2023 INVESTIGATOR MEETING & ANNUAL WORKSHOP

Seattle, Washington
FEBRUARY 18, 2023

leap

Long-Acting/Extended Release
Antiretroviral Research Resource Program

ABBREVIATIONS

Ab Antibody
ACTG AIDS Clinical Trials Group
ADME Absorption, distribution, metabolism, elimination
AE Adverse event
AfroCAB African Community Advisory Board
AIDS Acquired immunodeficiency syndrome
API Active pharmaceutical ingredient
ART Antiretroviral therapy
ARV Antiretroviral
ATLAS Antiretroviral Therapy as Long-Acting Suppression
AUC Area under the curve
AVAC AIDS Vaccine Advocacy Coalition
B or BIC Bictegravir
BDQ Bedaquiline
bHIV Background HIV
BioPIV Biomedical Prevention Implementation Collaborative
BMI Body Mass Index
bNAb Broadly neutralizing antibody
CAB Cabotegravir
CMO Contract Manufacture Company
CELT Centre of Excellence in Long-acting Therapeutics
cGLP Current good laboratory practices
cGMP Current good manufacturing practices
CHAI Clinton Health Action Initiative
CMC Chemistry, Manufacturing and Controls
COGs Cost of goods
CRO Clinical Research Organization
CYP Cytochrome P450
DAIDS Division of AIDS
DcNP Drug Combination Nanoparticles
DDI drug-drug interaction
DOR Doravine
DTG Dolutegravir
DSD Differentiated Service Delivery
EC50 Effective concentration 50%
EMA European Medicines Agency
ER Extended Release
ETR Etravirine
ETV Entecavir
FDA Food and Drug Administration
FIH First in human
F or FTC Emtricitabine
GBGMC Global Black Gay Men Connect
GLAD Global Long-Acting Drugs project
HBV Hepatitis B virus
HCV Hepatitis C virus
HIV Human immunodeficiency virus
HPTN HIV Prevention Trials Network
IC50 Inhibitory concentration 50%
IC90 Inhibitory concentration 90%
ID Intradermal
IM Intramuscular
IMPAACT International Maternal, Pediatric, Adolescent AIDS Clinical Trials
IND Investigational New Drug
INH Isoniazid
INSTI Integrase strand transfer inhibitor
IRB Institutional review board
ISFI In-situ forming implant
ISL Islatravir
ISR Injection site reaction
IV Intravenous
JHU Johns Hopkins University
LA Long-acting
LAI Long-acting injectable
LaPaL Long-acting technologies Patents and Licences database
LEAP Long-acting Extended-release Antiretroviral research resource Program
LEN Lenacapavir
LLOD Lower level of detection
LMIC Low-middle income country
LMNC Lymphoid mononuclear cells
LPV Lopinavir
MAP Microneedle array patch
MIC Minimum inhibitory concentration
MN Microneedle
MOH Ministry of Health
MPP Medicines Patent Pool
MR Modified release
Mtb Mycobacterium tuberculosis
NHP Non-human primate
NK Natural killer
NRTI Nucleoside reverse transcriptase inhibitor
NRTTI Nucleoside reverse transcriptase translocation inhibitor
OBR Optimized background regimen
OLI Oral lead in
PBMC Peripheral blood mononuclear cell
PBPK Physiology-based pharmacokinetic
PD Pharmacodynamic
PK Pharmacokinetic
PLGA Polylactic-co-glycolic acid
PLWH Person living with HIV
POC Point of care
PrEP Pre-exposure prophylaxis
QALY Quality-adjusted life year
R&D Research and development
RBT or RFB Rifabutin
RPT Rifapentine
RIF Rifampicin
RLS Resource-limited setting
RPV Rilpivirine
RTV Rotinavir
SAD/MAD Single/Multiple ascending dose
SC subcutaneous
SD subdermal
SDT Single-dose tablet
SOC Standard of Care
SR Sustained release
SVR Sustained virologic response
TAF Tenofovir alafenamide
TAG Treatment Action Group
TB Tuberculosis
TDF Tenofovir disoproxil fumarate
TFV Tenofovir
TGM Transgender man
TGW Transgender women
TLC-ART Targeted Long-acting Combinational ARV Therapeutic
TLD Tenofovir, lamivudine, dolutegravir
UNMC University of Nebraska Medical Center
VL Viral load
VS Virologic suppression
WHO World Health Organization
3TC Lamivudine

CONTENTS

OVERVIEW 4

OPENING REMARKS 5

PLENARY SESSION I Updates on Existing Technologies 6-12
- William Spreen, ViiV Healthcare – LA/ER CAB and RPV 6
- Jay Grobler, Merck & Co – ISL development 7
- Martin Rhee, Gilead Sciences – LEN 8
- David Margolis, Brii Biosciences – LA oral single-tablet regimen 9
- Simone Perazzolo, PBPK model for TLC-ART platform 10
- Ryan Donnelly – Update on transcutaneous MNs for ARV delivery 11
- Imelda Mahaka – Increasing access to LA formulations 12

PLENARY SESSION II Novel Technologies & Approaches 13-18
- Rodney Ho – TLC-ART Program updates 13
- Andrew Owen – Update from LONGEVITY project 14
- Vikram Arya – Conversion of approved oral ARV to LA formulation 15
- Kimberly Struble – Oral lead-in and LA ARV development 16
- Lasse Leino, DelSiTech – Silica-based platform for LA drug delivery 17
- Martina Kovarova – In-situ forming implants for TB 18

FOCUS GROUPS 19-27
- Overview 19
- Focus Group 1 – Lessons learned from ISL toxicity 20-21
- Focus Group 2 – Developing LA treatments for HCV 22-23
- Focus Group 3 – Developing LA therapeutics for TB 24-25
- Focus Group 4 – Commercial manufacturing of generic formulations 26-27

ANNEX A Focus Group Participants 28

Where will we LEAP next?

On February 18, 2023 clinicians, investigators, developers, community advocacy groups, not-for-profit institutions and regulatory authorities convened in-person and virtually for the annual LEAP Investigator Meeting and Workshop. The structure was the same as the previous two years. But this year, the atmosphere was particularly emotional, having the opportunity to be together in the same room after three or four years. Opening remarks from Drs Carl Dieffenbach and Charles Flexner were followed by two plenary sessions comprising updates on existing technologies and presentations on novel technologies and approaches. Presentations were 10 minutes. Four focus group discussions were held in advance of the meeting. These 90-minute sessions are intended to foster informative and provocative discussions on timely topics strategically selected to help collectively advance the long-acting field. This report summarizes the plenary session presentations and each focus group discussion.

Keynote

Carl W. Dieffenbach Director of DAIDS, NIAID at NIH

"LEAP facilitates development of new and existing compounds because our knowledge base is so much greater… each new product that has been conceived and developed teaches us something new."

Dr. Dieffenbach began with a proud announcement

In December 2022, injectable Cabotegravir for HIV prevention received a Grade A from the US Prevention Services Task Force, making it eligible for coverage by health plans under the Affordable Care Act.

He grounded the meeting, restating the potential for LA formulations to improve outcomes in chronic diseases and vulnerable populations through more even drug levels, which improves safety and minimizes side effects, and through supported medication adherence with longer dosing intervals and reduced stigma/privacy issues vs daily pill-taking. He acknowledged LA development as a complex and slow process with significant financial and scientific risks and emphasized LEAP's role. Centralizing and sharing information facilitates solutions to common problems and accelerates development – we learn from each success and failure. He concluded with future challenges: LA formulations for chronic diseases relevant to PLWH (single-dose hepatitis C virus cure and LA TB treatment); Progress in HIV should seed and facilitate more streamlined development in other fields; and Development of rules to guide medicinal chemistry and avoid rapid clearance and inherent long-term toxicities due to chemical structure.

Welcome

Charles Flexner Principal Investigator of LEAP

"For decades we have been saying in HIV… why isn't there one place you can go to know where an individual drug or formulation sits in clinical development, and today we have this for LA formulations."

2022 was another productive year

- **Supplement on LA in Clinical Infectious Diseases** published December 1, 2022 – a special thank-you to David Thomas and Susan Swindells (co-editors) and Jane McKenzie-White (editorial organizer).
- **Integrated Compounds Database** released within the LAPaL website *www.LAPaL.ch*. (MPP) – the online compound landscape includes a Compounds link to individual drugs and an Interactive visualization dashboard showing the stage of clinical development (brainchild of A. Olagunju and colleagues at Univ of Liverpool). Features include a list of all clinical studies for a particular drug and indication; color-coded clinical trials timeline; list of studies with a link to *clinicaltrials.gov* number, enrollment, and status; and a global summary of regulatory filings on a map and color-coded according to status.
- **LEAP publications.** Review on LA formulation development and implementation for PrEP; Cost-effectiveness analysis of LA Cabotegravir in LMICs; and Survey of patient preferences for LA formulations for HCV.

Where we are going in 2023

- Ongoing collaboration with two large UNITAID programs developing drugs for Phase I studies in HIV, TB, and HCV; Publish first systematic review of LA/ER ARVs in children, adolescents and pregnant women.
- Expand LAPaL Intellectual Property and Integrated Compounds Databases.
- Expect increased support for clinical development of new LA formulations for HIV, TB, and viral hepatitis; and Continued demand for the modelling and simulation core service headed by Andrew Owen at Univ of Liverpool.
- On July 1, 2023 LEAP will enter year 4 of a 5-year grant – began discussions about the possibility of renewal and priorities going forward.

PLENARY I

William Spreen Director of R&D and Medicine Development leader for CAB at ViiV Healthcare

"Current status of LA/ER Cabotegravir and Rilpivirine including a pipeline report on novel formulations"

Investigating self-injection, longer dosing intervals, and new combinations

Progress in CAB LA for HIV PrEP.

- Four regulatory approvals (US, Australia, Zimbabwe, and S Africa).
- Multiple submissions under active review (EMA, Brazil, and sub-Saharan African countries).
- WHO issued guidelines for use.
- At-risk individuals >35kg, optional OLI, no contraindication in pregnancy or lactation, HIV testing via RNA-based test at initiation in US or per national guidelines elsewhere.

HPTN-083 (MSM/TGW) and HPTN-084 (cis-women) illustrate staying power of LA HIV prevention.

- CAB LA has greater efficacy than oral TDF/FTC with consistent hazards reductions in incident HIV infection across blinded and unblinded phases.
  - ◊ 66% risk reduction in HPTN-083 (CROI 2022) and 89% risk reduction in HPTN-084 (AIDS 2022).
- ViiV and Medicines Patent Pool signed a voluntary licensing agreement in July 2022.
  - ◊ Selected generic manufacturers can supply CAB LA for PrEP in 90 countries.
- Multiple oral presentations at CROI 2023.
  - ◊ Susan H Eshleman et al. The LEVI syndrome: characteristics of early HIV infection with cabotegravir for PrEP.
  - ◊ Mark A Marzinke et al. Cabotegravir pharmacology in the background of delayed injections in HPTN 084.
  - ◊ Hyman Scott et al. Cabotegravir for HIV PrEP in US Black men and transgender women who have sex with men.
  - ◊ Sybil Hosek et al. CAB LA for HIV prevention in African cisgender female adolescents (HPTN 084-01).

Bi-monthly LAI CAB+RPV for HIV treatment.

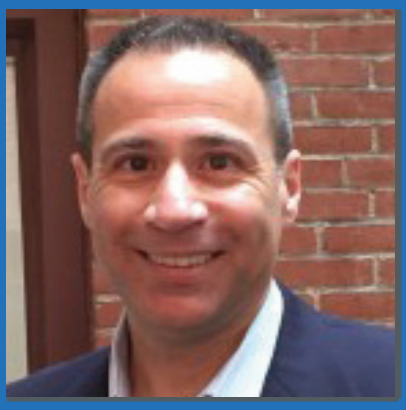
- SOLAR Study.
  - ◊ Phase 3b open-label RCT of CAB+RPV IM Q2M with and without OLI vs oral BIC/FTC/TAF QD for 12 months.
  - ◊ Metabolic endpoints are change in: BMI category; waist and hip circumferences; waist-to-height ratio; waist-to-hip ratio; and proportion with insulin resistance or metabolic syndrome.
  - ◊ CROI 2023 – **Moti N. Ramgopal et al.** Randomized switch trial of CAB + RPV LA vs oral B/FTC/TAF; **Darrell HS Tan et al**. Weight and metabolic changes with cabotegravir + rilpivirine long-acting or bictegravir.
- ATLAS-2M.
  - ◊ Phase 3b sub-study of CAB+RPV via IM thigh injection in virologically suppressed PLWH.
  - ◊ CROI 2023 – **Franco Felizarta et al**. Thigh Injections of CAB + RPV in Virally Suppressed Adults with HIV-1.

New opportunities to extend dosing intervals beyond Q3M.

- Novel double-concentrated CAB400 mg/mL formulation.
  - ◊ Phase I healthy volunteer study (212482) – CAB400 (multiple doses and routes) vs approved CAB200 (AIDS 2022).
  - ◊ Similar safety profile – Grade 1-2 ISRs common and short-lived.
  - ◊ Unexpected higher CAB400 absorption rate– higher C_{max} and shorter terminal half-life. Plasma concentrations within the range of CAB200 regimens, regardless of route.
  - ◊ **CAB400 practical for Q1M dosing, but dose/volume impractical for longer intervals**.
- rHuPH20-facilitated administration.
  - ◊ Halozyme's recombinant hyaluronidase temporarily expands the SC space (24-48 hrs) to allow larger injection volumes.
  - ◊ ViiV-Halozyme studies evaluate rHuPH20 with multiple HIV therapeutic targets (INSTIs, NRTIs, Capsid Inhibitors, bNAbs).
  - ◊ Study 218012 (NCT05418868) – safety and PK of CAB200 and novel CAB400 formulations (multiple doses and administration routes) with and without rHuPH20; no OLI required.

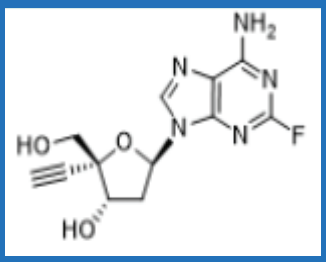
Other LA initiatives.

- Self-administration.
  - ◊ FLAIR sub-study LA CAB + RPV SQ to assess safety, tolerability, and PK in participants experienced with CAB+RPV LA via gluteal IM dosing (NCT02938520).
- Longer SC dosing intervals.
  - ◊ CAB + RPV LA SC in healthy participants (with Janssen).
- Other LA regimens.
  - ◊ ACTG 5357 Study of CAB LA + VRC07-523LS for HIV suppression (NCT03739996).
  - ◊ Upcoming study of CAB LA + bNAb N6-LS (VHC3810109).



Jay Grobler Associate Vice President of Infectious Diseases and Vaccines at Merck.

"Islatravir update: next steps for the Islatravir (ISL, MK-8591) program"



Comprehensive assessment of ISL toxicity has identified a pathway forward for LA oral ISL programs.

Background on Islatravir.

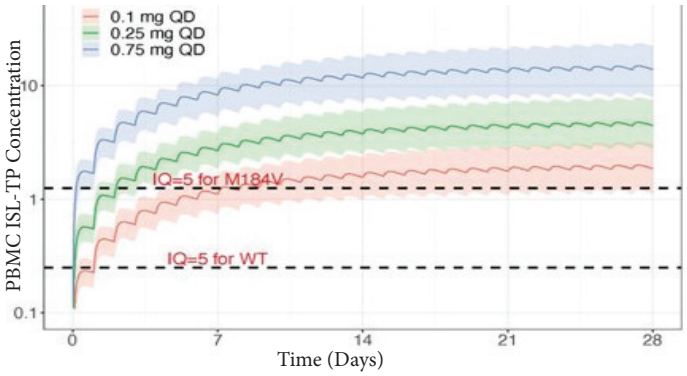
- Several Merck and joint ISL programs in 2021.
  - ◊ HIV treatment – daily and weekly oral and injectable 2-drug regimens.
  - ◊ HIV prevention – monthly oral and yearly implant as monotherapy.
- Full or partial FDA clinical holds across the ISL portfolio in Dec 2021.
  - ◊ Significant decreases in lymphocytes and CD4+ T-cells among participants receiving ISL in late-stage clinical studies.

Comprehensive assessment of the ISL lymphocyte effect was completed in 2022.

- Safety.
  - ◊ Magnitude of the effect is exposure-dependent – lower ISL doses are less likely to cause lymphocyte reductions.
  - ◊ Other hematologic cell lines are not affected.
  - ◊ No impact on incidence of infections.
- Mechanism.
  - ◊ Likely due to high intra-cellular ISL-TP exposures (or similarly high TP levels of other NRTIs), not mitochondrial toxicity.
- Lower ISL doses identified for daily (ISL+DOR) and weekly (ISL+LEN) oral HIV treatment.
  - ◊ Exposure-response models for lymphocytes and CD4+ T-cells found lower ISL doses with full efficacy and low to no risk of lymphocyte toxicity.
  - ◊ Unable to identify doses for monthly oral or injectable ISL formulations for HIV PrEP.

Phase 2 data and PK/PD modeling support ISL 0.25mg+DOR for daily oral HIV treatment.

- Phase 2b dose-ranging study (PN011) – QD oral ISL (0.25, 0.75, and 2.25 mg) + DOR (100mg) in treatment-naïve PLWH.
  - ◊ ISL 0.25mg maintained high virologic suppression through week 72; efficacy was comparable to higher ISL dose groups.
  - ◊ No ISL or DOR resistance variants were identified in any ISL dose group.
  - ◊ ISL 0.25mg could mitigate the lymphocyte effect – lymphocytes, CD4+ T-cells, CD8+ T-cells, B-cells, and NK cells were similar across ISL dose groups.
- Predictions from pooled PK/PD modeling of repeat daily dosing of ISL (0.1, 0.25, and 0.75 mg).
  - ◊ ISL 0.25mg will achieve therapeutic concentrations and CD4+ T-cell increases similar to comparators at week 48.



Programs for oral HIV treatment restarting in 2023 with lower ISL doses.

- P3 trials of QD ISL (0.25) + DOR (100) in virologically suppressed (VS) switch and ARV-naïve populations.
  - ◊ ISL/DOR vs baseline ART (051) in VS PLWH – open-label, randomized switch.
  - ◊ ISL/DOR vs BIC/FTC/TAF (052) in VS PLWH – blinded, randomized switch.
  - ◊ ISL/DOR vs BIC/FTC/TAF (053) in treatment-naïve PLWH – blinded, randomized.
  - ◊ ISL/DOR vs participants enrolled in earlier clinical trials (054) – single arm, dose de-escalation.
- P2 trial of QW ISL(2mg) + LEN in VS PLWH on daily BIC/FTC/TAF in the United States (PN045).
  - ◊ Primary endpoint is virologic failure at week 24.

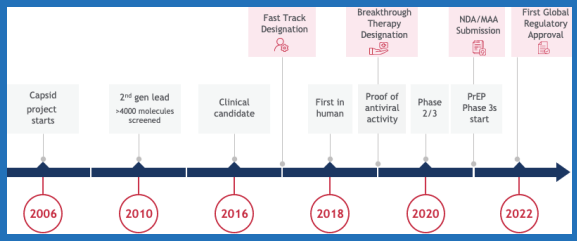
Summary and next steps.

- Comprehensive assessment of ISL toxicity identified lower ISL doses for oral QD and QW programs.
  - ◊ Daily P3 program will restart in 1Q2023.
  - ◊ Weekly P2 program restarted; first patient randomized in Feb 2023.
- Results from the P2 QD program and modelling work will be presented at CROI 2023.

PLENARY I

Martin Rhee Executive Director of Clinical Research at Gilead Sciences

"Current status of the Gilead LA/ER pipeline"



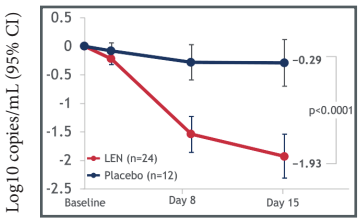
Gilead's Capsid Inhibitor project has been ongoing for more than 15 years.

LEN is the foundation of the LA portfolio.

- High potency (EC_{50}=100pM), multi-modal mechanism, no overlapping resistance with existing agents, excellent PK with long half-life, flexible dosing profile (oral or SC).
- Used in combination for HIV Treatment and as monotherapy for HIV Prevention.
- Weekly oral (300 mg t1/2= 12d) and Q6M SC dosing (927mg t1/2= 7 to 11 weeks) are feasible.

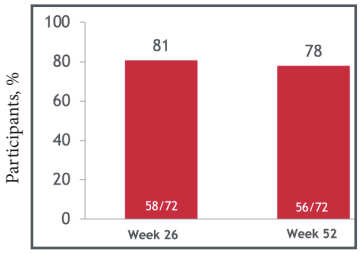
Early clinical data show LEN is potent and highly efficacious in people with multi-drug resistant HIV.

- P2 and P3 studies of LEN SC Q6M.
  - ◊ Functional monotherapy period x 14 days (QW oral LEN + failing regimen vs placebo+failing regimen vs QW oral LEN + OBR).
  - ◊ Maintenance Period x 52 weeks (LEN SC Q6M + OBR).
- Significant antiviral activity during the 14-day functional monotherapy period.



2-log$_{10}$ decline in VL
(oral LEN + failing regimen)

- High rate of virologic suppression (VL<50c/mL) achieved and maintained during maintenance period.



78% VS at 52 weeks
(LEN SC Q6M + OBR)

We are leveraging the efficacy and flexible LA profile of LEN to build a person-centric portfolio for LA HIV treatment.

- Studies of 2-drug regimens using oral and SC LEN (QD up to Q6M) in combination with diverse partner agents.
- Phase 2 study of oral LEN+ISL QW vs B/F/TAF QD in virologically suppressed PLWH.
  - ◊ Restarted screening using a lower 2mg ISL dose per US FDA.
- Proof of concept study for the first complete Q6M HIV treatment regimen.
  - ◊ Single-dose SC LEN + 2bNAbs (GS-5423 + GS-2872) in virologically suppressed PLWH.
  - ◊ Data presented at CROI 2023.
- P2/3 study of oral LEN + BIC QD in PLWH with a history of treatment failure, known resistance to ≥ 1 class of drugs, and virologically suppressed on a complex regimen.
  - ◊ potential as a simple, effective regimen in this population.
  - ◊ Enrollment complete.

Phase 3 studies evaluating LA LEN for HIV PrEP.

- PURPOSE 1 actively screening in South Africa and Uganda (sites with sufficient background HIV [bHIV]).
  - ◊ 5000 cis-gender adolescent girls and young women randomized 2:2:1 to LEN SC Q6M, oral F/TAF QD, and oral F/TDF QD (internal control).
  - ◊ Primary endpoint is LEN vs bHIV and F/TAF vs bHIV at 52 weeks.
- PURPOSE 2 actively recruiting in the US, Peru, Brazil, and South Africa (sites with sufficient bHIV).
  - ◊ 3000 cis-gender men, TGW, TGM, and gender non-binary individuals who have sex with men randomized 2:1 to LEN SC Q6M and oral F/TDF QD (internal control).
  - ◊ Primary endpoint is LEN vs bHIV at 52 weeks.

Presentations at CROI 2023.

- Eron J et al. Lenacapavir plus broadly neutralizing antibodies GS-5423 and GS-2872 for 6 monthly HIV-1 treatment.
- Hagins D et al. CALIBRATE LA LEN as comb treatment in treatment-naïve PWH, week 80 results.
- Obguabu O et al. CAPELLA LEN efficacy in heavily treatment experienced PWH at week 52.

David Margolis Vice President and Head of Infectious Diseases at Brii Biosciences

"Long-Acting ART programs"

Brii Biosciences
Breakthrough innovation & insight

Brii Biosciences is developing a weekly, oral single-tablet regimen for HIV treatment.

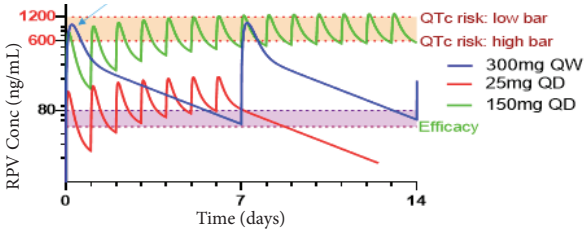
Overview of HIV program.

- Intended to support adherence and needs of PLWH who prefer an oral regimen over existing injectable LA ARV options.
- Weekly oral regimen for HIV treatment – P1 complete.
  - ◊ Modified-release (MR) LA RPV formulation (BRII-778).
  - ◊ Leverages relatively low RPV dose and long intrinsic $t_{1/2}$.
- Weekly low-dose tablet for HIV treatment and PrEP – initial P1 study complete.
  - ◊ Proprietary pro-drug formulation of EFdA (BRII-732).
  - ◊ Patent application published.
  - ◊ Clinical hold lifted for conduct of Phase 1 dose-finding study.

BRII-778 development hinges on achieving and sustaining target exposures within the safety window for RPV's known QTc effect.

- In silico human PK projections of QW BRII-778 (200 to 300mg) and QD RPV.

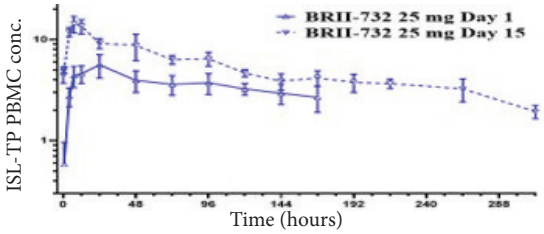
Goal: delay and blunt the C_{max} for QW dosing.



  - ◊ QW formulations may have a differential QTc effect due to relatively short time spent at Cmax compared to repeat QD dosing.
- Pre-clinical PK studies in dogs identified MR formulations with distinct in vitro dissolution profiles.
  - ◊ A21 (slow), A32 (intermediate), and A33 (fast) vs immediate-release RPV.
- Phase 1 SAD studies across selected formulations.
  - ◊ High doses of A3 achieve targets for QW dosing, but Cmax is above the QTc threshold.
  - ◊ Single 750 mg dose yielded Cmax> 700 ng/mL and maintained plasma RPV exposure above 60ng/mL at 1 week.
  - ◊ Generally safe and well-tolerated.
  - ◊ A concentration-dependent QTc effect was observed – no individuals met QTc stopping criteria.
  - ◊ Further optimization of the formulation is required.

BRII-732 is efficiently converted to EFdA (ISL) in vivo with comparable exposures, efficient intracellular uptake and safety profile.

- Phase I randomized, double-blind SAD (10mg to 200mg) and MAD (10mg and 25mg QW) of BRII-732 vs ISL in healthy volunteers.
  - ◊ Fast and efficient release of ISL from BRII-732 – no measurable systemic exposure to pro-drug with dosing up to 200mg.
  - ◊ Long half-life and dose-dependent PK.
  - ◊ Dose-dependent intracellular ISL-TP formation in PBMCs – long cellular $t_{1/2}$ and significant ISL-TP accumulation after three QW 25mg doses.



  - ◊ Well-tolerated at single doses up to 200mg and repeat doses up to 25 mg – no AEs > Grade 1 and no lymphocyte effect at 10mg and 25 mg QW.

Conclusions.

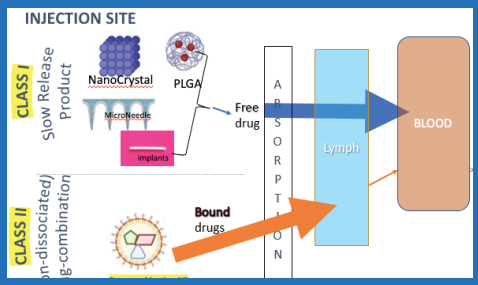
- QW oral dosing is important to provide options for PLWH.
- Further optimization of current BRII-778 formulations is required.
  - ◊ Unable to achieve sufficient C_{trough} exposures while remaining below the C_{max} required to minimize the QTc risk.
- Safety and PK data support further development of BRii-732 as part of oral weekly combination ART.
  - ◊ Phase I low-dose tablet study to begin 2Q2023 – dose will approximate daily ISL 0.25mg exposures (below threshold for observed lymphocyte toxicity).
  - ◊ A partner agent is required for a complete regimen for HIV treatment – in discussion with multiple companies across classes of agents.
  - ◊ Potential for use as monotherapy for HIV PrEP.

PLENARY I

Simone Perazzolo Modeling and Simulation

Scientist at the University of Washington

"PBPK modeling to Support a LA HIV Drug-combination formulation"



PBPK modeling is perhaps the best tool for assessing LA feasibility in humans.

TLC-ART platform (Class II) requires a different PBPK modeling approach than existing slow-release products (Class I).

- "Lag PK profile" of Class I products (e.g., LA CAB).
  - ◊ Nanocrystals, MNs, and implants are engineered to slowly and continuously release free drug from the injection site depot.
  - ◊ First Phase – free drug is released and quickly absorbed into the blood compartment.
  - ◊ Delay in treatment – requires time to achieve first peak therapeutic concentrations.
  - ◊ Key kinetic controller – slow release from the depot determines the LA profile.
- "No lag PK profile" of Class II non-dissociated drug-combination products (e.g., LA DTG in NHPs).
  - ◊ DcNPs (nanoparticles associated with a combination of ARVs) are formulated to remain stable. Physiochemical properties are not suited to stay at the injection site or directly cross into blood.
  - ◊ First Phase – bound drug is quickly absorbed into the lymph compartment. Sequential spread across lymph nodes exposes the whole lymphatic system to ARVs.
  - ◊ No delay in treatment – can achieve first peak therapeutic concentrations in 6 to 24 hours.
  - ◊ Key kinetic controller – slow release from the lymphatics determines the LA profile.

PBPK model in NHPs for SC TLC-ART 101 (DcNP containing LVP/RTV/TFV).

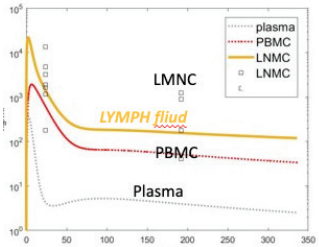
- Goals: explain LA mechanisms in NHPs; include elements of scaling to humans; feedback in formulation to optimize the fix-ratio for better LA; and evaluate feasibility in children.
  - ◊ Model 1 (free-drug mixture) – how the PBPK model needs to be adapted.
  - ◊ Model 2 (DcNP formulation) – the journey of NPs from the injection site, across the lymphatics, to the blood.
- Validated in NHPs – plasma (PBMCs), lymphatic system (LMNCs), tissues, etc.
- Validation using first-in-human (FIH) data would support scaling to humans and potentially children – we have approval to proceed.

PBPK modeling of TLC-ART 101 filled mechanistic knowledge gaps of our DcNP delivery system.

- Non-dissociated DcNPs remain bound during transit from the injection site to lymph nodes and are retained in the nodes for enhanced lymphocyte exposure.
- Modeling at 2 weeks (one half the interval dose).
  - ◊ High clearance rate at SC injection site (no depot) – fast absorption of DcNPs into the lymph nodes (70% of dose).
  - ◊ Low clearance rate at lymph nodes – excess DcNP enters the blood (30% of dose) with PBMC>plasma.
  - ◊ Intermediate clearance rate at blood – ARVs dissociate in the blood, and APIs are eliminated according to native clearance.
- IV administration of TLC-ART 101 in NHPs informs the PBPK model.
  - ◊ Useful for bioavailability considerations and to establish the in vivo association efficiency of the NPs (important to support scaling from in vitro to in vivo stability).

TLC-ART PBPK modeling can be used to "open the lymphatic system."

- Exposes all the nodes and provides time courses.
- Example of Protease Inhibitor (LA CAB) time course using axillary nodes collected from NHPs at necropsy.



Conclusions.

- PBPK modeling enabled us to fill knowledge gaps in the mechanisms of the TLC-ART delivery system (mono-clonal antibodies may have similar mechanisms).
- Published TLC-ART PBPK model supports DcNP development.
  - ◊ Offers lymphocyte and lymph node resolution, including traffic of lymphocytes in and out of the node.
  - ◊ Can track whether ARVs are free or bound to NPs at any timepoint.
- Clinical validation of the model will support formulation and dose selection for adults and PK scaling for children.

Ryan Donnelly Professor and Chair in Pharmaceutical Technology at Queen's University Belfast

"Update on transcutaneous microneedles for antiretroviral drug delivery"

Microneedles deposit nano-formulated drugs in viable skin layers for sustained release and absorption

Background.

- Desirable characteristics.
  - ◊ Avoid injections (enhance patient and HCW safety and patient acceptability); Support sustained drug delivery; Co-administration of several drugs is possible (suitable for HIV treatment and PrEP); and Self-application by patients is possible (no clinic visit).
- Formulation and application of LA ARV MAPs.
  - ◊ Load micron- and nano-particulate drugs at high concentration into aqueous gels; Cast into a mold and dry; Add adhesive and occlusive backing layer to form microarray patch (MAP).
  - ◊ Ideally baseplate should readily detach when MNs dissolve into skin for short wear time.

Pre-clinical PK studies of dissolving MNs for LA delivery of RPV, Etravine, CAB, and Bictegravir in rats.

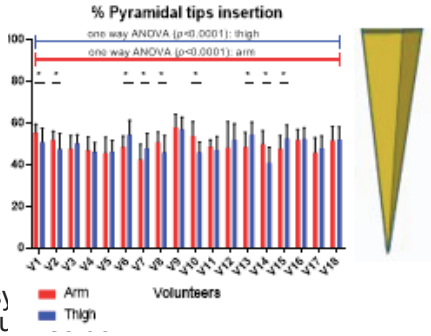
- SR for 28 to 56 days can be achieved.
- CAB MAP plasma levels were lower than CAB IM or ID, but above therapeutic targets, regardless of the formulation (free acid or sodium salt).
- Extrapolating from small animals to humans is challenging (flip-flop PK of most LA formulations).

PBPK modeling of MAP delivery of CAB and RPV for HIV treatment in children.

- Based on animal data and ex vivo skin deposition (in collaboration with PATH and Pharmetheus).
- Limited dosing interval in larger patients due to the patch size required to achieve therapeutic targets.
  - ◊ Smallest children (3 to <6kg) – QM dosing may be possible with a 14cm^2 patch for CAB and a 17cm^2 for RPV.
  - ◊ Patients ≥35 kg – QW dosing may be possible with 30 cm^2 patch for CAB and RPV (QM dosing would require a 119 cm^2 patch for CAB and 252 cm^2 for RPV).
- ARVs with higher potency may enable Q1M dosing in larger patients – two high potency HIV drugs have been recently evaluated.

Real-world usability of placebo MAP prototype with a feedback indicator for ARV delivery.

- MAP Prototype.
  - ◊ A series of smaller patches are mounted on a common backing (8 2.5cm^2-patches with 110 MNs each).
  - ◊ PATH developed a "bubble-type," removable applicator to provide visual and tactile feedback – depressed domes indicate sufficient MN insertion for drug delivery.
- 18 naïve MAP users actuated the prototype into simulated skin (8-layer parafilm applied to arm and thigh).
- Optical coherence tomography imaging measured MN insertion depth.
  - ◊ 50% of the length of the pyramidal tip was inserted into the simulated skin.
  - ◊ No variation based on location, gender, BMI, or age



- Users reported easy regarding successfu
- Implications.
  - ◊ All drug will need to be in that 50% of the tip length to ensure drug delivery.
  - ◊ For the two highly potent HIV drugs recently evaluated, this prototype should be sufficient for weekly and potentially monthly application for all patients, not just small children.

Considerations for next steps.

- Drugs studied to date are only suitable for weekly patch application in adults.
- PBPK modelling suggests feasibility of QM application in smaller children and QW in older children.
- Work with more potent drugs to enable longer duration of action or smaller patches than previous systems is promising.
- Macaque studies, clinical trials, and scalable manufacture.

PLENARY I

Imelda Mahaka Executive Director for Pangaea Zimbabwe AIDS Trust (PZAT)

"How do we increase access to LA formulations: a community perspective"

We cannot afford siloed conversations if we want to increase access to LA

Considerations to increase access to LA formulations from a community perspective.

- Community priorities.
  - ◊ Responsive to health needs, delivered in an acceptable manner, and results in better health outcomes.
  - ◊ Safety and ease of access (convenient, timely); affordability (access without financial burden); availability; and continuity of care.
- Leverage broad community engagement.
  - ◊ In the design, development and roll out of LA formulations.
  - ◊ Build mechanisms for ongoing participation to assess, adapt, and refine programs.
  - ◊ Fosters mutual respect, partnership, and accountability.
  - ◊ Advocates and civil society have driven the access agenda for CAB-LA (e.g., AVAC, AfroCAB, African Women Prevention Accountability Community Board, Sisterlove, GBGMC).
  - ◊ Bring various stakeholders into the discussion early in development (e.g., BioPIC, Coalition for LA-PrEP, WHO Think Tank).
- Choice matters.
  - ◊ Develop LA product options to meet the diverse needs and preferences of PLWH.
  - ◊ Learn from contraception – increased choice associated with increased persistence with chosen method; better health outcomes; and increased prevalence of contraceptive use (+12% for each additional method offered).

Understanding community needs and preferences for LA formulations and health care service delivery are key.

- Perspectives of PLWH – two meetings in Africa.
- HIV prevention and treatment advocates in Kampala (CHAI and Unitaid).
  - ◊ Strong preference for injectables (privacy and reduced stigma); questions arose about novel technologies (need to invest in advocacy and literacy to fill knowledge gaps); and there were groups that also preferred other methods.
- Peer-led meeting in Rwanda.
  - ◊ Interested in fewer clinic visits; preferred self-injections and self-administered options; LA viewed as a more discreet product form.

Differentiated service delivery models (DSD) – lessons from oral PrEP.

- Need for differentiated, simplified, integrated, and de-medicalized service delivery.
- Need to scale-up DSD models, replicate successful approaches, and prioritize those that help users access and stay on treatment.
- Build on models that have expanded due to COVID-19 (mHealth, multi-month dispensing, HIV self-testing), integrate PrEP and treatment with other services, and include peer/partner support interventions that are community led, accessible and non-discriminatory.

Cost of formulations and HIV testing protocols can be a barrier, especially in LMICs.

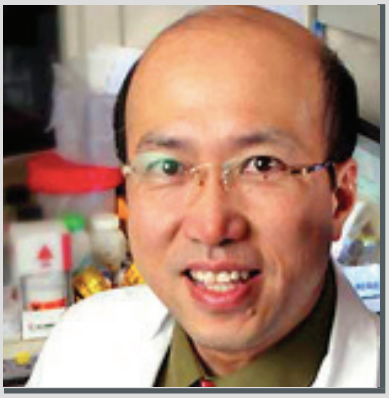
- Policymakers and funders generally base decisions on cost-effectiveness – the value of choice and reaching new users may be discounted when considering novel formulations.
- Negotiate licensing, patent pooling, and other IP agreements for better pricing – generic manufacturing can reduce price and increase product availability.
- Guidance on HIV testing protocols should balance safety and feasibility (e.g., impact on cost & feasibility of CAB).

Communities see the value in implementation research.

- Help with real-world programming and can guide funders, policymakers and other key decision makers.
- Communities are eager for earlier inclusion of pregnant and lactating women and adolescents in clinical trials – need a clear path of how to accomplish this.

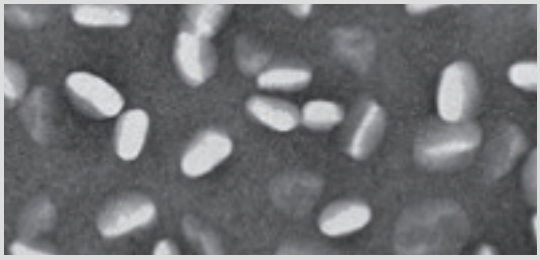
Conclusions.

- Fill product introduction gaps.
  - ◊ Communities need accelerated time from approval to introduction to impact.
  - ◊ Implementation studies to show how to deliver in real life.
  - ◊ Demand creation and program platforms.
  - ◊ Differentiated and integrated service delivery for treatment and prevention.
- Fill LA product development gaps.
  - ◊ Longer acting and event driven.
  - ◊ User-friendly and developed with users.
  - ◊ Dual-purpose and multi-purpose methods.



Rodney Ho Professor of Pharmaceutics and Engineering and Executive Director at WE-REACH

"Targeted Long-Acting Combination Antiretroviral Therapy (TLC-ART) program updates"



Can we introduce an HIV treatment program worldwide and knock out the virus?

TLC-ART Program from concept to initiating first in-human (FIH) studies for HIV treatment.

- HIV treatment indication chosen to advance U=U; uptake has also been considered; this work has been supported by public-private investment for 7-8 years.
- Discovery of DcNP technology enabled stable combination of 3 existing HIV drugs with incompatible properties.
- Determined how to assemble a stable product, simplified the manufacture process, and transferred to CMO.
- IND-enabling studies innovation leveraged known efficacy and safety profile of existing HIV drugs.
- Submitted IND application for HIV treatment indication to accelerate development.
  - ◊ Requires shorter, smaller studies than prevention (24 vs 48W).
  - ◊ Once sustained viral suppression is proven (1.5 to 2-log reductions sustained over 24 weeks), can move to prevention.

Leveraging TLC-ART 101 development and IND-enabling plans to inform TLC-ART 301 development.

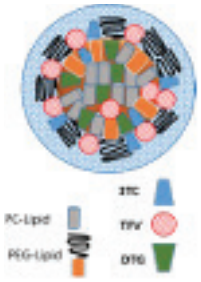
- Investigational New Drug status of TLC-ART 101.
  - ◊ 3 HIV drugs (TFV/LPV/r) in one self-administered SC injection.
  - ◊ Protease Inhibitor is useful for pediatrics and pregnant women, but HIV treatment has largely transitioned to integrase inhibitors.
- TLC-ART 301 combines TFV, 3TC, and DTG (TLD).

Global Long-acting Development (GLAD) project aims to transform short-acting TLD to LA TLD (supported by Unitaid and NIH).

- Use DcNP technology to combine TFV, 3TC, and DTG into stable DcNPs (TLC-ART 301) and synchronize fixed-dose combinations for collective exposures.
- A global funder has provided access to Dolutegravir.
- Start with one-month exposures: one SC TLC-ART 301 injection to replace 30 TLD pills.

Next Gen TLC-ART 301 development.

- Leverage DcNP technology to form a stable nanoparticulate TLD product at room temperature.
  - ◊ Lipid excipients are the glue (not novel).
  - ◊ Controlled solvent evaporation solubilization to form a stable DcNP TLD powder product (innovation).
  - ◊ Re-suspension and size reduction for final product.



- Pre-clinical PK studies of single-dose SC TLC-ART 301 in NHPs.
  - ◊ Plasma exposures of TFV, 3TC, and DTG are sustained for 4 weeks (to be published).
  - ◊ Need less drug in drug-combination, and there is no delay to peak concentration.
- Leverage PBPK modeling of TLC-ART 101 in NHPs (J of Pharm Sciences 2021).
  - ◊ TLC-ART 301 targets integrase inhibitor to the lymphocytes and remains stable for sustained total exposures.
  - ◊ Associated fraction of water-soluble and water-insoluble molecules is high throughout the body systems (TFV 99% and LPV/RPV 98%, respectively).
  - ◊ 70% of dose is first loaded in and exposes the lymphatic system, then excess to the blood.
- Scaling to humans requires data from FIH TLC-ART 101 studies (NHPs have limited lymph nodes).
- Future – assess study outcomes and potential impact of TLC-ART 301 on sustained viral suppression for HIV treatment.

Summary.

- Major milestones to reach Phase I treatment studies using TLC-ART 101 have paved the way for TLC-ART 301 (TLD).
- TLD is in development – DcNP technology enables transformation of oral TLD to LA TLD. First focus is HIV treatment, then prevention.
- We are looking for partners to develop NextGen LA TLD for global health benefit.

PLENARY II

Andrew Owen Director of the Centre of Excellence in LA Therapeutics (CELT) and Professor of Pharmacology and Therapeutics at Univ of Liverpool

"Update from LONGEVITY"

LONGEVITY aims to develop LA interventions for LMICs

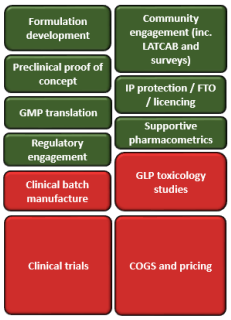
Project overview (Unitaid; Univ of Liverpool; JHU; UNMC; CHAI; Tandem Nano, LTD; TAG; MPP; Queen's Univ Belfast: LEAP).

- Indications.
  - ◊ Malaria prevention – atovaquone alone or in combination.
  - ◊ TB prevention –rifapentine + novel INH pro-drug.
  - ◊ HCV cure – glecaprevir/pibrentasvir combination.
- Drug selection based on similarity to other successfully developed LAIs.
  - ◊ Focused on target plasma concentration, aqueous solubility, and plasma half-life of oral products in humans.
  - ◊ Pro-drug strategy needed for INH to reduce aqueous solubility.
- Have access to several particle processing technologies to develop LAI medicines.
  - ◊ Emulsion-templated freeze drying; emulsion templated spray drying; nanoprecipitation; high pressure homogenization.

Indication-specific challenges.

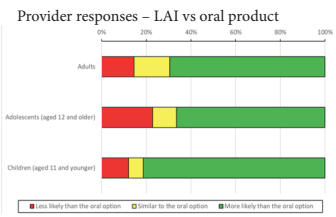
- Malaria – prevention of infection vs. disease.
  - ◊ Difficult to assess active infection in persons living in endemic countries.
  - ◊ Is a combination product needed to mitigate resistance risk?
    - * Research on the transmissibility of atovaquone-resistant parasites.
    - * Potential for combination with a monoclonal Ab.
  - ◊ Duration of the malaria season varies by region – need prevention for different periods of time (single vs multiple doses).
- Hepatitis C virus.
  - ◊ Current oral combinations have high cure rates, but huge benefits of LA expected with completion of therapy.
  - ◊ Access to glecaprevir and pibrentasvir and intellectual property challenges.
- TB – prevention of active disease in people with LTBI.
  - ◊ Is a combination product needed, particularly given the effectiveness of other preventive therapies?
  - ◊ One-month rifapentine + INH is as effective as 9-month INH.
  - ◊ Rifampicin already proven as a single agent for prevention.
  - ◊ P3 Asteroid Trial is underway for rifapentine as a single agent.

Structure of LONGEVITY activities and overview of progress with a focus on specific outputs.



Research and Development:
- Completed research to define transmissibility of clinically relevant atovaquone-resistant parasites (JHU).
- New formulations including glecaprevir/pibrentasvir combination (>500mg/mL) and rifapentine (>300mg/mL).
- Preclinical proof of concept achieved for all but isoniazid LAI.
- Exciting early preclinical data on newly incorporated MAPs.
- Prodrug identified and formulation activities initiated.
- New pharmacometrics tools developed to support human dose prediction.
- GMP drug donation for malaria (Hetero) and TB (Sanofi) prevention programmes.
- Multiple options being explored for HCV drug supply.
- Malaria patient / provide attitudes survey complete. TB and HCV surveys in mature development.
- Multiple patents files and licence executed with MPP.
- Two pre-IND meetings with FDA.
- GLP toxicology protocol developed.
- Product introduction framework for future planning.

- Research on the transmissibility of clinically relevant atovaquone-resistant parasites (Y268S) Preprint available online at https://www.biorxiv.org/content/10.1101/2023.02.07.527535v1.
  - ◊ Fitness cost evident throughout lifecycle and no detectable Y268S sporozoites in mosquito salivary glands.
  - ◊ Multiple failed attempts at transmission to humanized mice using Y268S-fed mosquitoes.
  - ◊ Provides evidence that resistance mutations cannot transmit with implications for a single-agent intervention.
- Patient/provider attitudes survey for Malaria.



◊ Most would "definitely try" injectable chemoprevention.
- * Patients (80%).
- * Parents/caregivers (84%).
- * Providers: adult patients (70%), adolescent patients (67%); and patients <12y (81%).

  - ◊ No obvious preference regarding frequency of LAI.
    - * Patients: Q1M (52%); Q2M (41%); and Q3M (55%).
    - * Providers: Q3M (71%) then Q1M (63%).
  - ◊ "Very Beneficial" attributes of LA therapy.
    - * Patients: improved effectiveness (87%); easier to take (85%); fewer side effects (76%); and discretion (75%).
    - * Providers: all benefits rated high, particularly long-term malaria prevention (90%).
- Preclinical PK studies of LAI glecaprevir/pibrentasvir in rats.
  - ◊ Linear dose-dependent PK; achieved plasma exposures above the human oral C_{trough} for 12 weeks (aiming for 8 weeks); similar hepatic-to-plasma concentration ratios between LAI formulations and oral delivery.
  - ◊ Different release kinetics observed for glecaprevir (quick absorption) and pibrentasvir (slower release into systemic compartment) – likely due to differences in aqueous solubility.

Vikram Arya Associate Director for Therapeutic Review, Division of Infectious Disease Pharmacology, Center for Drug Evaluation and Research at US FDA

"Conversion of an oral approved ARV drug to a LA formulation: a few considerations"

Over the past few years, there has been a considerable investment of regulatory time and effort to facilitate development of LA ARV formulations

cART has revolutionized HIV-1 treatment and the availability of several safe, convenient, generally well-tolerated, and effective treatment options has reduced mortality and morbidity rates and improved the overall quality of life. Although the currently available prevention and treatment options have markedly reduced the number of new infections and have ensured chronic viral load suppression for majority of patients, factors such as high pill burden, suboptimal adherence, and frequent dosing requirements present formidable barriers to realizing the full potential of prevention and treatment strategies.

Series of three peer-reviewed publications.

1. How the development of LA ARVs can present novel regulatory challenges (PMID # 26049954).
   - Determining the appropriate dosing regimen, the need for an oral lead-in (given the slower rate of drug release), and whether existing data with an approved oral formulation, if available, can be leveraged for a treatment or prevention indication.
2. Key considerations for the development of LAIs, implants, and patches for the treatment and prevention of HIV-1 infection (PMID # 31483323).
   - Utility of an oral formulation option for a LA product, the impact of residual drug(s) concentrations following discontinuation of the LA formulation, and use of the LA formulation in specific populations.
   - A "hybrid approach" can facilitate the transition from an oral formulation to a LA formulation while collecting the required PK, safety, and efficacy data.
     - ◊ The oral formulation can be used early in development to assess single and multiple dose PK, safety, and DDIs.
     - ◊ Results can generally be extrapolated to the LA formulation if similarity in systemic exposures between the oral and LA formulations can be adequately demonstrated.
     - ◊ Subsequent P2 trials can include LA formulation treatment arms +/-OLI. If similar safety and efficacy data are observed in both arms, then future Phase 2–3 trials can be conducted with only the LA formulation
3. How LA-ARVs have the potential to transform global implementation of HIV-1 prevention and treatment strategies (PMID # 36410378).
   - The latest in the series specifically discusses 3 drug development scenarios.

Scenario 1: Development of a novel LA-ARV (new molecular entity).

- General development paradigm is similar to the pathway for immediate-release oral products.
  - ◊ In-vitro antiviral activity, non-clinical data and PK/safety data from SAD/MAD studies inform selection of dosing regimens to be evaluated in proof-of-concept trials, followed by P2 and P3 trials.
  - ◊ ADME characteristics inform the need to evaluate the effect of intrinsic (e.g., hepatic and renal impairment) and extrinsic factors (e.g., DDIs) on PK.
  - ◊ Model-informed approaches are often used for optimizing dosing regimens, therapeutic individualization, and overall risk-benefit assessment.
- Considerations specific to LA ARVs.
  - ◊ Should an oral immediate-release formulation of the LA-ARV also be developed for administration in a lead-in phase prior to administration of the LA product?
  - ◊ What are the implications of the residual drug concentrations once dosing of a long-acting formulation is discontinued and the potential impact on future treatment or prevention options?

Scenario 2: Development of a LA formulation of an approved oral ARV product.

- Two overarching questions to consider under this scenario:
  1. What information may be leveraged?
  2. How much information may be leveraged?
- Initial dosing selection and dosing regimen optimization
  - ◊ Available PK/PD/ADME data from the oral product can be leveraged using quantitative methodologies to select the dosing regimen(s) of the LA product for characterizing its PK and safety.
- Comparison of systemic exposures of the ARV after administration of the LA product and the oral product.
  - ◊ Exposure-response information from the oral product can help to contextualize this comparison, especially related to assessing whether efficacy can be extrapolated across the two products.
  - ◊ The LA product may have unique safety-related considerations (e.g., ISRs) that need to be carefully considered.
- Existing information on the effect of intrinsic and extrinsic factors on the PK of the oral product can facilitate therapeutic individualization of the LA product.
- Available data with the oral product can be informative to determine management strategies for treatment interruptions and the impact of residual drug concentrations on subsequent therapeutic interventions.

Scenario 3: Development of a LA pro-drug of an approved oral ARV.

- If the LA pro-drug is being developed for a similar indication and assuming the pro-drug in itself does not exhibit any unique safety issues, development considerations are similar to scenario 2.
- Ability to leverage information depends on:
  - ◊ Availability of exposure-response information with the oral product.
  - ◊ Whether similarity in exposures between the immediate release product and the LA pro-drug of the immediate release oral product has been demonstrated.
  - ◊ Judicious selection and application of quantitative methodologies to address the clinically pertinent questions.

Summary.

- LA-ARVs have the potential to transform global implementation of HIV treatment and prevention strategies.
- Depending on the development scenario, development of LA ARVs can be streamlined by Identifying potential knowledge gaps early in development, actively generating missing information, and strategically leveraging available data.
- Efficient integration of multi-disciplinary knowledge, collaborative engagement of all stakeholders, and judicious use of quantitative tools has the potential to transform the availability and accessibility of LA therapeutics for HIV and other chronic viral infections.

PLENARY II

Kimberly Struble Senior Clinical Team Leader in the Division of Antiviral Products at US FDA

"Will an oral lead-in always be a part of long-acting ARV drug development?"

FDA U.S. FOOD & DRUG ADMINISTRATION

If you start with an oral lead-in, you are not stuck with an oral lead-in

Is an oral lead-in (OLI) needed?

- Sponsors can develop a new ARV de novo without an OLI , even if manufacturing an OLI is possible.
- FDA recognizes the additional feasibility and CMC considerations of developing two formulations up front before determining if OLI is needed.
- Consider the available non-clinical safety and PK data to decide if an OLI is needed.
  - ◊ Is there a safety concern (hypersensitivity, liver toxicity, etc.) – Consider the magnitude and severity of target organ toxicity.
  - ◊ Is PK sufficient – Is an OLI needed to reach target exposures before converting to LA?

Three approaches for development of LAI and implantable products.

- Always OLI due to PK or safety reasons.
  - ◊ Strategy depends on ability to reach target exposures and rule out safety concerns.
  - ◊ Dose oral to steady state then LAI (ensures target exposures are met).
  - ◊ Dose oral, overlap oral + injection dosing, then LAI (rule out safety concerns).
- No OLI is needed or available – not possible (i.e., monoclonal Abs) or a company may not want to pursue it.
  - ◊ Strategies surround risk mitigation.
  - ◊ Stringent enrollment criteria.
  - ◊ Start small – dose 1 or 2 patients and stagger dosing between patients for a specified interval.
  - ◊ Stringent stopping criteria for individual patients, cohorts, or the study.
  - ◊ Independent, unblinded medical monitor or data monitoring committee to oversee safety.
- Hybrid approach – it is possible to transition to no OLI early in development if no PK or safety concerns.
  - ◊ Strategize and prioritize the transition from OLI to all LA.
  - ◊ Example: OLI used for initial safety assessment.
    - * Safety – single and multiple dose PK studies assess target exposures in relation to EC_{90} to conduct DDI trials.
    - * OLI transition – dose-finding study +/- OLI arms. If no OLI needed for safety or PK reasons, then further trials can proceed without OLI.

Additional considerations when developing an oral ARV along with the LAI formulation.

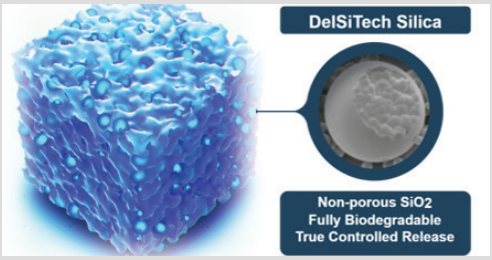
- Prioritize DDI assessment – may be able to more quickly move to the direct-to-injection phase.
  - ◊ Thoroughly evaluate data from in-vitro enzyme and transporter evaluations to prioritize in-vivo DDIs.
  - ◊ Conducting DDI assessments with index perpetrators and substrates first for CYP mediated interactions could save time and reduce the number of trials needed.
  - ◊ For transporter-mediated DDIs, need to strategize based on route of elimination and concomitant medications and safety considerations.
- An advantage of oral products is the ability to conduct DDI trials with a cross-over design.
  - ◊ LA ARVs have long half-lives – the amount of time needed for an adequate wash out could prolong trial duration.
- Renal and hepatic assessment can be done with oral or LA formulations – we do not expect PK differences.
  - ◊ PK trial duration may be shorter with oral formulations.
  - ◊ Data from the oral formulation can be applied to LA, but not necessarily vice versa (hepatic first pass would be missed with LAI).
- Leverage all available oral PK data.
  - ◊ Can use various quantitative clinical pharmacology approaches (such as modeling and simulation) to leverage PK data for addressing various "real life" scenarios, such as missed doses and LA treatment interruptions.
- Food effect assessment.
  - ◊ A preliminary food effect assessment is needed to guide oral dosing until a complete transition to all LA formulations is made.
  - ◊ If the development program does not include an OLI, then a dedicated food effect trial is not needed.

Summary.

- Three approaches for development of LA ARVs – with OLI, without OLI, and hybrid approach.
- The need for OLI depends on individual product PK and safety profile.
- A transition to direct-to-injection without OLI can be made early in development, providing no PK or safety concerns

Lasse Leino CEO of DelSiTech

"Biodegradable silica based platform for antiviral drug delivery"



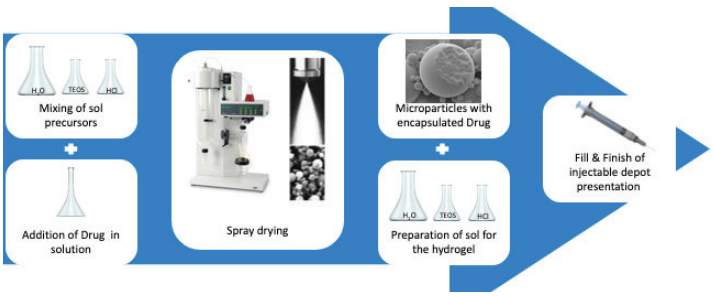
Biodegradable, amorphous, non-porous silica-based drug delivery

Overview of DelSiTech.

- Develops LAIs (SC,IM) that enable controlled release for days to months.
- Silica matrix technology is applicable to a large range of drugs – small molecules, peptides, proteins, oligonucleotides and vaccines.
- Multiple ongoing drug development projects for antiviral therapy – in-house and with external partners.
- DST1308 – first-in-house and first-in-class supergeneric/505(b)(2) drug product for chronic hepatitis B virus treatment.
  - ◊ FIH studies to begin early in 2024.
  - ◊ Entecavir-based Q3M SC injection.
  - ◊ Product protected by a global patent up to 2036 – several recent publications on the technology.

DelSiTech Silica matrix technology.

- Non-porous silica microparticles containing an encapsulated drug are combined with silica hydrogel forming an easily injectable silica-silica composite depot formulation.
- SiO_2-based biomaterial is non-porous and fully biodegradable for durable controlled release.
- Simple manufacturing process yields ready-to-use injectables.



Silica matrix for LA HIV bNAb delivery in collaboration with the Bill and Melinda Gates Foundation.

Preclinical studies indicate bNAb release for 4 months and the silica matrix protects the Ab for many months inside living tissue.

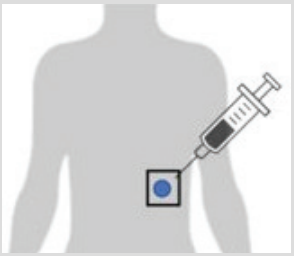
- Prototype depot formulation (#05D) developed for bNAb PGT-121.
  - ◊ PGT-121 was fully encapsulated in silica microparticles at 25% payload and formulated into silica hydrogel for an injectable product (25G needle).
  - ◊ In-house, in-vitro dissolution tests predict 5-month release of PCT-121 and full biodegradation of the silica matrix at 5 months in vivo with no burst release.
- Pre-clinical studies of single-dose SC PGT-121 in female SCID transgenic mice – in silica depot #05D vs saline bolus formulation.
  - ◊ Assessed PGT-121 serum concentrations up to day 125 (depot) and day 28 (bolus) via HIV-1 neutralization assay.
  - ◊ Analyzed PGT-121 depot remnant collected from sacrificed animals: SiO2 and PGT-121 content; biological activity of remaining PGT-121 (HIV-1 neutralization assay); and binding activity (ELISA).
  - ◊ PK – controlled release of PGT-121 up to day 40, followed by an elimination phase yielding serum exposure up to day 125 (half-life similar to bolus injection); no burst release.
  - ◊ Depot remnants collected at day 90 – PGT-121 from dissolved remnant retained full biological activity compared to samples of PGT-121 stock solution.

Conclusions.

- DelSiTech Silica Matrix technology offers an alternative to develop antiviral controlled-release products – small molecules and complex biologics.
- bNAb PGT-121 was successfully encapsulated and formulated at high payload (25%) in a silica-silica composite formulation.
- PK study in transgenic SCID mice showed controlled release of biologically active PGT-121 for at least 4 months after a single injection of PGT-121 silica depot formulation.
- PGT-121 retains full biological activity for at least 3 months encapsulated in the silica matrix within a living tissue.

Martina Kovarova Associate Professor of Medicine at University of North Carolina, Chapel Hill

"Long-acting in-situ forming implants (ISFI) for TB and other infectious diseases"



Biodegradable RFB formulation solidifies after SC injection - delivers high plasma drug concentrations for 16 weeks

Development of LA ISFI formulations for TB.

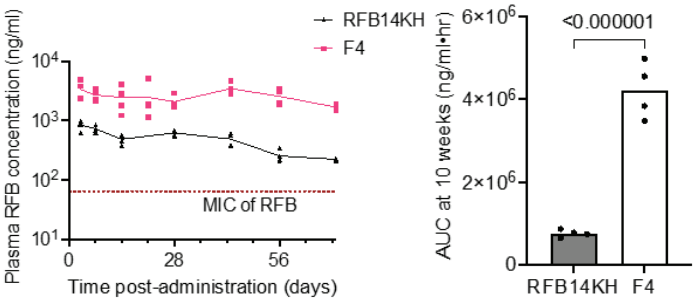
- Focus on rifamycins – rifampin (RIF), rifapentine (RFP), and rifabutin (RFB).
  - Potent bactericidal activity and ability to inhibit DNA-dependent RNA synthesis.
- RFB selected as a model drug for development of an ISFI formulation.
  - ◊ Reduced potential for DDIs – more suitable for TB-HIV coinfections.
  - ◊ Higher tissue uptake due to high lipophilicity, larger volume of distribution, longer terminal half-life, lower MIC.
  - ◊ Available as a low-cost generic medication.
- ISFI technology for a LA RFB formulation.
  - ◊ Several FDA-approved products.
  - ◊ A biodegradable implant is formed after direct injection – no need to remove, but can be removed to stop drug delivery.
  - ◊ Comprises three components that can be optimized – biodegradable polymer (PLGA), biocompatible solvent (DMSO/NMP), and the drug.

ISFI formulation release properties in mice.

- After injection into the hydrophilic SC space, there is an exchange between solvent and body fluid, and the implant becomes solid.
- A Single-dose yields plasma RFB concentrations above MIC for 18 weeks.
- Additives can increase RFB solubility and drug load (i.e., solubility in DMSO vs DMSO + additives) and improve release properties (in-vitro dissolution studies and in vivo studies).

Final optimized RFB-LA formulation (RFB14KH) in mice.

- PK and tissue penetration (SD + booster at month 2 or 3).
  - ◊ Plasma RFB concentrations above MIC for 36 weeks – exceeds duration of all treatment options for LTBI.
  - ◊ Better tissue penetration than previously published – nearly 20:1 lung to plasma ratio.
- In-vivo efficacy I.
  - ◊ Pre-exposure treatment or placebo for 14 days, exposed to Mtb aerosol at day 0, and necropsy at day 1 through 28.
  - ◊ Treated mice – all had bacterial load below level of detection in lung, liver, and spleen.
  - ◊ Placebo mice – all had high bacterial load (lung, liver, spleen).
- In vivo efficacy II – RFB14KH prevented dissemination and reduced burden in lung.
  - ◊ Exposed to Mtb aerosol at day 0, post-exposure treatment or placebo at day 7, and necropsy at day 1, 7 and 28.
  - ◊ Day 7– all mice have bacteria in the lung and no dissemination to liver or spleen.
  - ◊ Day 28 – all treated mice had bacterial load below level of detection in lung, liver, and spleen; all placebo mice had high bacterial load in all three tissues.
- Continued optimization efforts achieved increased drug load and plasma concentration after a single injection.
  - ◊ Over 4-fold increase in RFB exposure with F4 formulation.



Summary.

- Developed a LAI RFB formulation made of biodegradable polymer and biocompatible solvent that solidifies after SC injection.
- Addition of additives (amphiphilic compounds) increases drug solubility in organic solvent, allowing significantly increased drug load.
- Translational relevance in mice.
  - ◊ Delivered high plasma drug concentrations for 16 weeks without need for removal.
  - ◊ Prevented acquisition of Mtb infection.
  - ◊ Cleared acute Mtb infection from the lung and prevented dissemination to other tissues.
- A recently developed, optimized RFB-LA formulation (F4) delivers 4-fold more RFB.

Towards a collective agenda to advance the long-acting field.

Focus groups were convened virtually and lasted 90 minutes. Participants represented diverse perspectives, including clinicians, academia (some with links to industry), pharmaceutical industry, regulatory authorities, community advocacy organizations, and not-for-profit research and implementation institutions. Each group engaged in a crucial dialogue intended to inform how to collaboratively and strategically advance the LA field amidst a continually evolving landscape.

Focus Group 1
Lessons Learned from Islatravir Toxicity

Focus Group 2
Developing Long-Acting Treatments for HCV

Focus Group 3
Developing Long-Acting Therapeutics for TB

Focus Group 4
Commercial Manufacturing of LA Generic Formulations

FOCUS GROUP I

Rapporteur

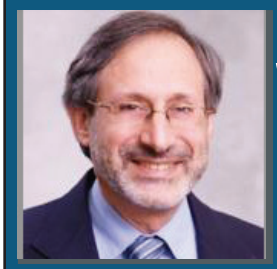
Polly Clayden

Co-founder of i-Base

Co-chairs

Joseph Eron

Vice Chief of Division of Infectious Diseases at UNC School of Medicine



Jeffrey Jacobsen

Professor of Medicine at Case Western Reserve University

"Lessons learned from Islatravir toxicity"

1. Timeline of events
2. Lessons learned
3. What is the unmet need?

Timeline of Events

Late 2021 - various ISL programs at different stages of development for HIV treatment and prevention.

- Lymphocyte toxicity observed in participants who received ISL.

Early 2022 - complete or partial hold across ISL programs.

Merck Program	Clinical Hold
QD ISL+DOR	Partial
QW ISL+MK-8507	Complete
LA oral ISL+LEN	Partial
LAI ISL+LEN	Complete
QM oral ISL	Complete
QY ISL implant	Complete

- Merck conducted a comprehensive assessment of the lymphocyte effect.
  - ◊ Not seen in animal, in vitro, or Phase I studies.
  - ◊ Isolated to lymphocytes and subsets – no effect on other hematologic cell lines.
  - ◊ Exposure-dependent, mostly seen at 120mg QM.
  - ◊ Likely related to high intracellular exposures, not mitochondrial toxicity.
  - ◊ No change in infection risk compared to control arm.
- Phase 2 dose-ranging studies identified lower QD and QW oral doses with efficacy and no lymphocyte toxicity.
  - ◊ ISL (0.25mg) QD and ISL (2mg) QW.
  - ◊ No dose identified for QM oral or injectable programs; implant on hold.
  - ◊ New MK-8527 may have potential for prevention.

Early 2023 - oral programs resume using lower ISL doses.

- Merck oral program (ISL 0.25mg +DOR QD)
  - ◊ Four studies (switch and treatment-naïve PLWH), including de-escalation for participants who received the ISL 0.75mg dose.
  - ◊ Women who become pregnant during the study can remain on ISL after consent (as before).
  - ◊ Study population does not include highly-experienced PLWH.

- Joint Gilead program (ISL 2mg +LEN QW)
  - ◊ Phase 2 trial (PN045) – 100 PLWH virologically suppressed on BIC/FTC/TAF.

Lessons Learned

Considerations were mostly focused on the ISL molecule, not LA development more broadly.

Do we need a better animal model?

- Accumulation of ISL-TP appears to be species-specific.
- Human cells phosphorylate ISL more effectively than animal cells.

Do we need to bank cells? Would it have made a difference?

- Merck did not bank cells, as the lymphocyte effect was not expected.

Could we develop another NRTTI that is not an adenosine analogue?

There was consensus that more attention should be paid to intracellular levels.

Focus on classical pharmacodynamic principles.

It took a long time to see the lymphocyte toxicity.

- It is unrealistic to expect that we would know everything about a 6-month dosing interval from a 24-week study in humans.

Not concerned the lymphocyte effect of ISL will pause development of LA formulations.

- Not seen previously with CAB-LA or RPV-LA.
- Merck is committed to publishing all findings from the evaluations – lessons learned will be in the public domain.

What is the Unmet Need?

Dosing interval.

- Knowing what is possible reframes what is considered useful or needed.
- Last year's focus group considered QW less useful than QM dosing – once we learn that QM is not possible, the QW option becomes more attractive.

Is the ISL implant worth taking forward?

Is postnatal prophylaxis a possibility?

Pediatric indications.

Stakeholder consultations are needed to identify unmet needs.

- A lot may be possible in terms of the science, but do people want and need it?
- Merck is conducting extensive stakeholder consultations.

FOCUS GROUP 2

Rapporteur

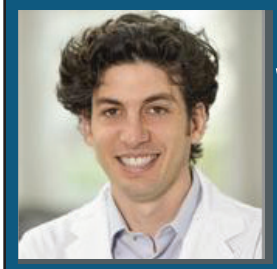
Ashwin Balagopal

Assistant Professor of Medicine at JHU

Co-Chairs

Meg Doherty

Director of Global HIV, Hepatitis and STIs programs at the WHO



Jordan Feld

Senior Scientist at Toronto General Hospital Research Institute

"The needs and challenges of developing long-acting treatments for hepatitis C"

1. Progress since LEAP 2022
2. Industry Perspective
3. Advocacy Perspective
4. Regulatory Perspective
5. Other thoughts
6. Summary

A single-shot cure is desired and would address those left behind - even if not for all patients.

Progress since 2022

- Estimates of dosing requirements.
- LONGEVITY project – progress with glecapravir glecapravir co-formulation.
- Broad consideration of use cases of LA agents (CID supplement 2022).
- Understanding patient preferences.
  - ◊ Survey by Weld ED and Thomas DL (CID 2022): pills (51%); injection (38%); implant (6%); GRD (6%).
  - ◊ UNITAID/Sue Swindells – study to better understand patient/provider preferences.
- Some understanding of best current candidates vs newer agents.
- Public-private partnership will be required – opportunity for funding agencies.

Industry Perspective

Considerations across drug development.

- Minimal monitoring approach pioneered by the ACTG is encouraging for POC cure.
- Viral kinetics – how to deliver two drugs to establish SVR (VS <LLOD for 28-30days after undetectable levels achieved).
  - ◊ Sofosbuvir considered – unique PK properties make this challenging.
  - ◊ Combination oral and injectable – resistance may develop if 8-12 weeks required.
- If 2 agents required (NS5A inhibitor and NS3 inhibitor), can expect DDIs.
- What is the unmet need given the success of oral antivirals?
- What would the reimbursement be?
- What reduction in SVR is acceptable?
- The pathway to development and approval might not be short, and there are legal aspects.
- Product development would be for bioequivalence
  - ◊ Need to show non-inferiority vs standard oral therapy?
  - ◊ Need for P1 studies in healthy volunteers?

Comments to Industry

- There is an unmet global need if all populations are considered.
  - ◊ There may be more itinerant populations than estimated – persons in prison are often a use case

for efficacy of oral therapies, but many are not there for the full duration of treatment.

- LA treatment is one necessary, complementary arm of an elimination strategy.
- What are the bottlenecks before industry advances on LA medicines?
  - ◊ No rapid POC test exists to effectively implement a POC HCV cure.
  - ◊ Some pharma questions exist that cannot be solved in isolation – Who pays? What are the regulatory benchmarks? How technically feasible is co-formulation?

Real-world experience with development of LA HIV treatment.

- CAB LA and RPV LA approval was slow. The "who pays?" question slowed progress.
- Unmet need may be similar to HIV. People who engage with LA HIV treatment really like it.
- Real-world surveys suggest equipoise – more people may take 1-2 shots if offered.
- LA treatments are being rolled out in LMICs.
- Timeline for HIV LA medicines.
  - ◊ P1 CAB/RPV studies presented at CROI 2012 (4-5 years of pre-clinical work) and approval in 2021.
  - ◊ LEN was faster – once the pipeline is built, there may be downstream advantages
- What gaps can academia and industry fill together
  - ◊ Quantify unmet need; What will be accomplished by delivery of these products?; POC HCV test; Modeling.

How mathematical modeling can help – Dr. Hoelek from Imperial College.

- Models can show impact.
- Consider incorporating the care cascade.
  - ◊ If the care cascade has an unmet need, then quantify it and how the opportunity you are offering will have an impact.
  - ◊ Certain populations are more vulnerable – likely geographically heterogeneous.
- Consider the overall cost of the product – every country values the opportunity and costs differently.
- What is the case for investment?
  - ◊ Individual gain? Societal gain? Benefits regarding transmission?
- It is cost-saving for payers to treat HCV.

Advocacy Perspective

- What will it take for funders to become interested in LA HCV treatment?
- How can we address transmission and treatment as prevention?
  - ◊ The care cascade is missing people, even with government buy-in.
- A rapid HCV test exists (1.5 hours) – roll out or optimization to make POC cure possible?
- Potentially a very important market – could be studied and characterized better.

Regulatory Perspective

- Oral adherence and tolerability is high – may be hard to get buy-in with an inferior SVR.
- Would pan-genotypic treatment be a requirement for a LA agent?
- What is the comparator – registrational trials or real-world experience?
- LA therapy will inherently give higher exposures (more safety data) or lower exposures (more efficacy data).
  - ◊ Original trials include duration-finding, but not much dose-finding – toxicity of higher doses?
- Non-inferiority trials are not always required, but there may be questions for lower SVR.
- Interested in working with academia, industry, and pharma to identify the right studies.
  - ◊ Proposed P3 "intent-to-cure" study (randomization at diagnosis to LA vs standard oral treatment) – the SVR would reflect real-world experience, accounting for theoretical loss of efficacy.

Other thoughts

- Is there a role for intensification for shorter duration?
- What types of co-formulations would be optimal?
- Manufacturing needs its own discussion – not touched on.
- Other formulations are important and were not fully discussed (i.e., aqua suspension; capsules; polymer-based products; injectables).

Summary Thoughts

- What are the individual and societal benefits?
- What is the unmet need?
- What is the investment case?
- What formulations would work?
- What will payers accept?
- What testing is required for POC cure?
- Perfect opportunity for funders to facilitate Public-Private partnerships.

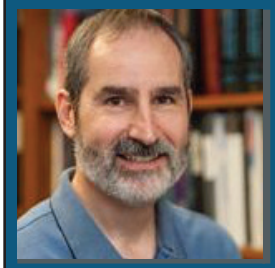
FOCUS GROUP 3

Rapporteur

Ethel Weld

Assistant Professor of Medicine at Johns Hopkins University

Co-Chairs



Charles Peloquin

Professor of Pharmacy and Medicine at University of Florida

Kim Scarsi

Professor in the College of Pharmacy at Univ of Nebraska Medical Center

"Long-acting therapeutics for TB: planning and prospects for future clinical development"

1. Considerations for development of LA LTBI treatment
2. Desirable attributes of a LA TB agent
3. Pharmaceutical considerations.
4. Regulatory challenges and solutions
5. Summary

Considerations for LA LTBI Treatment Development

Low-hanging fruit vs apples in the sky.

LTBI Treatment	TB Disease Treatment
One drug likely	≥3 drugs with aligned characteristics
Potency/loading issues less prominent	Potency/loading issues greater for induction therapy, which is 3+ drugs, but may be less of an issue for continuation therapy, which is usually 2 drugs
Safety is more clear	Toxicity from one component difficult to discern

General Considerations.

- RIF, INH, RPT have evidence as effective single agents, but may have adherence issues, especially when given for longer courses (e.g., <50% competion rates of 9-month INH).
- 2-drug combinations are likely NOT needed to mitigate resistance risk.
  - ◊ Data shows rates of incident DR-TB disease after LTBI treatment are similar to background rates.
- Sterilizing activity may not be needed, although preferable (e.g., RIF, BDQ, Pa, DLM).
  - ◊ INH took time, but worked – not a known sterilizer, but has good early bactericidal activity.
- Tissue levels are important.
  - ◊ A plasma gradient will "drive the drug to the bug" (no active transporters, just active diffusion).
  - ◊ Animal models are essential to understand where the organisms reside and drug levels in that compartment (cavity? tissue?) and in proxy compartments (plasma?)that are needed for efficacy.

Considerations for Children.

- Children under 2 years are highest priority.
  - ◊ Increased progression, higher risk of disseminated disease, and greater potential impact (in QALYs) of disease prevention.
- Are PK needs different in youngest children?
  - ◊ TB lives in tissues (and plasma when disease is disseminated), and tissue is not serum – are PKPD relationships the same?
- Objectives may be different in children vs adults.
  - ◊ Is there a specific drug that **only** works in young children (i.e., one that did not work in adults) that is still worth investigating?
  - ◊ Most children who develop TB did not receive LTBI treatment (lacked access) – if LA LTBI treatment expands ease of access, then it is a worthy goal for this population, which is already neglected in terms of gross undertreatment for LTBI globally.
- Is tolerability/acceptability of injections less of a concern in children? For the youngest kids who commonly receive multiple vaccine injections at once, perhaps it is?
  - ◊ Need to evaluate acceptability in an age-de-escalation manner?
  - ◊ PK should be evaluated in parallel to mitigate delays in treatment.

- ◊ Some technologies are easier in children than adults (e.g., microarray patches and injection, as less mg amount means less area and volume, respectively).
- Shorter duration makes rapid weight change less consequential for PK/clearance (Q1M or Q3M).

Desirable Attributes

Based on 2022 WHO TB preventive treatment case scenario.

More Suitable	Less Suitable
Sterilizing Activity?	Less Potent
Hydrophobic; Persists ≥3m or one year	Hydrophilic drugs; rapid clearance
Few DDIs	DDI-prone (e.g., with ARVs)
Match dosing intervals to existing LA ART products	
As safe as oral counterpart	
Single dissolvable implant	
Q1M dosing with no OLI	
No cold chain	
Delamanid, BDQ, RIF	Pyrazinamide

What PK is needed?

- LTBI may require lower exposures than TB disease treament because fewer bacilli in the body – lower, more tolerable, more feasible volumes?
- Emulate the oral concentration? AUC:MIC?Stay above C_{trough} of effective oral formulation?
  - ◊ Could this be different for each drug? (e.g., in LTBI Balb-C 104 CFU mouse model: trough >3x MIC active for RBT, not for RPT).
  - ◊ Stay in excess of MIC by 2- to 4-fold (given known variability in determining MIC)?
- Does concentration need to be > MIC for the entire dosing interval? Is high early concentration and lower later concentration ok? Is a long tail a concern? Less so for TB than HIV?
- Higher margin needed for possible resistant organisms?
  - ◊ If bacilli are truly non-replicating, then resistance is not possible.
  - ◊ Basic science info on Mtb under stress conditions would be useful.

Pharm. Considerations

- Potency, loading, physiochemistry, logP, rate of elimination, pro-drug approaches, volume, amphiphiles to alter solubility.
- Injectables.
  - ◊ Solid drug particle dispersions; microspheres; polymer approaches to control release of potent, water-soluble drugs.
- MAPs.
  - ◊ minimally invasive, more acceptable, but how big must the patch be? Need push thru to POC.
- Biodegradable implants (ISFI).
  - ◊ *Non*-biodegradable, surgically implanted possibly more trouble than it's worth for short-duration LTBI treatment?
  - ◊ For TB treatment, don't need all 3-4 drugs for the whole treatment duration, so tunability is needed.
- Hyaluronidase co-administration to allow larger injection volumes – impact on PK?
- Cold chain issue – easier to address with a solid product than liquid?
- Are new molecules worth investigating with all the regulatory hurdles?
  - ◊ Available therapeutics were chosen based on oral bioavailability, but lipophilic drugs with poor oral bioavailability are good for injectables.
  - ◊ Target something FDA approved in another dosage form.
  - ◊ Formulation fixes for stability issues: what are the goals? (e.g., RBT in solvent – stable for 3 months vs RBT formulated with polymer – no degradation at 2 years).
- End-user preferences determine use.
  - ◊ Need to assess preferences using interviews, focus groups, discrete choice experiments, and iterative processes to inform what products people will use.
  - ◊ Who participates in the surveys of safety, efficacy, etc. matters – Target Regimen Profiles survey: 1 of 100 stakeholders with lived experience of TB.
  - ◊ Need more rigorous patient preference work for TB drugs.

Regulatory Challenges

- Learn from LEAP process – leverage modeling and simulation and approved LA formulations.
- Orphan drug designation for LTBI (based on low incidence of conversions to active TB in US)?
- Breakthrough therapy designation?
  - ◊ RPV (11 years from P1 to clinical use) vs LEN (same journey was 4 years) because a precedent was set.
- What level of known adverse drug reactions from an oral formulation is acceptable with a LA one?
  - ◊ Is removability/reversibility mandated? Continual risk:benefit assessment.
- What level of data are needed to move from animals to humans?

Summary

- Goal is LA one-drug option for LTBI in all populations.
  - ◊ Build expedited pathway for other indications.
  - ◊ What does not work in adults may work in children – need parallel development.
  - ◊ Existing therapeutics preferred, but late pipeline should be considered.
- Continue to discuss appropriate targets – pre-clinical PKPD work and bridge to humans.
- Leverage learning from approved LA products in other disease states.
  - ◊ Eligard, Sublocade, Perseris, Atridox, etc.
- Measure lived experience (stakeholders' views).
- Balance regulatory issues.
- Public-Private partnerships are essential.

FOCUS GROUP 4

Rapporteur

Paul Domanico

Senior Director of Global Health Sciences at CHAI

Co-Chairs

Lobna Gaayeb

Head of Scientific & Medical Affairs at Medicines Patent Pool

Francois Venter

Head of Ezintsha at Univ of the Witwatersrand, Johannesburg

"Barriers to commercial manufacturing of generic LA formulations"

1. Scale-up and funding
2. Technology transfer
3. Innovative partnerships
4. De-risking mechanisms
5. Cost

Scale-up and Funding of LA Development

How to incentivize developers to take candidates forward?

- After discovery, cost of development and commercialization of a new drug can exceed USD 100M.
- Need alternative ways to fund costly and high-risk next steps.
  - ◊ Safety and efficacy in humans; product development to scale a safe, effective and low-cost product; and regulatory approval.
  - ◊ University of Washington – CROs.
  - ◊ University of Liverpool – Spinout and CROs.
  - ◊ University of Nebraska – Launched start-up to advance pre-clinical candidates to human studies.
- The real-world market for LA products is not known – innovators are interested, but cautious.
  - ◊ How many patients will be treated; how often do they need the treatment; if it is a cure, what does that mean about the size of that market.
- Need to understand the value of a LA product relative to the standard of care (SOC).
  - ◊ Detailed assessment of existing SOC and how the LA product would transform care.
  - ◊ Clear success criteria at every stage (product development, commercialization, introduction, and monitoring).

Technology Transfer

Ensuring smooth technology transfer is critical to reduce timelines and cost.

- Cannot predict if oral or LA approach will be more complicated, BUT many non-oral products involve a drug-device combination, which confer additional challenges and partnership complexities.
  - ◊ Each API is its own special case – difficult to set standards.
  - ◊ There may be value in setting platform standards (recent work by CHAI on matching API with delivery platforms to advance pediatric treatment).
  - ◊ Need to be able to anticipate the complexity – the team must represent the full suite of skills required to reach the endpoint.
  - ◊ Need clarity and agreement with regulatory or normative agencies on regulatory affairs strategies – begin discussions early regarding what evidence will be needed to approve generic products.
- What is necessary to generate a quality relationship?
  - ◊ Successful technology transfer requires a transparent and honest relationship – regular meetings, rigorous consideration of all aspects of business and science, and joint accountability for adhering to timelines.

Innovative Partnerships and De-risking Strategies

The innovation must account for the risk of introducing a new LA product that represents a new care paradigm for patients and infrastructure.

Accessible market and impact analysis is critical to engage manufacturers, but remains hypothetical for LA products.

- Single-administration glecapravir for HCV cure would simplify care and dramatically reduce transmission, but the overall market is not known.
- Analysis incorporates parameters associated with national guidelines, Ministry of Health (MOH) disease management strategy, existing approaches and SOC, funding envelopes, and actual and perceived value to patients and the system.
- Need to be cautious about the utility of cost-effectiveness analyses when building a business case for LA products – only one component of the decision to proceed on the national level.
  - ◊ Most useful for like-to-like comparisons.
  - ◊ Comparing oral and LA products is less useful – many aspects of the care cascade must evolve.
  - ◊ Learning from staged rollout will be useful – iteration and trial and error.
- LA products represent a fraction of the market.
  - ◊ Not all patients will migrate to LA, and this could affect manufacturer decision-making.

Scale.

- Generic manufacturers need product profiles to decide on the scale of manufacturing.
  - ◊ Dose per unit, duration of action, size of patient population at launch, and how it will scale.
- LA market needs to be better understood to determine the impact on the scale of manufacturing and what product margins are necessary to create competitive and stable markets.
  - ◊ What the cost of goods at launch is going to be, and given scale and assumptions around scale, what the cost or price is going to be at scale.
- The manufacturing industry is accustomed to the oral scenario (one or several tablets per day) – LA products are dosed less frequently and require fewer metric tons of active agent.
- The price of each LA administration may be higher than oral, but we do not know if the price per patient per year of LA treatment will be different.
  - ◊ In LMICs, this cost needs to be close to the current standard of care.
- Many patients prefer LA products, but the signal from MOHs is less clear.
  - ◊ Community activism must remain strong.
  - ◊ Additional operations research is probably needed to optimize care when LA products are introduced (i.e., adoption, adherence, outcomes, and systems).
- Markets may expand slowly.
  - ◊ Innovators and generic manufacturers will be cautious about how and where they enter the LA market.
  - ◊ Need to think in terms of introduction phases, and structure business relationships accordingly.

Next steps

- "CAB-LA is the canary in the coal mine"
  - ◊ Will transform our learning on how to roll out LA products.
- LA regimens will require funding well beyond what is needed to bring products to market.
  - ◊ Sources of funding must expand to include resources from MIC governments. Need to consider diagnostics, education to patients and community, etc.

Cost

How to justify higher potential cost to procurers?

- Market for LA products for ID is too nascent to know what prices will incentivize generic manufacturers or what procurers will be willing to pay.
  - ◊ MOH and finance may have different success criteria.
- Benefits of LA products might only be seen over time and when summed.
  - ◊ LA product and introduction may be more costly, but the overall cost of care may be lower.
  - ◊ Dramatically improved adherence translates to fewer instances of disease severity (avoiding more intensive care) and fewer infections (fewer people in care).
  - ◊ Simplified diagnosis, monitoring, and care cascade.
- Need transparent conversations with generic manufacturers about margins.
  - ◊ With fewer units per treatment or one injection to cure (e.g., glecapravir), what does the margin need to be for a manufacturer to "get in the game and stay in the game?"
- Capital investment may be necessary for LA technical platforms
  - ◊ To manufacture novel nano materials, etc.
  - ◊ Need to ensure capital expenditure is separate from the cost of treatment.
- What can we learn from other verticals? We will learn a lot from the infectious disease products we have heard about today.

ANNEX A

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Long-Acting/Extended Release
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