

# A Novel Oral Pyruvate Kinase M2 (PKM2) Modulator for Atopic Dermatitis (SYX-5219) Demonstrates Favorable Safety, Pharmacokinetics, Robust Target Engagement and Evidence of Type 2 Immunomodulation: Results from a First-in-Human Phase 1a Study



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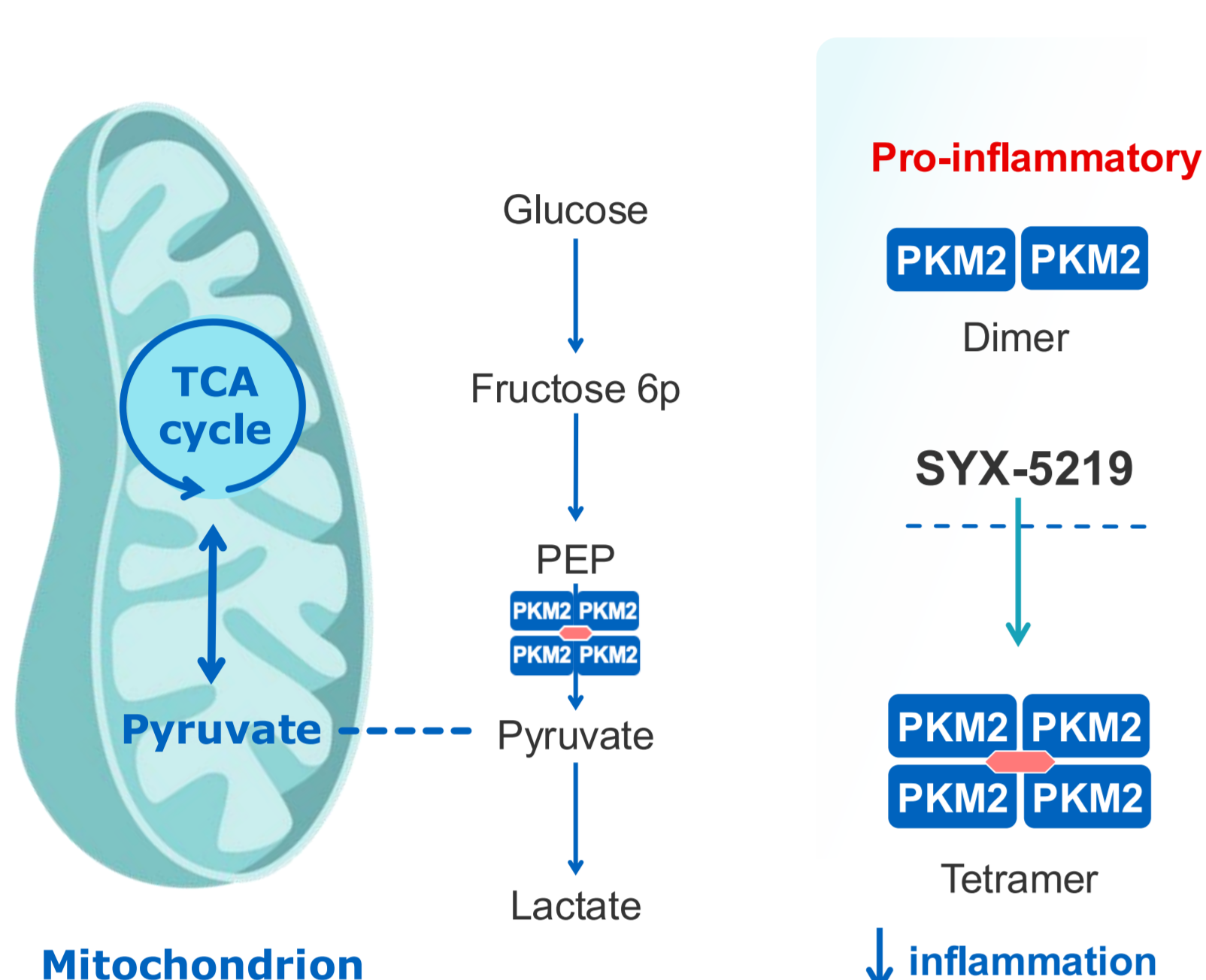
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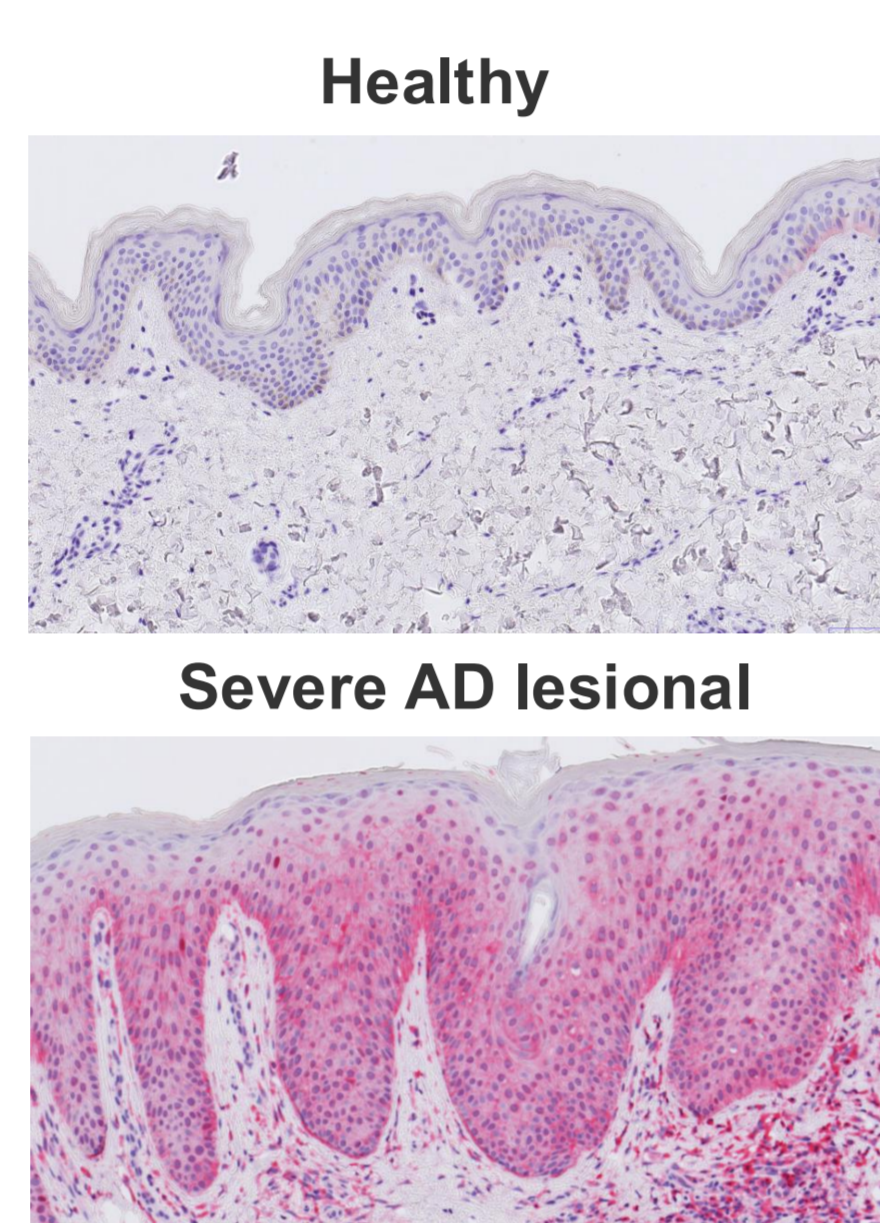
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## Introduction and background

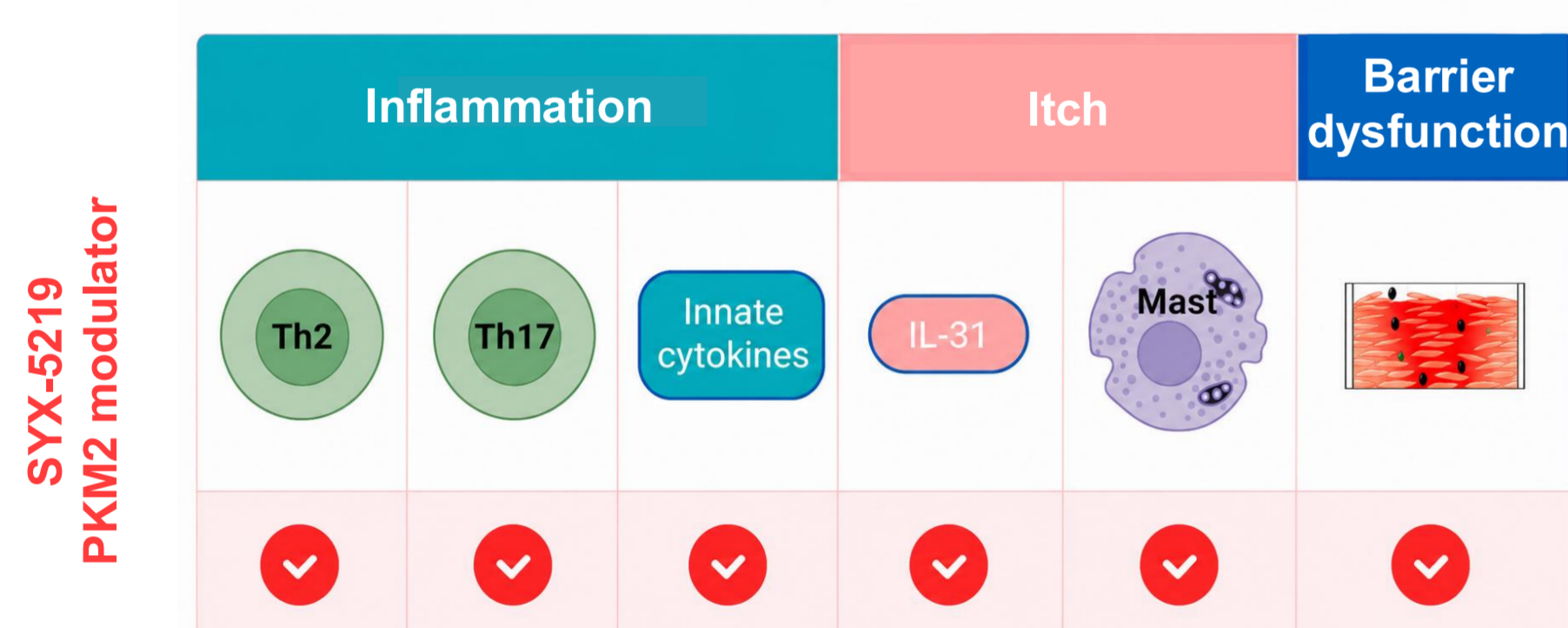
SYX-5219 promotes PKM2 tetramerization to reduce inflammation



PKM2 is upregulated in AD skin  
Representative PKM2 immunohistochemistry (IHC) staining of healthy and severe AD lesional skin



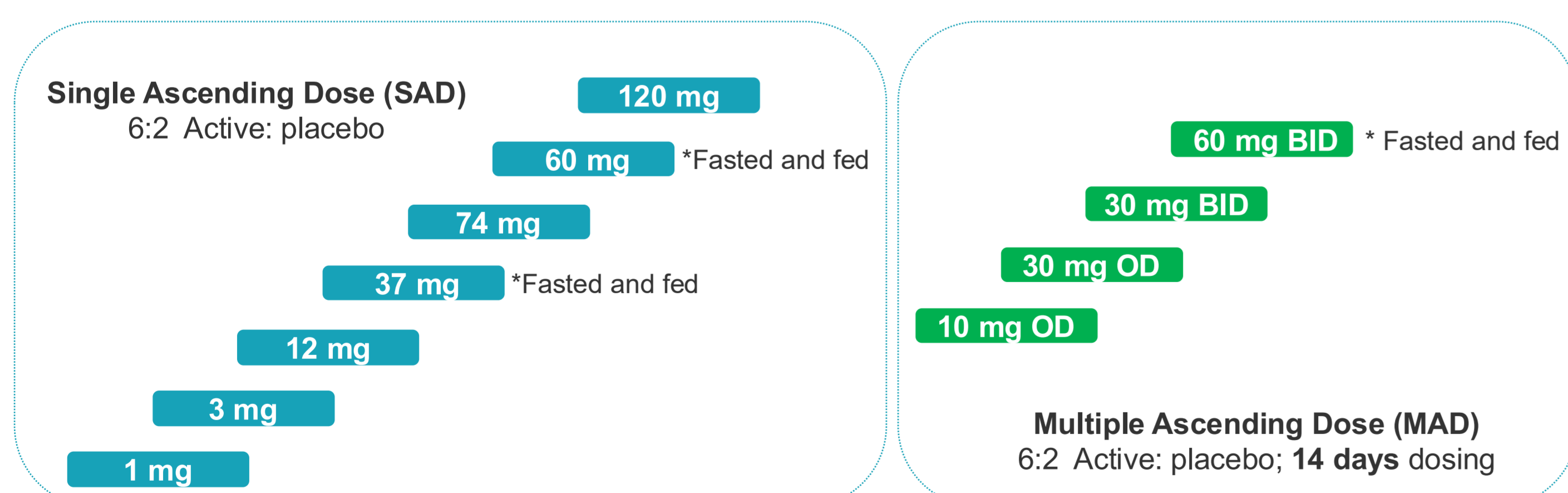
Modulation of PKM2 impacts multiple drivers of atopic dermatitis (AD) pathology



## Methods

- First-in-human, placebo-controlled study of oral SYX-5219 in healthy volunteers (aged 18-65y)
- 96 participants exposed overall; 72 received SYX-5219 (24 received placebo)
- Assessments included safety/tolerability, PK, PBMC pyruvate kinase activity, and serum TARC/CCL17

## Study design



## Results

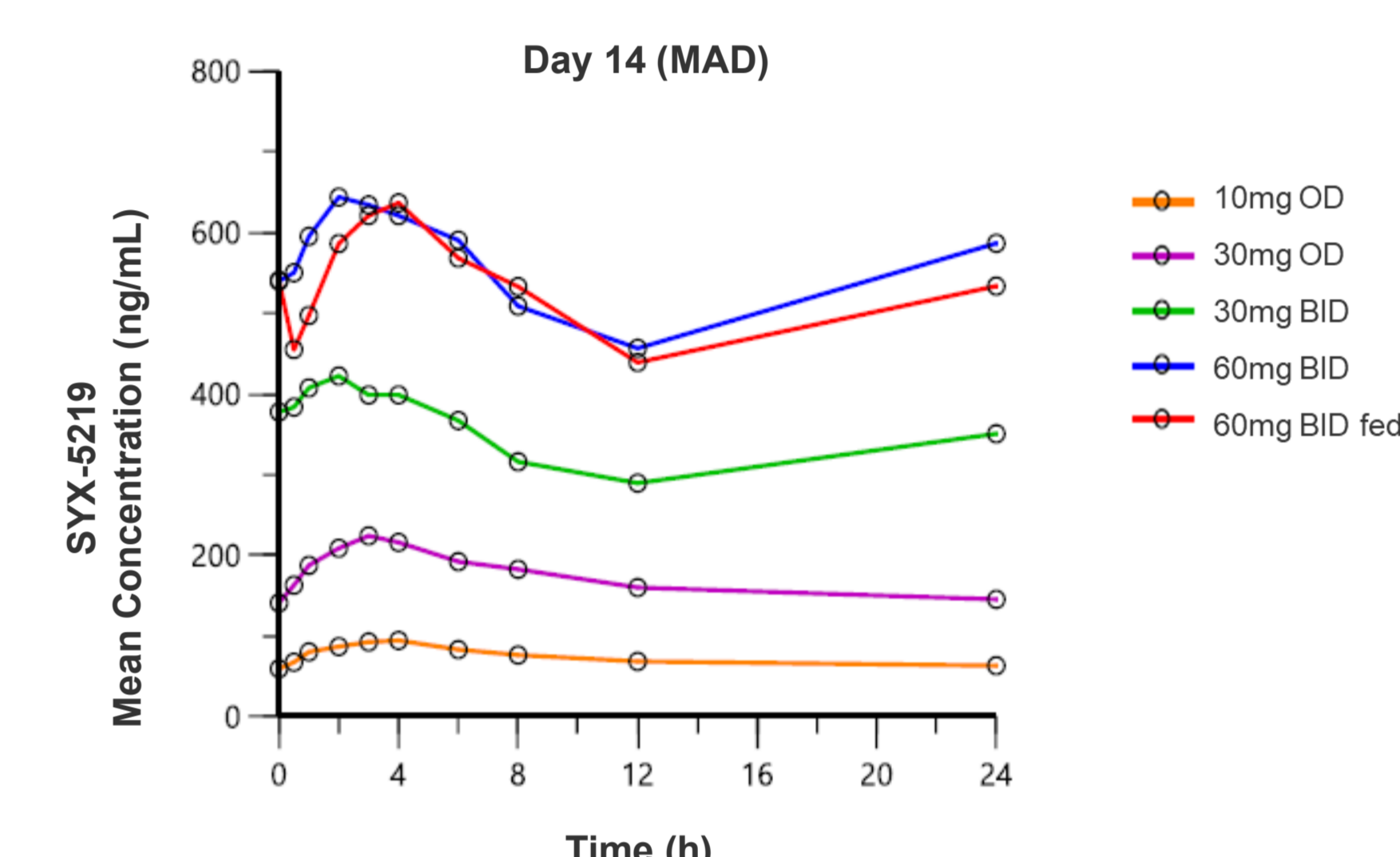
### Safety and tolerability

SYX-5219 was **safe and well tolerated** across all SAD and 14-day MAD cohorts in healthy adult participants. No serious or severe adverse events were reported, and no treatment-related withdrawals or laboratory abnormalities were observed.

n (%)	Placebo Overall (N=10)	SYX-5219 Overall (N=30)	10 mg QD		30 mg QD		30 mg BID		60 mg BID	
			Placebo (N=2)	SYX-5219 (N=6)	Placebo (N=2)	SYX-5219 (N=6)	Placebo (N=2)	SYX-5219 (N=6)	Placebo (N=4)	SYX-5219 (N=12)
Any TEAE	3 (30.0)	11 (36.7)	0	0	0	2 (33.3)	1 (50.0)	2 (33.3)	2 (50.0)	7 (58.3)
Serious TEAE	0	0	0	0	0	0	0	0	0	0
Mild	3 (30.0)	5 (16.7)	0	0	0	0	1 (50.0)	2 (33.3)	2 (50.0)	3 (25.0)
Moderate	0	6 (20.0)	0	0	0	2 (33.3)	0	0	0	4 (33.3)
Severe	0	0	0	0	0	0	0	0	0	0

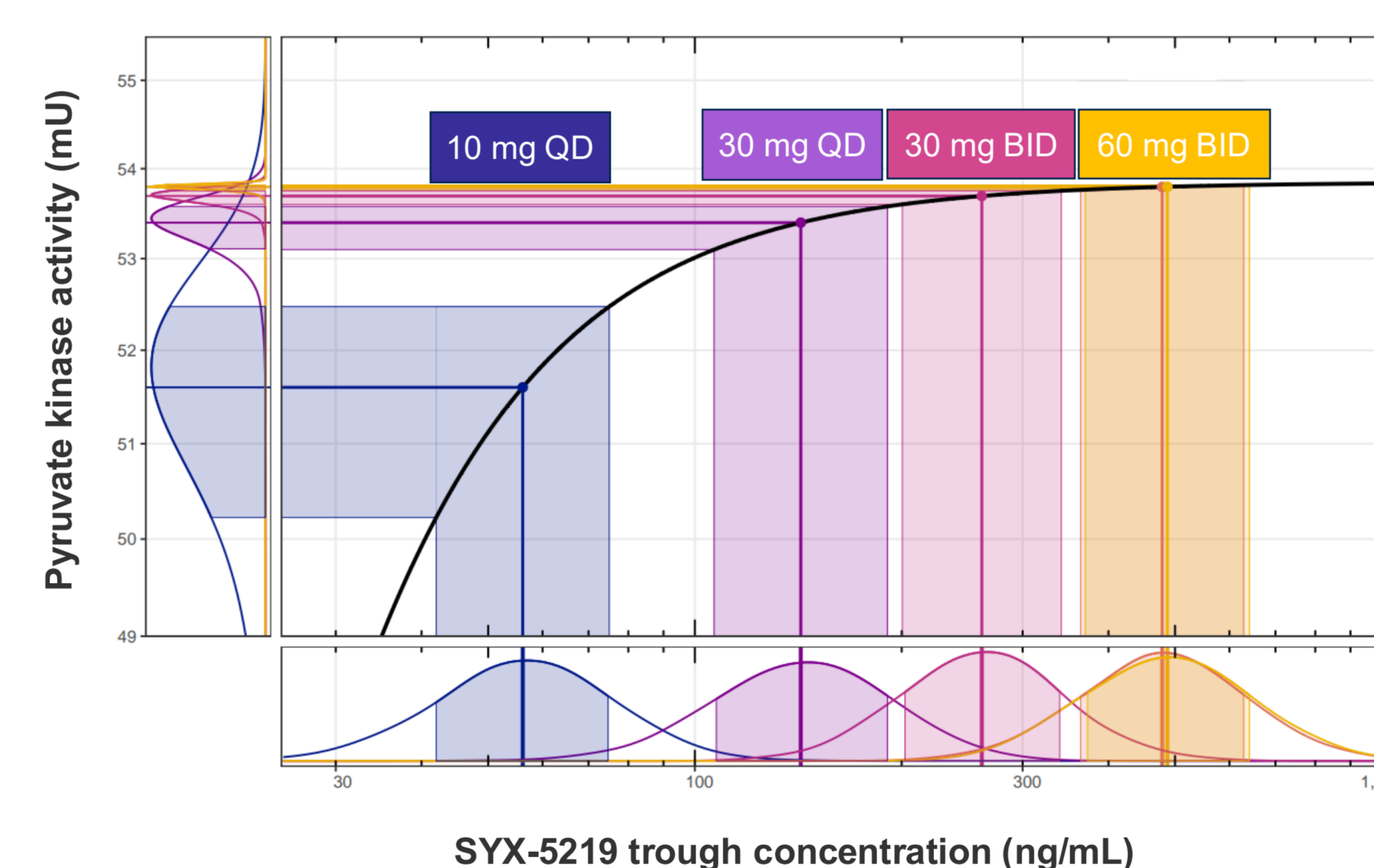
### Pharmacokinetics

- SYX-5219 showed sustained Day 14 plasma exposure across MAD cohorts.
- Single-dose exposure was dose-proportional up to 60 mg.
- Apparent half-life was ~60-70 h, with steady state estimated by Day 6-8.
- No food effect was observed at steady state.
- Steady state exposure consistent with preclinical human dose prediction.



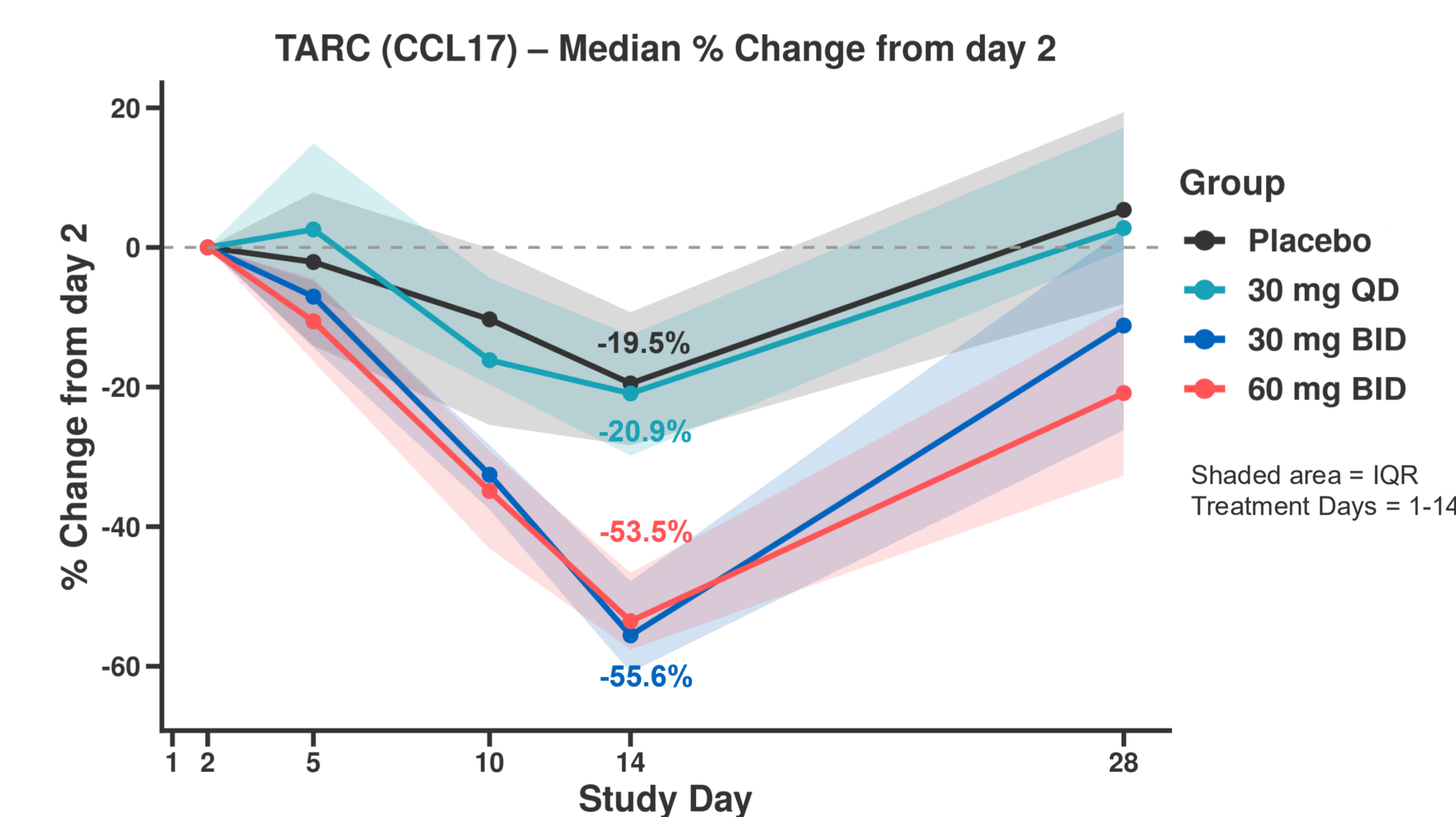
### Target engagement and Pharmacodynamics

SYX-5219 achieved exposure-dependent pyruvate kinase target engagement



- Pyruvate kinase activity increased with SYX-5219 exposure and plateaued at higher plasma concentrations.
- Model-derived PK/PD analysis indicated  $\geq$ EC95 target engagement at doses  $\geq$ 30 mg QD.
- BID dosing maintained exposures in the near-maximal target engagement range.
- These findings support robust pharmacologic engagement of PKM2 in humans.

SYX-5219 reduced AD inflammatory biomarker TARC/CCL17 in healthy adults



- SYX-5219 reduced serum TARC/CCL17 during 14-day dosing.
- Greatest median reductions were observed at Day 14 in BID cohorts: -55.6% with 30 mg BID and -53.5% with 60 mg BID.
- TARC/CCL17 levels trended back towards normalising at follow-up (Day 28) after treatment cessation.
- These data support systemic modulation of a type 2 inflammatory biomarker

## Conclusions

SYX-5219, a first-in-class oral PKM2 modulator, demonstrated a favorable Phase 1a profile in healthy adults supportive of progression into a Phase 1b study in AD.

Across SAD and 14-day MAD cohorts, SYX-5219 was safe and well tolerated, achieved sustained systemic exposures, and showed robust exposure-dependent target engagement. Treatment was associated with reductions in serum TARC/CCL17, supporting systemic modulation of type 2 inflammatory biomarkers. Together, these data support further clinical evaluation of SYX-5219 as a novel immunometabolic approach for AD.

### Future direction

An ongoing Phase 1b study is evaluating SYX-5219 in adults with moderate-to-severe AD.

The AD cohort will enroll up to 45 participants and assess safety, tolerability, PK, target engagement, clinical efficacy and disease-associated biomarkers following multiple dosing of SYX-5219 or placebo.

### Acknowledgements

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