Interpretation of early safety signals

- Do early safety signals exist ?

  Drawing the picture
- Why and how are they searched for ?

  The MTD story
- Making interpretation ?

  Questions and practice

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Drawing the picture !

1 Sanofi-Aventis survey

11 y (95-2005)

101 compounds

2 Data from other origins

Published articles on adverse events

Data from registers

Sanofi Aventis Survey

11 years (95-2005)

101 compounds → Phase I – FIMs

- all the compounds
  - * if available data from reports (SD&MD)
  - * excepted oncology and insulins
- 101 single dose (SD) studies

  87 multiple doses (MD) studies

  (14 stop)

Sanofi Aventis Survey
Early safety signals: **Types**

- Clinical AE
- Potentially clinically significant abnormality (PCSA)

  ie ECG, lab, vital signs ….

  using predefined threshold based on value and/or variation from baseline

Sanofi Aventis Survey

Early safety signals: **Characteristics**

n°1 Directly and immediately…

….safety relevant:

AEs or abnormalities « PCSAs »

For ex: vomiting, orthostatic hypotension, ALT increase…

Sanofi Aventis Survey:

Early safety signals: **Characteristics**

Not directly safety relevant: n°2&3

***2** → *Result predicting risk*

For ex: aPPT baseline x 2, 5 and anticoagulant

***3** → *Result limiting risk*

For ex: Cmax limitation when expected convulsions from preclinical data

Survey:

a big **Variety** of early safety signals

The most frequent examples:

Mainly GI AEs 17 compounds

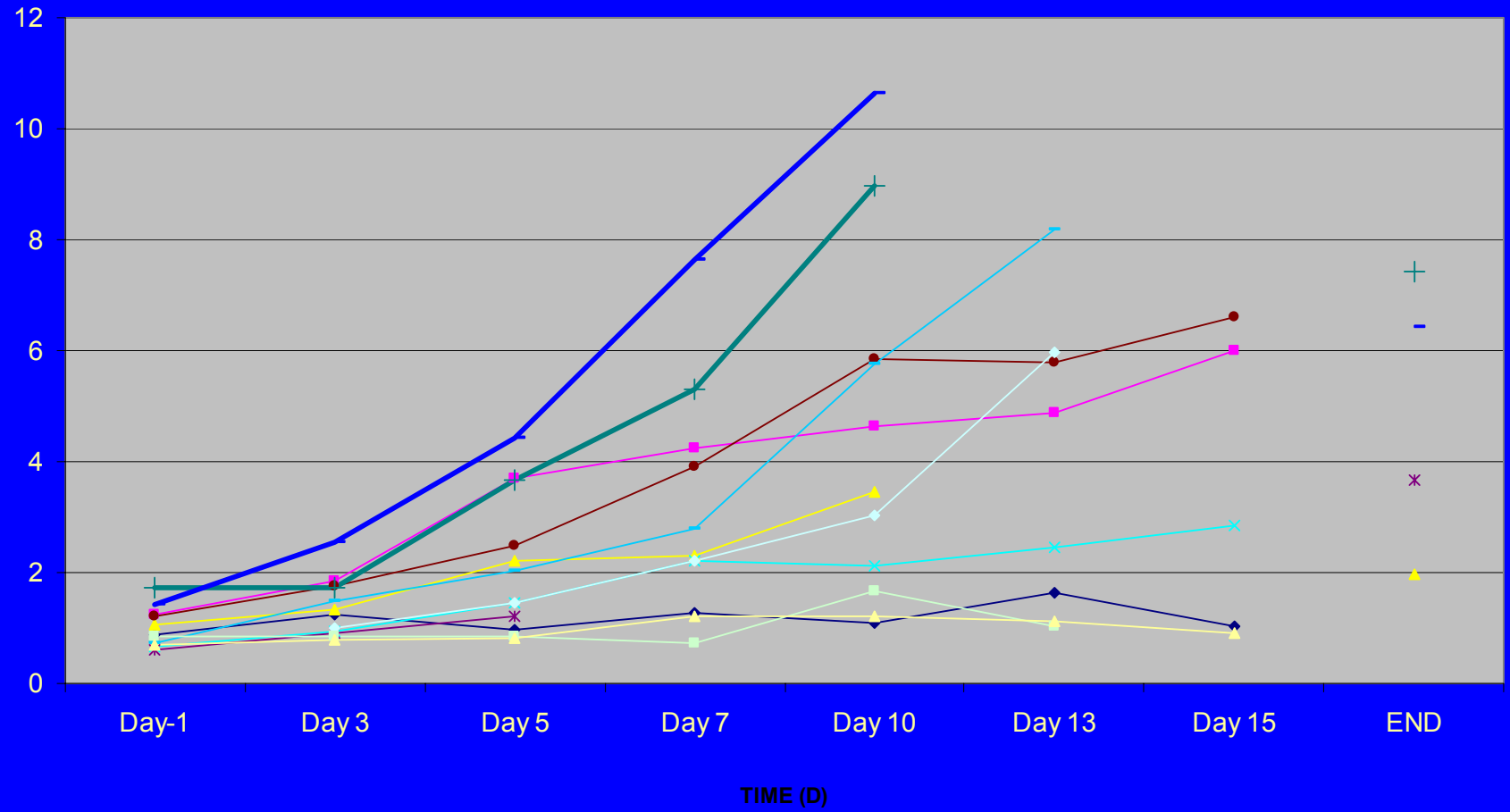
CNS AEs 17 c.

PCSAs: Liver enzymes 11 c.

QTc increase 7 c.

Ex	Gastro Intestinal	Early	Safety	Signals
	Digestive Event	Nausea	Vomit	Abdominal pain
100 mg	1			
150 mg	1			
225 mg	3	2		1
300 mg	7	2	1	4

Triglycerides (mmol/L) - Individual data



Survey: ESS **Seriousness** ?

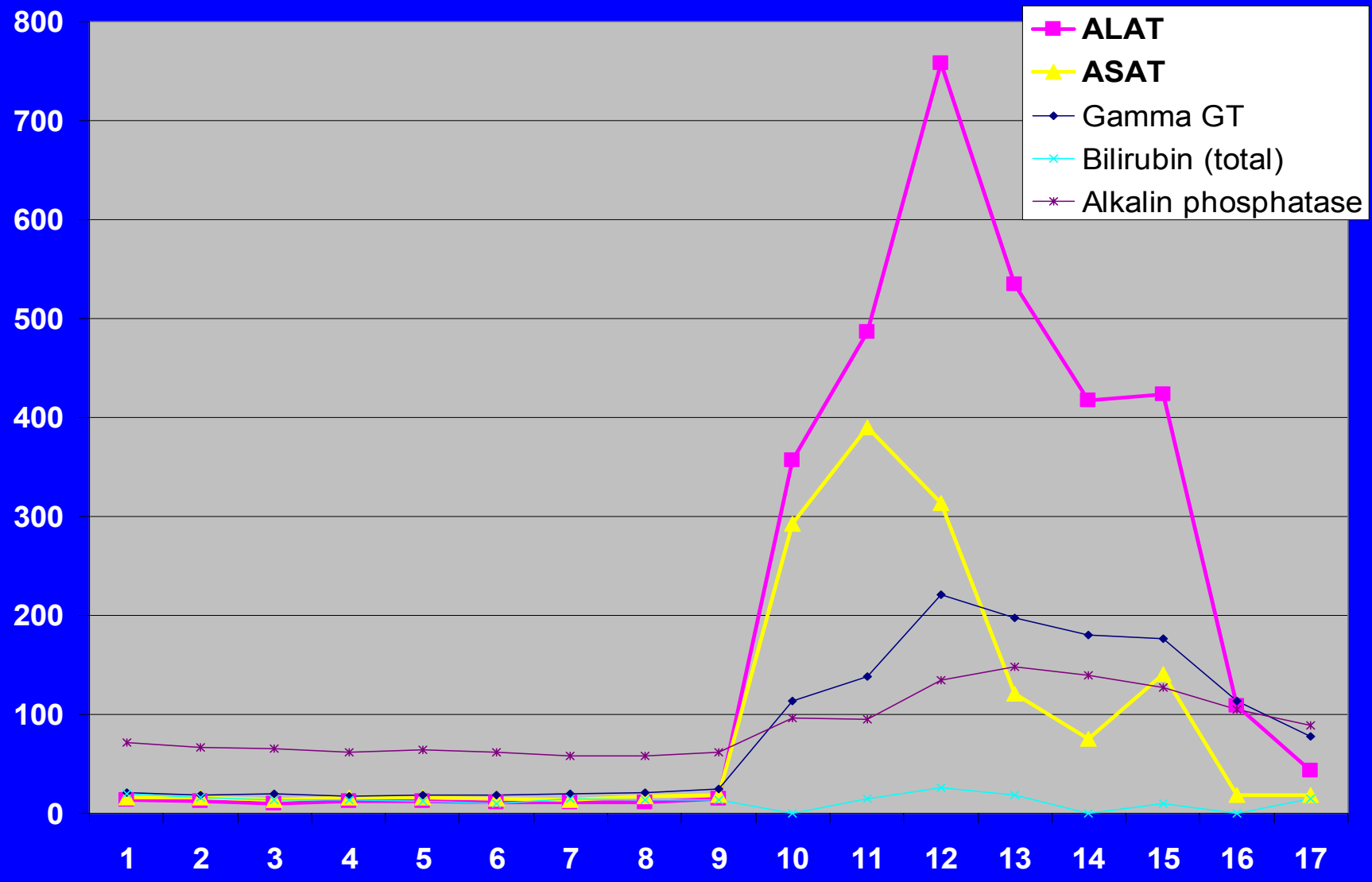
12 SAEs (12%)

no death

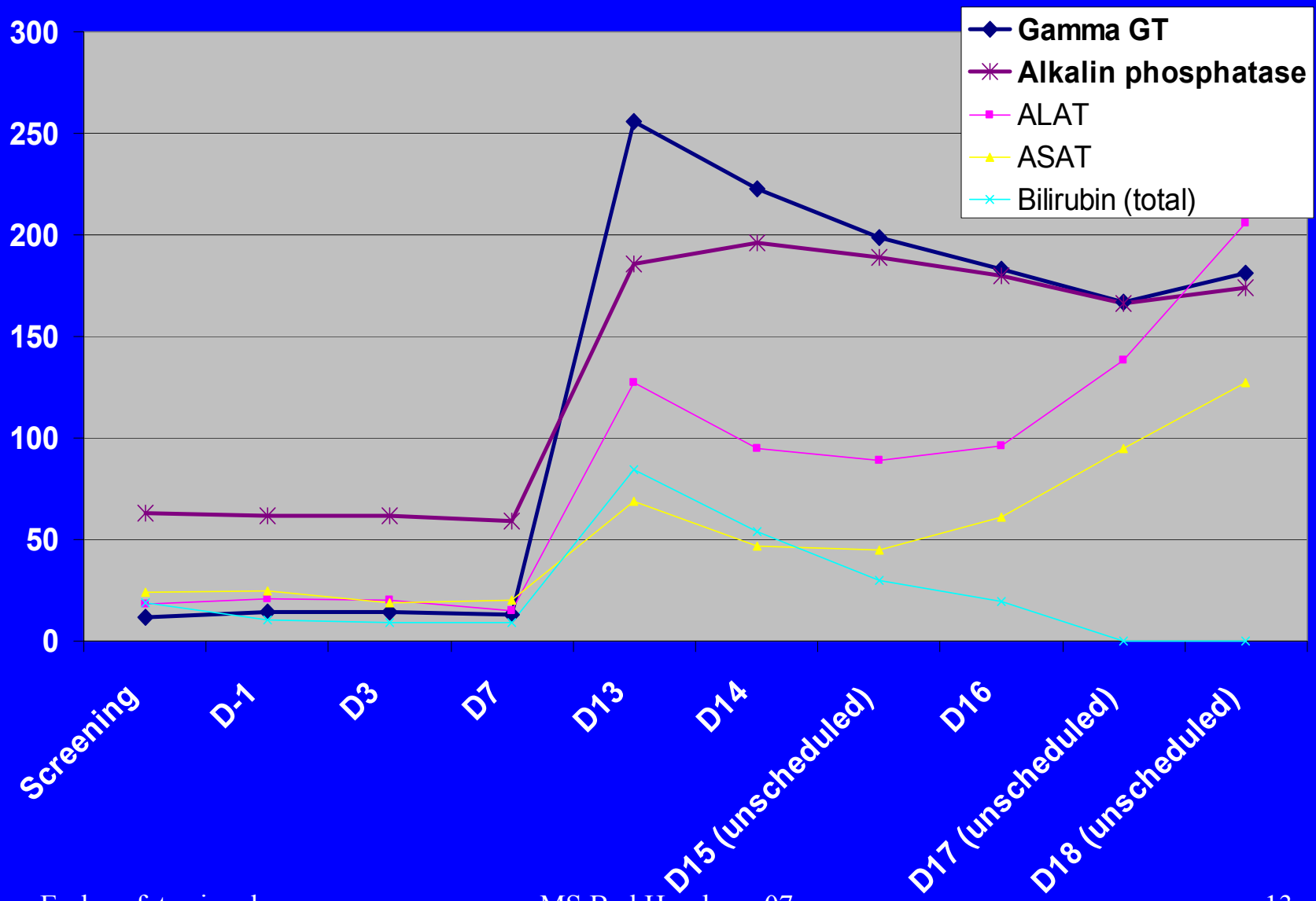
all, complete reversibility

- **3 in SD studies:** 3 syncopes from 3 compounds
- **9 in MD studies:**
  - * **Drug induced liver injury**
    6 reports from 3 compounds
  - * **Rhabdomyolysis**
    2 reports from 2 compounds
  - * **Rash, fever and bicytopenia**

Cytolytic hepatitis



Cholestatic hepatitis



B Early safety signals: other origins

Incidences - related to tested compound:

AEs	15 %
SAEs	0,4 ‰
Survey	*# 0,2 ‰*
Deaths	5 / 30 years / worldwide

® Rosenzweig Br J Clin Pharm 1999, 45: 19
® Sibille Eur J Clin Pharm 1992, 42: 389 & 1998, 54: 13
® Luftullin Int J Clin Pharm & Ther 2004; 43: 217
® Sibille Br J Clin Pharm 2006; 62:503
® Japan Clin Pharm & Therap 2006; 79:P71
® Club phase I www.clubphase1.org

Interpretation of early safety signals

- Do early safety signals exist ?

  Drawing the picture

- **Why and how are they searched for ?**

  The MTD story

  maximal tolerated dose

- Making interpretation ?

  Questions and practices

The MTD story

Phase I = first step of drug development

Phase I goal = jump to second step, by the way of Phase 2 dose selection

→ Active search of early safety signals to determine

MTD - Maximal Tolerated Dose

MTD definition

® CUTLER et al.

Defining the maximum tolerated dose

J Clin Pharmacol 1997;37:767 & 2000;40:1184

« The highest safe dose

and

maximal usable dose »

Survey: MTD rate of determination

MTD was defined in 58 out of the 101compounds **58%**

from SD st. 39%

from MD st. 31%

from both 12 %

in this last circumstance the MTD of MD study was identical (7) or lower (5)

MTD: 4 possible applications

- From **Direct** safety signals

N° 1 → « Genuine MTD »

- From **Indirect** safety signals:

N° 2 * predicting risk – biomarker

N° 3 * limiting risk – PK concentration

→ « Analogic MTDs »

- **No** safety signal: inhaled compound n.of actuations

N° 4 → « Derived MTD »

MTD: 4 types

- From Direct safety signals

N° 1 → « Genuine MTD » : 45/58 **78%**

- From Indirect safety signals:

N° 2 * predicting risk – biomarker: 5

N° 3 * limiting risk – PK concentration: 3

→ « Analogic MTDs »: (5+3) 8 **14%**

- No safety signal: inhaled compound n.of actuations

N° 4 → « Derived MTD »: 5 **8%**

Survey: Is MTD a ***secured*** strategy ?

12 SAEs (12%)

no death

all, complete reversibility

Survey: MTD …a **realistic timeline**

- Reaching MTD:
  median - 7 dose steps in SD
  - 3 in MD studies

Survey:

Is the choice of the first dose…

…of **SD** study accurate ?

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Criteria of accuracy : No ESS,

No activity

> LOQ

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Results: 96% no ESS, no activity

67% concentration > LOQ

Survey:
Is the first dose of SD study…safe?

A major question after the London story …

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Is the first dose of SD study…safe?

A major question after the London story …

101 SD studies: no SAE

only 4 related safety issues

all mild & reversible AEs

- Orthostatic hypotension 2 (CV&CNS area)
- Digestive low tolerability (antibiotic)
- Local irritation (infused vein)

Survey:

Is the first dose of SD study…safe?

A major question after the London story …

If * rules and regulations

* prudence on choice of doses

…an answer far from the tragedy !

Survey:

Is the first dose of MD…safe ?

….MD could be more at risk!

2 SAEs

1. Rhabdomyolysis
2. Hepatitis

Survey:
Exceeding the NOAEL Human Equivalent Dose

*Is it …**useful** ?*

- Actual frequency: 42 compounds in SD
  21 in both SD and MD

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Exceeding the NOAEL Human Equivalent Dose

*Is it …**useful** ?*

- Actual frequency: 42 compounds in SD
  21 in both SD and MD
- Results: improving MTD determination ?

  YES:

  if not, MTD score is **39%**

  if yes, MTD score increased to **58%**

Survey:
Exceeding the NOAEL Human Equivalent Dose

*Is it ….**safe** ?*

Survey:
Exceeding the NOAEL Human Equivalent Dose

*Is it ….**safe** ?*

- SD studies

42 SD studies: *YES - no SAE up the top dose*

Survey:
Exceeding the NOAEL Human Equivalent Dose

*Is it ….**safe** ?*

MD studies

- 21 MD studies: *Mild over-risk*

*** 3 SAEs **14%**

Hepatitis (2 reports 1 compound)

Rhabdomyolysis (1 report)

*** versus 6/66 rest of cohort **9%**

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- **Making interpretation ?**

  Questions and practices

In fact, three scenarios:

1. High frequency/intensity of ESS
2. Dose dependent occurrence of ESS
3. Low frequency of ESS

Scenarios and …

…decision process

1. High frequency/intensity of ESS
2. Dose dependent occurrence

CLARITY

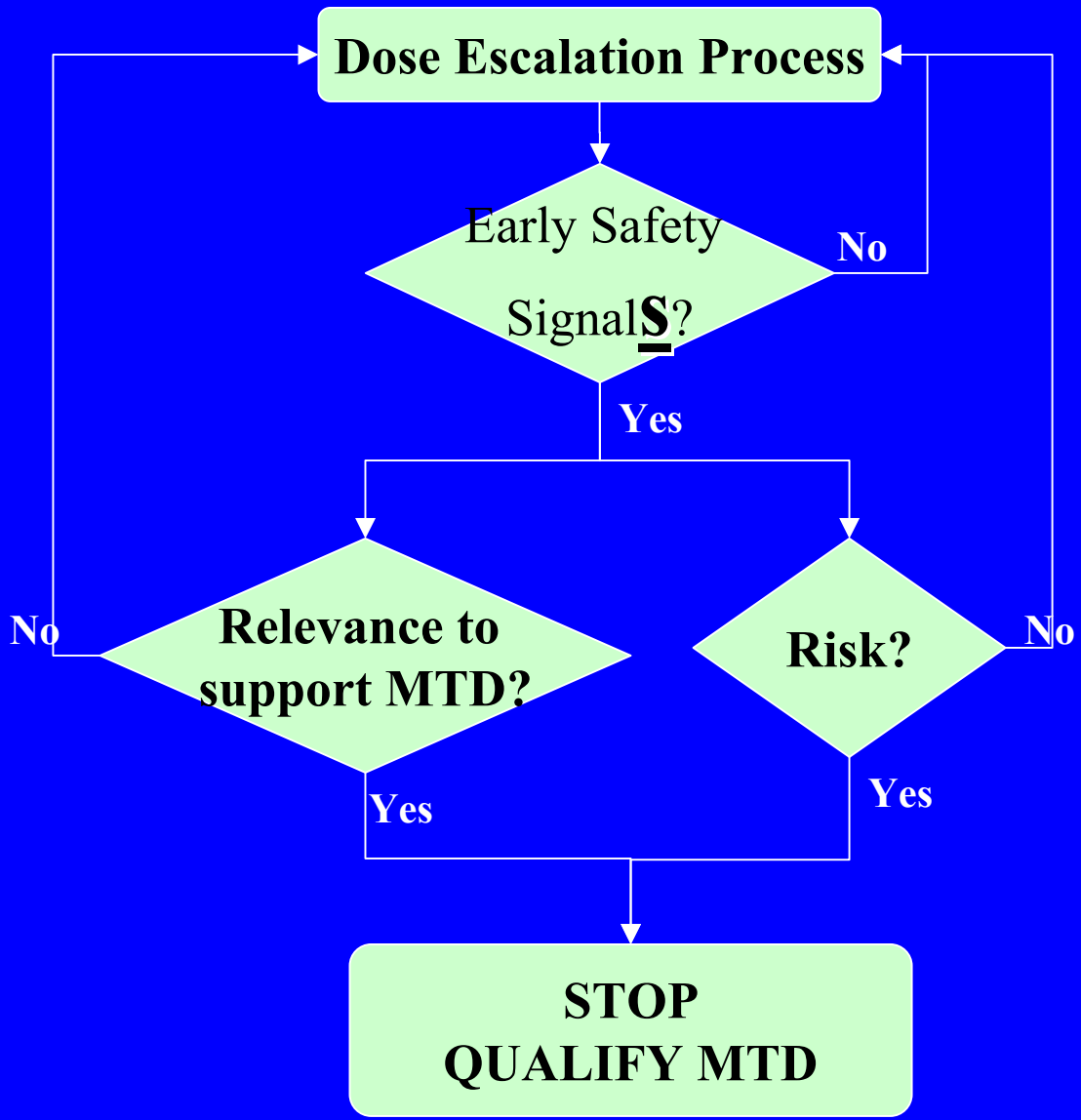
1st Ex.	Digestive Event	Nausea	Vomit	Abdominal pain
100 mg	1			
150 mg	1			
225 mg	3	2		1
300 mg	7	2	1	4

2d Ex	Digestive Event	Nausea	Diarrhea	Meteorism
400 mg	0			
600 mg	2			2
800 mg	5	2	1	2
1000 mg	12	2	5	5

Multiple dose - 14 days 12 subjects per dose

Rash: Acnea-like syndrom

Dose	Men	Women
20 mg	0	ND
50 mg	3 mild	6 mild
80 mg	5 (3mild/2moderate)	ND


Dose Escalation Process
Early Safety Signals?
No
Yes
Relevance to support MTD?
No
Yes
Risk?
No
Yes
STOP
QUALIFY MTD

Scenarios and …

…decision process

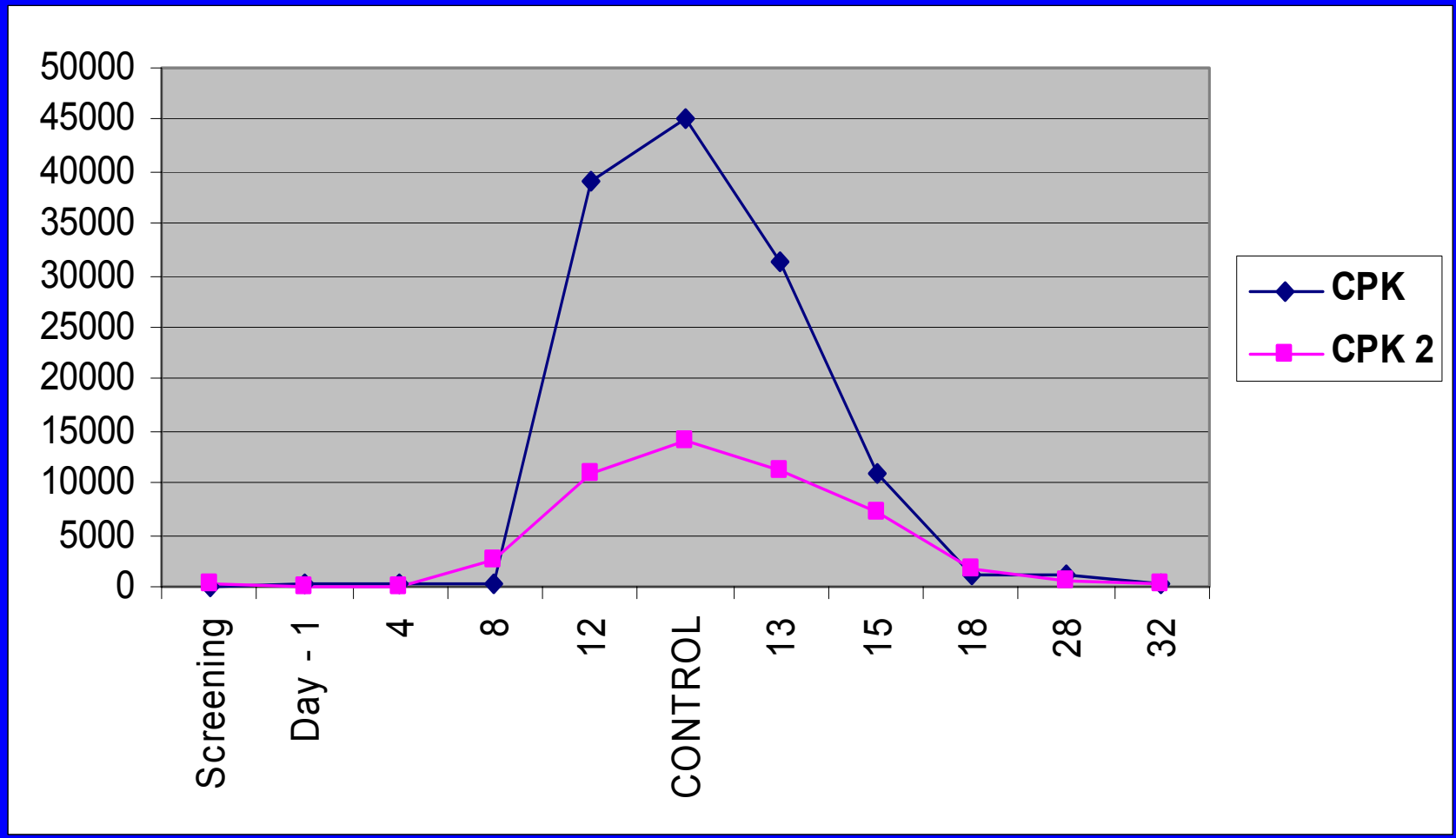
1. High frequency/intensity of ESS
2. Progressive dose dependent occurrence

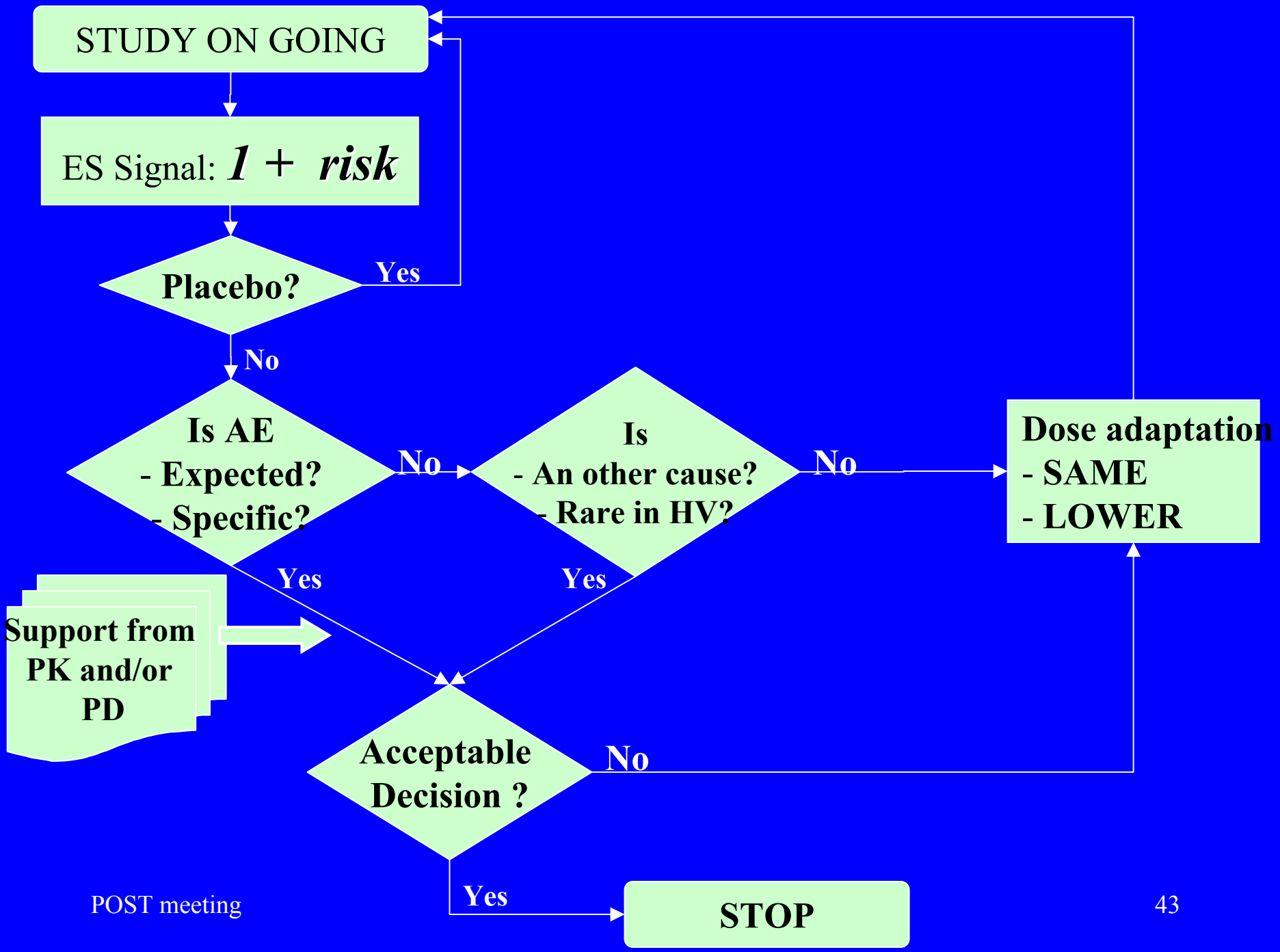
CLARITY

3. ***Low frequency of ESS***

PERPLEXITY

Perplexity: 1verum - 1placebo




STUDY ON GOING
ES Signal: 1 + risk
Placebo?
Yes
No
Is AE
- Expected?
- Specific?
No
Is
- An other cause?
- Rare in HV?
No
Dose adaptation
- SAME
- LOWER
Yes
Yes
Support from PK and/or PD
Acceptable Decision ?
No
Yes
STOP

Conclusions (1)

1. ESS do exist,

   thus MTD determination is:

- Realistic
- Safe
- Even if, NOAEL HED exceeded in **SD** study

Conclusions (2)

2. ESS interpretation is supported by simple algorithms:

- If **Several ESS**: Intensity and number of early safety signals → MTD
- If **Unique ESS**: More difficult decision making process

Conclusion (3): a subtle balanced strategy between…

1. Minimizing risk and keeping priority to subject protection
2. Testing the highest possible dose on the biggest number of subjects

to

→ Obtain Early Safety Signals

→ Have significant intensity

→ Have significant frequency

→ Support MTD relevance