A Brief Overview/Summary on the status of the Cidofovir Post-Authorisation-Safety-Study (PASS) initiated by the European Medicines Agency (EMA)- Final Annual Report on Study Progress

The European Medicines Agency (EMA) informed Marketing Authorization Holder (MAH) Tillomed Laboratories Ltd (herein after referred as Tillomed) in the third quarter of 2017 to register into the EU PAS Register for a Post Authorisation Safety Study (PASS) of the product Cidofovir: **EUPAS33124**. EMA requested Tillomed to conduct a PASS of Cidofovir to identify the indications and patient populations for the use of Cidofovir, as well as to evaluate patterns and compare rates of adverse events occurring in the on-label group with events occurring in the off-label group, and to assess patient outcome following treatment in the specified indication. Countries involved in this joint PASS are the United Kingdom, Germany, Belgium and Spain.

On 10th August 2018, Tillomed submitted the protocol version 1.0 to the EMA for approval and the protocol version 1.0 was approved by the EMA on 13th June 2019. PASS protocol Version 2.0 was prepared to update the annexes and milestones and this protocol version 2.0, dated 10-May-2021 was further approved by EMA on 02-Sep-2021.

Milestones that are outlined in latest approved protocol are shown below:

Milestone	Planned date	Comment
Registration in the EU PAS register	Q4 2018	Last updated on 03-Aug-2023
Start of data collection	End of Q1 2019	The data collection will be initiated within 6 months of the protocol being approved
Interim Report	Nov-2021 and annually thereafter	-
End of data collection	31-Aug-2024	-
Study progress/Annual report	Annual submission by 30th November of every year	-
Final report of study results	30-Nov-2024	-

In parallel to the protocol being approved, a website was developed by Tillomed as described in the approved protocol and implemented for the sole purpose of healthcare professionals being able to register patients who have been prescribed Cidofovir onto the study after the patient had provided their informed consent in all member states. The website went live in August 2019.

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In order to inform and encourage healthcare professionals to register their interest onto the study an initial dissemination of the educational materials (in the form of protocol synopsis) was initiated. Country wise status can be found in the table below:

Countries	**Dissemination Status**
United Kingdom	Dissemination done in July 2019 and again in November 2019 From Feb-2024 till Aug-2024, cover letter and synopsis were disseminated with each Cidofovir pack via distributor.
Germany	Dissemination done in November 2019.
Spain	No dissemination done.
Belgium	Cidofovir is not yet marketed, therefore no dissemination.

As per approved protocol, total sample size of 2951 patients was proposed and data collection end date was 31-Aug-2024. However, no patients could be recruited until Aug-2024.

In 2023 company decided to initiate feasibility study first to understand that if this study could be completed with the existing process in protocol or not. Tillomed submitted this feasibility report to National authorities on 07-Sep-2023 as well as EMA PRAC on 18-Sep-2023 for their

further advice. BfArM suggested to submit the feasibility report via type II variation category C.I.z. BfArM also advised to seek a work sharing procedure, which includes both DE/H/6139/001 and FI/H/1060/001 in order to get a harmonized assessment. Type II work-sharing application (DE/H/xxxx/WS/1581) was then submitted by Tillomed on 29-Dec-2023. Based on the feasibility report, the RMS concluded that conduct of the study according to the approved PRAC protocol in version 2.0 dated 10-May-2021 is likely not feasible. During evaluation of procedure as asked by authority Tillomed provided two commitments. Namely, one commitment to submit a protocol amendment for the imposed category 1 Cidofovir PASS with regards to an "Exposure Registry Study" and another commitment to prepare a feasibility exercise to identify appropriate European, United States and Canadian data sources for a drug utilisation study based on healthcare claims data. Tillomed also provided assurances that this feasibility exercise will be submitted together with the amended PASS protocol and coordinated with the PRAC Rapporteur for the Cidofovir PASS protocol. The work-sharing procedure was closed on 17-Aug-2024. Tillomed contacted PRAC Rapporteur on 29-Jul-2024 to inform that Tillomed is working with CRO IQVIA for preparation of feasibility of Drug Utilisation study (DUS) model and updated PASS protocol and based on current estimation of this project duration, Tillomed had proposed a submission date for this as 31-Dec-2025. Response from PRAC Rapporteur was received on 04-Sep-2024 wherein by they accepted the proposal.

The PASS study as per current protocol has ended in Aug-2024 and Tillomed also informed PRAC rapporteur that the final study report as per PASS protocol 2.0 shall be submitted before Nov-2024. MHRA was also notified about this on 21-Aug-2024.

Hence this is the final study report and Tillomed had stopped all activities mentioned in study protocol v2.0. Now Tillomed will continue study as per updated protocol with new study design after authority approval.

Reviewed by:
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