

April 2025



Preventing Transplantation-Associated CMV Reactivation and Disease with Ex Vivo Perfusion

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Very common

human pathogen

DNA virus

of the herpesvirus family

60-100% of all humans

have a life-long persistent CMV infection

Immunosuppression

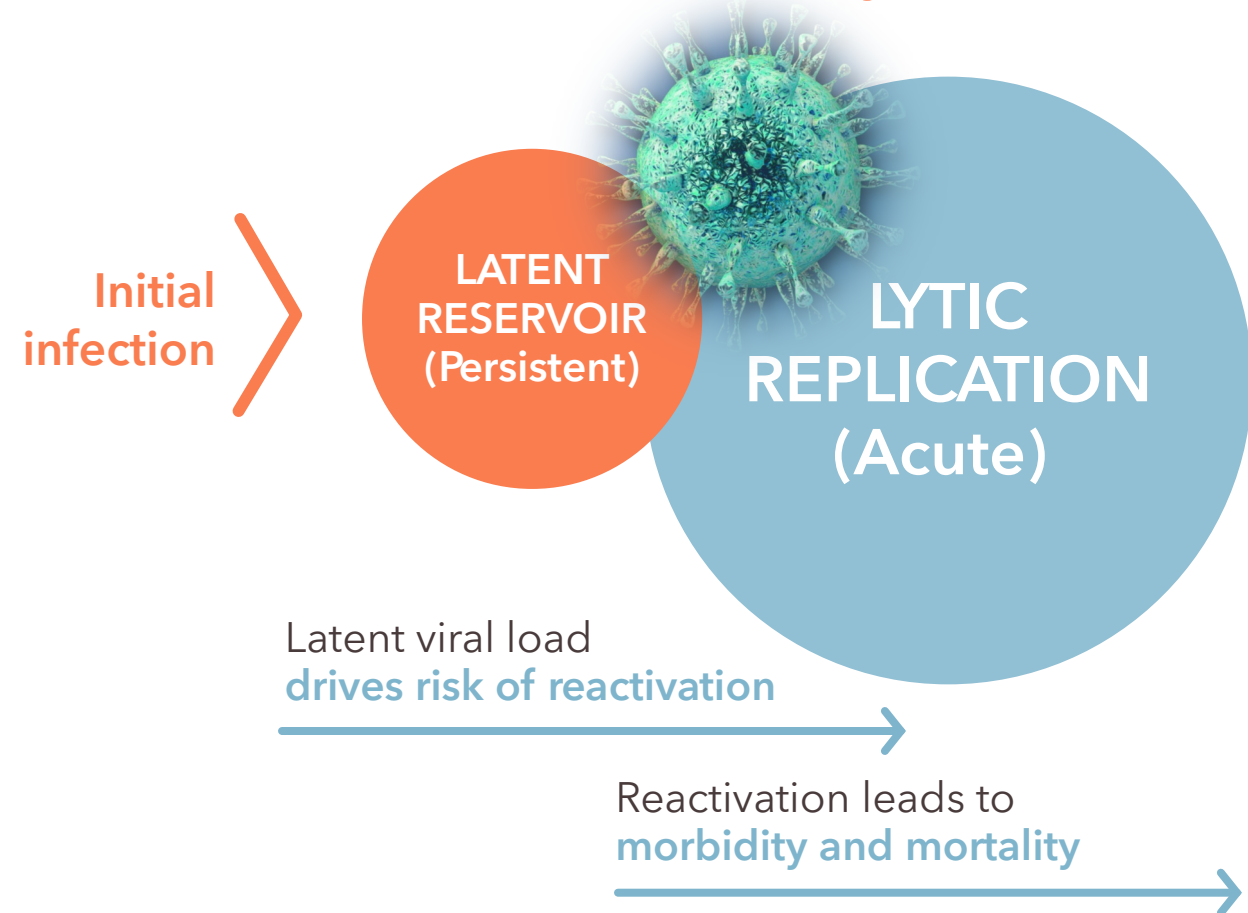
leads to virus reactivation from latency

Current CMV prophylaxis insufficient

with up to 30% of kidney transplant patients experiencing CMV reactivation

LATENT RESERVOIR
ENSURES LIFELONG PERSISTENCY AND RISK

The CMV lifecycle





LATENT
RESERVOIR
(Persistent)

Clear correlation between
CMV latent load and
reactivation^{1,2}

"The copy number of latent viral genome in tissues was identified as the key parameter that determines the overall and organ-specific risks of recurrence"³

RISK OF CMV REACTIVATION 6 MONTH AFTER ESTABLISHMENT OF LATENCY DEPENDS ON THE LATENT LOAD³

Low latent virus load

→ CMV reactivation in 7% of animals

– ≤20 copies in 10⁶ tissue cells

High latent virus load

→ CMV reactivation in 63% of animals

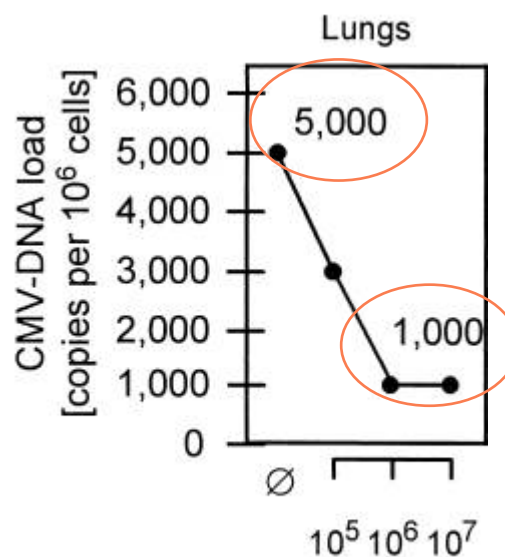
– ≥200 copies in 10⁶ tissue cells

¹Holtappels R et al. J. Virol. 2000, ²Simon CO et al., J. Virol 2006, ³Reddehase MJ et al., J. Exp. Med., 1994

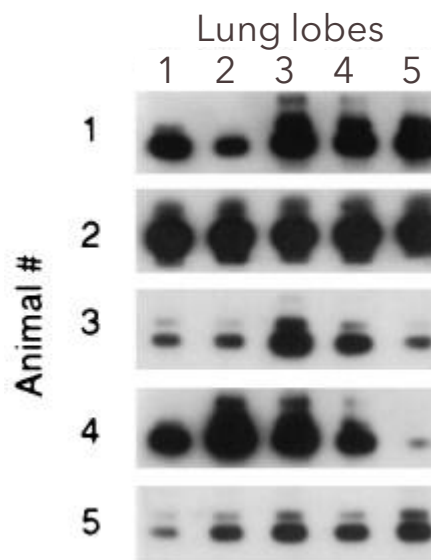
LATENT LOAD DRIVES RISK OF REACTIVATION

High viral load drives in vivo reactivation in more individual animals compared to low latent load

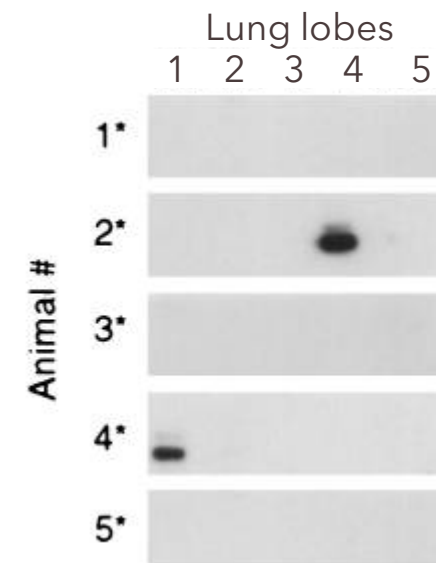
Latent load reduced by 80%¹



8 months



8 months

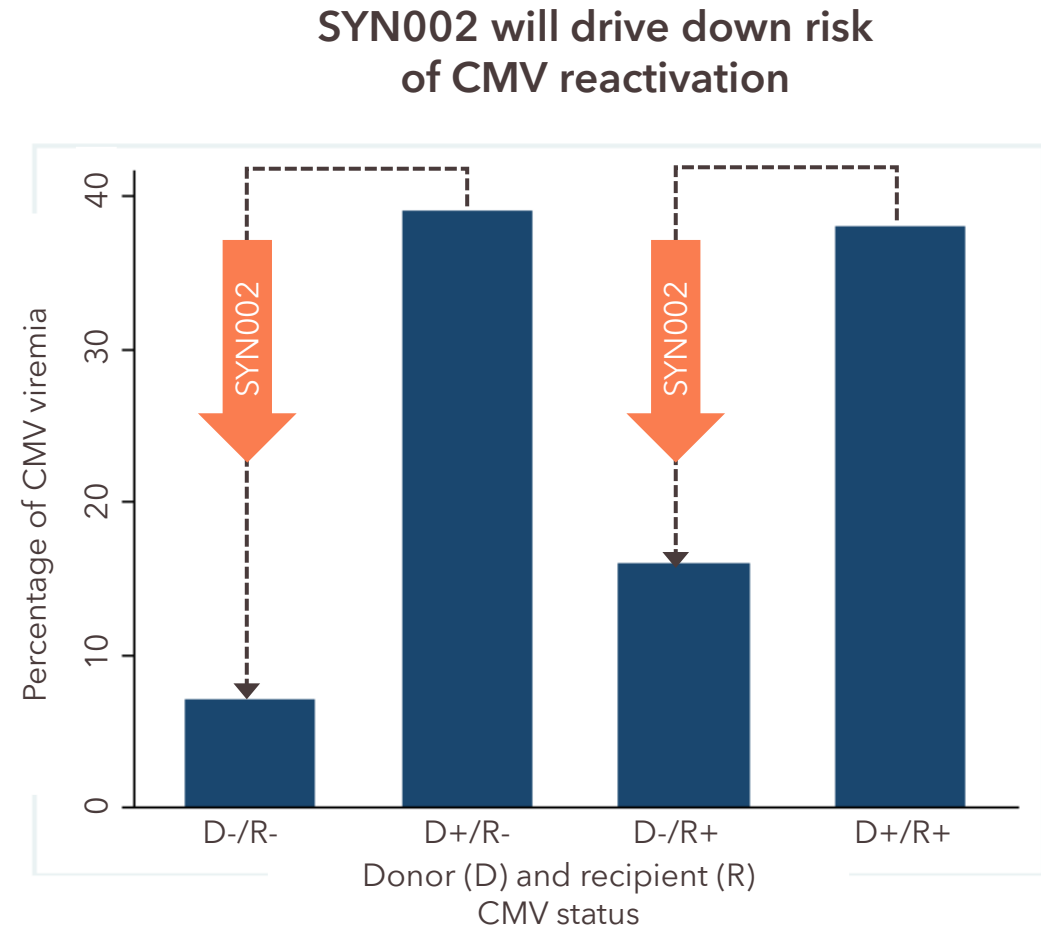
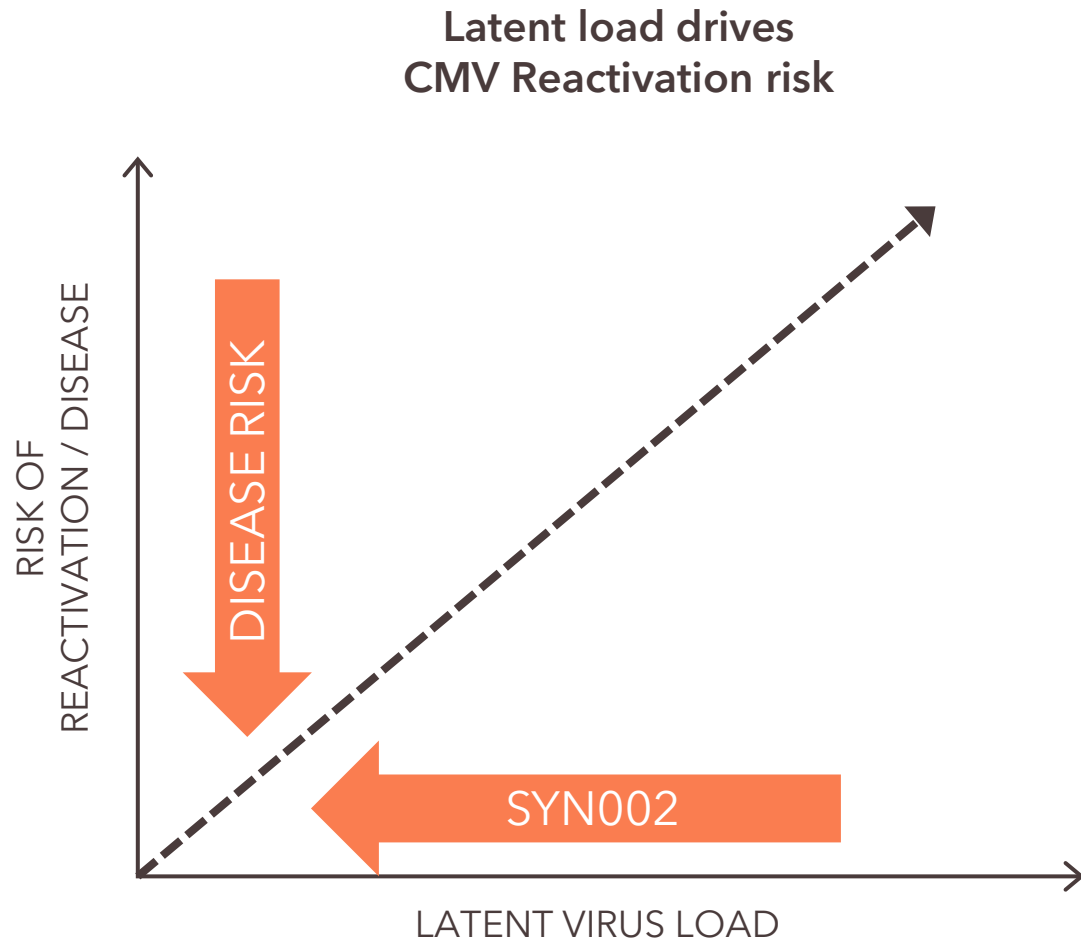


Polyclonal antiviral CD8⁺ T cell therapy

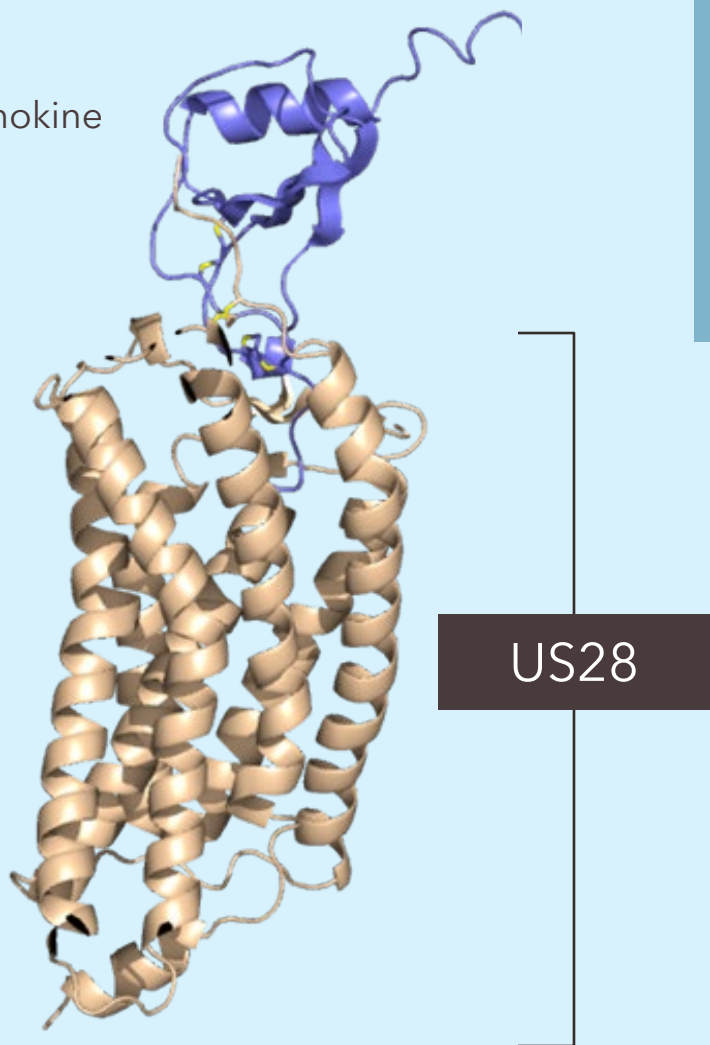
¹Steffens HP et al., J Virol. 1998

LATENT VIRUS LOAD DICTATES RISK OF REACTIVATION AND DISEASE IN IMMUNOCOMPROMIZED PATIENTS

SYN002 targets the main CMV reactivation risk driver – the donor organ latency pool



Chemokine



US28 is a novel CMV-specific target

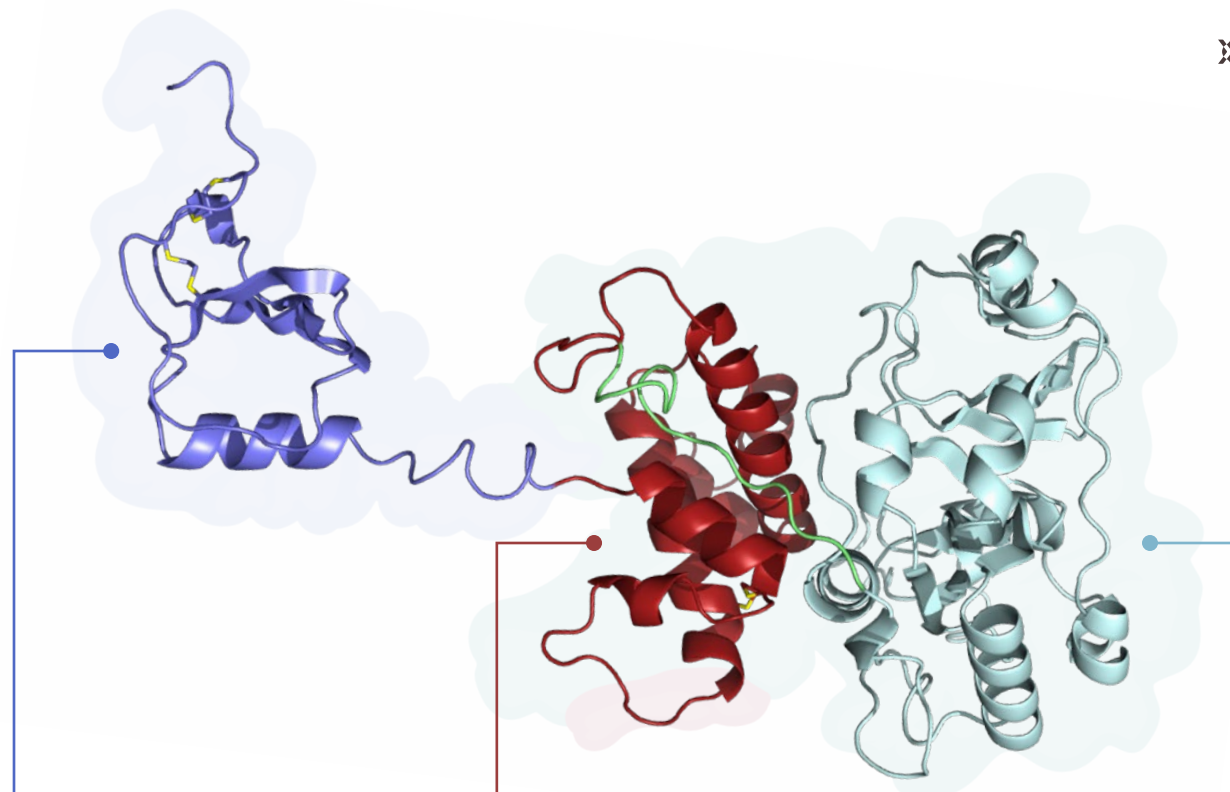
INNOVATION IN TARGETING CMV

Leveraging the active function of US28 to gain access to CMV infected cells

- Membrane protein encoded by the virus
- Exclusively expressed on virus infected cells
- Expressed during both lytic and latent phase
- Continuously internalizing
- Acts as a chemokine scavenger

SYN002 DESIGN

Selectively kills
infected cells
without impacting
organ function



DOCKING

**Chemokine scaffold
optimized for selective
binding to CMV US28**

Enables internalization
of SYN002 in all CMV
infected cells

ACTIVATOR

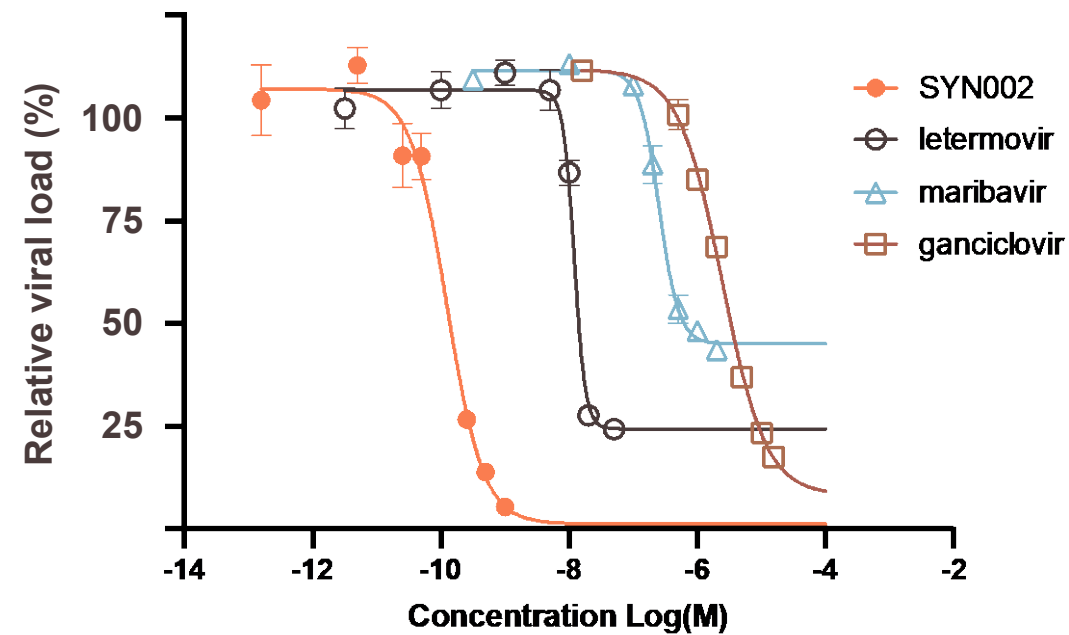
Furin cleavage site
results in intracellular
release

EFFECTOR DOMAIN

**Catalytic domain of
pseudomonas exotoxin**
Blocks protein synthesis,
driving CMV-infected cells
to undergo apoptosis

SYN002 EFFICACY AND ANTIVIRAL CELL-KILLING POTENCY

Superior efficacy and potency of SYN002 compared to SOC in lytic infected cells



Wild Type CMV

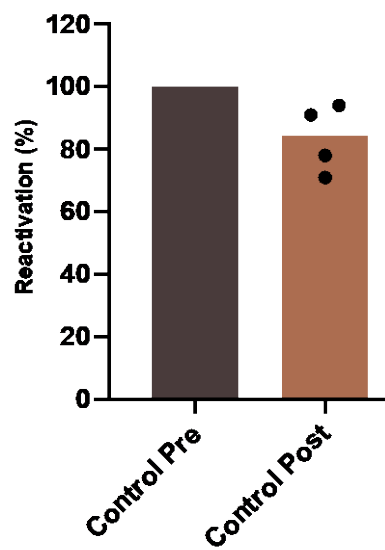
	SYN002	Letermovir	Ganciclovir	Maribavir
		nM		
IC50	0.13	8.8	1800	230

SYN002 is **14,000 times more potent** than Ganciclovir and **1,800 times more potent** than Maribavir, and **68 times more potent** than Letermovir

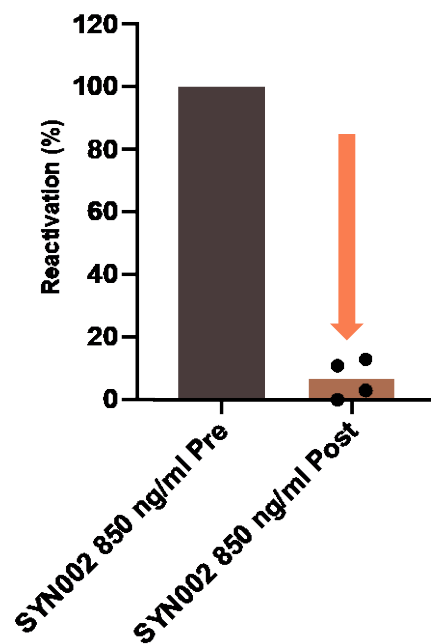
SYN002 IS HIGHLY EFFICACIOUS AND WELL TOLERATED IN A HUMAN KIDNEY EX VIVO MODEL

Latent CMV infection is
reduced by >90%
after single, 4-hour treatment

Control kidneys



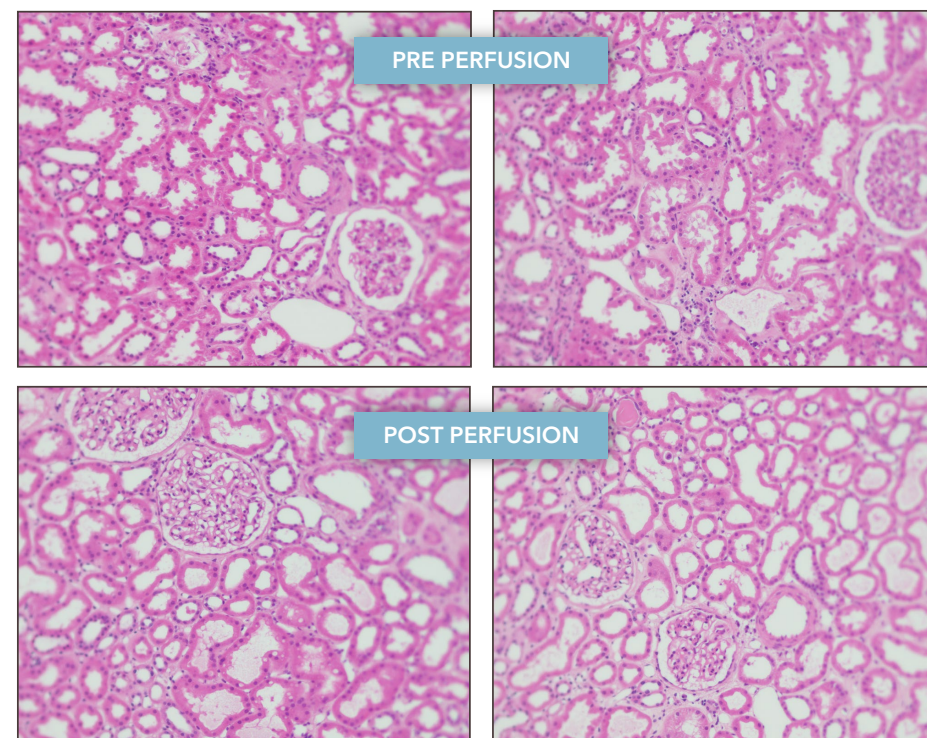
Treated kidneys



No acute histopathological changes after
SYN002 treatment

Control treated

SYN002 treated



SYN002 Phase 1 Study

Clinical study outline

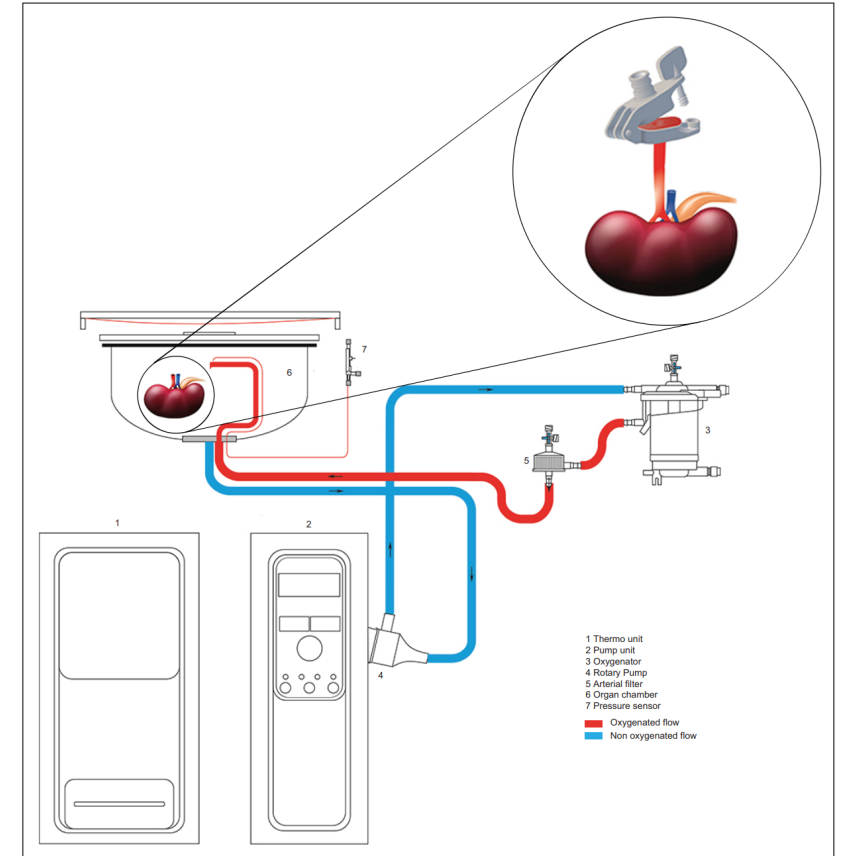
Study title: A Phase 1 Safety, Acceptability, Pharmacokinetic, and Pharmacodynamic Study of SYN002 Administered *Ex Vivo* to Renal Transplant Patients

Parameter	Description
Patient population	CMV positive donor kidneys from deceased donors CMV positive or negative transplant recipients
Dose levels	4 dose levels equivalent to IC10 (25ng/mL), IC50 (75ng/mL), IC90 (225ng/mL), and IC99 (450ng/mL) (based on preclinical <i>ex vivo</i> studies)
Number of patients (N=24)	Cohort 1 (IC10): 3:1 Cohort 2 (IC50): 3:1 Cohort 3 (IC90): 6:2 Cohort 4 (IC99): 6:2
Primary objective	Safety and tolerability
Secondary objective	Confirm lack of SYN002 exposure systemically
Exploratory objective	Assess changes in CMV levels pre- and post-transplantation - In recipient patients (CMV DNA PCR)

KIDNEY PRESERVATION PRIOR TO TRANSPLANTATION

Ex vivo machine perfusion is used to preserve and recondition/repair organs

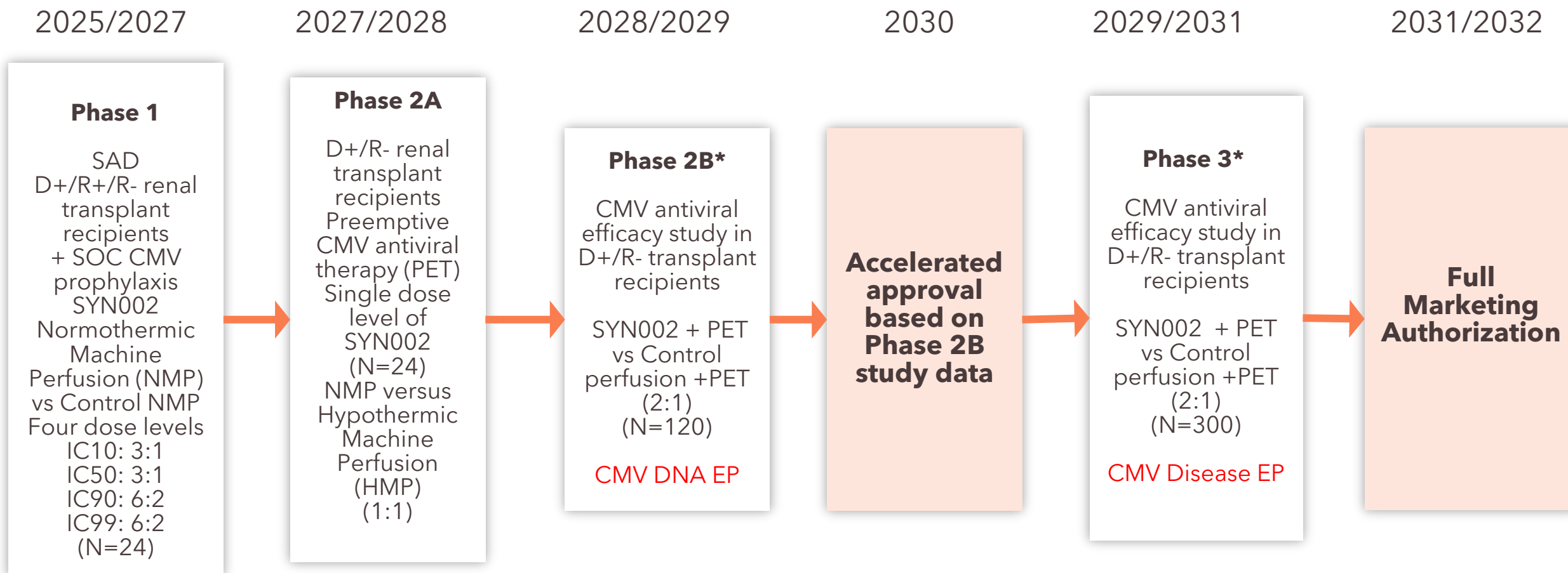
- Kidneys harvested for transplantation are preserved by **cold storage** or **machine perfusion**
- Organs that are perfused during preservation have a reduced incidence of delayed graft function, an overall improved graft survival, and an increased rate of use



Perfusion circuit of the XVIVO Kidney Assist
(Rijkse et al., Int J Surg Protoc., 2021)

CURRENT CLINICAL DEVELOPMENT PLAN FOR SYN002 *EX VIVO* RENAL TRANSPLANT

Accelerated pathway



*Choice of perfusion parameters (NMP or HMP) will be based on Phase 1/2 data

Summary

- CMV reactivation and disease remains a significant problem in transplantation
- Current standard of care only targets lytic infection and is still associated with high rates of CMV reactivation
- Novel antiviral and immunotherapeutic strategies offer promise but will only address lytic infection
- SYN002 is the first drug to be developed that specifically targets both the latent and lytic CMV compartments
- Preclinical translational studies in human CMV-positive kidneys have shown the potential to reduce the CMV latent reservoir by 95% in the absence of safety issues

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