

# Safety in Phase I

After the London tragedy....

...more & more attention on safety in Phase I,  
... particularly the First-In- Man studies

UK expert group – final report (Nov 30)

AFSSAPS – recommendations (Sept 5)

Analysis of the real data is the most accurate  
way to support such safety assessment

# Serious Adverse Events in Phase I

Club Phase I French register

# The French Register

- Sponsor: Club Phase I
- Creation: 2003 → data available on 2004/5<sup>®</sup> & 6
- Mode: Survey sent to CROs
- Scope: Phase I studies  
Healthy subjects  
SAEs (GCP definition)

<sup>®</sup> 2004/5 Brit J Clin Pharm, 2006; 62: 502-3

<sup>®</sup> [WWW.clubphase1.org](http://WWW.clubphase1.org)

# The Club Phase I French Register Notes

## 1. “SAEs”

- Easy to identify
- Recover all “serious”
- But, do not always mean major “seriousness” associated to real or potential danger
  - “Worrying” criteria is used

# The Club Phase I French Register Notes

## 2. Related or not to tested drug ?

“Related” often used by default if no other identified cause...

... “Related” is not proof !

## 3. Survey completeness

Data collection score > to 90% of french activity in healthy subjects included in phase I studies

<b>Population</b>	<b>All</b>
<b>healthy subjects</b>	
2004	5458
2005	9928
2006	5927
<b>TOTAL</b>	<b>21313</b>

<b>Population healthy subjects</b>	<b>Young men</b>		<b>All</b>
2004	4312		5458
2005	7189		9928
2006	3599		5927
<b>TOTAL</b>	<b>15100</b>	<b>71%</b>	<b>21313</b>

<b>Population healthy subjects</b>	<b>Young men</b>	<b>Young women</b>		<b>All</b>
2004	4312	783		5458
2005	7189	2445		9928
2006	3599	1618		5927
<b>TOTAL</b>	<b>15100</b>	<b>4846</b>	<b>94%</b>	<b>21313</b>

<b>Ratio</b>	<b>Young: Female/ male</b>	
<b>2004</b>	<b>15%</b>	
<b>2005</b>	<b>25%</b>	
<b>2006</b>	<b>31%</b>	
<b>TOTAL</b>	<b>24%</b>	
	<b>Increasing</b>	

<b>Population</b>	<b>Elderly</b>	<b>Elderly</b>		<b>All</b>
<b>healthy subjects</b>	<b>men</b>	<b>women</b>		
2004	169	194	7%	5458
2005	141	153	3%	9928
2006	436	274	12%	5927
<b>TOTAL</b>	<b>746</b>	<b>621</b>	<b>6%</b>	<b>21313</b>

<b>SAEs</b>	<b>ALL</b>
2004	25
2005	35
2006	44
<b>TOTAL</b>	<b>104</b>

<b>SAEs</b>	<b>ALL</b>	<b>Incidence</b>
2004	25	4 per 1000
2005	35	3 per 1000
2006	44	7 per 1000
<b>TOTAL</b>	<b>104</b>	<b>5 per 1000</b>

<b>SAEs</b>	<b>RELATED</b>	<b>UNRELATED</b>	<b>ALL</b>
2004	10	15	25
2005	20	15	35
2006	10	34	44
<b>TOTAL</b>	<b>40</b>	<b>64</b>	<b>104</b>
%	<b>38%</b>	<b>62%</b>	

<b>SAEs</b>	<b>RELATED</b>	<b>Incidence</b>
2004	10	2 per 1000
2005	20	2 per 1000
2006	10	2 per 1000
<b>TOTAL</b>	<b>40</b>	<b>2 PER 1000</b>

# SAEs RELATED & WORRYING

NUMBER: 8

1. Long lasting atrial fibrillation—elderly w.
- 2/3 Rash and fever – young.
- 4 Agranulocytosis – young.
5. Cholecystectomy/lithiasis – young m.
- 6/7/8 Acute hepatitis DILI – young

**None with after effects**

<b>SUBJECTS</b>	<b>RELATED</b>		<b>RELATED &amp;</b>	<b>INCIDENCE</b>
	<b>SAEs</b>		<b>WORRYING</b>	<b>PER 1000</b>
5458	10		0	0,0
9928	20		3	0,3
5927	10		5	0,8
<b>21313</b>	<b>40</b>		<b>8</b>	<b>0,4</b>

# DEATHS

Number = 4      Incidence = 0,2 per thousand

1. Cancer (lung): elderly woman
2. Motorbike accident: 1 young man
3. Suicide: elderly
4. Suicide: middle-aged man

**None being related to the drug**

## SAEs: most common types

- Intercurrent diseases :

**35 (related 0)**

Kc (4), Infection (5), Traumatism(15), Surgery ( 11)

- Liver:

**28 (related 25 (90%))**

**including 3 Acute Hepatitis**

# Incidence/age

	Population	SAEs	Related & worrying	Deaths (unrelated)
Young	19946	80 <b>4/1000</b>	7	2
Elderly	1367	<b>24 17/1000</b> <b>x 4 !!!</b>	1	2 <b>x 15 !!!</b>
<i>Male</i>	<i>746</i>	<i>9 12/1000</i>		1
<i>Female</i>	<i>621</i>	<b>15 24/1000</b> <b>x 6 !!!</b>	1	1

# SAEs French Register: Comparison to other registers

1. Japan (93-2004) – 95780 subjects  
# 8000/year

Ⓜ Clin Pharm & Therap 2006; 79:P71

2. UK (AICRC 92-2001) – 92510  
# 9000/year
3. France # 7000/year

# Comparison of registers

	France	UK	<i>Japan</i>
SAEs incidence per 1000	<b>5</b>	<b>2</b>	<b>0,5</b>
<b>Related SAEs incidence per 1000</b>	<b>2</b>	<b># 1</b>	<b>0,2</b>
Worrying & related	<b>8</b> <b>0,4 ‰</b>	<b>? +6</b> <b>London</b>	<b>?</b>
Death	<b>4</b>	<b>3</b>	<b>None</b>
<b>Related deaths</b>	<b>no</b>	<b>no</b>	<b>No</b>

# LUTFULLIN®

1559 Healthy subjects

2604 Adverse events

**SAEs 6 /1559    4 ‰**

**Worrying & related : 2**

**Long lasting orthostatic hypoTA**

**Pseudo allergic shock (due to excipient)**

® Int J Clin Pharm & Ther 2004; 43: 217-226

# Learning from deaths

Worldwide 4 last decades

## Deaths in Phase I and experimental research

N°	Year	Country	Phase I	Exp. Research	Reference
1	1980	US	X		Hastings - Center, 1980, 10:5
2	1985	Ireland	X		Lancet, 1985, I:93
3	1985	UK	X		BMJ, 1985, 290:1359
4	1999	US	X		No publication
5	2004	US	X		Indianapolis Star, 10 Feb. 2004
6	1992-2001	UK	X		AICRC Survey
7	1992-2001	UK	X		AICRC Survey
8	1992-2001	UK	X		AICRC Survey
9	1978	US		X	CPT, 1978, 24:127
10	1996	US		X	NY State Dpt of Health - 96 Press release
11	2000	Australia		X	Med. J. Aust, 1998, 168 (9):449
12	2001	US		X	Science, 2001, 293, 5532:1013
13	2002	US		X	Arterioscler. Thromb. Vasc. Biol. 2002, 22:1
14	2004	France	X		Club Phase I French register
15	2005	France	X		Club Phase I French register
16	2006	France	X		Club Phase I French register
17	2006	France	X		Club Phase I French register

## Deaths in Phase I Studies

Year	Country	Phase I	Related		
1980	US	X	+		
1985	Ireland	X	+		
1985	UK	X	+ ?		
1999	US	X	+		
2004	US	X	+		
1992-2001	UK	X	-		
1992-2001	UK	X	-		
1992-2001	UK	X	-		
2005	FR	X	-		
2005	FR	X	-		
2006	FR	X	-		
2006	FR	X	-		
		<b>12</b>	<b>5</b>		
			<b>&lt; 1/2</b>		

3. Aplastic anemia (8 months after study)  
Treatment: **midazolam**

## Deaths in Phase I Studies

Year	Country	Phase I	Related		
1980	US	X	+		
1985	Ireland	X	+		
1985	UK	X	+ ?		
1999	US	X	+		
2004	US	X	+		
1992-2001	UK	X	-		
1992-2001	UK	X	-		
1992-2001	UK	X	-		
2005	FR	X	-		
2005	FR	X	-		
2006	FR	X	-		
2006	FR	X	-		
		<b>12</b>	<b>5</b>		
			<b>&lt; 1/2</b>		

## Deaths in Phase I Studies

Year	Country	Phase I	Related	Elderly	
1980	US	X	+		
1985	Ireland	X	+		
1985	UK	X	+ ?		
1999	US	X	+	X	
2004	US	X	+	X	
1992-2001	UK	X	-		
1992-2001	UK	X	-		
1992-2001	UK	X	-		
2005	FR	X	-	X	
2005	FR	X	-		
2006	FR	X	-		
2006	FR	X	-	X	
		<b>12</b>	<b>5</b>	<b>4</b>	
			<b>&lt; 1/2</b>	<b>1/3</b>	

## Deaths in Phase I Studies

Year	Country	Phase I	Related	Elderly	Screening &/or study misconduct
1980	US	X	+		X
1985	Ireland	X	+		X
1985	UK	X	+ ?		
1999	US	X	+	X	x
2004	US	X	+	X	x
1992-2001	UK	X	-		
1992-2001	UK	X	-		
1992-2001	UK	X	-		
2005	FR	X	-	X	X
2005	FR	X	-		
2006	FR	X	-		X
2006	FR	X	-	X	X
		<b>12</b>	<b>5</b>	<b>4</b>	<b>7</b>
			<b>&lt; 1/2</b>	<b>1/3</b>	<b>&gt; 1/2</b>

## Deaths in Phase I Studies

Year	Country	Phase I	Related	Elderly	Screening &/or study misconduct
1980	US	X	+		X
1985	Ireland	X	+		X
1985	UK	X	+ ?		
1999	US	X	+	X	x
2004	US	X	+	X	x
1992-2001	UK	X	-		
1992-2001	UK	X	-		
1992-2001	UK	X	-		
2005	FR	X	-	X	X
2005	FR	X	-		
2006	FR	X	-		X
2006	FR	X	-	X	X
		<b>12</b>	<b>5</b>	<b>4</b>	<b>7</b>
			<b>&lt; 1/2</b>	<b>1/3</b>	<b>&gt; 1/2</b>

# General conclusions

1. Phase I is safe
2. Major risks **rarely related** to tested drug use:
  - Only 0,4 ‰ worrying & related SAEs
  - < 50% of related SAEs
  - No related deaths in the three registers
  - Only 5 related deaths (worldwide)
  - Only one not associated to screening default and/or study misconduct

# General conclusions

3 . Safe but .... risks if:

# Default in subject screening and /or study misconduct

# Elderly people

# Specific: any compound with lack (or low) predictability of animal data  
- TGN1412 story

# Recommendations

**Common:** Strict adherence to safe rules  
(screening & study conduct)

**New:** Prudence & Scrutiny on elderly people

**Specific:** Accurate rule of first dose choice  
required for some compounds  
ie TGN1412

UK expert group – final report (Nov 30)  
AFSSAPS – recommendations (Sept 5)