Implementation of Patient Centric Microsampling to Support Paxlovid PK

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Clinical Bioanalytics, Clinical Pharmacology, Pfizer

Outline

Clinical Development Demands Tools to Support Decentralized Trials

- PK Strategy to Support Outpatient Studies
- Patient Centric Microsampling Brings Flexibility/Convenience to Special Populations with Reduced Patient Burden

Bioanalytical Support for Decentralized Trials

- Selection of Devices
- Method Dev and Validation
- Bridging Strategy and Results
- B/P Ratio

Implementation of Tasso M20 for PK

- Device Approval Status
- Central Lab Workflows
- Patient Facing Document and Site Training
- Patient Acceptance

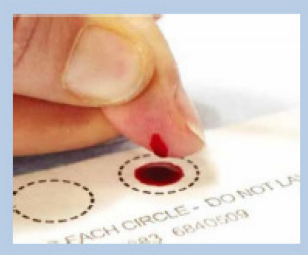
Paxlovid Clinical Development for EUA

- COVID-19 pandemic requires expedited development of antiviral therapies to prevent disease progression and stop transmission. Nirmatrelvir (PF-07321332) is an orally bioavailable protease inhibitor with potent antiviral activity. It entered phase I clinical trial in March 2021.
- Out-patient studies were needed because of quarantine requirements for COVID-19 patients to reduce spread of the infection to site staff or other patients.
- With out-patient study design, PK sampling at-home using Tasso M20 device was implemented in three Phase 3 studies used to support the emergency use authorization (EUA).
- The at-home sampling complemented venous blood sampling procedures to enrich the PK dataset and to improve patients on-study experience by allowing different sampling approaches (e.g, home health visits, site visit, or self-collection).
- Paxlovid (Nirmatrelvir/ritonavir) was granted emergency use authorization in Dec 2021 by FDA and it has since received authorization/approval in several countries.

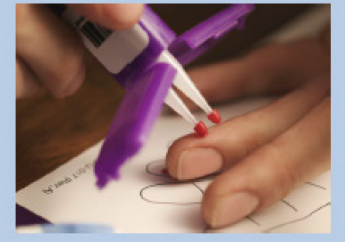
Enabling Technologies for At-home PK Sampling

Traditional Venous Collection

Fingerstick Collection



https://cleancompetition.org/2016/05/11/whats-next-wednesday-dried-blood-spot-sampling/



https://www.neoteryx.com/mitra-cartridge-blood-sampling-device-dbs

https://www.trajanscimed.com/pages/hemapen

Mobile Phlebotomy

www.sciencedirect.com/science/article/pii/S0167701217303287?via%3Dihub

ehp.niehs.nih.gov/doi/pdf/10.1289/ehp.6264

Capillary Collection

https://www.tassoinc.com/

http://www.7sbio.com/

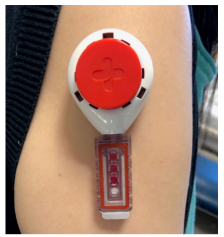
https://www.drawbridgehealth.com/

Patient Centric Sampling: How the COVID-19 Pandemic is Shifting the Landscape, IQ CPLG/TALG PCS Working Group, 2021.

PK Assay Feasibility Evaluation with Different Devices

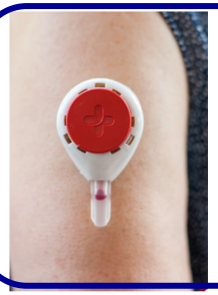
Parallel PK samples were collected at the same sampling time point from the same subject for comparison.

Venous Plasma



Tasso M20
Dried Blood

<100 µL of blood

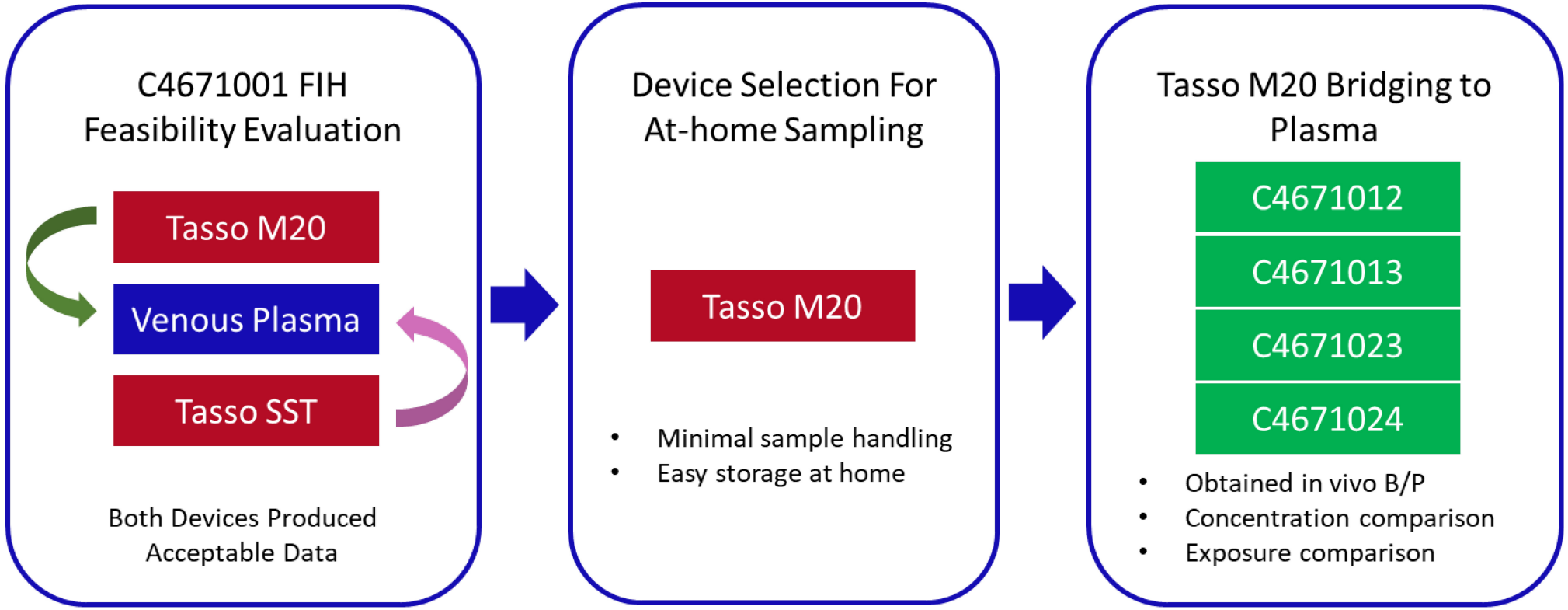


Tasso SST
Liquid Serum

~ 100 µL of serum

Tasso M20 Video Link:
https://vimeo.com/409226805?embedded=true&source=vimeo_logo&owner=96725381

Bioanalytical Bridging Strategy

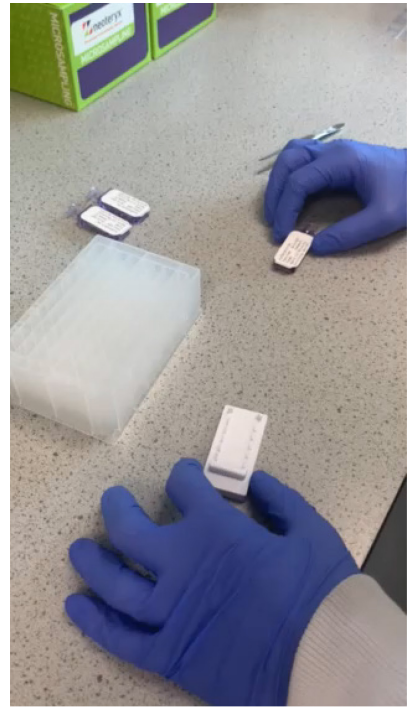


1. Enaksha R Wickremsinhe, Qin C. Ji, Carol R. Gleason, Melanie Anderson, and Brian P. Booth, Land O'Lakes Workshop on Microsampling: Enabling Broader Adoption, ***AAPS J.*** (2020) 22: 135.

Bioanalytical Method Validations

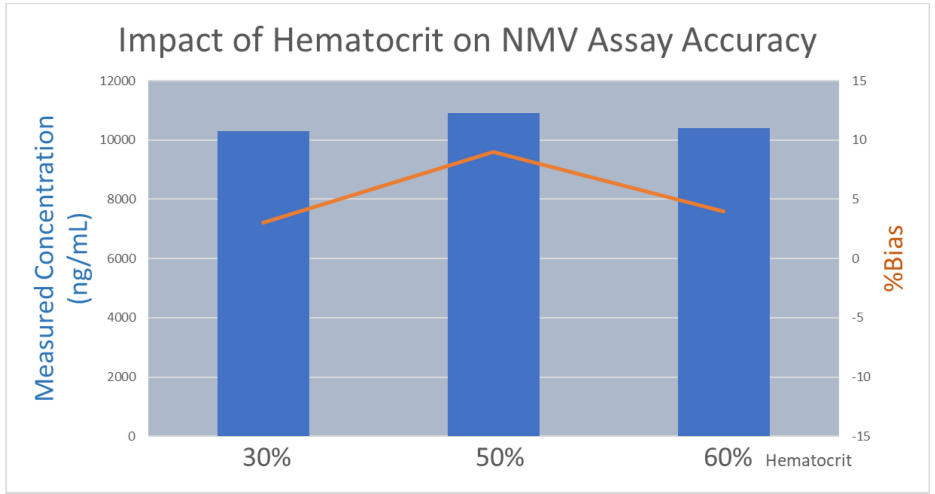
Three assays are needed:

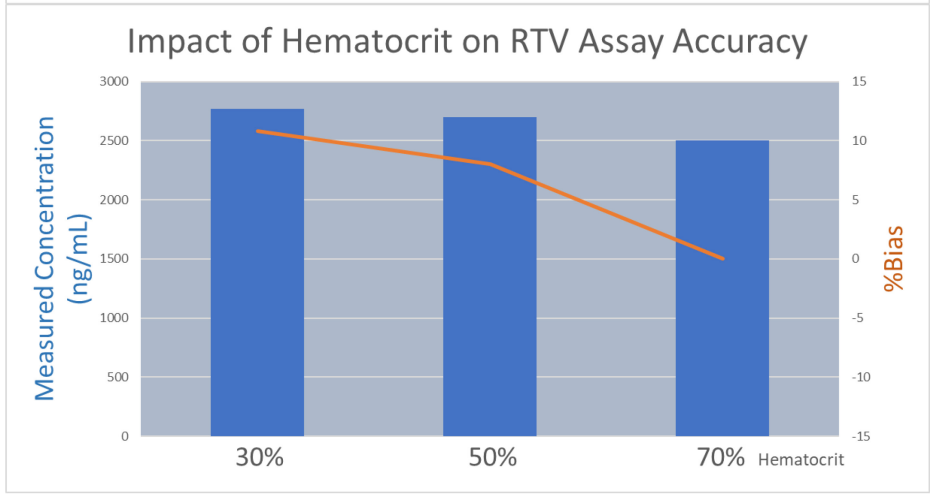
- Plasma Assay
- Whole Blood Assay
- Dried Blood Assay (for the analysis of Tasso M20 samples
  - Hematocrit impact to assay accuracy
  - Lot-to-Lot Variation
  - Comprehensive stability evaluations (including elevated humidity and temperature conditions) to cover the entire life cycle of a sample

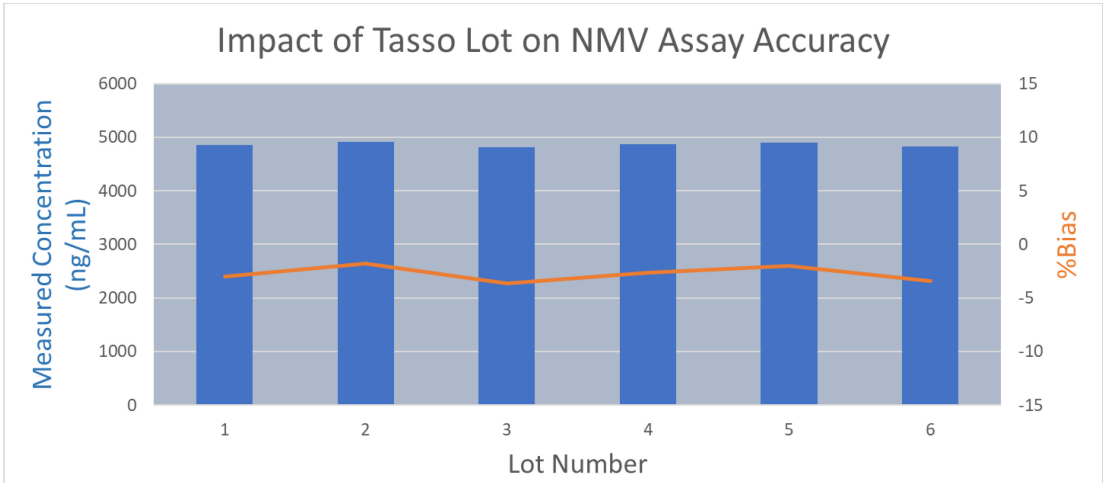


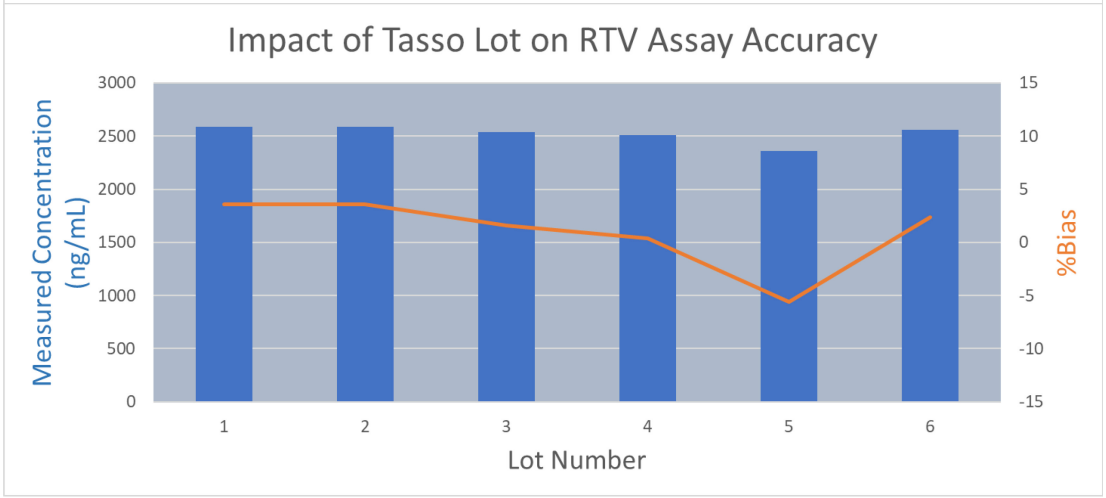
Store ambient @ patient home until pickup by Courier → Dry Ice or RT → Central Lab → Dry Ice or RT → Analytical Lab

Paxlovid Assay: Hematocrit Levels and Lot-to-Lot Variations









Summary Bridging Results for NMV

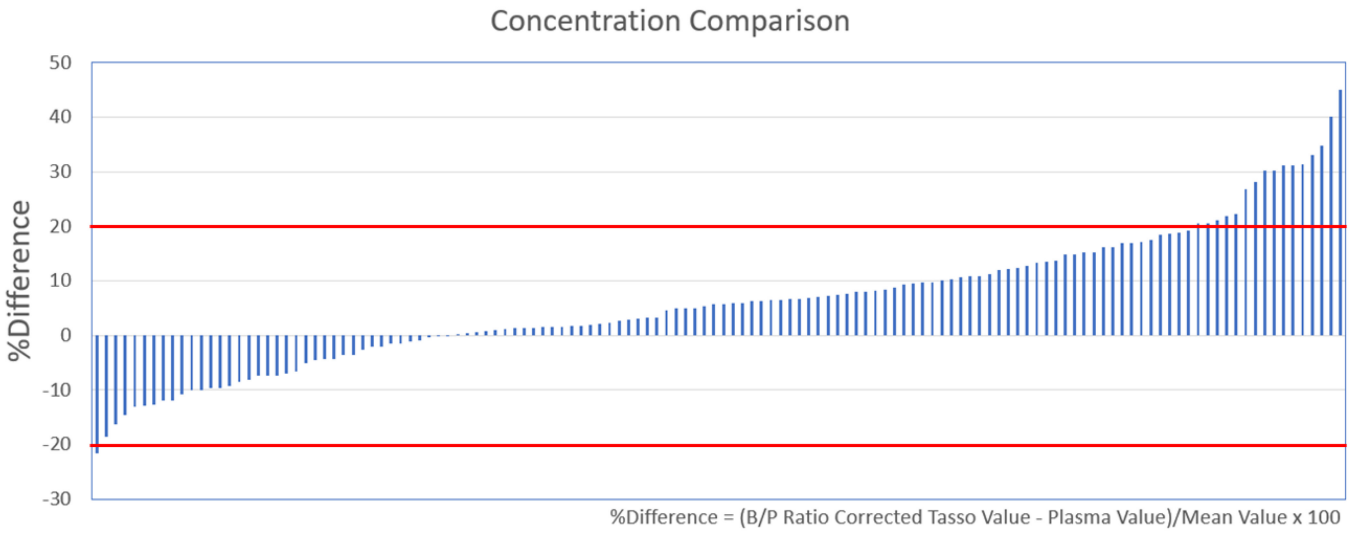
- Dried blood concentrations measured from samples collected via Tasso M20 device were converted to equivalent plasma concentrations by applying B/P ratio.
- Tasso equivalent plasma concentrations and traditional venous plasma concentrations were paired up for concentration and exposure comparisons to establish assay concordance.

Study	Number of Data Pairs	Concentration Comparison (% Passing)*	Bland-Altman Plot Bias (%)	Bland-Altman Plot SD of Bias	Correlation r	AUC within BE Criteria**	Cmax within BE Criteria**
C4671001	35	62.9%	-5.853	18.9	0.9557	N/A	N/A
C4671012	138	79.7%	-7.947	17.75	0.8814	23/23	21/23
C4671013	66	81.8%	9.963	14.47	0.9539	10/10	8/10
C4671023	132	87.1%	6.190	12.37	0.9625	22/22	22/22
C4671024	128	80.5%	7.513	14.76	0.9430	22/22	18/22

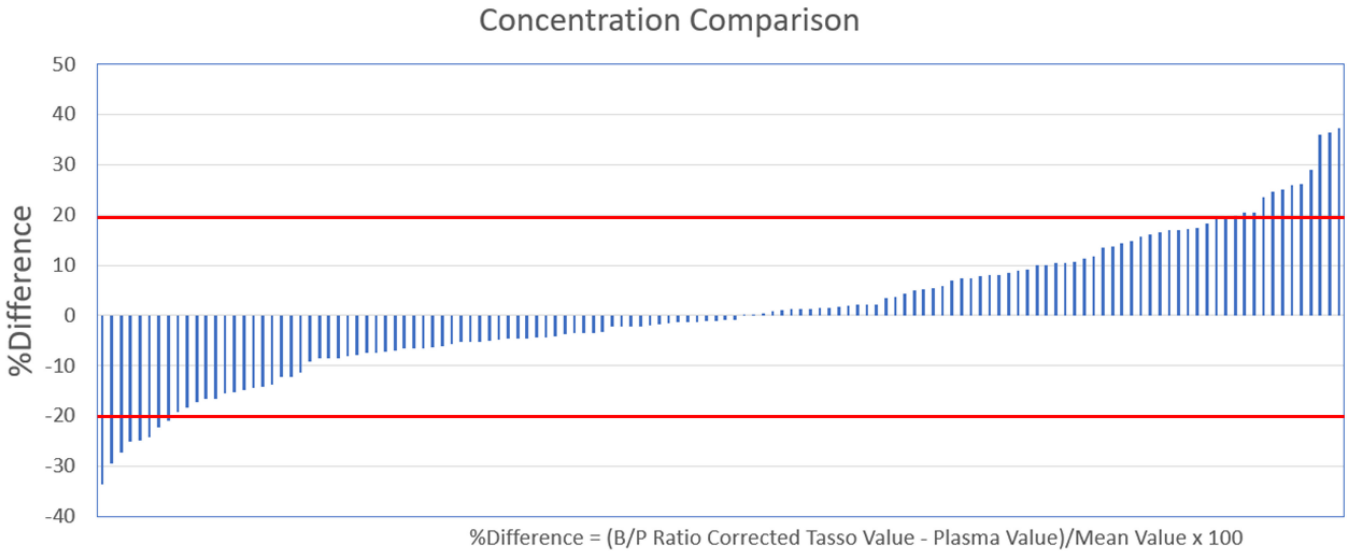
* Percent of data pairs where their difference is within +/- 20% of their mean
** Tasso/Plasma exposure ratio within 80-125%

Bridging Results In C4671023 – Waterfall Plot

NMV – %Diff from 115 out of 132 (87.1%) data pairs are within +/- 20% of their mean.

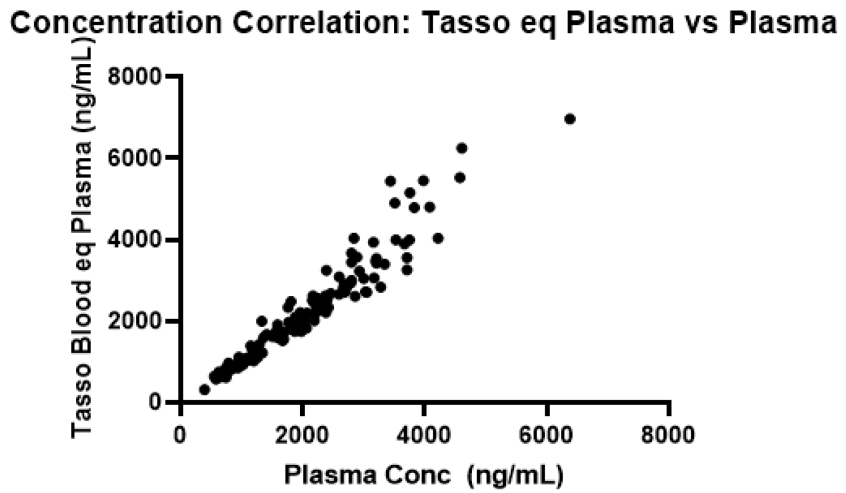


RTV – %Diff from 113 out of 132 (85.6%) data pairs are within +/- 20% of their mean.

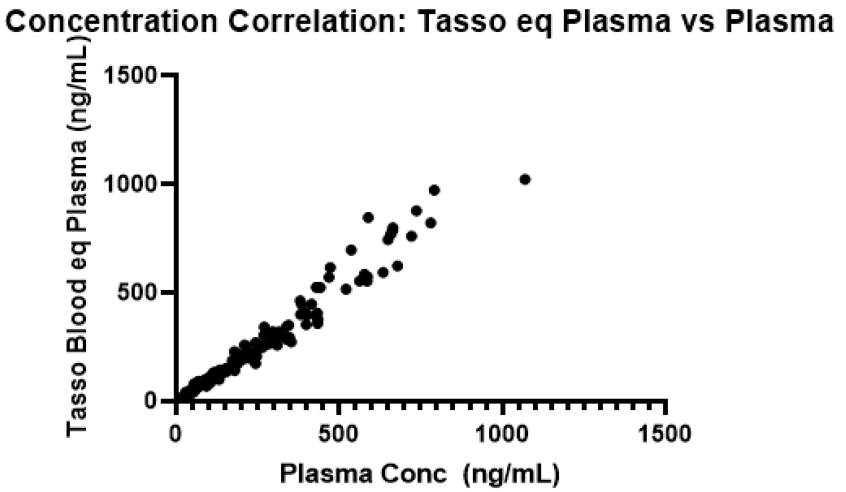


Bridging Results In C4671023 – Correlation Analysis

NMV
r = 0.9625
P < 0.0001

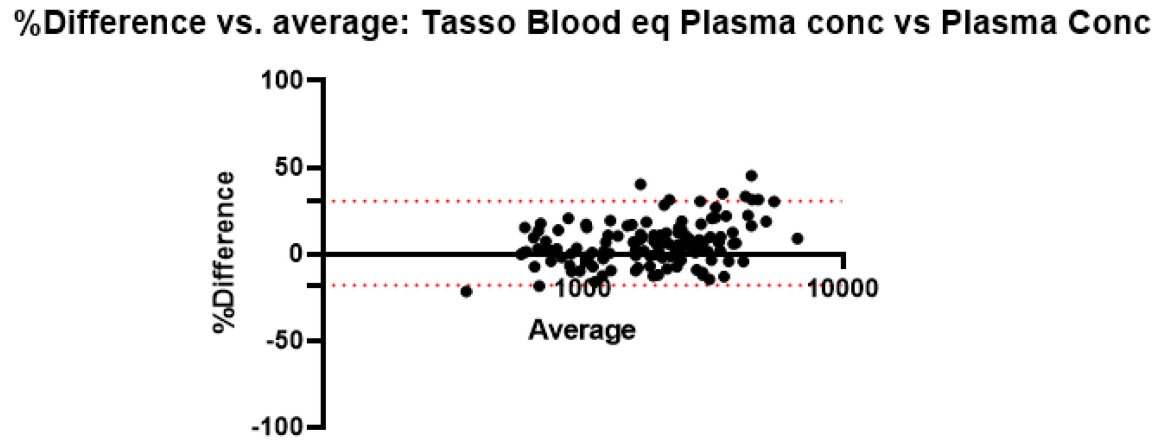


RTV
r = 0.9777
P < 0.0001

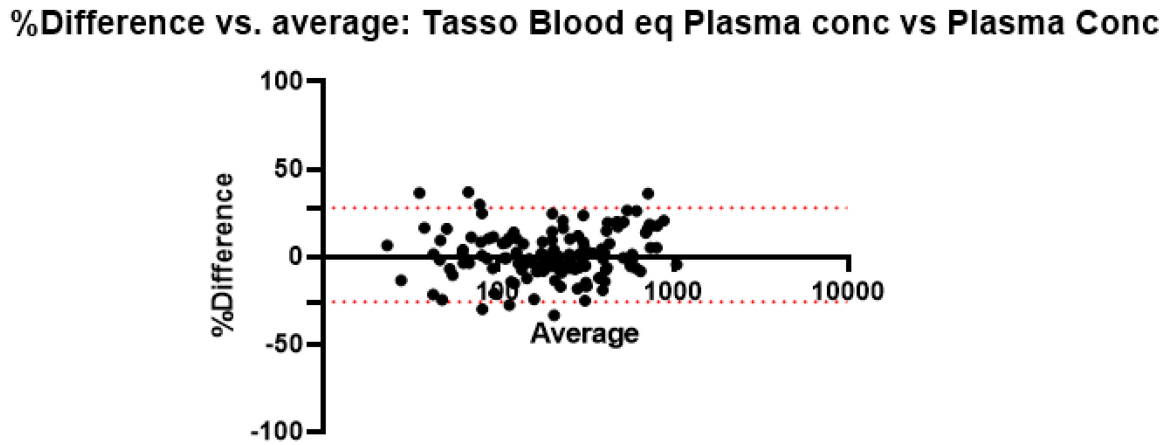


Bridging Results In C4671023 – Bland-Altman Plots

NMV
Bias = 6.190
SD of bias = 12.37



RTV
Bias = 1.002
SD of bias = 13.66



NMV Tasso M20 Assay Performance and Sample Quality

Study	Study Title	Number of Samples Collected	Number of Results Not Reportable due to Sample Quality Issues	ISR Passing Rate	Run Passing Rate
C4671001	A Phase 1 Single Ascending Dose and Multiple Ascending Dose Study of PF-07321332 in Healthy Adult Participants	58	4	75.8%	100%
C4671002	A Phase 2/3 Efficacy and Safety Study of PF-07321332/Ritonavir in Nonhospitalized Low-Risk Adult Participants With COVID-19	31	2 (overfilled)	50%*	100%
C4671005	A Phase 2/3 Efficacy and Safety Study of PF-07321332/Ritonavir in Nonhospitalized High Risk Adult Participants With COVID-19	102	0	82.6%	100%
C4671006	A Phase 2/3 Postexposure Prophylaxis Study of PF-07321332/Ritonavir in Adult Household Contacts of an Individual with Symptomatic COVID-19	293	11 (underfilled)	90.5%	54.5%**
C4671012	A Phase 1 Study to Estimate the Effect of PF-07321332/Ritonavir and Ritonavir on the PK of Dabigatran in Healthy Participants	138	0	100%	100%
C4671013	A Phase 1 Study to Estimate the Effect of PF-07321332/Ritonavir and Ritonavir on the PK of Midazolam in Healthy Participants	66	0	95.2%	100%
C4671023	A Phase 1 Relative Bioavailability Study of Nirmatrelvir/Ritonavir 4 Different Fixed Dose Combination Tablets Relative to the Commercial Tablets in Healthy Participants	132	0	100%	100%
C4671024	A Phase 1 Relative Bioavailability Study of PF-07321332/Ritonavir Oral Powder	132	4 (overfilled)	69.6%	100%

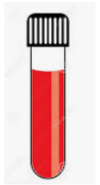
* Only 12 samples are eligible for ISR; ** MS detector saturation resulted in 2 run failures. Upon reinjection with reduced volume, the affected runs passed.

Blood to Plasma Ratio (B/P)

Day 1 On-site Collection

Venous Blood

1. Aliquot ~XX µL into a separate tube before processing the remaining blood in vacutainer



Venous Blood

2. Centrifuge the remaining blood to harvest plasma

Venous Plasma

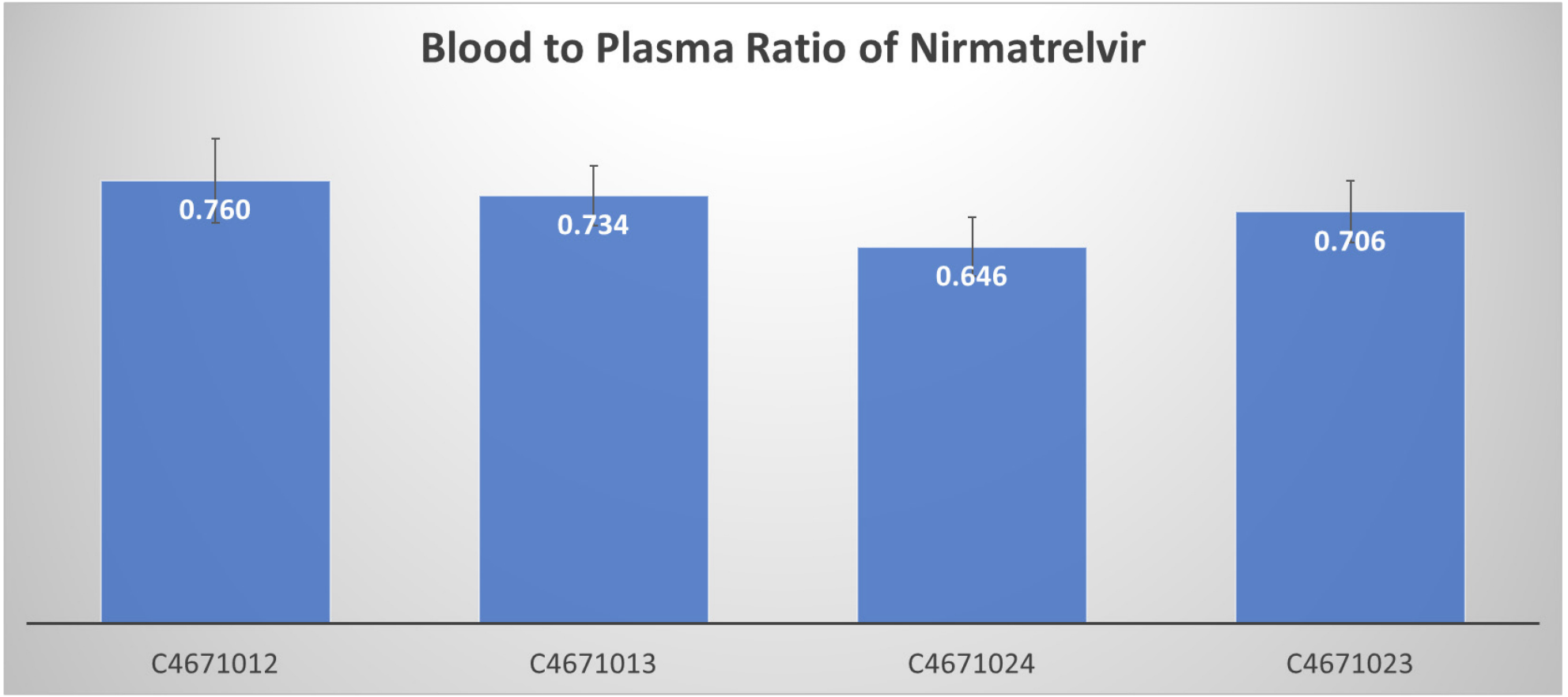
Freeze, Store, and Ship to Central Lab

Ship to Analytical Lab for concentration measurements in both blood and plasma to calculate B/P

It is imperative to obtain/check B/P in target populations.

Consistent B/P Obtained for NMV

- B/P ratio samples were collected from different subjects at different time points. There is minimal subj-to-subj difference. There is no concentration/time point dependance.



Tasso M20 Implementation in Phase 2/3 Trials

- Device Approval Status

  Tasso M20 is approved in US, EU, Switzerland and UK. For global studies in countries where M20 has not been approved, consider work with local RA team to obtain IUO (investigational use only) of Device as part of the CTA.

- Central Lab Workflow

  Need to form a close partnership with central lab and device provider to map out the process

  1) Supply sites with device, patience facing documents, label instructions

  2) Coordinate courier pick-up service (from patient home) and timely identify missing samples

- Patient Facing Document and Other Assistance

  1) Translation is needed for non-English speaking countries; device vendor can provide this.

  2) Pictorial instructions and preferably video demos are provided

  3) Help line is useful

- Site Training

  1) Training sessions followed by Q&A were conducted for sites

  2) Training slides and demo videos are made available to site staff

  3) Site staff is encouraged to demo the process to consented patients on Day 1 when they are on-site

Beyond EUA: Continued Tasso M20 Implementation

Pfizer continued to implement Tasso M20 in Paxlovid program because patients demand and deserve “patient centric” experience on trial.

- Pediatric population – small blood volume, less invasive and almost painless collection given by caregiver

- Pregnant and lactation studies – minimize travel to site, flexible collection at the comfort of patient's home
- Severely renal impairment study – lessen patient’s burden to travel

Conclusions

- Tools to collect PK samples outside clinical visit by patients, caregivers or home health service providers have enabled accurate quantitation of drugs in biological matrix.

  Our journey with Paxlovid Program has demonstrated the current technology and infostructure can be adapted to support at-home PK sampling to enrich PK dataset.

- Integration of digital health with patient centric sampling device is more likely to overcome some of the current challenges.
- At-home sampling will become the “new norm” and used broadly in clinical trials beyond just PK.

Acknowledgement

Pfizer Clinical Pharmacology

- Olga Kavetska and Haihong Shi
- Donna Cox, Ravi Shankar Singh, Bharat Damle and Brian Corrigan

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- Pilar Gonzalez
- Daniel Potts and Ian Smith

Tasso, Inc.

- Erwin Berthier
- Trish Kan Brown

Pfizer PCRU

- Kay Criswell
- Tracy M Orlinski

Questions?

AAPS Microsampling and Patient Centric subgroup (Part of AAPS Bioanalytical community)

Partnership with different organizations

- PCSIG
- NC3Rs
- European bioanalytical forum
- IQ consortium on patient centric sampling

Open Scientific discussion

- Foster awareness
- Share expertise across bioanalytical community
- Webinars

Team members includes

- Pharma
- CRO
- FDA
- EBF
- Consultants

Contact us

https://community.aaps.org/communities/community-home

Co-chairs

Shefali Patel- spatel31@its.jnj.com
Enaksha Wickremsinhe -enaksha@lilly.com

Patient Centric Sampling Interest Group

A not-for-profit organization that brings together a variety of interested parties who wish to develop & promote the use of patient centric blood sampling technologies for the advancement of human healthcare & well-being

- Clinical trial
  - Understand whether home vs in-clinic blood sampling has an impact on clinical trial recruitment & retention
- Diagnostics Working Group
  - Publications
    - Economic use cases
    - Summary of guidelines for bridging diagnostic test with PCS
  - Buyers guide
- Surveys
  - Clinician
  - Patient
- Education
  - Engaging key stakeholders at international conferences
  - PCSIG webinars
- Contact us
  - https://www.pcsig.org/
  - contact@pcsig.org