Freedom of Information Appeal: design of MHRA-approved First in Man studies, and associated reporting of Suspected Serious Adverse Reactions

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In response to Freedom of Information appeal, Dr Martyn Ward, on behalf of MHRA, extracted summary information on the designs of First in Man studies approved by MHRA during the first three months of 2005 for **Chemical compounds** {55 studies: 23 in patients and 32 in healthy volunteers} and in the 30 months from May 2004 to end October 2006 for **Biologicals** {32 studies; 15 in patients and 17 in healthy volunteers}. Dr Ward also provided information about suspected serious adverse reactions (SUSARs) which MHRA was aware of as having occurred in these approved studies. Please see**: Freedom of Information Table** on 87 MHRA-authorized First in Man study designs.

SUSARs were reported for four of the 55 First in Man studies of **Chemical compounds**. All four were non-placebo studies in **patients with cancer**, and designed to test an Investigational Medicinal Product (IMP) until toxicity: a single SUSAR was reported for three studies (in final cohort (1) or by-design-intermediate cohorts (2)), while the fourth study reported four SUSARs in three patients in 3rd, 5th and 8th cohorts of a study which was originally designed to recruit up to seven cohorts only.

SUSARs were reported for two of the 32 First in Man studies of **Biologicals**: placebo-controlled TGN1412 study in **healthy volunteers**, which reported SUSARs in each of its six volunteers who received IMP in the 1st cohort of eight subjects; and placebo-controlled study in **patients with cystic fibrosis**, which reported a single SUSAR in the multiple dosing phase of its 1st cohort of six patients, four of whom received IMP.

For 34 First in Man studies in healthy volunteers which randomized between IMP and placebo/control, medians were: six cohorts (mean = 5.3, sd = 2.4), 48 healthy volunteers in total, of whom 36 received IMP, and eight in the 1st cohort, of whom six received IMP. As in TGN1412, randomisation ratios strongly favoured IMP.

Thirty month census of MHRA's 32 First in Man studies of biologicals needs to be extended, including by international collaboration of regulators, for analysis to be robustly informative; and likewise for approved First in Man studies of chemical compounds. In particular, the proneness of First in Man studies of biologicals to SUSARs in their initial cohort should be investigated.

Chemical compounds: patients

One of the 23 studies was a 2-period cross-over trial in 24 patients with asthma, half of whom were randomized to receive placebo in the first period. A single-cohort trial randomized 75 patients with eczema to investigational medicinal product (IMP) or active comparator or placebo, so that 25 patients were assigned to each. Nineteen other studies (17 cancer-related, one in a single cohort of six patients with multiple sclerosis and one in two cohorts of 12 asthma patients) had no controls. Nine of the 17 cancer studies were explicitly designed to recruit a maximum of x1 cohorts 'until toxicity'. Of these nine

studies, four studies reported SUSARs as follows: 1, 1, 1 and 4. The study with four SUSARs observed them (febrile, tachycardia, shortness of breath, thrombocytopenia) in three patients in cohorts 3, 5 and 8 – although the study design was reported as a maximum of six to seven cohorts, with three to six patients in the initial cohort, and a maximum of 25 to 40 patients studied. The latter format of design summary, see **Freedom of Information Table**, was typical for the subset of 'until toxicity' studies.

The final two studies were: in 27 patients with psoriasis, of whom nine were recruited to each of three cohorts and, within cohort, six patients were randomised to IMP versus three to placebo; and a single cohort of 32 patients with eczema, half of whom were randomized to IMP.

Chemical compounds: healthy volunteers (HVs)

Five of 32 studies in healthy volunteers recruited as follows to IMP only: two cohorts of 12 HVs (24HVs), three cohorts of 6 HVs (18 HVs), two cohorts of 8 HVs (16 HVs), single cohort of 6 HVs, and single cohort of 4 HVs. These studies recruited a mean (median) of 13.6 (16) healthy volunteers. Design details for the other 27 First in Man studies in healthy volunteers can be summarized as follows:

Mean (median) number of cohorts recruited = 5.3 (median is 6)
(1, 4@2 cohorts, 3@3, 4@4, 1@5, 4@6, 4@7 cohorts, 3@8, 2@9, and 1@10 cohorts)

Overall IMP: placebo ratio across cohorts = 859: 303 = 2.8:1
Mean (median) for total number of HVs recruited = 43.0 (median is 48)
Mean (median) for number of HVs randomized to IMP = 31.8 (median is 36)
(81, 80, 3@64, 4@56, 54, 48, 3@48, 44, 40, 32, 32, 27, 2@27, 2@24, 18, 2@16, 12)
(54, 60, 3@48, 4@42, 36, 40, 3@36, 32, 30, 28, 24, 21, 2@18, 2@18, 12, 2@12, 6).

Overall IMP: placebo ratio in 1st cohort = 171: 62 = 2.8: 1
Mean (median) for number in 1st cohort of HVs = 8.6 (median is 8)
Mean (median) for number of HVs randomized to IMP in 1st cohort = 6.3 (median is 6)
(15, 12, 12, 11, 4@9, 8, 17@8, 3)
(12, 10, 6, 8, 4@6, 7, 17@6, 2).

Randomization ratio strongly in favour of the IMP characterized the majority of First in Man studies of chemical compounds in healthy volunteers. Substantial heterogeneity is evident in the number of cohorts recruited, ranging from one to 10, with standard deviation of 2.55 about mean of 5.3. There were no reported SUSARs in the above set of 32 First in Man studies of chemical compounds in health volunteers.

Biologicals: patients

Eight of the 15 studies assigned patients to IMP only: one used Bayesian logistic regression - presumably to determine next dose after an initial cohort of three patients had been studied out of the envisaged recruitment of 22, three used stem cells, one targeted

patients with allergic rhinitis, and three were cancer-related, one of which also individualized treatment after a first cohort of three patients had been studied. The remaining seven First in Man studies had a placebo or control group and designs as follows:

Mean (median) number of cohorts recruited = 5.0 (median is 5)
(3, 4, 4@5, 8 cohorts)
Overall IMP: placebo ratio across cohorts = 180: 69 = 2.6:1
Mean (median) for total number of HVs recruited = 35.6 (median is 36)
Mean (median) for number of HVs randomized to IMP = 25.7 (median is 25)
(18, 40, 36, 30, 30, 25, 64)
(12, 20, 30, 25, 25, 20, 48)

Overall IMP: placebo ratio in 1st cohort = 29: 10 = 2.9: 1
Mean (median) for number in 1st cohort of HVs = 5.6 (median is 6)
Mean (median) for number of HVs randomized to IMP in 1st cohort = 4.1 (median is 4)
(6, 2, 6, 2@6, 5, 8)
(4, 1, 4, 2@5, 4, 6).
One SUSAR was reported in the 3-cohort study on 18 patients with cystic fibrosis, two-thirds of whom were randomized to IMP.

Biologicals: healthy volunteers (HVs)

Eight of the 17 studies in healthy volunteers assigned to IMP only, and had designs as follows: seven cohorts which ranged from 3 HVs in 1st cohort to 10 in final cohort (vaccine study), three cohorts of 10 (prophylaxis re HVI/AIDS), four cohorts of 6 (condylomata acuminatum), two cohorts of 12 (diabetes mellitus), two cohorts of 8 (gram-positive bacterial infection), one cohort of 10 (diabetes mellitus), one cohort of 8 (micro-dose platelets study), and one cohort of 7 (allogenic fibroblasts).

The other nine studies included TGN1412 which randomized six HVs to IMP versus two to placebo per intended four cohorts, and a reproductive health study which adopted a 3-way randomization (6: 2: 1) in each of its six cohorts of 9 subjects. The remaining seven studies in healthy volunteers had the following designs, one of which was composite in the sense of placebo allocation only after the 1st cohort:

Mean(median) number of cohorts recruited = 5.3 (median is 6)
(2@3, 3@6, 8, 5 cohorts)
Overall IMP: placebo ratio across cohorts = 261: 109 = 2.4:1
Mean (median) for total number of HVs recruited = 52.9 (median is 51)
Mean (median) for number of HVs randomized to IMP = 37.3 (median is 36)
(24, 2@48, 51, 60, 64, 75)
(18, 2@36, 33, 30, 48, 60)

Overall IMP: placebo ratio in 1st cohort = 50: 18 = 2.8: 1
Mean (median) for number in 1st cohort of HVs = 9.7 (median is 8)

Mean (median) for number of HVs randomized to IMP in 1st cohort = 7.1 (median is 6)
(8, 16, 8, 3, 10, 8, 15)
(6, 12, 6, 3, 5, 6, 12)

The only SUSARs reported were the six for HVs who were randomized to IMP in the TGN1412 study's initial cohort of eight HVs.

Freedom of Information Table on 87 MHRA-authorized First in Man study designs

Initial cohort size (active: placebo)	Proposed number of cohorts	Proposed total subjects	Notes/**SUSARs**
Chemical compounds: patients (23 study designs, January to March 2005)			
24 (12: 12)	2	24	Asthma, cross-over
75 (25: 25: 25)	1	75	Eczema, 3-way
No placebo/control group			
12	2	24	Asthma: different doses of IMP
6	1	6	Multiple sclerosis: 6 doses per patient
3	Up to 12	36	Cancer
3 – 6	Up to 10	35 – 40	Cancer
3 – 6	Approximately 10	30 – 40	Cancer
3 – 6	6 to 8	24 – 32	Cancer
1 – 6	6 to 7	15 – 25	Cancer
8	1	8	Cancer
3	6 (sizes: 3, 3, 6, 6, 6, 18)	42	Cancer
24	1	24	Cancer vaccine
3	5 to 7	15 – 21	Cancer: until toxicity **SUSAR = 1, cohort 3**
3	5 to 7	20 – 40 approximately	Cancer: until toxicity
3 - 6	?6	35 approximately	Cancer: until toxicity
3	?6 to 7	20 approximately	Cancer: until toxicity
3 - 6	6 to 7	56 maximum	Cancer: until toxicity
3 - 6	6 to 7	40 approximately	Cancer: until toxicity **SUSAR = 1, cohort 5**
3 - 6	6 to 7	50 approximately	Cancer: until toxicity
1 - 3	6 to 7	18	Cancer: until toxicity **SUSAR = 1, cohort 7**
3 - 6	6 to 7	25 – 40	Cancer: until toxicity **SUSARs = 4, affecting three patients in 3rd, 5th and 8th *(sic)* cohorts.**
IMP versus placebo/control			
32 (16: 16)	1	32	Eczema
9 (6: 3)	3	27	Psoriasis – oral

Chemical compounds: healthy volunteers (32 study designs, January to March 2005)			
Initial cohort size (active: placebo)	Proposed number of cohorts	Proposed total subjects	Notes/**SUSARs**
No placebo/control group			
4	1	4	
6	1	6	
6	3	18	
8	2	16	
12	2	24	
IMP versus placebo/control			
9 (6: 3)	9	81	
8 (6: 2)	10	80	
8 (6: 2)	8	64	
8 (6: 2)	8	64	
8 (6: 2)	8	64	
8 (6: 2)	7	56	
8 (6: 2)	7	56	
8 (6: 2)	7	56	
8 (6: 2)	7	56	
9 (6: 3)	6	54	
12 (10: 2)	4	48	
8 (6: 2)	6	48	
8 (6: 2)	6	48	
8 (6: 2)	6	48	
11 (8: 3)	4	44	
8 (6: 2)	5	40	
8 (7: 1)	4	32	
8 (6: 2)	4	32	
15 (12: 3)	2	27	Note that 2nd cohort randomized 12 healthy volunteers (9: 3)
9 (6: 3)	3	27	
3 (2: 1)	9	27	
8 (6: 2)	3	24	
8 (6: 2)	3	24	
9 (6: 3)	2	18	
8 (6: 2)	2	16	
8 (6: 2)	2	16	
12 (6: 6)	1	12	

Initial cohort size (active: placebo)	Proposed number of cohorts	Proposed total subjects	Notes/**SUSARs**
Biologicals: patients (15 study designs, May 2004 to end October 2006)			
No placebo/control group			
10	1	10	Stem cells
10	1	10	Stem cells
2	5	18	Stem cells – liver disease, 5th cohort of 10 patients, otherwise two per cohort
3	4	18	Cancer – 3rd and 4th cohort of 6 patients, otherwise three per cohort
3		20 maximum	Cancer – individualized treatment after 1st cohort
3		22	Bayesian logistic regression
24	1	24	Allergic rhinitis – intranasal
24	1	24	Cancer vaccine
IMP versus placebo/control			
8 (6: 2)	8	64	Allergic rhinitis – intravenous
2 (1: 1)	4	40	Stem cells – 3rd and 4th cohorts of 4 and 16 patients, matched pairs within cohort
6(4: 2)	5	36 approximately	Alzheimers – 4th and 5th cohorts of 8 (6:2) and 10 (7:3) patients, 2nd and 3rd as 1st.
6 (5: 1)	5	30	Alzheimers
6 (5: 1)	5	30	HIV
5 (4: 1)	5	25	Ulcerative colitis
6 (4; 2)	3	18	Cystic fibrosis **SUSAR = 1, in 1st cohort's multiple dosing phase**
Biologicals: healthy volunteers (17 study designs, May 2004 to end October 2006)			
No placebo/control group			
7	1	7	Allogenic fibroblasts
8	1	8	Micro-dose platelets study
10	1	10	Diabetes mellitus
8	2	16	Gram +ve bacterial infection
12	2	24	Diabetes mellitus
6	4	24	Condylomata acuminatum
10	3	30	Prophylaxis of HIV/AIDS
3	7	35	Vaccine - 6th and 7th cohorts each of 10 healthy volunteers

Initial cohort size (active: placebo)	Proposed number of cohorts	Proposed total subjects	Notes/**SUSARs**
Biologicals: healthy volunteers (17 study designs, May 2004 to end October 2006): continued			
IMP versus placebo/control			
8 (6: 2)	4	32	TGN1412 **SUSARs = 6. All six healthy volunteers randomised to TGN1412 in 1st cohort**
9 (6: 2: 1)	6	54	Reproductive health: 3-way randomization
15 (12: 3)	5	75	Influenza vaccine
8 (6: 2)	8	64	Allergic rhinitis – intravenous
10 (5: 5)	6	60	Vaccine
3 (3: 0)	6	51 composite	Stroke – 2nd to 6th cohorts, each of 8 (6:2)
8 (6: 2)	6	48	Rheumatoid arthritis
16 (12: 4)	3	48	Staphylococcal infection
8 (6: 2)	3	24	Labour stimulation