European Investment Bank (EIB) Luxembourg, 20 December 2018

Environmental and Social Completion Sheet (ESCS)

Overview

Project Name:	BIAL INOVACAO RDI II
Project Number:	2015-0078
Country:	Portugal

Project Description: Funding of BIAL Group's R&D-activities, with a focus on drugs for epilepsy, cardiovascular and Parkinson's diseases, covering the period 2015-2017.

Summary of Environmental and Social Assessment at Completion

EIB notes the following key Environmental and Social outcomes at Project Completion.

The project concerns investments in research and development that have been carried out in existing facilities without changing their already authorised scope. An Environmental Impact Assessment (EIA) was therefore not required by Directive 2011/92/EU. The Promoter has an integrated environmental management policy and effective operating procedures in place which are in line with industry standards.

In the framework of the project, Bial was developing BIA 10-2474, a drug with potential for the treatment of a range of different medical conditions such as pain relief, anxiety disorders, and movement disorders. A Phase I first-in-human clinical trial with this drug was underway in Rennes, France, in January 2016, when serious adverse events occurred affecting six participants, including the death of one man. The trial was conducted by the French contract research organisation (CRO) Biotrial on behalf of Bial. The trial had been approved by the regulatory authority, the Agence Nationale de Sécurité du Médicament (ANSM), on 26 June 2015, and by the Brest regional ethics committee on 3 July 2015.

Immediately after the tragic incident, Bial suspended the clinical trial and subsequently abandoned the development of the concerned molecule. The incident has been investigated by the ANSM through a Temporary Specialist Scientific Committee (CSST) and by the Inspection générale des affaires sociales (IGAS) commissioned by the French Ministry of Health. A judicial investigation against unknown persons for involuntary manslaughter and involuntary injury was also initiated by the Office of the Chief Prosecutor of Paris to determine whether criminal deficiencies contributed with certainty to the death and injury of the victim or if the facts fall under the scientific risks. The judicial investigation is still ongoing and the conclusions of said investigation have not yet been made public.

The final report from the ANSM Committee (CSST) appointed to investigate the matter concluded in April 2016 that the most likely hypothesis to date is that of toxicity specific to the molecule via its binding to other brain cell structures, facilitated by (1) its low specificity for its target enzyme; (2) use of multiple doses a lot higher than those leading (at least in humans) to complete and lasting FAAH[1] inhibition and; (3) its probable gradual accumulation in the brain, undoubtedly related to the specific pharmacokinetic features of BIA 10-2474. The

[1] Fatty Acid Amide Hydrolase

European Investment Bank (EIB) Luxembourg, 20 December 2018

Committee made recommendations to European and International regulators with the aim to improve the conduct of future trials.

In July 2017, the European Medicines Agency (EMA) issued a new guideline for first-in-human clinical trials, aiming to address risks posed by complex trials, such as the one undertaken in Rennes. The new guideline that took effect in February 2018 emphasises that drug developers must perform comprehensive preclinical tests of a new compound, including how it binds to its target and whether it has so-called off-target effects. EMA also provides more detailed guidance on dosing and how to monitor subjects' safety. Trial sponsors need to have strategies to minimise risks at every step and have to deal with adverse events timely and adequately.

The Promoter has been cooperating with the Bank to allow the close monitoring of any further developments regarding the incident and has also shared all studies conducted since January 2016 and the list of publications and presentations to date.

Summary opinion of Environmental and Social aspects at completion:

EIB is of the opinion based on reports from the promoter, that the Project has been implemented in line with EIB Environmental and Social Standards, applicable at the time of appraisal.