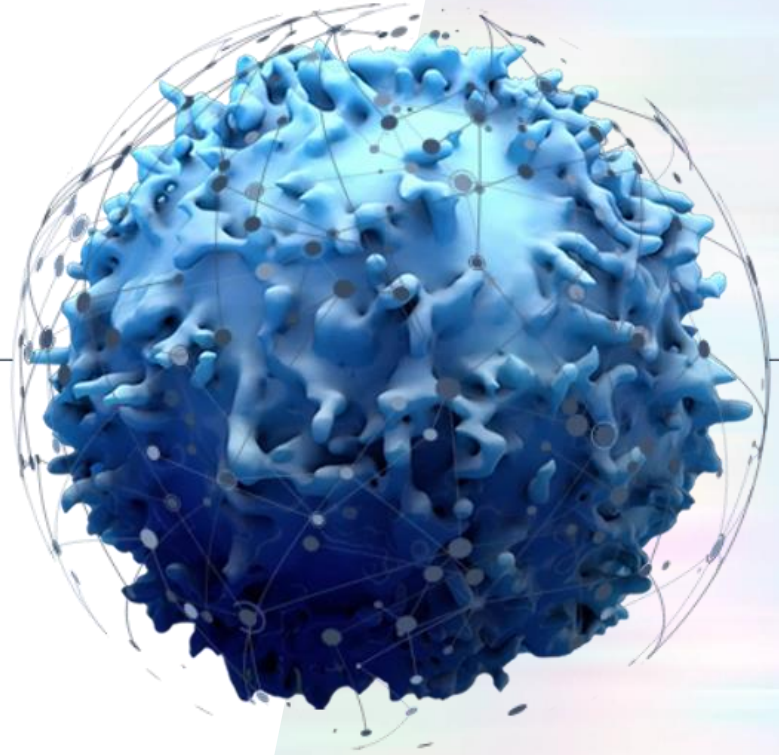
CARGO THERAPEUTICS

Comparability Considerations when In-Licensing an Early-Stage Academic Program



Annie Chiu, PhD
Associate Director, Process Development

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- The Phase 1clinical trial for firi-cel referenced herein was conducted by Stanford using their formulation of CRG-022†. The Company has made additional process and analytical improvements to the Stanford process to create the intended commercial manufacturing process for firi-cel in an effort to improve manufacturing yields and efficiency.
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†See footnote in Appendix.

CARGO – developing and delivering potentially curative cell therapies

Q1'24 Key takeaways

- **Strong execution and momentum of potentially pivotal Phase 2 clinical study (FIRCE-1), with interim results expected in 1H 2025**
  - >20 patients dosed; 26 sites activated
  - Independent Data Monitoring Committee (IDMC) recommended continuation of FIRCE-1 without modifications to protocol
  - Continued impressive manufacturing success
- **Impressive, ongoing follow-up from Stanford Phase 1 study for firi-cel†** in CD19 CAR T R/R LBCL patients
  - No add'l relapses from patients who achieved CR at 31.4m median follow up; mOS of 25.7m with 29.8m of follow-up for DL1*[1]. For LBCL patients who are R/R to CD19 CAR T cell therapy, median OS is less than 6m[2].
- **Pipeline advancement** – ongoing IND-enabling studies for CRG-023 platform

**Dose being evaluated in CARGO's ongoing FIRCE-1 Phase 2 clinical study of firi-cel*

Source: [1] Kramer et al. EHA 2024; [2] Blood Adv (2023) 7 (12): 2657–2669.

†Firicabtagene autoleucel (firi-cel) (CRG-022) is CARGO Therapeutics' autologous CD 22 CAR T-cell product candidate. The underlying CAR of which the Company exclusively licensed was the construct evaluated by Stanford University in a Phase 1 clinical trial in patients with large B-cell lymphoma whose disease relapsed or was refractory to CD19 CAR T-cell therapy. The Company's CRG-022 Investigational New Drug application included a comprehensive package in which CARGO performed and demonstrated analytical CRG-022 produced using the intended commercial process to the CRG-022 produced using the process used for the Stanford Phase 1 clinical trials. CARGO cannot assure that the FDA will agree with its claim of comparability and the sufficiency of the data to support it when it files its Biologics License Application.

History of Firicabtagene autoleucel (Firi-cel)

- Autologous, CD22 directed CAR T cells
- 120+ patients dosed across multiple clinical trials and firi-cel (CRG-022) was generally well-tolerated

Year	Study Site	Description
2014	National Cancer Institute (NCI)	• CD22 CAR made from human CD22 antibodies • first-in-human studies • Open manufacturing process
2019	Stanford University	• Clinical trial for relapse/refractory large B cell lymphoma (R/R LBCL) • Positive Phase 1 results in CD19 CAR T R/R LBCL impressive durability and safety • Granted Breakthrough Therapy Designation (BTD) by FDA • Closed manufacturing process
2022	Cargo Therapeutics	• In-licensed CD22 CAR from NCI • Initiated potentially pivotal Phase 2 clinical trial; multiple patients dosed with successful manufacturing to date • Leveraging readily transferrable, closed manufacturing process intended towards commercial

Process changes from v1.0 to v2.0 to balance speed to pivotal and line of sight to commercialization

Aspects	Process Change
Lentiviral Vector	Vector CDMO 2: commercially-suitable, scalable platform providing increased titer
Analytical Methods	Phase appropriate analytics developed assays to assess dose, safety, and functionality (potency)
Manufacturing Site	Drug Product CDMO 2: enable pivotal-ready technical development and GMP manufacture; includes commercial launch option
Starting Material Status	Change in starting material status increases process consistency and manufacturing flexibility
T Cell Expansion	Optimized cell culture conditions to minimize number of cell doublings, enable flexible harvest window, and increase likelihood of meeting target dose for consistent turnaround time (TAT)
Concentration	Closed automation improves process consistency, lower failure risk; synergistic with automated formulation and fill system
Filling	Closed and automated formulation improves consistency and microbial control
Final Product Container	New vendor intended for commercial container configuration

Increased drug product characterization with newly developed analytical methods (v2.0)

Drug Product Attributes

- Cell Count & Viability
- CAR Expression
- Vector Copy Number (VCN)
- Mycoplasma
- Sterility
- Potency
- T Cell Phenotypes; Memory Activation Exhaustion

Analytical Comparability Complications

- For phase appropriate testing, v2.0 analytical methods were qualified prior to completion of comparability studies
- Release and extended characterization assays needed re-development for going straight into pivotal studies (v2.0 methods)
- No potency method existed in Phase I, development needed to establish mechanism of action (MoA) reflective assay matrix prior to start of comparability studies
- New v2.0 analytical methods needed to bridge original v1.0 methods prior to establishment of comparability study criteria
- Re-testing drug product retains from Phase 1 clinical studies using v2.0 analytical methods to build pre-change data set for comparison to post-change drug product

Comparability can demonstrate clinical data before process changes remains applicable post-changes

Comparability study executed by CARGO allows leveraging Phase 1 clinical data, specifically for safety, dose, and efficacy, to facilitate further clinical development.

Due to the product complexity, health authority starting point for gene therapies (such as CAR-T products) means that the product is the process.

For CAR-T programs, studies should include side-by-side analyses of the pre- and post-change vector. Additionally, there should also be side-by-side analyses of CAR-T cells manufactured using the same cellular starting material with pre- and post-change vector (e.g., splitting the leukapheresis starting material from the same donor)[2, 3].

Comparability studies should be analyzed using appropriate statistical methods using predefined acceptance criteria based on lots shown to be safe and effective [2]. Appropriate statistical methods are for the sponsor to determine, but FDA current thinking is that an equivalence approach is most appropriate for setting acceptance criteria[4].

1. ICH Q5E: Comparability of Biotechnological/Biological Products (ICH, June 2005)
2. Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products: Draft Guidance for Industry (US FDA, March 2022)
3. Questions and answers Comparability considerations for Advanced Therapy Medicinal Products (ATMP). (EMA, December 2019)
4. Dr K. Schultz, Branch Chief, Gene Therapy 2, CBER OTAT, CASSS CGTP, Arlington Virginia, June 8, 22

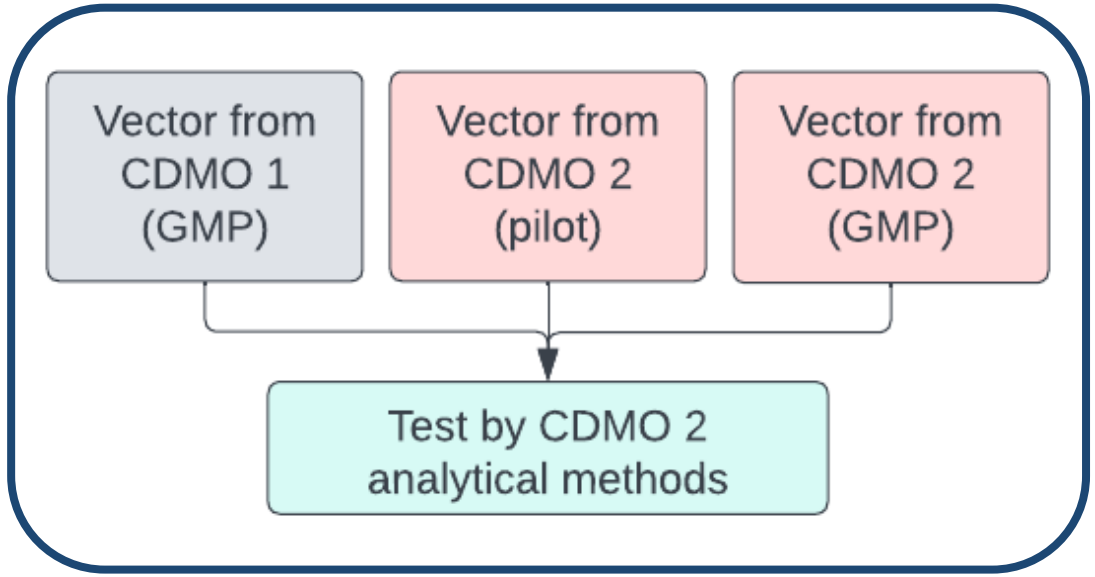
Comparability Study Rationale

- CARGO's intention to leverage Phase I clinical data required demonstration of comparability between Stanford initiated v1.0 CD22 drug product and the CARGO developed v2.0 CRG-022 drug product (firi-cel)
- Assessment of potential Critical Quality Attributes (pCQA) and risk ranking of pCQAs into tiers based on availability of historical data and SME technical rationale resulted in four Tier 1 attributes:
  - Cell Viability (%)
  - Transduction Efficiency (%)
  - Vector Copy Number (VCN) (copies per CAR+ cell)
  - Purity (%)
- Phase I study objective = determine maximum tolerable dose (MTD) and product safety
- CARGO proposed to supply phase 2 study with v2.0 drug product, so v1.0 and v2.0 drug products need only be established as sufficiently comparable with respect to Tier 1 attributes (viability, TE, VCN, Purity)
  - Tier 2/3 attributes assessed for extended characterization to supplement package

Vector Comparability: Analytical Assessment of Vector Changes by v2.0 Analytical Methods

Strategy
Aim to leverage Ph I clinical data
Critical Quality Attribute (CQA) assessment
Risk assessment
Study Design (integrated evaluation with donor matched runs)
Strategy verification with FDA

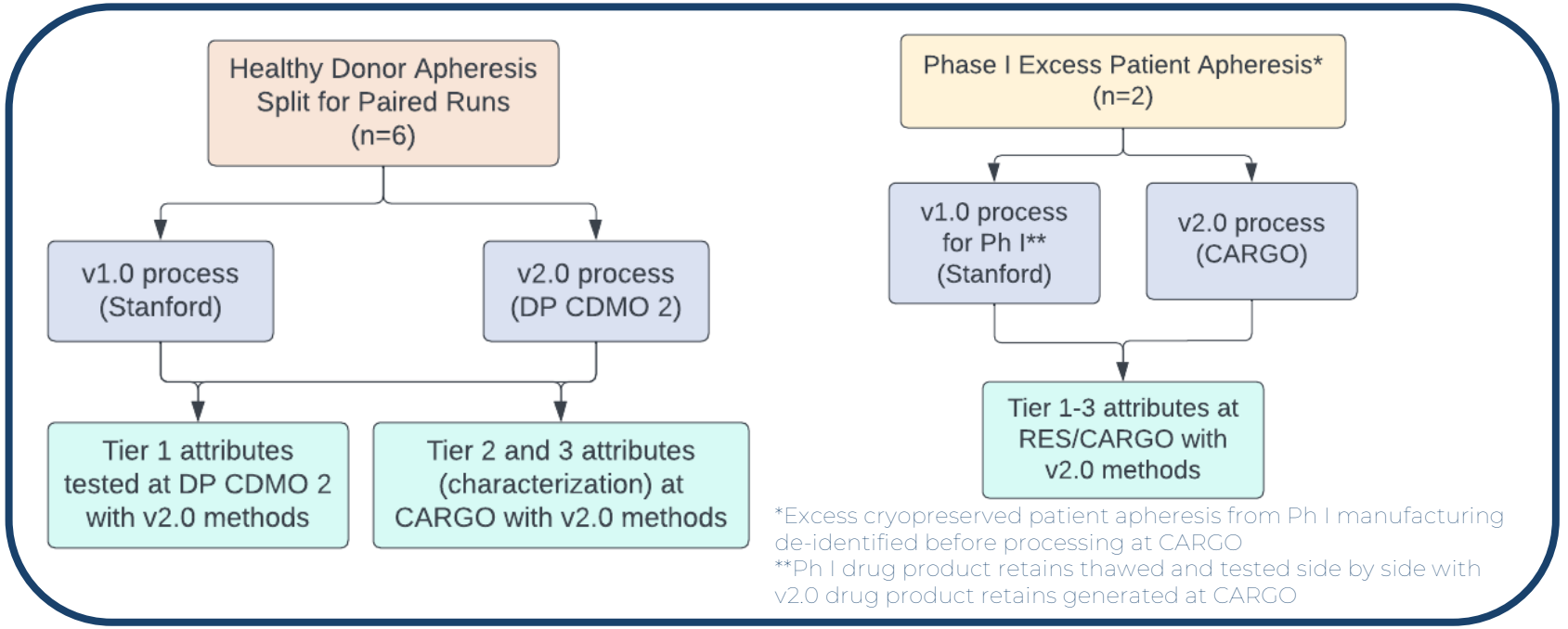
Constraints
Limited v1.0 vector supply
Vector CDMO 1 platform not scalable for commercial readiness



Drug Product Comparability: Integrated evaluation of all process changes by v1.0 vs v2.0 drug product testing

Justification for Study Size:

- Power calculations for Tier 1 attributes evaluated with EAC:
  - assumed mean paired difference between v1.0 and 2.0 process
  - standard deviation for paired difference
- Based on significance level of $\alpha = 0.05$ and power of >80%, comparability study is sufficiently powered when executing n=6 healthy donor runs.



*Excess cryopreserved patient apheresis from Ph I manufacturing de-identified before processing at CARGO
**Ph I drug product retains thawed and tested side by side with v2.0 drug product retains generated at CARGO

Constraints
Limited v1.0 drug product retains for side-by-side comparison
Limited excess patient apheresis for v2.0 process to supplement comparability package
v2.0 analytical methods needed redevelopment and qualification
Lack of historical data and implementation of new v2.0 assays require different statistical approach

FDA Feedback on Proposed Comparability Strategy

- Received valuable feedback from FDA consistent with comparability guidance

- No significant changes to study design in process flow or analytical testing

Critical Quality Attribute (CQA) Assessment Strategy

- Preliminary critical quality attributes (pCQA) determined to have potential impact on drug product safety and/or efficacy used to assess v1.0 vs v2.0 drug product comparability

- pCQA scored for severity and uncertainty based on patient safety and product efficacy and ranked by SMEs
  - Tier 1 = could impact product safety and/or efficacy
  - Tier 2/3 = extended characterization

- v1.0 clinical data used to assess potential equivalence acceptance criteria (EAC) for paired runs, but too tight and not biologically meaningful
- No paired runs and method variability data so subject matter experts (SMEs) established "practical significant differences (PSD)" based EAC
- PSD based EAC = interval within which difference is not anticipated to be clinically or scientifically meaningful, set by SME manufacturing history and product safety and/or efficacy

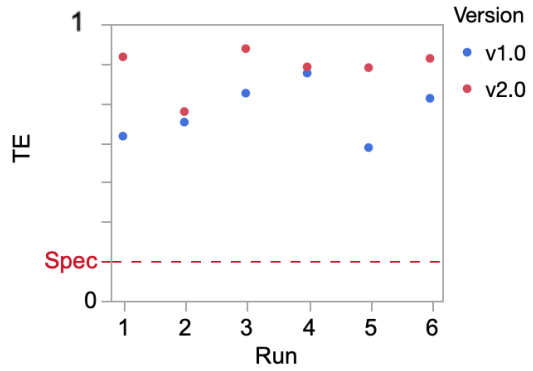
Key Comparability Attributes and Acceptance Criteria

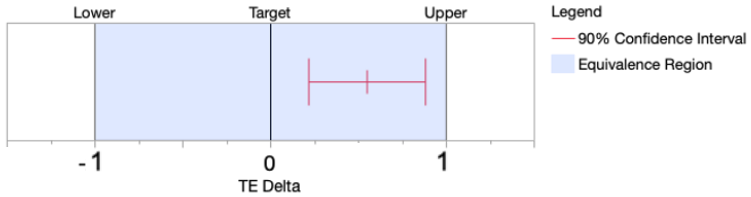
Comparability Assessment Approach	Attribute	pCQA Tier	Comparability Acceptance Criteria
Equivalence Test (TOST)[1]	Transduction efficiency	1	EAC of ± X%
	Vector copy number		EAC of ± X copies/CAR+ cell
	Viability		EAC of ± X%
	Purity		EAC of ± X%
Meet v2.0 acceptance criteria	Dose	1	± X% of target dose
Graphical/ Tabular Assessment of paired runs	Primary Potency	1	Report Results
	Orthogonal Potency		
	T Cell Memory	2	
	T Cell Activation		
	T Cell Exhaustion	3	

[1]Equivalence Acceptance Criteria (EAC) determined using SME determined practical significant difference
[2]Appearance test only performed for v2.0 due to fresh sample requirement

Tier 1 Equivalence Test Possible Outcomes

Calculated using Two One-Sided T-test (TOST), 90% Confidence Interval (CI)

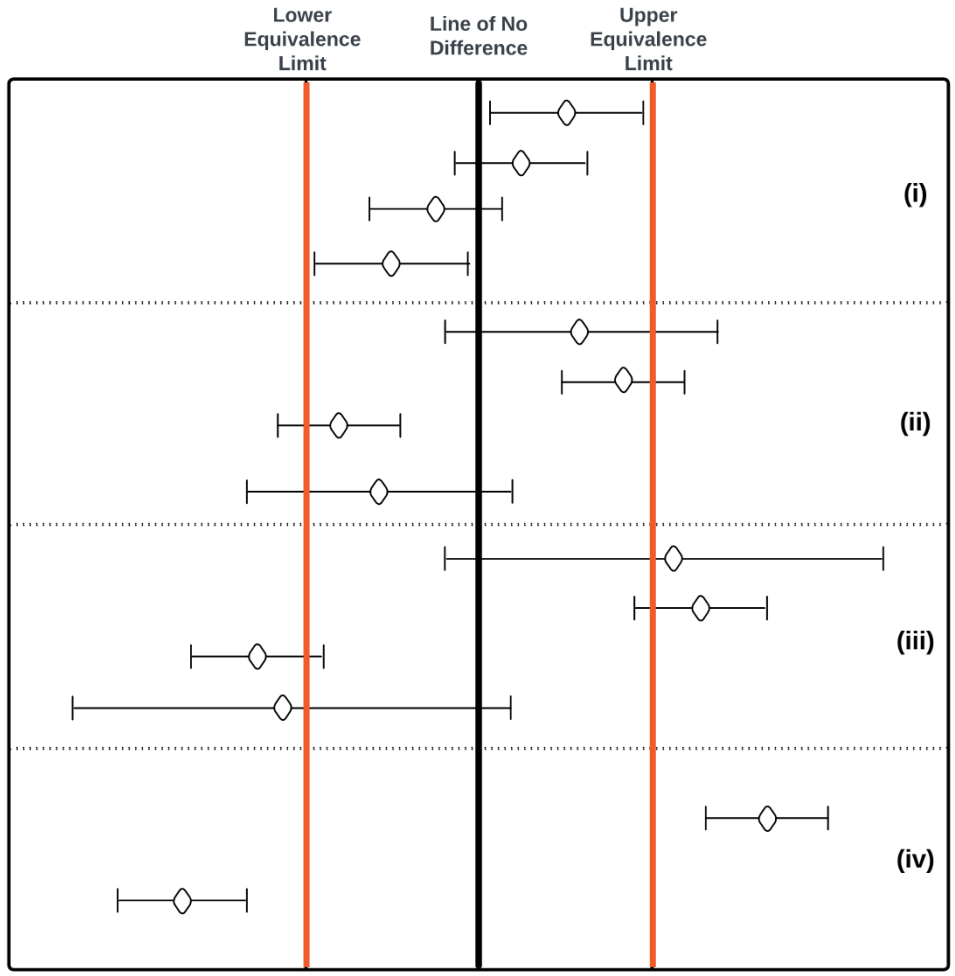




Null Hypothesis	DF	t Ratio	p-Value
Mean ≤	5	9.3975	0.0001*
Mean ≥	5	-2.735	0.0205*

The maximum p-value of both tests is 0.0205.

Mean is equivalent to 0.



✓ PASS

Probable Equivalent

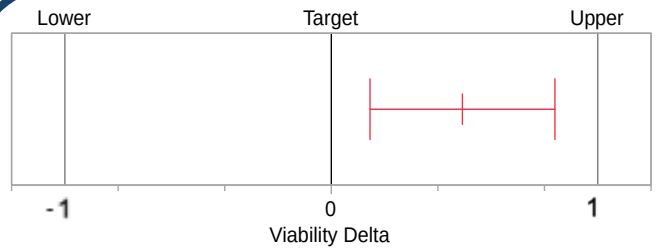
Probable Non-Equivalent

✗ Fail

Tier 1 Equivalence Test Results: Viability, Purity, TE, VCN

- All four Tier 1 attributes met EAC with PSD considerations, and thereby, v1.0 and v2.0 drug products are considered comparable

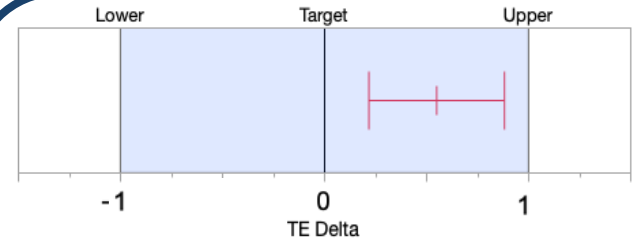
Calculated using Two One-Sided T-test (TOST), 90% Confidence Interval (CI)



Null Hypothesis	DF	t Ratio	p-Value
Mean ≤	5	8.6656	0.0002*
Mean ≥	5	-2.95	0.0159*

The maximum p-value of both tests is 0.0159.
Mean is equivalent to 0.

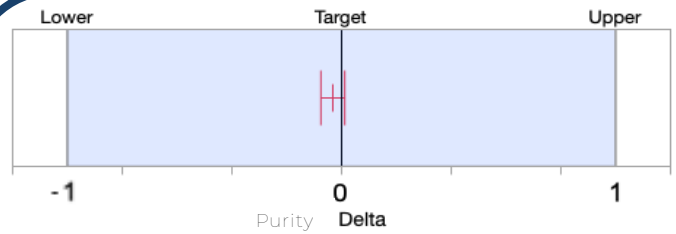
✓ PASS
Viability



Null Hypothesis	DF	t Ratio	p-Value
Mean ≤	5	9.3975	0.0001*
Mean ≥	5	-2.735	0.0205*

The maximum p-value of both tests is 0.0205.
Mean is equivalent to 0.

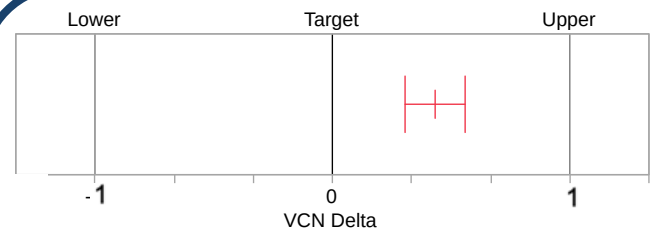
✓ PASS
TE



Null Hypothesis	DF	t Ratio	p-Value
Mean ≤	5	44.759	<.0001*
Mean ≥	5	-47.72	<.0001*

The maximum p-value of both tests is <.0001.
Mean is equivalent to 0.

✓ PASS
Purity

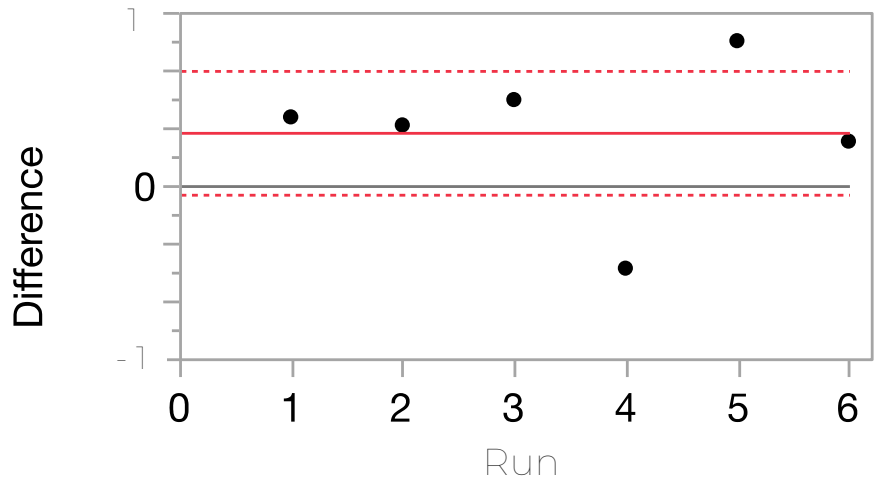


Null Hypothesis	DF	t Ratio	p-Value
Mean ≤	5	22.821	<.0001*
Mean ≥	5	-9.035	0.0001*

The maximum p-value of both tests is 0.0001.
Mean is equivalent to 0.

✓ PASS
VCN

Tier 1 Equivalence Test Results: Potency Assay 1



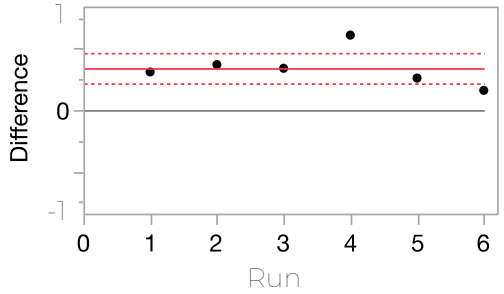
t-Ratio	1.729682
DF	5
Prob > |t|	0.1443
Prob > t	0.0721
Prob < t	0.9279

Solid Red Line = Mean
Dashed Red Lines = 90% Confidence Interval

- No statistically significant difference observed between v1.0 and v2.0
- Graphical/tabular assessment due to implementation of new assay, lack of historical data, and leveraging efficacy data was not necessary to start phase 2 studies

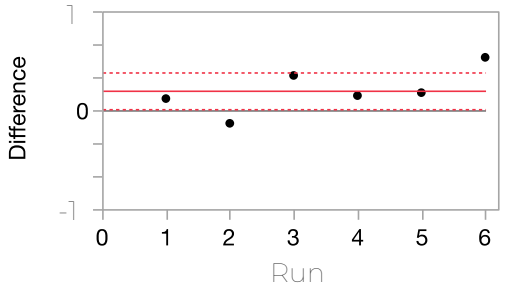
Tier 2 Equivalence Test Results: T Cell Phenotypes

T Cell Phenotype A
v2.0 increase



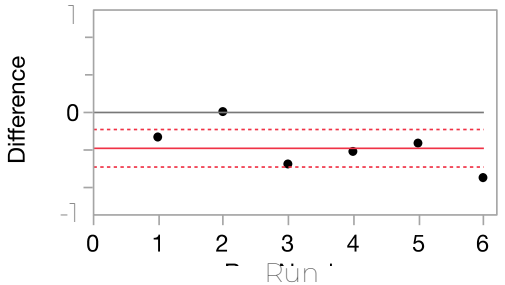
t-Ratio	5.555168
DF	5
Prob > |t|	0.0026*
Prob > t	0.0013*
Prob < t	0.9987

T Cell Phenotype B
v2.0 increase



t-Ratio	2.151063
DF	5
Prob > |t|	0.0841
Prob > t	0.0421*
Prob < t	0.9579

T Cell Phenotype C
v2.0 decrease



t-Ratio	-3.84287
DF	5
Prob > |t|	0.0121*
Prob > t	0.9940
Prob < t	0.0060*

- T cell phenotypes include assessment of memory, activation and exhaustion
- Tier 2 attribute -impact on safety and efficacy is expected to be minimal
- Variability in patient material given line of therapy could mask observing differences

Solid Red Line = Mean
Dashed Red Lines = 90% Confidence Interval

Key Comparability Outcomes and Conclusions

Comparability Assessment Approach	Attribute	pCQA Tier	Result
Equivalence Test (TOST)[1]	Transduction efficiency	1	Pass Equivalence
	Vector copy number		Pass Equivalence
	Viability		Pass Equivalence
	Purity		Pass Equivalence
Meet v2.0 acceptance criteria	Dose	1	Pass Release Specification
Graphical/ Tabular Assessment of paired runs	Potency Assay 1	1	Comparable
	Orthogonal Potency		No EAC established; highly similar between v1.0 and v2.0
	T Cell Phenotype (memory, activation, exhaustion)	2, 3	No EAC established; highly similar between v1.0 and v2.0

[1]Equivalence Acceptance Criteria (EAC) determined using SME determined practical significant difference

Learnings for Comparability of In-Licensed Academic Process

- Anticipate and strategize for comparability exercise in advance
  - Think “outside the box” to maximize limited supply while balancing risk (materials for current treatment, prioritized attributes based on risk assessment, SME input)
  - Reserve critical materials (i.e., drug product retains) for future testing

- Vector Control Strategy
  - Plan early and thoroughly for all contingencies (i.e., material overage for repeat)

- Integration of Automation in Drug Product Process
  - Automated platforms have potential for equipment failure, ensure back-up or buffer time/resources available for repeat runs if necessary
  - Cross-functional collaboration to identify potential failure modes in operations and develop recovery plans for clinical manufacturing

Acknowledgements

- Big thanks for the guidance and oversight from different functions at CARGO (Process Sciences, MSAT, Quality, Regulatory) in study design, planning, scheduling, and sample testing for extended characterization.

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- Thanks to cross-functional efforts and input at CARGO in statistical analysis and data summary for final assessment of drug product comparability.

- Thank you to the organizers of CASSS for the invitation to speak here at the CGTP Summit and thank you to everyone for attending this presentation!