Statistical issues in first-in-human studies on BIA 10-2474: neglected comparison of protocol against practice

Sheila M. Bird (sheila.bird@mrc-bsu.cam.ac.uk), MRC Biostatistics Unit, CAMBRIDGE CB2 0SR

Rosemary A. Bailey, School of Mathematics and Statistics, University of St Andrews, ST ANDREWS KY16 9SS

Andrew P. Grieve, ICON plc, MARLOW SL7 1HZ

Stephen Senn, Competence Center for Methodology and Statistics, Luxembourg Institute of Health, LUXEMBOURG

ABSTRACT

By setting the regulatory-approved protocol for a suite of first-in-human studies on BIA 10-2474 against the subsequent French investigations, we highlight six key design and statistical issues which reinforce recommendations by a Royal Statistical Society Working Party which were made in the aftermath of cytokine release storm in six healthy volunteers in the UK in 2006.

The six issues are: dose determination; availability of pharmacokinetic results; dosing interval; stopping rules; appraisal by safety committee; clear algorithm required if combining approvals for single and multiple ascending dose studies.

KEYWORDS

BIAL 10-2474; protocol; design; statistical issues; combined approvals

Background

Cytokine release storm in six healthy volunteers in 2006: In the United Kingdom (UK), Te Genero's highly novel monoclonal antibody TGN1412 caused a cytokine release storm in all 6 healthy male volunteers who received it in an initial first-in-human (FIH) cohort of eight subjects, two of whom were randomized to placebo [1]. Cytokine release storm was an anticipated serious adverse event but the chance of its occurrence was presumed low. A contract research organization, Parexel, had conducted the TGN1412 study on behalf of

Germany's Te Genero. The UK regulator and ethics committee had permitted an inter-administration interval of only 10 minutes between subjects.

The Royal Statistical Society's (RSS) Working Party on Statistical Issues in First-in-Man Studies therefore recommended the justification ***always*** of a proper inter-administration interval between successive subjects, and also specification of the waiting time for laboratory-based results which pertained to subjects' 'safety'[2], see **BOX 1**. As we shall see, both issues recurred in the suite of FIH studies in France on BIA 10-2474, an inhibitor of fatty acid amide hydrolase (FAAH).

The Duff report on TGN1412[3] led to a revised European guideline on strategies to identify and mitigate risks for FIH trials[4], but its provisions on inter-administration intervals had been weakened through consultation[5]. The European Medicines Agency is consulting until February 2017 on its November 2016 revision[6] which, although substantially improved, remains insufficiently strict in section 8.2 on precautions to apply between treating subjects within a cohort, see below; and between cohorts, see **BOX 2**.

Fatality and four other serious-adverse-event hospitalizations in healthy volunteers in 2016: France's Agence Nationale de Securite du Medicament et des Produits de Santé (ANSM) gave approval on 26 June 2015 for a contract research organization, Biotrial, to conduct a suite of healthy volunteer FIH studies in Rennes on the Portuguese firm BIAL's FAAH-inhibitor, BIA 10-2474[7].

Despite seven single ascending dose (SAD) escalations (6 of them doublings from 1.25 mg to 240 mg; then 100 mg) and a shift to multiple ascending doses (MAD) which were unspecified in the protocol but entailed once-daily administration for 10 days, ***only two subjects (one actively treated, one placebo) in the initial lowest-dose SAD cohort (0.25 mg)*** were administered their assigned medication 24 hours ahead of the remaining six volunteers in the SAD-1 cohort (five actively treated, one placebo). Subsequent SAD and MAD cohorts of eight subjects (six actively treated, two placebo) lacked even a single sentinel-pair, see **BOX 3**.

Tragically, on 10 January 2016, the fifth day of daily dosing at 50 mg in the MAD-5 cohort, BIA 10-2474 caused the sudden onset of symptoms (including blurred vision and severe headache; also slurred speech and ataxia, as recently revealed [8]) and, by evening, hospitalization of a healthy male volunteer who became comatose by late morning on 11 January and died on 17 January 2016[7]. Notwithstanding his hospitalization (and clinical symptoms in a second volunteer on Day 5[8]), the remainder of the MAD-5 cohort received their sixth dose at around 8 o'clock in the morning of 11 January. Of the five who were actively treated on Day 6, two developed neurological symptoms and were hospitalized that day, two more on 12 January, with the fifth hospitalized on 13 January as a precaution.

Chronology, disclosures and investigations in France

Biotrial/BIAL suspended the MAD-5 cohort on 11 January 2016 after the condition of the first hospitalized volunteer worsened and symptom onset in two others; ANSM was informed on 14 January; the Biotrial protocol[9] was published on 22 January 2016, after Le Figaro had leaked it[10]; preliminary and final reports by Inspection Generale des Affaires Sociales (IGAS) were made on 4 February and 23 May[7 11 12]; and by France's Temporary Specialist Scientific Committee (TSSC) on 7 March and 19 April[13]. The TSSC had access to the Investigator Brochure (IB) which describes dose-related adverse events in four animal species[13]. The IB has also been leaked but, even 11 months after the fatality on 17 January 2016, BIAL has failed to publish the IB despite repeated calls for its publication [7 14-16]. The French press [17-20] has made important disclosures at the behest of volunteers and in defence of Biotrial's duty-doctor, some of which conflict with the investigatory accounts.

The TSSC strongly suspected that an off-target effect of BIA 10-2474 was responsible [13]. If BIA 10-2474's mode of action was solely FAAH-inhibition, TSSC questioned the exposure of healthy volunteers to doses higher than 5 mg, as FAAH inhibition had already occurred although extrapolation from pre-clinical studies had suggested 10-40mg could be needed for FAAH-inhibition. Pharmacodynamic (PD) analyses showing 100% FAAH inhibition by 5mg should have been available to inform dose escalation decisions in subsequent SAD cohorts, let alone in MAD cohorts [16]. The testing of very high non-pharmacological doses to establish a Maximum Tolerated Dose is ill-advised in healthy volunteers [6].

The TSSC noted steepness in the dose-escalation curve and apparent lengthening of the half-life so that dose-escalation should have been moderated and informed by the preceding cohort's PK results, see **BOX 3**. The TSSC also cautioned that individual variation in pharmacokinetic (PK) parameters, not just means, matters: see Bayesian methods in pharmaceutical practice [21].

Lacking from the investigatory accounts: As statisticians, we had expected critical examination of the ANSM-approved BIAL/Biotrial protocol including comparison of what was written in the protocol with what was done; an audit-trail of dates for the receipt at BIAL/Biotrial of each cohort's analysed PK and/or PD results; clear documentation of the data (PK and/or PD, adverse events, external) that were appraised by the BIAL/Biotrial safety committee at each dose-escalation decision – especially the decision to administer 50 mg daily for 10 days when the approved protocol had made no explicit mention of a 50 mg dose; and an unambiguous account (by assigned treatment, volunteer code, and ideally with consent) of the adverse events experienced. In extremis in FIH studies, as here, medical confidentiality should be balanced by the wider public good, as some volunteers and families have demonstrated.

Focus on key statistical issues

By setting the ANSM-approved protocol against the subsequent investigations, we highlight six key design and statistical issues which reinforce recommendations by the RSS working party, see **BOX 1**. The six issues are: dose determination; availability of PK results; dosing interval; stopping rules; appraisal by safety committee; clear algorithm if combining SAD/MAD approvals.

Dose determination – rationale and in practice: No dose was pre-specified in the ANSM-approved protocol for any MAD cohort: if the maximum tolerated dose was not reached after completing MAD-4, ANSM permitted that up to four additional MAD cohorts could be added**.** The Ethics Committee, which gave approval on 3 July 2015, had queried what information would be given to MAD volunteers about the scheme for determining which doses to administer. Re-assurance was given to the Ethics Committee that volunteers would be told the assigned dose [7], but this is not the same as explaining the rationale for how that dose was determined.

On 24 April 2016, De Pracontal reported that volunteer 2508 (who subsequently died) had recounted to his partner that the team at Biotrial had decided to increase the administered dose in MAD-5 from 40 mg to 50 mg "because they had estimated that there would not be enough of effects at 40 mg" [18]. For this dose-escalation in particular, investigatory reports should have clearly specified: i) the PK (and, see **BOX 2**, PD [6]) analyses from previous SAD and MAD cohorts that were actually considered by the safety committee, ii) the adverse events from previous SAD and MAD cohorts that were appraised by the safety committee, iii) pertinent other information considered and iv) the written final rationale by which the safety committee authorized escalation from 20 mg daily for 10 days in MAD-4 to 50 mg daily for 10 days in the MAD-5 cohort.

Safety precautions – PK results, per-protocol versus in practice: The ANSM-approved protocol had clearly stated that the dose levels for the first 4 MAD cohorts would be determined: ***"after evaluation of the safety, tolerability and available pharmacokinetic (PK) results of previous SAD and MAD (when applicable) dose groups."*** As the interval between SAD and MAD cohorts was 7 to 14 days except for the SAD-2 cohort (31 days) and MAD-5 cohort (18 days), Eddleston et al.[22] concluded: "Except for the second cohort, the delay between cohorts did not allow the previous cohort's pharmacokinetics to be considered before starting another, something recommended in the RSS report". The planned last study in the FIH suite of four was for PD analyses.

Collection schedules (for blood and urine samples) and a data analysis plan were set out. But there was no schedule for Biotrial's receipt of PK results. And despite calling for a debate on open data from FIH studies [13], the TSSC did not disclose the actual PK results from SAD-cohorts at 20 mg, 40 mg and 100 mg; nor from MAD-cohorts at 10 mg and 20 mg; ***nor precisely when*** the latter results were received at Biotrial[7] for review by its safety committee as, ***per-protocol for the MAD cohorts*** (see **BOX 3: PRECAUTION**), they should have been before determining that MAD cohort-5 would receive 50 mg daily for 10 days.

Divergence from what was written in the protocol for MAD versus SAD cohorts (see **BOX 3**) was not highlighted when the TSSC reported that, in practice, from the MAD-3 cohort (10 mg), administration to MAD-n cohort was based on the PK information from the MAD-(n-2) cohort. For the MAD-5 cohort (50 mg), this delay was 40 days but, as Eddleston et al. [22] have pointed out, the delay was only 18 days between the end-date of the MAD-4 (20 mg) and initiation of MAD- 5: too short for the PK information from the MAD-4 cohort to have been taken into account [2 3].

Safety precautions – dosing interval and escalation stopping rules, per-protocol versus in practice: The protocol stated that, if there were drug safety concerns for MAD-cohorts, the subjects' dosing would be staggered (a maximum of 4 subjects dosed on the same day and 24 hours of follow-up necessary before dosing the remaining subjects). This did not happen and so we may infer that the safety committee had no such concerns.

Stopping rules for safety, given as a guideline only in the protocol, stated that the dose should not be escalated further if one of four circumstances occurred in subjects *within the same cohort* (our italics), unless it was obvious that the occurrence was not related to the administration of the treatment. First of these four circumstances was: drug-related severe adverse event of the same character in *4 or more subjects*. The other three (laboratory abnormalities; changes in vital signs; confirmed changes in ECG) required clinically significant drug-related occurrence in *6 or more subjects* – ***despite each cohort having only 6 actively treated subjects.***

Biotrial claimed that its FIH designs were in line with current regulatory guidance. If so, stopping rules for safety in FIH studies need to be reviewed since the approved protocol permitted drug-related severe adverse events to be observed in half the healthy volunteers without necessitating a stay on dose-escalation. By contrast, several published designs use dose-response models to curb the adoption of dangerously high doses by predicting safety outcomes for future cohorts [23-25].

Appraisal by safety committee– per-protocol versus in practice: As is required in Phase I studies, dose-escalation in the MAD stage was also conditional on the absence of toxic effects in volunteers at the preceding dose-level upon appraisal by an advisory committee. Unlike in Phase II/III studies, there is no requirement for independent membership of Phase 1 safety committees. The BIAL/Biotrial advisory committee judged that double-vision, later described by TSSC as blurred vision [13] (compare page 18 in second report versus page 10 in first), on two separate occasions in each of two volunteers in MAD-3 (10 mg) was unrelated to the study drug and so permitted MAD-4 (20 mg) to proceed.

In combination, a lack of transparent audit by BIAL/Biotrial and inconsistent documentation by TSSC about adverse events necessitated recourse to newspaper reports. In May 2016, Le Figaro reported that magnetic resonance imaging (MRI) in 2016 for volunteers in the suite of BIA 10-2474 FIH studies had revealed that an actively-treated volunteer 2305, one of the two with visual disturbances in MAD-3 (10 mg), had had a cerebral vascular accident which may have occurred proximal to his participation in MAD-3. Le Figaro, citing an unpublished ANSM report, also claimed prolonged headache for one volunteer in each of MAD-cohorts

10 mg or 20 mg, which TSSC classed as non-severe [13]. The neurological symptoms on 10 January presented by the volunteer who subsequently died included double-vision and headache among others [8], as confirmed by Mediapart's publication of correspondence by the duty-doctor at Biotrial who referred this volunteer to hospital. On referral, the duty-doctor asked whether the patient's condition might be related to the study drug [20]. The IB was made available to the intensivists during their treatment of the hospitalized volunteers but how quickly remains to be established.

To date, there is no properly-dated, consistent account of which PK evaluation reports were received when, and which of them - alongside which adverse-event reports – were considered by the BIAL/Biotrial safety committee prior to approving the next dose escalation. Press reporting of volunteers' experience of adverse events (blurred vision or double-vision; duration; severity of headaches) can appear at odds with the investigatory-teams on what transpired in terms of the evolution of adverse events - including on the morning, afternoon and evening of 10 January 2016 [8] - which led to the hospitalization of a volunteer who had received five 50 mg daily doses of BIA 10-2474.

Combined-approval of SAD and MAD stages needs clear algorithm: The suite of FIH studies on BIA 10-2474 combined SAD and MAD stages. Had the latter been independently presented for regulatory and ethical approval, the SAD results would need to have been presented to justify the conduct of the MAD stage. By putting these two stages together, the sponsor made such a review impossible. It thus behoved the sponsor to make sure that a clear algorithm for proceeding to, and through, the MAD stage - based on previous results - was provided.

Flexible trials[26], in which the information gained early on is used to modify subsequent conduct, have received much theoretical attention in recent years. Regulators do not permit their use in Phase II/III without explicit rules covering modfication and the provision of stringent safeguards. Similar safeguards ought to apply in Phase I.

Discussion

A common expectation in multiple dose studies is that, based on the available PK information, the steady state concentration that a chosen regimen is expected to reach should not be higher than that already tested in single dose studies. Given that the highest SAD dose had been 100 mg, a 50 mg daily dose over 10 days would be hard to justify unless it were known that elimination of the drug was fairly rapid (say, linear with a half-life of at most one day). Instead, according to TSSC, BIA 10-2474 had a long half-life which extended with increased doses [13] but the actual PK results were not disclosed.

To enable others to do better, it is important that information on the design and conduct of the BIAL/Biotrial trial, and its results, are shared widely.

Conclusions: If there is high inter-volunteer variation in susceptibility to risk, a single sentinel-pair {active; placebo}, treated 24 hours ahead of other volunteers in the lowest dose FIH cohort only, as in BIA 10-2474, will be generally insufficient. Implementation of the current [4] (and future draft [6]) European guideline on risk mitigation needs to be more thoughtful: both between volunteers within a cohort; and in determining dose-level per-cohort. Regulators should specifically assess how well safeguarding is justified ***per-cohort*** (eg reliance on single or multiple sentinel-pairs, each at 24 hour intervals); and should appraise the principles (eg on inhibition; maximum occupancy) and precautionary practice by which the dose-level per-cohort will be decided in the light of pharmacological effects at preceding dose-levels. Guidelines serve to assist, not abrogate, thoughtfulness.

In the UK, clinical research organizations are registered by the regulator. European regulators should be able to de-register contract research organizations if the safety precautions that were written into approved protocols are weakened in practice.

Regulators should be extremely wary of stopping rules for dose-escalation in FIH studies which require at least two-thirds of the actively-treated healthy volunteers to experience severe adverse events before stopping is invoked. The occurrence of possibly related events in preceding cohorts should be taken into consideration [2]. Consideration might be given to whether having a written charter [27], which sets out the independent membership, role and responsibilities of safety committees for FIH studies, would assist them.

By offering staged approvals, regulators could enable pharmaceutical companies to invoke adaptive designs for FIH studies which use Bayesian methods formally to incorporate PK information from all preceding cohorts. Properly used, and with explicit assumptions, these designs hope to optimize both the number of subjects and the active: placebo ratio for the next cohort of healthy volunteers exposed to higher doses [2].

Latitude in approved protocols should never extend to wholly unspecified dose-levels [6]. A mechanism is needed for an approved protocol-variation if later dose levels are to be escalated exceptionally (for example, supra-pharmacologically) in the light of data from earlier cohorts; or for another reason.

Conflicts of Interest: All authors were members of Royal Statistical Society's Working Party on Statistical Issues in First-in-Man Studies, which SS chaired.

SMB holds GSK shares.

APG is a statistician working for a CRO providing services for pharmaceutical sponsors, is a past-chairperson of Statisticians in the Pharmaceutical Industry and a past-president of the Royal Statistical Society. APG holds shares in ICON plc.

SS holds shares in Novartis and regularly consults for the pharmaceutical industry.

Funding: nil.

References

1. Sunthalingan G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, Panoskaltsis N. Cytokine release storm in a phase 1 trial of anti-CD28 monoclonal antibody TGN1412. *New England Journal of Medicine* 2006; 355: 1018 – 1028.
2. Senn S, Amin D, Bailey RA, Bird SM, Bogacka B, Colman P, Garrett A, Grieve A, Lachmann P. Statistical issues in first-in-man studies (Report of a Royal Statistical Society Working Party, chairman: Professor Stephen Senn). *Journal of the Royal Statistical Society Series A (Statistics in Society)* 2007; 170: 517 – 579.
3. Expert Scientific Group on Phase One Clinical Trials (Final report of a group convened by UK's Medicines and Healthcare Regulatory Authority and chaired by Professor Sir Gordon Duff). Final report online 6 December 2006, see http://webarchive.nationalarchives.gov.uk/+/dh.gov.uk/en/publicationsandstatistics/publications/publicationspolicyandguidance/dh_063117 (accessed 16 March 2016).
4. European Medicines Agency Committee for Medical Products for Human Use (CHMP). *Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medical Products*, as finalized in 2009 (see page 10 of http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002988.pdf; last accessed 16 March 2016).
5. European Medicines Agency Committee for Medical Products for Human Use (CHMP). *Guideline on Requirements for First-in-Man Clinical Trials for Potential High-Risk Medicinal Products*. Draft for consultation in 2009 (see page 9, at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002989.pdf; last accessed 16 March 2016).
6. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). *Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products.* 10 November 2016 draft: EMA/CHMP/SWP/28367/07 Rev. 1 (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/11/WC500216158.pdf. Last accessed 29 December 2016).
7. L'Inspection Generale des Affaires Sociales (IGAS). Enquete sur des incidents graves survenus dans le cadre de la realisation d'un essai Clinique. Premieres Constatations (5 February 2016). See http://social-sante.gouv.fr/IMG/pdf/fevrier_2016_-_note_etape_-_accident_essai_clinique.pdf (accessed 16 March 2016). Final report in two volumes was published in French on 23 May 2016, see http://social-sante.gouv.fr/IMG/pdf/2016-012r_tome_1_rapport_definitif_rect_20_05.pdf [page 28-30 re questions raised by Ethics Committee] and http://social-sante.gouv.fr/IMG/pdf/2016-012r_tome_2_rapport_definitif_enquete_incident_grave_essai_clinique.pdf (last accessed 4 July 2016).

8. Kerbrat A, Ferre J-C, Fillatre P, Ronziere T, Vannier S, Carsin-Nicol B, Lavoue S, Verin M, Gauvrit J-Y, Le Tulzo Y, Edan G. Acute neurologic disorder from an inhibitor of fatty acid amide hydrolase. *New England Journal of Medicine* 2016; 375: 1717-1725. (doi: 10.1056/NEJMoa1604221).
9. L'Agence Nationale de Securite du Medicament et des Produits de Sante (ANSM). For time-line and reports, see http://ansm.sante.fr/Dossiers/Essai-Clinique-Bial-Biotrial/Essai-clinique-BIA-102474-101-du-laboratoire-BIAL/%28offset%29/0. Including English version of *Clinical Study Protocol No BIA 102474-101: A double-blind, randomised, placebo-controlled combined single and multiple ascending dose study including food interaction, to investigate the safety, the tolerability, pharmacokinetic and pharmacodynamic profile of BIA 10-2474, in healthy volunteers*. See http://ansm.sante.fr/var/ansm_site/storage/original/application/3968769c8773917a7eb56202e18a6ae4.pdf. Also **ansm**.sante.fr/.../**protocol**e_**BIAL**_102474+101-22012016131259.pdf, accessed 16 March 2016.
10. Hawkes N. Details of French drug trial must be released urgently, say UK experts. *British Medical Journal* 2016; 352: i319.
11. Hawkes N. French drug trial had three major failings, says initial report. *British Medical Journal* 2016; 352: i784.
12. Casassus B. France releases interim report on drug trial disaster. *Lancet* 2016; 387: 634-635.
13. Temporary Specialist Scientific Committee (TSSC). Minutes of TSSC meeting on "FAAH (Fatty Acid Amide Hydrolase) Inhibitors" on 15 February 2016 (released on 7 March 2016; English version on 8 March 2016). See http://ansm.sante.fr/Dossiers/Essai-Clinique-Bial-Biotrial/Essai-clinique-BIA-102474-101-du-laboratoire-BIAL/%28offset%29/0; accessed 9 March 2016. TSSC published its second report on 19 April 2016, the English translation of which was released on 24 April 2016, see http://ansm.sante.fr/content/download/88057/1108293/version/1/file/CSST_FAAH_Rapport-Final_Version-Anglaise_18-04-2016.pdf; last accessed on 4 July 2016.
14. Royal Statistical Society. Royal Statistical Society Statement on the publication of study protocol BIA-102474-101 for the French "first-in-man" trial in healthy volunteers. See http://www.rss.org.uk/Images/PDF/about/press-releases/2016-01-22-rss-statment-BIA-102474-101-french-first-trial-in-healthy-volunteers.pdf (last accessed 20 March 2016).
15. Alexander S, Cohen A, Pirmohamed M, Webb D. Improve early access to data from catastrophic clinical trials: a statement on behalf of the British Pharmacological Society, 22 January 2016. See https://www.bps.ac.uk/news-events/news/society-news/articles/improve-early-access-to-data-from-catastrophic-cli (accessed 20 March 2016).
16. Randerson J. Fatal French clinical trial failed to check data before raising drug dose. Revelation from drug firm Bial prompts criticism from pharmacologists. *Nature* 2016;

22 December: News.
(http://www.nature.com/news/fatal-french-clinical-trial-failed-to-check-data-before-raising-drug-dose-1.21190; last accessed 29 December 2016).
17. Jouant A, Mascret D. Essai Clinique: le document qui accable Biotrial et L'ANSM. Le Figaro, 13 April 2016 See http://sante.lefigaro.fr/actualite/2016/04/13/24857-essai-clinique-document-qui-accable-biotrial-lansm. (accessed 20 April 2016).
18. De Pracontal M. Essai de Rennes: comment Biotrial s'est moqué de l'Igas. Mediapart 2106; 24 April.
19. Jouant A. Essai clinique de Rennes : quand le CHU réécrit les comptes rendus d'IRM. L'hôpital confirme l'information du « Figaro » selon laquelle un des volontaires a eu un AVC lors de la période de l'essai. *Le Figaro* 2016; 2 June: 12. See also sante.lefigaro.fr/actualite/2016/05/12/24963-essai-clinique-rennes-novembre-volontaire-avait-deja-eu-avc (last accessed on 4 July 2016).
20. De Pracontal M. Essai clinique mortel de Rennes: la lettre qui trahit le laboratoire Biotrial. *Mediapart* 2016; 1 June.
21. Racine A, Grieve AP, Flühler H, Smith AFM. Bayesian Methods in Practice: Experiences in the Pharmaceutical Industry (with Discussion). *Applied Statistics* 1986; 35: 93-150.
22. Eddleston M, Cohen AF, Webb DJ. Implications of the BIA-102474-101 study for review of first-into-human clinical trials (Editorial). *British Journal of Clinical Pharmacology* 2016; 81: 582-586.
23. Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. *Statistics in Medicine* 1998; 17: 1103 - 1120.
24. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. *Statistics in Medicine* 2008; 27: 2420 - 2439.
25. Whitehead J, Patterson S, Webber D, Francis S, and Zhou Y. Easy-to-implement Bayesian methods for dose-escalation studies in healthy volunteers. *Biostatistics* 2001; 2: 47-61.
26. Food and Drugs Administration. *Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics.* February 2010. See http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf; last accessed 4 July 2016.
27. DAMOCLES Study Group. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet* 2005; 365: 711 – 722.

BOX 1: Royal Statistical Society's Working Party on Statistical Issues in First-in-Man Studies [2] made 21 recommendations, of which we list 11 below.

R4. Before proceeding to a first-in-man study, there should be:

(a) quantitative justification of the starting dose—based on suitable preclinical studies and relevant calculations;

(b) *a priori* assessment of the risk level for the recommended study dose(s);

(c) appraisal of the uncertainty about these recommendations.

R9. Unless arguments have been provided that the risk is so low that simultaneous treatments are acceptable, in order to allow early evidence of toxicity to halt the trial without risk to subsequent subjects, a proper, or sufficient, inter-administration interval needs to be proposed and observed.

R*10.* First-in-man study protocols should provide:

(a) justification of the proper interval between administration to successive subjects;

(b) justification of the dose steps the trial will use;

(c) operational definition of 'safety' if investigating safety and tolerability;

(d) delay between receiving biomarker or other laboratory results which determine 'safety' and having obtained the relevant biological sample;

(e) prior estimates of the expected number (or rate) of adverse reactions by dose, especially those serious enough to raise questions about 'safety'.

R11. Appropriate sample sizes for first-in-man studies can be better justified statistically—rather than by mere custom and practice—when 'safety' has been given an operational definition.

R12. First-in-man study protocols should discuss their chosen design and its limitations together with the implications for analysis. For example, if an unequal allocation between treatment and placebo per dose step is chosen, this affects the ability of the data safety monitors to assess tolerability most efficiently before proceeding to a further dose escalation step.

R13. First-in-man study protocols should describe their intended analysis in sufficient detail to allow protocol reviewers (and the independent research ethics committee) to determine whether the objectives, design and proposed analyses are compatible.

R*14.*The design of first-in-man trials and the analysis of the data should reflect realistic models of the pharmacokinetic data.

R16. For first-in-man studies, the standard of informed consent to be observed is ‘open protocol, hidden allocation’—i.e. all aspects of the trial design shall be shared with subjects to be recruited.

R17. Public debate and research are needed about the maximum acceptable level of risk for first-in-man studies in healthy volunteers, and about whether there should be risk-adjusted remuneration of healthy volunteers.

R18. Competent drug regulatory authorities should provide a mechanism for the pharmaceutical industry to collect and share data on serious adverse reactions in first-in-man studies—to improve *a priori* risk assessment.

(a) For example, separate syntheses of study designs and of the occurrences of predicted, theoretical and unprecedented harms—either as serious adverse events or distributional changes in biomarkers—should be considered for healthy volunteers and for patients, by type and novelty of compound, and by *a priori* assessed level of risk.

(b) In particular, for the UK, the MHRA should report annually on the designs of, and serious adverse events (whether for the first exposed cohort or at a dose escalation step) in, first-in-man studies in healthy volunteers (*versus* patients) that involved administration of a biological or biotechnology, and for those that involved a chemical compound.

(c) The MHRA should also take responsibility for maintaining a central registry of participating volunteers in the UK.

R19. Statistical reporting of preclinical studies should be improved to be comparable with the requirements by the International Conference on Harmonisation for the reporting of clinical trials.

BOX 2: European guidelines on strategies to identify and mitigate risks for First-in-Human trials.

2.1 Draft for consultation [5], page 9 (***our italics***):

"For trials with high-risk medicinal products, an initial sequential dose administration design should be employed ***within each cohort*** in order to minimise any risks. Any non-sequential dose administration within each cohort should be justified . . . "

2.2 As finalized in 2009[4], page 10 (***our italics***):

"***It will usually be appropriate to design the administration of the first dose so that a single subject receives a single dose of the active IMP***. Further dose administration should be sequential within each cohort to mitigate the risk. Any non-sequential dose administration within each cohort should be justified . . ."

2.3.1 European Medicines Agency November 2016 draft Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (IMPs) [6], section 8.2.6 on Precautions to apply between treating subjects within a cohort (***our italics***):

"***It is considered appropriate to design the administration of the first dose in any cohort so that a single subject receives a single dose of the active IMP***. When the study design includes the use of placebo it would be appropriate to allow for one subject on active and one on placebo to be dosed simultaneously ***prior to dosing the remaining subjects in the cohort***.

There should be an adequate period of time between the administration of treatment to these first subjects in a cohort and the remaining subjects in the cohort to observe any reactions and adverse events. The duration of the interval of observation should be justified and will depend on the properties of the IMP and the interpretation of the available data, including non-clinical PK and PD. Experience and . . . "

2.3.2 European Medicines Agency November 2016 draft Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (IMPs) [6], section 8.2.7 on Precautions to apply between cohorts (***our italics***):

"Administration in the next cohort should not occur before participants in the previous cohort have been treated and PK data, ***where available***, or possible adverse events from those participants are reviewed in accordance with the protocol. Thus all relevant data from cohort "n" should be reviewed prior to allowing dosing of cohort "n+1". ***Review of all previous cohorts' data in a cumulative manner is preferred.*** Late emerging safety issues that may have occurred after the time-point for the dose escalation decision (***for example, 48 hour safety data for each subject set as the minimum data required*** but significant event(s) happening at 7 days post dose) can then be considered.

All emerging PD, PK and safety data should be critically reviewed against the pre-defined stopping criteria (see section 8.2.10), including exposure limits that are not to be exceeded.

Account should be taken of any signs related to potential PD or toxicity targets identified in non-clinical studies. While there can be no delay for safety data, a lack of PD information or a reduced PK data set could be justifiable in some cases, such as a short duration of the PD effect.

The review should include comparison of PK, PD or PK/PD data from any previous cohorts with known non-clinical data and safety information to inform the decision, as well as . . . "

BOX 3: Suite of four First-in-Human studies on BIA 10-2474 approved by France's Agence Nationale de Securite du Medicaments et des Produits de Sante (ANSM).

Phase and Cohort	**Design** {randomly assigned; with between-subject interval of 10-minutes}	**Dose**	**Neurological Adverse Events:** according to investigatory reports, press or volunteer accounts
Single Ascending Dose (SAD) Cohorts: 8 SAD cohorts, & approval for 4 more . . . Pharmacokinetic (PK) PRECAUTION: PK results for SAD cohort (n-2) must be available for review before the start of SAD cohort n [9].			
SAD- 1 ***Begun on 9th July 2015***	{1 active; 1 placebo} ***24-hours' delay, then*** {5 active; 1 placebo}	0.25 mg, 1/400th no-observed-adverse-effect-level (NOAEL) in rats	***None reported as far as we know***
SAD- 2	{6 active; 2 placebo}	1.25 mg	
SAD- 3	{6 active; 2 placebo}	2.5 mg	
SAD- 4	{6 active; 2 placebo}	5 mg	
SAD-5	{6 active; 2 placebo}	10 mg	
SAD-6	{6 active; 2 placebo}	20 mg	
SAD-7	{6 active; 2 placebo}	40 mg	
SAD-8	{6 active; 2 placebo}	100 mg, the human equivalent of NOAEL in rats	
SAD-9 ***Not done***	{6 active; 2 placebo}	150 mg, maximally	***Not done***
SAD-10 ***Not done***	{6 active; 2 placebo}	225 mg, maximally	
SAD-11 ***Not done***	{6 active; 2 placebo}	337 mg, maximally	
SAD-12 ***Not done***	{6 active; 2 placebo}	505 mg, maximally	
Food Interaction (FI) Cohort			
FI-cohort ***Begun on 12th September 2015***	12 healthy volunteers: ***Study-day & condition (fasted/not fasted) were confounded.***	Not pre-specified ***In practice, dosed at 40 mg on each of two study-days***	***None reported as far as we know***
Multiple Ascending Dose (MAD) Cohorts with daily dosing for 10 days: 4 MAD cohorts but with conditional approval for 4 more [9] . . . Pharmacokinetic (PK) PRECAUTION: Protocol stated that the dose levels for the first four MAD cohorts would be determined **"after the evaluation of safety, tolerability and available PK results of previous SAD and MAD (when applicable) dose groups".**			
MAD-1 ***Begun on 6th October 2015***	{6 active; 2 placebo}	***Not pre-specified*** but 2.5 mg	***None reported as far as we know***
MAD-2	{6 active; 2 placebo}	***Not pre-specified*** but 5 mg	
MAD-3 ***Begun on***	{6 active; 2 placebo}	***Not pre-specified*** but 10 mg in	Volunteer 2305, who received BIA 10-2474 had

17th November 2015		practice	blurred vision twice, also headache by press-account, and subsequently had cerebral vascular accident diagnosed by MRI. Another volunteer had blurred vision twice.
MAD-4	{6 active; 2 placebo}	***Not pre-specified*** but 20 mg in practice	One or two volunteers each had headache twice.
*The ANSM-approved protocol [9] stated that**, if the maximum tolerated dose was not reached after completing the fourth MAD cohort,** up to 4 additional MAD cohorts could be added.*			
MAD-5 ***Begun on 6th January 2016.*** ***Suspended on 11th January 2016 after the remaining seven volunteers had received their Day 6 dose.***	{6 active; 2 placebo}	***Not pre-specified*** but 50 mg in practice	Onset of neurological symptoms, including diplopia and headache, in volunteer 2508 after dosing on Day 5. This volunteer was hospitalized in the evening of 10th January 2016, became comatose in the morning of 11th and died on 17th January 2016. Four other volunteers who each received a sixth 50 mg dose of BIA 10-2474 became symptomatic and were hospitalized. The fifth was not symptomatic but was hospitalized as a precaution [8].
MAD-6 ***Not done***	{6 active; 2 placebo}	***Not pre-specified***	***Not done***
MAD-7 ***Not done***	{6 active; 2 placebo}	***Not pre-specified***	
MAD-8 ***Not done***	{6 active; 2 placebo}	***Not pre-specified***	
Pharmacodynamic study on 20 healthy volunteers: *Not done*			

497