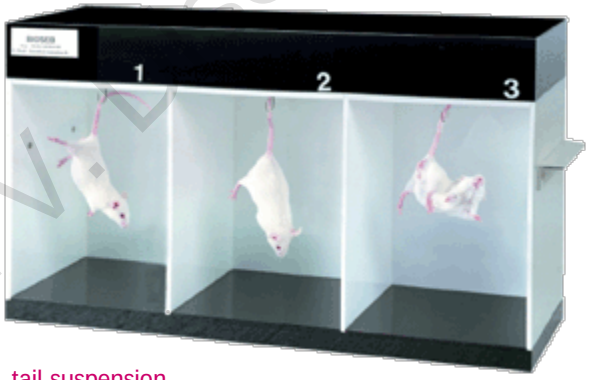
Product Properties:
Preclinical Efficacy (*in vitro/in vivo*)

- Pharmacological target characterization
  - affinity, EC_{50}, E_{max}
  - distribution (autoradiography)
  - functional relevance
- Animal models
  - drug class validation
  - pathophysiological validation

learned helplessness



tail suspension

forced swim

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Extrapolation to Humans:
drug concentrations as information vector

- physicochemical predictions

Lipinski's Rule of Five:

- octanol-water coefficient more than 5
- molecular weight <= 500
- number of hydrogen bond acceptors <= 10
- number of hydrogen bond donors <= 5
- not an acid
- pKa between 7.5 to 10.5

BBB-penetrating drug do not violate more than one rule; modified from C. Lipinski, 1997

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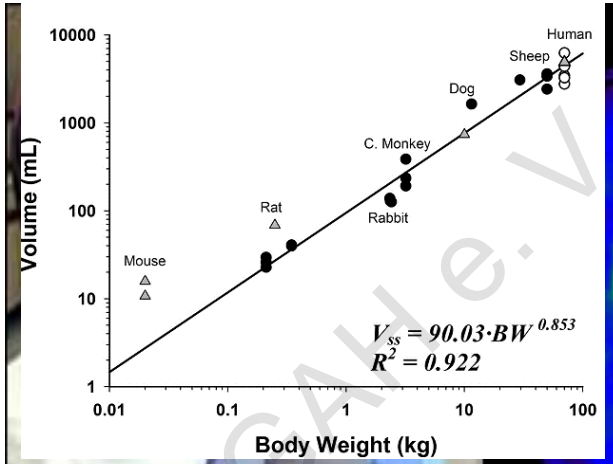
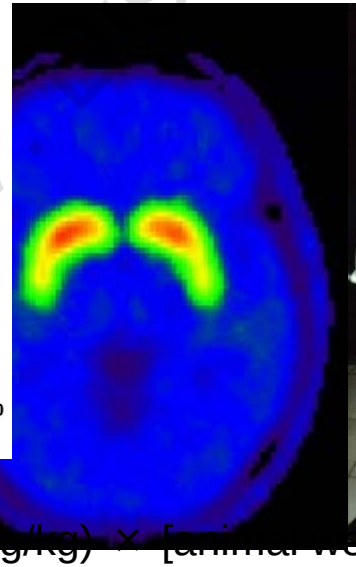
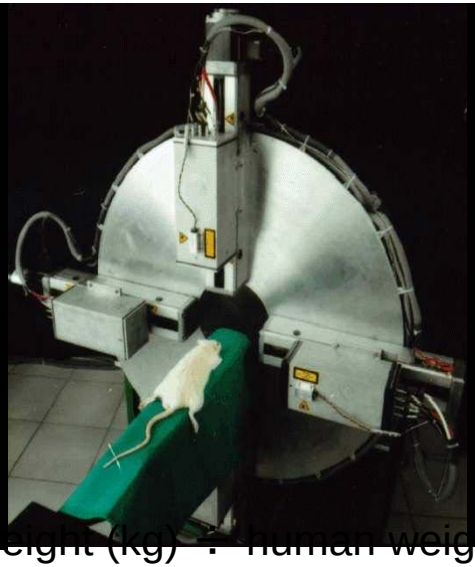
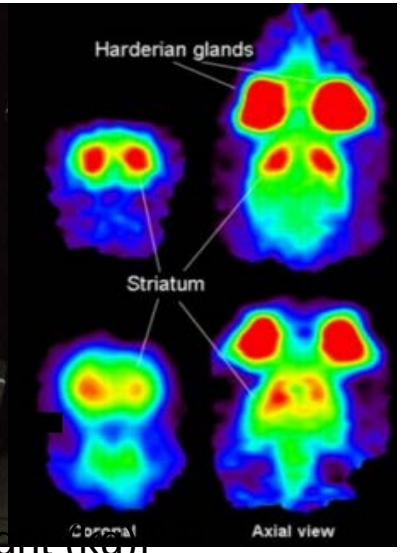
Extrapolation to Humans:
drug concentrations as information vector

- physicochemical predictions
- allometric scaling
- *in vitro* intestinal absorption models
- *in vitro* blood brain barrier models
- CYP450 preparations/ hepatocyte suspensions
- *in silico* computational organ exposure models
- autoradiography/PET-imaging









Human dose = Animal dose (mg/kg) × [animal weight (kg) ÷ human weight (kg)]

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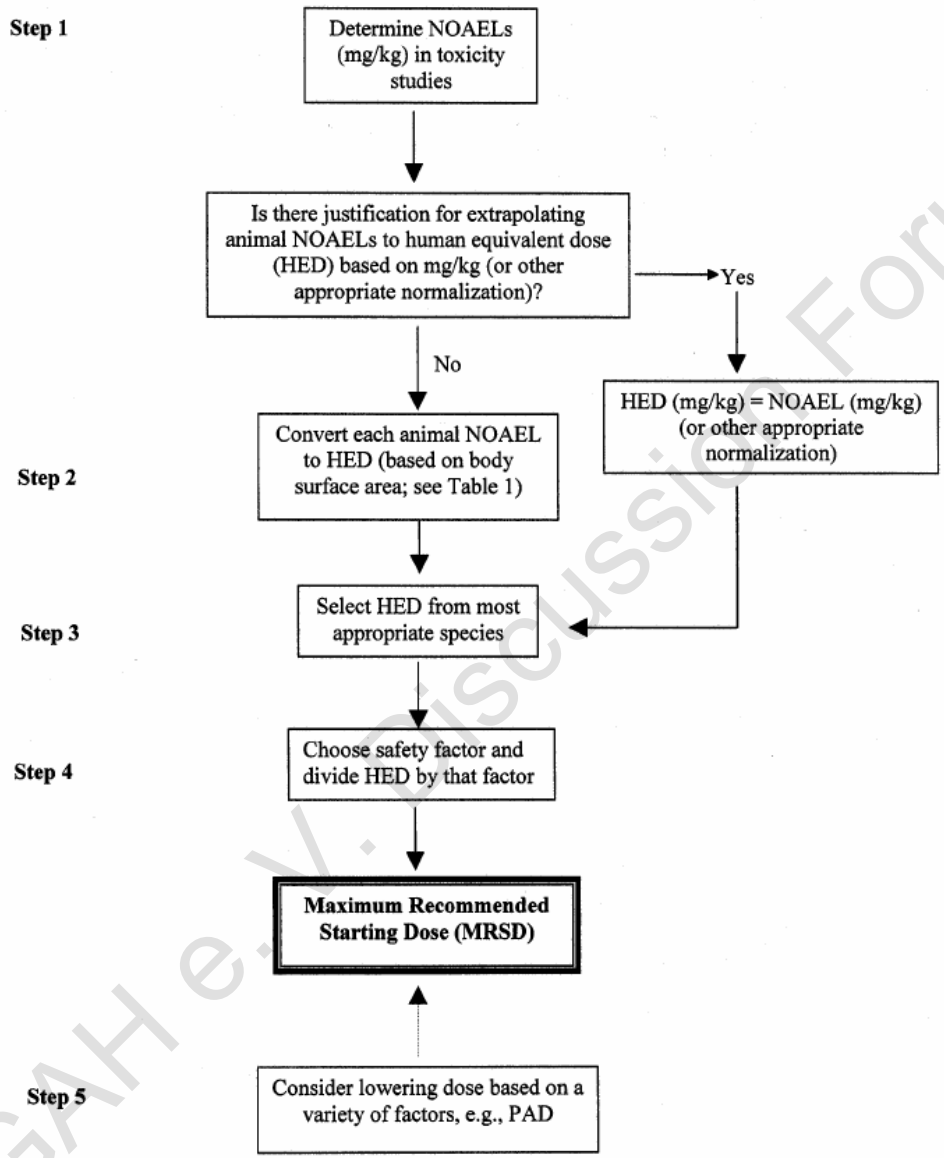
Selection of Maximum Recommended Starting Dose for Drugs Administered Systemically to Normal Volunteers



FDA. Guidance for Industry - Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. J:\!GUIDANC\5541fnlcln1.doc July 2005

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Tegenero Incident: tragedy in 2006

- TGN1412: CD28 superagonist specifically targeted at regulatory T-cells
- very large therapeutic window in animals
- starting dose was calculated from NOAOL with extra safety factor
- cytokine storm in first-in-man trial

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Tegenero Incident: analysis

- TGN1412 was highly selective in animals but not in humans:
- in humans, not only regulatory but also memory T-cells have CD28 receptors, causing massive cytokine release after activation
- starting dose in 2006 already caused 90% receptor occupancy
- new study in 2010 with 1000-fold lower dose caused regulatory IL10-production without pro-inflammatory cytokine release

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12605

Editorial

The return of the prodigal son and the extraordinary development route of antibody TGN1412 - lessons for drug development and clinical pharmacology

Marcel J. H. Kenter[1]* & Adam F. Cohen[2]

[1]The Netherlands Organisation for Health Research and Development (ZonMw) and [2]Centre for Human Drug Research, Leiden, the Netherlands
*The author's views do not necessarily reflect the viewpoint of his employer.

Kenter MJ, Cohen AF. Establishing risk of human experimentation with drugs: lessons from TGN1412. Lancet. 2006 Oct 14;368(9544):1387-91.

Kenter MJ, Cohen AF. The return of the prodigal son and the extraordinary development route of antibody TGN1412 - lessons for drug development and clinical pharmacology. Br J Clin Pharmacol. 2015 Apr;79(4):545-7.

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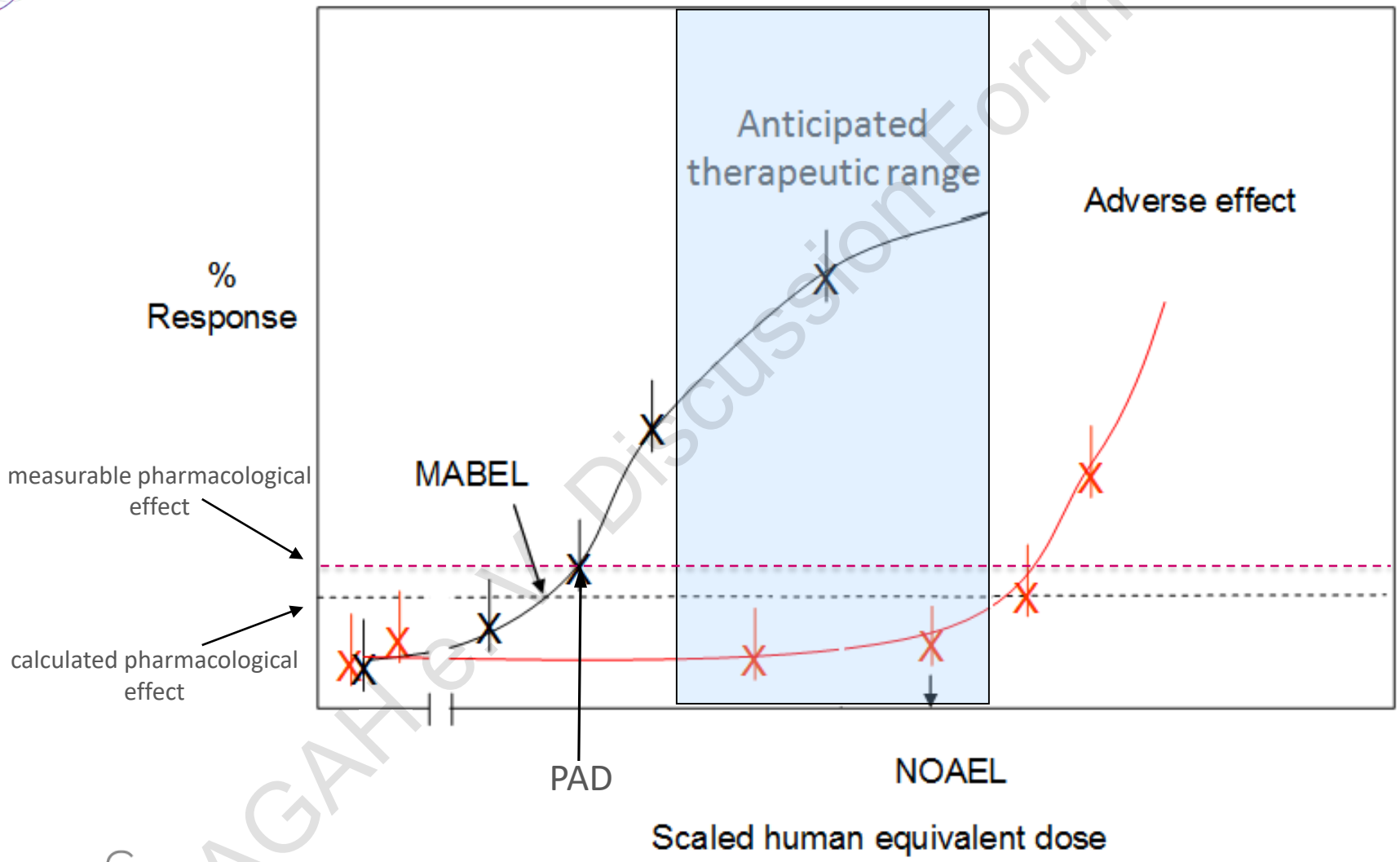
MABEL (EMA) vs PAD/NOAEL (FDA):



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Summary of Product Characteristics: Investigator's Brochure

- 'Compilation of clinical and non-clinical data on investigational product(s) that are relevant to the study of the product(s) in human subjects'
- Concise, simple, objective, balanced, non-promotional
- Should contain all available information to facilitate understanding of study rationale and protocol

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How do we integrate this information to design a first-administration-in-man study?

compiling concentration-effect relationships

Study Identifier	HED (mg)	Dose/F (mg/kg)	Cmax (ng/mL) *po*	Day of observation	Animal	Effects
PK STUDY	calculated HED	administered dose	measured Cmax			NO MEASURED/REPORTED EFFECT
PK STUDY	calculated HED	administered dose				NO MEASURED/REPORTED EFFECT
SAD STUDY	administered dose		measured Cmax			OBSERVED EFFECT
PD STUDY	calculated HED	administered dose	*calculated Cmax*			PHARMACOLOGICAL EFFECT
Human Predictions	calculated HED	administered dose	*calculated Cmax*			ANTICIPATED HUMAN DOSE
DISEASE MODEL	calculated HED	administered dose	*calculated Cmax*			THERAPEUTIC-LIKE EFFECT
PK / PD / TOX STUDY	calculated HED	administered dose	*calculated Cmax*			TOLERABLE/MONITORABLE SIDE EFFECT
PK / PD / TOX STUDY	calculated HED	administered dose	measured Cmax			UNACCEPTABLE/UNMONITORABLE/IRREVERSIBLE SIDE EFFECT
PK / PD / TOX STUDY	calculated HED	administered dose	measured/calculated Cmax			SEVERE TOXICITY
PK / PD / TOX STUDY	**calculated HED**	administered dose	measured/calculated Cmax			DEATH

ib-derisk.org

sort on (interpolated) Cmax

Van Gerven JMA, Cohen AF. Integrating data from the Investigational Medicinal Product Dossier/investigator's brochure. A new tool for translational integration of preclinical effects. Br J Clin Pharmacol. 2018 Jul;84(7):1457-1466

Van Gerven JMA, Bonelli M. Commentary on the EMA Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. Br J Clin Pharmacol. 2018 Jul;84(7):1401-1409

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PAD

Anticipated Therapeutic Dose (ATD)

NOAEL

Cmax (ng/mL)	Dose (mg/kg)				CNS Effects	Cardiovascular Effects
	Rats M	Rats F	Dogs	Humans		
3						
66		3				
53-303	9.7					
75/225			5			
143		5			reduction in ACTH levels after CRH/dDAVP challenge	
165/93			5 MD			
202	3					
200				2	anticipated lowest pharmacologically active dose	
282	2					
7	2.7 MD				antagonism of CRF/dDAVP-stimulated ACTH release	
216/183			10			
245-328	2					
286-371	10					
295/669			5			
307/125			10 MD			
340		5 MD			no clinical/pathological effects NOAEL (rats, MD)	
373				5	minimum effective human concentration; Cmaxss 1000 ng/mL	
300-400				5	human NOAEL equivalent dose	
352/352			5 MD			
551/211			10			
437	5					
459		10				
480/467			20			
550	5 MD				no clinical/pathological effects	
619/666			20 MD			
866	10					
7	10				improvement of mechanical allodynia in the Chung model of neuropathic pain	
7	10				reduction in ACTH levels after CRH/dDAVP challenge	
1222/1329			10			
1600				20	NOAEL (rats, SD)	
1583	25 MD				no clinical/pathological effects	Increased urinary production
1649/1035			10 MD			CV: mild QT prolongation (1 male)
7			10 MD		moderate tremors	
1675		25 MD			no clinical/pathological effects	Increased urinary production
2604/2241			20 MD		Mortality: 1 female died from sedation on day 14 of dosing; CNS: mild changes in behavior, posture and locomotion – reduced motor activity and bodily tremors	CV: mild QT prolongation
2945	75 MD			40	Mortality: 1/20 males on day 15	
3913		75 MD			Mortality: 1/20 females on day 6	
3983		125 MD			Mortality: 3/20 females on day 1,2,3; CNS: staggered gait, muscular weakness, incidentally reduced activity, vocalization	
			31 MD		Mortality: 1 male sacrificed on day 4 of dosing; CNS: restlessness	
7	250 MD				Mortality: 1/4 male (1/4) on day 3; CNS: sedation, tremors	
7		250 MD			Mortality: 2/4 females on day 2; convulsions in 1 dying female	
			100 MD		Mortality: 1 male died on day 1, and 1 female sacrificed on day 3 of dosing; CNS: mild tremors, mildly reduced activity and restlessness on the third day	
7		450			Mortality: 1/6 females died 2 days after dosing	
7	600				Mortality: 2/6 males died on the day of dosing, 1/6 died the day after dosing, 2/6 males and 5/6 females were sacrificed intercurrently 2 days after dosing, 1/6 males was found dead 4 days after dosing	
7		600			Mortality: 1/6 females died on the day of dosing, 5/6 females were sacrificed intercurrently 2 days after dosing	
77	600				Mortality: 6/15 animals died 24m-64h after dosing; serious ECG changes as clearly observed prior to EEG drop in 4 out of 6 non-survivors (bradycardia, sinoatrial block, ventricular escape complexes and sinoatrial arrest)	

new anxiolytic

PD: neuroendocrine CNS

steep C/E for toxicity!

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10% NOAEL

NOAEL

Cmax (ng/mL)	Dose (mg/kg)						CNS Effects
	Rats L/E	Rats S/D M	Rats S/D F	Dogs	Monkey	Humans (70kg)	
						0.005-0.0125	*improved well-being/performance*
0.03						0.02	marginal improvement RVPA CANTAB
0.07						0.02	improvement RVPA, PAL-TE, RTI-SRT/SCRT CANTAB
0.1						0.08	no significant CANTAB effect
0.3						0.08	no significant CANTAB effect
0.4						0.24	no CANTAB effect
0.55		0.01					significant improvement of social exposure time in social recognition retention model
0.69		0.013					Ki = 2,2 nM (MW 313)
0.8						0.24	no CANTAB effect
0.8						0.50	PSG
8.0						5.00	PSG
5.5		0.1					significant improvement of social exposure time in social recognition retention model
	0.3						no effects on 5-Choice Serial RT
	0.3						no effects on Morris Water Maze (scopolamine)
		0.3					no effects on n attempts at radial maze (scopolamine)
55		1	1				
		1					47% decrease in n errors induced by scopolamine
		1					30% decrease in latency to complete radial maze
73	1						5CSRT: increase in magazine latency
	1						no effects on Morris Water Maze (scopolamine)
		3					39% decrease in n errors induced by scopolamine
		3					36% decrease in latency to complete radial maze
155		3	3				
		3					'well tolerated in rats'
207					1		
220	3						
	3						no effects on 5-Choice Serial RT
	3						no effects on Morris Water Maze (scopolamine)
230				3			
248		3	3		1		
255		3					significant increase in wake time (ca. 30 min/4h)
270- 493		1-3	3		3		
760					3		
					3		NOAEL in cynomolgus
767		10	10				
798*	3						
798		1					
		10					significant increase in wake time (ca. 60 min/4h)
872		3					
823-1217		10	10	10			
1505		30	30				
1753		30					max brain concentrations 4450 ng/g at T=1h
1819		30	30				
		30					significant increase in wake time (ca. 120 min/4h)
2037					10		slight tremor in cynomolgus D1-13
2294		30					
2747		30					
		30					stained eyes, salivation
		30-56					dose-dependent increase in waking activity, rats
		56					dose-dependent increase in waking activity, rats
					20		tremor, ataxia
					30		tremor, ataxia, 3/n seizures on D1-4
					60		after SD tremor, ataxia, lethargy, seizure in 1/6 cynomolgus
4700		100					'well tolerated in rats'
		100					irritability, mydriasis and increased responsiveness to handling
			100				stained eyes, salivation
		100	100				1+1/n dead at D4/24
		100					dose-dependent increase in waking activity, rats
		178					dose-dependent increase in waking activity, rats
		178					convulsions in 1/5 rats, decreased seizure threshold
		200					abnormal gait, abnormal stance, body quivering, decreased body tone/staub tail in rats
		300					dose-dependent increase in waking activity, rats
		300					irritability, mydriasis and increased responsiveness to handling
		300					convulsions in 1/5 rats, decreased seizure threshold
		300					tremor, convulsions in 1/3 rats, decreased seizure threshold
		200	200				2+3/n dead at D2

new cognitive enhancer

SAD ⇨SDD!

no no-effect level?

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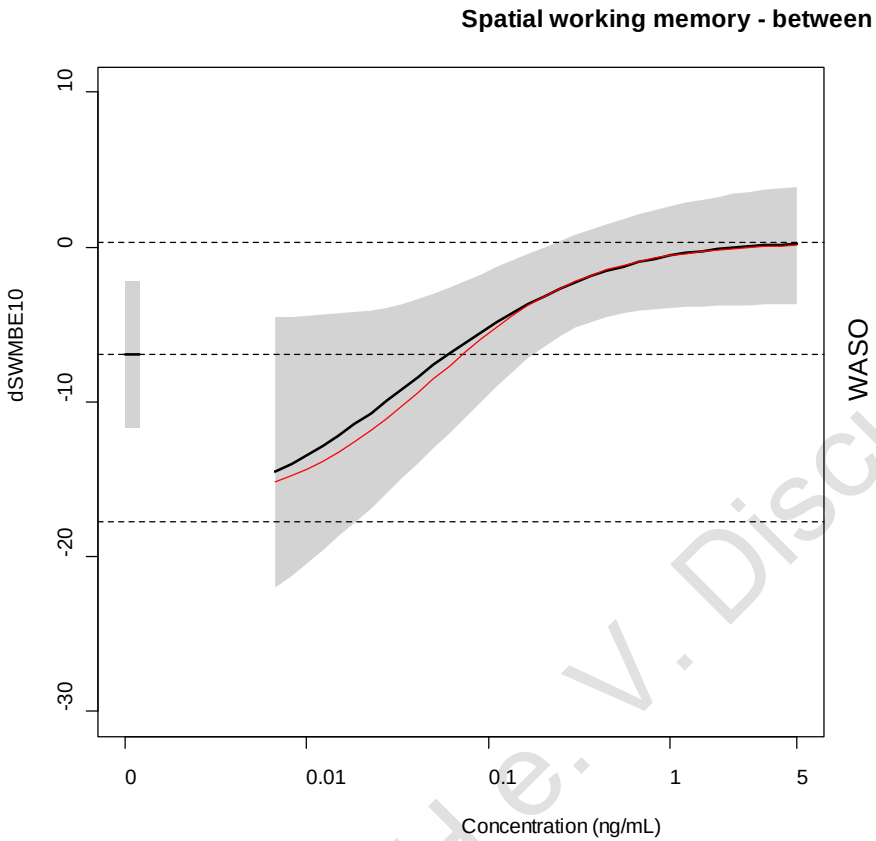
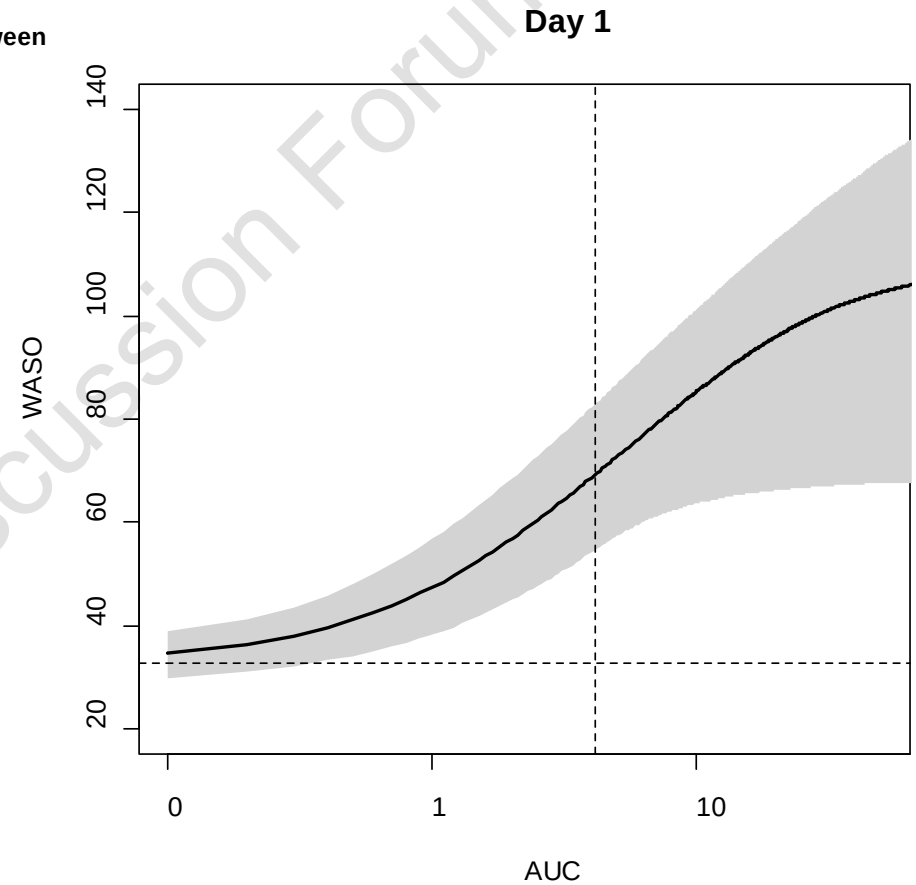
PK/PD-modeling



cognitive improvement < 1 mg/mL



sleep disturbance > 1 mg/mL

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10% NOAEL

NOAEL

anticipated therapeutic dose

Cmax (ng/mL)	AUC (ng*h/ml)	Dose (mg/kg)	mg/kg	µg/kg	µg	µg	CNS Effects
		Rat (Sex?)	Rat M	Monkey	Humans	Humans	
0.0362	0.07		6.6		2.27		
0.0724	0.15		59.9		4.54		
0.080						5.00	
0.145	0.30				9.07		
0.160						10.00	
0.20	0.30			1			NOAEL
0.24					237		maximum tolerated estimated equipotent concentrations for cannabinoid with 100-fold lower potency*efficacy vs
0.289	0.59				18.1		
0.319						20.00	
0.579	1.18				36.3		
0.639						40.00	
0.869	1.77				54.4		
0.957						60.00	
1.03					10000.00		maximum tolerated estimated equipotent THC-concentrations (assuming 390-fold lower potency*efficacy vs
1.278						80.00	
1.20	2.00			10			minor reductions in heart rate and body temperature, some reduction in locomotor activity
1.50					670-1800		anticipated effective human dose (1°C temp reduction)
2.17					80		maximum tolerated estimated equipotent concentrations for compound with equal potency and efficacy vs
4.65**		0.072 SD/INF					no reduction infarct size
		0.1 SD bolus					transiently decreased locomotor activity
8.7*	12.20			0.01 SD			
10.90					80		observed dose-limiting estimated equipotent concentrations for cannabinoid with equal potency and efficacy vs
14.85**		0.24 SD/INF					significant reduction infarct size
15.**					146250		therapeutically equivalent estimated equipotent THC-concentrations (assuming 230-fold lower potency*efficacy)
		0.24 MD					non-toxic dose
18.56		0.3 SD bolus					transiently decreased locomotor activity, convulsions
				0.048 MD			non-toxic dose (Male: decrease in body temperature)
48.20					80		observed dose-limiting estimated equipotent concentrations for compound with 100-fold lower potency*efficacy vs
56.7**		0.72 SD/INF					significant reduction infarct size
		0.72 MD					non-toxic dose
87.8*	70.40		0.03 SD				
				0.144 MD			non-toxic dose
		1 SD bolus					transiently decreased locomotor activity, convulsions
		2.4 mg/kg*24h					reduced infarct size, 4°C temp reduction
189.00		2.4 MD					decreases in locomotor activity, body weight, food consumption, blood lymphocyte count, thymus & speen weights, decrease in or necrosis of lymphocyte in thymus, spleen and lymph node
417.60				0.48 MD			vomiting, tremors, decreases in body weight, food consumption, white blood cell and lymphocyte counts, thymus weigths, and lymphocytes in the thymic cortex and in the marginal zone of spleen

new neuroprotectant

contradictory animal models!

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new breathing stimulator

HED (mg/kg)	GAL-160-022	Vd (L/kg) (dose iv/ Cmax	Vd (L/kg) (dose po/ Cmax	Cmax (mg/L) (HED (mg/kg)	Dose	Cmax (mg/L)	C mean (mg/L)	AUC (mg*h/l) in plasm	Animal	Effects
3.2				1.6	10 mg/kg PO	**0.0205**		0.107	cynomolgus monkey	no emesis
0.48					3 mg/kg PO	*0.13701*	**0.04**		rat	**required for efficacy in central sleep apnea and obstructive apnea**
2.85			11.7	1.4	3 mg/kg PO SD (ds1) A	**0.257**		2.087	mini pigs	no abnormalities
5.7			24.5	2.9	6 mg/kg PO SD (ds1) A	**0.245**		1.888	mini pigs	no abnormalities
8			251.9	4.0	50 mg/kg PO SD	**0.1985**			rat	
	1.6				10 mg/kg PO SD	**0.27**		0.742	rat-022	
4			89.0	2.0	25 mg/kg PO SD	**0.281**		1.1745	rat	
5.4			17.5	2.7	10 mg/kg PO SD	**0.573**		0.476	dog	
11.4			21.1	5.7	12 mg/kg PO SD (ds1) A	**0.5685**		7.9255	mini pigs	no abnormalities
0			34.5	0.0	25mg/kg/dose MD (ds1) C	**0.725**		3.7975	mini pigs	**NOAEL male/female mini pigs DRF** (however, one female had isolated perivascular inflammation of spinal co
1.6				0.8	10 mg/kg PO				rat	decreased hindlimb splay
3.2			8.2	1.6	20mg/kg PO	**2.436**		7.125	rat	**NOAEL male/female rats DRF**
3.2				1.6	20 mg/kg PO				rat	decreased hindlimb splay, increased respiration
4.8			23.1	2.4	30 mg/kg PO	**1.2985**			rat	decreased hindlimb splay, decreased hindlimb grip strength, increased respiration, decreased body temp
			19.2		24 mg/kg PO	**1.25**		10.6285	mini pigs	emesis (also in controls)
2.16				1.1	27mg/kg PO				mouse	acutely impaired gastric emptying
4.8			23.1	2.4	30 mg/kg PO, during 5 days	**1.3**			rat	impaired gastric emptying at 1 and 6 hr post dose, but dissipated at 24 hr post dose
5.4			7.7	2.7	10 mg/kg PO	**1.3**			dog	emesis
16			75.7		100 mg/kg PO SD	**1.32025**		16.27	rat	
	4.8				30 mg/kg PO SD	**1.73**		5.09	rat-022	
34.2			19.3	17.1	36 mg/kg	**1.87**		13.4155	mini pigs	emesis
8				4.0	50 mg/kg PO		2.6		rat	acutely impaired gastric emptying
							3.7		rat	muscle laxity and loss of righting reflex
4.75		1.3			5 mg/kg IV		3.8		mini pigs	no emesis
47.5				23.8	50 mg/kg PO (followed by 40 mg/kg) MD (ds1) C				mini pigs	minimal to moderate perivascular/vascular inflammation at necropsy in extremis in 2/6 animals; decreased acti
71.25			33.8	35.6	75 mg/kg PO(follow-up from 90 mg/kg)	**2.22**		11.22	mini pigs	minimal to moderate perivascular/vascular inflammation at necropsy in extremis; decreased activity, vomitus, a
32			74.0	16.0	200 mg/kg PO SD	**2.702**		11.292	rat	
85.5			24.2	42.8	90 mg/kg MD (ds1) A	**3.715**		29.348	mini pigs	
16.2			9.8	8.1	30 mg/kg PO	**3.06**		2.26	dog	
32.4			19.5	16.2	60 mg/kg PO	**3.08**		2.78	dog	
		1.4			5 mg/kg IV	**3.62**			dog	emesis
48			80.6	24.0	300 mg/kg PO SD	**3.7225**		65.666	rat	
							5.325		rat	ataxia
57			9.6	28.5	60 mg/kg PO SD (ds1) A	4.17		34.52	mini pigs	vomitus, material around eyes (brown) on ds1
		1.0			5 mg/kg IV	**5.15**		1.34	rat-022	
54			19.2	27.0	100 mg/kg PO	**5.21**		3.91	dog	
					90 mg/kg PO SD (ds1) A			41.918	mini pigs	decreased activity, vomitus, and material around eyes (brown) on ds 1; inappetence on ds2; minimal to modere
		0.9			5 mg/kg IV	**5.34**		1.88	rat-012	
		0.8			5 mg/kg IV	**6.54**		3.82	cynomolgus monkey	emesis
					100 mg/kg PO				rat	acutely impaired gastric emptying stilll evident at 24 hr,
					0.25 mg/kg/min IV for 30 min, thus 7.5 mg/kg				rat	acutely impaired gastric emptying
81			18.5	40.5	150 mg/kg PO	**8.1**		7.54	dog	
	9.6				60 mg/kg PO	**8.64**		7.54	rat-022	
	16				100 mg/kg PO	**10.1**		316	rat-022	
					150 mg/kg PO				rat	acutely impaired gastric emptying
					150 mg/kg PO SD (ds1) A			178.307	mini pigs	decreased activity, vomitus, salivation, skin warm to touch, tremors, ataxia, material around eyes (brown), and
							24.124		rat	ataxia, material around eyes (brown), and thin body condition on the day of and the
					0.75 mg/kg/min IV for 30 min, thus 22.5 mg/kg				rat	impaired gastric empting day after dosing
					300 mg/kg PO				rat	acutely impaired gastric emptying, 2 animals death
	48				300 mg/kg PO	**67**		145	rat-022	
					2.25 mg/kg/min IV for 30 min, thus 67.5 mg/kg				rat	acutely impaired gastric emptying

idiosyncratic toxicity?

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Conclusions

- Evaluation of preclinical data for early human drug studies mainly consists of intelligent integration of information
- The most important objective of early human drug studies is to understand the drug's clinical pharmacology
  - pharmacokinetics
  - safety pharmacology
  - efficacy pharmacology

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