

Amendment – Section VIII.D

Scientific Studies and Analyses

Clinical Studies

This amendment provides additional information to VIII.D.4.vii of 22nd Century Group Inc.'s PMTA; STNs PM0000491 and PM0000492 and MRTPA; STNs MR0000159 and MR0000160.

Reason for Amendment: On an August 2, 2019, teleconference with the FDA, the Agency requested additional information on the Significant Adverse Event (SAE).

Confidentiality: A version with proposed redactions is also being submitted.

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VIII. Scientific Studies and Analyses

D. Clinical Studies

4. Adverse Events

- vii. *A Longitudinal Ambulatory Study to Assess Changes in Cigarette Consumption Behavior and Biomarkers of Exposure during a 6-Week Switch to Very Low Nicotine Cigarettes (NCT03571724).*

A 51-year-old female, subject 001023, experienced a subarachnoid hemorrhage after study completion. She initiated use of non-mentholated (regular) VLN cigarettes on August 2, 2018 and completed usage on September 14, 2018. She was scheduled for a follow-up call on September 21, 2018. On (b) (6) she was admitted to the hospital after suffering severe headache and a syncopal episode. The event was reported to Celerion on September 17, 2018 (Attachment 1) and the sponsor's representative ((b) (6), (b) (4)) was notified on that date (Attachment 2). The medical monitor, Natascha Fladischer, concluded that this was a Significant Adverse Event (SAE) (Attachment 3). A follow-up report on the SAE was recorded on September 21 (Attachment 4) assigning the causality as unlikely. Assign DMB, the medical monitor company,

created a narrative (Attachment 5) on September 21, 2018. The subject made a complete recovery.

Attachment 1 contains the SAE Report form from Celerion. The event was described as follows: "Based off medical records received on November 14, 2018, subject presented to ER with a history of severe headaches, syncopal episode, nausea and vomiting on (b) (6). A CT showed a large subarachnoid hemorrhage and a CT angiogram showed an aneurysm of the right internal carotid artery. An external ventricular drain (EVD) was placed and subject underwent coil embolization of a right supraclinoid internal cerebral artery aneurysm. Symptoms improved, the EVD was weaned and subject was discharged to home on October 2, 2018 and remained symptom free." The SAE was assessed as unrelated since the event of subarachnoid hemorrhage was due to a rupture of right internal cerebral artery aneurysm (Attachment 6). The subject returned to the site on October 10, 2018 to sign a medical release form. Dr. Mathew concluded that the SAE had been resolved (Attachment 7), and Assign DMB created a narrative (Attachment 7-1). A clarification follow-up SAE report was created on October 18 (Attachment 8), along with a narrative by Assign DMB (Attachment 8-1). The SAE was considered closed by the sponsor on November 20, 2018 (Attachment 9). The SAE was assessed as unrelated since the event of subarachnoid hemorrhage was due to a rupture of the right internal cerebral artery aneurysm (Attachment 6).

A copy of the subject's hospital records may be found in Attachment 10.