Chronology of the evaluation and performance of the clinical trial sponsored by BIAL laboratories and conducted by BIOTRIAL in Rennes

Background-reminder:

The clinical trial entitled "Double-blind, randomised, placebo-controlled, combined single and multiple ascending dose study including food interaction, to investigate the safety, tolerability, pharmacokinetic and pharmacodynamic profiles of BIA 10-2474 in healthy volunteers" is **a phase I clinical study, involving a stage of first administration to humans** of the medicinal product "BIA 10-2474" (chemical medicinal product in capsule form) (ANSM ref: 150565A-31 - EudraCT no. 2015-001799-24).

It was conducted only in France (at the BIOTRIAL research site in Rennes) and involved healthy volunteers, men and women aged between 18 and 55 years.

The objectives of the trial were to assess:
- the safety and tolerability of BIA 10-2474 after single and multiple oral doses;
- the effect of food on the pharmacokinetics (PK) of BIA 10-2474;
- the pharmacokinetics (PK) and pharmacodynamics (PD) profile of BIA 10-2474.

To be conducted in France, a clinical trial must first obtain authorisation from ANSM and a favourable opinion from a Comité de protection des personnes (CPP) [Ethics Committee]. The authorisation and opinion are legally independent and may be obtained in parallel or sequentially.

1. PRELIMINARY INSPECTIONS OF THE BIOTRIAL RESEARCH SITE

Phase I research sites (except health facilities) undergo administrative authorisation issued by the regional health agency (ARS).

Independently of the implementation of this trial, BIOTRIAL underwent several inspections by ANSM.
Latterly, an inspection was conducted:
- in October 2014 to appraise compliance with legislative and regulatory provisions relating to the performance of clinical trials and the observance of "good clinical practice" (GCP);
- in December 2014 to appraise compliance with legislative and regulatory provisions relating to the performance of pre-clinical trials and the observance of "good laboratory practice" (GLP).

It should be pointed out that the pre-clinical trials relating to the medicinal product BIA 10-2474 were not conducted by BIOTRIAL.

2. REQUEST FOR CLINICAL TRIAL APPLICATION (CTA)

- The request for clinical trial application (CTA) was submitted to ANSM by BIOTRIAL on behalf of the sponsor BIAL on 30 April 2015.
- This request for CTA was evaluated with regard to pre-clinical and clinical aspects and pharmaceutical quality. Exchanges took place with the sponsor and changes to the protocol were requested by ANSM. Following these exchanges and these changes to the protocol, the trial was authorised by an ANSM decision of 26 June 2015.
- Favourable opinion issued by the CPP OUEST VI [West VI Ethics Committee] in Brest on 3 July 2015, emailed to ANSM by BIOTRIAL on 9 July 2015.

3. PERFORMANCE OF THE CLINICAL TRIAL, OCCURRENCE OF SERIOUS ADVERSE EVENTS AND MANAGEMENT OF THE SITUATION

The protocol envisages three parts for this trial:

1st part: administration of single ascending doses (SAD)

The volunteers participating in this study receive a single treatment dose: verum (investigational medicinal product) or placebo.

Eight ascending doses were tested, each dose being tested in a cohort of 8 volunteers (i.e. 64 subjects in total).

For the 1st cohort of subjects testing the first dose, 2 volunteers first received the treatment (1 verum and 1 placebo), then, 24 hours later, the other 6 volunteers (5 verum and 1 placebo).

For the next 7 cohorts, the 8 volunteers received one treatment dose at the same time (6 verum and 2 placebo).

9 July 2015:
Start of cohort 1: first administration of the 0.25 mg dose to 2 volunteers of cohort 1

10 July 2015:
Continuation of cohort 1: administration of the 0.25 mg dose to 6 other volunteers of cohort 1 (24 h after the first 2 volunteers of cohort 1)

11 August 2015:
Start of cohort 2: administration of the 1.25 mg dose to cohort 2 (31 days after cohort 1)

19 August 2015:
Start of cohort 3: administration of the 2.5 mg dose to cohort 3 (8 days after cohort 2)

26 August 2015:
Start of cohort 4: administration of the 5 mg dose to cohort 4 (7 days after cohort 3)

3 September 2015:
Start of cohort 5: administration of the 10 mg dose to cohort 5 (8 days after cohort 4)

16 September 2015:
Start of cohort 6: administration of the 20 mg dose to cohort 6 (13 days after cohort 5)

30 September 2015:
Start of cohort 7: administration of the 40 mg dose to cohort 7 (14 days after cohort 6)

9 October 2015:
Start of cohort 8: administration of the 100 mg dose to cohort 8 (9 days after cohort 7)

No serious adverse event was brought to the knowledge of ANSM during this first part of the trial.

2nd part: Interaction with food

A cohort of 12 volunteers receives on 2 occasions one 40 mg verum dose, once in the morning on an empty stomach, and once after a fat-rich breakfast.

21 October 2015: Administration on an empty stomach of a 40 mg verum dose.

10 November 2015: Administration after breakfast of a 40 verum dose (20 days after the administration on an empty stomach).

3rd part: administration of multiple ascending doses (MAD)

Each volunteer receives one treatment dose once a day for 10 days.

Five ascending doses (2.5 mg, 5 mg, 10 mg, 20 mg then 50 mg) are tested, each dose being tested in a cohort of 8 volunteers. In each cohort there are 6 verum and 2 placebo.

1st cohort (2.5 mg dose): from 6 October to 15 October 2015

2nd cohort (5 mg dose): from 28 October to 6 November 2015

3rd cohort (10 mg dose): from 17 to 26 November 2015

4th cohort (20 mg dose): from 9 to 18 December 2015

No serious adverse event was brought to the knowledge of ANSM from cohort 1 up to the end of cohort 4.

5th cohort (50 mg dose)

Wednesday 6 January 2016:

Start of treatment with 50 mg dose in cohort 5 (19 days after the end of cohort 4).

Sunday 10 January 2016:

- 5th day of administration of a 50 mg dose to the 8 volunteers of cohort 5;
- Date of onset of the symptoms in one of the volunteers in the cohort – hospitalisation of this volunteer in the evening.

Monday 11 January 2016:

- The 7 other volunteers of cohort 5 receive the 6th treatment dose in the morning;
- MRI on the hospitalised volunteer whose clinical condition became worse (coma);
- Discontinuation of the clinical trial by agreement between the sponsor and BIOTRIAL.

Between Wednesday 13 and Friday 15 January 2016:

Hospitalisation of the 5 other volunteers of cohort 5 treated with the verum.

Thursday 14 January 2016:

ANSM is informed by BIOTRIAL of the occurrence of serious adverse events in the trial.