Cardiovascular

Model Informed Drug Development Approach to Support the Approval of Camzyos

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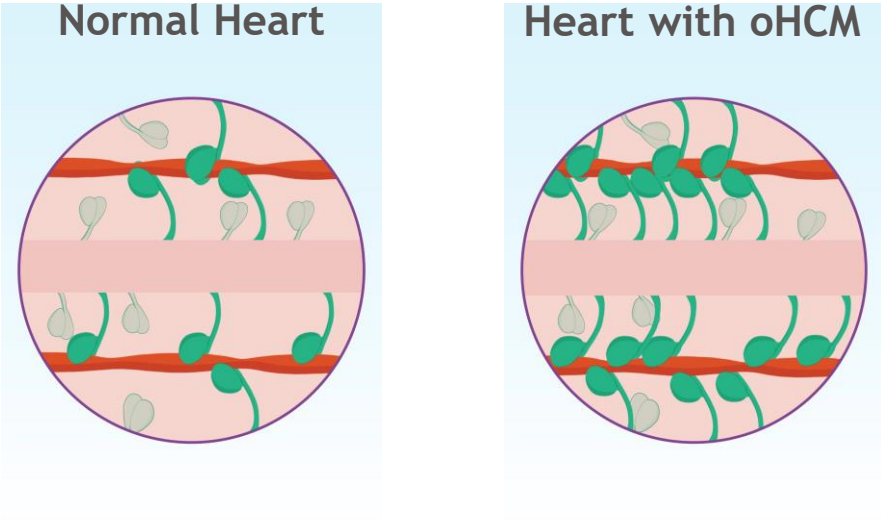
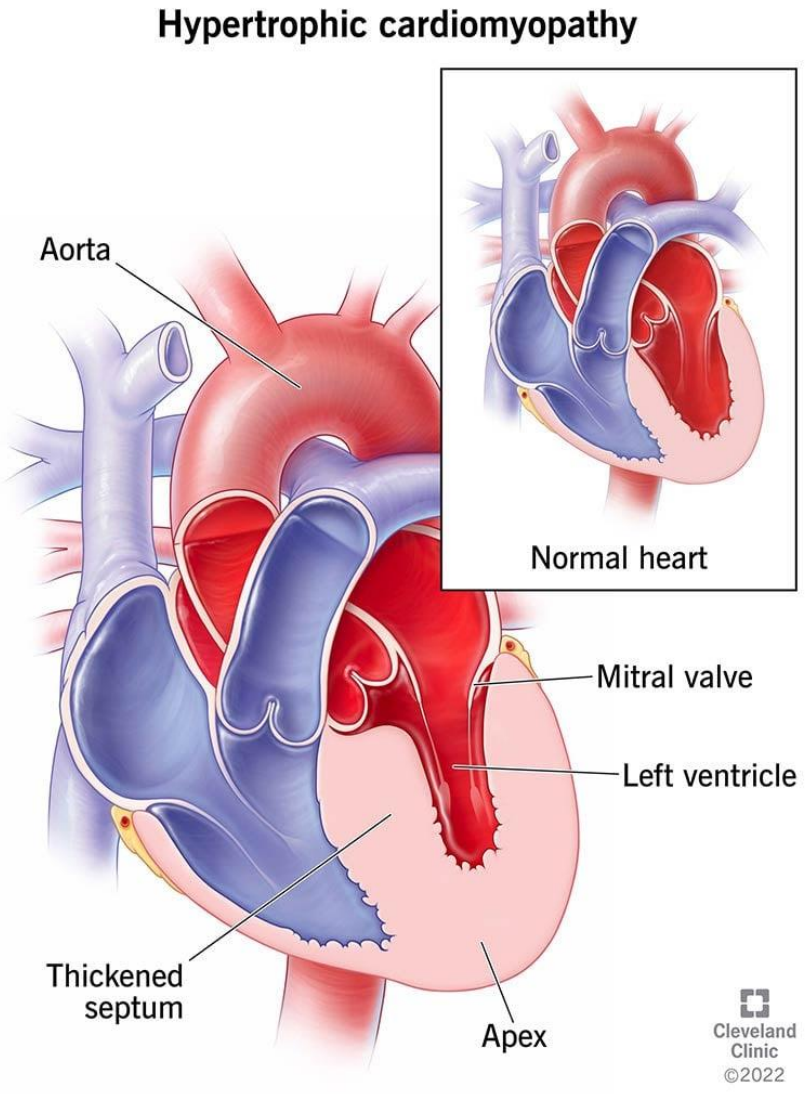
- Obstructive Hypertrophic Cardiomyopathy and Camzyos (Mavacamten)
- Clin Pharm Package & Clinical Development Program
- Population PK and E-R Analysis
- M&S Framework to Optimize the Posology

Symptomatic Obstructive Hypertrophic Cardiomyopathy





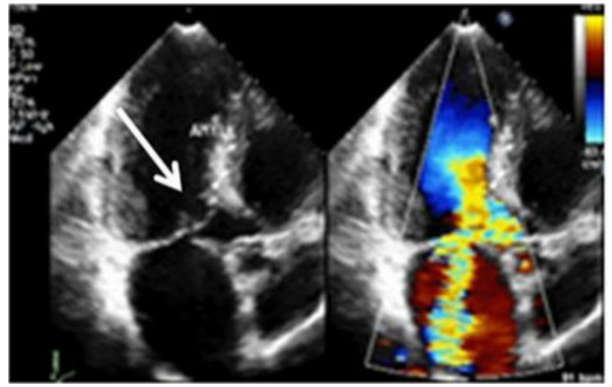
- Obstructive Hypertrophic Cariomyopathy (oHCM): Genetic disorder, rare disease
  - Prevalence: 0.36 per 10,000 in those under 18 to 4.82 per 10,000 in those 55–65
- Common Symptoms
  - Chest Pain, Shortness of Breath, Fatigue, Rapid/Irregular heartbeat, Fainting
- Commonly prescribed Beta-blockers, Calcium Channel Blockers

https://www.camzyos.com/what-is-camzyos

Key Clinical Parameters/Targets in oHCM

LVOT gradient

- Left Ventricular outflow tract gradient
- Measured by Echocardiogram



pVO_2

- peak Oxygen Consumption
- Cardiopulmunary Exercise Testing (CPET)

NYHA Class

- New York Heart Association Class
- Class I, II, III, IV

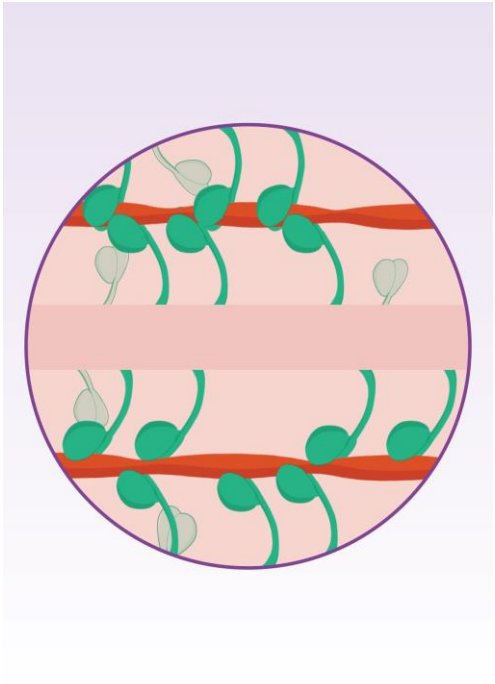
LVEF

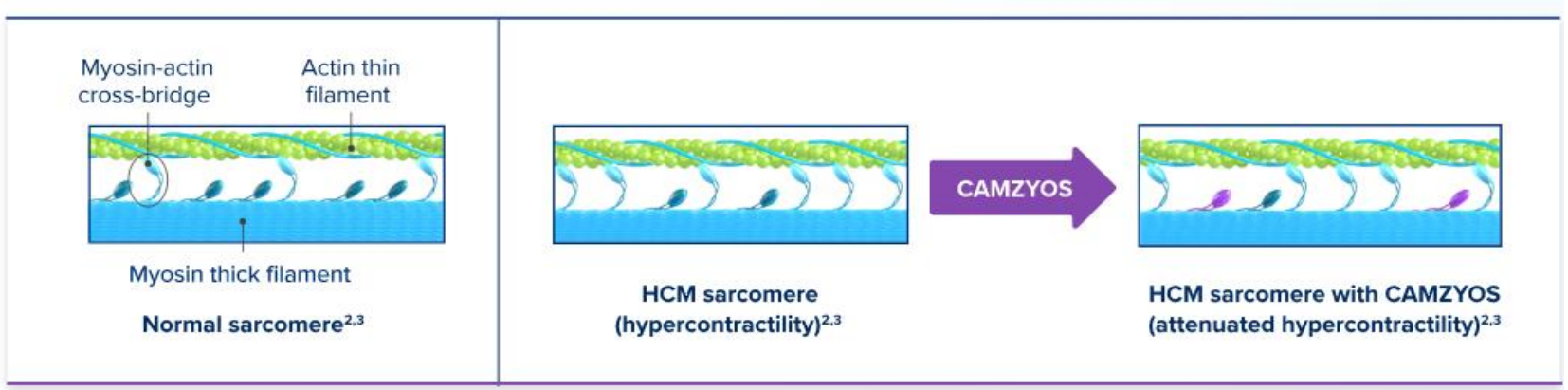
- Left Ventricular Ejection Fraction
- Measured by Echocardiogram

CAMZYOS: First and Only Approved Cardiac Myosin Inhibitor

- CAMZYOS, selective reversible allosteric inhibitor, is a prescription medicine used to treat:
  - Adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM)
  - Approved in 43 countries including the US, Canada, the EU, the UK, and South Korea

How CAMZYOS works in a Heart with oHCM





Decreasing the number of excess myosin-actin cross-bridges:

- Reduced dynamic LVOT obstruction[1]
- Improved cardiac filling pressures[1]
- Improved energy consumption[1,2]
- Reduced cardiac contractility[2,3]

https://www.camzyos.com/what-is-camzyos

CAMZYOS The 2023 Prix Galien USA Award Winner

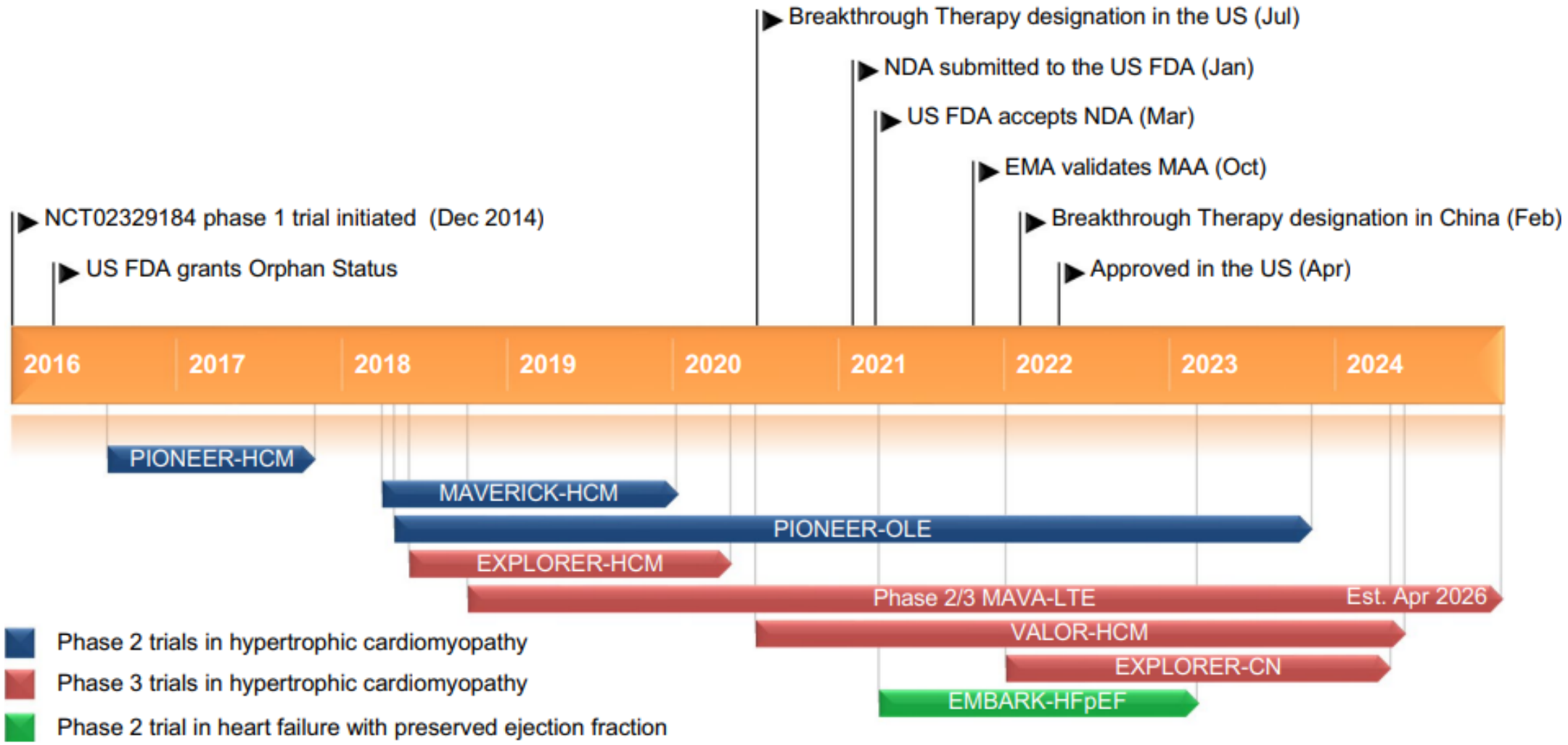
The 2023 Prix Galien USA Award Winners

Best Biotechnology Product	Bristol Myers Squibb	Camzyos™ (mavacamten)
Best Pharmaceutical Product	Eli Lilly and Company	Mounjaro® (tirzepatide) Injection
	Novo Nordisk Inc.	Ozempic® (semaglutide)
Best Product for Rare/Orphan Diseases	Boehringer Ingelheim	Spevigo® (spesolimab)
	CSL / uniQure	HEMGENIX®
Best Medical Technology	Guardant Health	Guardant360® CDx
Best Digital Health Solution	Medable	Medable Decentralized Clinical Trials (DCT) Platform
Incubators, Accelerators and Equity	Villgro Africa	Incubating Healthcare Startups in Africa

PRIX GALIEN USA

PRIX GALIEN AFRICA

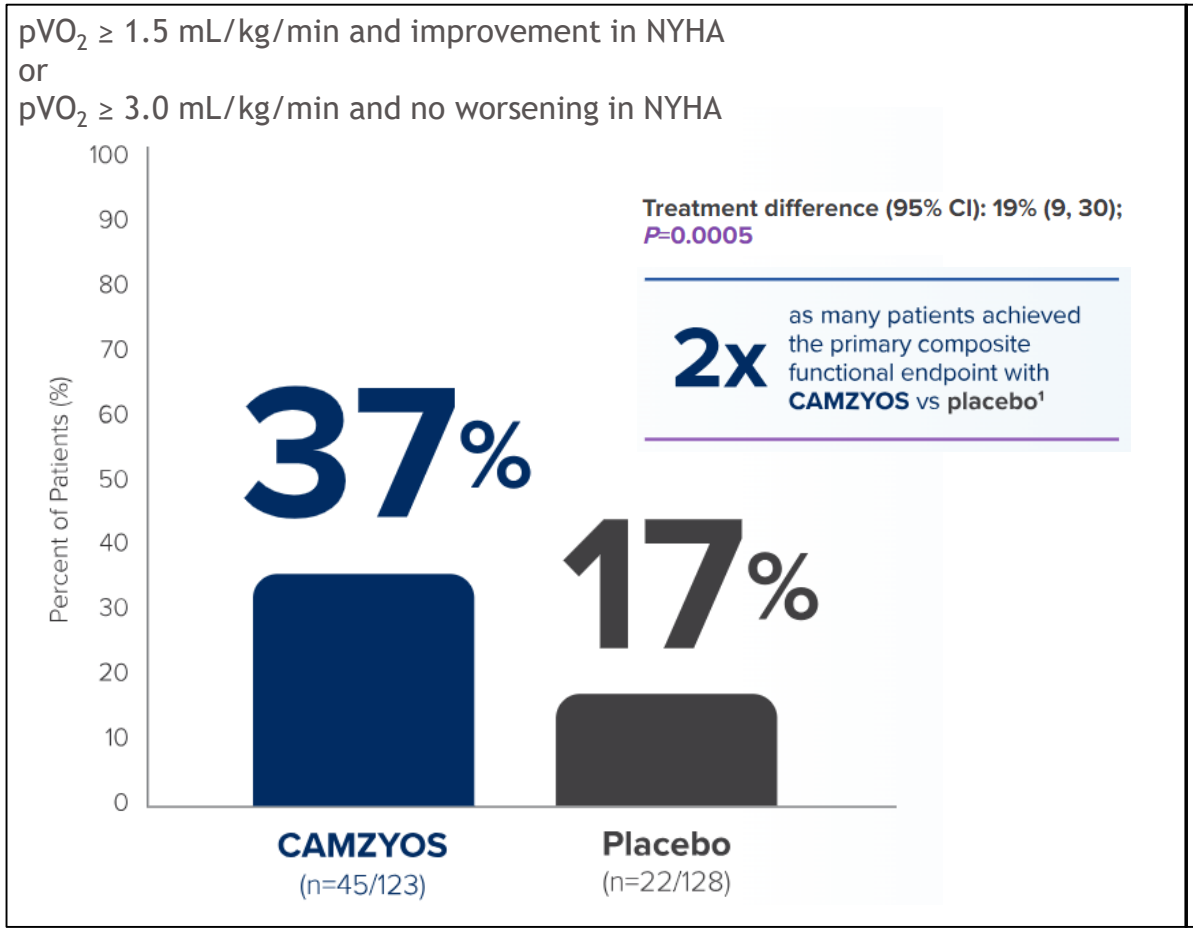
Overview of Clinical Development Program



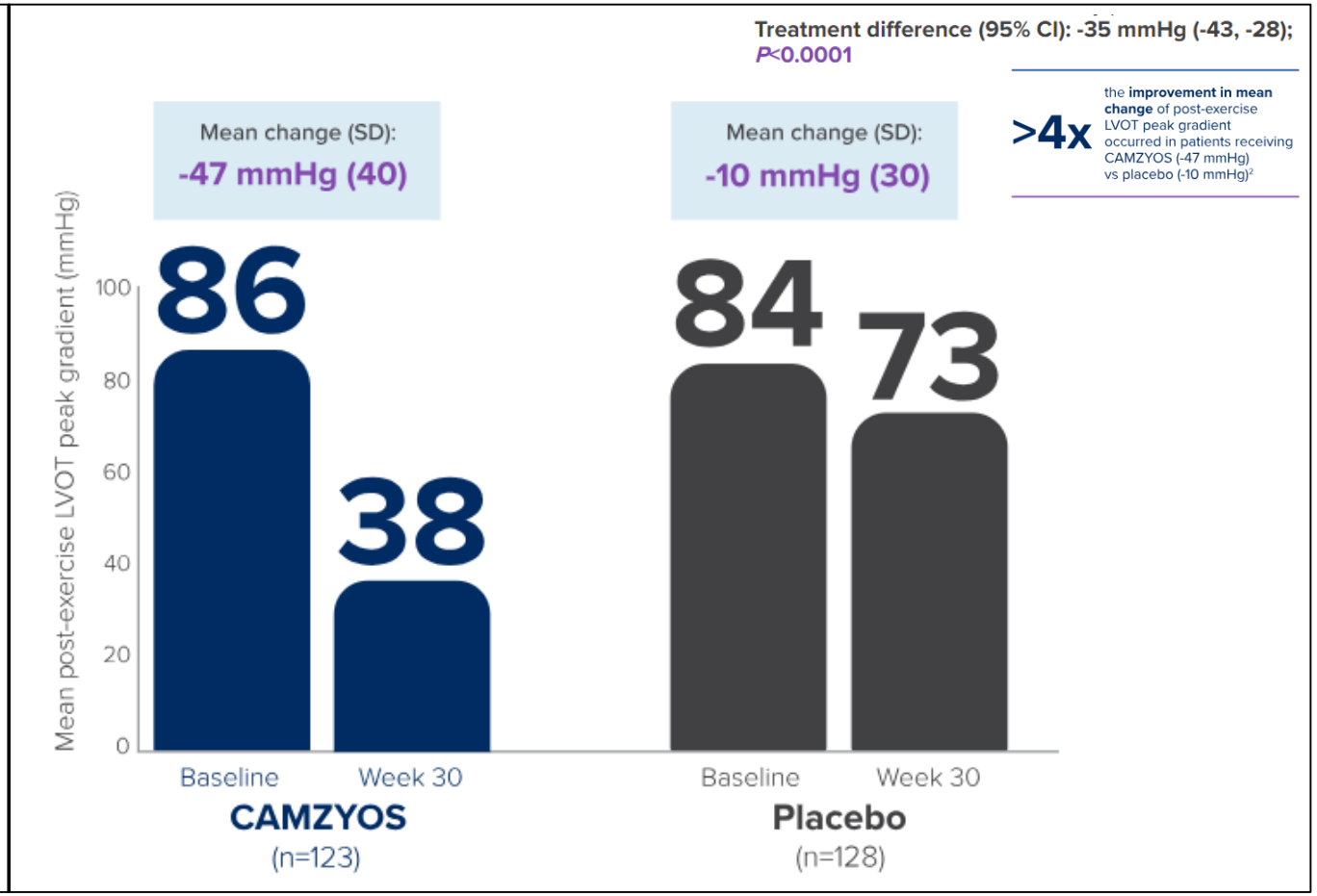
Susan et al, Drugs 2022 82(10)

EXPLORER-HCM, A Randomized, double blind, placebo-controlled trial showed Successful Results

Composite Primary Endpoint



Key Secondary Endpoint: Reduced LVOT



CAMZYOS® (mavacamten) EXPLORER-HCM Secondary & Exploratory Endpoints | Safety Profile (camzyoshcp.com)

Population PK analysis to characterize the Mavacamten PK

- Data from 12 Clinical studies (Total n= 497, 9244 measurable PK observations)
  - HV: 192, HCM Patient: 305
- Two-compartment model with first order absorption was used to characterize the Mavacamten PK
  - Full model covariate modelling approach

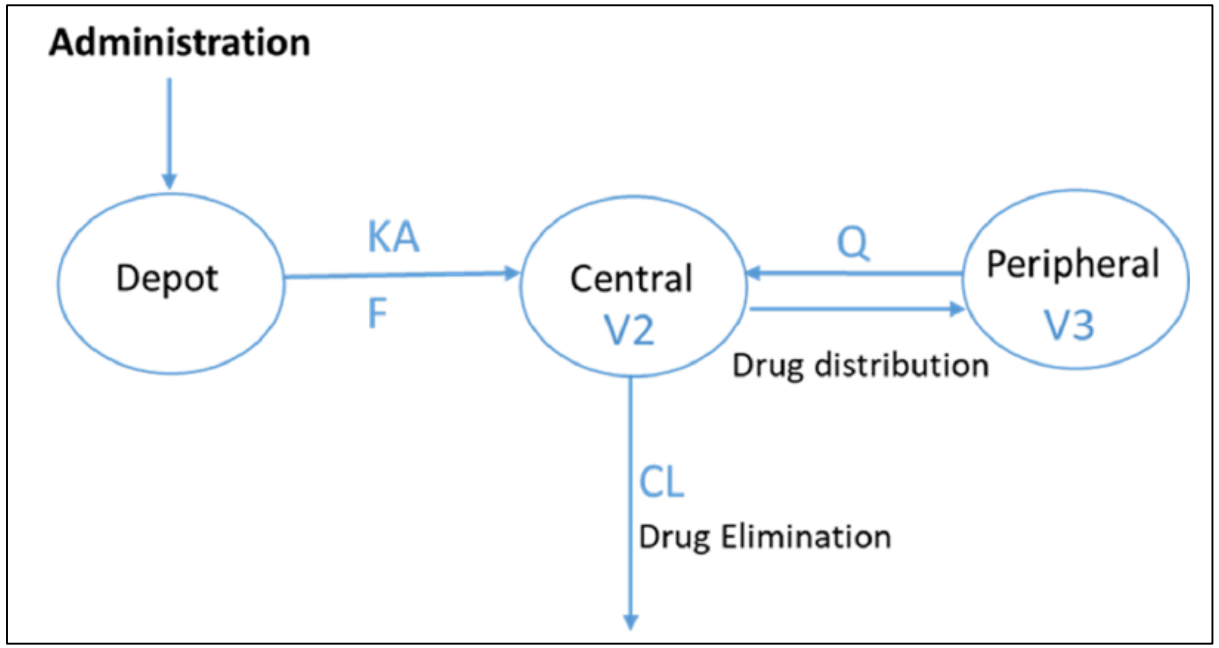


Table 2. Estimated structural model parameters (final model, reference participant)

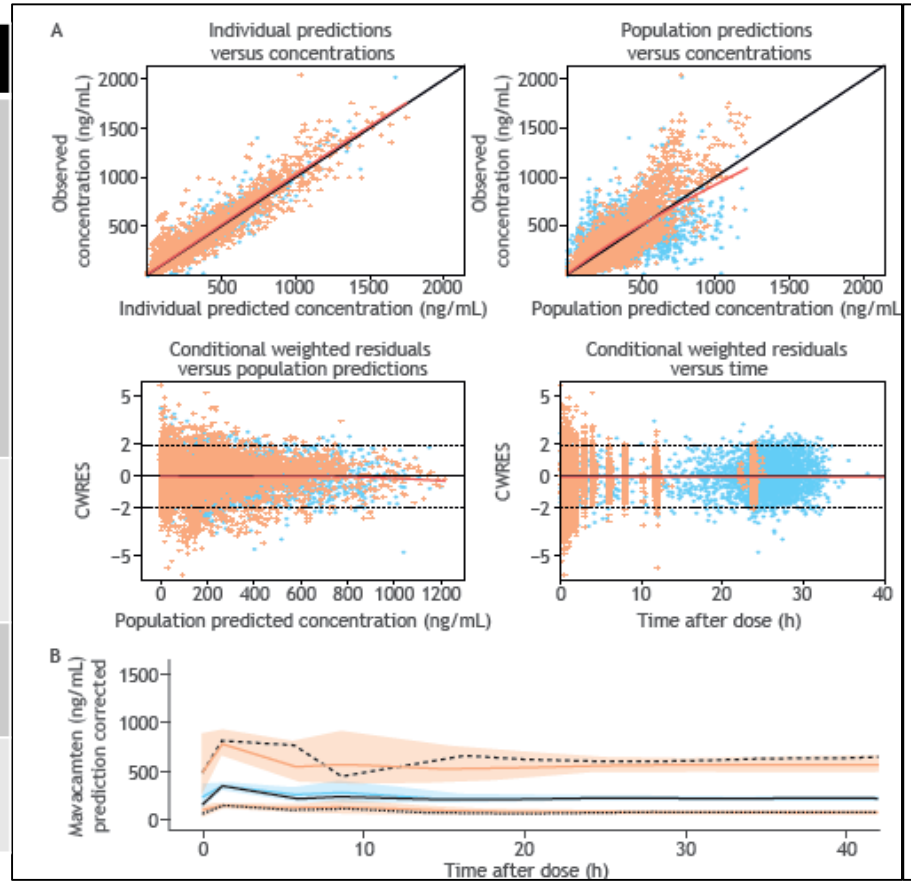
Parameter	Estimate	%RSE
CL/F, L/h	0.914	3
V2/F, L	6.63	14
V3/F, L	252	2
Q/F, L/h	16.3	4
KA, h^{-1}	0.301	25
ALAG1, h	0.192	5
F	1 (fixed)	-
IIV	**Estimate %**	**%RSE**
CL/F	57.2	3
V2/F	217	8
V3/F	22.9	5
KA	42.9	14
Q/F	23.3	8
Residual Error	0.0292	5

Identify the intrinsic/extrinsic effect using Pop PK analysis and utilize it for E-R analysis

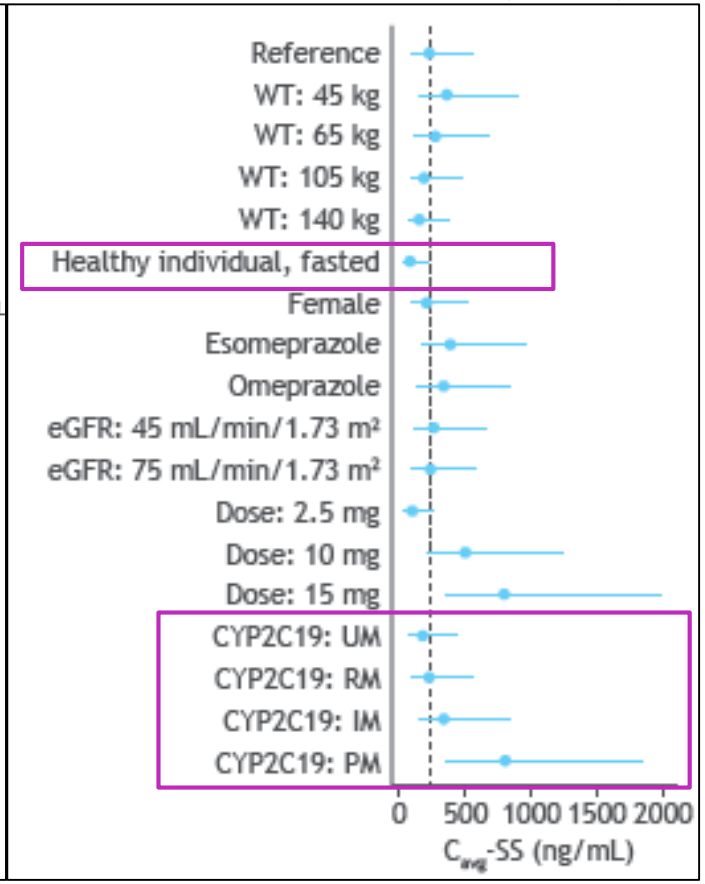
- Identified key covariate effects were used to derive the exposure for E-R analysis

Parameter	Selected Covariates
CL/F	CYP2C19 Phenotype (PM, IM, NM, RM, UM), Population (HV vs Patient), Body weight, Sex, eGFR, CYP3A4 / CYP2C19 inhibitor
V2/F, Q/F, V3/F	Body weight
KA	Dose amount, Formulation, Food status
Relative BA	Dose amount, Formulation, Food status

GOF and pcVPC of the final model



Effect of covariates on exposures (Cavg-SS)



Exposure-Response Modeling of Mavacamten in Adults with HCM

- E-R model for VLVOT and LVEF were characterized by nonlinear mixed-effect model with Cavg168
- Data for efficacy: 272 Patients & safety: 331 Patients
- Time (weeks since dose initiation) was also explored to determine if there was
- Placebo (background treatment) effect over time on VLVOTg

Table 1. Clinical studies used as data source

Study	Phase	Patient population	Endpoint	Status
PIONEER-HCM (NCT02842242)	2	Obstructive HCM	LVEF and VLVOTg	Completed
MAVERICK-HCM (NCT03442764)	2	Nonobstructive HCM	LVEF	Completed
EXPLORER-HCM (NCT03470545)	3	Obstructive HCM	LVEF and VLVOTg	Completed
PIONEER-OLE (NCT03496168)	2	Obstructive HCM	LVEF and VLVOTg	Ongoing
MAVA-LTE (NCT03723655)	3	Obstructive HCM	LVEF and VLVOTg (EXPLORER-LTE cohort)	Ongoing
	2	Nonobstructive HCM	LVEF (MAVERICK-LTE cohort)	Ongoing

LTE, long-term extension; OLE, open-label extension.

EFFICACY

$$VLVOTg(t) = (VLVOTg_0 \times VLVOTg_{PBO}(t)) \times exp(-k_{MAVA} \times C_{avg168}(t)), \text{ where}$$

$$VLVOTg_{PBO}(t) = VLVOTg_{PBOMAX} + (1 - VLVOTg_{PBOMAX}) \times exp(-k_{PBO} \times t)$$

	Estimate (SE)
Parameters	
$Log(VLVOTg_{0.REF})$, log(mm Hg)	4.22 (0.0248)
$Log(VLVOTg_0)$ ~ $log(VLVOTg_0/69)$	0.521 (0.0319)
$Log(VLVOTg_0)$ ~ log(NT-proBNP/736)	0.108 (0.0152)
$Log(k_{MAVA,REF})$, log(1/(ng/mL))	−5.66 (0.0343)
$Log(k_{MAVA})$ ~ $log(VLVOTg_0/69)$	0.438 (0.0506)
Placebo parameters	
k_{PBO}, 1/wk	0.0373 (0.0205)
$VLVOTg_{PBOMAX}$	0.8767 (-)

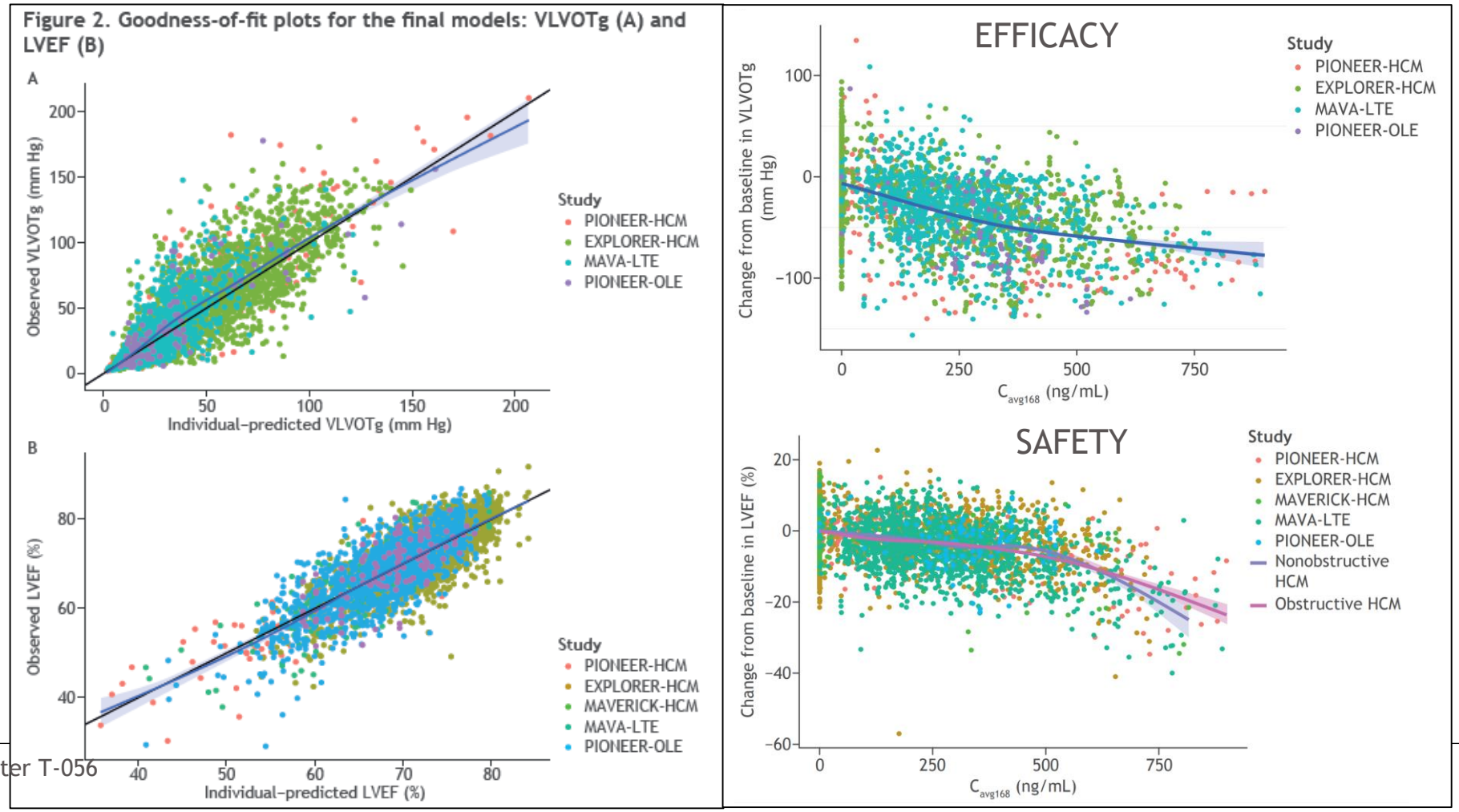
SAFETY

$$LVEF(t) = LVEF_0 \times (1 - k_{MAVA} \times [C_{avg168}(t)]^{qq})$$

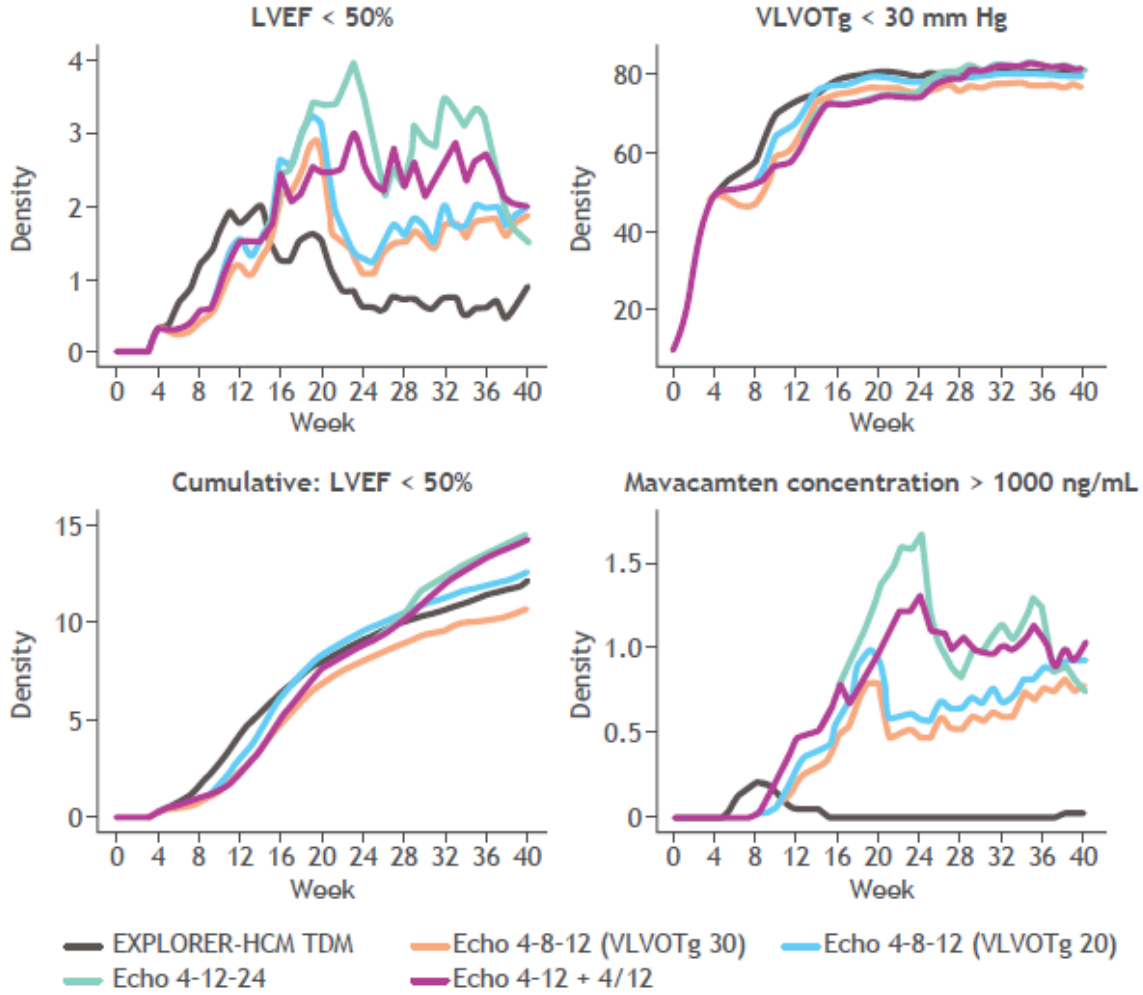
	Estimate (SE)
Parameters	
$LVEF_{0.REF}$, %	74.0 (0.243)
$LVEF_0$ ~ $log(LVEF_0/74)$, %	33.6 (1.73)
$LVEF_0$ ~ nonobstructive HCM, %	−3.24 (0.485)
$LVEF_0$ ~ female, %	1.40 (0.345)
$Log(k_{MAVA,REF})$, 1/(ng/mL)	−12.8 (0.901)
$Log(k_{MAVA,REF})$ ~ all studies except EXPLORER-HCM	4.29 (0.869)
$Log(k_{MAVA,REF})$ ~ $log(LVEF_0/74)$, 1/(ng/mL)	1.73 (0.418)
qq_{REF}	1.69 (0.146)
qq_{REF} ~ all studies except EXPLORER-HCM	−0.64 (0.142)

E-R models characterized both Mavacamten Efficacy and Safety endpoints well in patients with oHCM

- These E-R models, together with a pop pk model, form the basis of a simulation tool that was used to identify an optimized dose titration regimen for Mavacamten



M&S Framework to optimize Titration Regimen considering multiple factors



Cumulative LVEF < 50% counts patients only at the first instance of reaching that threshold.

- CYP2C19 Phenotype
- Benefit/Risk Profile
- Different Titration used Phase 3 study
- Real World Clinical Practice

2022 ACoP13 Poster T-056

Extensive M&S Analysis Throughout oHCM Development Program Led to ECHO Guided Titration Without PK TDM

ECHO Guided Titration is expected to have a similar Benefit/Risk as the titration regimen in EXPLORER

- NO PK TDM-guided dose titrations
- **Week 4 & 8:** Down-titrate if VLVOT gradient <20 mmHg or
- **Week 12 & 24:** Up-titrate if VLVOT gradient ≥ 30 mmHg and LVEF ≥ 55%
- **Follow up:** Every 12 weeks unless up-titration or dose interruption, in which case the follow-up is in 4 weeks.
- **Temporary dose interruption:** if LVEF <50%