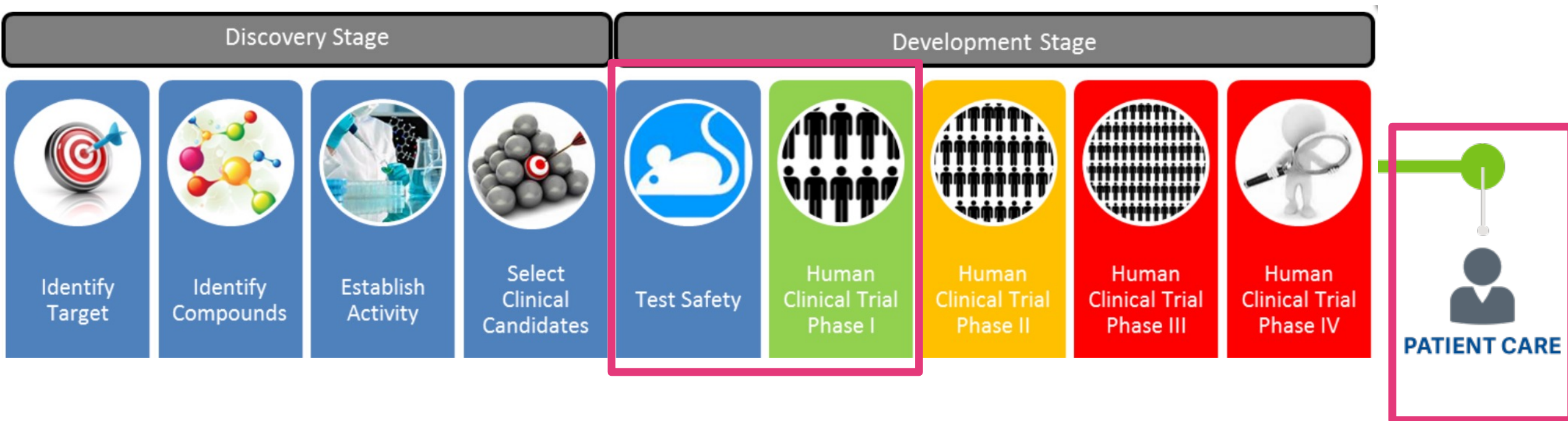


# IB derisk – Pitch KlinFarm

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# How to choose the clinical dose

## Drug development



- Best chance of taking the right dose to patients:
  - Determine safe starting dose for FIH
  - Determine effective dose range in early clinical trials

# Pre-clinical studies

## Drug development

- *In vitro* and *in vivo* work in different species
  - Toxicology
  - Pharmacokinetics
  - Pharmacodynamics
- Combined in the Investigators Brochure (IB)
- Crucial document for FIH trial



# IB-derisk

Tool to structure IB information

IB information:

Title:

Protein binding:

**+** Graphs menu

exclude	dose
<input type="checkbox"/>	100
<input type="checkbox"/>	101
<input type="checkbox"/>	102
<input type="checkbox"/>	103
<input type="checkbox"/>	104
<input type="checkbox"/>	105
<input type="checkbox"/>	106

add study

Study ID:

#25

Study duration(in days):

18

Study design:

knowledge

☐ In Vitro

☒ Effect study

pagenumber in pdf:

1

Species:\*

Select species:

Gender:

Select gender

Dose:\*

200

Dose unit:\*

mg/kg

cmax(ng/mL):

12

AUClast in plasma(ng.h/mL):

13

Administration route:

Select route

Color code:

























Select colorcode

Safety and efficacy description:

Safety and efficacy description

# Colour coding

IB-risk

	100	Study without clinical observations			
	103	Desirable effect			
	104	Undesirable but acceptable effects			
	105	More severe adverse effects			
	106	Serious irreversible toxicity and/or death			
	102	Intended human dose			





## Pre-clinical data

study ID	study design	study duration	species	route/dose/form	MOA/mechanism of action and efficacy description	ministration route	ED <sub>01</sub> /mg/kg	ED <sub>50</sub> /mg/kg	ED <sub>99</sub> /mg/kg	ED <sub>99.99</sub> /mg/kg	remarks	observed	type	notes	
Table 4.2	Inhibition of PARH in liver EDSB	mouse		10 mg/kg	EDSB Liver after 1h	Oral	0.881	0.833	0.853	Wide Clot door		0.881	Efforal study	Halalalilal	
Table 4.2	Inhibition of PARH in liver EDSB	mouse		20 mg/kg	EDSB Liver after 1h	Oral	0.882	0.881	0.882	Wide Clot door		0.882	Efforal study	Halalalilal	
Prevalent	Human SD	1 human	male	0.883 mg/kg	1	Unknown	0.883	0.881	0.88	Dosed upon Vd 2.51/kg		0.883	Efforal study	Halalalilal	
Prevalent	Human SD	1 human	male	0.887 mg/kg	7	Unknown	0.887	0.823	1.82	Dosed upon Vd 2.51/kg		0.887	Efforal study	Halalalilal	
Prevalent	Human SD	1 human	male	0.893 mg/kg	19	Unknown	0.893	1.221	1.38	Dosed upon Vd 2.51/kg		0.893	Efforal study	Halalalilal	
Prevalent	Human SD	1 human	male	0.867 mg/kg	27	Unknown	0.867	2.473	4.82	Dosed upon Vd 2.51/kg		0.867	Efforal study	Halalalilal	
4.5	Dose dependent brain AER from plasma DIB	mouse		1 mg/kg	35	EDSB was administered	Oral	0.88	0	0		0.88	0	0	0
4.8	Formulation test	1 mouse		1 mg/kg	35	Administration of oral only in combination with intraperitoneal	Oral	0.88	0	0		0.88	0	0	0
EDS Abnormal	Lowest PARH inhibition	1 mouse/kg [Cyanomycin, chroma, allopurinol]	male	0.1 mg/kg	37	Max PARH inhibition	Unknown	0.832	0.2	0.32		0.832	0.2	0.32	0.32
EDS Abnormal	PARH inhibition study	1 mouse/kg [Cyanomycin, chroma, allopurinol]	male	0.1 mg/kg	37	EDSB PARH inhibition peripherally	Oral	0.832	0.2	0.32		0.832	0.2	0.32	0.32
Prevalent	Human SD	1 human	male	0.133 mg/kg	53	Unknown	0.133	0.321	7.38	Dosed upon Vd 2.51/kg		0.133	Efforal study	Halalalilal	
Prevalent	Human SD	1 human	male	0.267 mg/kg	185	Unknown	0.267	0.321	16.82	Dosed upon Vd 2.51/kg		0.267	Efforal study	Halalalilal	
EDS Abnormal	Lowest PARH inhibition	1 mouse/kg [Cyanomycin, chroma, allopurinol]	male	0.3 mg/kg	117	EDSB PARH inhibition	Oral	0.836	0.6	0.76		0.836	0.6	0.76	0.76
4.2.1	Pharmacokinetic study	1 day	male	0.1 mg/kg	154	EDSB PK study	IV	0.816	0.6	0.86		0.816	0.6	0.86	0.86
Prevalent	Human SD	1 human	male	0.1 mg/kg	182	EDSB PK study	IV	0.854	2	0.24		0.854	2	0.24	0.24
4.5	Dose dependent brain AER from plasma DIB	mouse		0.533 mg/kg	243	Unknown	0.533	0.521	31.38	Dosed upon Vd 2.51/kg		0.533	Efforal study	Halalalilal	
Abnormal EDS	PARH in low range	1 mouse/kg [Cyanomycin, chroma, allopurinol]	male	1 mg/kg	583	Maximal inhibition of PARH peripheral	Oral	0.32	0	0.32		0.32	0	0.32	0.32
Prevalent	Human SD	1 human	male	1.333 mg/kg	534	Unknown	1.333	0.521	73.38	Dosed upon Vd 2.51/kg		1.333	Efforal study	Halalalilal	
4.5	Dose dependent brain AER from plasma DIB	mouse		10 mg/kg	1127	EDSB was administered	Oral	0.8	0	0		0.8	0	0	0
4.7	Mouse tail flick test	mouse		10 mg/kg	1127	Administration of 1h	Oral	0.8	0	0		0.8	0	0	0
Table 4.2	Inhibition of PARH in brain EDSB	mouse		34 mg/kg	1161	EDSB brain after 1h	Oral	0.888	0.282	0.451	Wide Clot door		0.888	Efforal study	Halalalilal
4.2	Brain PARH inhibition	1 mouse		180 mg/kg	1163	EDSB brain PARH inhibition	Oral	0.888	0.3	0.48		0.888	0.3	0.48	0.48
EDS/ED	Three month Toxicology	31 mouse/kg [Cyanomycin, chroma, allopurinol]		0.25 mg/kg	4256	EDSB was administered	Oral	2	75	128		2	75	128	128
EDS/ED	Repeat administration toxicology	28 mouse/kg		0.25 mg/kg	2385	EDSB was administered	Oral	0.8	0	0.8		0.8	0	0.8	0.8
37/53	Toxicology 6 month PK at day 185 average m	180 rat		0.25 mg/kg	5241	EDSB was administered	Oral	1.5	0	0		1.5	0	0	0
EDS/ED	Up to 100% up to 100% in 100% in 100%	28 mouse/kg [Cyanomycin, chroma, allopurinol]		10 mg/kg	5153	EDSB was administered	Oral	0.32	0	0.32		0.32	0	0.32	0.32
EDS/ED	Repeat dose toxicology	18 rat		28 mg/kg	5648	EDSB was administered	Oral	0.8	0	0.8		0.8	0	0.8	0.8
4.1.3	Cardiovascular maximum animal study	1 day	male	28 mg/kg	8878	No CVS effects	Oral	0.8	0	0.8		0.8	0	0.8	0.8
37/53	Toxicology 6 month PK at day 185 average m	180 rat		0.25 mg/kg	5241	EDSB was administered	Oral	1.5	0	0		1.5	0	0	0
EDS/ED	Up to 100% up to 100% in 100% in 100%	28 mouse/kg [Cyanomycin, chroma, allopurinol]		10 mg/kg	5153	EDSB was administered	Oral	0.32	0	0.32		0.32	0	0.32	0.32
EDS/ED	Repeat dose toxicology	18 rat		28 mg/kg	5648	EDSB was administered	Oral	0.8	0	0.8		0.8	0	0.8	0.8
4.1.3	Cardiovascular maximum animal study	1 day	male	28 mg/kg	8878	No CVS effects	Oral	0.8	0	0.8		0.8	0	0.8	0.8
EDS/ED	Up to 100% up to 100% in 100% in 100%	28 mouse/kg [Cyanomycin, chroma, allopurinol]		10 mg/kg	5153	EDSB was administered	Oral	0.32	0	0.32		0.32	0	0.32	0.32
EDS/ED	Repeat dose toxicology	18 rat		28 mg/kg	5648	EDSB was administered	Oral	0.8	0	0.8		0.8	0	0.8	0.8
4.1.3	Cardiovascular maximum animal study	1 day	male	28 mg/kg	8878	No CVS effects	Oral	0.8	0	0.8		0.8	0	0.8	0.8
Table 4.2	Inhibition of PARH in brain EDSB	mouse		34 mg/kg	1161	EDSB brain after 1h	Oral	0.888	0.282	0.451	Wide Clot door		0.888	Efforal study	Halalalilal
4.1.3	Safety pharmacology CNS	1 rat	male	30 mg/kg	11865	Minor changes in body temp and piloerection	Oral	4.8	188	288		0.888	0.282	0.451	0.451
4.1.3	Safety pharmacology Respiratory	1 rat	male	30 mg/kg	11865	No effects Respiratory/Respir	Oral	4.8	188	288		0.888	0.282	0.451	0.451
4.2.2	Pharmacokinetic	1 rat	male	30 mg/kg	11865	EDSB PK study	Oral	4.8	188	288		0.888	0.282	0.451	0.451
4.3.1	Three month toxicology	28 mouse		25 mg/kg	12188	EDSB was administered	Oral	2	75	128		0.888	0.282	0.451	0.451
EDS/ED	Toxicology up to 100%	31 mouse/kg [Cyanomycin, chroma, allopurinol]		0.25 mg/kg	14288	EDSB was administered	Oral	12	458	728	Up to 100% 6.25 - 12.5 - 25 mg/kg then 37.5	0.888	0.282	0.451	0.451
EDS/ED	Toxicology up to 100%	28 mouse/kg		30 mg/kg	17488	EDSB was administered	Oral	4.8	188	288		0.888	0.282	0.451	0.451
4.1.3	Cardiovascular maximum animal study	1 day	male	58 mg/kg	15235	No CVS effects	Oral	27	1888	1628		0.888	0.282	0.451	0.451
EDS/ED	Repeat dose toxicology	28 mouse/kg		180 mg/kg	11588	EDSB was administered	Oral	54	2888	3248	EDSB was administered	0.888	0.282	0.451	0.451
EDS/ED	Up to 100% up to 100% in 100% in 100%	31 mouse/kg [Cyanomycin, chroma, allopurinol]		25 mg/kg	28688	EDSB was administered	Oral	24	588	1448	6.25 - 12.5 - 25 - 58 mg/kg up to 100% then 75	0.888	0.282	0.451	0.451
EDS/ED	Up to 100% up to 100% in 100% in 100%	28 mouse/kg [Cyanomycin, chroma, allopurinol]		30 mg/kg	24867	EDSB was administered	Oral	16	688	368	EDSB was administered	0.888	0.282	0.451	0.451
4.1.3	Safety pharmacology CNS	1 rat	male	180 mg/kg	22488	Minor changes in body temp and piloerection	Oral	16	688	368		0.888	0.282	0.451	0.451
4.1.3	Safety pharmacology Respiratory	1 rat	male	180 mg/kg	22488	No effects Respiratory/Respir	Oral	16	688	368		0.888	0.282	0.451	0.451
4.1.3	Cardiovascular maximum animal study	1 day	male	180 mg/kg	22488	EDSB was administered	Oral	54	2888	3248		0.888	0.282	0.451	0.451
EDS/ED	Up to 100% up to 100% in 100% in 100%	31 mouse/kg [Cyanomycin, chroma, allopurinol]		25 mg/kg	27625	EDSB was administered	Oral	16.2	688	372		0.888	0.282	0.451	0.451
EDS/ED	Repeat dose toxicology	28 mouse/kg		30 mg/kg	27625	EDSB was administered	Oral	32	1288	1528	EDSB was administered	0.888	0.282	0.451	0.451
4.3.1	Three month toxicology	28 mouse		25 mg/kg	28635	EDSB was administered	Oral	14.4	548	808	EDSB was administered	0.888	0.282	0.451	0.451
EDS/ED	Up to 100% up to 100% in 100% in 100%	31 mouse/kg		30 mg/kg	36488	EDSB was administered	Oral	6	225	368	EDSB was administered	0.888	0.282	0.451	0.451
EDS/ED	Repeat dose toxicology	28 mouse/kg		30 mg/kg	38388	EDSB was administered	Oral	14.4	548	808	EDSB was administered	0.888	0.282	0.451	0.451
4.3.3	Dose dependent brain AER from plasma DIB	14 rat		158 mg/kg	52388	EDSB was administered	Oral	24	588	1448		0.888	0.282	0.451	0.451
EDS/ED	Up to 100% up to 100% in 100% in 100%	28 mouse/kg		158 mg/kg	52388	EDSB was administered	Oral	24	588	1448		0.888	0.282	0.451	0.451
4.3.1	Dose dependent brain AER from plasma DIB	14 rat		180 mg/kg	53288	EDSB was administered	Oral	8	388	488		0.888	0.282	0.451	0.451
4.3.3	Dose dependent brain AER from plasma DIB	14 rat		180 mg/kg	53288	EDSB was administered	Oral	32	1288	1528		0.888	0.282	0.451	0.451
4.3.1	Dose dependent brain AER from plasma DIB	14 rat		158 mg/kg	72388	EDSB was administered	Oral	12	458	728		0.888	0.282	0.451	0.451
4.3.3	Dose dependent brain AER from plasma DIB	14 rat		158 mg/kg	81235	EDSB was administered	Oral	48	2388	2748		0.888	0.282	0.451	0.451

Starting dose

Adverse effects  
(~ 5000 ng/mL)

## Pre-clinical data

 MABEL ( $\sim 1$  ng/mL)  
 Starting dose  
  
 ATD ( $\sim 100$  ng/mL)  
  
 Adverse effects  
 ( $\sim 5000$  ng/mL)

# IB derisk as educational tool

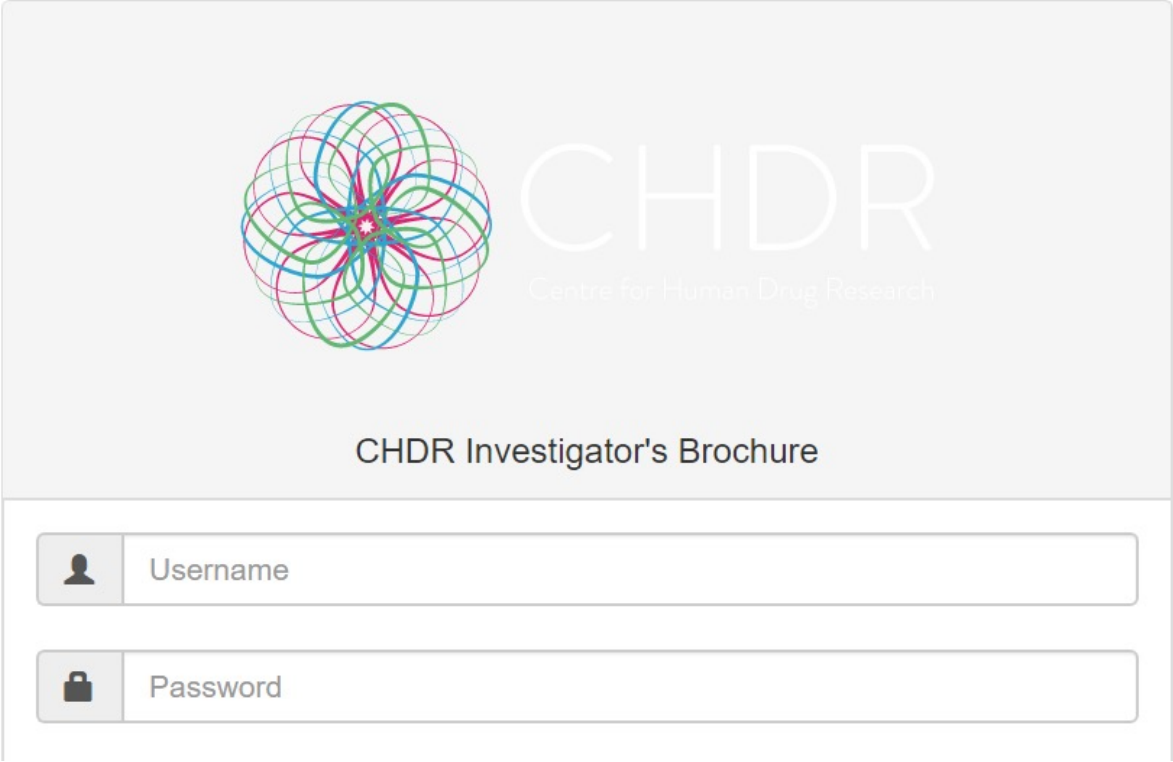
NVKFB

## Why?

- Understanding of pre-clinical and clinical pharmacology
  - Toxicology
  - Pharmacokinetics
  - Pharmacodynamics
  - Translation
  - Protein binding
  - Interpretation
- Crucial step in drug development
  - Translation from Pre-clinical → Clinical

## How to implement in education centres?

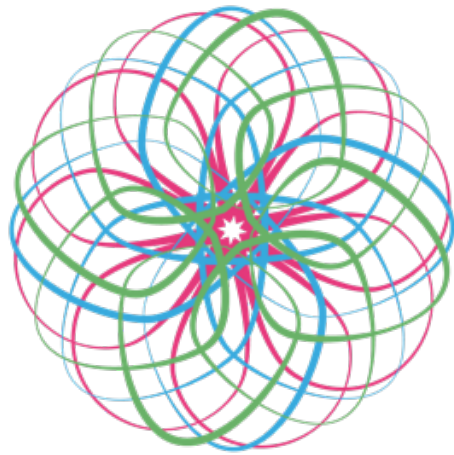
- IB-derisk tool freely available
- CHDR could make a set of IB's for this educational purpose available
- Comparison possible between student and study team outcome / dosing plan



The image shows a login interface for the CHDR Investigator's Brochure. At the top, there is a logo consisting of a colorful, multi-layered sphere with lines radiating from the center, followed by the text 'CHDR' in large, white, sans-serif font, and 'Centre for Human Drug Research' in a smaller, lighter font below it. Below the logo, the text 'CHDR Investigator's Brochure' is centered. The login section contains two input fields: the first is labeled 'Username' with a user icon on the left, and the second is labeled 'Password' with a lock icon on the left. Both fields are empty and have a light gray border.

# WWW.IB-DERISK.ORG

<https://youtu.be/jPvXk7yiuxw>



# CHDR

Centre for Human Drug Research