FROM INNOVATION TO IMPLEMENTATION: OVERCOMING CHALLENGES IN PATIENT CENTRIC SAMPLING IN CLINICAL TRIALS

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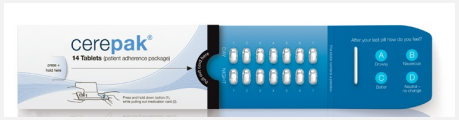
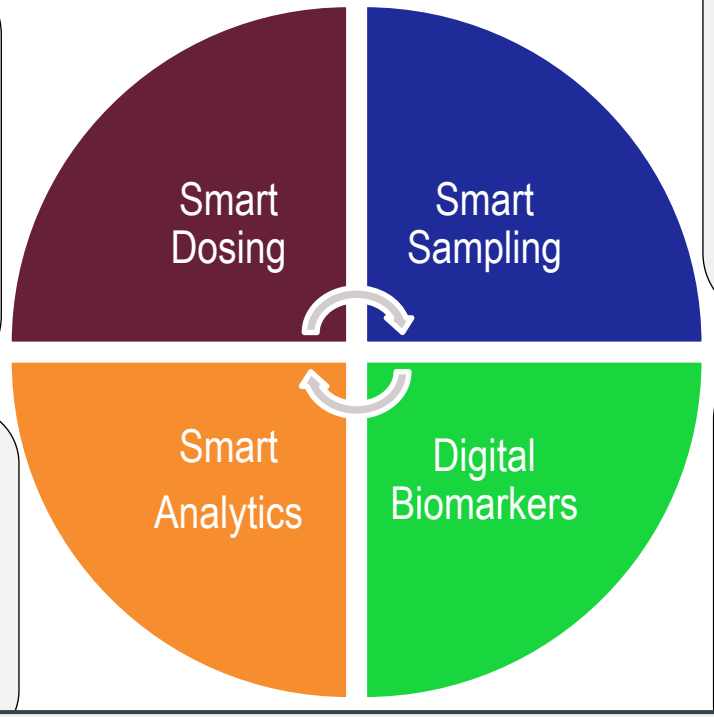
Smart Trials: A Patient Centric Approach to Enriching Clinical Trial Data

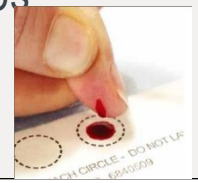
Smart Trials is a cross-functional, multi-year innovation project at Merck & Co., Inc. aimed at **enriching clinical trial datasets** and enabling more **rapid and informed clinical decisions** through a **patient-centric approach**

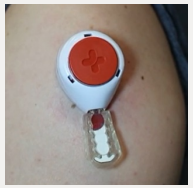
Smart Dosing: technologies to record and transmit dosing information (i.e. if and when the patient took the drug)



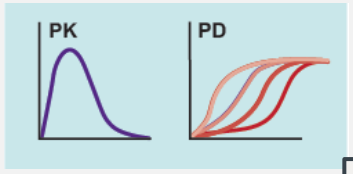


Smart Sampling: technologies for use in the outpatient setting to collect PK, PD, or biomarker samples coupled with date/time stamps





Smart Analytics: analytic platforms that can integrate and visualize data in real-time



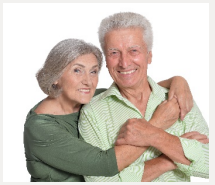
Digital Biomarkers: objective measures collected using digital devices that reflect physiological responses to disease progression or therapeutic intervention

Clinic

HIGH Cost, Skill, Burden

LOW Cost, Skill, Burden

Patients



Site Centric Approach: *Bring the **patient** to the trial*

Patient-Centric Approach: *Bring the trial to the **patient***

Disclaimer: These are just a few examples of the technologies and not an endorsement of any product.

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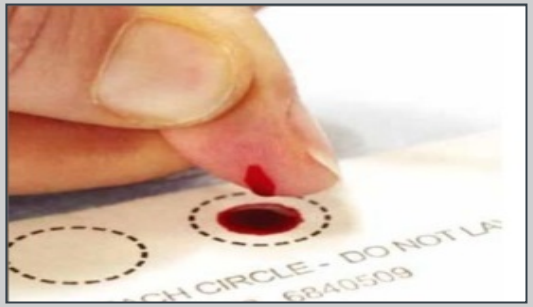
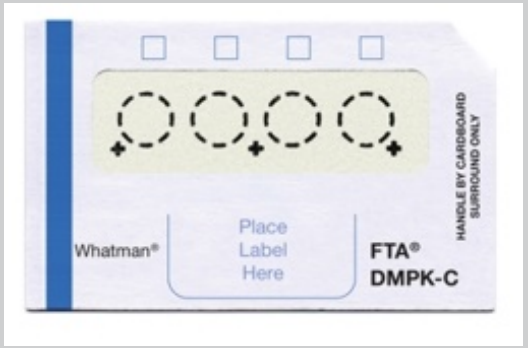
Conclusions and Future Directions

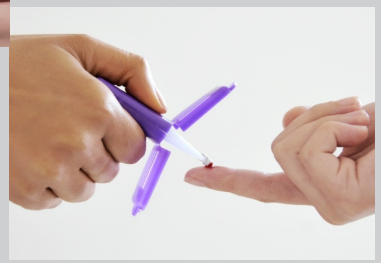
- Smart Trials initiative is aimed at modernizing clinical trials in order to:
  - improve data quality
  - enrich data s
  - drive a mor ic approach
- Pilot study results de sibility and subject acceptance of "smart" approaches for future use a d identify areas of focus for further investigations:
  - automated date/time stamps for sampling, pa f sampling, more streamlined data integration
- Future directions:
  - Continue evaluating digital health technologies & outpatient sampling approaches in pilot trials to enable readiness for implementation in clinical development programs
  - Inclusion of Smart Trials approaches into clinical development programs

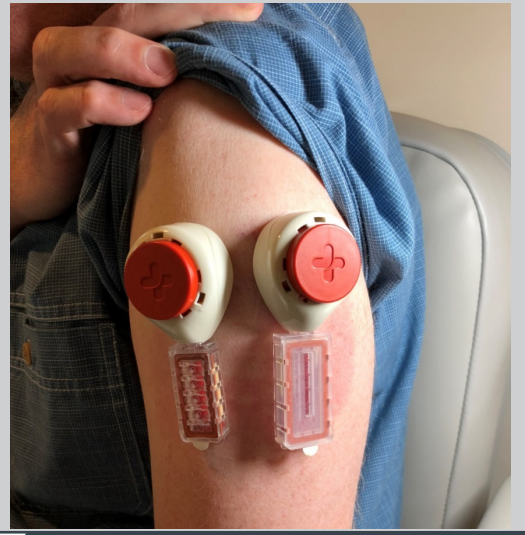
At-Home Sampling Approaches

Dried Blood Spot (DBS)	Volumetric Absorptive Microsampling (VAMS™)	Microneedle Based Approaches
• Blood spotted onto DBS card • ~10-20 µL/spot, 4 spots/card	• Polymer absorptive tip that collect defined volume of blood (10-20 µL) • 4 VAMS tips/sample	• Painless, no sharp exposure • Can include automated collection from device → DBS or VAMS™ • Can include automated date/time stamp









Patient Centric Sampling Challenges

Bioanalytical

- Sensitivity – low sample volume may prevent detection of analyte
- Stability in the dried state – this is a bigger concern in later trials when samples may ship from multiple clinical sites and storage may occur for longer at central laboratories
- Extractability of aged or stressed dried samples
- Appropriate automation for device handling not yet established (chicken and egg story)
  - Tedious sample handling and storage
- Lot-to-Lot variability of sampling matrix
  - Logistics requirement

Patient-centric sampling will not work for all compounds

Feasibility to Replace Wet Blood for GLP and Clinical Studies

Compound specifics:

- Extensive blood to plasma partitioning
- Strong impact of hemolysis on plasma concentrations
- Complicated sample processing due to high viscosity of whole blood
- Low extraction recovery from blood

Validation process

- Accuracy and precision
- Extraction Recovery (101-105%) and Matrix Effect (1.05)
- Hematocrit - % bias (-13.1 to 2.7) from 25-85% HTC
- Dilution QC
- Long term stability at RT and 40°C/75%RH

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First VAMS Study in GLP and Clinical

GLP

Initiate conversion with Preclinical

- Share previous VAMS work
- Present feasibility result

Demo and proposal on sampling

- Pilot study for bridging

Pilot study and training

- Hands on training for pilot and GLP studies

VAMS in GLP study

- Positive feedback from biologists and the team

Clinical

Recommend to Clinical team

- Feasibility result to reach Requested LLOQ

Operational Brochure

- Assessment of storage conditions to ensure stability

Training at Clinical site

- Order supplies for clinical site
- Hands on training

VAMS Clinical FIH

- Initial data was included for IND filing

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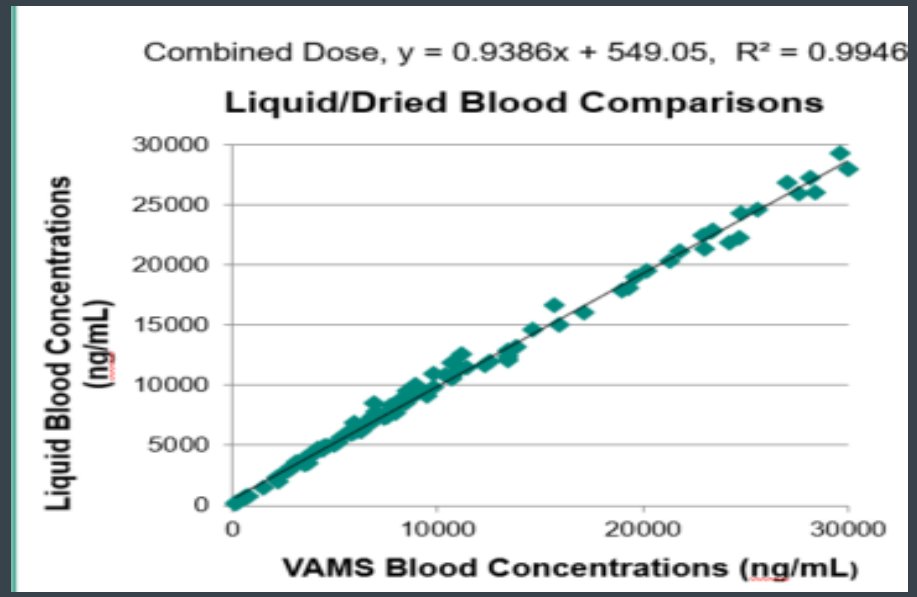
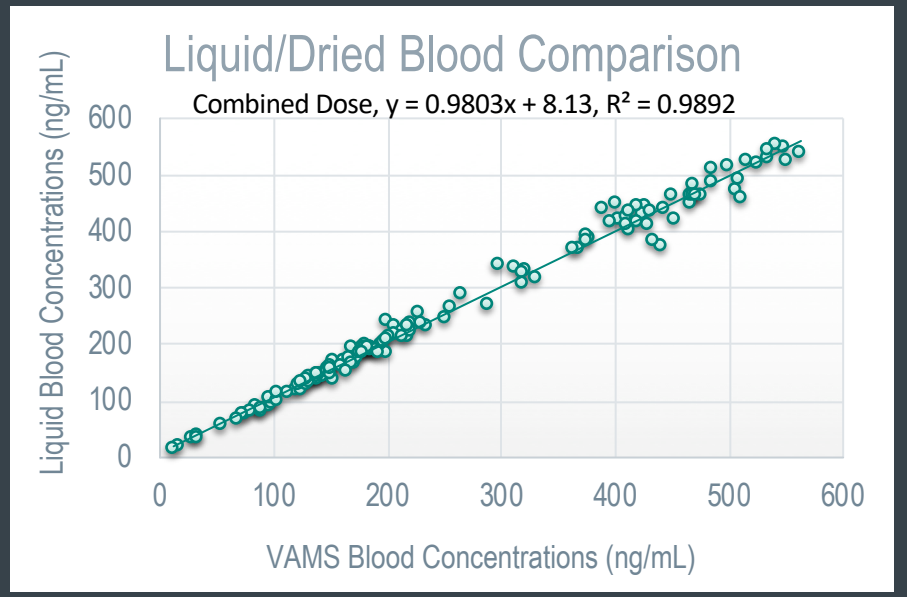
Good Correlations Achieved in Rat, Dog and Human

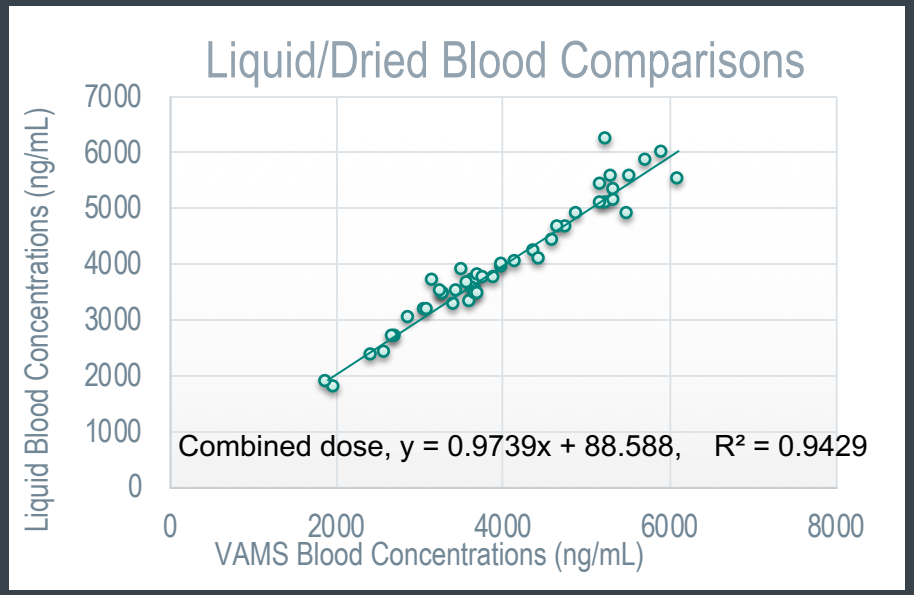
Rat



Human



Dog



- All PK values demonstrated good agreement between wet and dried blood
  - Only Venous Blood
- Positive feedback from the Agency eliminated the need for wet blood sampling in later studies

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Consideration of VAMS Lot Differences

In one panel of the clinical bridging study, dry blood concentrations were 10% higher than in wet blood

- Standard VAMS lot: 9.9 uL
- Unknowns VAMS lot: 10.9 uL

Corrections:

- Apply a correction factor
- Manage the lot variability for standards, QCs and unknowns to ensure data agreement in clinical studies

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Feasibility for Monoclonal Antibody using VAMS

Monoclonal Antibody Drug:

- A fully humanized mAb (IgG1)

PK samples from First in Human clinical study with IM and IV doses

- Serum
- Venous VAMS
- Fingerstick VAMS

IS response in Fingerstick samples showed a different trend compared to Std/QC

- EDTA blood was initially used for Std/QC preparation
- Validation and analysis with Na heparin blood

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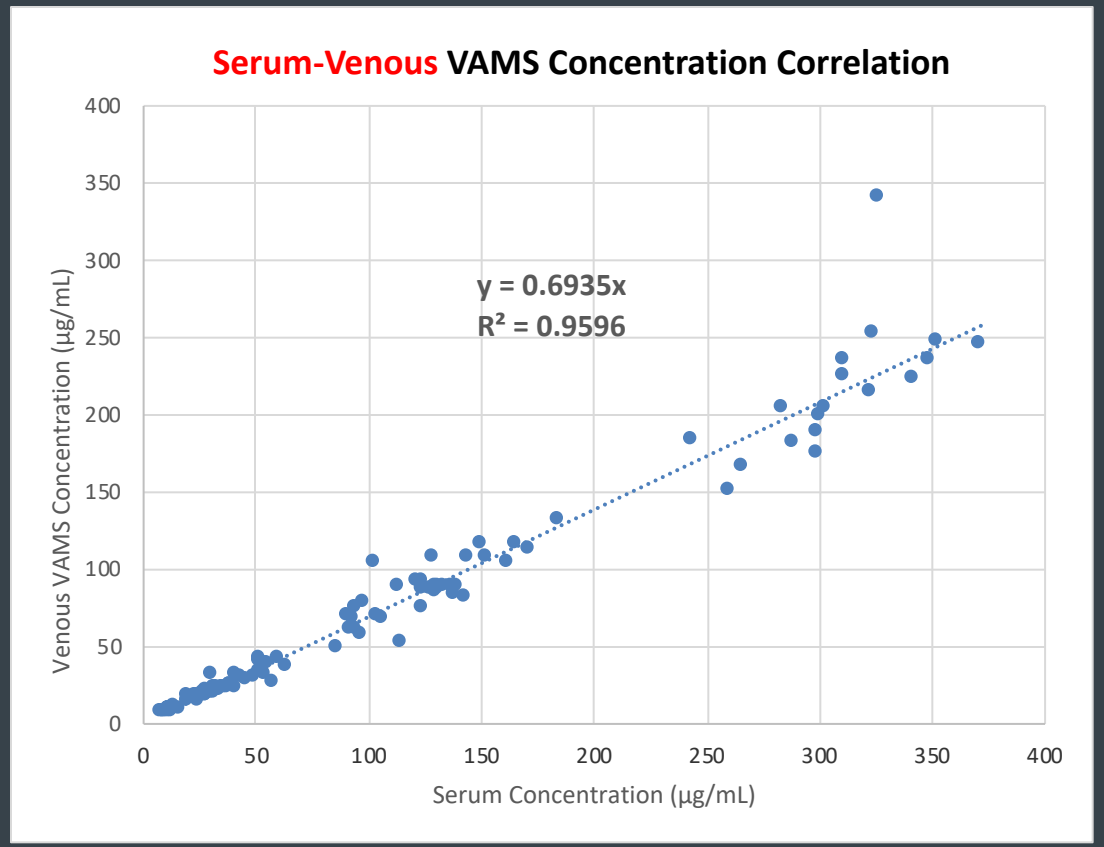
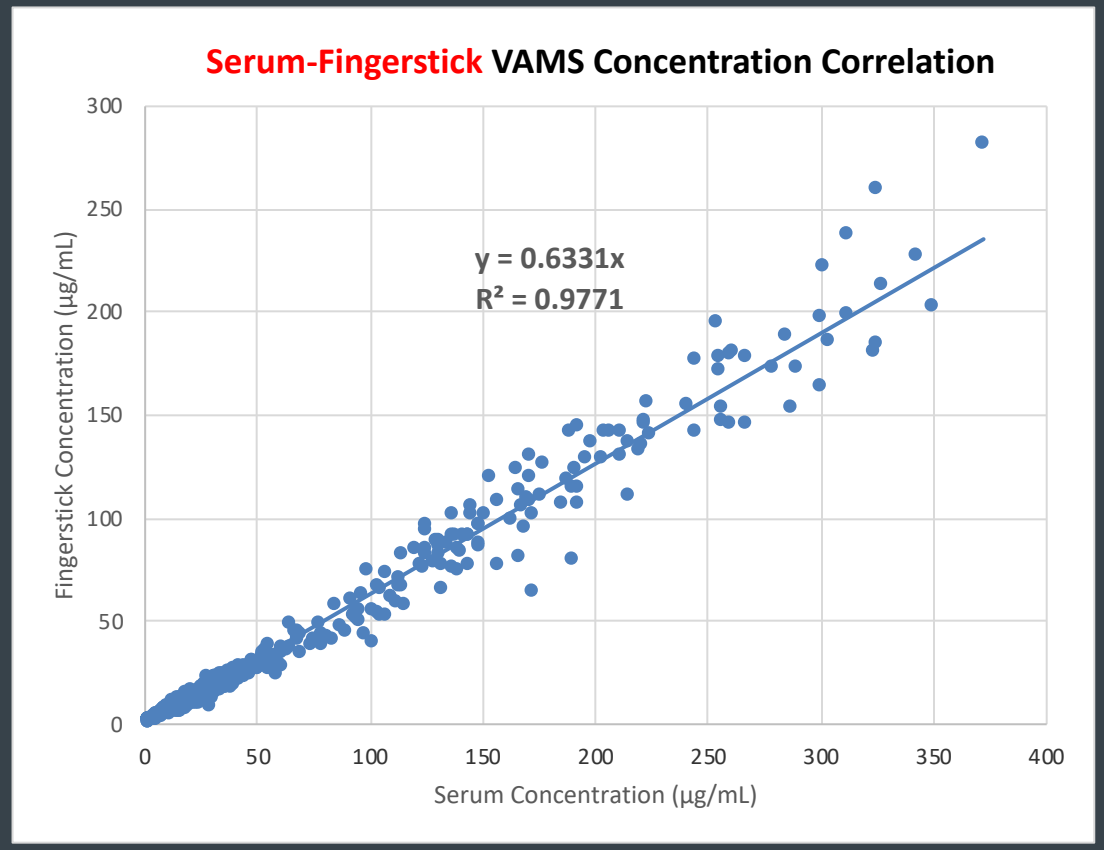
Clinical Study Result
Serum to Venous/Fingerstick VAMS Concentration Correlation





- The study result qualified for future pediatric study using VAMS

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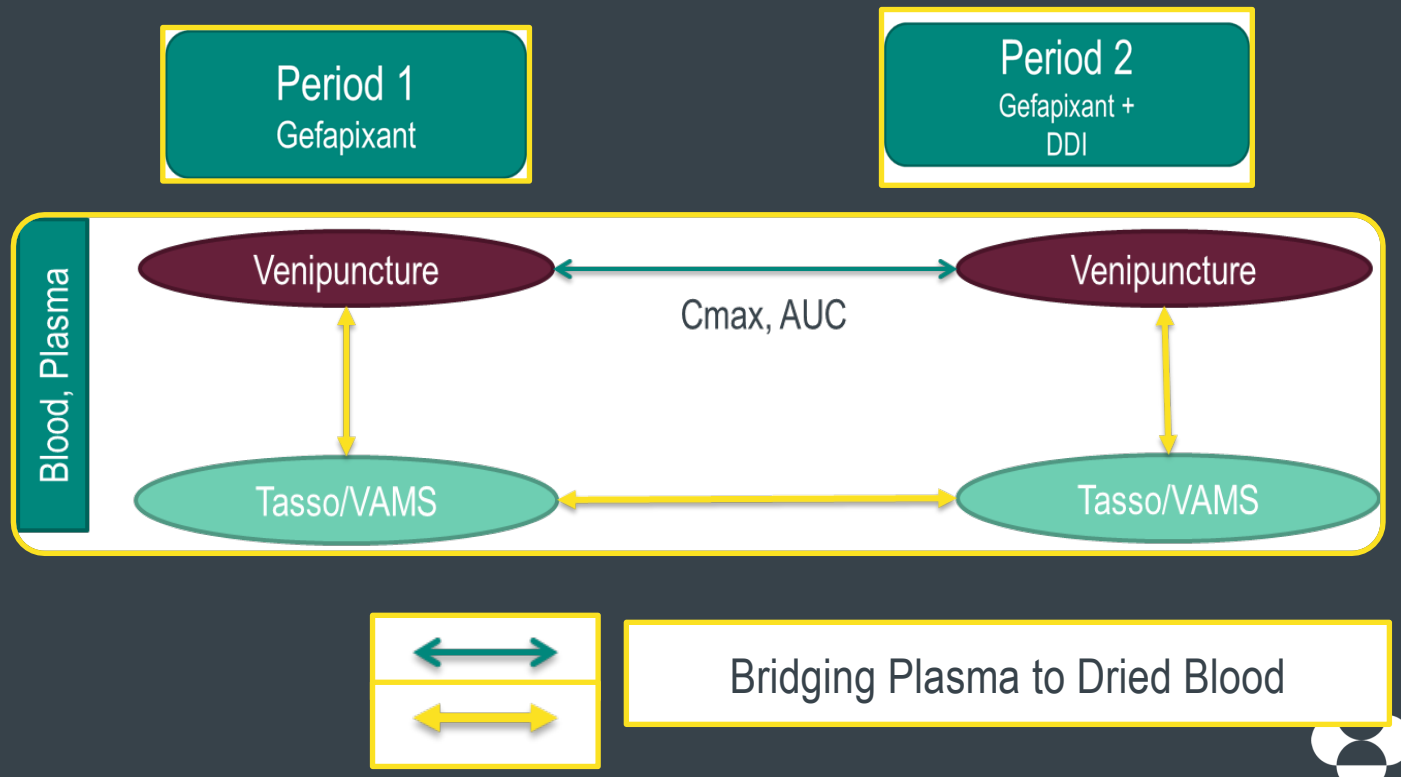
Study Background

- Gefapixant is a nonnarcotic, P2X3 antagonist being developed for the treatment of chronic cough
- Microsampling arm was added to a DDI study with the plan to eventually have at home sampling to monitor compliance – 1st use of Tasso Device in a Merck Program Study



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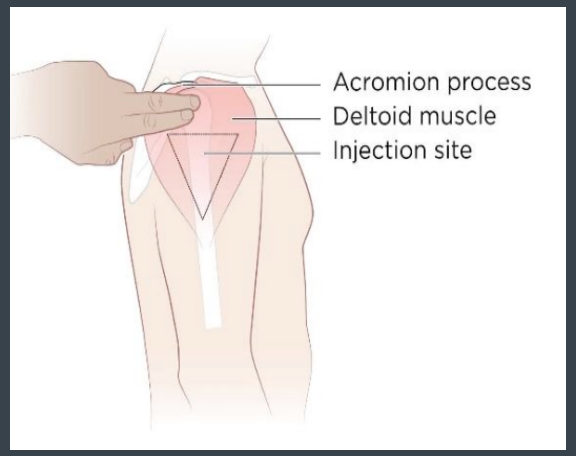
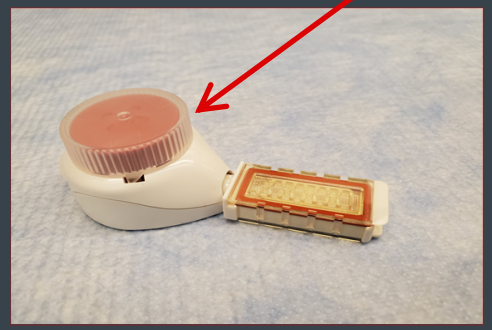
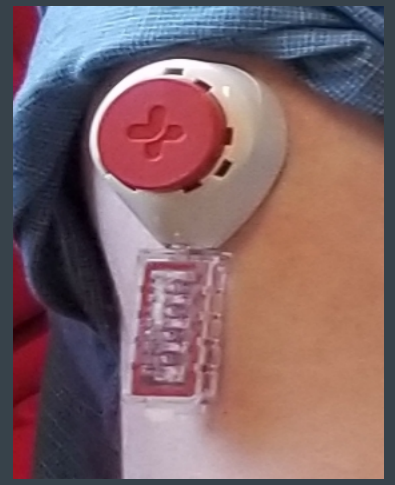
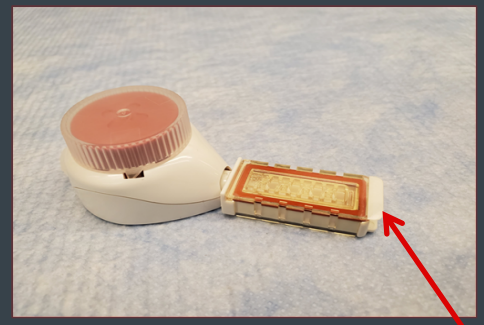
Tasso Sample Collection Procedure



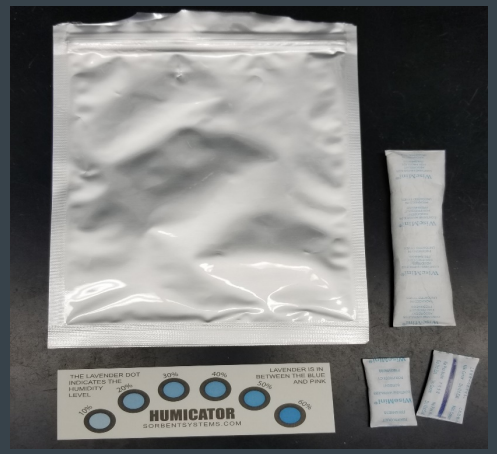
Transparent protective cover







Clear film covering sample pod vents



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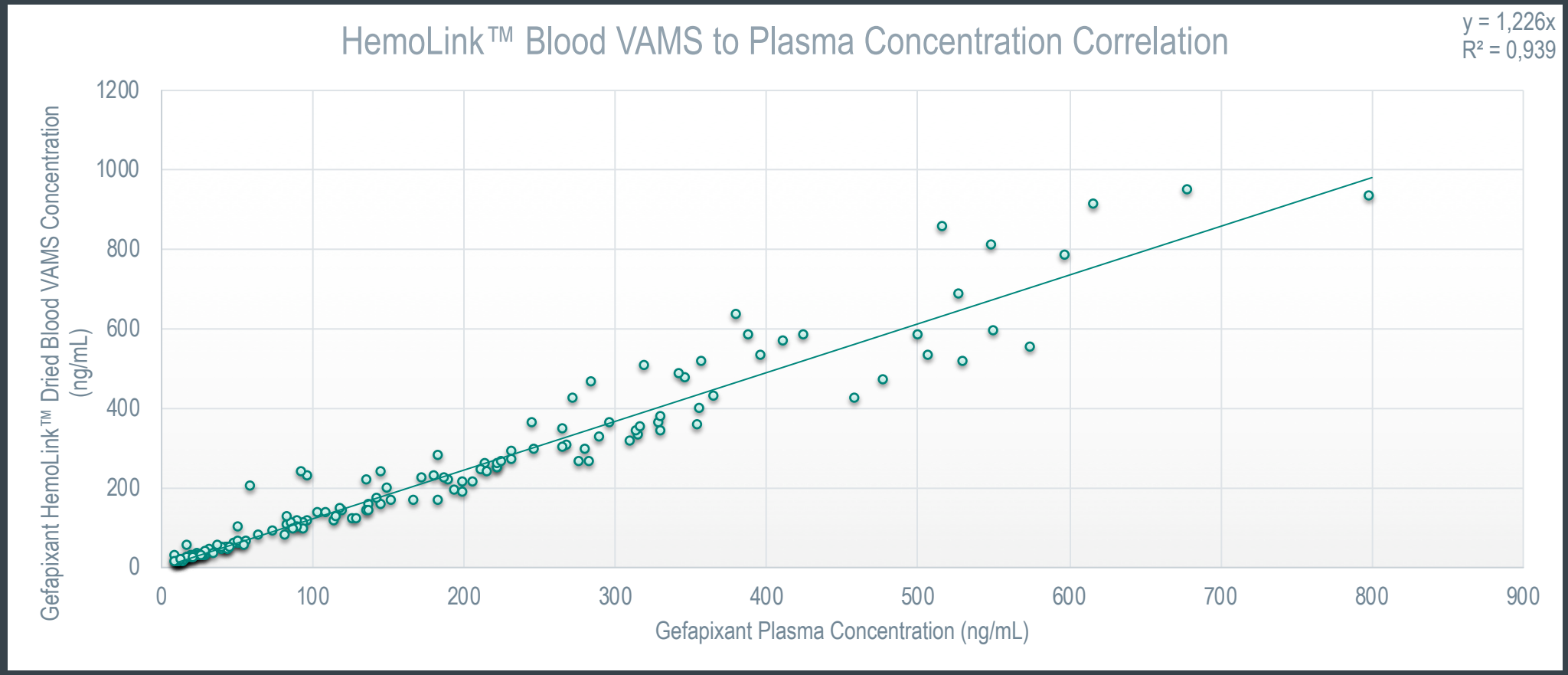
Comparison of HemoLink™ VAMS Data to Plasma



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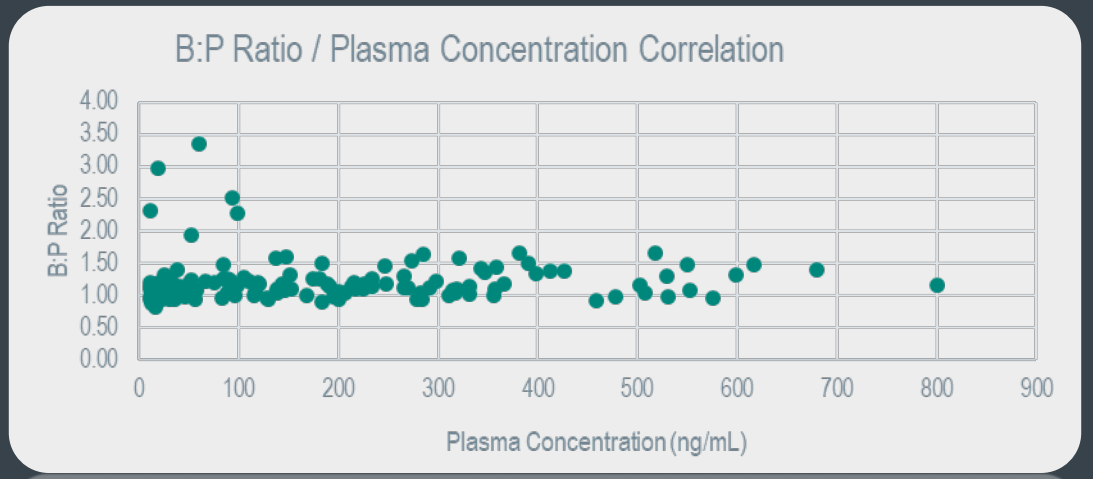
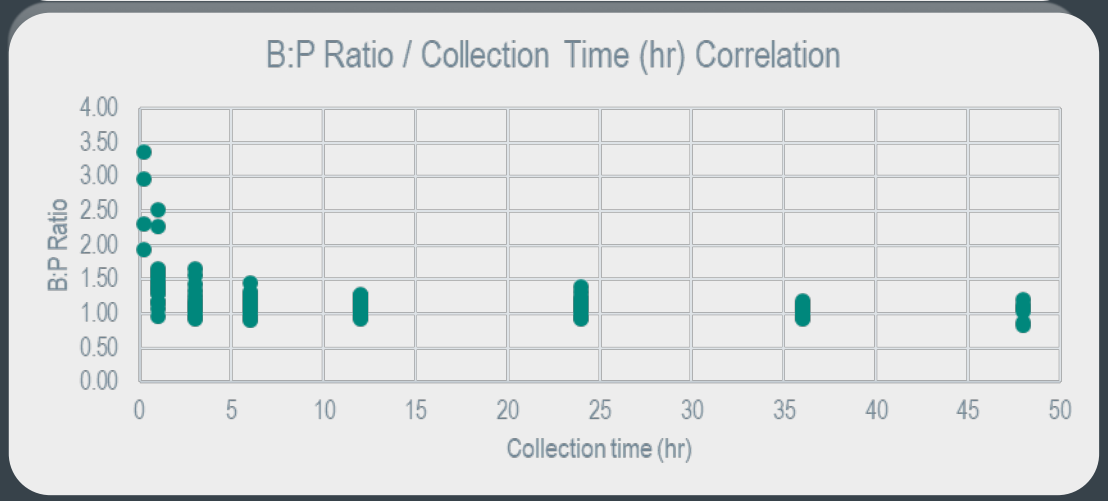
Data Observations

- B:P ratio of *in vivo* samples were similar to that seen in *in vitro* studies
- Samples with higher B:P ratio seems independent of concentration
- Most samples with higher B:P ratio occurred at the earlier time points (0.25 hr, 1 hr)





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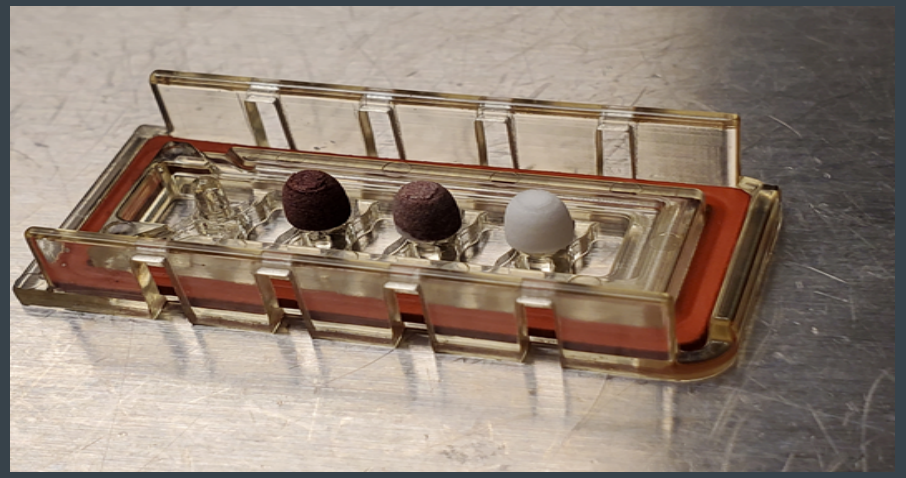
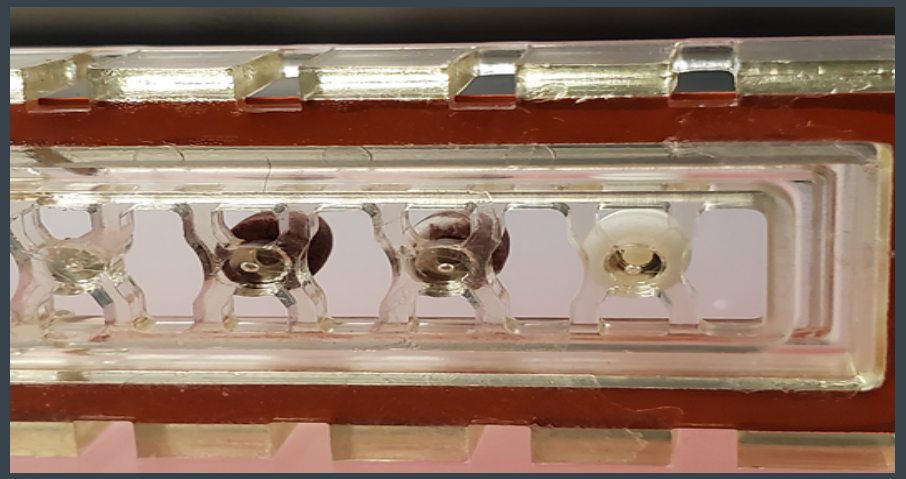
Minor Sampling Issues

240 HemoLink™ samples collected

- 1 instance of incomplete sampling (2 out of 4 VAMS tips had full volume)
- 2 instances of “caking” (early BLOQ timepoints, so impact is difficult to determine)
- Instances of device not actuating in clinic (device was replaced and sample collected)





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Feedback from Clinical Site

They generally felt that the collection devices worked correctly/effectively

- There were a few instances where they did have to try recollection due to no sample being collected on the first attempt
- There were also several instances where the VAMS filled up quite quickly and we removed within < 1min/2min.
- Some did find that the activation button was a little difficult to engage (push harder than anticipated)

Some positives:

- Participant complaints were extremely minimal and there were no complaints of pain when performing the procedure.
- The devices were easily removed and overall was a very simple process from start to completion of packaging.
- The heat packs did seem to assist with blood flow.

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Feasibility for Triplet Combination in VAMS (Ongoing Clinical Study)

- Triplet co-dosing
  - All three compounds with long half lives (at home sampling to assess trough drug levels)
- Challenges for simultaneous extraction
  - To achieve high recovery for all three compounds with different physical/chemical properties
  - Sensitivity requirement on Lower limit of quantitation(LLOQ)

Compound	LogD@pH3.0	LLOQ (ng/mL)
A (Nucleoside analogue with phosphate)	-4.02	0.2-0.5
B	-0.42	100
C	0.51	0.1

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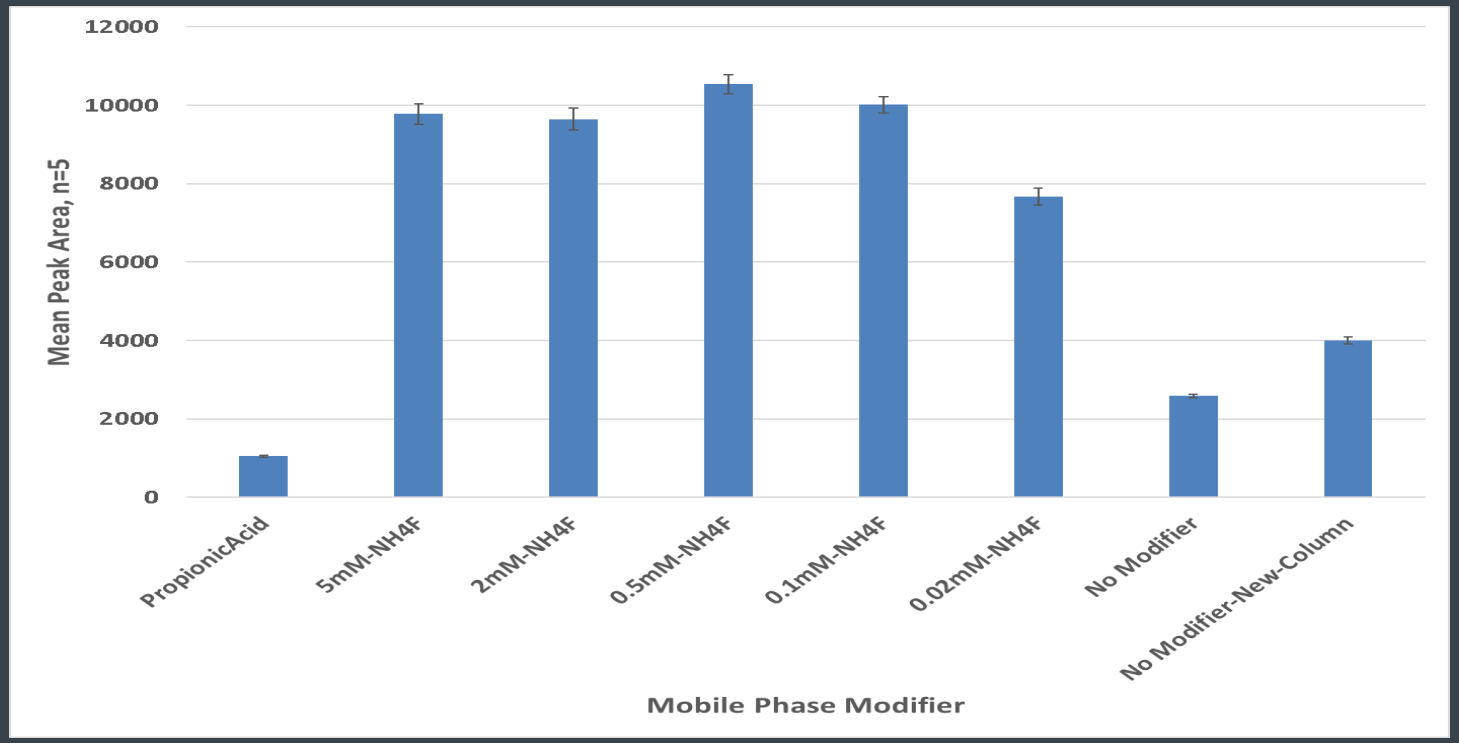
To Improve LC/MS/MS Sensitivity (Compound C, 0.1 ng/mL LLOQ)

Mobile phase modification to increase MS ionization



Using NH_4F modifier in the LC mobile phase, MS sensitivity was significantly improved

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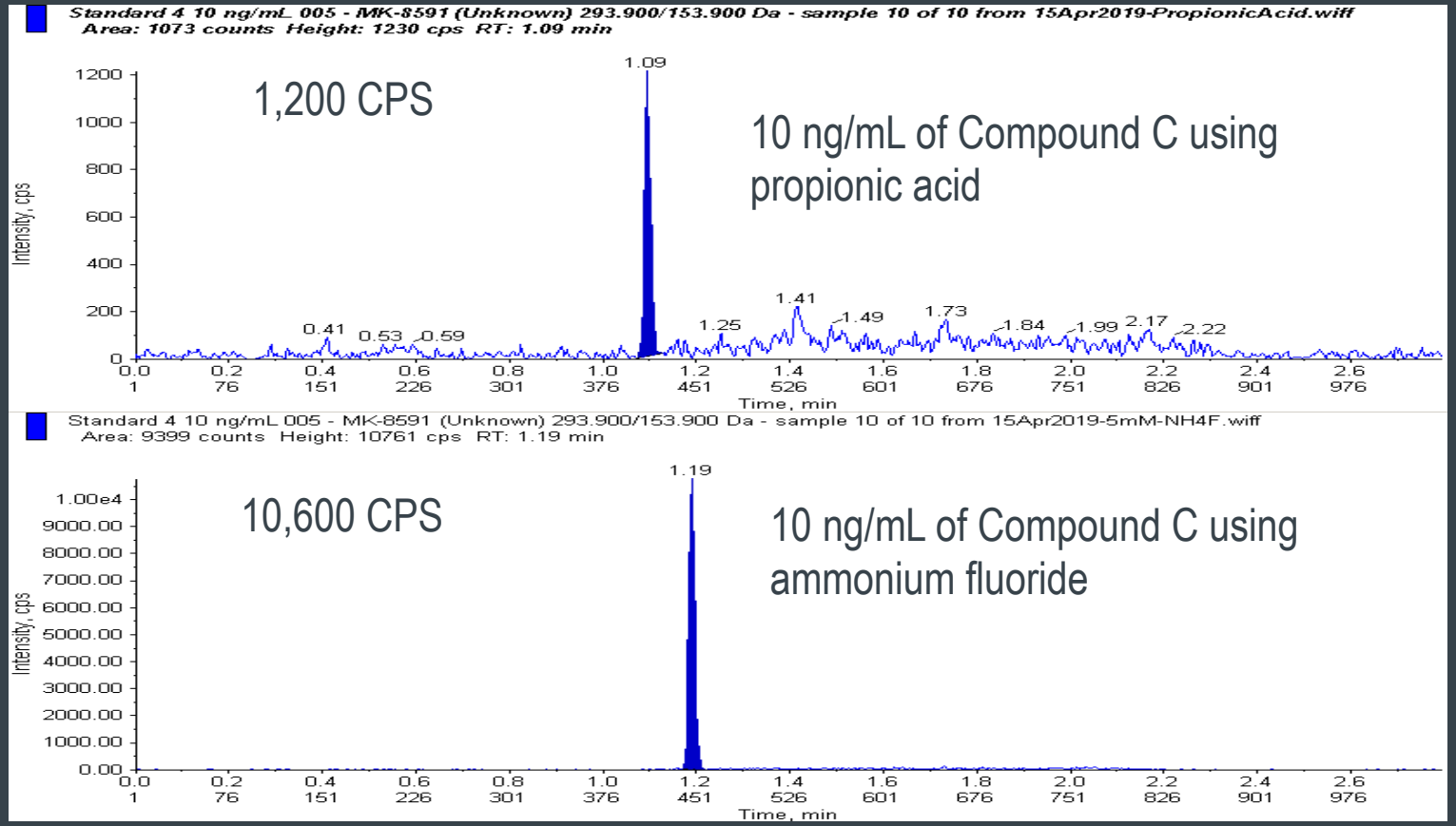
Sensitivity Achieved with Mobile Phase Containing Ammonium Fluoride (Compound C)



Signal to noise is >25x higher using 5mM ammonium fluoride vs 0.1% propionic acid on a API4500

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Patient Centric Sampling Challenges

Logistical (real and/or perceived)

- Clinical site and Patient training – this can involve several clinical sites all over the world and require language translation.
- Technology access for use in remote/underserved geographies if using an eDiary/App based data collection approach is used.
- Shipping requirements within a country and country to country?
- How do we reliably collect a time stamp and how will the data flow?
- Patient compliance and sample collection reliability, at home sampling needs to be as simple and straightforward as possible.

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Patient Centric Sampling Challenges

Business/Regulatory Related

- "If it can't be used at 100% of sites, it can't be used at all" attitude.
- Increases the cost of conducting the trial.
- Requires bridging from liquid plasma to dried blood.
- Increases the complexity of the protocol for the trial and this may impact enrollment?
- No definitive data that shows return on investment for Patient-Centric Sampling.
- How are devices treated and what regulatory approval is needed in each country?
- How do you show the sample is from the person enrolled in the trial?
- Can you define inclusion/exclusion criteria using adherence data from at home sampling? What about intent to treat criteria?

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Protocol Development for At Home Sampling Technologies

- We include all participant facing materials (including training materials and any surveys) in our IRB submission and include mention of the device in the Informed Consent.
- The use of Tasso is described in the protocol which was submitted to the IRB.
- The Tasso device and blood collection in general are considered “low risk” procedures so we don’t need to explicitly seek IRB approval.

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Protocol Components of the Study

- Include rationale for conducting bridging and using novel PK devices
- Describe devices to be used
- Include timepoints at which devices will be used for PK sampling
- Decide whether sampling will be done in the clinic or at home
- Decide how safety events related to device will be captured
  - For Tasso devices, AEs (e.g. bruising) are captured as study AEs in clinic database similar to a hematoma from a blood draw or rash due to ECG leads
- Decide how device malfunctions will be captured and whether these need to be reported to manufacturer or regulators
  - For Class I devices like Tasso, no reporting to FDA required

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The Regulatory Path Followed with the Team

Statement from our internal Regulatory Group:

"The Tasso OnDemand™ when used to collect blood samples for PK, is considered an investigational device. In the USA, it is classified as a Class I device (low risk) and exempt from both a clinical as well as a commercial application prior to use. It does not require a separate IND or IDE, nor does it require IRB approval outside of the protocol in which it is being used."

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Study Rationale Language

outside of planned clinic visits. Given that Phase 2 and 3 trials are large, multi-center studies, it is desirable to pilot these novel technologies in a smaller study or in a subset of participants. To support these technologies in later studies, this study will estimate the relationship between MK-[redacted] plasma PK and PK in dried blood, and the relationship between MK-[redacted] plasma, [redacted], and total MK-[redacted] in dried blood. PK will be measured using venous and fingerstick blood samples collected in the clinic and compared to capillary blood collected using the Tasso OnDemand™ device both in the clinic and at-home. In particular, this will facilitate evaluation of the reliability of participants using the OnDemand™ for at-home PK sampling.

Protocol Language

8.6.2.2 OnDemand™ Blood Samples

The OnDemand™ device is a blood collection tool that will be used to obtain capillary blood samples from participants' arms. The OnDemand™ device adheres to the participant's upper arm and employs lancets to pierce the skin and a delicate vacuum to flow blood into the tool. The blood is then collected onto an absorptive material, which can then be analyzed for drug concentrations. Further instructions on use of the OnDemand™ device will be provided in the laboratory/study operation manual.

Malfunctions or AEs directly related to the OnDemand™ device should be communicated to the manufacturer by the Investigator. Additionally, AEs involving the OnDemand™ device should be recorded on the appropriate eCRF.

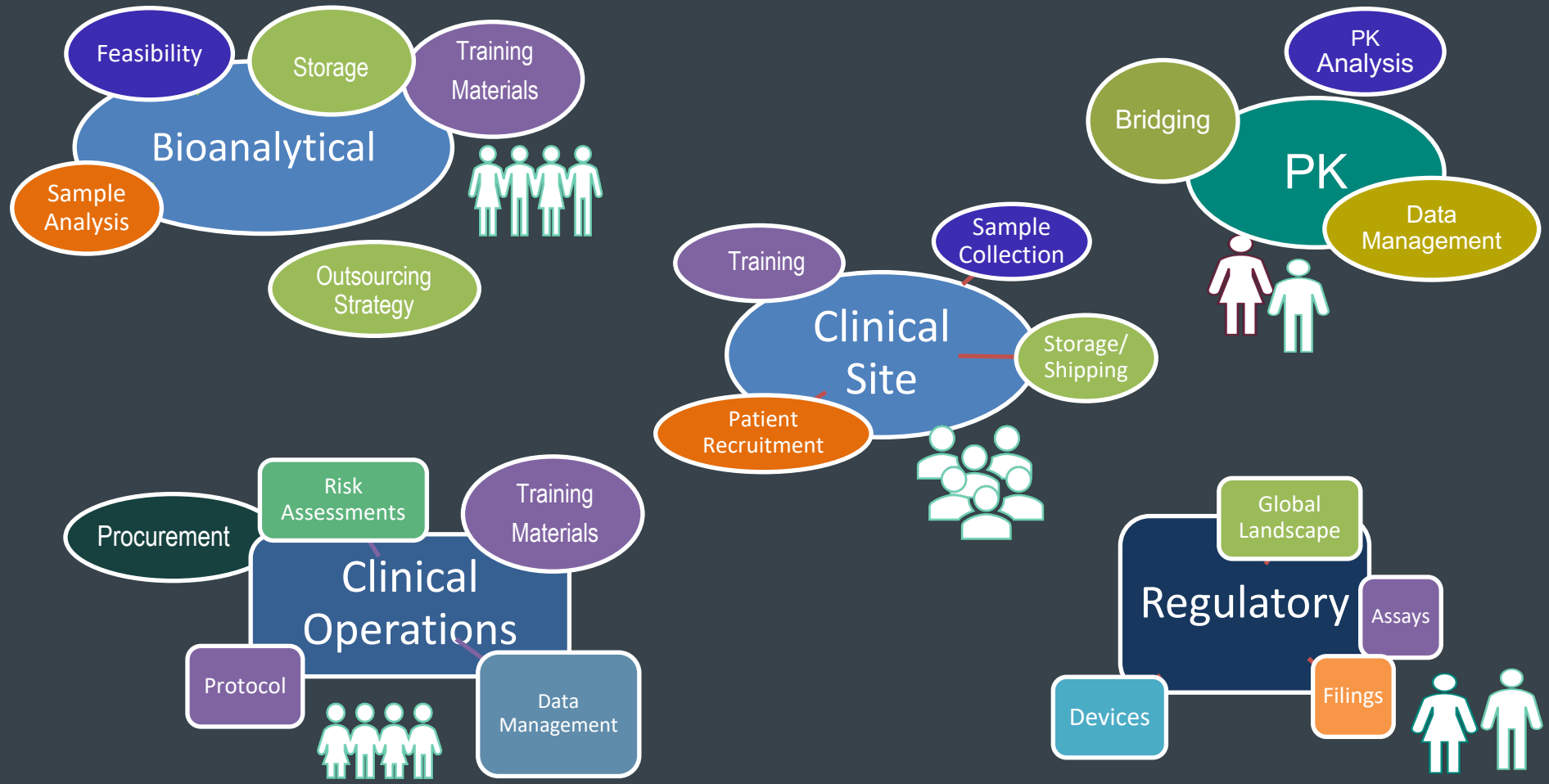
Description of Blood Sampling

8.6.3 Peripheral Blood Collection for MK-[redacted] and Total MK-[redacted] Dried Blood Assays

Blood drawn via fingerstick and sampled using the VAMS™ collection kit will be collected by the study participants in the clinical research unit. Capillary blood drawn via Tasso OnDemand™ will be collected by the study participants in the clinical research unit and at home. Study participants will be trained by the study site staff; collections done in the clinic will be observed by the study site staff. For timepoints at which both venous and fingerstick and/or Tasso OnDemand™ blood is collected at the same scheduled time, the venous and non-venous collections should occur within 15 minutes of each other.

Study participants will be discharged with a pre-labeled collection kit and be instructed to collect PK samples at the timepoints specified in the SoA. Study participants will also be provided with a paper diary card to record date and time of sample collection. All at home PK samples will be returned to the clinical research unit at the next scheduled study visit, or if more convenient, at an earlier time agreed upon mutually by the study site and the participant. Detailed instructions will be provided by the study staff to each participant.

Logistical Roles and Responsibilities for Patient Centric Clinical Studies



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