Letter to the editors

After the London tragedy, is it still possible to consider Phase I is safe?

Michel Sibille, Yves Donazzolo, Franck Lecoq & Emmanuel Krupka on behalf of Club Phase I members

The recent London tragedy [1] induces a huge emotion in the clinical pharmacology world. As decided by the Medicines and Healthcare products Regulatory Agency, the main point is to redefine the acceptable conditions for fully humanized agonist monoclonal antibodies in man. Such anxiety could also be reinforced by the fact that three deaths in healthy subjects have recently been reported in the USA [2–4].

Therefore, based on all the available data, it is necessary to reassess whether Phase I – early drug development in healthy subjects – is still safe:

1. In the literature, only 15 deaths have been published during the last 30 years in Western countries, although probably 100 000 healthy subjects are dosed every year; moreover, only three deaths could not have been avoided if accurate common rules had been strictly adhered to. However, there is probably a higher risk in elderly subjects [5, 6].
2. Recently, a register has been initiated in France under the responsibility of the 'Club Phase I' (<http://www.clubphase1.org/>). This annual register is focused on serious adverse events (SAEs) and is limited to healthy subjects – young and elderly, men and women – and to Phase I studies. SAE refers to good clinical practice (GCP): death, life-threatening, requires hospitalization, disability, congenital anomaly and medically important event. It was implemented in 2004 and 2005; 15 386 healthy subjects have been included and dosed during the 2-year period (see Table 1). Two deaths occurred: one motorbike accident in a young man within a wash-out period and one lung cancer in an elderly woman undetected at screening in a study without drug administration (biomarker pilot study). No deaths were related to the tested drug. Sixty other SAEs

were reported (not including the two above-mentioned deaths) (see Table 2). Only eight SAEs were really clinically serious, i.e. worrying with high risk, three out of eight only being related to the study drug: rash and fever, agranulocytosis and long-lasting atrial fibrillation. The others were not related: unstable angina, peritonitis, thrombosis (retina central vein), coma (car accident) and acute leukemia. Total SAE incidence is 0.4%, including worrying SAE 0.05%, of which related SAE 0.02%. In young subjects SAE incidence is 0.3%, but it is much higher in the elderly 2%, particularly in elderly women (3%). This register reporting more than 90% of the actual French activity in healthy subjects suggests clear conclusions: Phase I is safe, without related deaths and only 0.02% worrying and related SAEs; but a higher risk incidence is reported in elderly subjects, particularly in women.

3. A recent Japanese register draws the same conclusions: from 1993 to 2004, 95 780 subjects, no deaths, low incidence of SAEs [47 (0.05%)], of which only 23 (0.02%) were related to drugs, all reversible without sequelae [7].

Thus, one can conclude:

1. The risk of SAE in a Phase I study is low when common safety rules are applied: quality of drug supplies, use of a relevant method for the choice of doses, prudent progression from dose to dose using stopping criteria defined in protocols and approved by an ethics committee, resuscitation track and permanent presence of trained physicians on site . . . all, in fact, from GCP.
2. The new data suggest reinforcing safety rules in two areas:
  - Drug administration practice: define the number of subjects to administer at the same time, especially for first-in-class compounds, parenteral route, or possible immunogenicity of the drug. The same prudent approach is relevant in the case of possible

Table 1

French register: number of subjects

Population: Healthy subjects	Young men	Young women	Elderly men	Elderly women	All
2004	4 312	783	169	194	5 458
2005	7 189	2445	141	153	9 928
Total	11 501	3228	310	347	15 386

Table 2

French register: SAE incidence

Serious adverse events	Related (incidence)	Unrelated (incidence)	All (incidence)
2004	10	15	25
2005	20	15	35
Total	30 (0.2%)	30 (0.2%)	60 (0.4%)

low predictability of animal data: CNS, immune targets, fully humanized and recombinant compounds.

- Elderly subjects: special scrutiny and a more prudent approach are required.

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