THU0185

Safety, Pharmacokinetics and Proof-of-Mechanism of an Oral Bruton's Tyrosine Kinase Inhibitor HM71224 in Healthy Adult Volunteers

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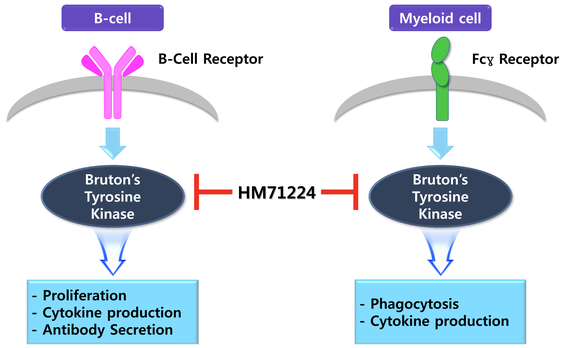
Introduction

- Bruton's Tyrosine Kinase (BTK) plays key roles in B-cell receptor (BCR) and Fc receptor (FcR) signaling cascades and B cell development and activation1-8
- HM71224 is an orally available, irreversible and highly selective small molecule inhibiting BTK protein
- HM71224 may provide therapeutic opportunities in autoimmune diseases



Objectives

- **Primary Objective:** To evaluate the safety and tolerability and if possible to determine the maximum tolerated dose of HM71224 after single and multiple ascending dose administration in healthy subjects
- **Secondary Objective:**
  a. To determine the pharmacokinetics(PK) of HM71224 and selected metabolites (M1 and M2) following single and multiple oral dose administration of HM71224
  b. To assess whether the PK of HM71224 is affected by food
  c. To assess the occupancy by HM71224 after multiple oral administration of HM71224 (Multiple Ascending Dose Part only)

Methods

- Phase 1 study is consisted of 3 parts; a single ascending dose (SAD) part, a single food effect (FE) part and a multiple ascending dose (MAD) part
- The SAD, FE and a part of MAD part results were revealed previously
- In the MAD part, once daily dosing and twice daily dosing were evaluated in placebo controlled manner under fasted conditions

Sing Ascending Dose (n=18)	Food Effect (n=8)	Multiple Ascending Dose QD, 14-day (n=40)	Multiple Ascending Dose BID, 14-day (n=24)
10mg	60mg	10mg	40mg
20mg		20mg	5, 20mg
40mg		40mg	60mg
80mg		80mg	
140mg		120mg	
200mg			

Results

1. Subject Demography

Characteristics	SAD Part (n=18)	FE Part (n=8)	MAD Part	
			QD (n=40)	BID (n=24)
Race (N, %)				
Caucasian	17 (94.4%)	6 (12.5%)	32 (80.0%)	22 (91.7%)
Black	-	1 (12.5%)	3 (7.5%)	1 (4.2%)
Asian, American Indian or Alaska naïve	1 (5.6%)	1 (75.0%)	3 (7.5%)	1 (4.2%)
Others	-	-	2 (5.0%)	-
Age, median (yr)	52.5 (±10.0)	28.5 (±19.8)	33.5 (±15.0)	33.0 (±12.6)
Height (cm)	182.4 (±7.8)	179.3 (±8.6)	179.6 (±9.7)	180.5 (±5.2)
Weight (kg)	81.7 (±11.5)	75.6 (±10.7)	79.3 (±11.8)	78.4 (±10.0)
BMI (kg/m²)	24.5 (±2.4)	23.5 (±3.0)	24.5 (±2.5)	24.1 (±2.9)

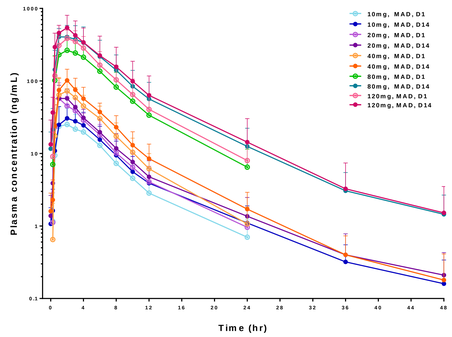
- Total 90 subjects were included in the Phase 1 study
- 2 subjects were withdrawn due to adverse events in the MAD part; 88 subjects completed the study per protocol

2. Adverse Events in Multiple Ascending Dose Part

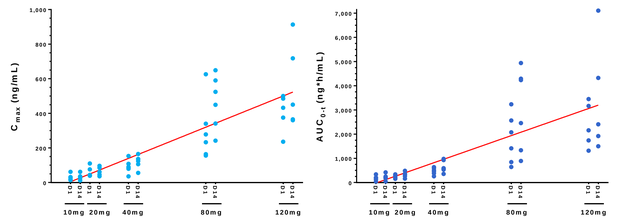
	QD dosing						BID dosing					
	Placebo N=10 n (%) [#AEs]	10 mg N=6 n (%) [#AEs]	20 mg N=6 n (%) [#AEs]	40 mg N=6 n (%) [#AEs]	80 mg N=6 n (%) [#AEs]	120 mg N=6 n (%) [#AEs]	Placebo N=6 n (%) [#AEs]	5 mg N=3 n (%) [#AEs]	20 mg N=3 n (%) [#AEs]	40 mg N=6 n (%) [#AEs]	60 mg N=6 n (%) [#AEs]
TEAEs	6 (60%) [13]	3 (50%) [3]	5 (83.3%) [7]	3 (50%) [3]	5 (83.3%) [20]	5 (83.3%) [18]	3 (50%) [5]	2 (66.7%) [3]	2 (66.7%) [3]	4 (66.7%) [7]	5 (83.3%) [16]
Any ADRs	-	-	-	-	1 (16.7%) [1]	4 (66.7%) [12]	-	-	-	1 (16.7%) [2]	-
Severity											
Mild	-	-	-	-	-	3 (50%) [7]	-	-	-	1 (16.7%) [1]	-
Moderate	-	-	-	-	-	1 (16.7%) [1]	-	-	-	1 (16.7%) [1]	-
Severe	-	-	-	-	1 (16.7%) [1]	3 (50%) [4]	-	-	-	-	-
By System Organ Class (SOC)											
Skin/Subcutaneous tissue disorders	-	-	-	-	-	4 (66.7%) [6]	-	-	-	1 (16.7%) [1]	-
Nervous system disorders	-	-	-	-	-	1 (16.7%) [2]	-	-	-	1 (16.7%) [1]	-
Gastrointestinal disorders	-	-	-	-	-	1 (16.7%) [1]	-	-	-	1 (16.7%) [1]	-
General disorders/ Administration site conditions	-	-	-	-	-	1 (16.7%) [1]	-	-	-	-	-
Immune system disorders	-	-	-	-	1 (16.7%) [1]	-	-	-	-	-	-
Musculoskeletal /Connective tissue disorders	-	-	-	-	-	1 (16.7%) [1]	-	-	-	-	-
Vascular disorders	-	-	-	-	-	1 (16.7%) [1]	-	-	-	-	-

- No serious adverse events were reported in the Phase 1 study
- No clinically relevant changes in vital signs, ECGs and clinical laboratory tests
- All treatment emergent adverse events (TEAEs) were transient and resolved without sequelae by follow-up
- Most common TEAEs were reported in Gastrointestinal system classified by system organ

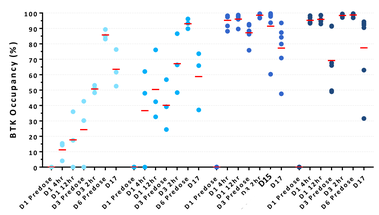
3. Pharmacokinetic Profiles



- HM71224 showed increasing PK profiles as ascending dose levels in QD dosing
- HM71224 indicated slight accumulation after multiple dosing for 14 days
- Inter subject variability in exposure was relatively large
- Excretion of HM71224 and metabolites in urine was limited (data not shown)



4. BTK Occupancy



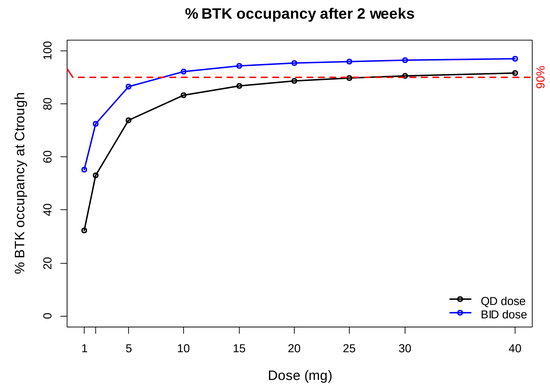
Study Drug Administration

Day	Morning dose	Evening dose
1	O	X
2	X	X
3-13	O	O
14	O	X

* Only active data is included above.

- BTK occupancy was evaluated with BID dosing cohorts in MAD part
- More than 80% of BTK occupancy was maintained until 48 hours after the single dose (Day 3, pre-dose)
- At steady state, more than 90% of BTK occupancy was achieved above 20mg BID dosing
- BTK occupation lasted more than 7 days after completion of dosing (data not shown)

5. PK-PD Modeling



- A PK-PD model for HM71224 showed a steep dose response relationship with BTK occupancy
- According to the PK-PD model above 10mg BID dosing or 20mg QD dosing shows 90% of BTK occupancy with HM71224

Conclusions

- HM71224 demonstrated well-tolerated safety profile in healthy volunteers and desirable PK and PD properties
- The data support the potential for HM71224 to be evaluated for treatment of autoimmune diseases such as rheumatoid arthritis

Reference

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Acknowledgement

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HM71224, a Selective BTK Inhibitor, Ameliorates Murine Lupus Development

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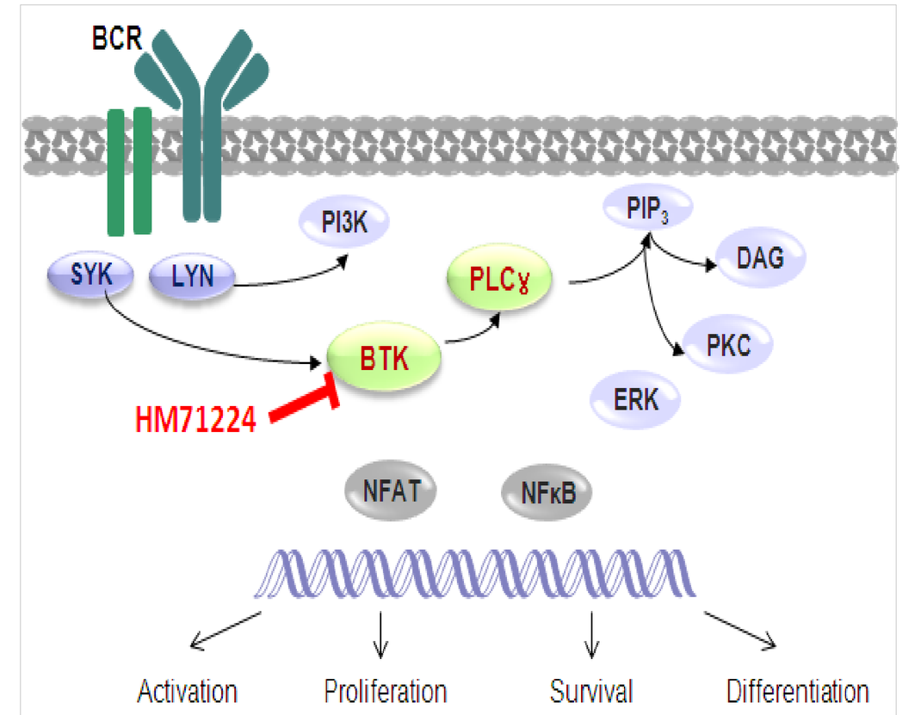
Introduction

‡ Systemic lupus erythematosus (SLE) is known to be associated with the formation of autoantibodies by B cell hyperactivity.

‡ % U X WRQ¶V tyrosine kinase(BTK) is a member of TEC family tyrosine kinases important in B cell activation, proliferation, survival and differentiation.



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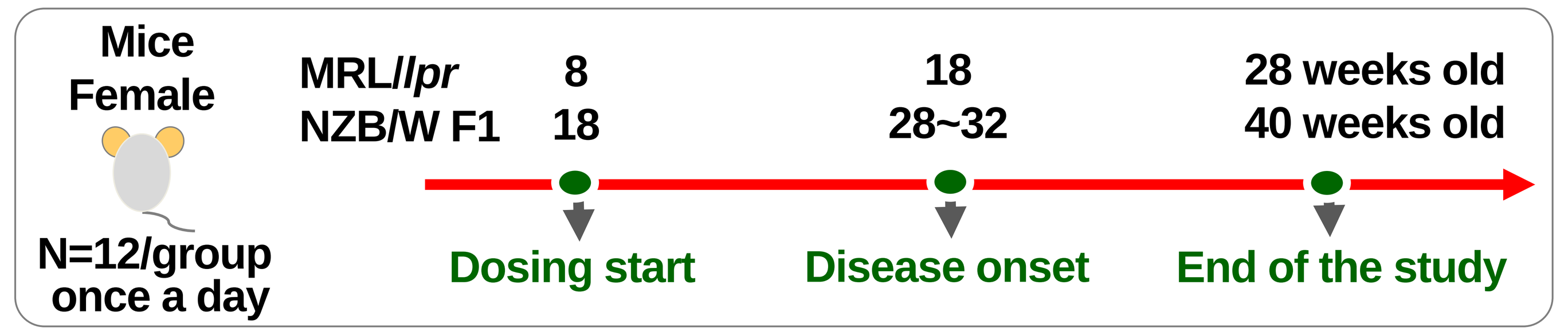
‡ HM71224 is an orally irreversible BTK inhibitor with IC_{50} of 2.6 nM in kinase inhibition assay and IC_{50} of 1 nM in phosphorylation inhibition assay.

‡ Commonly used model for SLE drug discovery is the spontaneous lupus mice model, MRL/*lpr* with the lymphoproliferation mutation(Fas^{lpr}) and New Zealand Black and White F1 hybrid (NZB/W F1) strain with co-expression of several sle susceptibility genetic loci.

‡ **The aim of this study is to evaluate the impacts of therapeutic intervention on the development of SLE like disease features by HM71224 in MRL/*lpr* and NZB/W F1 mice lupus models.**

Methods

1. Animals and Administration



2. Observations

‡ **The measurements of urine protein with urine strip, blood urea nitrogen and creatinine with chemical analyzer and anti-dsDNA IgG with ELISA were conducted.**

‡ **Relative organ weights of spleen, cervical lymph node and kidney were measured.**

‡ **Phenotyping of splenic B cells were performed by flowcytometry.**

‡ **Renal histopathology was scored in H&E and PAS stain.**

‡ **Survival rates were calculated with the Kaplan-Meier method.**

‡ **Statistical significance between groups was evaluated by one-way ANOVA with 'XQQHWW¶V test or Kruskal-Wallis with 'XQQ¶V test.**

Results

1. In vitro Cellular Activity

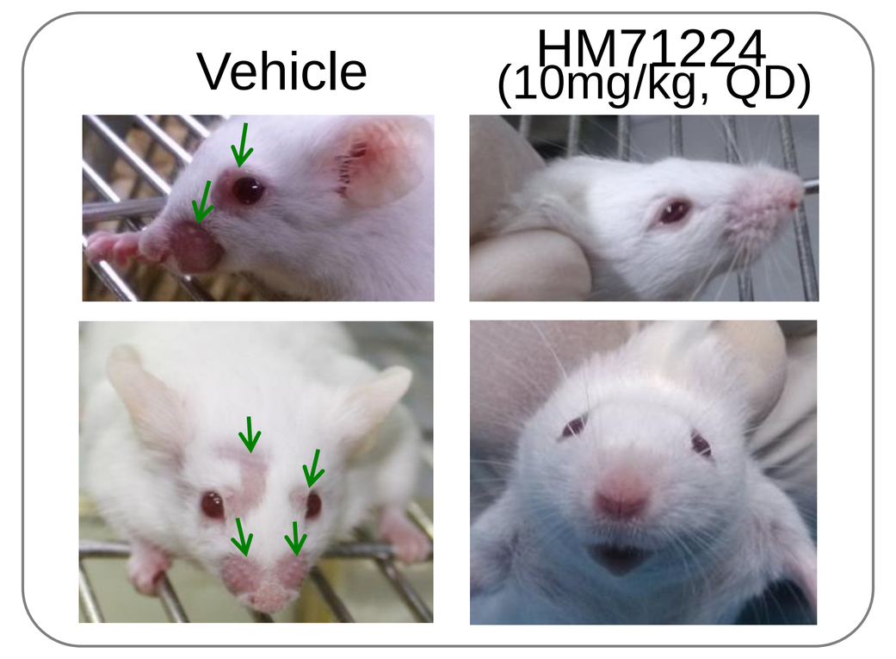
‡**HM71224 is a potent and selective BTK inhibitor**

Cell	Inhibition of phospho-kinase (IC_{50}, nM)		
	Stimulant	p-Kinase	HM71224
Ramos [1)]	anti-IgM	p-BTKY223	1.0
		p-PLC 2	1.0
	IL-4	p-STAT6	445
CTLL-2 [2)]	IL-2	p-STAT5	>1,000
A431 [3)]	EGF	p-EGFR	800

1) Human Burkitt's lymphoma B-cell line, 2) murine cytotoxic T-cell line, 3) human epidermoid carcinoma cell line

2. Results in MRL/*lpr* Mice

‡ **HM71224 prevents the development of skin lesions**



‡ **HM71224 inhibits the B cell activation, autoantibody production and enlargement of lymphatic organs**

a. **Splenic Activated B cells**

b. **Splenic Germinal Center B cells**

c. **Autoantibody**

d. **Organ weights**

‡ **HM71224 ameliorates the renal injury and inflammation from SLE**

a. **Serum BUN**

b. **GN score**

c. **IN score**

3. Results in NZB/W F1 Mice

‡**HM71224 inhibits the activation of B lymphocytes**

a. **Splenic Activated B cells**

b. **Splenic Plasma B cells**

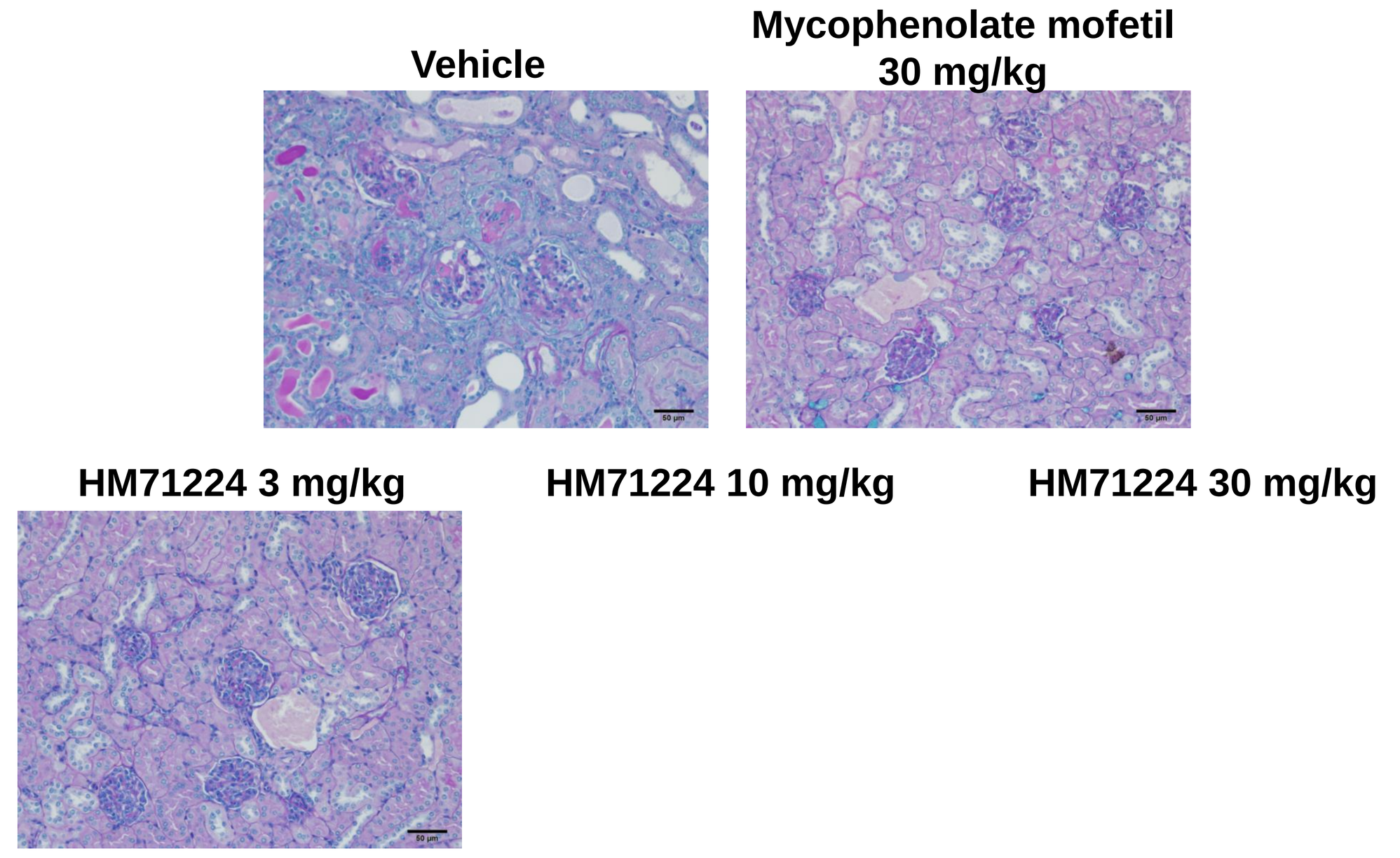
c. **Urine Protein**

d. **Survival Rates**

Survival rate
Vehicle 66.7%
MMF (30mpk) 91.7%
HM (3mpk) 75.0%
HM (10mpk) 100%
HM (30mpk) 100%

‡**HM71224 reduces renal damages and lymphocyte infiltration**

a. **Renal Histopathology**



The thickening of basement membrane(arrow) and tubule distended with proteinaceous fluid(asterisk) were ameliorated in HM71224 treated groups.

Conclusion

‡ **BTK inhibition by HM71224 in MRL/*lpr* and NZB/W F1 mice**

- **Effectively dampened splenic B cells and autoantibody.**
- **Significantly decreased the development of SLE like manifestations such as skin lesions, enlargement of lymph node, splenomegaly, urine protein and renal injury.**
- **Markedly decreased mortality from SLE in NZB/W F1 mice model.**

‡ **HM71224 can efficaciously ameliorate lupus developments in murine disease model that resembles human SLE.**

References

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