Priftin®: sNDA submission in progress

- **FDA e-submission on May 30, 2014:**
  - eCTD + data sets CDISC converted
  - Claimed new indication: Treatment of LTBI in combination with INH (3RPT/INH once-weekly regimen) in patients > 2 years at high risk of progression to TB disease.

- **FDA agreement for a priority review designation on July 9, 2014:**
  - Application sufficiently complete for a substantive review
  - The user fee goal date is **November 30, 2014 (D180)**

- **Process of Questions/Answers**
Priftin®: 3HP regimen assessed in other studies

● **iAdhere Study (TBTC S33)**
  - **International multicenter, randomized clinical trial comparing**
    - Control arm → 3HP by DOT
    - Investigational arm 1 → 3HP by SAT
    - Investigational arm 2 → 3HP by enhanced SAT
  - 1,002 participants enrolled. Analysis is in progress.

● **Investigator Sponsored Trials**
  - Taiwan - United Kingdom - Australia

● **Dossier to be submitted for registration outside US**
  - RSA – Taiwan - Latin America - Europe
Priftin® in active TB: an upcoming phase 3 trial

- **Public/private collaboration**
  - CDC-TBTC with ACTG partnership
  - Principal investigators Susan Dorman, JHU and Payam Nahid, UCSF
  - **Sanofi** member of the study team, provider of ALL study drugs

- **Towards a shortened regimen for an international, multicenter, randomized, controlled, open-label, 3-arm phase 3 non-inf. trial**

- **Primary Endpoints:**
  - Efficacy: TB disease-free survival at 12 months after study treatment assignment.
  - Safety: Proportion of participants with grade 3 or higher adverse events during study drug treatment
S31 design

Primary objectives:

- To evaluate the efficacy of a RPT-containing regimen to determine whether the single substitution of P for R makes it possible to reduce to 17 weeks the duration of treatment for DS pulmonary TB.

- To evaluate the efficacy of a RPT-containing regimen that in addition substitutes M for E and continues M during the continuation phase to determine whether it is possible to reduce to 17 weeks the duration of treatment for DS pulmonary TB.
Interaction Priftin™ /Atripla™

**DDI Atripla™/Priftin™**

- Open-label, randomized, 2 periods, parallel groups,
- PK-DDI study, repeated doses in HIV infected volunteers (otherwise healthy) receiving chronic Atripla (CD4>350)

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Atripla™

3 weeks Screening Atripla™

2 weeks Period 1 Atripla™

3 weeks Period 2 Atripla™ +Priftin™

EOS

3-5 days after last dose of RPT

Cohort 1: Priftin™ daily regimen: 15mg/kg OD for 21 days

Cohort 2: Priftin™ weekly regimen: 900mg OW (3 weekly administrations)
Interaction Priftin™/Atripla™: results

- Co-administration of 1 tablet per day of Atripla™ with a single 15 mg/kg dose of RPT
  - No change in steady state efavirenz exposure ($C_{\text{min}}$, $C_{\text{max}}$, AUC$_{0-24}$ and AUC$_{0-10}$) compared to ATRIPLA administered alone.

- Co-administration of 1 tablet per day of Atripla™ with daily 15 mg/kg dose of RPT for 21 days
  - Decrease in steady state efavirenz exposure: 17% for $C_{\text{max}}$, 37% for $C_{\text{min}}$ and 33% for AUC$_{0-24}$.
  - The magnitude of this interaction between efavirenz and RPT could be considered as modest taking into account the observed high inter-subject variability of efavirenz exposure (CV% on AUC$_{0-24}$ ranged from 77 to 85%).
  - The co-administration was well tolerated and no clinically significant changes of CD4 cell counts or viral loads were observed.
Update on Industrial Activities

August

- Week 34
- Adult FDC Tech. lot
- Adult FDC analyses Tech. lot

September

- Week 35
- Adult FDC GMP lot
- Adult FDC pk biopharm Evaluation - Tech. lot
- WDT FDC Tech. lot

- Week 36
- Adult FDC packaging & Release - GMP lot
- WDT FDC analyses Tech. Lot (incl. Biopharm)

- Week 37
- Adult FDC shipment GMP lot
- WDT FDC GMP lot
- WDT FDC Packaging & release GMP lot

- Week 38
- WDT Rif. Only GMP lot
- WDT Rif. Only Packaging & release GMP lot

- Week 39
- WDT FDC
- Rifapentine only
- Manufacturing steps
- Analyses & release

- Week 40
- WDT FDC
- Rifapentine only
- Manufacturing steps
- Analyses & release

- Week 41
- WDT FDC
- Rifapentine only
- Manufacturing steps
- Analyses & release

- Week 42
- WDT FDC
- Rifapentine only
- Manufacturing steps
- Analyses & release

- Week 43
- WDT FDC
- Rifapentine only
- Manufacturing steps
- Analyses & release

- Week 44
- WDT FDC
- Rifapentine only
- Manufacturing steps
- Analyses & release

CPTR meeting - Washington 24 Sep 2014  I.Cieren-Puiseux | 8
Film coated FDC 300/300 for LTBI: Bioequivalence study to be performed

- Open label, randomized, cross-over and safety study comparing
  - 1 FDC tablet RPT 300/INH 300
  - standalone formulations of 2 drugs administered concomitantly at the same dosage ie 2 Priftin tablets 150mg + 1 INH tablet 300 mg
  - in healthy male and female subjects

- 46 PK evaluable subjects

- Tentative timelines:
  - Mid-November 2014: Clinical supplies ready
  - Study start: as soon as approvals obtained
  - Completion/results of the study by 3 months later
TB Vaccine

The only TB vaccine (BCG) used in the world today was developed over 80 years ago. Sanofi is one of several manufacturers that produce and distribute BCG.

- A TB vaccine is critical in areas of the world where TB is highly prevalent and the chances of an infant or young child becoming exposed to an infectious case are high.

- Although BCG is effective in protecting infants against childhood forms of the disease, a more effective vaccine is needed for protection of adolescents and adults against pulmonary TB.

In 2008, Sanofi Pasteur signed a collaborative agreement with Denmark’s Statens Serum Institut to develop a new TB vaccine.

- Enrollment in the Phase I clinical trial was completed in 2008 and analysis of the clinical samples is ongoing.
Sanofi Pasteur, in collaboration with Aeras, is currently conducting two clinical studies with H4:IC31 TB vaccine candidate:

- **Phase I/II DR finding study in South Africa to assess safety and immunogenicity when administered in an EPI vaccination schedule.**
  
  Initiated in July 2013, Interim results are expected 2H 2014, with additional results in 2015 and final study report in 2017.

- **Phase II study to evaluate TB prevention in young adolescents in South Africa.**
  
  Initiated in February 2014, this study intends to provide proof-of-concept to inform initiation of an efficacy study. Preliminary results are anticipated late 2015 with study report scheduled for 2017.

The immune-response profile elicited by the vaccine is believed to be protective against TB and safe when administered in close timing proximity to BCG.
THANK YOU