

**IRISH MEDICINES BOARD  
RIMCAZOLE CLINICAL TRIAL AT SHANDON CLINIC  
FINAL REPORT (3 OCTOBER 2011)**



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## 1 INTRODUCTION

The purpose of this report is to detail the findings of the Irish Medicines Board's investigation into the conduct of a clinical trial using rimcazole hemifumarate at the Shandon Clinic in August 2010. This investigation was initiated by the IMB after three subjects participating in the trial experienced seizures. All three subjects recovered fully when the administration of the trial medication was discontinued.

## 2 PARTIES INVOLVED IN THE CONDUCT OF THE TRIAL

The Sponsor, Modern Biosciences, is based in the UK. Modern Biosciences is a drug development company which sources late stage discovery projects from academia, conducts early proof of principle clinical trials and subsequently licenses out the results of these trials to the pharmaceutical industry.

Shandon Clinical Trials Ltd ('Shandon Clinic') was a clinical research organisation based at 9 John Redmond Street, Cork. It was founded in 1990 as a clinical pharmacology unit and expanded its services over the years to include bioequivalence testing and pharmacokinetic studies.

On 20 October 2010, the IMB received notification that the Clinic went into liquidation citing the main reason as a significant downturn in its business. As a result, no further trials will be conducted at Shandon Clinic.

Both the Sponsor (Modern Biosciences) and the Investigators (Shandon Clinic) cooperated fully throughout the IMB investigation.

## 3 SUMMARY OF TRIAL

The IMB received a clinical trial application under the IMB reference number CRN 2081124 on 13 April 2010 and it is cited as *CT1460/1/2 – A two-part bioavailability study of rimcazole hemifumarate 100 mg immediate release capsules, including initial dose escalation (single dose) followed by multiple dosing to steady state*

This trial was a Phase 1 human pharmacology<sup>1</sup> trial of an unauthorised medicinal product containing the active substance rimcazole hemifumarate. Shandon Clinic was the only site at which this trial was carried out.

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<sup>1</sup> This is data gathered by the studying of the actions and metabolism of drugs in human beings.

The trial involved the administration of rimcazole hemifumarate in two parts. The first part involved the administration of increasing single doses of rimcazole hemifumarate to healthy subjects. The second part of the trial involved the administration of multiple doses (i.e. twice daily) of rimcazole hemifumarate in order to reach steady state.<sup>2</sup> The doses to be administered in the second part of the trial were to be determined by the pharmacokinetic<sup>3</sup> and safety data obtained from the first part of the trial.

Another salt of rimcazole, rimcazole dihydrochloride, was investigated for treatment of schizophrenia in Phase 1 and 2 clinical trials in the 1970s and 1980s in another jurisdiction. A seizure occurred in two patients with schizophrenia at a dose of 600 mg per day, and lower doses were used in further trials in this patient population. The sponsor and investigators of these early trials considered that patients with schizophrenia were more likely to experience seizures than others. In a separate trial, a seizure occurred in one healthy subject at a single dose of 800 mg. The investigation of the dihydrochloride salt was discontinued at that time.

Following renewed interest in its potential as a possible treatment for cancer, a trial was conducted in 2008 at Shandon Clinic under the IMB reference number, CRN 2045121, CT1460/1/1, with rimcazole dihydrochloride. During this trial, the maximum single dose was 300 mg (immediate release and prolonged release tablets) and the substance was well tolerated. However, it was found that the pharmacokinetic properties of rimcazole dihydrochloride were highly variable, and this led the company to use the hemifumarate salt in this 2010 trial (CT1460/1/2), to determine if its pharmacokinetics were more predictable.

CT1460/1/2 was approved on 11 June 2010 by the IMB, in accordance with the clinical trials legislation.<sup>4</sup> During the course of the assessment of the application, the IMB raised queries, required amendments particularly as regards the informed consent form, and also sought clarification of the protocol and details of the facilities for resuscitation (see section 5(iv) of

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<sup>2</sup> When a person is taking a medication on a regular basis, there is an ongoing process of drug absorption from each dose of the drug and, concurrently, an ongoing process of drug removal with the drug's metabolism and clearance. Eventually, there comes a point when the amount of drug absorbed in is the same as the amount of drug metabolised and excreted. This is known as "steady state."

<sup>3</sup> Pharmacokinetics may be simply defined as what the body does to a drug, as opposed to pharmacodynamics which may be defined as what a drug does in the body. Pharmacokinetics includes the study of the mechanisms of absorption and distribution of an administered drug, the rate at which a drug action begins and the duration of the effect, the chemical changes of the substance in the body and the effects and routes of excretion of the metabolites of the drug.

<sup>4</sup> European Communities (Clinical Trials on Medicinal Products for Human Use) 2004 (SI No. 190 of 2004), as amended, which transposed into Irish law the requirements of European Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and for investigational medicinal products for human use and Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

this report). The clinical trial was also approved by the Clinical Research Ethics Committee of the Cork University Teaching Hospitals.

The trial commenced on 27 July 2010 and a total of 14 healthy subjects received doses of rimcazole hemifumarate. The trial protocol foresaw administration to 12 trial subjects and the total figure of 14 individuals arose as two of these subjects were replacements for 2 subjects from the first part of the trial who did not wish, for personal reasons, to complete the trial. The investigational medicinal product, rimcazole hemifumarate, appeared to have been well-tolerated in the first part of the trial when single doses were administered. However, serious adverse events occurred in the second (multiple-dose) part of the trial following the administration of the third dose.

#### **4 OCCURRENCE OF SERIOUS ADVERSE EVENTS**

On 27 August 2010, the second day of multiple dosing, three of twelve healthy subjects who received rimcazole hemifumarate experienced seizures. One of these was a replacement subject as referred to section 3 above. The three subjects were transferred to Cork University Hospital (CUH) by ambulance and one subject had a second seizure while hospitalised. These serious adverse events resolved without treatment. The subjects were detained in hospital under observation overnight and returned to Shandon Clinic on 28 August. All 12 subjects remained in the Clinic for observation for the following 48 hours and were discharged on 30 August following medical examination. No further trial medication was administered to any of the subjects following the dose on the morning of 27 August, i.e. third dose of the second part of the trial, and as a result of the serious adverse events, the trial was terminated on that date. Written notice of termination was received by the IMB on 30 August. The emergency procedures at Shandon Clinic were effective and patients were monitored appropriately until discharge. All of the subjects recovered fully following the seizures.

#### **5 IMB INVESTIGATION**

The IMB was informed of the serious adverse events by Shandon Clinic during the afternoon of the 27 August 2010 and an investigation, under the legislation, into the conduct of the trial began immediately. This included:

- (i) A Good Clinical Practice inspection was undertaken to examine the conduct of the trial.
- (ii) The human pharmacology data relating to the trial was obtained and examined by the IMB. An external pharmacokinetic expert from another European medicines regulatory agency was engaged to carry out an independent review of these data.
- (iii) A review of the investigational medicinal product was carried out and samples were taken from Shandon Clinic for analysis.

- (iv) A review of the IMB's assessment of the clinical trial application was carried out.
- (v) Advice was sought from the IMB Scientific Committees, and the Management Committee of the IMB and the Board were kept informed.
- (vi) A review of the end of trial report received from Modern Biosciences was carried out.

In addition, the responsible ethics committee (Clinical Research Ethics Committee of the Cork Teaching Hospitals) was formally notified that the trial had been terminated and that an investigation was under way.

### **5(i) Good Clinical Practice Inspection**

An inspection of the conduct of the trial was carried out from 31 August to 2 September 2010. One critical deficiency<sup>5</sup> and five major deficiencies<sup>6</sup> were identified.

The critical deficiency was the finding that two subjects were entered into the trial as replacement subjects at escalated doses without the clinic having obtained initial safety or pharmacokinetic data for them. One of these replacement subjects entered the trial at an escalated dose in the first part of the trial and the other entered the trial only at the second part (see section 3 for clarification).

The major deficiencies were as follows:

- (i) A Safety Review Committee at Shandon Clinic played a key role in evaluating the data generated during the trial and in deciding the doses that subjects should receive. However, this Committee had not been described in the protocol or procedures, and the Committee's records were inadequate.
- (ii) Shandon Clinic was not compliant with the protocol submitted to and authorised by the IMB. This was due to the use of metaboliser status (genotyping)<sup>7</sup> to determine dosing in the multiple-dose part. This was not clearly specified in the protocol. According to the protocol authorised by the IMB, the decision on the dose that subjects would receive during the multiple-dose part of the trial, and the number of

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<sup>5</sup> Conditions, practices or processes that adversely affect the rights, safety or well being of subjects and / or the quality and integrity of data.

<sup>6</sup> Conditions, practices or processes that might adversely affect the rights, safety or well being of subjects and / or the quality and integrity of data (Major observations are serious deficiencies and are direct violations of Good Clinical Practice principles).

<sup>7</sup> Genotype testing for polymorphisms can identify variants of specific genes associated with abnormal and normal drug metabolism. The theory is that individuals with certain gene variants may potentially be able to receive higher or lower doses of some drugs to improve the likelihood of achieving clinical goals as well as lessening the risk of adverse drug effects.

subjects to be given a particular dose, was to be based on pharmacokinetic data and safety data from the single-dose part of the trial.

- (iii) The management and delegation of sponsor responsibilities were not clearly documented.
- (iv) The quality checks carried out during the trial were inadequate to ensure the quality of the pharmacokinetic and safety data.
- (v) The use of genotyping to determine dosing in the multiple dose part of the trial was not clearly specified in the genotyping informed consent form.

A report outlining these deficiencies was sent to Modern Biosciences and Shandon Clinic. A joint response was received which led to further comments from the IMB. This was followed up with a teleconference and meeting at the IMB offices to discuss outstanding issues. At the meeting, the Sponsor (Modern Biosciences) indicated that it disagreed with the IMB's classification of the critical deficiency and, specifically, the interpretation of the protocol (refer to point (ii) above in this section). The IMB advised that it was satisfied with its classification of this point as a critical deficiency. The Sponsor acknowledged that the protocol, as written, was open to an interpretation other than that taken by them. The Sponsor confirmed that it has taken corrective action to ensure protocols for future trials are more clearly written.

Other preventative actions in relation to the major deficiencies have been implemented by the Sponsor and these are considered to be acceptable to the IMB.

The Sponsor has also taken corrective action for future trials which require review of pharmacokinetic data. For such clinical trials, more than one pharmacokinetic expert will be employed to review the pharmacokinetic data (see section 5(ii) below). This is acceptable to the IMB.

The Sponsor has confirmed that they do not intend to pursue further development of rimcazole.

## **5(ii) Human Pharmacology Data and Expert Review**

The IMB carried out a preliminary analysis of the human pharmacology data obtained from the trial. The data were also forwarded to an independent expert for review. The main conclusion drawn was that the data from the first part of the trial indicated that non-linear kinetics<sup>8</sup> applied to the excretion of rimcazole. The pharmacokinetic model used by the

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<sup>8</sup> Linear pharmacokinetics implies that the rate of elimination of a drug is proportional to the amount of drug present in the plasma (blood), whereas in non-linear pharmacokinetics the rate of elimination is constant and, dependent on the size of subsequent doses, may lead to accumulation of the drug substance in the body.

Clinic/Sponsor to determine the dose subjects received for the second part of the trial was considered inadequate. This led to the subjects being given a larger dose of rimcazole hemifumarate exposing them to an increased risk of accumulation of the medication and seizure activity. However, the independent expert noted that the extent of accumulation seen in the second part of the study would have been difficult to predict.

#### **5(iii) Review of the Investigational Medicinal Product and Analysis of Samples**

A review of the pharmaceutical quality of the investigational medicinal product (IMP) used in the trial was conducted. Following this review, which included analysis of the product carried out by the IMB's contract laboratory, there was no concern regarding the quality of the investigational medicinal product.

#### **5(iv) Review of the IMB's assessment of the Clinical Trial Application**

The IMB conducted a full review of the initial assessment of the trial application that was carried out prior to its approval. The initial assessment involved a full evaluation of all of the clinical, pre-clinical and pharmaceutical data submitted in support of this clinical trial in line with normal practice.

It was noted by the IMB at this initial assessment of the application that the information in the subject consent form regarding seizures had been considered to be insufficient. The applicant was requested by the IMB to indicate in the patient consent form that seizures had occurred previously following the administration of a single dose of 800 mg to healthy subjects. It was noted that the maximum proposed dose for the second part of the trial was not to exceed 400 mg twice daily and the dose regime was to be determined following evaluation of the pharmacokinetic and safety data obtained from each subject during the first part of the trial (refer to Section 3 of this report). It was considered by the IMB to be reasonable that the maximum dose of 400 mg twice daily proposed in the protocol was likely to be safer than 800 mg once daily (the dose associated with the seizure in a previous clinical trial involving healthy subjects).

In addition, clinical queries raised by the IMB during the initial assessment of the trial included a request for clarification of the protocol and details of the facilities for resuscitation, in the event of a medication-induced seizure. The IMB had inspected the facility in July 2010, in relation to the conduct of two other clinical trials, with a positive outcome and there were no critical or major findings during this audit.

All issues raised during the assessment of the application were resolved satisfactorily and the trial was approved by the IMB on 11 June 2010.

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The review of the initial IMB assessment confirmed that the clinical trial application was evaluated appropriately and in line with the relevant European and national legislation.

#### **5(v) Consideration by IMB Scientific Committees**

Following the termination of the trial, the Scientific Committees of the IMB analysed and considered all the information pertaining to the rimcazole trial at a number of meetings.

The Committees concluded that the two-part trial design proposed by the sponsor was considered appropriate for a medicinal product at this stage of development and provided an appropriate level of protection for the subjects. It was considered reasonable that the maximum dose of 400 mg twice-daily proposed in the protocol was likely to be safer than 800 mg once daily. They were also satisfied that the appropriate facilities were available at Shandon Clinic in the event of a seizure and that staff had been adequately trained and that there had been two medical staff on duty in Shandon Clinic on the day that the serious adverse events occurred.

Results of the previous inspections of trials conducted at Shandon Clinic were summarised and the generally good record of compliance with Good Clinical Practice was noted.

#### **5(vii) Review by the IMB Management Committee and the Board**

The IMB's Management Committee considered the termination of the rimcazole trial and initiated the IMB investigation into the conduct of the trial. They also considered the implications for the conduct of further trials at Shandon Clinic as a result of the termination of the rimcazole trial. However with the closure of the site, in October 2010, the latter point was resolved. The recommendations/advice from the Scientific Committees was discussed at the Management Committee and it was updated regularly in relation to the status of the investigation.

The Board of the IMB was also kept informed of the progress of the investigation.

## **6 CONCLUSIONS**

- (i) The three subjects who experienced seizures recovered fully, as confirmed by the Sponsor, Modern Biosciences, and Shandon Clinic.
- (ii) The emergency procedures at Shandon Clinic were effective and patients were monitored appropriately until discharge.
- (iii) The trial design was considered appropriate for a medicinal product at the stage of development. It was reasonable to consider from the trial design (rising single dose followed by review of safety and pharmacokinetic data and then multiple dose to a maximum of 400 mg twice daily) that the maximum dose of 400 mg twice-daily

proposed in the protocol was likely to be safer than 800 mg as a single dose (the dose associated with a seizure in a previous clinical trial).

- (iv) The IMB concludes that this clinical trial was not conducted in full compliance with its approved protocol, particularly in respect of:
  - a. The inappropriate introduction of the replacement subjects into the study
  - b. The use of metaboliser status (genotyping) to determine dosing in the multiple dose part of the trial was not clearly specified in the protocol and in the genotyping informed consent form.
- (v) The IMB concluded that the single dose data clearly indicated non-linearity and therefore the pharmacokinetic modelling employed for the calculation of the dose for the multiple dose part of the trial was not adequate and led to an increased risk of accumulation of rimcazole in the healthy subjects. However, the extent of accumulation observed would have been difficult to predict.
- (vi) There is no concern regarding the quality of the investigational medicinal product (IMP) used in the trial.
- (vii) The review of the initial IMB assessment confirmed that the clinical trial application was evaluated appropriately and in line with the relevant European legislation.
- (viii) Both the Sponsor (Modern Biosciences) and the Investigators (Shandon Clinic) cooperated fully throughout the IMB investigation.
- (ix) In relation to the preparation for and conduct of future clinical trials, Modern Biosciences has put in place corrective and preventative actions that, as set out, are considered by the IMB to be acceptable.
- (x) The Sponsor has confirmed that they do not intend to pursue further development of rimcazole.
- (xi) It is noted that, due to a significant downturn in its business, Shandon Clinic has gone into liquidation and no further trials will be conducted there.