# A First-In-Human Investigation Of MAU868, A Novel Monoclonal Antibody Against BK Virus

Steven J Kovacs[1], Johanna R Abend[2], Xiaoying Xu[1], Sachin Desai[1], Amanda Nguyen[1], Laura M Sterling[3], Michael R Hodges[4], Peter Pertel[1]

## Introduction

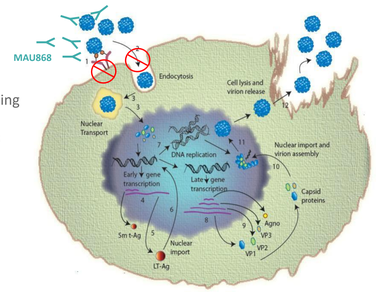
- BK virus (BKV) is one of 13 known human polyomaviruses. Infection is essentially ubiquitous (estimated seroprevalence 80-90% of adults).
- Primary infection occurs during childhood and is usually asymptomatic or associated with mild, non-specific, upper respiratory symptoms.
- Persistent infection is established in the epithelial cells of renal tubules, ureters, and bladder but effectively controlled by the immune system.
- Compromised immune function can lead to uncontrolled BKV replication and development of disease, the best characterized of which is BKV nephropathy (BKVN).
- BKVN is a leading cause of early allograft loss in kidney transplant recipients.
- The need for specific and effective anti-BKV therapies remains unmet.

## MAU868

- A novel, human monoclonal antibody that binds to the BKV major capsid protein (VP1) and blocks virion binding to host cells.
- pM binding affinity and sub-nM neutralizing potency against the four major genotypes of BKV (pan-genotype activity) (Table 1)
- High barrier-to-resistance *in vitro*.
- Neutralizing activity against the closely related JC virus, the cause of progressive multifocal leukoencephalopathy.

**Figure 1. MAU868 mechanism of action**

MAU868 disrupts binding of BKV to the host cell receptor and prevents infection of new cells.




## Study Design

- Randomized, blinded, placebo-controlled, single ascending dose study conducted at a single center in the United States.
- MAU868 was administered in five intravenous (i.v) dosing cohorts (1, 3, 10, 30, and 100 mg/kg) of five participants each (4 active:1 placebo) and one subcutaneous (s.c) dosing cohort (3 mg/kg) of eight participants (6 active:2 placebo).
- The i.v. doses were administered as 1-hour infusions through a peripheral vein.
- Subjects were observed for 24 hours and followed for 106 days with routine safety monitoring and PK assessments.
- Safety monitoring included routine clinical laboratory tests (chemistry, hematology, urinalysis) and single 12-lead electrocardiograms were performed before and at various times after the infusion. Adverse events were graded according to the Common Terminology Criteria for Adverse v5.0.
- *Ex vivo* neutralizing activity of serum was measured using samples collected prior to dose administration and at Day 29 after dosing.

## Rationale for Dose Selection

- Doses investigated included and exceeded the predicted clinically efficacious doses for the prevention of BKV disease.
- Predictions of efficacious doses were based on the *in vitro* neutralizing activity of MAU868 across BKV genotypes and assumed:
  i. typical IgG pharmacokinetics
  ii. that maintaining trough concentrations ≥10 times the $EC_{50}$ against the least susceptible genotype would be required for clinical efficacy
  iii. that 10-20% of the circulating antibody concentrations penetrated the interstitial spaces of the kidney and 1-2% penetrated the bladder tissue

**Table 1. *In vitro* binding affinity and neutralizing activity of MAU868 across BKV genotypes**

| | $K_D$ (pM) | $EC_{50}$ (µg/mL) | $EC_{50}$ (nM) |
|---|---|---|---|
| BKV genotype I* | 5.8 ± 1.8 | 0.009 ± 0.010 | 0.062 ± 0.068 |
| BKV genotype II | 2.8 ± 0.6 | 0.040 ± 0.025 | 0.278 ± 0.175 |
| BKV genotype III | 8.4 ± 3.7 | 0.093 ± 0.057 | 0.645 ± 0.397 |
| BKV genotype IV* | 4.1 ± 1.3 | 0.021 ± 0.020 | 0.143 ± 0.135 |

* BKV genotypes I and IV comprise 95% of global seroprevalence.
Data presented as arithmetic mean ± standard deviation across replicates (n=4 for $K_D$; n=3 for $EC_{50}$).

## Results

### Demographics

- A total of 33 participants were enrolled, randomized, and completed the study.

**Table 2. Study participant demographics by treatment group**

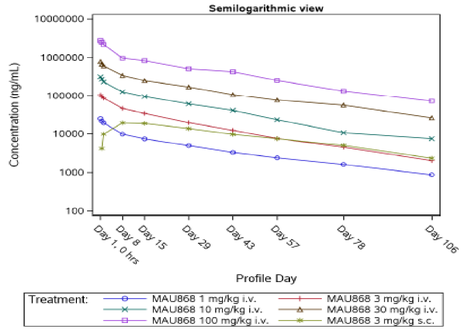
| | MAU868 1 mg/kg i.v. (n=4) | MAU868 3 mg/kg i.v. (n=4) | MAU868 10 mg/kg i.v. (n=4) | MAU868 30 mg/kg i.v. (n=4) | MAU868 100 mg/kg i.v. (n=4) | MAU868 3 mg/kg s.c. (n=6) | Placebo i.v. & s.c. (n=7) |
|---|---|---|---|---|---|---|---|
| Age (years) | 42.8 ± 14.97 | 39.0 ± 16.25 | 44.3 ± 12.79 | 38.3 ± 10.59 | 58.0 ± 3.56 | 45.7 ± 8.91 | 51.9 ± 12.21 |
| Sex | | | | | | | |
| Male | 3 | 3 | 3 | 3 | 2 | 2 | 5 |
| Female | 1 | 1 | 1 | 1 | 2 | 4 | 2 |
| BMI (kg/m²) | 28.7 ± 3.66 | 38.8 ± 4.49 | 29.7 ± 4.36 | 28.8 ± 4.90 | 27.7 ± 4.16 | 33.3 ± 4.90 | 30.8 ± 5.55 |
| Race | | | | | | | |
| White | 3 | 4 | 3 | 4 | 3 | 6 | 7 |
| Black or African-American | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| Ethnicity | | | | | | | |
| Not Hispanic or Latino | 4 | 3 | 4 | 4 | 3 | 6 | 7 |
| Hispanic or Latino | 0 | 1 | 0 | 0 | 1 | 0 | 0 |

Data presented as arithmetic mean ± standard deviation

### Pharmacokinetics

- The time course of exposure to MAU868 was typical of a human IgG with a half-life of 23 to 30 days (Figure 2).
- AUC and Cmax were dose-proportional, ranging from 9880 to 1060000 µg*hr/mL and 24.7 to 2740 µg/mL (ie, no evidence of FcRn saturation).
- Day 29 plasma MAU868 concentrations, adjusted for extravascular distribution to estimate parenchymal exposure, were approximately 7- to 751-fold higher than the highest *in vitro* $EC_{50}$ (0.093 µg/mL) across the dose range.
- Bioavailability after s.c. injection was 57.6%.

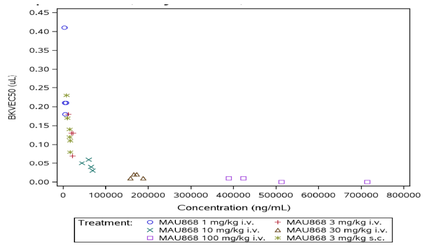
**Figure 2. Time course of exposure to MAU868 following i.v. or s.c. administration**




### MAU868 *Ex Vivo* Neutralizing Activity

- Increasing serum neutralizing activity, as demonstrated by decreases in the volume of serum required to reduce infection *in vitro* by 50%, was observed with increasing doses of MAU868 (Figure 3).

**Figure 3. *Ex vivo* serum neutralizing activity versus serum MAU868 concentration**




BKVEC50 = volume of serum required to neutralize *in vitro* infection by 50%; BKV genotype I

### Safety and Tolerability

- A total of 31 adverse events were reported in 12 (36.4%) participants.
- All reported adverse events were grade 1 and resolved.
- The most commonly reported adverse events were nasal congestion (n=3, 9.1%), oropharyngeal pain (n=3, 9.1%), and injection site hemorrhage (n=2, 6.1%), all of which occurred following administration of the two lowest doses in the study.
- There were no infusion or injection site reactions.
- No subject discontinued the study due to an adverse event or developed anti-drug antibodies.
- No changes in clinical laboratory tests, vital signs, or ECGs.

## Conclusions

- Single intravenous and subcutaneous doses of MAU868 were safe and well tolerated with PK typical of a human IgG.
- The *ex vivo* neutralizing activity data may be suggesting where the therapeutic range is for the treatment and/or prevention of BKV disease but further clinical investigation in patients is warranted.
- MAU868 has the potential to be the first specific therapy for the treatment and/or prevention of BKV disease.

[1]Translational Medicine, Novartis Institutes for BioMedical Research, East Hanover, NJ, USA; Cambridge, MA, USA; [2]Infectious Diseases - Virology, Novartis Institutes for BioMedical Research, Emeryville, CA, USA; [3]Celerion, Lincoln, Nebraska, USA; [4]Amplyx Pharmaceuticals, San Diego, California