SYNERGY-1: A phase 1, first-in-human, safety, tolerability, immunogenicity, PK and PD study of KP104 in escalating single and multiple doses in healthy subjects

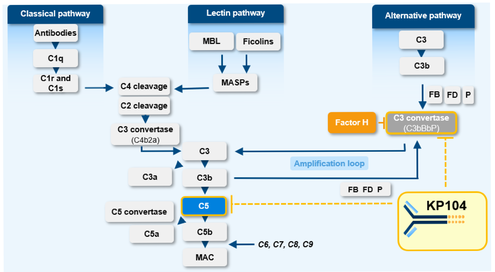
Paul Wabinitz[1], Xiang Gao[2], Jay Ma[2], Ping Tsui[2], Martin Rabe[2], Helen Fu[2], Chaomei He[2], Jingtao Wu[2], Brian York[2], Qing Yu Christina Weng[2,3], Jon Rankin[4], Frederick Beddingfield[2,5], Wenru Song[2], Nicholas Farinola[1], Richard Lee[2]

[1]Cancer Research Institute, University of South Australia, [2]Kira Pharmaceuticals, [3]Massachusetts General Hospital – Harvard Medical School, [4]Syneos Health, and [5]David Geffen School of Medicine - UCLA

Introduction

- Kidney diseases, especially those with limited or no approved therapy, such as IgA nephropathy, complement 3 glomerulopathy, and lupus nephritis, are known to be mediated by aberrant complement activation (Walport 2001, Dunkelberger 2010).
- KP104 is the first known single agent bifunctional complement inhibitor fusion protein comprised of humanized anti-C5 monoclonal antibody and a truncated complement factor H that is capable of inhibiting both the alternative pathway (AP) and terminal pathway (TP) (Figure 1). This dual-pathway inhibition may provide an advantage over a single pathway blockade (Notaro, 2022).
- KP104 is being developed for treatment of patients with multiple diseases in which the complement cascade is implicated such as renal, rheumatologic, and hematologic therapeutic areas.

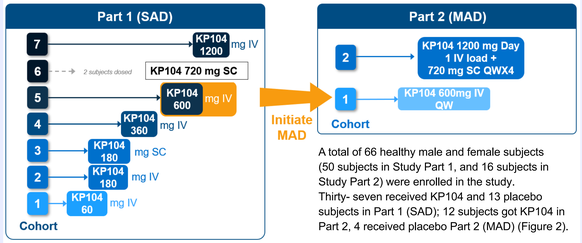
Figure 1. KP104 with its unique MOA represents breakthrough in complement therapy



Methods

- This is a first-in-human, randomized, double-blind, placebo-controlled, single center study of KP104 in healthy volunteers following intravenous (IV) and subcutaneous (SC) administrations. The same KP104 formulation was used for both IV and SC administrations.
- Safety, tolerability, anti drug antibody (ADA) development, pharmakokinetic (PK), and pharmacodynamic (PD) were assessed in single ascending dose (SAD) and multiple ascending dose (MAD) cohorts.
- To evaluate the KP104's function as a bifunctional complement inhibitor, PD markers including free C5, C3b depositions and rRBC inhibition are evaluated. Free C5 and C3b measure anti-C5 and factor H activities; rRBC inhibition measures combined AP/TP inhibition by KP104. Total C5 and factor H levels were also measured.

Figure 2. Study schema

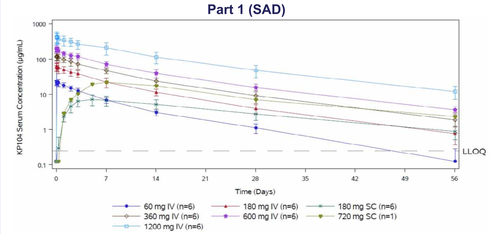


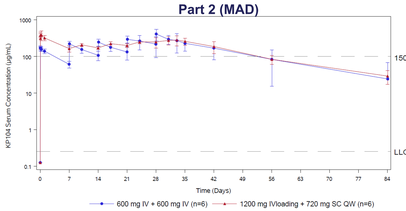
A total of 66 healthy male and female subjects (50 subjects in Study Part 1, and 16 subjects in Study Part 2) were enrolled in the study. Thirty- seven received KP104 and 13 placebo subjects in Part 1 (SAD); 12 subjects got KP104 in Part 2, 4 received placebo Part 2 (MAD) (Figure 2).

Table 1. Demographic characteristics

	Part 1 (SAD)										Part 2 (MAD)				
Category	All Placebo (N=13)	KP104 60 mg IV (N=6)	KP104 180 mg IV (N=6)	KP104 180 mg SC (N=6)	KP104 360 mg IV (N=6)	KP104 600 mg IV (N=6)	KP104 720 mg SC (N=1)	KP104 1200 mg IV (N=6)	Overall KP104 (N=37)	Overall (N=50)	All Placebo (N=4)	KP104 600 mg IV QW (N=6)	KP104 1200 mg IV loading + 720 mg SC QW (N=6)	Overall KP104 (N=12)	Overall (N=16)
Age (years)															
Mean ± SD	31.5 ± 9.90	32.0 ± 13.16	24.0 ± 8.49	26.7 ± 7.76	31.2 ± 12.77	31.8 ± 13.20	42.0	33.5 ± 16.15	30.2 ± 11.86	30.5 ± 11.30	36.3 ± 11.67	34.8±10.65	31.8 ± 8.06	33.3 ± 9.14	34.1 ± 9.50
Sex, n (%)															
Male	7 (53.8)	4 (66.7)	4 (66.7)	4 (66.7)	3 (50.0)	2 (33.3)	1 (100.0)	2 (33.3)	20 (54.1)	27 (54.0)	2 (50.0)	5 (83.3)	3 (50.0)	8 (66.7)	10 (62.5)
Female	6 (46.2)	2 (33.3)	2 (33.3)	2 (33.3)	3 (50.0)	4 (66.7)	0	4 (66.7)	17 (45.9)	23 (46.0)	2 (50.0)	1 (16.7)	3 (50.0)	4 (33.3)	6 (37.5)
Race, n (%)															
Asian	1 (7.7)	0	1 (16.7)	0	1 (16.7)	1 (16.7)	0	1 (16.7)	4 (10.8)	5 (10.0)	0	3 (50.0)	1 (16.7)	4 (33.3)	4 (25.0)
White	9 (69.2)	6 (100.0)	5 (83.3)	5 (83.3)	4 (66.7)	5 (83.3)	1 (100.0)	5 (83.3)	31 (83.8)	40 (80.0)	4 (100.0)	3 (50.0)	5 (83.3)	8 (66.7)	12 (75.0)
Other	3 (23.1)	0	0	1 (16.7)	1 (16.7)	0	0	0	2 (5.4)	5 (10.0)	0	0	0	0	0
BMI at Screening (kg/m^2)															
Mean ± SD	28.1 ± 6.97	24.6 ± 6.08	25.2 ± 4.63	27.0 ± 5.37	28.7 ± 6.57	30.3 ± 6.24	30.4	29.0 ± 8.22	27.6 ± 6.11	27.7 ± 6.28	25.3 ± 5.74	25.5 ± 6.16	24.1 ± 2.78	24.8 ± 4.61	24.9 ± 4.72
Weight at Screening (kg)															
Mean ± SD	81.0 ± 19.48	78.6 ± 18.45	72.1 ± 19.88	86.6 ± 16.21	84.9 ± 19.99	85.6 ± 11.16	106.3	79.3 ± 20.02	81.9 ± 17.61	81.6 ± 17.91	72.6 ± 22.03	78.4±21.79	66.9 ± 11.66	72.7 ± 17.72	72.6 ± 18.09

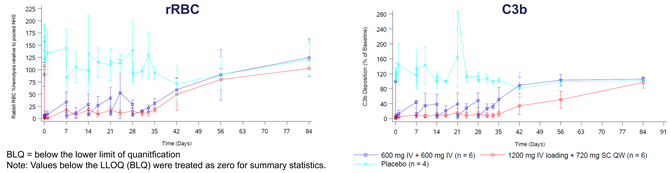
Figure 3. Mean KP104 concentration-time profiles (semi-logarithmic scale)





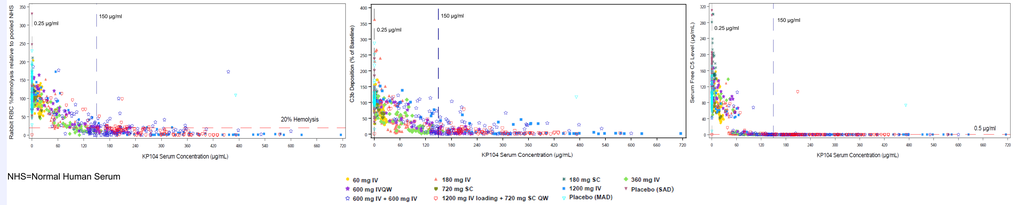
LLOQ = lower limit of quantification 0.25 µg/mL; IV = intravenous; SC = subcutaneous
Note: Mean concentrations below the limit of quantification were set to 1/2 the LLOQ. Single liquid formulation was used for IV and SC.

Figure 4. Mean (SD) serum rRBC, C3b, and free C5 versus time by dosing regimen in MAD cohorts



BLQ = below the lower limit of quantification
Note: Values below the LLOQ (BLQ) were treated as zero for summary statistics.

Figure 5. Scatter plot of serum rRBC, C3b, and free C5 versus KP104 concentrations in all subjects



NHS=Normal Human Serum

Table 2. Most frequently reported treatment-emergent adverse events

	Part 1 (SAD)									Part 2 (MAD)			
MedDRA® Preferred Term n (%)	Placebo (N=13)	KP104 60 mg IV (N=6)	KP104 180 mg IV (N=6)	KP104 180 mg SC (N=6)	KP104 360 mg IV (N=6)	KP104 600 mg IV (N=6)	KP104 720 mg SC (N=1)	KP104 1200 mg IV (N=6)	KP104 Overall (N=37)	Placebo (N=4)	KP104 600 mg IV QW (N=6)	KP104 1200 mg IV loading + 720 mg SC QW (N=6)	Overall KP104 (N=12)
Headache	1 (7.7)	2 (33.3)	1 (16.7)	0	1 (16.7)	3 (50.0)	1 (100)	2 (33.3)	10 (27.0)	2 (50.0)	2 (33.3)	3 (50.0)	5 (41.7)
Catheter site pain	0	1 (16.7)	0	0	0	1 (16.7)	0	2 (33.3)	4 (10.8)	-	-	-	-
Injection site erythema	1 (7.7)	0	0	4 (66.7)	0	0	0	0	4 (10.8)	-	-	-	-
Nausea	0	1 (16.7)	0	1 (16.7)	1 (16.7)	1 (16.7)	0	0	4 (10.8)	-	-	-	-
Diarrhoea	2 (15.4)	1 (16.7)	0	0	1 (16.7)	0	0	1 (16.7)	3 (8.1)	1 (25.0)	1 (16.7)	1 (16.7)	2 (16.7)
Fatigue	1 (7.7)	0	0	1 (16.7)	0	1 (16.7)	0	1 (16.7)	3 (8.1)	0	1 (16.7)	1 (16.7)	2 (16.7)
Pruritus	0	1 (16.7)	0	1 (16.7)	1 (16.7)	0	0	0	3 (8.1)	-	-	-	-
Injection site induration	-	-	-	-	-	-	-	-	-	0	0	2 (33.3)	2 (16.7)
Abdominal distension	0	1 (16.7)	0	0	0	1 (16.7)	0	0	2 (5.4)	-	-	-	-
Abdominal pain lower	0	0	1 (16.7)	0	1 (16.7)	0	0	0	2 (5.4)	-	-	-	-
Catheter site bruise	0	0	1 (16.7)	0	1 (16.7)	0	0	0	2 (5.4)	-	-	-	-
Decreased appetite	0	0	0	0	1 (16.7)	0	0	1 (16.7)	2 (5.4)	-	-	-	-
Dizziness	0	0	0	0	0	1 (16.7)	0	1 (16.7)	2 (5.4)	-	-	-	-
Erythema	0	0	0	1 (16.7)	0	1 (16.7)	0	0	2 (5.4)	-	-	-	-
Lethargy	0	0	0	0	1 (16.7)	0	0	1 (16.7)	2 (5.4)	-	-	-	-
Migraine	0	0	0	0	2 (33.3)	0	0	0	2 (5.4)	-	-	-	-
Neutropenia	0	1 (16.7)	0	0	1 (16.7)	0	0	0	2 (5.4)	-	-	-	-
Rash	0	0	1 (16.7)	0	0	1 (16.7)	0	0	2 (5.4)	-	-	-	-
Rash papular	0	0	0	0	1 (16.7)	1 (16.7)	0	0	2 (5.4)	-	-	-	-
Vaccination site pain	0	0	0	0	0	2 (33.3)	0	0	2 (5.4)	-	-	-	-
Vessel puncture site bruise	0	0	0	0	1 (16.7)	1 (16.7)	0	0	2 (5.4)	-	-	-	-

N = number of subjects dosed; n (%) = number and percent of subjects with treatment-emergent adverse events; - = not reported. KP104 Overall: Included all subjects who took KP104.
Note: Most frequent TEAE are defined as TEAEs experienced by at least 2 subjects in the KP104 overall group.

Results

Demographics:
- In Part 1 (SAD), demographic characteristics in the placebo group (n=13) were similar to those in the combined KP104 group (n=37) (Table 1).
- In Part 2 (MAD), all placebo subjects (N=4,100%) were white, while 66.7% (N=8) of KP104 subjects were white. Subjects receiving KP104 600 mg IV weekly are predominantly male (83.3%). Otherwise, the demographic characteristics were similar in combined placebo and combined KP104 group (Table 1).

Safety:
- There were no deaths or serious TEAEs reported in the study; no subjects were discontinued from the study drug due to drug-related TEAEs. The majority of the TEAEs are mild (Grade 1) and no severe (Grade 3) TEAEs were reported. No dose-limiting toxicities occurred.
- There was no clear dose-related trend observed across treatment groups in the incidence of individual TEAE preferred terms, and no drug-related changes were noted in clinical safety laboratory values, vital signs, or ECGs.

Pharmacokinetics:
- The KP104 PK generally behaves like IgG with approximately dose-proportionality and distributing primarily intravascularly (Figure 3).
- With 600 mg IV weekly for 5 doses, KP104 peak concentrations increased after each dose, indicating accumulation. After the last dose at Week 5, KP104 generally displayed a biphasic profile with a rapid distribution followed by a slow elimination phase, which was measurable up to 8 weeks after the last dose.
- With 1200 mg IV Day 1 + 720 mg SC weekly, steady state appeared to be achieved after the fourth dose, and the mean terminal elimination half-life was 15.7 days.
- Following 4 weekly doses of SC administration, serum KP104 estimated bioavailability was approximately 67% using a population PK modeling approach.

Pharmacodynamic:
- Inhibition of RBC lysis and C3b deposition increased with the concentration of KP104 and reached at least 80% inhibition from baseline at drug concentrations >150 µg/mL. The inhibition on free C5 by KP104 achieved >99.5% at drug concentraion >150 µg/mL.
- Free C5 levels were maintained below 0.5 µg/mL from Day 1 post dose to Day 35, which is 8 days following the last dose of KP104 with MAD 1200 mg IV Day 1 + 720 mg SC weekly for 4 weeks (Figures 4 and 5).
- There was no significant impact of KP104 dosing on total C5 and endogenous factor H levels observed throughout the study (data not shown).

Immunogenicity:
- Seven out of 49 (14%) subjects who received KP104 tested positive for anti-KP104 antibodies. Two from the Part 1 (SAD) tested positive transiently on Day 15 or 57, with titers ranging from 0 to 60. Five from the Part 2 (MAD) tested positive between Day 57 and Day 85 with titers ranging from 60 to 7680.
- The presence of ADAs after single or multiple KP104 IV or SC doses did not impact safety, and had no relevant impact on PK and PD.

Conclusion

KP104 was safe, well tolerated, and showed proof of mechanism with potent TP and AP inhibition in the SYNERGY-1 study. The data supports planned future clinical trials in complement-mediated kidney diseases.

References
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Disclosures
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