A Phase 1, Randomized, Double-Blind, Placebo-Controlled Study, To Evaluate the Safety, Tolerability and Pharmacokinetics of Single and Multiple Ascending Doses (SAD-MAD) of AJ201 in Healthy Volunteers

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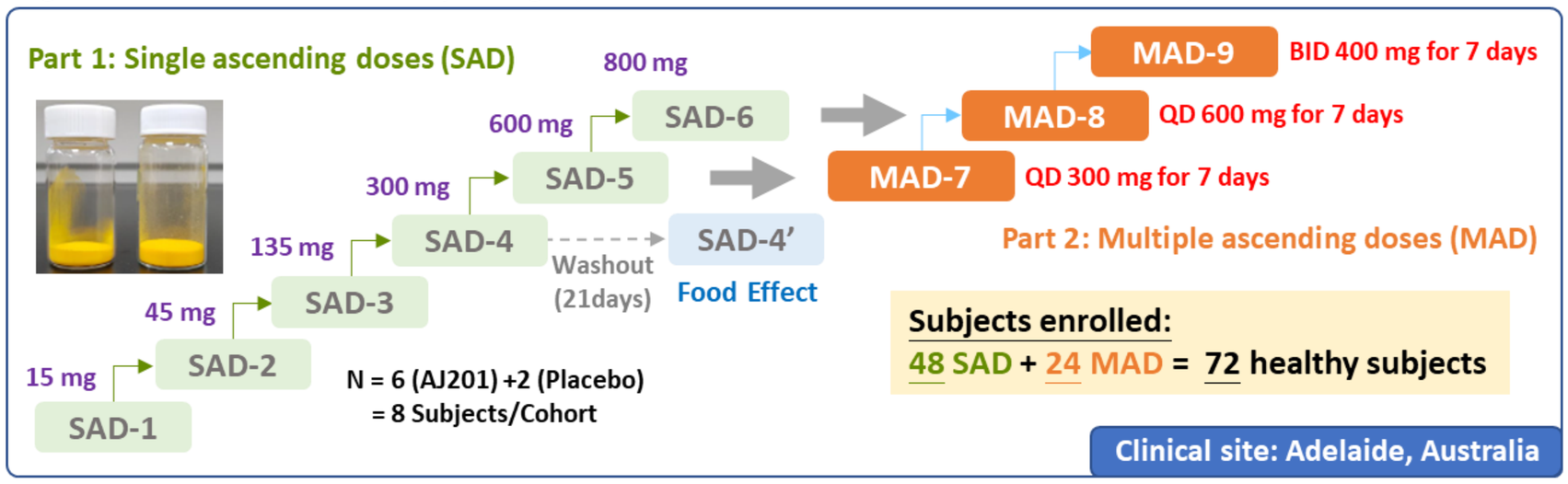
BACKGROUND:

Spinal and Bulbar Muscular Atrophy (SBMA) is a rare, X-linked hereditary lower motor neuron disease with an abnormal expansion of the CAG repeat (>37) in the androgen receptor (AR) gene, resulting in a polyglutamate (polyQ) expansion in the AR protein. AJ201 is a curcumin analog and preclinical studies have shown that AJ201 increased Nrf2-mediated antioxidant gene expressions and reduced mutant AR accumulation in muscles[1]. The study aims to establish the safety, tolerability, and pharmacokinetics (PK) of AJ201 in humans.

MATERIAL and METHOD:

This is a randomized, double-blind, placebo-controlled study to assess AJ201's safety, tolerability (primary objective), and PK (secondary objective) after single (15, 45, 135, 300, 600, 800 mg) and multiple oral dosing (300 mg [QD], 600 mg [QD], 400 mg [BID] for consecutive 7 days) in **healthy volunteers**. Food effect was evaluated in the single-dose cohort of 300 mg.

Figure 1. AJ201 Phase 1 Study Design (Protocol No.: ALZ002-101; NCT04392830)



RESULT:

- A total of 72 healthy volunteers were enrolled and randomized to receive either AJ201 (54 subjects) or Placebo (18 subjects).

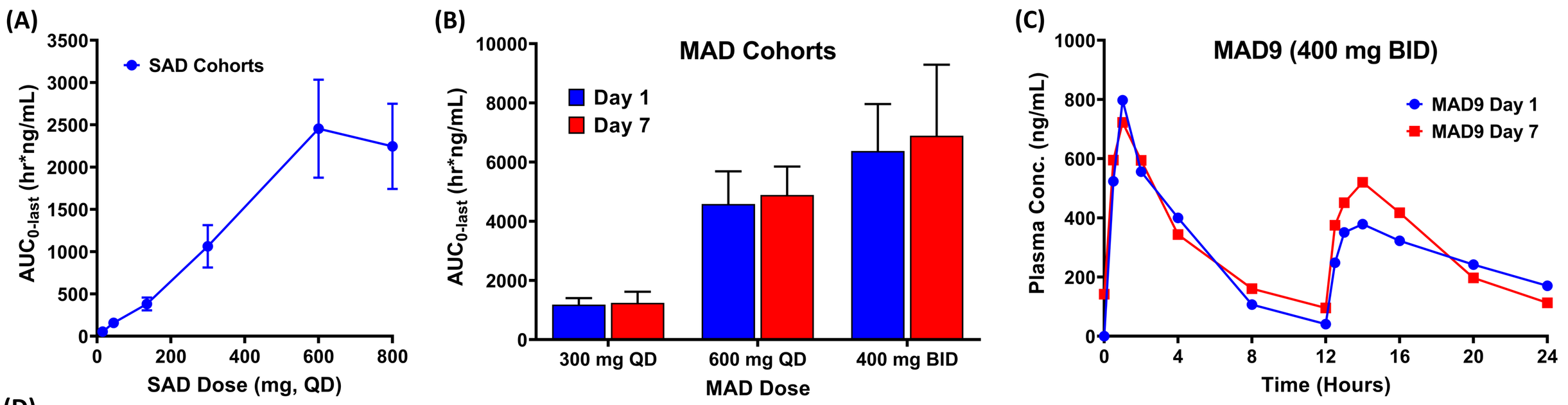
Safety Summary:

- A total of 146 TEAEs (Treatment Emergent Adverse Events) were reported by 39 subjects (72.2%) who received AJ201 and 43 TEAEs were reported by 10 subjects (55.6%) who received placebo. There was no dose-related trend observed across treatment groups with regards to the number of subjects who reported TEAEs and the number of TEAEs reported. Common TEAEs included nausea (14%), diarrhoea (13%), headache (10%), abdominal distension (5%), and vomiting (3%). Most TEAEs (>99%) were mild to moderate and resolved without intervention. No clinically relevant changes were observed in clinical laboratory and ECG results.
- No serious adverse events were reported. No adverse events led to AJ201 discontinuation or subject withdrawal.

PK Summary:

- Both single and repeated administration of AJ201 showed a dose-dependent increase in systemic exposure. Absorption appeared to approach saturation at >600 mg/day.
- The plasma AJ201 concentrations were almost negligible and approaching pre-dose levels after 12 hours post-dose on Day 7 in all the multiple dosing cohorts. No apparent accumulation in systemic exposure after repeated dosing.
- Consumption of food did not significantly affect the PK profile of AJ201.

Figure 2. Pharmacokinetics (PK) of AJ201 in Healthy Volunteers. Dose-exposure relationship of AJ201 in (A) SAD Cohorts and (B) MAD Cohorts. (C) PK profiles of AJ201 in Day 1 and Day 7 after 400 mg twice daily dose. (D) Food effect of AJ201. All data were presented as mean (± SD).



DISCUSSION:

- AJ201 was **safe** and **well-tolerated** in humans up to 800 mg/day dose.
- There was no accumulation in systemic exposure of AJ201 from repeated dosing, and AJ201 demonstrated a favorable drug-like PK profile over a broad dosing range.

NEXT STEP:

- A Phase 1/2a first-in-patient international study to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of AJ201 in **SBMA patients** to be initiated **in Q4 2022**.
- **If any inquiry, please contact: Cheng-Lung (Andy) Chen 陳承龍 (andy.chen@ajpharm.com)**

REFERENCE:

1. Bott et al., Human Molecular Genetics, 2016, 25(10): 1979–1989