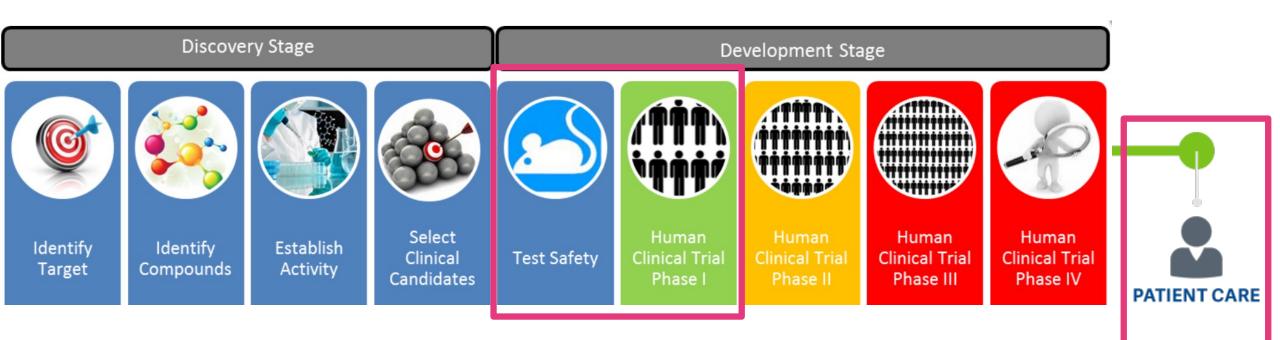
IB derisk – Pitch KlinFarm

Jules Heuberger Senior Clinical Scientist, klinisch farmacoloog Centre for Human Drug Research



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

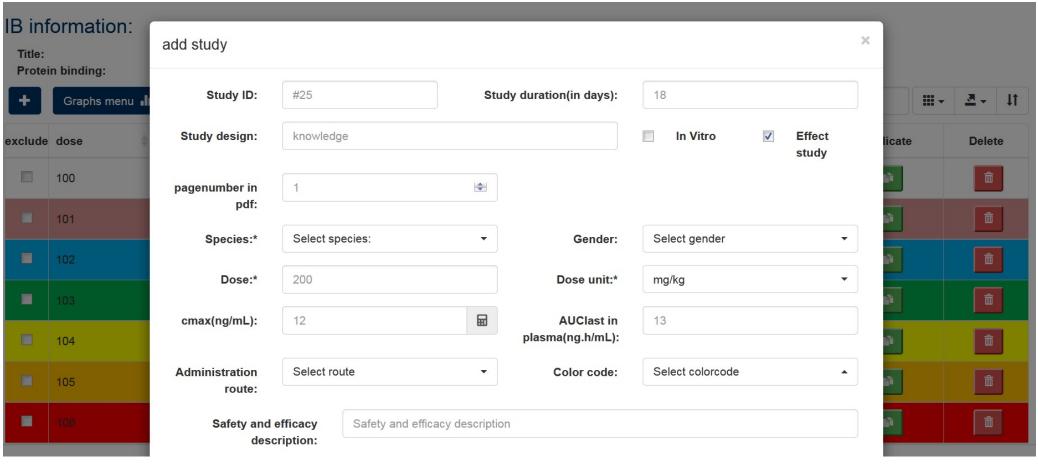






IB-derisk

Tool to structure IB information





Colour coding IB-derisk

Intended human dose

102

100	Study without clinical observations	Ø		
103	Desirable effect	Ø		â
104	Undesirable but acceptable effects	Ø	1	â
105	More severe adverse effects	Ø		â
106	Serious irriversible toxicity and/or death	Ø	100	Ê

Ø



Colour pattern

Pre-clinical data

alady id		ladą darali:	apraira prai	1012700000		Classafely and officery denociplies	1000	100000		To be the state of	alarand		siles els
Mr 4.2	Inhibition of PAAH in lines EDSS	*****		11 pg/kg		EDSB Lines after 16	Oral	1.09	1.111	8.859 Wide Chaf dase			Hallie ailes
N+4.2	labibilian of FAAH in lines EDSE			27 pg/kg		EDS# lines affect # \$	Oral	1.02	1.004	8.45 Wide Chaf dage	arrerer c	ffeel slade	Hall in eilen
level	Haman SD	1 house	-al-	Little my/kg	- 1		Unknown	1.00	8.444	E.18 Panedapon V42.50/kg	HIDITE E	Secolulula.	Helicailes
decel	Haman SD	1 keman	mate	8.887 mg/kg	7		Unknown	0.017	8.625	1.82 Paned apon Vd 2.51/kg	HIPPET C	Seculately.	Helicailes
decal	Haman SD	1 kense	wall	1.000 mg/kg	12		Unknown	0.033	1.221	1.58 Basedopos Vd 2.51/kg	HIRITE E	Seculately.	Helicailes
level	Haman SD	1 house	walt	1.867 mg/kg	27		Unknown	0.067	2,475	4.82 Panedapon Vd 2.51/kg	HIGHT C	Seculately.	Hallia ailea
	.5 Dane dependence brain AEA from plants DI	in maner		1 -9/69	95	BSX man annulamide	Oral	1.00		6.0	arrerer E	Seculated,	Hallis ailes
	A Permalia pasa Iral	1		1 mg/kg	95	Autioniusplies effect only in combination :	Interpreliment	1.00		63	HIPEST E	Secolululy.	Hallis alles
Sakulraul	Leanuagle PARH inhibition	1 maskega [Case	malgan, eleman, alamphail[male	. It's my/kg	97	SE Han 72X (natibilities	Unkerne	0.002	1.2	1.52			Hallie ailes
Sakelearl	PARKINGSINGSINGS	1 maskega [Cyan	ondges, ekensy damphailf mah		57	BEX PARK intitition prelipherally	Oral	0.052	1.2	1.52	4.5	Secolulula	Hall in eilen
alesal	Haman SD	1 kmm	-ali		55		Unknown.	8,199	4.521	7.58 Panedapon Vált.5176q			Helia eiles
alasal	Haman SD	1 kense		8.257 mg/kg	186		Unknown	8.267	5.875	16.62 David open Vd 2.517kg			Hallis ailes
Sabelrael	Leanungle PARH inhibition		malgan, chemn, alamplail), male			452.2 38 X (a4/40) as	Oral	(8.836	3.6	5.76			Hal is siles
		ral	-41			14111 PK slada	IV	8.846	1.6	1.16			Halia siles
2.1	Pharmanshinelinalodg	1 444	-41		182	And the Committee of the Control of	iv	1.154		1.24			Halisailes
elevel	Hamas SD	1 kmm		8.555 mg/kg	213	121 PK SISSA	Unknown	8.555	15.721	31.38 Paned apon Vd 2.51/kg			Halia siles
						400							
	.S. Daar dependence brain AEA from planta Bl		The second of the second	S my/kg	274	B1X was assertantle	Oral .	1.24		16.1			Halicailea
	PARH in Ironneyles		malgan, ekenna, alamplail mala		585	1886.5 Hanimalinkikilinnuf PRAN preigheral	Oval	8.52	12	11.2			Hal is siles
-desel	Heman SD	1 kense	-ali		594		Unknown	1.555	49,521	75.58 Pased upon Vd 2.51/bg			Hal is siles
	.S. Duur dependense krain AEA feun planna Pl	IA manar		10 mg/kg	1127	188X was awardamide	Oral	1.0					Hal is ailes
	.7 Hanne fail flink leaf			18 mg/kg	1127	Autininius pline at # k	Oral	1.0	- 11	0	INDEST E	Seculateda	Halia siles
Me 4.2	labibilian of FAAH in besin EDSE			34 parks	1161	EDS8 beain after 16	Oral	1.00	8.282	8.451 Wide Chaf dage	arrerer c	Fire I slade	Hallis ailes
	.2 Prais PAAH ishibilisa	1		100 pg/kg	1165	SSX beste PAAH telibilise	0 eal	100	8.0	1.0	atterer E	Seculately.	Hallia siles
2765	Three world Taxinalogy	35 markege Cyan	malgan, ekenan, alamphill	5.25 mg/bg	4256	24994 Hawrence of Fruit and all convenible	Oral	2	75	128	HIDIST E	Effect study	Hallis ailes
1/65	Repeal administration funishing	28 day		28 mg/kg	5255	2011	Oral	10.0	- 01	FOL	BELLEVIS E	Seculated.	Halis siles
/65	Taninalogy Empells, PK aliday 185 apreage of	401 est		18 mg/kg	5241	18458 HOAEL RATEMO	Oral	1.6	68	16 organ weight absorre	AFFFFRA E	Secolulula.	Helia eilea
5/65	Up literline experiment in agreemely se	28 mashrqu [Cqua	malgan, chessa, alamptail]	18 mg/kg	6465	33833 Effects is single asimals	Oral	5.2	128	192	STEETERS E	Secol alada	Helia eilea
2/65	Repealed door looiselegg	28 day		28 mg/kg		28588 DOGHOAEL [Jankliful]	Oral	11.1	411	648 arequisitable process of signs in l			
1.3	Cardinaanslar sensines asimal sledg	1 44	e als	. 28 mg/kg		Ha CVS efficials	Oral	11.1	(1)	548			Halisailes
/69	Tonioslagg Smooth, PK at day 485 accesses			28 mg/kg		33583	Oral	6.1	111	200 organ weight abangen weight toon afini			
/69		28 day		SE my/kg		SIRR HOAELDOG	Oral	27	100	1628			Helie eilee
51-4.2	Inhibition of FAAH in bruin EDSE			27 paths	11146	EDSB beain after 8 b	Oral	0.002	1.011	1.43 Wide Class date			Hal is siles
1.5	Safely pharmaning CHS	1 ral	-al-		11866			6.1	111	211			
			=41			Histor abangen inhada later and piloreralism							Halisailes
.5	Safely pharmanilogy Respiratory	1 rat		- 38 mg/kg	11866	Ha officula Respiratory/Resal	Oral	9.0	401	201			Hallia ailea
5.1	Pharmanshineline	ral	=41			HIII PK alada	Oral	4.1	111	211			Helissiles
la .	Three would be include	21 mm		25 mg/kg		SEREE HOAELHOUSE	Oral .	- 2	75	101			Halia siles
5/65	Taninalogy op licalian		malgan, ekenna, alampiaili	57.5 mg/bg		78862 Haurrissa effests	Oral	12	451	728 Up literation 6.25 - 12.5 - 25 mg/kg liber			
4765		28 val		SE my/kg	17/00	SASSE RATHOAEL SAI HOEL SAI FALLSIISSAN	Oral	- 61	100	211	INDEST E	Secolulula.	Halia siles
1.5	Cardinaanular ununinu asimal aladq	1.44	mali mali	Si my/kg	17585	HO CYS effects	Oral	27	100	1628	BELLEVISE E	Stratulada	Halis siles
2765	Repeal Inninulugy	28 day		100 -9769	19588	113588	Oral	54	2000	\$248 Jermann, January Kalanan, abanemal ga	II, des APPORTS E	Secolulada	Halisailes
1/65	Up litration tonionlogy	31 maskrya (Cyan	malgan, chessa, alamphill	75 mg/kg	28688	194519 Hankey HOREL?	Oral	24	388	1448 6.25 - 12. 5 - 25 - 58 mg/kg ap literation l	er 75 SPPCSSS E	Secolulula.	Helie eiles
1/63	Up litration alody in Communique	28 mashran [Cana	malgan, chemm, alamplaill	58 -9/69	24867	141451	Oral	15	588	358 Englation 18-25-58, All officiarrors	willie SPFCSSS E	Secol slade	Helia siles
1.5	Safely pharmanilogy CHS	1 eal	-al-			Hisse shanges inhedglese and pilocerolise		15	611	358			Halisailes
1.5	Safely pharmanology Respiratory	1 rat	wall		22488	Ha effects Respiratory/Resul	Oral	46	iii	368			Halis siles
1.5	Cardinaanular uunninn asimal olody	1 day	-ale		22488	Innerancia arlegial PP	Oral	54	2111	5248			Halisailes
		4.9	-41			SERRE PK alada	Oral	16.2	611	572			Halis siles
1/69	Up litration study in agreembles		malana, ekenan, alamphiill	188 44/64		174834 Husbra HOAEL2	Oral	92	1200	1928 HOREL stated despite buy mortalities			
			malana, rarana, alimplanti										
69	Trainalogy Corolls, PK al day 185 are raye o			10 m/0s		(\$1738	0x4	163	500	ESE angus weight shanges weight lass after			
.1	Three would be included	21		75 mg/bg		11111	Oral		225	368 Weight gain Denceard bennglubin lan			
1/65	Teninelogg eledg 28d	28 eat		28 mg/kg		276111	Oral	16.4	548	864 Budg weight gain Denerated CDS- and	belger SFFFFSS E	Ffral alada	Helieniles
1.5	Descringed	16 ral		158 -4/64	25388	COMMIT Stiff and absormal gail	Oral .	24	311	166	IFFCHI E	Ffral slade	Halisailes
765	Tanianlagg aladg 28d	28 ral		158 mg/kg	52588	ean	Oral	24	111	1000 Designing hind links and abserved gail	Edra SPECIAL E	ffeel slade	Helicailes
.1	Dane earging lunionlygg PK dag 28 man	*****		488 -9769	59288	SESSE HOAEL HOUSE	Oral		311	400 Innersard lines weight dearesard than	SFFFFEE	FFral slade	Halisailes
3	Descripting out	10 sal		288 mg/kg	55474	Stick and above and guilt Atabata	Oral	92	1288	1928 Weightland	1771111 5	Seculateds.	Hall in willow
.1	There would be included	28		158 mg/kg	72588	212111	Oral	12	651	728 Weight gain Deureaned bennglubin lan			
4	Dance ranging ral	10 v.d		255 mg/hg	84255	Sliff and above wal gail Alabaia	0-4	- 40	4588	2400 Weight has Death and saveifines			Hallie will-se
		-10 101		100 -100		Annual and a second a second and a second and a second and a second and a second an			1000	A SAME TO PERSON AND ADDRESS OF THE PERSON ADDRESS OF THE PE			

Starting dose

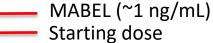
Adverse effects (~ 5000 ng/mL)

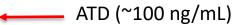


IB-derisk and dose range

Pre-clinical data

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Table 4.2	labibilian of PAAH in lines EDSS		11 parks	EDSB Lines after 16	Oral	1.09	1.033	8.859 Wide Chafdane		Effectulate Halicailes		INIADEF (T
Table 6.2 Peologal	Habibilian of PARH in lines EDSE Haman SD	1 hours	27 pg/kg male 1.000 mg/kg	EDSB lines affect # h	Oral Unknown	1.112	1.111	8.45 Wide Chafdoor 8.48 Paned apon Vd 2.51/bg		Effectulate Halicailes		Ctarting do
Prolocal	Haman SD	1 bears	male 8.847 mg/kg		Unbanan	0.017	1.625	1.82 Paned apon Vd 2.51/bg		Effectulated Helicailes		Starting do
Peulanal	Haman SD	1 house	male \$1833 mg/kg		Unknown	0.000	1.221	1.58 Panedapan V42.5I/by		Effentalule Helinnilen		•
Professi	Haman SD	1 house	male \$1867 mg/kg	27	Unknown	0.007	2.475	4.82 Paned agen V4 2.51/bg		Effentululg Halinailes		
	I.S. Dune dependence beain AEA from planta DI		1 =9/69	95 BSX man anandamide	Oral	1.01		C.I		Effectately Helicaites		
	Cl Fernalis pau Irel	1	1 mg/kg	95 Aufinnierplier effent aufg in ann	finalisms Intraprellment	1.01	1	G G	HIPESI	Effentulutg Halinniten		
PPS abeliant	Leannight FAAH intibilian	1 markeys Cyannalyse, els		57 SE Han 72X (mbibilion	Unknown	0.032	1.2	4.92		Effectulutg Halicailes		
PPS abeliant	PARKINGSINGSING	1 markeys Cyssus Igns, els	enn, slauptailf male 8.4 mg/kg	57 BEX FRANCISCH peripherally	Oral	0.002	1.2	1.52		Effectulute Halicailes		
Professi	Haman SD	1 house	male 8.133 mg/kg	55	Unknown	8.455	4.521	7.58 Basedopes V4 2.51/kg	HIPPY	Effectulute Helicailes		
Professi	Haman SD	1 house	male 8.267 mg/kg	46	Unknown	8.257	5.875	16.82 David spec V42.5I/bg		Effectululg Halicailes		ATD (~100
DPS abeleast	Leanungle FRAH inhibition	1 markeys Cyssus styre, els	enn, elemptail) male 8.5 mg/kg	197 452.2 SEX (abibilities	Oral	0.00	1.6	5.75	Berrer	Effectululy Helicailes		AID (100
		ral	male 8.1 mg/kg	454 B4BB PK-I-44	IV	1.116	1.6	1.16	BFFFFFF	Effectulate Halicailes		
4.2.1	Pharmannhinelin olodq	1 day	male 8.1 mg/kg	182 751 PK alady	IV	1.154	2	5.24	BFFFFFF	Effectateda Halicailes		
Professi	Haman SD	1 keess	male 8.555 mg/kg	245	Unknown	8.555	15,721	31.38 Paned apon Vd 2.51/kg	HIPPY	Effectululg Halicailes		
1000	I.S. Duur dependense krain AEA fenn planna DI	A	2 mg/kg	271 B1X man anandamide	Oral	8.24		164	HITTER	Effentulutg Halinnilen		
Abeliant PPS	FAAH is Iranasyles	1 markeys Cyssonilyss, ek	rees, elemptail) mate — 1 mg/kg	585 1886.5 Hanimalinkibilian of PAAH preiph	real Oral	8.52	12	15.2	HITTER	Effectululed Helicailes		
Professi	Haman SD	1 keese	male 1.333 mg/kg	594	Unknown		45.521	75.58 Paned upon V42.51/kg		Effectulate Halicailes		
	I.S. Duur dependense krain AEA feun planna Pl	A	10	1127 188X man anandamide	Oral	1.1			mini	Effectululy Halicailes		
	CP Hanne fail (flink leaf		48 mg/kg	1127 Autininiusplies at 8 k	Oral	1.1	- 11			Effentuludg Halinnilen		
Table 4.2	labibilian of PAAH in bruin EDSE	*****	26 pg/kg	1161 EDSB keals after 16	Oral	0.00	8.282	8.451 Wide Chaf dage		Effentuludg Halinailen		
	C.2 ProjetAAH jebibilise	1	400 pg/kg	1165 95X keale PARH lebibilies	Oral	1.00	1.0	1.0		Effentuludg Halinnilen		
852/65	There would Taxicalage	34 markeys Cyssonilyss, ek		4256 21994 Haururer officials and all eroresis			75	128		Effenfuluig Halinnilen		
848/65	Repeal administration funioning	28 day	28 mg/kg	5285 24888	Oral	11.1	-01	10		Effectulutg Halicailes		Adverse eff
37/63	Tonionlogg & woolb. PK at dag 185 annrage w		18 mg/kg	SZ41 18458 HOAELRATEMO	Oral	1.6	61	36 organ wright absogra		Effectulated Halicailes	-	Adverse en
845/65	Up litration representation agreemely on	28 manbren Cennanders, rbs		6163 33833 Effects is single asimals	Oral	5.2	128	192		Effectulated Halicailes		/a. F000
842/65	Repealed door looiselegg	31 day	28 mg/kg	EE48 28588 DOGHOAEL Januari 6-11	Oral	11.1	411	641 arequisited present of signs is the q				(~ 5000 ng/
4.1.1	Cardinaannolar nooninno animal olodo	1 444	male 28 mg/kg	8878 Ha CVS +66+ala	Oral	11.1	401	141		Effentulude Halinnilen		(33336/
37/63	Tanianlagg Emails, PK al dag 185 annsagn m		31 mg/kg	3428 33583	Oral	6.1	111	211 organ weight absorper weight formulining				
61/63		21 day	58 -4/44	1858 S1888 HOAELDOG	Oral	27	100	1628 8.15 Wide Charles		Effectululat Halicailea		
Table 4.2 4.1.5	Inhibition of FAAH in house EDSI		27 pg/kg male 38 mg/kg	11145 EDSI brain after II b	Oral C 0 1	6.1	101	211		Effectulated Halicailes		
4.1.3	Safely pharmanology CHS Safely pharmanology Respiratory	1 ral	male 38 mg/kg	11865 History shanges in budg lear and pile 11866 Hay of feels Respiratory/Resul	Oral	6.0	101	211		Effectulada Halianilea Effectulada Halianilea		
4.2.2	Pharmanoline Pharmanobiarline	ral	male 38 mg/kg	11855 B4888 PK-slady	Oral	C.I	111	211		Effectated Helicailes		
4.1.1	There must be included	21	25 mg/kg	12188 SEZER HOREL HOUSE	Oral	2.7	25	121		Effectulate Halicailes		
859/69	Taninalogg op licalina	31 manbras Canamalans, ebs		14288 78862 Haurrissandfrala	Oral	12	458	728 Up literline 5.25 - 12.5 - 25 mg/kg lbro 57.				
831/63		28 ral	38 -9/69	17488 E4588 RAT HOAEL ball HOEL and raduablic		6.1	188	211		Effentulute Halinailes		
6.1.3	Cardinganular appositus asimal sludg	1 444	male SE mg/kg	17595 HO CVS +66++la	Oral	27	100	1628		Effentuluig Halinnilen		
842/65	Repeal Instituting	28 day	101 -1/41	19588 119588	Oral	54	2111	5248 Jermers, January balance, abovemal gail, d				
852/69	Up literline lanicalogy	31 mashras [Cannadan, ch.		28688 194519 Hankey HOREL?	Oral	24	111	1448 5.25 - 12. 5 - 25 - 58 mg/bg ap literation then				
858/69	Up litration alodg in Communique	28 montres Canamalans, rh.		21867 141461	Oral	16	111	368 Equalation 18-25-58. All officely reservable				
4.1.5	Safely pharmanology CHS	1 ral	male 100 mg/kg	22488 Histor shanges inhedg last and pile		16	611	358		Effectatedy Halicailes		
4.1.5	Safely pharmanology Respiratory	1 rel	male 100 mg/kg	22488 Haleffeels Respiratory/Resul	Oral	16	601	368		Effectatule Halicailes		
4.4.5	Cardinganular monoine animal sludg	1 444	male 188 mg/kg	22488 Ingresse in arterial PP	Oral	54	2111	5248		Effectulate Halicailes		
		4-1	male 38 mg/kg	27588 358888 PK-1-44	Oral	16.2	688	572		Effectatedy Halicailes		
819789	Up lite alian abody in agreemation	28 markega Cyannalyse, ek-		27625 174854 Houtey HORELS	Oral	52	1288	1928 HOREL stated despitation modalities and				
92759	Training County, PK at day 185 annuage of	101 vol.	25 -9759	28455 458755	deal	16.6	548	Hit organizatish abangsa unight ban alialiad				
4.5.4	There would be included	28	75 mg/kg	3600 3000	Oral		225	358 Weight gain Denreased benngtobin laurea		Effectatedy Halicailes		
851/65	Tesiselegg sledg 284	28 eat	28 mg/kg	31311 275111	Oral	14.4	548	864 Budg weight gain Dearraned CDS- and bely				
6.5.5	Descrangingral	14 ral	158 mg/kg	S2200 424000 Sliff and above maligail	Oral	24	111	160	BPFCBB	Effectululy Halicailes		
892/69	Testeslagg sledg 28d	28 eat	158 -9769	521H 424H	Oral	24	311	1668 Designing bind limbs and absormal gail Edu	- IPPCINI	Effectulated Halicailes		
1.1.1	Door ranging lunionlogg PK dag 28 man	*****	101 mg/kg	SEZEE SESEE HOAEL HOUSE	Oral		311	411 Increased lines weight dearerared lignon	ur STTTTSS	Effectulate Halicailes		<u>~</u>
4.5.5	Dance cauging call	90 (4.4)	281 mg/kg	\$5474 Sliff and above mat gail Ataluia	Oral	92	1288	1928 Weightland	100000	Effectately Halicalter		
1.5.1	There would be included	28	158 mg/kg	72511 212111	Oral	12	458	728 Weight gain Deurraand bennglubin laurra	or HYCHH	Effectululy Halicailes		(
1.5.3	Dane cauging cal	90.64	258 mg/kg	84255 Sliff and above maliquit Atabita	Oral	- 0	1300	2008 Weight have Death and naveiffines	100000	Effectately Helicaltee		\sim





effects g/mL)



IB derisk as educational tool

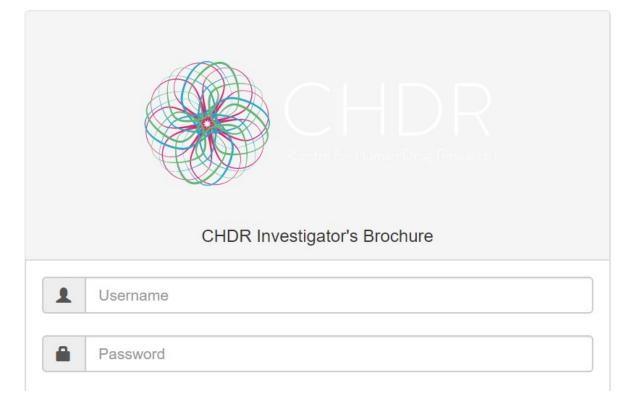
NVKFB

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



WWW.IB-DERISK.ORG

https://youtu.be/jPvXk7yiuxw



