Nurix Therapeutics

Blazing a New Path in Medicine

Exploring NX-5948: A CNS Penetrant Selective Degrader of BTK that Significantly Reduces Inflammation in Mouse Models of Autoimmune Disease

3rd Annual B & T Cell-Mediated Autoimmune Disease Drug Development Summit

July 27th, 2022

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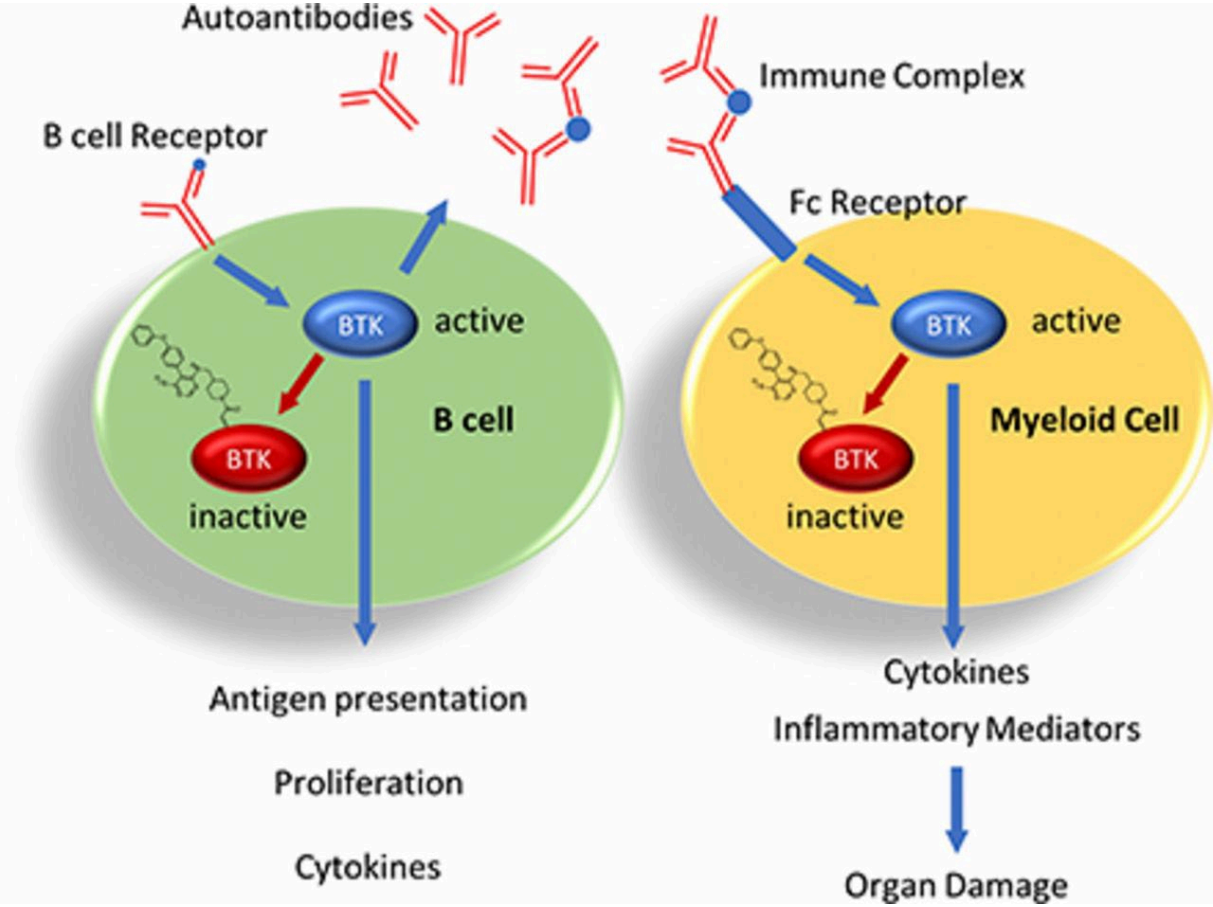
Nurix Is Advancing Four Wholly Owned Clinical Programs with a Deep Pipeline of Proprietary and Partnered Novel Targets

MOA	Drug Program	Target/ Delivery	Therapeutic Area	Pre-Clinical	Phase 1	Phase 2	Phase 3
TPD	**NX-2127** Degrader	BTK-IKZF *Oral*	B-Cell Malignancies				
TPD	**NX-5948** Degrader	BTK *Oral*	B-Cell Malignancies				
TPE	**NX-1607** Inhibitor	CBL-B *Oral*	Immuno-Oncology				
TPE	**DeTIL-0255** Cell Therapy	Adoptive Cell Therapy *Ex vivo CBL-B Inhibition*	Gynecologic Malignancies				
TPM	Wholly owned	5 targets	Multiple				
TPD	Gilead Sciences	5 targets	Multiple				
TPD	Sanofi	5 targets	Multiple				

MOA, Mechanism of action; TPD, Targeted Protein Degradation; TPE, Targeted Protein Elevation; TPM, Targeted Protein Modulation

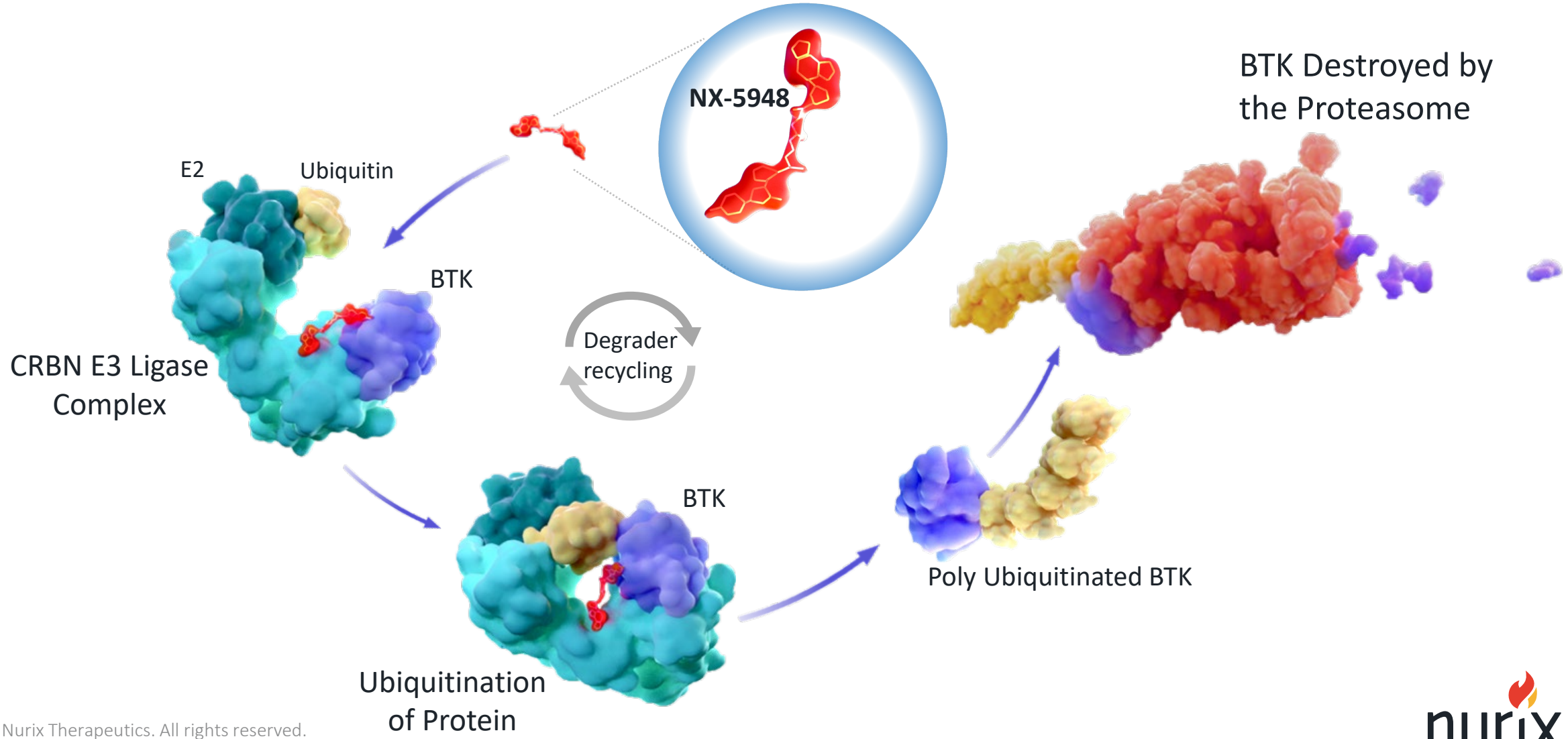
BTK Regulates Signaling Pathways in B cells and Myeloid Cells that Contribute to Autoimmunity



(Haselmayer, JI, 2019)

- BTK transduces signals downstream of the B cell receptor, toll-like receptors, and Fc receptors in B cells and myeloid cells
- BTK regulates B cell maturation, autoantibody production, and antigen presentation to T cells
- BTK regulates immune-complex mediated activation of myeloid cells which directly damages tissues

NX-5948 Promotes Proteasomal Degradation of BTK

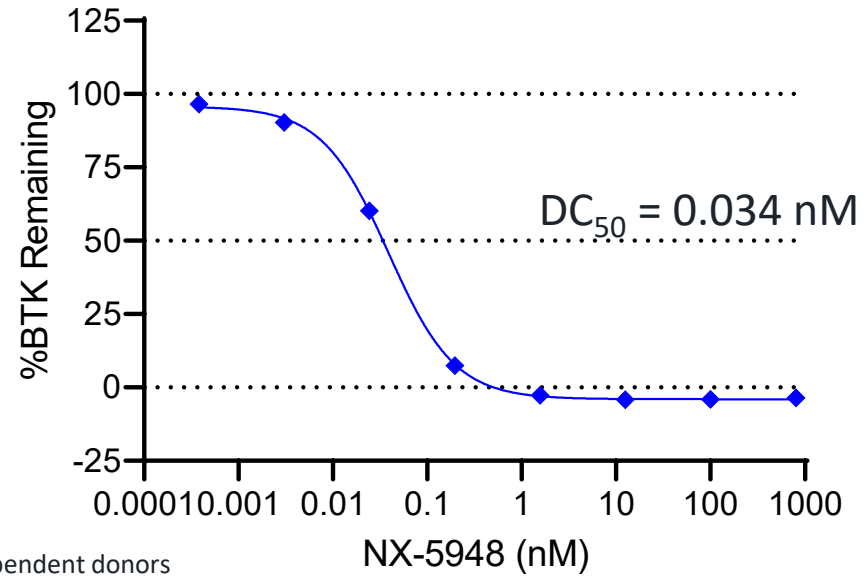


Presentation Overview

- NX-5948 potently degrades BTK *in vitro* and suppresses B cell activation in human cell lines and primary human B cells
- NX-5948 rapidly degrades BTK *in vivo* in circulating B cells following oral administration to mice and non-human primates (NHP)
- Daily oral administration of NX-5948 provides efficacy in multiple preclinical models of autoimmune disease
  - Collagen induced arthritis (CIA)
  - Autoimmune lymphoproliferative disease (ALPS)
  - Experimental autoimmune encephalomyelitis (EAE)
- NX-5948 mediates degradation of BTK in brain-resident microglia and macrophage following oral administration to naïve mice

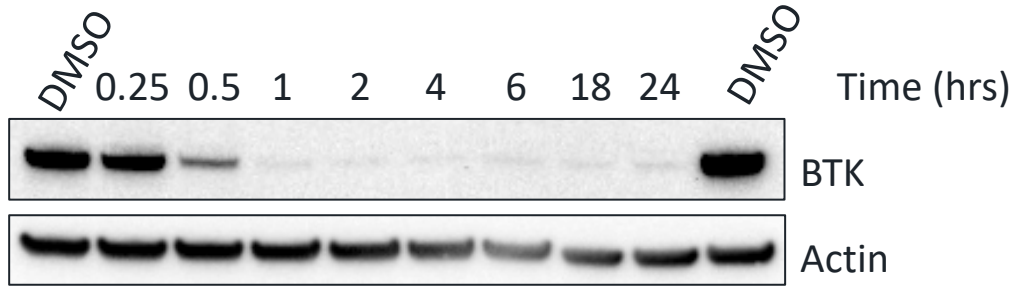
NX-5948 is a Potent and Rapid BTK Degrader

Dose Titration on Primary Human B cells



N=3 independent donors
SEM error bars are smaller than symbols

Degradation Time-Course

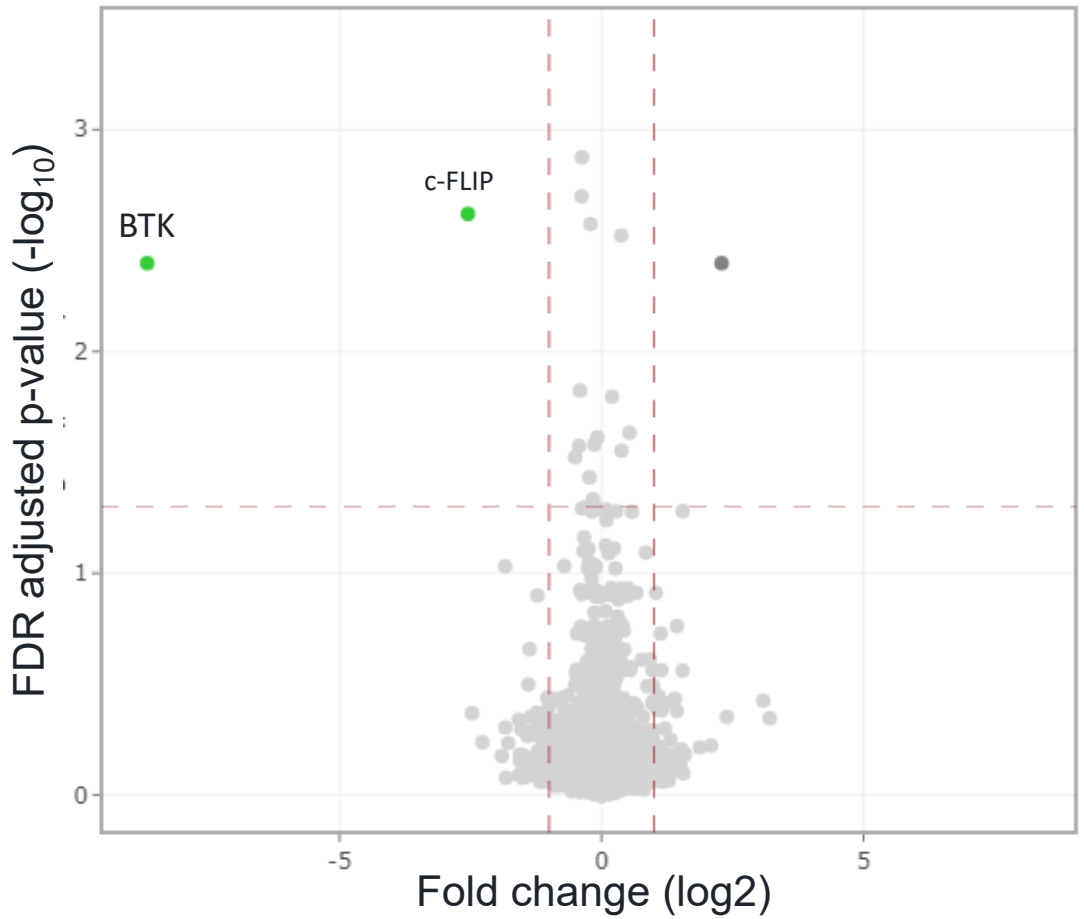


Ramos human Burkitt's lymphoma B cells
incubated with 10 nM NX-5948

- Robust BTK degradation observed in primary human B cells after 4 hours of NX-5948 treatment
- BTK degradation is observed within 1 hour and is complete within 2 hours in Ramos cells

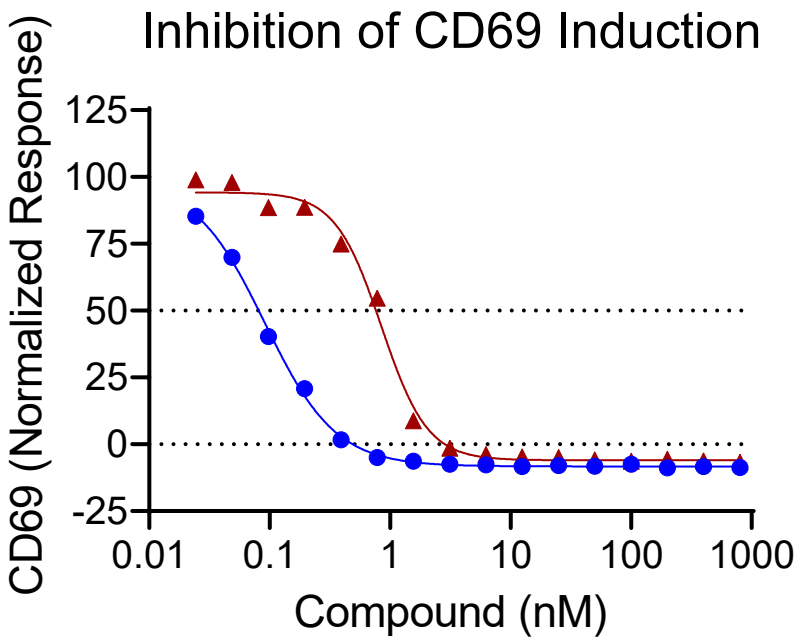
NX-5948 is a Selective BTK Degrader

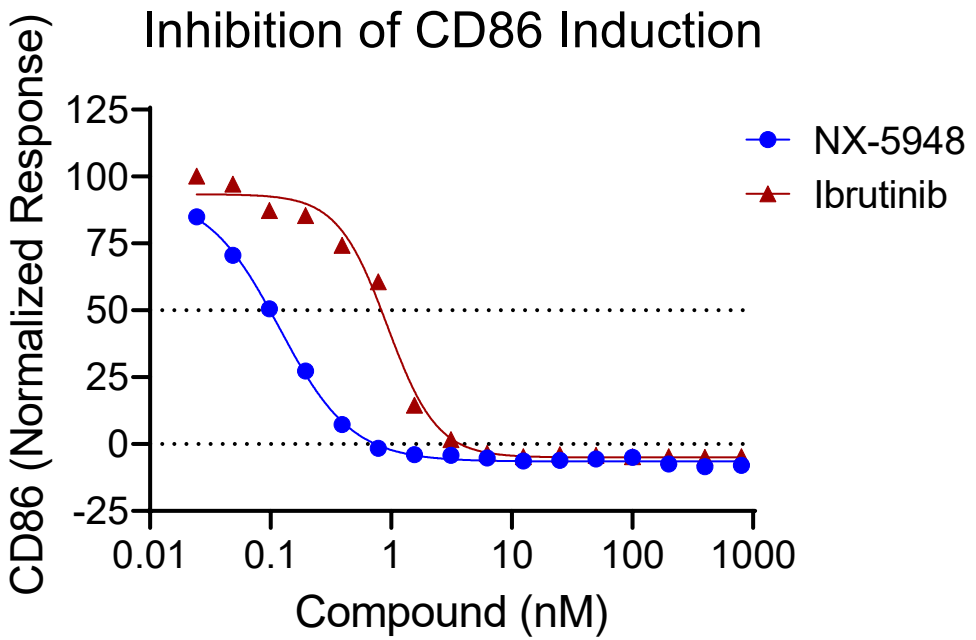
Human TMD8 ABC DLBCL cells incubated for 6 h with 50 nM NX-5948



- NX-5948 is highly selective for BTK degradation by proteomic analysis
- c-FLIP is an anti-apoptotic protein required to maintain survival of ABC DLBCL cells that is regulated by the BCR/NF-κB signaling axis
- BTK inhibition by ibrutinib also downregulates c-FLIP in TMD8 cells (Nurix data and Nagel; *Onco Target*; 2015)
- Therefore, c-FLIP reduction is believed to be a secondary effect of BCR/BTK signaling loss

NX-5948 is a Potent Inhibitor of Anti-IgM-Mediated B Cell Activation

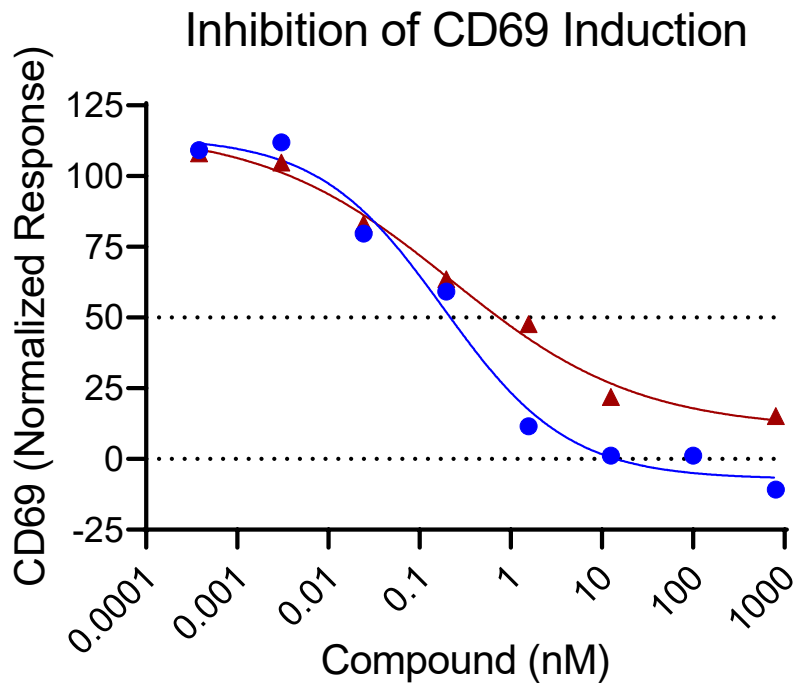


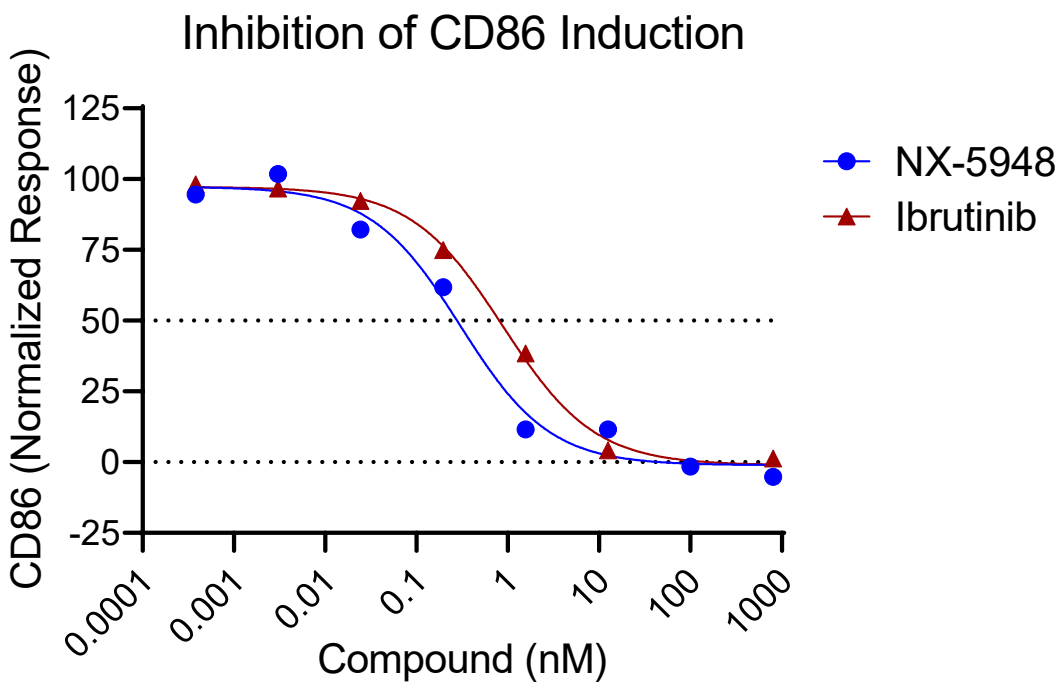


N=1 donor
Data representative of 3 independent donors

- NX-5948 is more potent than ibrutinib at inhibiting B cell activation following BCR stimulation

NX-5948 is a Potent Inhibitor of TLR7-Mediated B Cell Activation

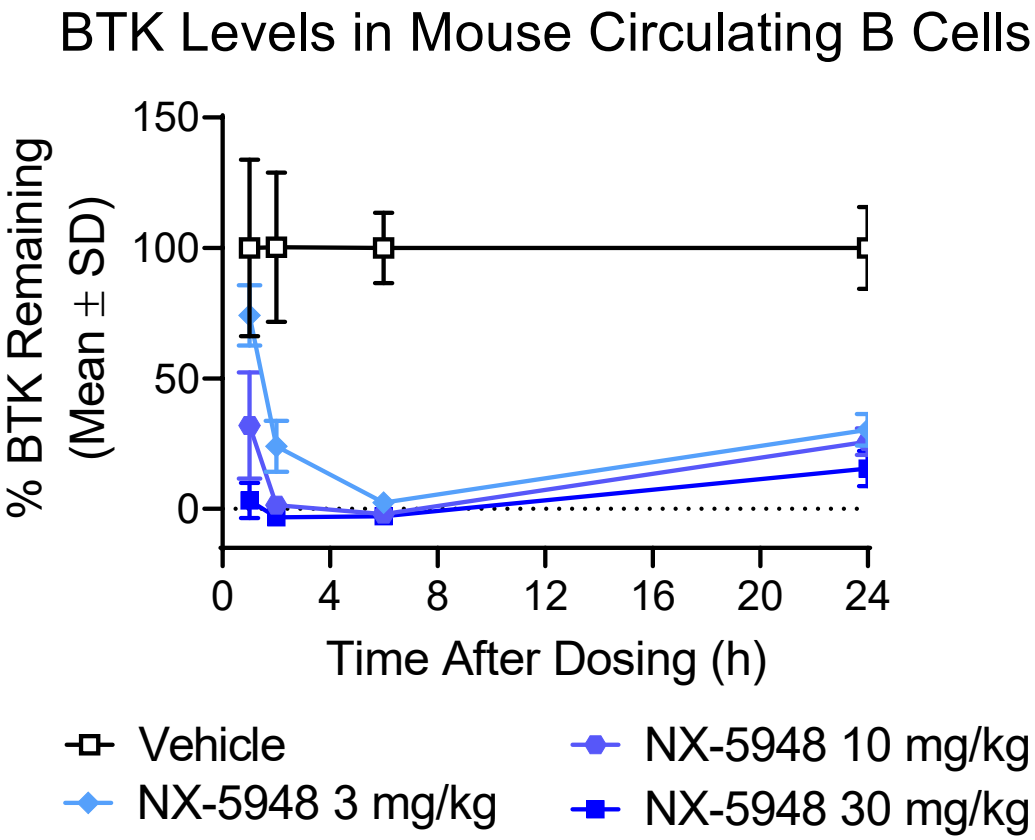


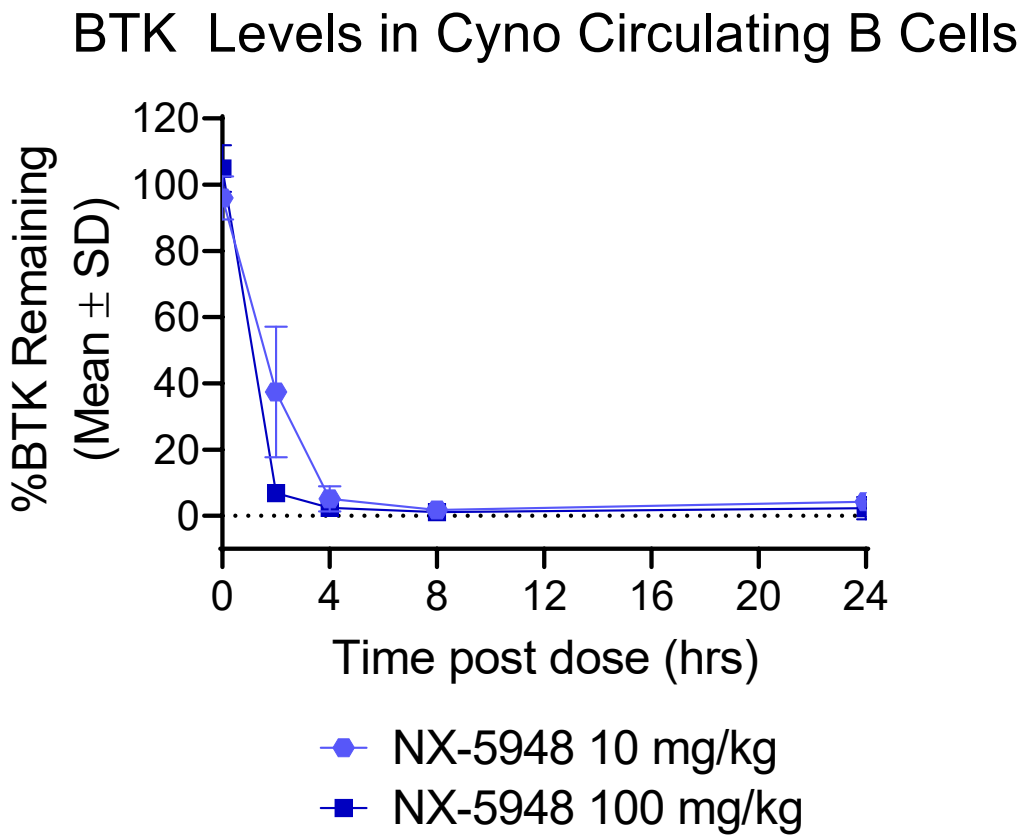


N=1 donor
Data representative of 3 independent donors

- NX-5948 is more potent than ibrutinib at inhibiting B cell activation following TLR7 (Imiquimod) stimulation

A Single Oral Dose of NX-5948 Promotes Rapid and Compete BTK Degradation in Mouse and NHP B cells

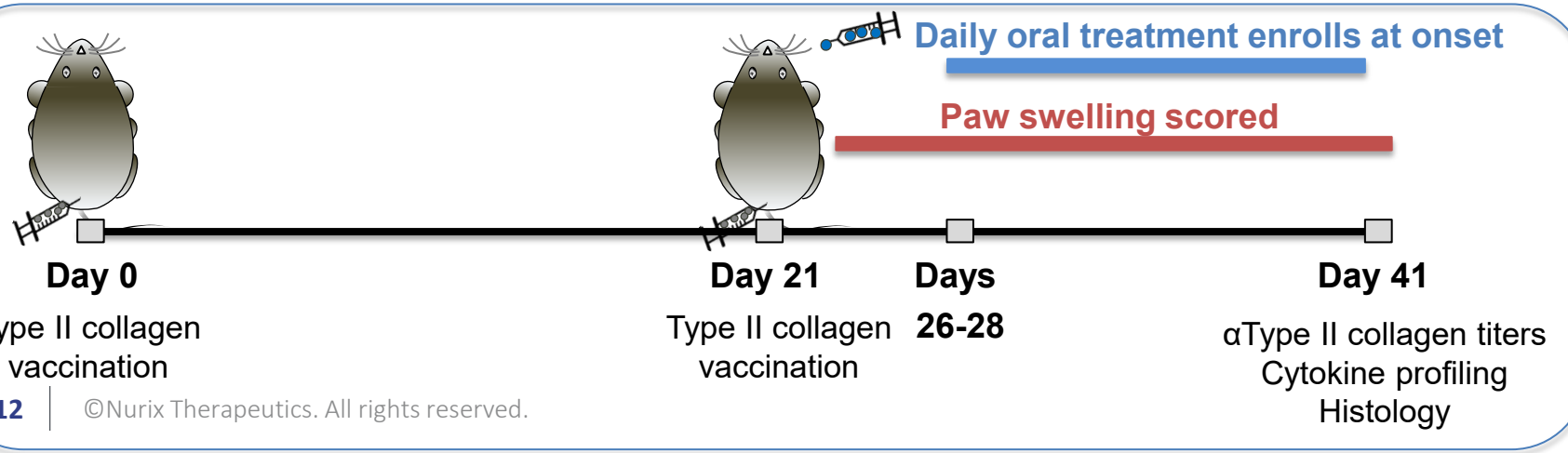




- In mice, BTK levels increased 24 hours after dosing from BTK resynthesis
- In cynomolgus monkeys, BTK levels remained suppressed at 24 hours

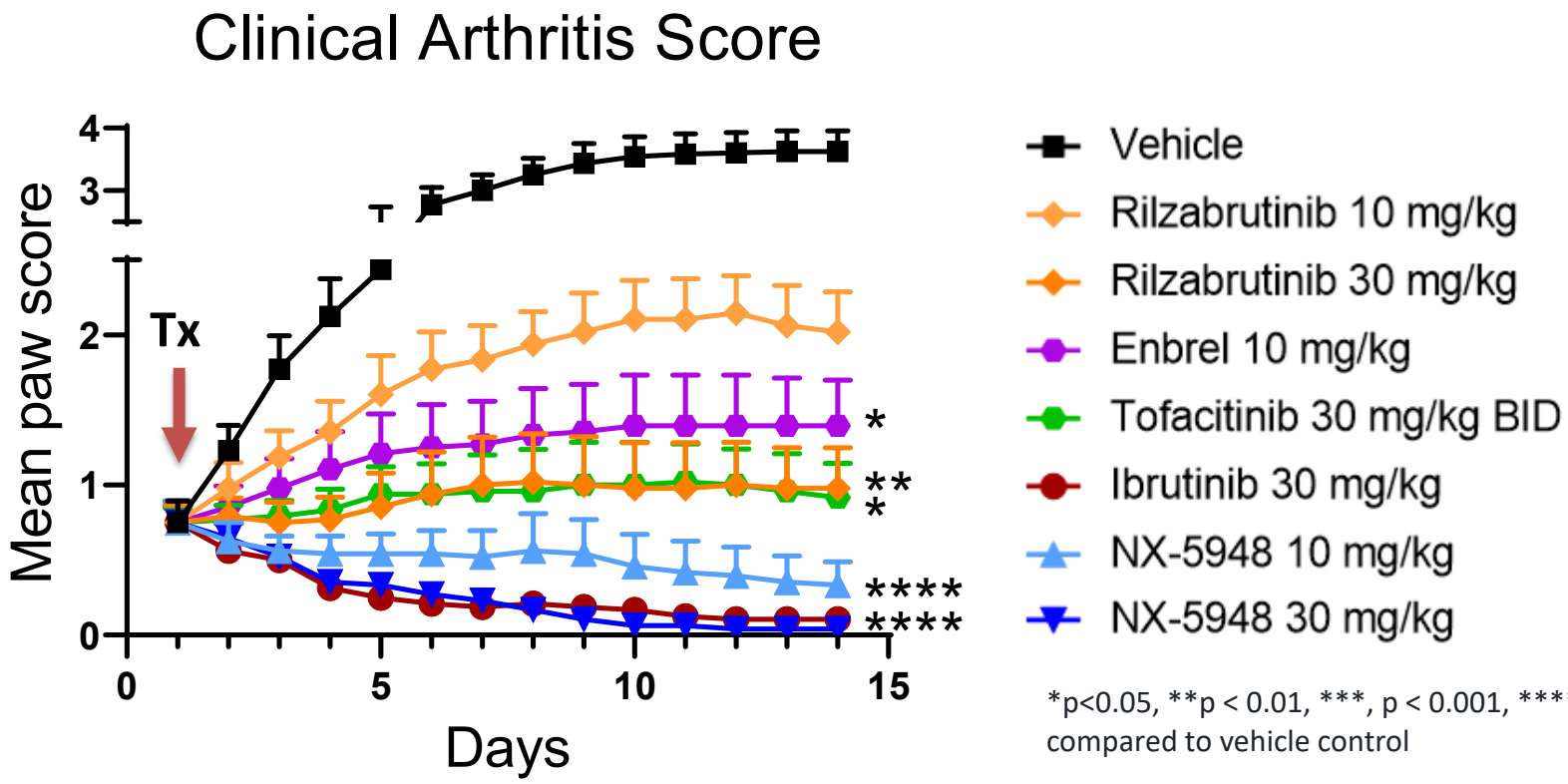
Comparison of NX-5948 to BTKi or Standard of Care Agents in Mouse Model of Established CIA

Group	N	Treatment	Dose (mpk)	Regimen
1	10	Naive	N/A	N/A
2	12	Vehicle	0	Oral, QD, At onset of symptoms ~Day 26
3	12	NX-5948	10	
4	12	NX-5948	30	
5	12	Rilzabrutinib (BTKi)	10	
6	12	Rilzabrutinib (BTKi)	30	
7	12	Ibrutinib (BTKi)	30	
8	12	Tofacitinib (JAKi)	30	PO, BID
9	12	Enbrel (TNFi)	10	IP, QD



- Immunization against type II collagen induces autoreactive T and B cells leading to a disease model for rheumatoid arthritis
- Antibody immune complexes deposited on cartilage promote joint inflammation and tissue damage mediated by myeloid cells
- BTK functions downstream of the B cell Receptor to promote B cell activation, produce anti-type II collagen antibodies, and present antigen to autoreactive T cells
- BTK also functions downstream of the Fc Receptor to activate myeloid cells against immune complexes leading to cartilage destruction and bone resorption

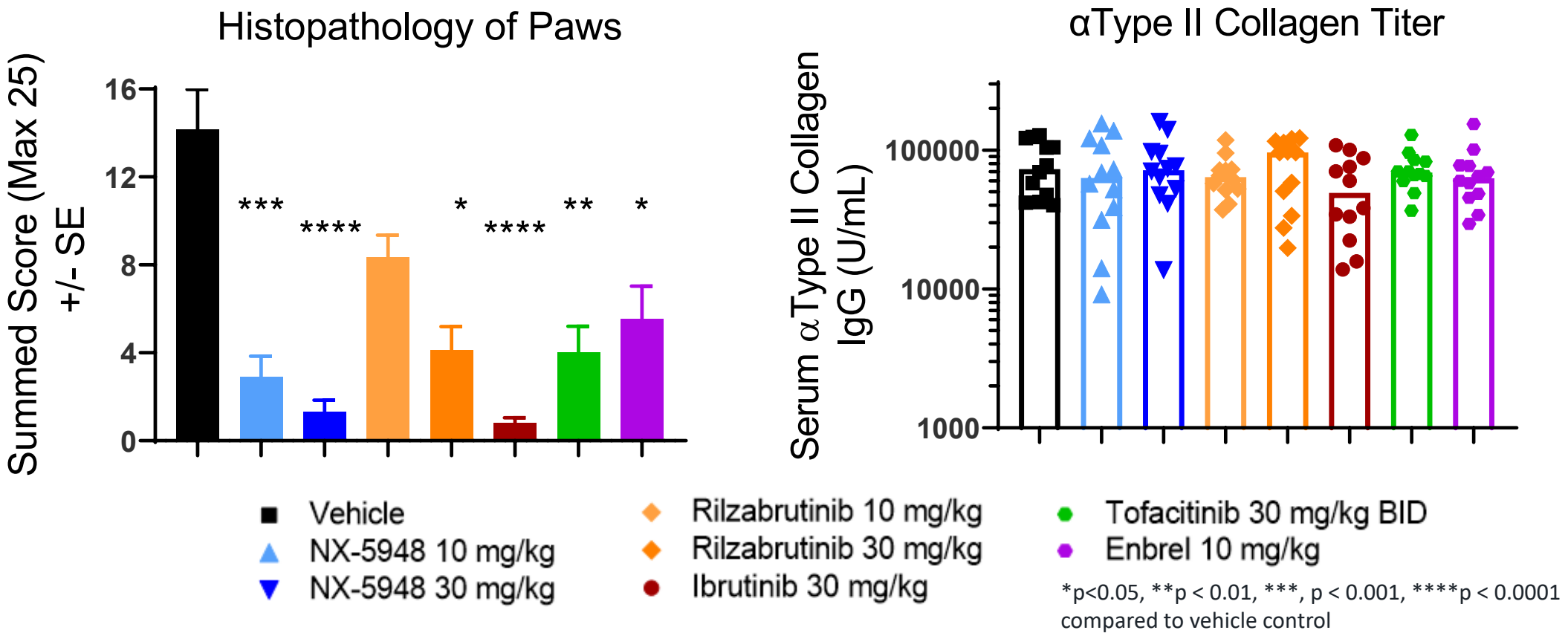
NX-5948 Improves Arthritis Clinical Scores and Provides a Similar or Greater Benefit as BTKi or Standard of Care Agents



*p<0.05, **p < 0.01, ***, p < 0.001, ****p < 0.0001 compared to vehicle control

- 30 mg/kg NX-5948 resulted in complete resolution of symptoms in 10/12 mice
- 30 mg/kg ibrutinib resulted in complete resolution of symptoms in 7/12 mice
- Oral NX-5948 treatment resulted in lower mean clinical score than Rilzabrutinib, Tofacitinib, or Enbrel

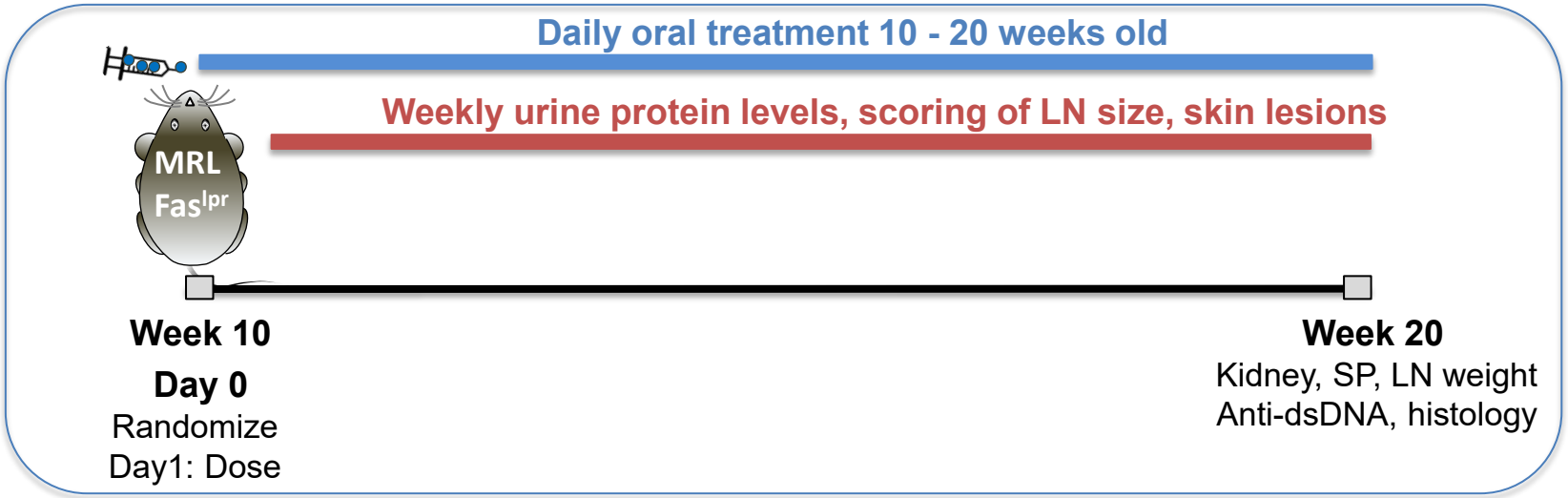
NX-5948 Improves Histopathology of Arthritis and Provides a Similar or Greater Benefit as BTKi or Standard of Care Agents



- Improved histopathology despite high αType II collagen titers suggests inhibition of other B cell functions or Fc receptor signaling in myeloid cells

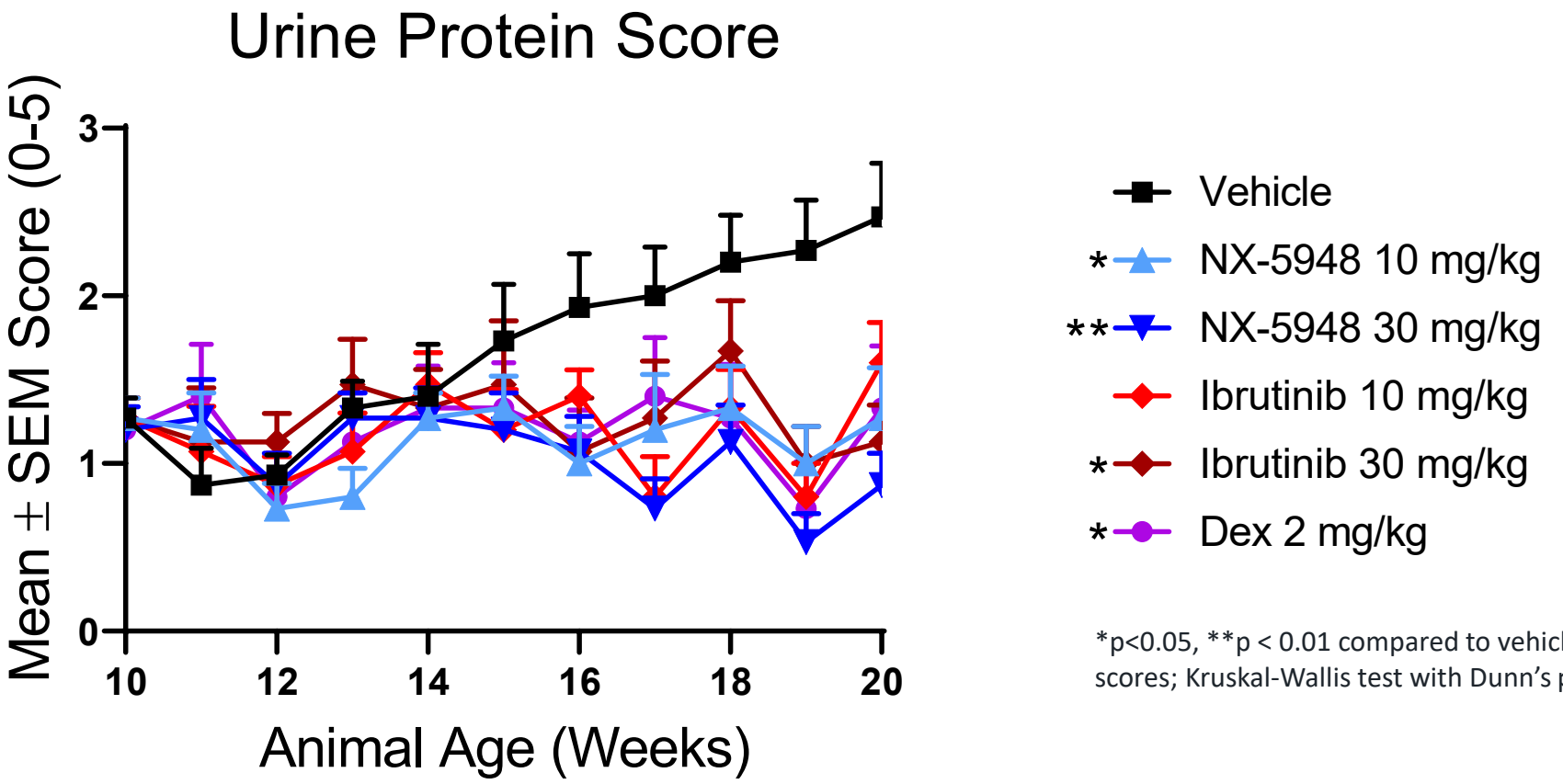
Comparison of NX-5948 to Ibrutinib in Mouse Model of Autoimmune Lymphoproliferative Syndrome (ALPS)

Group	N	Treatment	Dose (mpk)	Regimen
1	15	Vehicle	0	Oral, QD, starting at 10 weeks old (Study Day 0) until 20 weeks old
2	15	NX-5948	10	
3	15	NX-5948	30	
4	15	Ibrutinib	10	
5	15	Ibrutinib	30	
6	15	Dexamethasone	2	



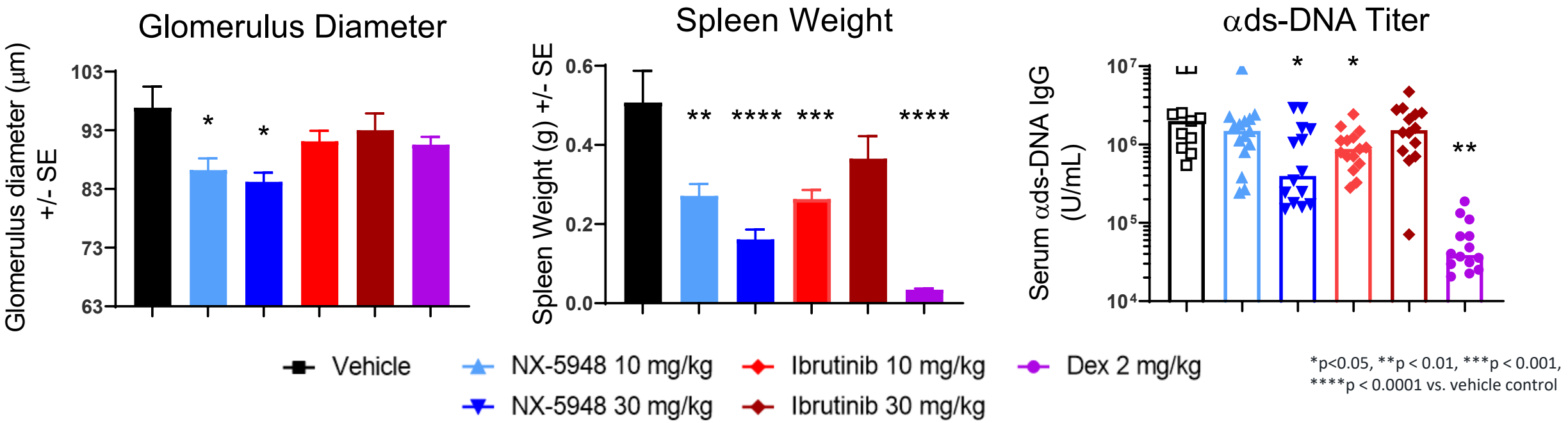
- Genetic mutation of the FAS death receptor causes systemic autoimmunity due to hyperproliferation of autoreactive B and T cells
- Mice develop a spontaneous lupus-like disease characterized by hyperactive B and T cells and high titers of autoantibodies
- Antibody immune complexes deposited in the kidney promote inflammation and tissue damage
- BTK functions downstream of the B cell Receptor to promote B cell activation
- BTK also functions downstream of the Fc Receptor to activate myeloid cells against immune complexes leading to kidney damage

NX-5948 Improved Urine Protein Score and Was Well Tolerated for 10 Weeks



*p<0.05, **p < 0.01 compared to vehicle control (Week 20 scores; Kruskal-Wallis test with Dunn's post-hoc analysis)

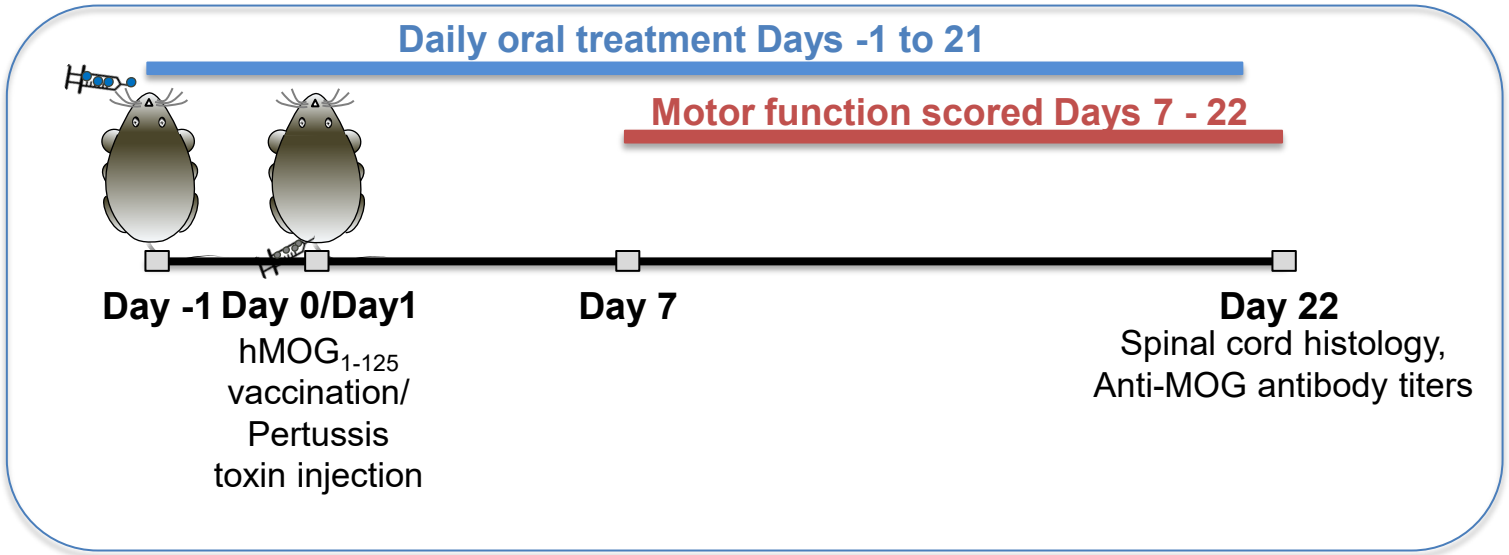
NX-5948 Significantly Improved Kidney Histopathology, Spleen Weight, and Anti-dsDNA IgG Titers



- NX-5948 improved glomerulus diameter more strongly than ibrutinib or dexamethasone, despite dexamethasone strongly suppressing anti-dsDNA titers
- Suggests NX-5948 has superior ability to suppress Fc Receptor signaling and reduce tissue damage from myeloid cells responding to immune complex deposition

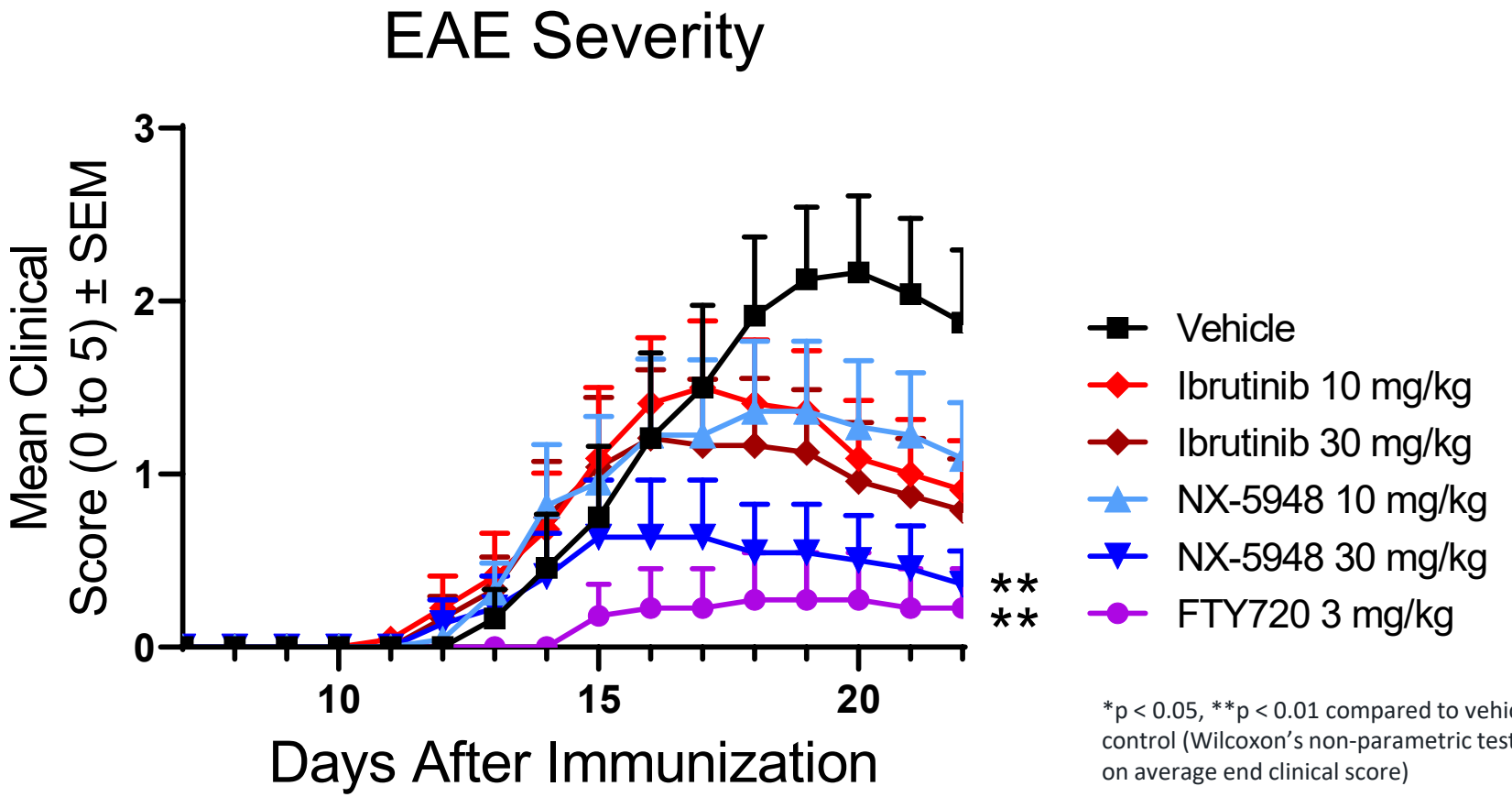
Comparison of NX-5948 to Ibrutinib in Antibody-Dependent EAE model

Group	N	Treatment	Dose (mpk)	Regimen
1	12	Vehicle	N/A	N/A
2	12	FTY720	3	Oral, QD, Days -1 to 22
3	12	Ibrutinib	10	
4	12	Ibrutinib	30	
5	12	NX-5948	10	
6	12	NX-5948	30	



- EAE is induced by immunization with full-length human MOG (myelin oligodendrocyte glycoprotein) to initiate an autoimmune reaction similar to multiple sclerosis
- This particular EAE model is dependent upon B cells, T cells, anti-MOG Ab, and myeloid cells
- BTK functions downstream of the B cell Receptor to promote B cell activation, produce anti-MOG antibodies, and present antigen to autoreactive T cells
- BTK also functions downstream of the Fc Receptor to activate myeloid cells such as microglia against anti-MOG antibodies bound to myelin, promoting demyelination

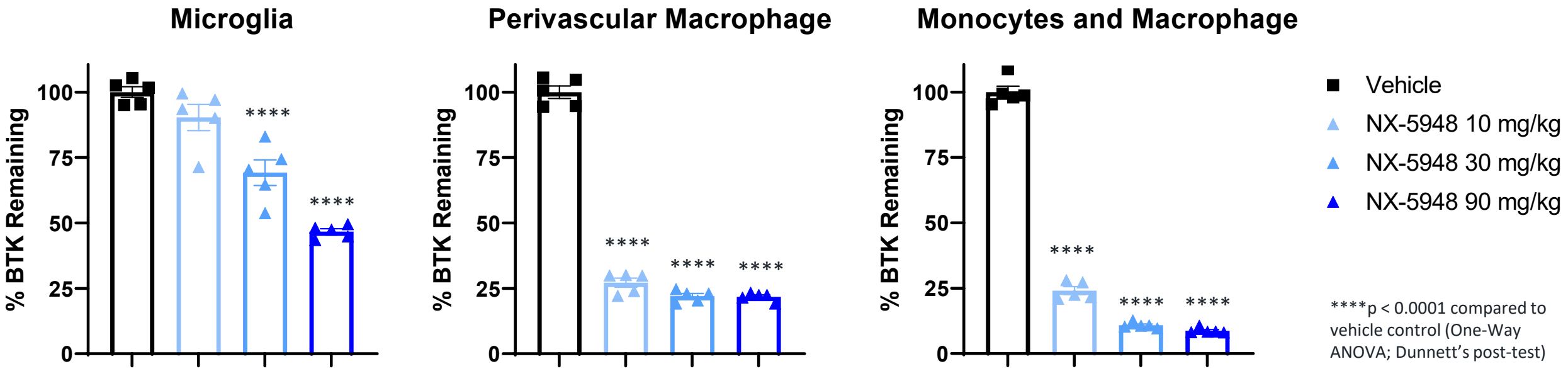
NX-5948 Improves EAE Clinical Scores and Provides More Benefit Than Ibrutinib



*p < 0.05, **p < 0.01 compared to vehicle control (Wilcoxon's non-parametric test on average end clinical score)

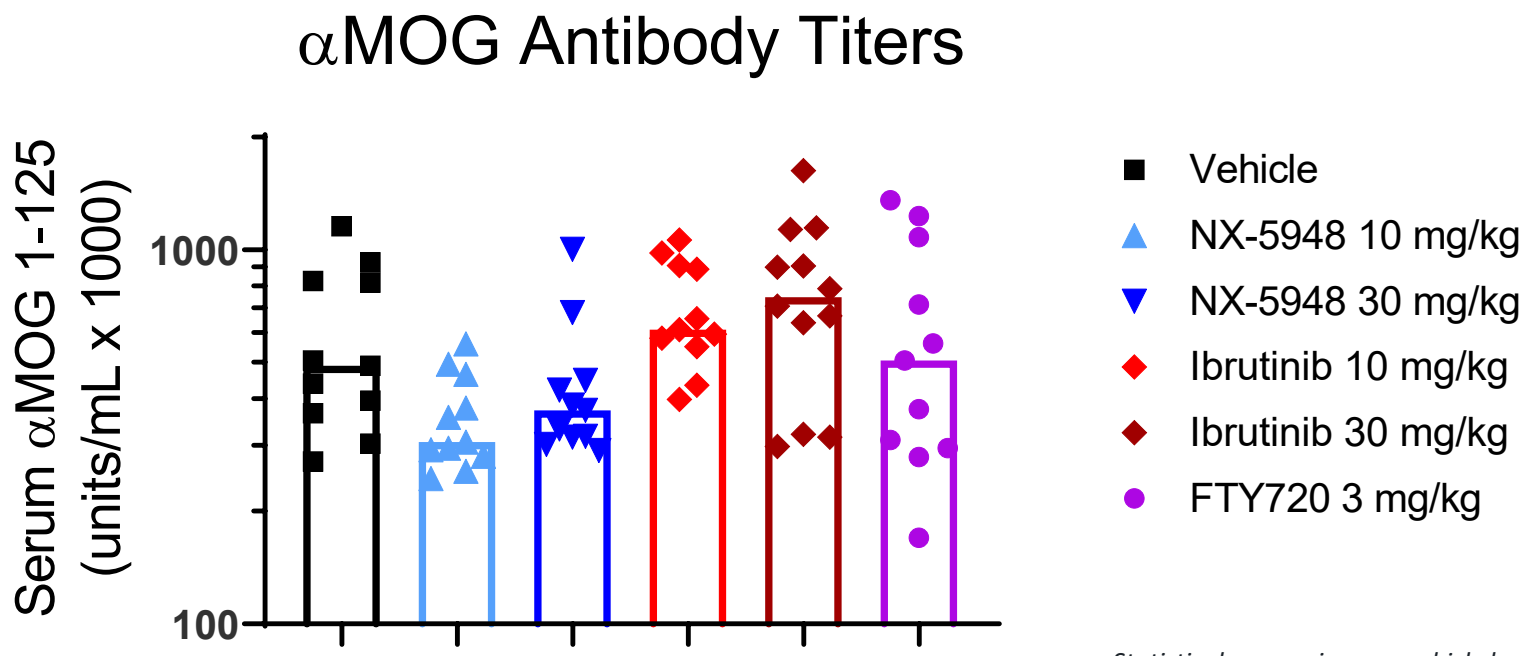
NX-5948 is Brain Penetrant and Degrades BTK in Microglia and Macrophage in Mouse Brains

NX-5948 administered orally QD x 3 days to naïve mice.
BTK levels assessed 8 h after 3rd dose by flow cytometry.



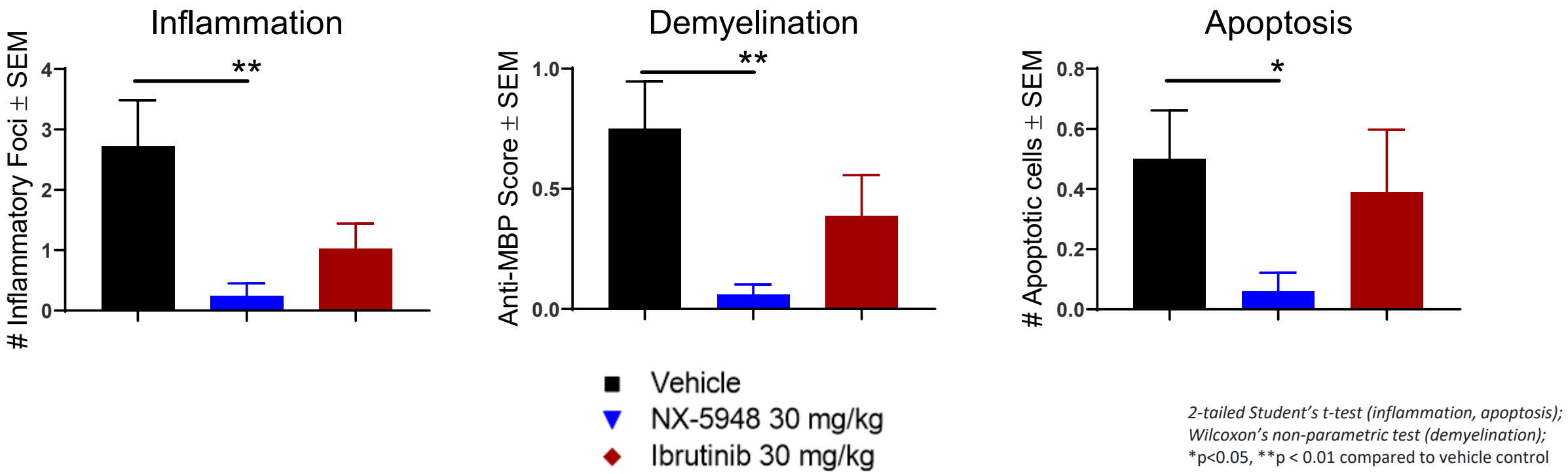
- NX-5948 drives dose-dependent BTK degradation in cells isolated from brains
- Magnitude of BTK degradation depends on dose and cell type

NX-5948 Treated Groups Have Trends of Lower αMOG Antibody Titers



Statistical comparison vs. vehicle by One-Way ANOVA with Dunnett's multiple comparison test (significance not reached)

NX-5948 Improved Histological Findings Associated with EAE More Strongly Than Ibrutinib



2-tailed Student's t-test (inflammation, apoptosis); Wilcoxon's non-parametric test (demyelination);
*p<0.05, **p < 0.01 compared to vehicle control

- NX-5948 dramatically reduced inflammation, demyelination, and apoptosis in the spinal cords of treated mice

Summary

- NX-5948 is a highly potent, CNS penetrant, targeted protein degrader of BTK in Phase 1 clinical development for B cell malignancies
  - NX-5948 potently degrades BTK in primary human B cells (DC_{50} = 0.034 nM) and cancer cell lines
  - NX-5948 inhibits BCR and TLR7 mediated B cell activation
  - NX-5948 promotes BTK degradation in microglia and periventricular macrophage of naïve mice
- Daily oral administration of NX-5948 provides efficacy in multiple preclinical models of autoimmune disease
  - NX-5948 showed similar or superior activity to BTK inhibitors or standard of care agents in mouse models of CIA, ALPS, and EAE
- NX-5948 preclinical data supports further exploration of NX-5948 to treat autoimmune diseases

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