AIC468 Phase 1 Safety and Pharmacokinetic Data

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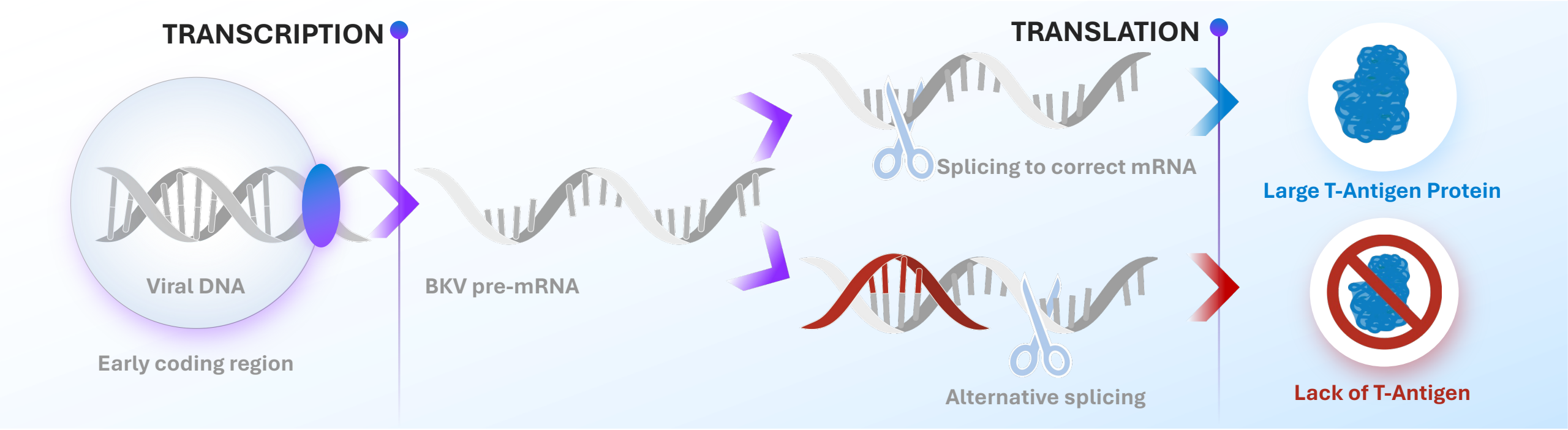
AIC468 Background

Splice-modulating 2nd generation antisense oligonucleotide (ASO)

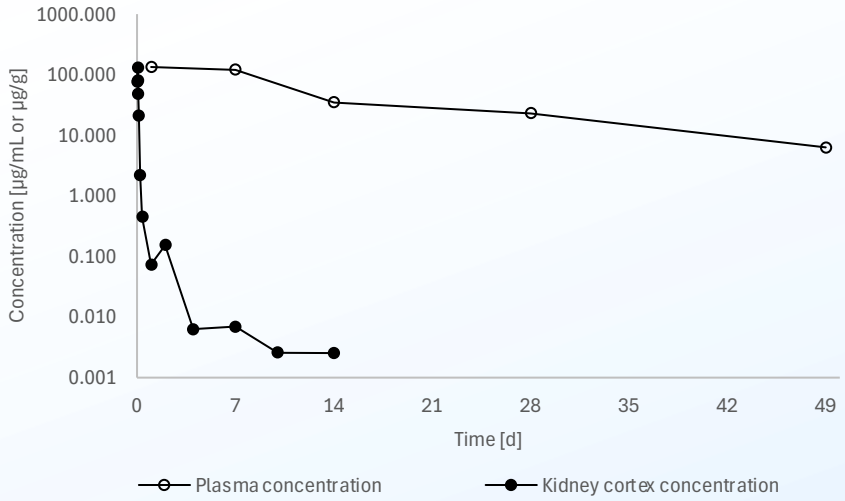


- **As a direct-acting agent, AIC468 targets the virus intracellularly**
- **Inhibition of correct splicing** prevents formation of large T-Antigen
- The large T-Antigen is essential for **BK virus replication**

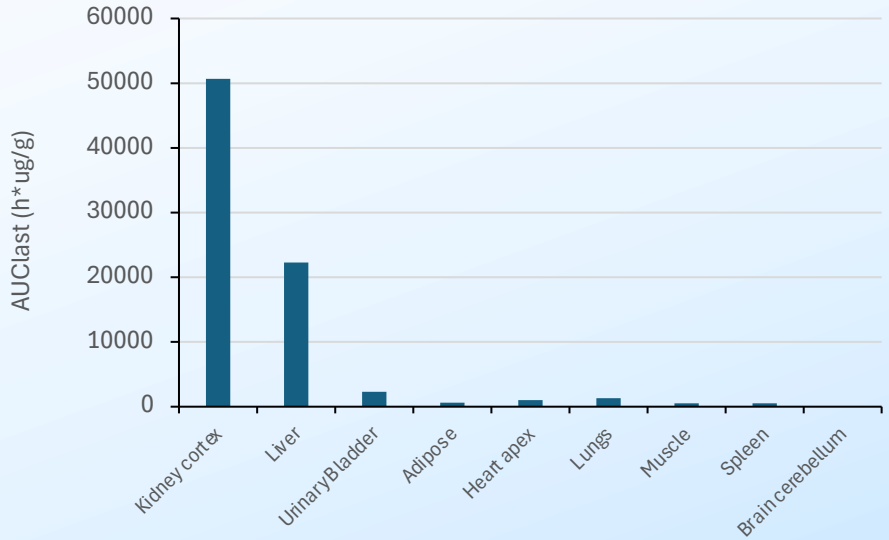
AIC468 Background

Pre-clinical PK and tissue distribution (IV and SC administration)

Pharmacokinetics



Tissue distribution



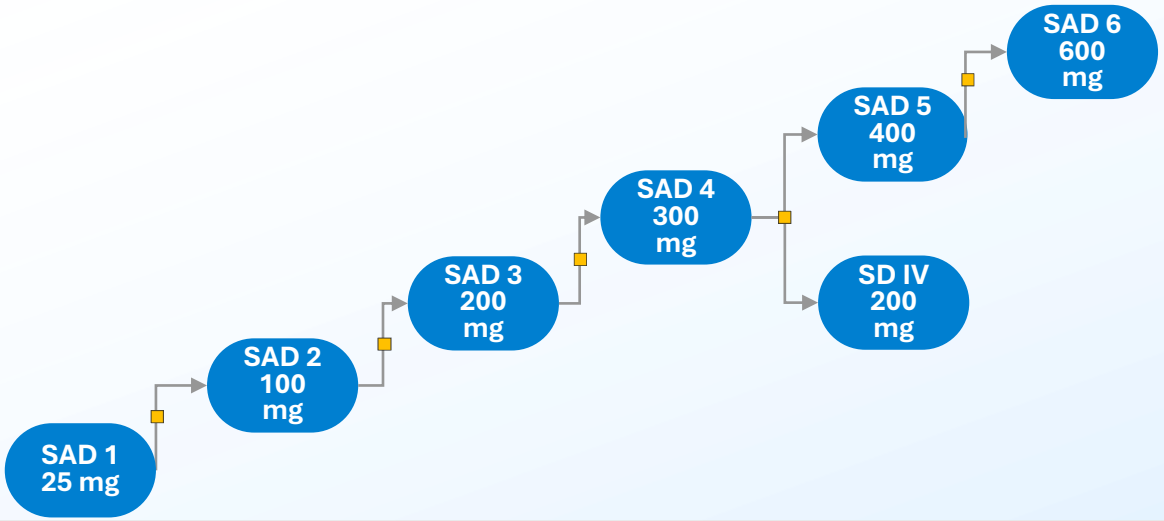
- Rapid distribution from systemic circulation into tissues
- Long terminal tissue half-life (approx. 2-3 weeks)

- Highest tissue exposure observed in the kidney cortex

Phase 1 Study Design

Single center, randomized, placebo-controlled, first-in-human trial (EUCT 2023-510074-13-00)

Single Ascending Dose; N=56



Population: Healthy volunteers, 18-45 years of age

Objectives: Safety/tolerability, pharmacokinetics

Design: 6 SAD cohorts SC, 1 single dose IV cohort

8 subjects per cohort (6 active: 2 placebo)

Multiple Ascending Dose; N=24

Population: Healthy volunteers, 18-45 years of age

Objectives: Safety/tolerability, pharmacokinetics

Design: 3 MAD cohorts (5 doses QW SC)

8 subjects per cohort (6 active : 2 placebo)

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Demographics

- 80 healthy volunteers (HVs) enrolled across 10 cohorts
- Demographics well-balanced in general; only males were enrolled in MAD
- Majority of HVs were male, white, age 20-45 years, body weight 51-99 kg

Table 1. Participant Demographics

	SAD cohorts								MAD cohorts		
	25 mg SC n=6	100 mg SC n=6	200 mg SC n=6	300 mg SC n=6	400 mg SC n=6	600 mg SC n=6	200 mg IV n=6	Placebo SC n=14	120 mg SC n=8	230 mg SC n=8	330 mg SC n=8
Age, mean (SD) years	39.0 (5.18)	34.2 (5.08)	39.2 (3.60)	31.7 (4.63)	37.7 (6.41)	31.7 (7.45)	33.5 (7.66)	33.7 (4.92)	32.1 (8.15)	31.6 (7.44)	30.5 (6.61)
Male, n (%)	2 (33.3)	4 (66.7)	4 (66.7)	2 (33.3)	3 (50.0)	2 (33.3)	3 (50.0)	6 (42.9)	8 (100)	8 (100)	8 (100)
Weight, mean (SD) kg	76.3 (6.51)	71.6 (10.22)	74.0 (14.12)	68.8 (7.87)	74.6 (13.44)	67.0 (11.55)	72.6 (10.68)	72.2 (9.34)	75.7 (6.75)	83.8 (12.22)	81.7 (10.89)
BMI, mean (SD) kg/m²	25.4 (2.33)	22.9 (1.63)	24.1 (1.73)	22.8 (2.48)	24.4 (2.15)	21.7 (1.97)	24.4 (1.82)	22.7 (2.26)	23.1 (1.92)	25.1 (2.74)	24.1 (2.44)
Race, n (%)											
White	5 (83.3)	6 (100)	6 (100)	4 (66.7)	6 (100)	6 (100)	6 (100)	13 (92.9)	8 (100)	7 (87.5)	8 (100)
Others	1 (16.7)	0	0	2 (33.3)	0	0	0	1 (7.1)	0	1 (12.5)	0

Safety and Tolerability

- Majority of treatment-emergent adverse events (TEAEs) were mild in intensity, and unrelated to IMP
- There were no treatment-related SAEs, Grade 3-5 TEAEs, or treatment/trial-related discontinuations
- One SAE (skin laceration) was considered unrelated to IMP

Table 2. Summary of Treatment-Emergent Adverse Events

	SAD cohorts								MAD cohorts*		
	25 mg SC n=6	100 mg SC n=6	200 mg SC n=6	300 mg SC n=6	400 mg SC n=6	600 mg SC n=6	200 mg IV n=6	Placebo SC n=14	120 mg SC n=8	230 mg SC n=8	330 mg SC n=8
Any AE	5 (83.3)	6 (100.0)	3 (50.0)	6 (100.0)	4 (66.7)	6 (100.0)	4 (66.7)	10 (71.4)	8 (100)	7 (87.5)	8 (100)
Treatment-related	2 (33.3)	2 (33.3)	2 (33.3)	2 (33.3)	3 (50.0)	3 (50.0)	1 (16.7)	2 (14.3)	7 (87.5)	4 (50.0)	6 (75.0)
Grade 1 (mild)	4 (66.7)	6 (100.0)	2 (33.3)	5 (83.3)	4 (66.7)	6 (100.0)	4 (66.7)	6 (42.9)	8 (100)	7 (87.5)	8 (100)
Grade 2 (moderate)	1 (16.7)	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	2 (33.3)	1 (16.7)	7 (50.0)	2 (5.0)	4 (50.0)	4 (50.0)
Serious AEs	0	0	0	0	1 (16.7)	0	0	0	0	0	0

*MAD data presented blinded, as trial part is ongoing

Safety and Tolerability

- Most common TEAEs (28-33% participants) were Nasopharyngitis, Injection Site Reactions (ISRs) and Headache
- ISRs were most frequently erythema, and all were mild-moderate intensity
- No ASO class effects (e.g. renal, liver, coagulation abnormalities) were observed.
- There were no dose/exposure related trends in the safety parameters (AEs, labs, ECGs, vital signs)

Table 3. Common Treatment-Emergent Adverse Events (occurring in >20% participants per group)

	SAD cohorts								MAD cohorts		
Adverse Event	**25 mg SC n=6**	**100 mg SC n=6**	**200 mg SC n=6**	**300 mg SC n=6**	**400 mg SC n=6**	**600 mg SC n=6**	**200 mg IV n=6**	**Placebo SC n=14**	**120 mg SC n=8**	**230 mg SC n=8**	**330 mg SC n=8**
Nasopharyngitis	1 (16.7)	3 (50.0)	1 (16.7)	3 (50.0)	2 (33.3)	1 (16.7)	2 (33.3)	6 (42.9)	4 (50.0)	1 (12.5)	2 (25.0)
Headache	2 (33.3)	2 (33.3)	2 (33.3)	0	1 (16.7)	3 (50.0)	2 (33.3)	2 (14.3)	4 (50.0)	3 (37.5)	1 (12.5)
Injection site reaction	0	1 (16.7)	1 (16.7)	4 (66.7)	2 (33.3)	2 (33.3)	0	0	6 (75.0)	4 (50.0)	5 (62.5)
Blood CPK increased *	0	1 (16.7)	0	0	0	1 (16.7)	0	3 (21.4)	1 (12.5)	2 (25.0)	1 (12.5)
Nausea	1 (16.7)	0	0	0	0	0	0	0	0	2 (25.0)	0
Diarrhea	0	0	2 (33.3)	0	0	0	0	0	0	0	0
Oropharyngeal pain	0	0	0	0	0	0	0	0	0	2 (25.0)	0

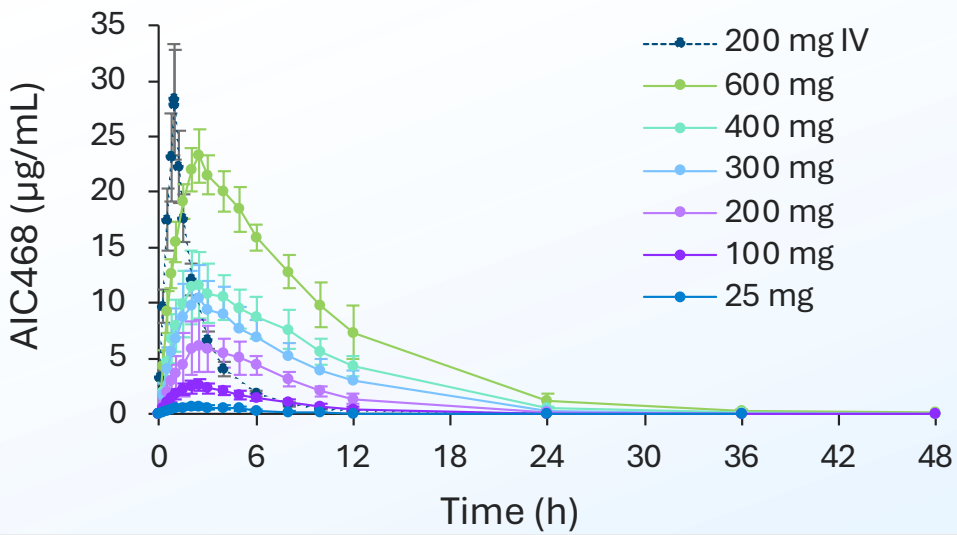
* CPK elevations: transient self-limiting, considered unrelated to IMP, attributed to alternative etiological factors (e.g. physical activity)

Plasma Pharmacokinetics

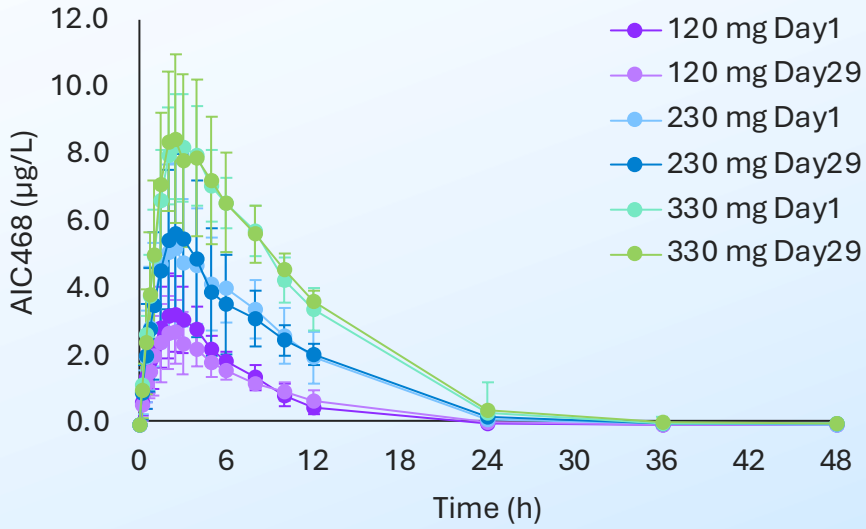
- AIC468 was rapidly absorbed with median T_{max} of 2–5 hours; AIC468 not quantifiable beyond 168 hours
- Plasma exposure ($AUC_{0\text{-}24h}$ and C_{max}) increased in a supra-proportional manner
- Systemic clearance decreased with dose, indicating non-linear kinetics likely due to tissue uptake saturation
- The estimate of the absolute bioavailability was 82%
- No accumulation was observed for AIC468 in plasma

Figure 1. AIC468 Plasma Concentration Profiles

A. After single dose



B. After multiple doses



Data shown as mean +/- SD; LLOQ, lower limit of quantification

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Urine Pharmacokinetics

- Less than 2% of AIC468 dose was excreted in urine unchanged during the first 24 hours post dose
- Excreted amount during subsequent 24 hours was negligible (<0.04% of dose)
- Amount excreted in urine increased with dose level, reflecting supra-proportional exposure increase in plasma

Table 4. Urine PK Parameters for AIC468

	25 mg SC	100 mg SC	200 mg SC	300 mg SC	400 mg SC	600 mg SC	200 mg IV
Plasma $AUC_{0\text{-}24h}$ h·µg/mL	4.00 (32.94)	18.5 (17.00)	49.9 (18.79)	89.3 (20.17)	115 (20.0)	216 (14.8)	60.5 (14.24)
Ae 0-24h, % of dose	0.037 (59.4)	0.0475 (55.1)	0.056 (59.3)	0.291 (75.4)	0.514 (97.4)	1.56 (80.4)	1.72 (29.0)
CL_{Renal} mL/h	2.5 (65.6)	2.7 (69.0)	2.0 (60.9)	8.9 (73.0)	14.8 (92.3)	40.7 (71.1)	2.5 (65.6)

All parameters are displayed as arithmetic mean (CV%); Ae 0-24h, amount excreted from 0 to 24h post-dose; CL_{Renal}: renal clearance

Phase 1 Data Summary

- AIC468 administration for up to 4 weeks was safe and well-tolerated in HVs
- Most common AEs were mild/moderate ISRs, there was no evidence of ASO class related toxicities
- Favorable PK characteristics are consistent with expected profile for a 2nd generation ASO
- Renal excretion is a negligible elimination route of AIC468. Tissue uptake and subsequent metabolism seems to be the primary route of systemic clearance
- Estimated renal exposures from MAD cohorts are within the predicted efficacious range based on preclinical model

- A Phase 2/3 trial in kidney transplant recipients with BKV infection is scheduled to begin in H1 2026

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