Do we need pharmacokinetic data during each data review meeting in adaptive first-in-human trial? From guideline to practice

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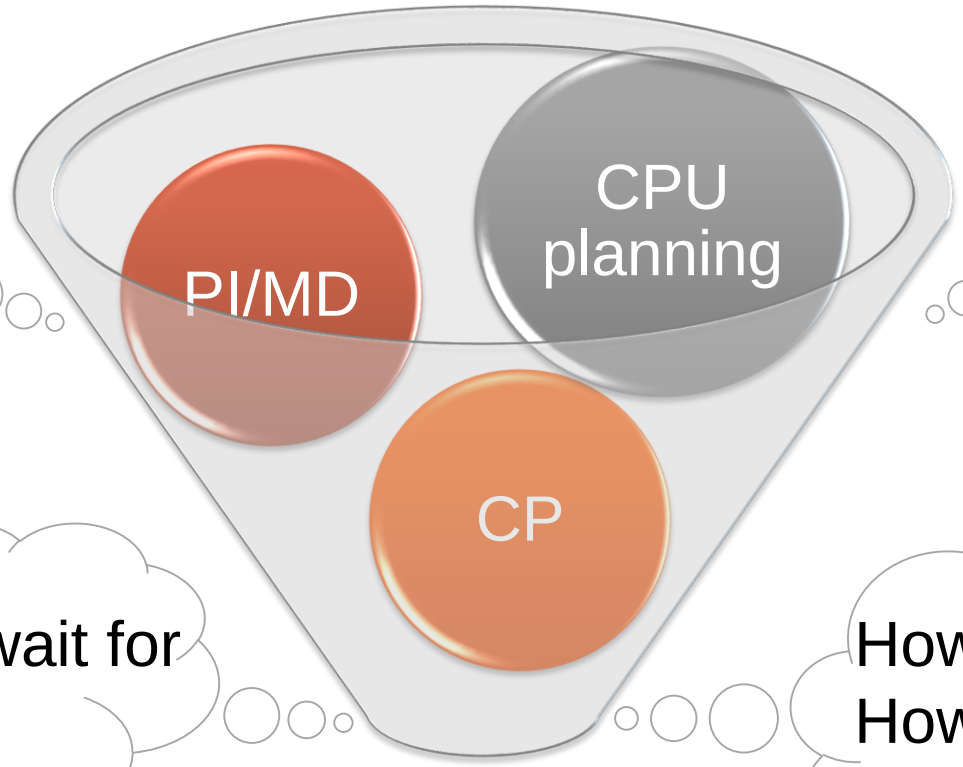
SUMMARY

- Introduction
- Methods
- Results and access on guideline
- Results - Discussions
- Take-home messages

INTRODUCTION TO TOPIC

How much time between doses?

Safety review: obviously!



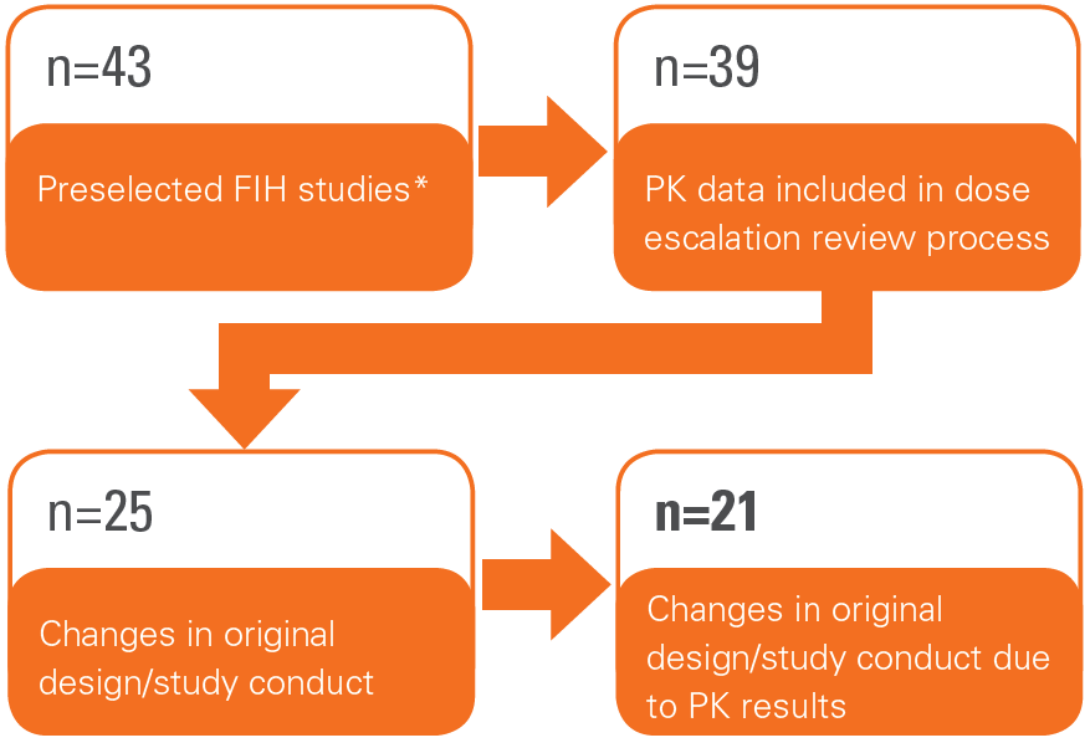
Should we wait for PK review?

How frequently PK?
How long PK?
Is it decisive?

FIH (SAD) will start in our CPU

PI = Principal Investigator
MD = Medical Director
CP = Clinical Pharmacologist

METHODS: TARGET FIH STUDY GROUP SELECTION PROCESS



Source = Clinical Study Database of our CPU

* Primary selection criteria: FIH studies performed at SGS CPU between 2010 and 2018, final report available

RESULTS: CHARACTERISTICS OF TARGETED FIH STUDIES

ITEM	N (%)
STUDY TYPE#	
SAD	17 (81%)
MAD included	10 (48%)
Food effect included	15 (71%)
DDI included	9 (43%)
POC included	6 (27%)
Age effect included	5 (24%)
Formulation effect included	4 (19%)
AMENDMENT INTRODUCED TO DESCRIBE THE CHANGES IN STUDY CONDUCT/DESIGN	
Yes (substantial)	14 (67%)
No (CSP flexibility allowed the adaptation)	7 (33%)
PK DATA REVIEW AT EACH DOSE-BY-DOSE STEP	
Yes	10 (48%)
No (cumulative or after one part)	11 (52%)
IMP PROPERTIES	
First-in-class	5 (24%)
Other	16 (76%)
Biological[&]	2 (9.5%)
PRECISE PK CRITERIA DEFINED FOR STOPPING/DOSE ESCALATION	
Yes	13 (62%)
No	8 (38%)
TYPE OF PHARMA COMPANY	
Big/mid-size Pharma	8 (38%)
Small Biotech	13 (62%)

Complex FIH

Amendment

Intensive PK review

First-in-class / Biological

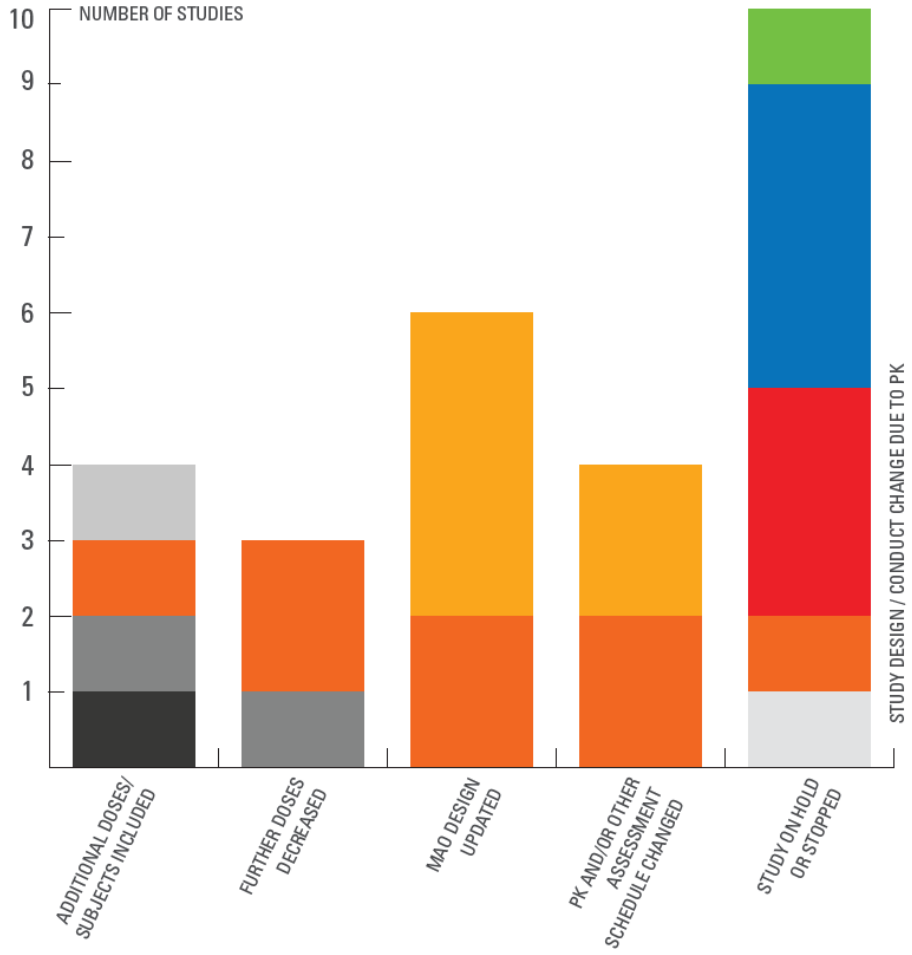
PK stopping criteria

Big *vs* small Pharma

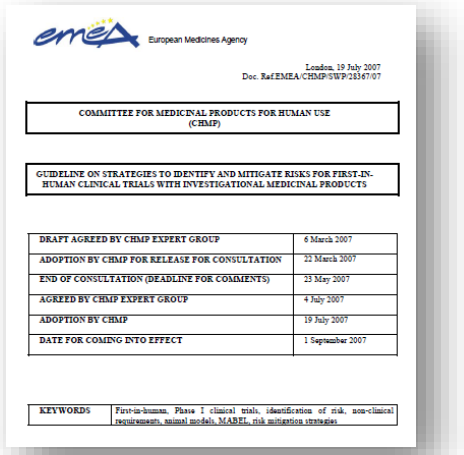
One or more design types may be included in a FIH study in addition to SAD. Four FIH studies were MAD (without SAD)

[&] One biological molecule was first-in-class

RESULTS: FIH STUDY DESIGN CHANGES DUE TO PK REASONS



WHAT IS WRITTEN IN GUIDELINE?



European Medicines Agency

London, 19 July 2007
Doc. Ref.EMEA/CHMP/SWP/28367/07

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

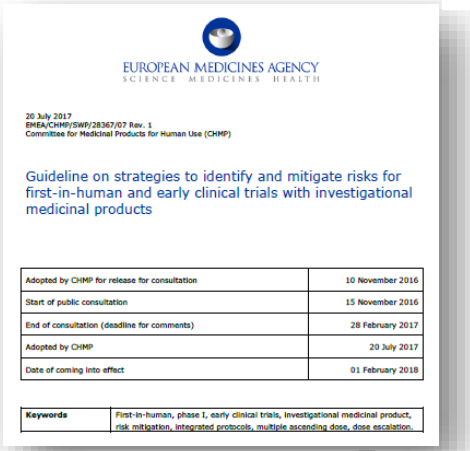
GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

DRAFT AGREED BY CHMP EXPERT GROUP	6 March 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	22 March 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	23 May 2007
AGREED BY CHMP EXPERT GROUP	4 July 2007
ADOPTION BY CHMP	19 July 2007
DATE FOR COMING INTO EFFECT	1 September 2007

KEYWORDS	First-in-human, Phase I clinical trials, identification of risk, non-clinical requirement, animal models, MABEL, risk mitigation strategies

IS THERE MORE ACCESS TO PK DURING DIFFERENT REVIEW STEPS?

…(DRAFT VERSION NOV/2016 – FEB/2017)…



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2017
EMEA/CHMP/SWP/28367/07 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

Adopted by CHMP for release for consultation	10 November 2016
Start of public consultation	15 November 2016
End of consultation (deadline for comments)	28 February 2017
Adopted by CHMP	20 July 2017
Date of coming into effect	01 February 2018

Keywords	First-in-human, phase I, early clinical trials, investigational medicinal product, risk mitigation, integrated protocols, multiple ascending dose, dose escalation.

- ✓ Access on sentinel approach
- ✓ Access on PK stopping criteria
- ✓ Cumulative PK data review concept

…

RESULTS - DISCUSSIONS

- High interest of PK data review in FIH dose escalation steps (n=39 from 43)
- PK as a frequent reason of FIH design/conduct change (n=21 from 25)
- Amendment to FIH protocols for PK change (n=14 from 21)
- Justified PK stopping criteria = regulatory acceptance (n=13 from 21)

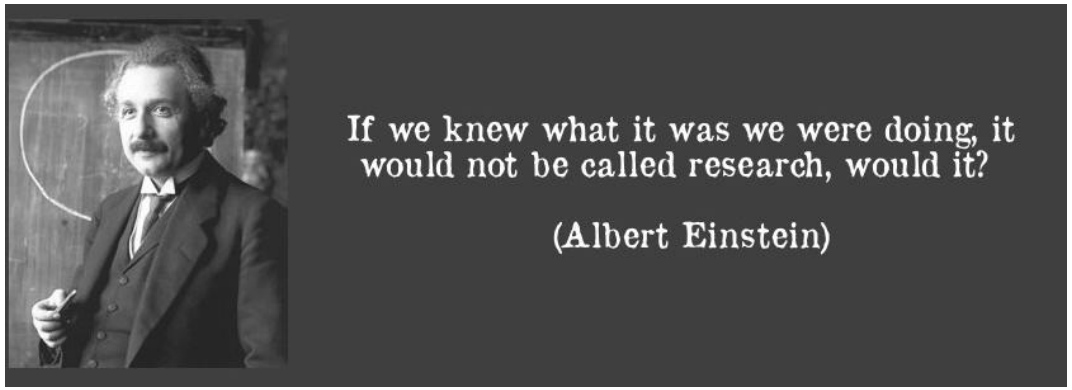
RESULTS - DISCUSSIONS

- Various PK reasons and related design/conduct changes of FIH ➞ Scientific and clinical justification required
- PK data review after each SAD (n=10 from 21) is not mandatory for all molecules in FIH ➞ case-by-case approach
- Are PK related changes in design/conduct related to company size/experience? (small Biotechs n=13 from 21)
- We could not prove influence of new EMA guidance on the PK review approach (initiated before July 2017 n=18 from 21)

TAKE HOME MESSAGES

Rationale of PK dose escalation scenarios and stopping criteria in the protocol will avoid amendments.

A more tailored PK review may increase the cost-effectiveness whilst keeping the crucial information to continue next steps of complex adaptive FIH trials.



ACKNOWLEDGEMENTS

We, as **CRO**, would like to **THANK** the **Pharma companies** considering our input on FIH study design/conduct during protocol development !

Thank you for your attention!

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WHEN YOU NEED TO BE SURE