Stopping rules in First entry into human studies

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Club Phase 1 Working Party

WHY

- To improve decision making in dose escalation as requested by regulatory authorities after TGN 1492 incident on 13 MAR 2006 in the UK
- Needs:
  - Standardisation of quotation…then accurate and relevant «Grading»
  - Clinically relevant & accepted «Stopping rules»

To-day : Current guidelines available

Nothing relevant and accepted fitting well to healthy subject participating in FIHs

1. **WHO** Recommendations for grading Acute & subacute toxic effects *WHO Handbook for reporting results of cancer treatment* (1979) → Oncology
2. **NCI** Common Terminology for Adverse Events (CTCAE v3 Aug 2006) → Oncology
3. **NIH** Division of AIDS (Dec 2004) : *Table for grading the severity of adult and pediatric adverse events*
4. **FDA** Guidance for Industry (Sept 2007) : *Toxicity grading scale for adult and adolescent volunteers enrolled in preventive vaccine clinical trials*

Club Phase 1 Goal(s)

1. **Method of quotation – clinical AEs and non clinical abnormalities (vital signs, ECG & lab tests)**
2. **Applications (thresholds/grades)**
3. **Method supporting stopping rules determination**
   - Individual level
   - Cohort level (including MTD)

Scope

- **FIMs dose escalation studies – single & multiple dose**
- **Healthy (young) subjects as a first step**

What is an Adverse Event (1)

Adverse Event: ICH def

- « any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship to this treatment»
- Any spontaneously reported or observed AE → to be collected

Is the Event Related ? (2)

- Investigator judgement: « unrelated, unlikely, possible, probable, (likely) or definite »
- Final judgement / coding : binary process (related or not related)
- Low imputability power due to small number of subjects →
  - Clear proof of intercurrent disease: non-related
  - If not => related

Types and Kinds of Event (3)

- Two types and kinds:
  - Clinical AEs (discontinuous variables) → quotation directly derived from observed severity or daily life consequences
  - Non-clinical «abnormalities» (continuous numerical variables) → quotation derived from an «estimated likelihood» of risk or consequence → quotation based on thresholds to be determined

Proposed quotation

1. Responsible: Investigator
2. Criteria: Severity
3. Grading: use the NIH/FDA 4-level scales:
    1. Grade 1: mild: Does not interfere with activity
    2. Grade 2: moderate: Interferes with activity; no ttt, excepted acetaminophen (limited amount)
    3. Grade 3: severe: Prevents daily activity or requires ttt (or medical intervention FDA)
    4. Grade 4: life-threatening: Emergency room visit or disabling or hospitalization

Intensity	1 Mild	2 Moderate	3 Severe	4 Potentially life-threatening
General definition	Does not interfere with activity	Interferes with activity, no treatment except acetaminophen	Prevents daily activity or requires treatment	Emergency room visit or hospitalization
Possible modulations based on:	*number of episodes and/or*	*duration of symptoms and/or*	*associated malaise or*	*general effects.*
Headache	Transient	Interferes with activity, no treatment except acetaminophen Several hours but less <12 hours.	Prevents daily activity or requires treatment > 12 h, presence during the night.	Emergency room visit or hospitalization
Pain (whatever location)	Transient	Interferes with activity, no treatment except acetaminophen Several hours but less <12 hours.	Prevents daily activity or requires treatment > 12 h, presence during the night.	Emergency room visit or hospitalization
Malaise/syncope ®	Does not interfere with activity	Interferes with activity, no treatment	Syncope®, or prevents daily activity, or requires treatment	Repeated syncopes. Emergency room visit or hospitalization

Intensity	1 Mild	2 Moderate	3 Severe	4 Potentially life-threatening
General definition	Does not interfere with activity	Interferes with activity, no treatment except acetaminophen	Prevents daily activity or requires treatment	Emergency room visit or hospitalization
Possible modulations based on:	*number of episodes and/or*	*duration of symptoms and/or*	*associated malaise or*	*general effects.*
Asthenia	Does not interfere with usual and social activity	Interfere with usual and social activity, no treatment	Prevents daily activity or requires treatment	Emergency room visit or hospitalization
Cognitive disturbances Concentration or memory disorder	Idem	Idem	Idem	Idem
Confusion or disorientation or attention disorder	Idem	Idem	Idem	Idem
Somnolence/ drowsiness	Idem	Idem	Idem	Idem
Dizziness or vertigo or light headedness	Idem	Idem	Idem	Idem

Intensity	1 Mild	2 Moderate	3 Severe	4 Potentially life-threatening
General definition	Does not interfere with activity	Interferes with activity, no treatment except acetaminophen	Prevents daily activity or requires treatment	Emergency room visit or hospitalization
Possible modulations based on:	*number of episodes and/or*	*duration of symptoms and/or*	*associated malaise or*	*general effects.*
Nausea/meteorism or dyspepsia	Keep normal intake	Intake significantly decreased	No intake. Requires treatment	Parenteral support or hospitalization
Vomiting	1 episode	2 to 4 episodes/day or 2/day x 2 days	> 4 episodes per day or 2 or more per day prolonged on several days	Parenteral support or hospitalization
FDA°°°	*1-2*	*>2*	Idem*Prevents daily activity or requires treatment*	*Parenteral support or hospitalization*
Diarrhea	Increase of 2-3 stools/day over normal pre-study flow	Increase of 4-5 stools/day or moderate cramping	Increase of 6-8 or severe cramping or incontinence	Increase > 8 or Bloody diarrhea or parenteral support
FDA°°°	*2-3 loose stools*	*4-5 loose stools*	*6 or more watery stools*	*Parenteral support or hospitalization*

Threshold(s) ? Relevant method

Major difficulty and weakness of previous guidelines (FDA-NIH controversy): no method have been described and used !!!

- Two possible approaches:
  - Existing & recognized threshold or rules:
    - Disease definition (diabete, HTA, anemia)
    - Published rule: Hy's law
  - Use a relevant method to determine the threshold between spontaneous variation and potentially clinically significant abnormality in healthy subjects

Grade I Threshold ?

«Combined method» based on:

**** a value – out of range (reference values)**

if associated to

**** a variation from baseline – out of change range (reference changes)**

is basically designed to define the grade 1 thresholds.

Table 2: Determination of the “Grade I threshold” using Combined Method:

Healthy subject database* (unpublished data, see also 9)

Some examples …

Parameters LAB	Unit	Reference Values** (Lower/ Upper limit of Normal ranges)	Reference changes Decrease: (-) Increase (+) Median value*	Relative values to NR Lower	Higher
ALT	IU/L	10 - 58	(+10)	NA	+1.3
AST	IU/L	10 - 43	(+9)	NA	+1.2
Bilirubin	µmol/L	5 – 27	(+12)	NA	+1.3
Creatinin	µmol/L	78 – 113	(+15)		+1.1
Potassium	mmol/L	3.5 – 4.9	(-0.2) (+0.8)	-0.9	+1.1
CPK	IU/L	53 - 400	(+72) mean : - 29		+1.2
Neutrophils	giga/L	1.7 - 6.5	(-0.5) (+1.8)	- 0.7	+1.3
Platelets	giga/L	153 - 324	(-20)	- 0.8	

* These data are applicable for young male subject. On some parameters, an **adaptation** is required for females or elderly or black people.

** The **reference values (normal ranges) shoud not necessarely be used as inclusion criteria**. *** Due to frequency of Gilbert disease in young men the inclusion limit is 27.

Grade 2, 3, 4 Thresholds ?

- Except for some cases – for ex Hy's law, nothing is recognized to define such tresholds !!!
- Proposal: consensus approach
  - CPI seniors : investigators & sponsors - consensus
  - Consider CTCAE, WHO, FDA and NIH grades
  - Submit proposals for agreement – internal submission
  - Publish & collect remarks, criticizisms and finalize

Application

1. Lab
2. ECG
3. Vital sign
4. …

Table 3: Lab abnormalities grading

- Conditions:
  - Accurate sampling and assay conditions
  - Any abnormality requires a control before validation
  - U(L)LN = upper (lower) limit of laboratory normal range of the local lab of the Clinical Pharmacology Unit
  - Association to clinical symptoms or concomitant changes of other lab parameters induces an upgrading

Table 3: Lab abnormalities grading Liver

Intensity	1 Mild	2 Moderate	3 Severe
ALT	**1.3/3 ULN**	**3/5 ULNR***	**5/10 ULNR**
FDA°°°	*1.1/2.5*	*2.6/5*	*5/10*
NIH	*1.25/2.5*	*205/5*	*5/10*
AST	**1.2/3ULN**	**3/5 ULN***	**5/10**
FDA°°°	*1.1/2.5ULN*	*2.6/5ULN**	*5/10ULN**
Bilirubin	**1.3/2ULN if change from baseline > 10 mmol/L**	**2/2.5***	**2.5/3***
FDA°°° if ALT nl.	*1.1/1.5ULN*	*1.6/2**	*2/3**
Alkaline phosphatase	**1.1/2ULNR**	**2.1/3**	**3.1/10**
FDA°°°	*1.1/2ULNR*	*2.1/3*	*3.1/10*
Hy's Law (10)			ALT>3ULN and Bili>2ULN

Intensity	1 Mild	2 Moderate	3 Severe
Creatinin	**1.1/1.5 ULNR**	**1.5/2 ULNR***	**2/2.5 ULNR**
FDA°°°mg	*1.5/1.7*	*1.8/2*	*2.1/2.5*
NIH	*101/1.3*	*1.4/1.8*	*1.9/3.4*
Neutrophils decrease Caucasian	**LLN to 0.7LLN and decrease >0.5**	**0.7LLNR to 1.0 giga**	**< 1.0**
FDA°°°ALL	*2.5/3.5*	*1.5/2.4*	*1/1.4*
Black Giga/L	**LLN to 0.7LLN and decrease >0.5**	**0.7LLNR to 0.8 giga**	**< 0.8**
CPK Assuming in housed conditions and no physical exercise	**450/1000 or 1.1/2.5ULN**	**1000/2000 or 2.5 to 5ULN**	**2000/5000 or 5 to 10 ULNR**
FDA°°°	*1.25/1.5ULN*	*1.6/3*	*3.1/10*
NIH	*3/5.9*	*6/9.9*	*10/19.9*

Intensity	1 Mild	2 Moderate	3 Severe	4 Life-threatening
Potassium: Hypokalemia if sampling without tourniquet	**LLNR to -0.9 LLNR or 3.4 to 3.1 mEq and decrease > 0.2 mEq**	**No relevance**	**ECG signs or <0.9LLNR or 3mEq and below**	**<2 or dysrythmias or muscle weakness or ileus of gut**
FDA°°°	*3.5/3.6*	*3.3/3.4*	*3.1/3.2*	
NIH	*3.4/3*	*2.9/2.5*	*2.4/2*	
Hyperkalemia if sampling without tourniquet	**ULNR to 1.1 ULNR or 5 to 5.5 mEq and increase >0.8mEq**	**No relevance**	**ECG signs or >1.1ULNR or sup to 5.5mEq**	**>7 or dysrythmias or muscle weakness**
FDA°°°	*5.1/5.2*	*5.3/5.4*	*5.5/5.6*	
NIH	*5.6/6*	*6.1/6.5*	*6.6/7*	
Glucose: Hypoglycemia mmol/L	**LLNR to 0.8 LLNR or LLNR to 3mmol/L and decrease over 0.5**	**No relevance**	**< 3 mmol/L or clinical signs**	**Clinical signs**
FDA°°°	*3.5 / 3.8*	*3/3.4*	*2.5/2.9*	*<2.5*
Hyperglycemia mmol/L - fasting	**ULNR to 1.1ULNR and increase over 1**	**1.1ULNR to 7mmol**	**> 7**	**Insulin requirement**
FDA°°°	*5.6/6.1*	*6.2/6.9*	*>6.9*	*Insulin requirement/ hyperosmolar coma*

Remarks

* FDA draft guidance:

The “appearance of worsening of fatigue, nausea, vomiting, fever, rash, eosinophilia or right upper quadrant pain or tenderness” or the “association to INR superior to 1.5” induces an upgrading (2).

** Trend: significant & fast worsening of results also induces an upgrading

Ambiguity

If **potential PD effect**:

ie decreasing the glucose level with an antidiabetics will not be considered as a worrying AE but as a beneficial effect and the accepted lower limit of the glycemia will be very different

increasing aPTT with an anticoagulant drug is a beneficial effect and therefore threshold may be greater (3 ULNR used as stopping rule)

	Mild	Moderate	Severe	Life-threatening
Haemoglobin decrease in male g/dL *	**LLNR to 12 and decrease >1.5**	**11.9 to 10**	**< 9.5**	Clinical signs ** Take care of blood amount sampling*
FDA°°°	*12.5/13.5*	*10.5/12.4*	*8.5/10.4*	*<8.5*
FDA°°° change	*<1.5*	*1.6/2*	*2.1/5*	*>5*
Haemoglobin decrease in female g/dL	**LLNR to 11 and decrease > 2**	**10.9 to 9.5**	**< 9.5**	Clinical signs
FDA°°°	*11/12*	*9.5/10.9*	*8/9.4*	*<8*
FDA°°° change	*<1.5*	*1.6/2*	*2.1/5*	*>5*
Eosinophils**	**620/750 or 1.3/1.5 ULN**	**750/1500 or 1.5/3ULN**	**>1500 or >5ULN**	Clinical signs
FDA°°° cell/mm3	*650/1500*	*1500/5000*	*>5000*	Clinical signs
Platelet Giga/L ***Assuming lack of platelet cluster***	**125/100**	**100/75**	**75/25 or minor bleeding**	**<25 or major bleeding**
FDA°°°	*125/140*	*100/124*	*25/99*	*<25*

ECG	Mild	Moderate	Severe	Life-threatening
PR interval msec	**220/250 and increase from baseline > 20**	**>250**	**Mobitz 2 or syncope**	**Complete AV block**
NIH	210/250	>250	Mobitz 2 or ventricular pause > 3 sec	Complete AV block
QTc interval msec young male using the most accurate QTc formula	**460/479 and increase superior to 40**	**476/499**	**Exceed 500 or QTc over 450 and increase > to 60**	**Ventricular dysrhythmias or torsade de pointe**
QTc interval Female or elderly people	**20msec addition Threshold moved to 470**			

Heart Rate	**Mild**	**Moderate**	**Severe**	**Life-threatening**
Bradycardia bpm	**NA**	**< 40 and decrease from baseline exceeds minus 20**	**Clinical lack of tolerability and/or ECG abnormalities**	**Emergency room visit or Hospitalization Arrythmias or conduction disorder**
FDA	50-54	45-49	< 45	
Tachycardia bpm	**101/115**	**116/130**	**>130 or dysrythmias (ventricular)**	**Emergency room visit or hospitalization Dysrrythmias or**
FDA	100/115	116/130	>130	

Supine blood pressure mmHg	**Mild**	**Moderate**	**Severe**	**Life-threatening**
Systolic increase	**140/150 and > +20**	**150/160**	**>160 or headache**	**Emergency room visit or hospitalization**
Diastolic increase	**95/99 and > +10**	**100/110**	**>110**	**Emergency room visit or hospitalization**
FDA°°° SBP *DBP*	*141/150* *91/95*	*151/155* *96/100*	*>155* *>100*	
NIH SBP *DBP*	*140/159* *99/90*	*160/179* *100/109*	*>180* *>110*	
Systolic decrease	**90/80 and variation from baseline over minus 25**	**80/70**	**<70 or symptomatic**	
Postural hypotension Systolic BP mmHg	**Decrease > to 20,** association to reflex tachycardia	**Cannot stay standing.**	**Syncope or prevents daily activity, or requires treatment**	**Repeated syncopes. Emergency room visit or hospitalization**
Fever				
"central" adapt values to the type of measure	**38/38.4 °C** **100.4/101.1°F**	**38.5/39.4 °C** **101.2/102/9 °F**	**39.5/40.4 °C** **103.1/104.7 °F**	**>40.5 °C** **>104.8 °F**

Decision process
Stopping rules

Difficulty due to conflict-of-interest:

- **Subject protection → caution**
- **Learning on drug → pushing dose escalation**

Decision process Stopping rules

Three criteria will lead the process

- **AE Grades**
- **Number of similar AEs**
- **Drug relationship :Active or Placebo**

Stopping Rules : Individual level

- if any event of grade equal or greater than 3

Stopping rules at cohort level (1)

1. **No adverse event → dose escalation**
2. **AE(s) → grading**

   if intensity < 3 → dose esc.

   if intensity = or > 3

   – **Stop treatment of the(se) subject(s)**

   – **Unblinding (sponsor resp.): limited to the grade 3 subject(s).**

Stopping rules at a cohort level (2)

- ***AE severity equal or greater than 3 : Unblind***
  - ***Only placebo → dose esc.***
  - ***Placebo and active → dose adaptation***
  - ***No placebo & frequency < 50% → dose adaptation***
  - ***No placebo & frequency = or > 50% → stop & MTD qualification***

Stopping rules at a cohort level (3)

Dose Adaptations:

- ***50% or less or more***
- ***Predefined criteria:***

  PK, supraproportionality, PD,

  AE of special interest

Stopping rules at a cohort level (4)

- Adaptations: Grade 2 or 3 to support stopping rules
- Ambiguity of PD effect → need two different levels
- Grade « 2+ » = upgrading
    - * magnitude of variation from baseline
    - * trend (big or fast increase/decrease)
    - * association to clinical signs
    - * association to other abnormality (ie Hy's law)