A Deimmunized, Half-life Extended Anti-TNFα/IL-23p19 Bifunctional Antibody for Inflammatory Diseases

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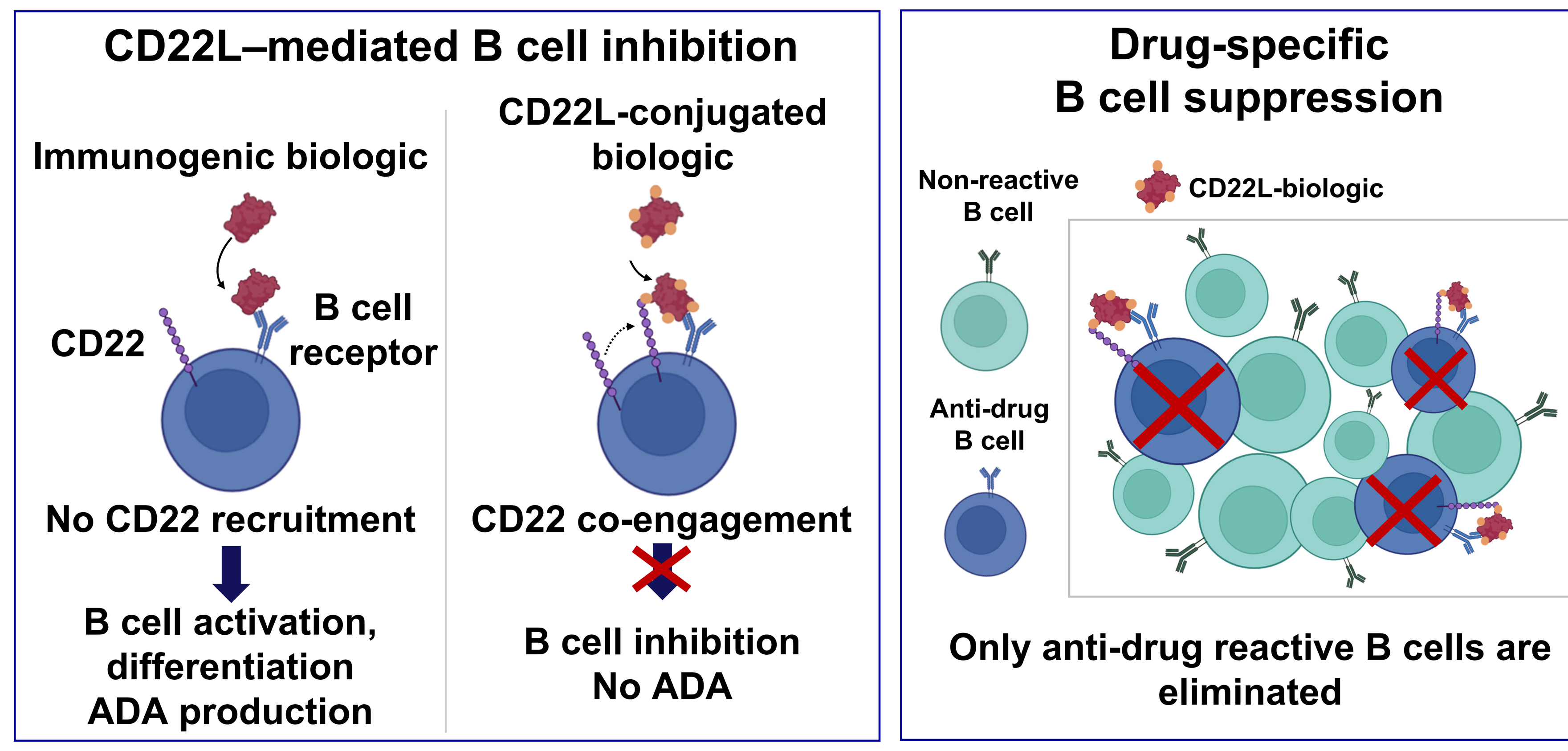
Background

- Dual blockade of TNFα and IL-23 using coadministration of monospecific antibodies has shown additive clinical benefit in ulcerative colitis and psoriatic arthritis.
- Several bispecifics containing an anti-TNFα arm failed due to strong anti-drug antibody (ADA) responses driven by the TNFα-neutralizing arm.
- A half-life–extended anti-TNFα/IL-23p19 hIgG1 bispecific was engineered with lysine-conjugated CD22 ligands (CD22Ls) to suppress drug-specific B-cell responses and prevent ADA formation, and streamline development compared to combination therapies.

Unsuccessful development of anti-TNFα containing bispecific antibodies

Target	Drug	Status (year reported)	ADA incidence
TNFα x p19	SAR442999	Ph1 - disc. (2022)	100% [1]
TNFα x IL17	JNJ-61178104	Ph1 - disc. (2020)	100% [2]
TNFα x TL1A	AMG 966	Ph1 - disc. (2021)	98% [3]
TNFα x IL-6	SAR444419	Ph1 - disc. (2023)	100% [1]

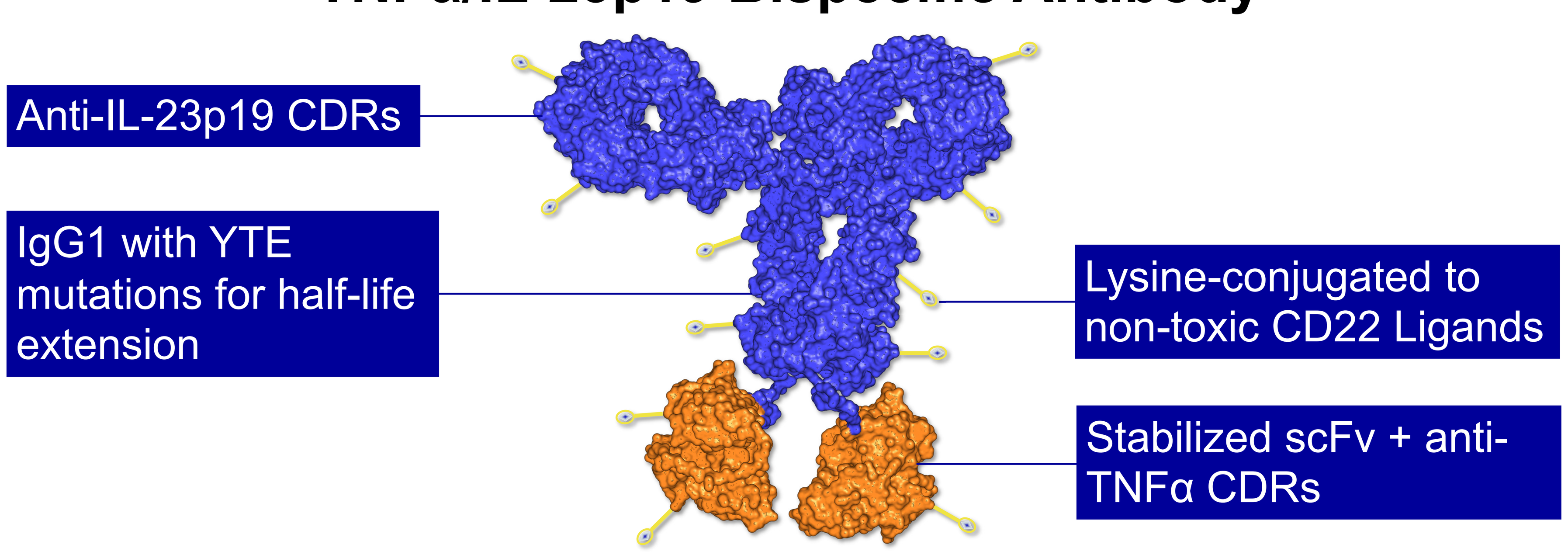
ADAx Platform



CD22L conjugation to an immunogenic biologic drug aims to eliminate or prevent the proliferation of drug-reactive B cells.

Results

ADX-001: A CD22L-Deimmunized, Half-Life Extended TNFα/IL-23p19 Bispecific Antibody



ADX-001 demonstrates potent binding of TNFα and IL-23 *in vitro* and enhanced FcRn binding

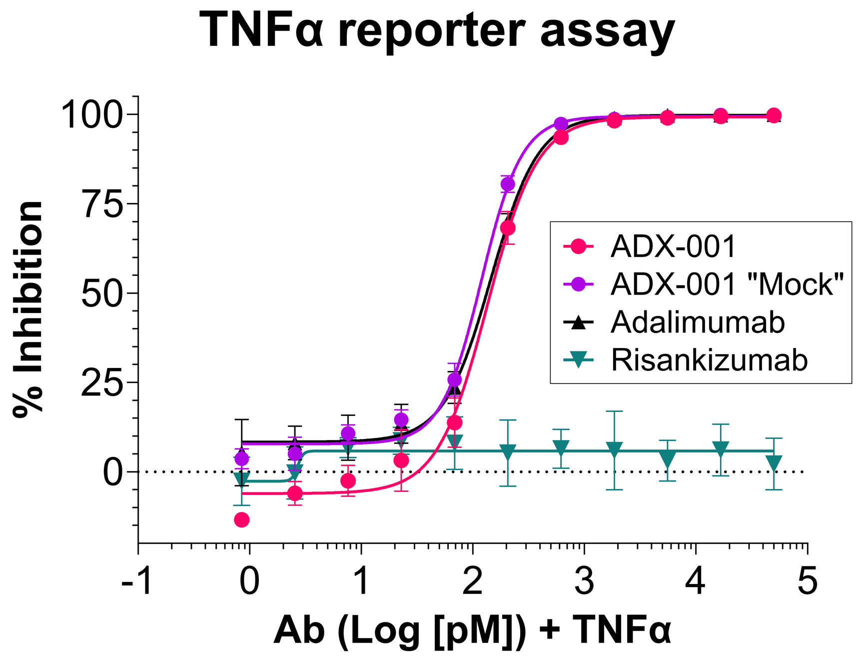
Binding measured by Surface Plasmon Resonance (SPR)

Antibody	TNFα (nM)	IL-23 (nM)	FcRn (nM)
Adalimumab	0.2	NB	380
Risankizumab	NB	0.21	95*
Bispecific	0.57	0.14	160
ADX-001	0.45	0.21	133

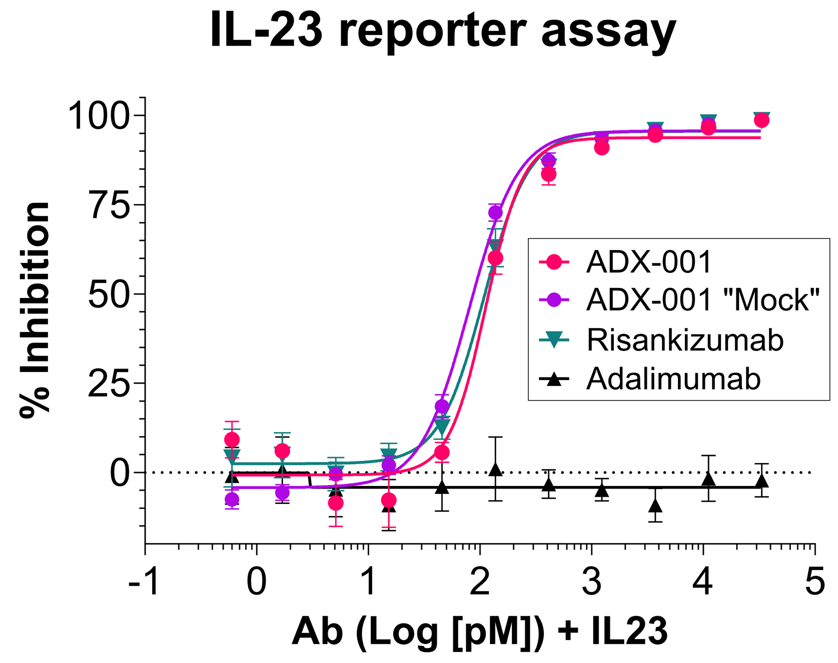
** Risankizumab with YTE mutation; NB – No binding*

ADX-001 demonstrates potent neutralization of TNFα and IL-23

TNFα reporter assay



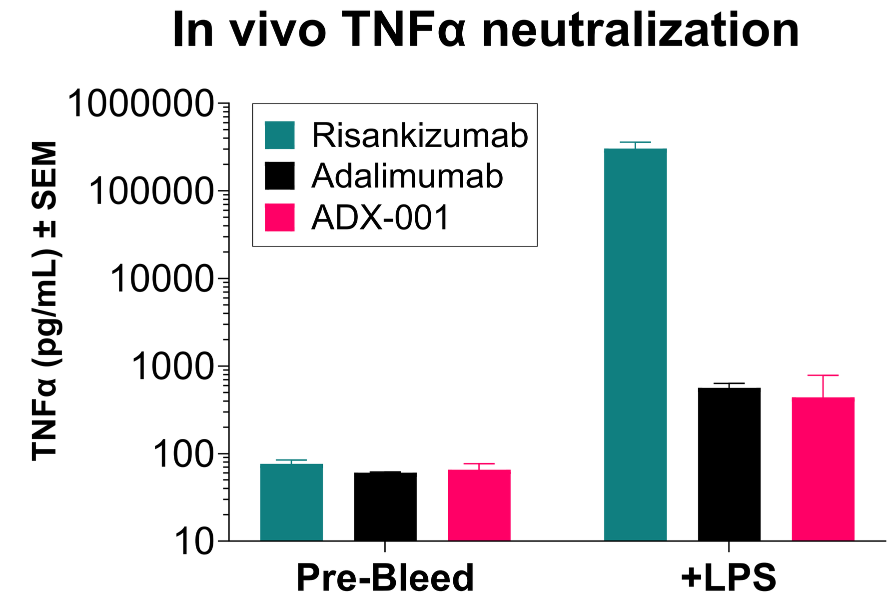
IL-23 reporter assay



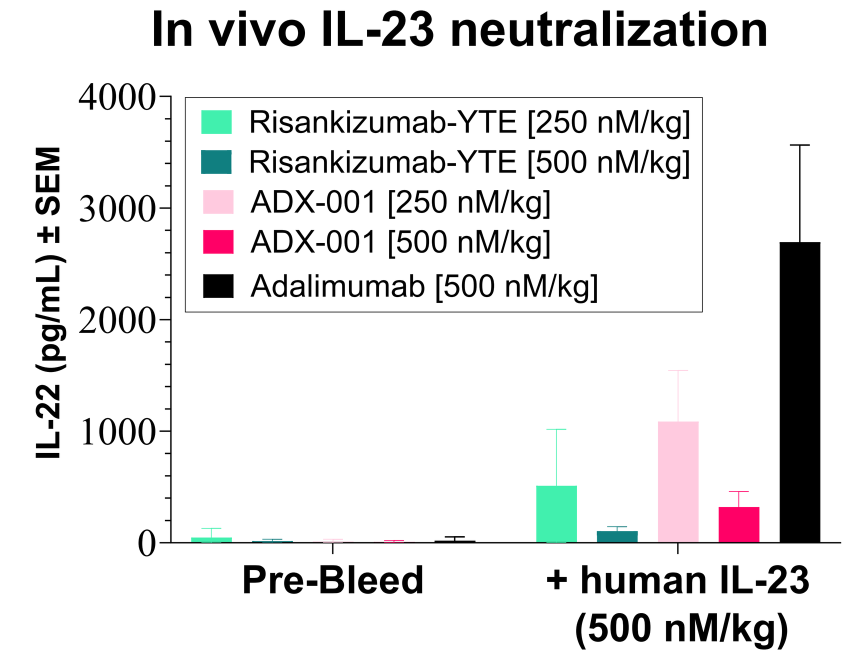
ADX-001 neutralizes human TNFα and IL-23 with IC_{50} values comparable to its “Mock” non-conjugated form and reference antibodies.

ADX-001 effectively neutralizes human TNFα- and IL-23–induced cytokine responses *in vivo*

In vivo TNFα neutralization

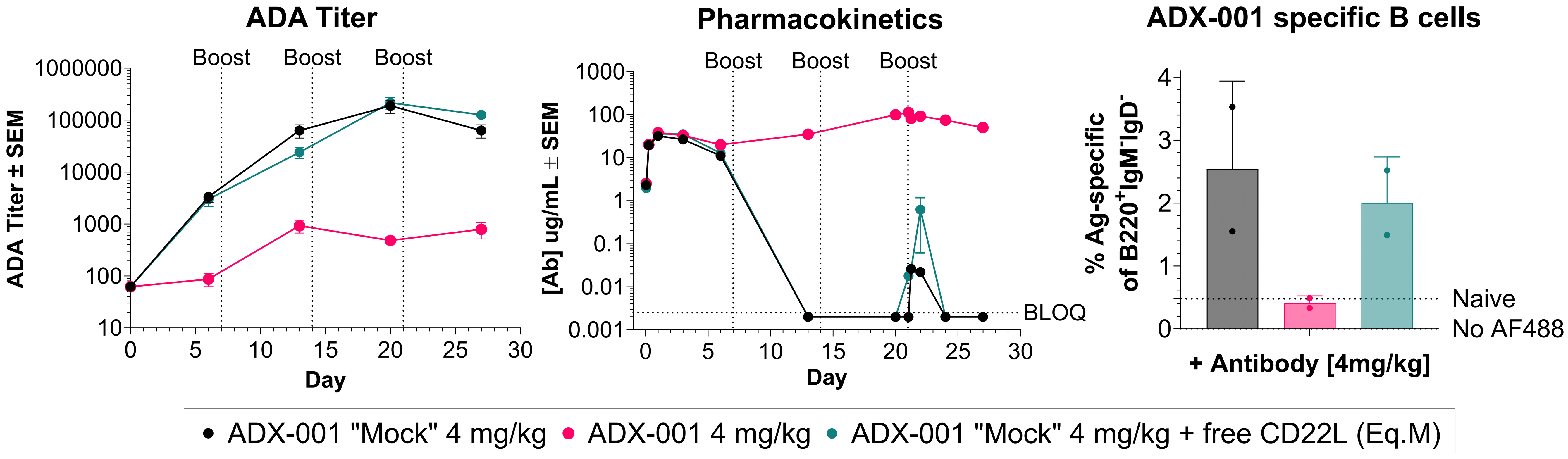


In vivo IL-23 neutralization



Inhibition of human TNFα in B6-hTNFa KI mice post challenges with LPS. Blockade of human IL-23–driven mouse IL-22 production.

ADX-001 exhibits CD22 ligand-dependent ADA suppression in B6-hFcRn KI mice



ADA suppression: CD22L-conjugated ADX-001 effectively suppresses anti-drug antibody responses.

Restored PK: ADA suppression by ADX-001 enables sustained antibody exposure over time.

B cell inhibition: ADX-001 reduces anti-TNFα/IL-23 specific B cells in a conjugation-dependent manner.

Conclusions

- ADX-001 is a deimmunized, half-life–extended anti-TNFα/IL-23p19 bispecific antibody using the proprietary CD22L platform to reduce anti-drug antibody formation and enable less frequent dosing.
- ADX-001 demonstrates potent dual neutralization, low immunogenicity, and high stability suitable for subcutaneous administration, supporting its advancement into clinical development with Phase I expected to start in Q4 2026.

References

1. www.trialsummaries.com; SAR442999 = Trial TDR16643 ; SAR444419 = Trial SAD17663
2. Akpalu, 2019.
3. Kroenke, 2021a.

Poster Number: 86