

# Financial Results Q1 FY2023

(January to March 2023)

Carna Biosciences, Inc.



# AGENDA

- 1** FY2023 Q1 Results
- 2** Updates on Pipelines in Clinical Development
- 3** Updates on Licensed Pipelines
- 4** Appendix



# FY2023 Q1 Results by Business Segment



(JPY million)	Q1FY2022 Actual	Q1FY2023 Actual	YoY Change	FY2023 Plan as of Feb 10	vs. FY Plan	
Total Sales	554	226	-327 -59.1%	902	25.1%	
ddSP business	268	226	-41 -15.5%	902	25.1%	<ul style="list-style-type: none"><li>Sales were on track to achieve FY plan.</li><li>While sales of kinase proteins were solid, overall sales declined YoY as revenue related to the license agreement with Gilead contributed to FY2022 sales.</li></ul>
ddRD business	286	—	-286	—	—	<ul style="list-style-type: none"><li>Received an upfront payment from FRTX and a milestone payment from BioNova in FY2022.</li></ul>
Total Operating Profit/Loss	1	-505	-506	-1,890	—	
ddSP business	109	64	-44 -41.0%	221	29.1%	<ul style="list-style-type: none"><li>Operating profit was on track to achieve FY plan.</li><li>Operating profit declined due to a decrease in sales.</li></ul>
ddRD business	-107	-570	-462	-2,111	—	<ul style="list-style-type: none"><li>Received an upfront payment and a milestone payment in 2022.</li><li>Operating loss increased YoY due to the increase in R&amp;D expenses.</li></ul>
Ordinary Profit/Loss	4	-513	-517	-1,911	—	
Net Profit/Loss	-15	-519	-504	-1,936	—	
R&D Cost	346	535	+188	1,968		<ul style="list-style-type: none"><li>Invested in the programs in clinical trials.</li></ul>

Business plan for FY2023 in ddRD does not include potential milestone payments or upfront payments as the timing or the amounts are difficult to predict.

Note : Rounded down to the nearest million yen

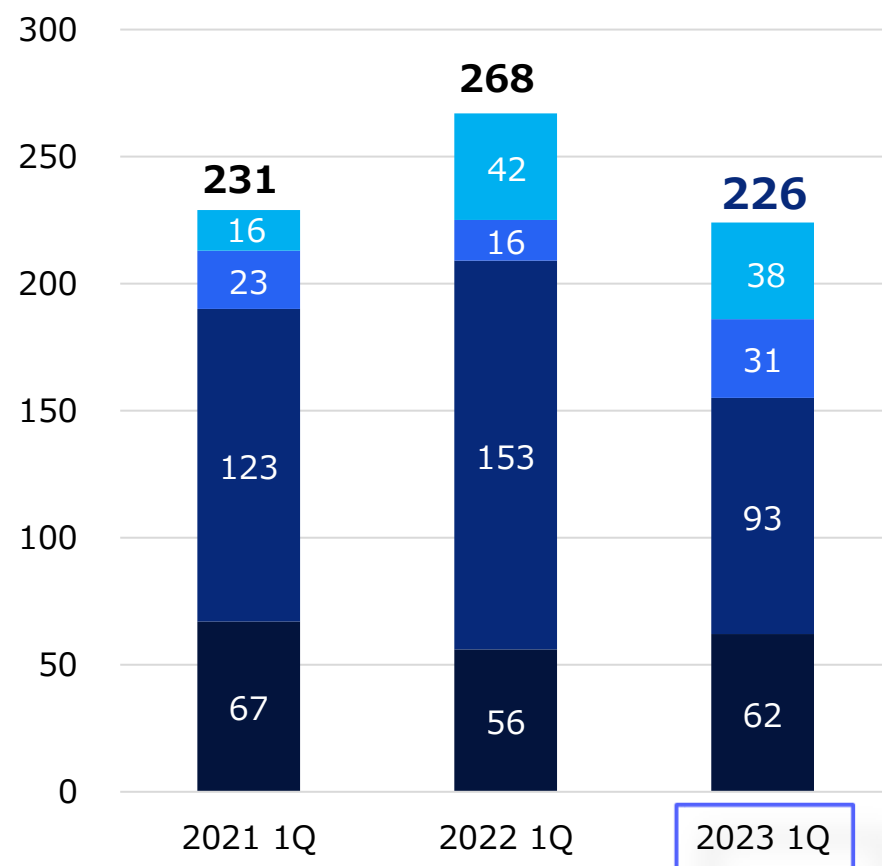


# FY2023 Q1 Drug Discovery Support Business Sales Trend



Drug Discovery Support Business Sales Trend by Region  
(Consolidated)

(JPY million)    Other   Europe   North America   Japan



## Japan

### Increased 11.2% YoY

- Sales of Cell-based assay service including NanoBRET service and assay development were robust.

## North America

### Decreased 38.9% YoY

- Sales of kinase proteins were strong while overall sales declined YoY as sales from Gilead contributed to FY2022 sales.

## Europe

### Increased 95.4% YoY

- Sales of kinase proteins and profiling service were both very strong.

## Other

### Decreased 9.4% YoY

- In China, the overall demand is still robust but sales declined YoY compared to the same period last year when sales were very strong.



# Consolidated Balance Sheet



(JPY million)	As of Dec.31, 2022	As of Mar.31, 2023	Change	Reason for changes
Current assets	4,104	4,794	+690	Cash and deposits +702
Cash and deposits	3,379	4,082	+702	Amount raised from exercised share options +1,274
Non-current assets	162	150	(11)	
Total assets	4,266	4,945	+678	
Current liabilities	436	389	(47)	Accounts payable -13 Current portion of long-term debt -14
Non-current liabilities	188	158	(30)	Long term loans payable-29
Total liabilities	624	547	(77)	
Total net assets	3,641	4,397	+755	Capital stock and capital surplus +1,283 Retained earnings -519
Total liabilities and net assets	4,266	4,945	+678	

Shareholders' equity ratio	85.0%	88.8%
BPS	255.0yen	258.4yen
PBR	2.0x	1.8 x
Share price of Carna	520yen	475yen

Note: Share price is the closing price of the term end.



## <20th Subscription Rights to Shares >

	DEC. 2022	2023 1Q	Apr. 2023	Total
Amount raised (JPY)	300 mil.	<b>1,274mil.</b>	<b>28mil.</b>	<b>1,602mil.</b>
No. of shares exercised (Shares)	550,000	<b>2,775,000</b>	<b>61,000</b>	<b>3,386,000</b>
No. of Exercised rights/No. of total rights issued	16.2 %	<b>81.9%</b>	<b>1.8%</b>	<b>100%</b>

**Cash and deposits as of the end of March 2023 : 4,082million JPY.**

## Financing

Additional financing may be considered as necessary in order to accelerate the clinical trials of AS-1763, our most important asset.





# Updates on Pipelines in Clinical Development

**1 AS-1763**

**2 AS-0871**

**3 AS-0141**



Compound	Target	Indication	Status
AS-1763	BTK	Blood Cancer	<ul style="list-style-type: none"><li>Phase 1 SAD and BA part in healthy volunteers were completed in the Netherlands.</li><li>In preparation to initiate Phase1b study in the U.S. The first patient is expected to be dosed in Q2 2023.</li></ul>
AS-0871	BTK	Immune-inflammatory diseases	<ul style="list-style-type: none"><li>Phase 1 study in healthy volunteers is in progress in the Netherlands.</li><li>SAD study and BA part of MAD study were completed.</li><li>Dosing in MAD part of MAD study has been completed. The top-line results will be available in Q3 2023.</li></ul>
AS-0141	CDC7/ ASK	Cancer	<ul style="list-style-type: none"><li>Phase 1 study in cancer patients is in progress in Japan.</li><li>Dose escalation part is on going.</li></ul>





## Mechanism/ Indication

AS-1763 is an **orally available** Bruton's Tyrosine Kinase (BTK) inhibitor targeting B cell malignancies.

## To overcome drug resistance

AS-1763 is a **non-covalent inhibitor** that reversibly inhibits BTK, **having a potential to be effective for patients who have developed resistance to ibrutinib**, the first BTK inhibitor in the market.

## To minimize a risk of side effects

AS-1763 is designed to selectively inhibit BTK **to reduce a risk of potential side effects.**



## Objectives of the study

### **AS-1763 was administered orally to healthy volunteers to evaluate:**

- plasma concentration of AS-1763
- safety assessments (clinical laboratory, ECGs, or vital signs, etc)
- inhibitory potency on B cell activation

## Result of the study

### **After a single-dose administration of 5 mg, 25 mg, 100 mg, 300 mg, 500 mg, and 600 mg of AS-1763:**

- plasma concentrations of AS-1763 were increased in a dose dependent manner
- no safety issues were reported in all safety assessments
- dose-dependent inhibition in B cell activation assays was observed

## New tablet formulation for Phase 1b study

### **Relative oral bioavailability was evaluated after administering newly developed tablet formulation containing 100 mg of AS-1763 to healthy volunteers.**

- the new tablet formulation demonstrated good oral bioavailability, supporting that the tablet formulation can be used for Phase 1b study.



Planned clinical study

Phase 1b study of AS-1763 will be conducted in the U.S.

Indication

Patients with CLL(Chronic Lymphocytic Leukemia), SLL(Small Lymphocytic Leukemia), and B-cell NHL(B-cell non-Hodgkin Lymphoma).

Schedule

First clinical site is ready to enroll patients.  
**The first patient is expected to be dosed in Q2 2023.**



# AS-1763: Potential Market Size (B-cell Malignancies)



Present

**Covalent BTK inhibitors including ibrutinib, acalabrutinib, and zanubrutinib** are key therapeutic options.

Est. market size

Estimated sales of covalent BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib)

Est. sales for 2021 **\$9 billion**

Est. sales for 2029 **\$17 billion** ※Expected CAGR is 8%

## Opportunity

Patients treated with covalent BTK inhibitor drugs are reported to develop resistance to the drugs



High unmet needs for new therapeutic options to treat patients with B-cell malignancies who have developed resistance to covalent BTK inhibitor drugs



- The next generation **non-covalent BTK inhibitors** including AS-1763 are expected to be a promising therapeutic option for the patients who have developed resistance to covalent BTK inhibitors. We aim to make AS-1763 a blockbuster drug by taking a certain share of this potential large market.
- We regained the development and commercialization rights in Greater China from BioNova, aiming to partner with major pharmaceutical companies for global license.



## Competitors: other non-covalent BTK inhibitors in clinical development

Compound	Company	Development Phase
pirtobrutinib (LOXO-305)	Lilly (Loxo)	Approved/P3
nemtabrutinib (ARQ 531)	Merck (ArQule)	P2
TT-01488	TransThera	P1
HMPL-760	HutchMed	P1

- FDA granted accelerated approval to pirtobrutinib, the most advanced non-covalent inhibitor, in the U.S early 2023.
- Focused differentiation strategy is the key to the success of AS-1763.
- In preclinical studies, AS-1763 demonstrated to be effective for mutant BTKs that confer resistance to pirtobrutinib in addition to ibrutinib.

*\*N. Engl. J. Med. 2022;386(8):735–743.*





## Mechanism/ Indication

AS-0871 is an **orally available** Bruton's Tyrosine Kinase (BTK) inhibitor to treat autoimmune diseases by inhibiting activation of immune cells such as B cells, macrophages, and mast cells.

## To minimize a risk of side effects

AS-0871 is designed to selectively inhibit BTK **to reduce a risk of potential side effects**.

## Characteristics

AS-0871 is a **non-covalent BTK inhibitor** that reversibly inhibit BTKs to reduce safety concerns associated with covalent inhibitors.



## Objectives of Single Ascending Dose (SAD) study

### **AS-0871 was administered orally to healthy volunteers to evaluate:**

- plasma concentration of AS-0871
- safety assessments (clinical laboratory, ECGs, or vital signs, etc)
- inhibitory potency on B cell and basophil activation

## Result of SAD study

### **After a single-dose administration of 5 mg, 25 mg, 100 mg, 300 mg, 600 mg, and 900 mg of AS-0871:**

- plasma concentration of AS-0871 were increased in a dose dependent manner
- no safety issues were reported in all safety assessments
- Sufficient inhibition of B cell and basophil activations was observed at 100 mg or above.

## New formulations for Multiple Ascending Dose (MAD) study

### **Plasma concentration was evaluated after administering newly developed capsule formulation and tablet formulation containing 50 mg of AS-0871 to healthy volunteers:**

- the new tablet formulation was shown to be safe and demonstrated good oral bioavailability, and the tablet formulation was selected for the MAD part.



## Status

**Dosing in MAD part of MAD study was completed as planned. Unblinded top-line results will be available in Q3 2023.**

## MAD part of MAD Study

**Repeated dosing of AS-0871 for 14 days in healthy subjects:**

- double blind and placebo-controlled study
- 3 dose levels

## Objectives

- plasma concentration of AS-0871
- safety assessments (clinical laboratory, ECGs, or vital signs, etc)
- inhibitory potency on basophil activation



# AS-0871: CSU is a skin disease with unmet medical needs



**Chronic Spontaneous Urticaria (CSU)** is a distressing skin disorder that characterized by itching and hives lasting for more than 4 weeks with unknown causes. The symptoms can last months or years, affecting on QoL of patients.

## Challenges of CSU

- Curative treatment is not available
- High socio-economic costs for patients with high disease activity\*
- Large number of patients; approximately 1% of the global population is affected\*

**High unmet medical needs with large potential market**

\* Br J Dermatol 2021;184:226-36.

## Competitors

Compound	Company	Development Phase
Remibrutinib (LOU064)	Novartis	P3

Positive Ph 2b results were disclosed that remibrutinib rapidly and effectively improved the symptoms of patients whose CSU was inadequately controlled. \*

\*J Allergy Clin Immunol.2022;150:1498-506.

## Opportunity

- The potential for market expansion in CSU would be considerable when new treatment option is approved.
- The key to the success of AS-0871 is to demonstrate the difference between remibrutinib (covalent) and AS-0871 (non-covalent) in terms of safety and efficacy.



## Mechanism/ Indication

AS-0141 is an **orally available** CDC7 kinase inhibitor targeting cancers.

## To minimize a risk of side effects

AS-0141 is designed to selectively inhibit CDC7 kinase **to reduce a risk of potential side effects.**

## Potentially effective for various cancers

AS-0141 exhibited **a potent anti-proliferative activity against a wide range of cancer cell lines in preclinical studies.**

## Potential first-in-class molecule

AS-0141 has a potential to become the first-in-class drug as no CDC7 inhibitors have been approved.





**Clinical trails in progress**

Phase 1 dose escalation study targeting cancer patients is ongoing.

**Objectives of the study**

The primary objectives of the dose escalation study is to assess safety, tolerability, maximum tolerated dose (MTD), preliminary anti-tumor activity, and pharmacokinetics (plasma concentration, duration) of AS-0141.

**Dosage**

Oral administration, twice a day

**Potential first-in-class molecule**

Patients were treated with AS-0141 at dose levels of 20 mg, 40 mg, 80 mg, 150 mg, 250 mg, 300 mg BID. Dose-limiting toxicities were observed at 300 mg BID, therefore additional patients are being enrolled at a lower dose level to evaluate safety and tolerability and to determine MTD and recommended dose level for the expansion part.



# Updates on Licensed Pipelines

- 1 DGK $\alpha$  Inhibitor** (Gilead Sciences, Inc.)
- 2 STING Inhibitor** (Fresh Tracks Therapeutics, Inc.)
- 3 Joint Research with Sumitomo Pharma**



# Out-licensed Programs

Program/ Partner	Compound (Target)	Upfront payment	Total milestone payments expected	Royalty	Region	Contract date	Milestones received
<b>DGKα inhibitor</b> Gilead Sciences (Out-license)	GS-9911 (Immuno- oncology)	\$20M	\$450M	Undisclosed	Worldwide	Jun. 2019	\$10M (Dec. 2021)
<b>STING inhibitor</b> Fresh Tracks Therapeutics (Out-license)	FRTX-10 (Immune- inflammatory diseases)	\$2M	\$258M	Up to 10%	Worldwide	Feb. 2022	
Joint Research with Sumitomo Pharma	Kinase inhibitor (Psychiatric and neurological disorders)	JPY80M (including research milestone)	JPY10.6B	Undisclosed	Worldwide	Mar. 2018	



Partner



GILEAD

**Gilead Sciences, Inc.**  
**Out-licensed in June 2019** (worldwide rights)

Deal size

- Upfront payment \$20 million
- Maximum of \$450 million potential milestone payments upon achievement of certain development and commercial milestones

Royalties

- Royalties on future net sales

## 1. Investigational DGK $\alpha$ inhibitor: GS-9911

- GS-9911, as well as its target kinase, was first introduced by Gilead in its presentation “Oncology Deep Dive” held in April 2022.

## 2. Indication: Cancer (immunotherapy)

- The presentation suggested that GS-9911 potentiated anti-tumor immunity by activating T cell function and demonstrated anti-tumor immune responses in mouse models in combination with anti-PD-1 antibody.



Partner



**Fresh Tracks Therapeutics, Inc.**  
**Out-licensed in February 2022** (worldwide rights)

Deal size	<ul style="list-style-type: none"><li>• Upfront payment \$2 million</li><li>• Maximum of \$258 million potential milestone payments upon achievement of certain development and commercial milestones</li></ul>
Royalties	<ul style="list-style-type: none"><li>• Tiered royalty payments ranging up to 10% of net sales</li></ul>

- 1. Investigational STING inhibitor : FRTX-10**
- 2. Indication: autoinflammatory and rare monogenic diseases**  
(Systemic Lupus Erythematosus, dermatomyositis, non-alcoholic steatohepatitis, etc.)
- 3. Characteristics: FRTX-10 is a novel orally available covalent STING inhibitor that blocks the palmitoylation site of STING.**
- 4. Preclinical IND-enabling development activities are in progress.**





Partner



**Sumitomo Pharma Co., Ltd.**  
**Joint Research Agreement in March 2018**  
(worldwide rights)

Deal size	<ul style="list-style-type: none"><li>• Upfront payment + Research milestone JPY80 million</li><li>• Maximum of JPY10.6 billion potential milestone payments upon achievement of certain development and commercial milestones</li></ul>
Royalties	<ul style="list-style-type: none"><li>• Royalties on future net sales</li></ul>

- 1. **Joint research to discover novel kinase inhibitors to treat psychiatric and neurological disorders.**
- 2. **The term of the joint research was extended in December 2021.**
- 3. **Joint research is ongoing to identify preclinical candidates.**

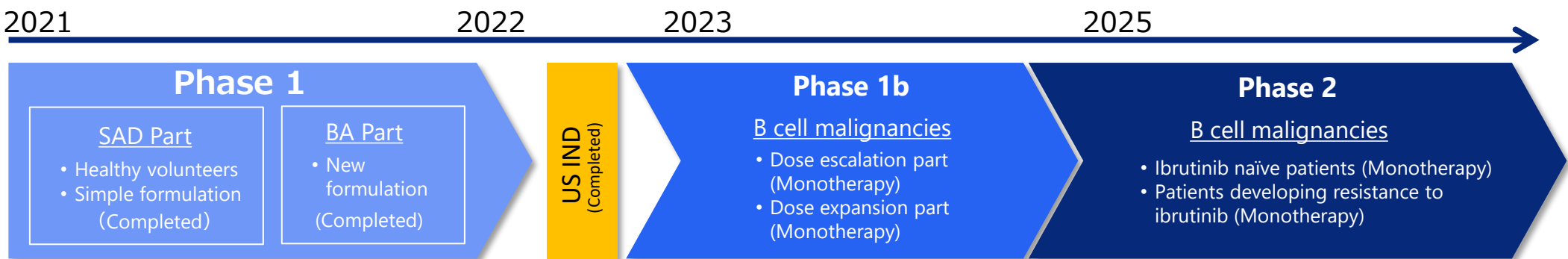


# Appendix



## AS-1763 : Targeting Blood Cancer

- Small molecule BTK inhibitor
- Non-covalent/reversible
- High kinase selectivity
- Inhibits both BTK wild type and ibrutinib resistant BTK C481S mutants
- Orally available
- Displayed strong anti-tumor effects in lymphoma model with both wild type and C481S mutant BTK
- Displayed efficacy in immuno-oncology model
- Completed an IND application process in the U.S.
- FPI in the U.S. is expected in Q2 2023.



IND application: Investigational New Drug application

FPI: First Patient In

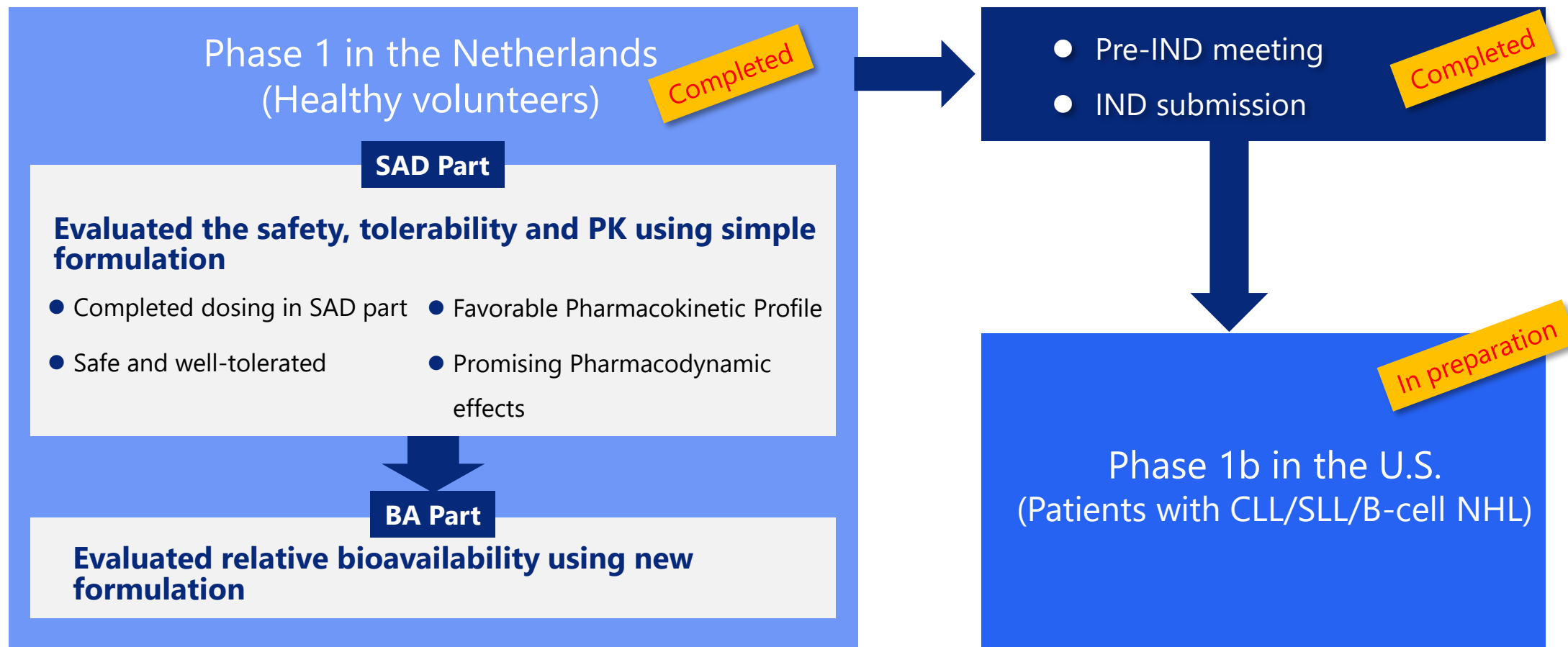
SAD: Single Ascending Dose

BA: Bioavailability

B-cell malignancies: Chronic Lymphocytic Leukemia (CLL), Small Lymphocytic Lymphoma (SLL), and B-cell non-Hodgkin Lymphoma (B-cell NHL), etc.



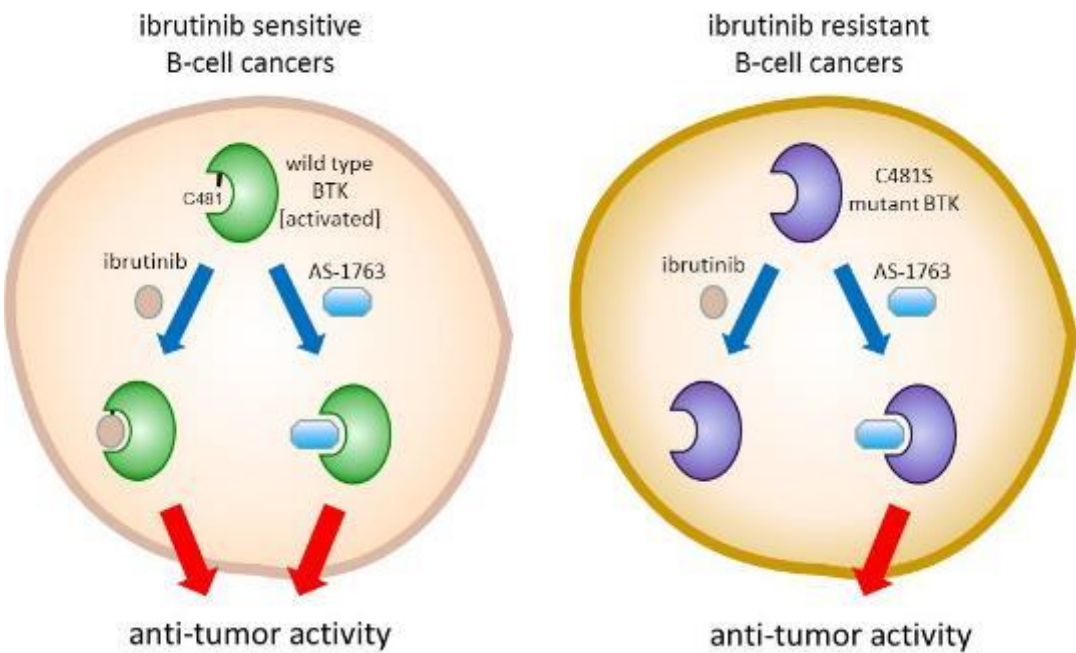
# AS-1763: Phase 1 Clinical Trial in Progress



- ◆ In May 2022, Carna received an approval for an IND to initiate Phase 1 study in the U.S.
- ◆ FPI in the U.S. is expected in Q2 2023.



# AS-1763: Potent Inhibitor of C481S mutant BTK



Journal of  
**Medicinal  
Chemistry**

pubs.acs.org/jmc

Drug Annotation

## Discovery of AS-1763: A Potent, Selective, Noncovalent, and Orally Available Inhibitor of Bruton's Tyrosine Kinase

Wataru Kawahata,\* Tokiko Asami, Takao Kiyoi, Takayuki Irie, Shigeki Kashimoto, Hatsuo Furuichi, and Masaaki Sawa

Cite This: *J. Med. Chem.* 2021, 64, 14129–14141

Read Online

### ◆ IC<sub>50</sub> values of AS-1763 against wild-type and C481S-mutant BTK

	IC <sub>50</sub> (nM)	
	BTK[A]	BTK <sup>C481S</sup>
AS-1763	0.85	0.99

*J Med Chem.* 2021 Oct 14;64(19):14129-14141.



# AS-1763: Strong Cellular Activity and High Kinase Selectivity

## ◆ In vitro pharmacological activities of AS-1763

	IC <sub>50</sub> (nM)	
	AS-1763	Ibrutinib
Autophosphorylation BTK (Ramos)	1.4	1.1
CD69 activation (Human whole blood)	11	8.1
Cancer cell growth OCI-Ly10 cells	1.8	0.75
Cancer cell growth OCI-Ly10 [BTK C481S] cells	20	1030
Normal cell growth HEL299 cells	6370	6870

50-fold Stronger activity

Ramos: human Burkitt lymphoma cell line

OCI-Ly10: human B-cell non-Hodgkin lymphoma cell line

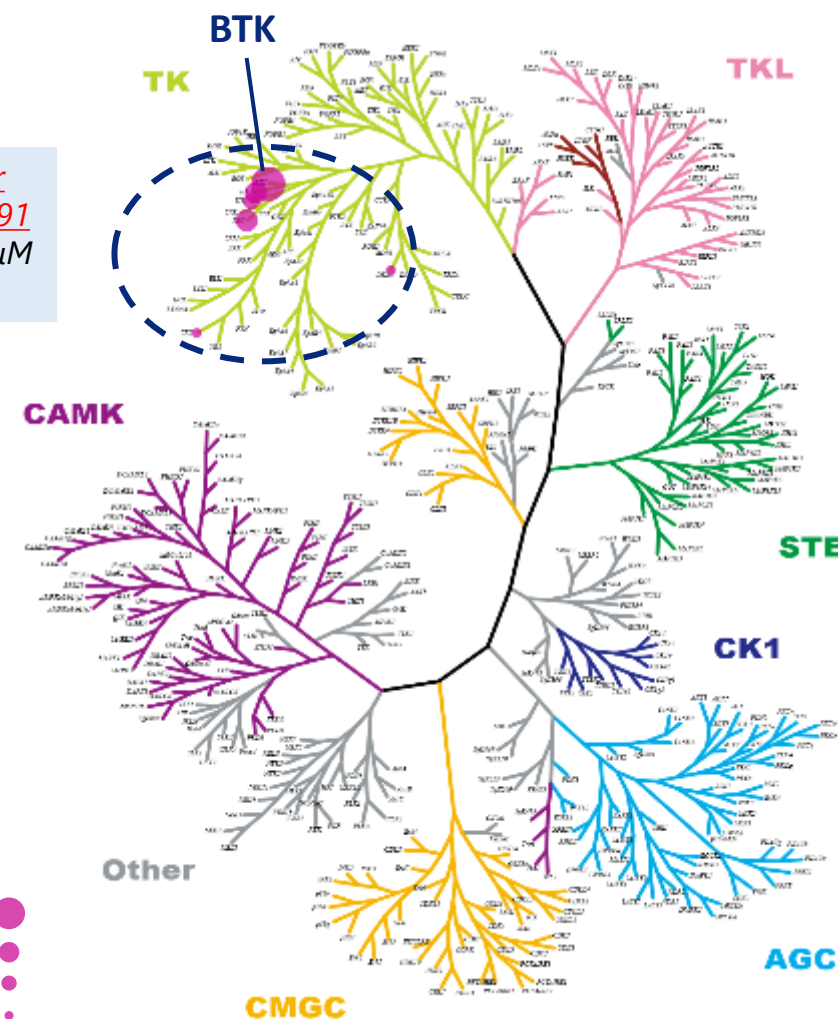
OCI-Ly10 [BTK C481S]: BTK[C481S] knock-in OCI-Ly10 cells

HEL299: human embryo lung cell line

J Med Chem. 2021 Oct 14;64(19):14129-14141.

## ◆ Kinase selectivity profiling

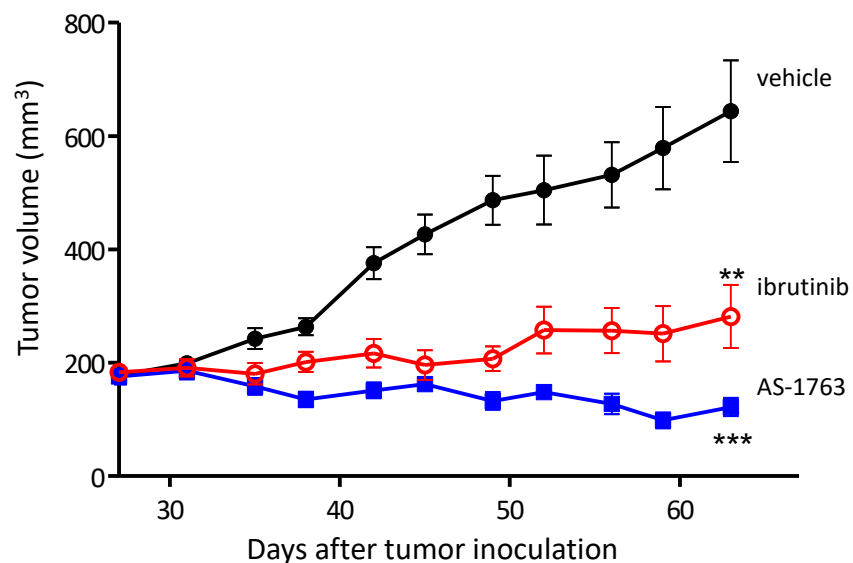
Only inhibited 6 other kinases in a total of 291 kinases tested at 0.3  $\mu$ M concentration.





# AS-1763: In Vivo Antitumor Effect against BTK<sup>C481S</sup> Mutant

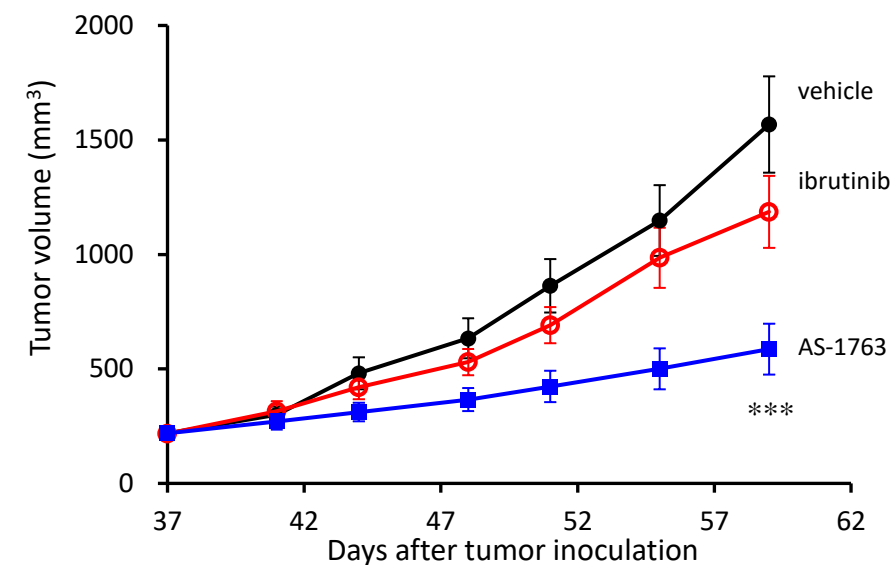
- ◆ In vivo antitumor effects of AS-1763 on human B-cell non-Hodgkin lymphoma cell line, OCI-LY10 tumor xenograft mouse model (n=8-10)



Ibrutinib: 25 mg/kg QD  
AS-1763: 60 mg/kg BID

\*\*: p<0.01  
\*\*\*: p<0.001

- ◆ In vivo antitumor effects of AS-1763 on ibrutinib-resistant BTK<sup>C481S</sup> knock-in OCI-LY10 tumor xenograft mouse model (n=11)



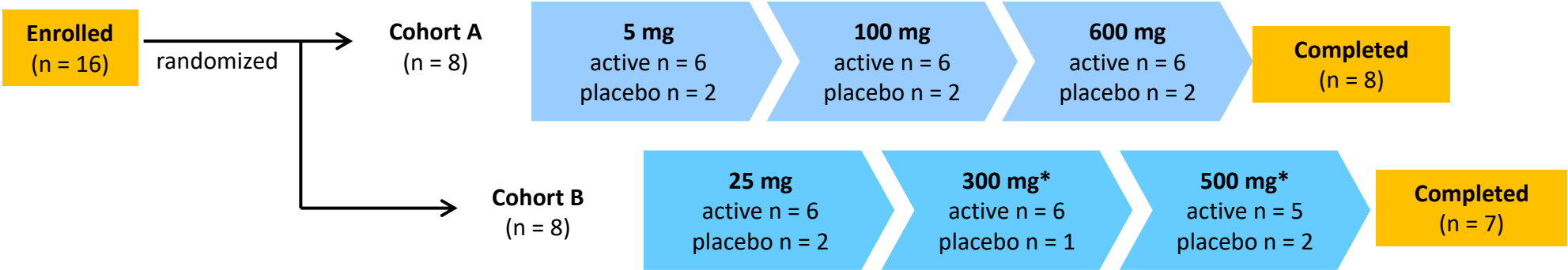
Ibrutinib: 25 mg/kg QD  
AS-1763: 60 mg/kg BID

\*\*\*: p<0.001



## Study Design

Step 1 Single Ascending Dose (SAD) Part	Step 2 Relative Bioavailability (BA) Part
<ul style="list-style-type: none"><li>• Double-blind, placebo-controlled, randomized FIH study</li><li>• Simple formulation (solution)</li><li>• 6 dose levels (8 subjects/cohort A, 8 subjects/cohort B)</li><li>• 6 active / 2 placebo for each dose level</li><li>• Safety and tolerability</li><li>• Pharmacokinetics and pharmacodynamics (PD; CD69 upregulation on naïve B cells )</li></ul>	<ul style="list-style-type: none"><li>• Open label study</li><li>• Another cohort of 8 subjects</li><li>• The subjects were dosed with a single dose of AS-1763 100-mg tablet, and relative bioavailability with simple formulation was evaluated</li></ul>



\*One subject was withdrawn from the study on Day 1 of 300-mg period before the intake of treatment medication (placebo) by physician's decision. This subject showed AEs (Grade 2 lymphocytosis and Grade 2 neutropenia) which were considered treatment-emergent but not trial medication-related. No replacement was done at 300-mg and the following 500-mg periods.



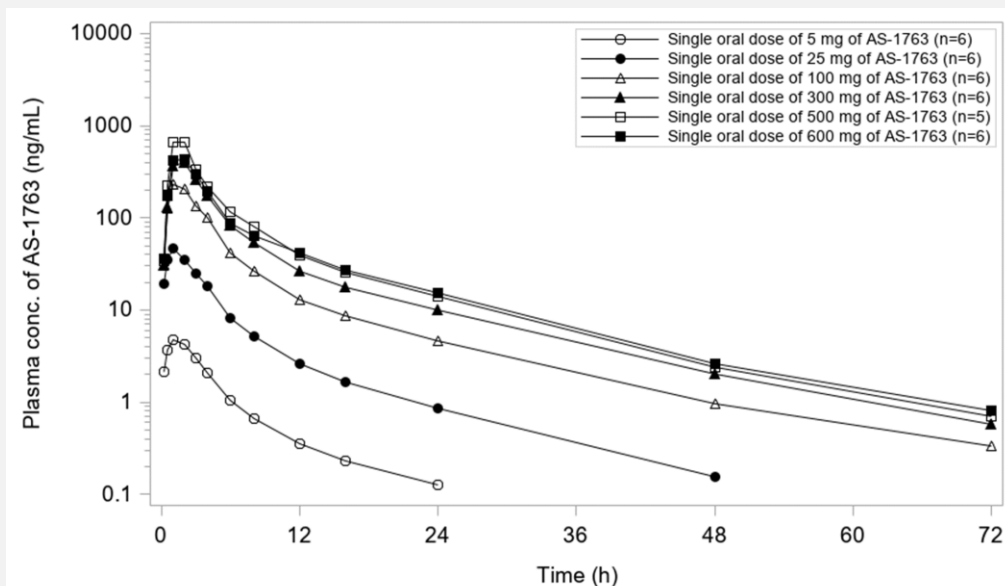
## Safety and tolerability

- AS-1763 was well-tolerated after single dose administration up to the maximum dose level (600 mg).
- No serious adverse events (AEs) were reported during the trial.
- Two Grade 2 AEs were reported in one subject, which were considered not related to trial medication.
- Other AEs reported were of mild intensity and showed no apparent dose-relationship in frequency.
- No clinically relevant changes from baseline were observed in all other safety parameters assessed (clinical laboratory, 12-lead safety ECGs, vital signs, or physical examinations).

## Pharmacokinetics

- After a single-dose oral administration, plasma concentration of AS-1763 rapidly reached the maximum and then declined in a biphasic manner across the dose range (median  $t_{max}$  between 0.5 and 1.5 hours; mean  $t_{1/2}$  between 8.4 and 12.1 hours).
- Mean AS-1763 exposures generally increased with dose up to 500 mg.

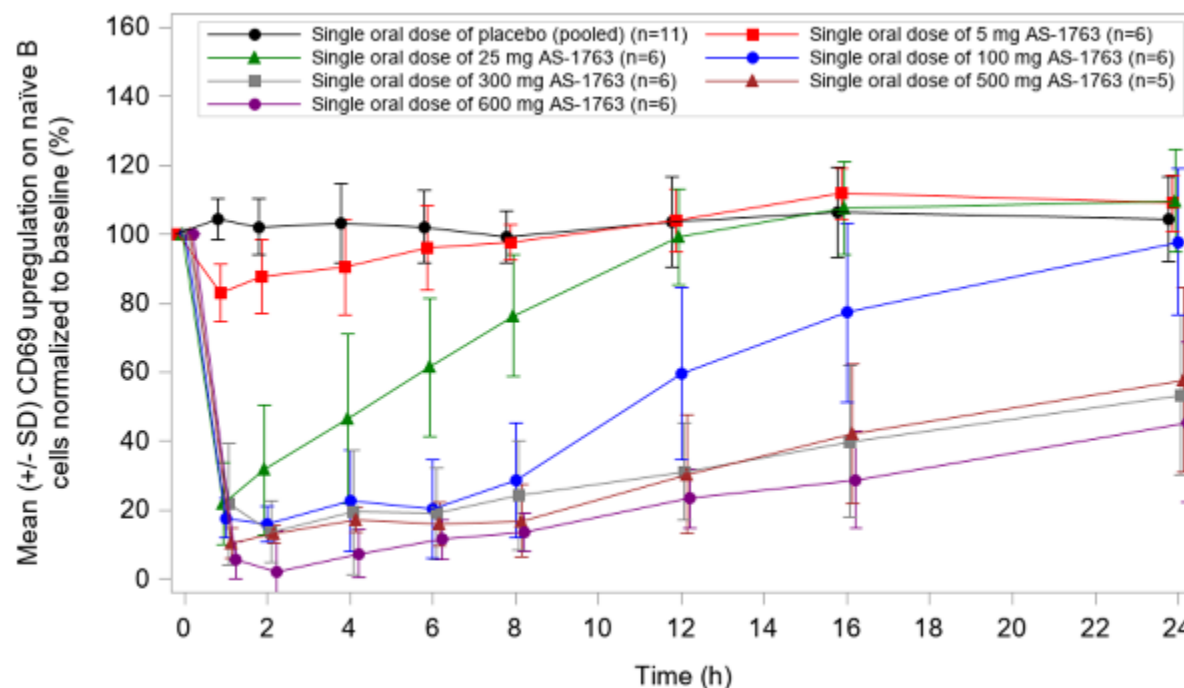
### < Plasma concentration of a single oral dose of AS-1763 >



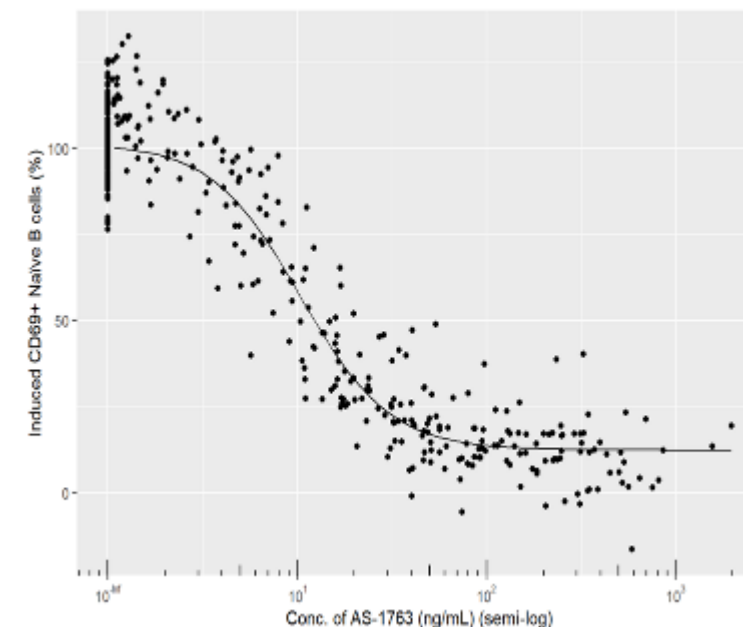


- Inhibition of B cell CD69 upregulation was observed for 5 mg onwards.
- Maximum inhibition (arbitrarily defined as  $\geq 80\%$ ) was observed at 1-2 hours post-dose from 100 mg to 600 mg, and the duration of inhibition was dose-dependent with values of 2, 6, 8 and 8 hours for 100, 300, 500, and 600 mg, respectively.
- Based on a PK/PD correlation analysis, the IC<sub>50</sub> value of AS-1763 on CD69 upregulation was calculated to be 10.5 ng/mL.

## < B cell CD69 upregulation after a single oral dose of AS-1763 >



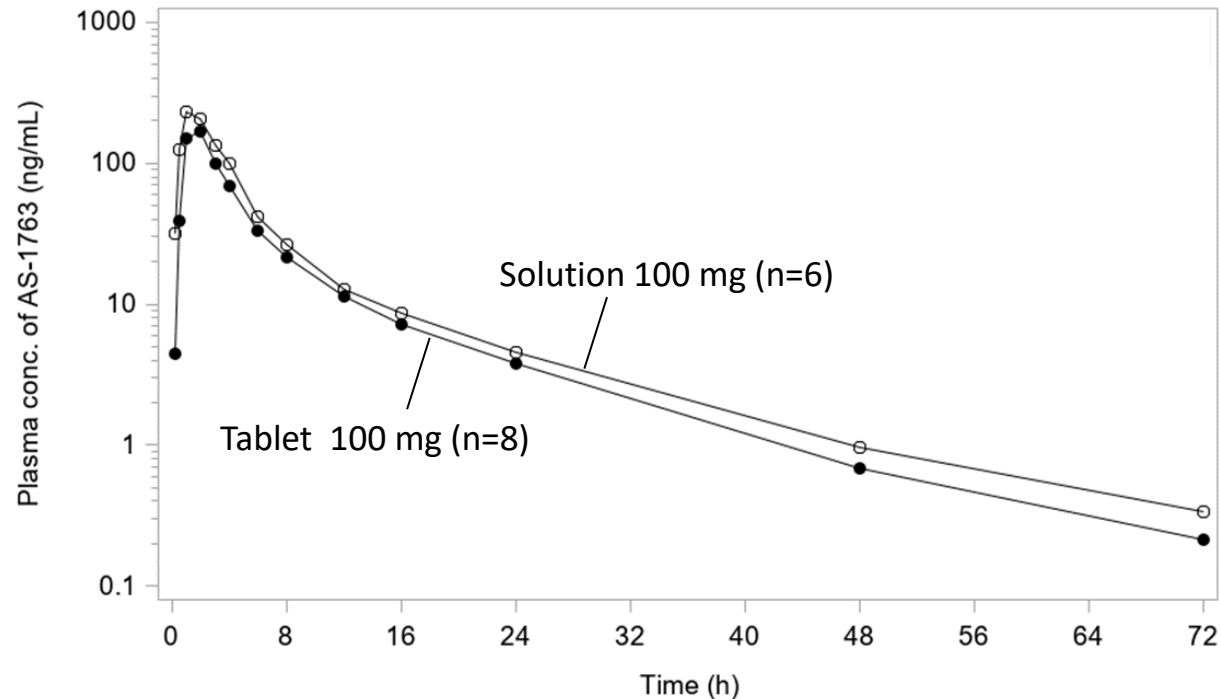
## < PK/PD correlation analysis >





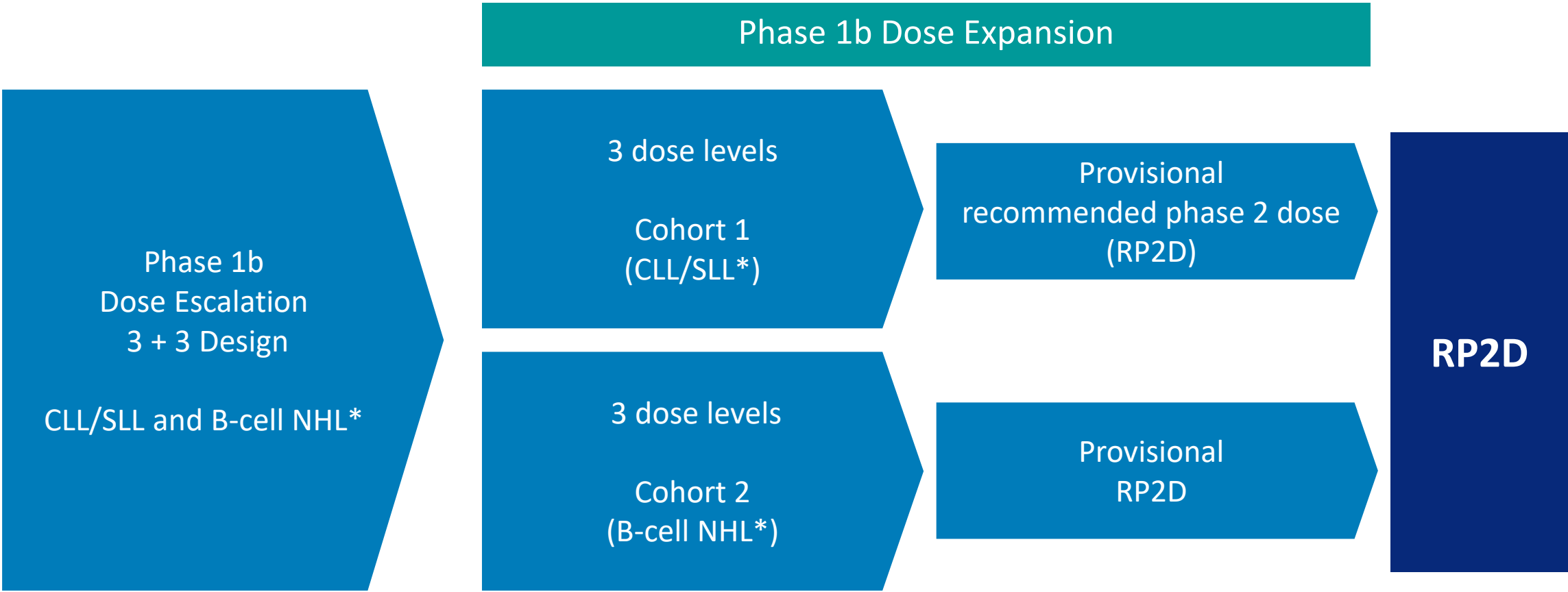
- In the BA part, 100 mg tablet and the solution showed almost the similar PK profile while the exposure of 100 mg tablet was slightly lower than the that of the solution.
- The PK/PD data and favorable safety profile in healthy volunteers support a planned Phase 1b clinical study with AS-1763 tablet twice daily dosing in relapsed/refractory CLL and B-cell NHL.

<PK of Tablet vs Solution after a Single oral dose AS-1763>





# AS-1763: Phase 1b Schema (US)



\*Previously treated patients

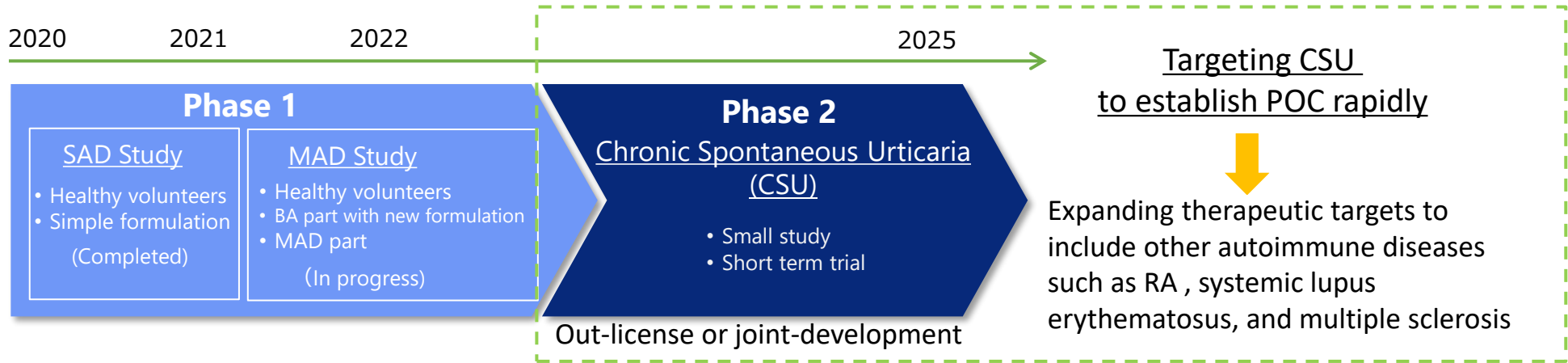
◆ FPI in the U.S. is expected in Q2 2023.





## AS-0871 : Targeting Immune-inflammatory diseases

- |   |  |
|---|--|
| <ul style="list-style-type: none"><li>• Small molecule BTK inhibitor</li><li>• Non-covalent/reversible</li><li>• High kinase selectivity</li><li>• Orally available</li></ul> | <ul style="list-style-type: none"><li>• Demonstrated significant efficacies in arthritis models</li><li>• Showed efficacy in systemic lupus erythematosus model</li><li>• Phase 1 MAD study is in progress</li><li>• Find a partner to conduct further development after completing Ph 1 study</li></ul> |
|---|--|



SAD: Single Ascending Dose  
MAD: Multiple Ascending Dose  
BA: Bioavailability  
POC : Proof of Concept



Completed

## Phase 1 in the Netherlands SAD study (Healthy volunteers)

- Safe and well-tolerated at all dose levels
- Favorable Pharmacokinetic (PK) Profile
- Promising Pharmacodynamic(PD) effects
- Conducted using simple formulation



Developed multiple new formulations



## Phase 1 in the Netherlands MAD study (Healthy volunteers)

### BA Part

Evaluate the relative bioavailability of multiple new formulations to select the best formulation

Completed



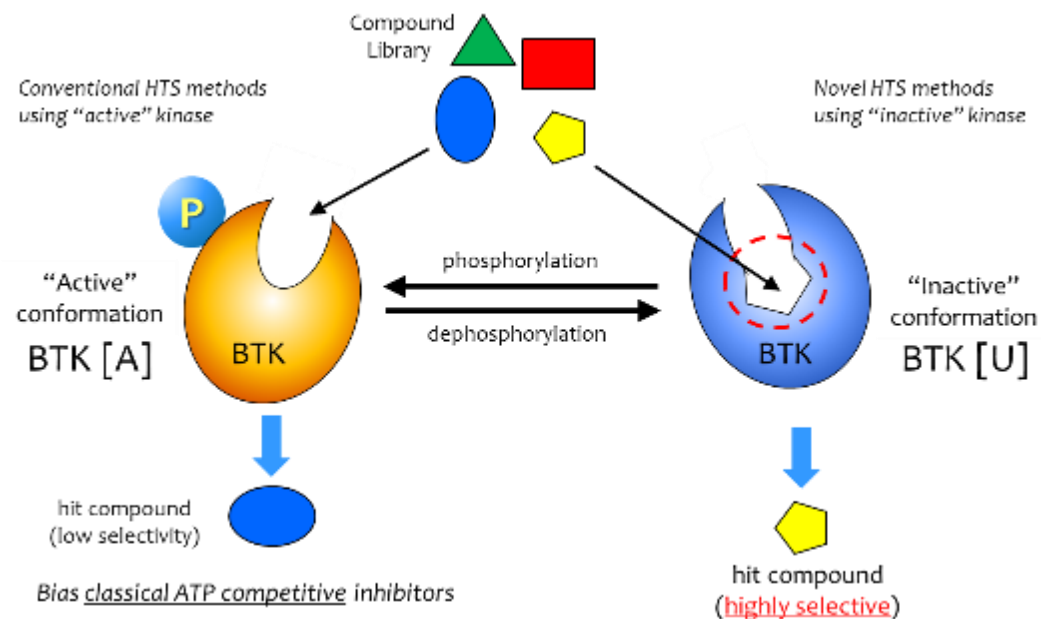
### MAD Part

Evaluate the safety, tolerability, PK and PD in the 2-week multiple ascending dose of AS-0871

Dosing completed

\*The protocol has been amended to skip the SPT (Skin Prick test) part based on the recent clinical outcomes of competing BTK inhibitor drug candidates, which enable us to predict the efficacy from the PD effects.

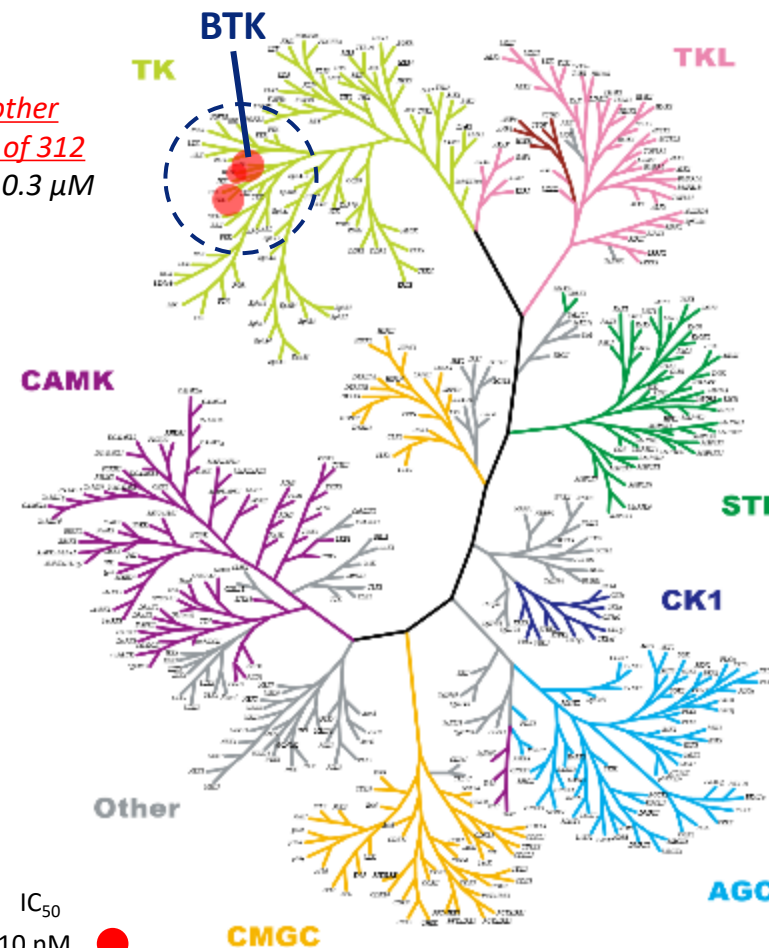
## ◆ Targeting Inactive Conformation of BTK



	BTK IC <sub>50</sub> (nM)	
	BTK[A]	BTK[U]
AS-0871	3.4	0.3

## ◆ Kinase Selectivity Profiling

Only inhibited 2 other kinases in a total of 312 kinases tested at 0.3  $\mu$ M concentration.



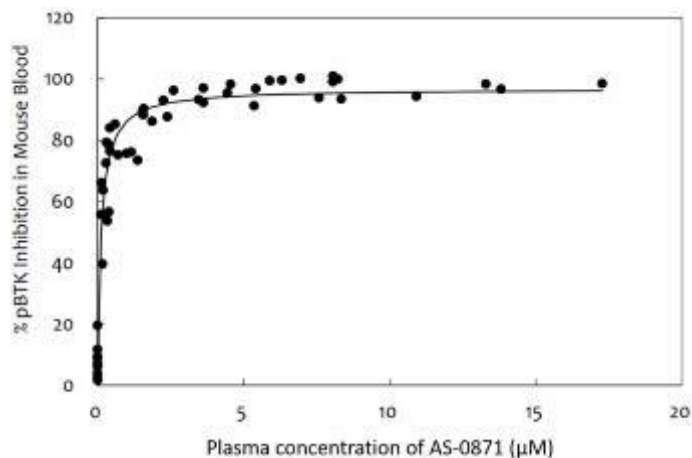
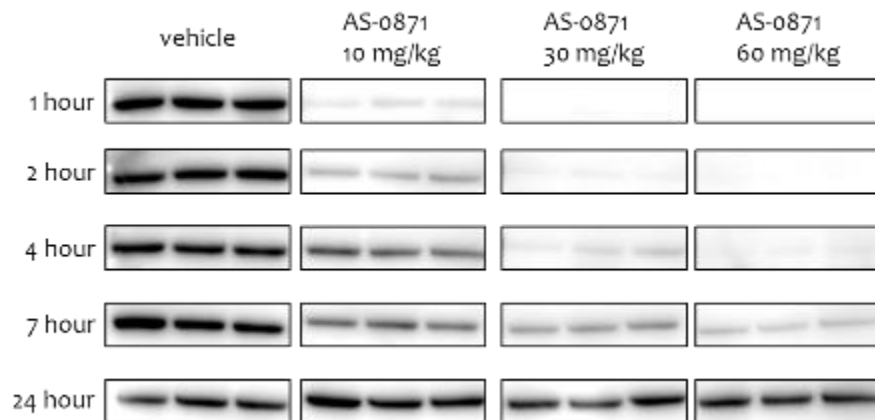
IC<sub>50</sub>  
 < 10 nM ●  
 10 – 100 nM ●  
 100 – 1000 nM ●



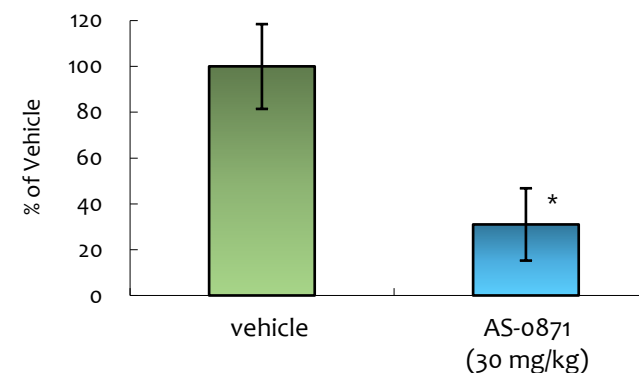
# AS-0871: In Vivo Therapeutic Efficacy

## ◆ PK/PD Study

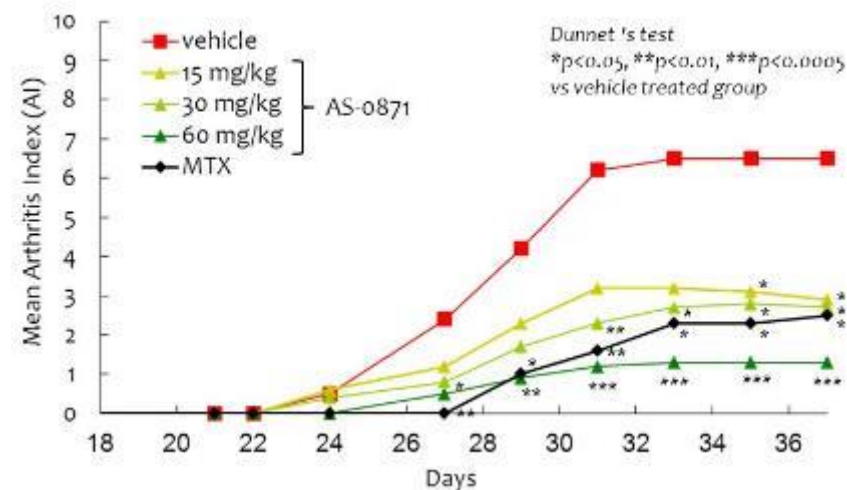
Auto-phosphorylation status of BTK was measured following oral single administration of AS-0871



## ◆ Passive cutaneous anaphylaxis (PCA) mouse model (n=5)



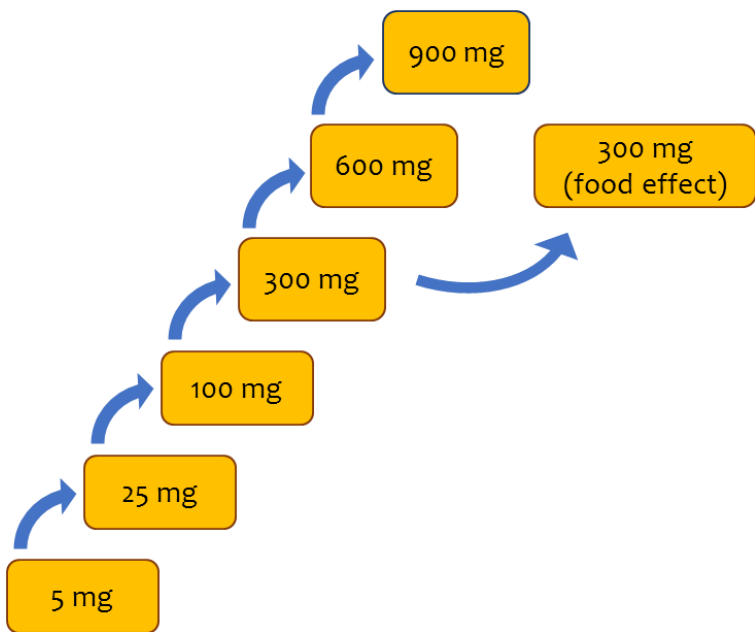
## ◆ Collagen-induced arthritis (CIA) mouse model (n=10)





## SAD Part (Completed)

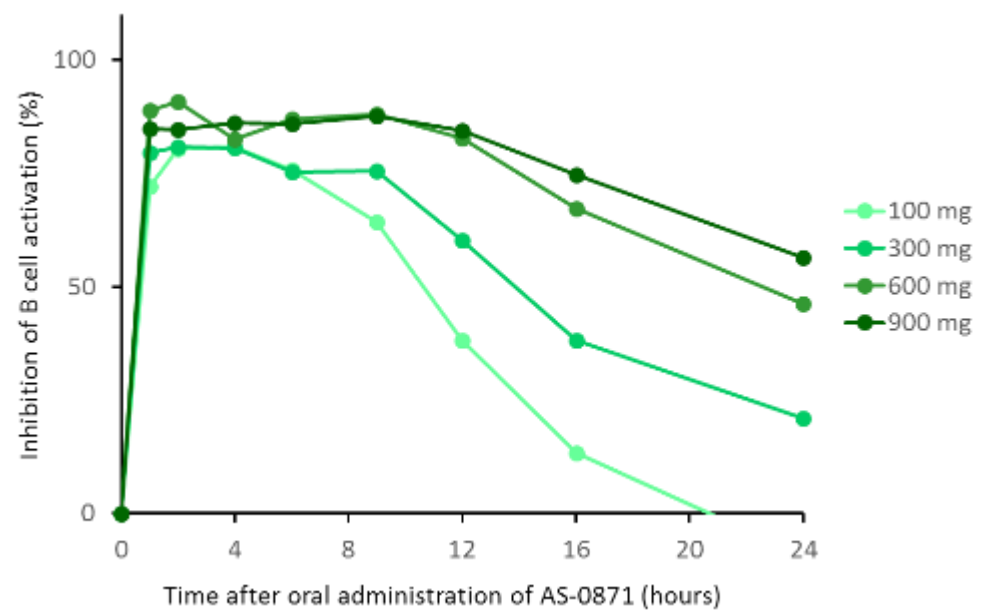
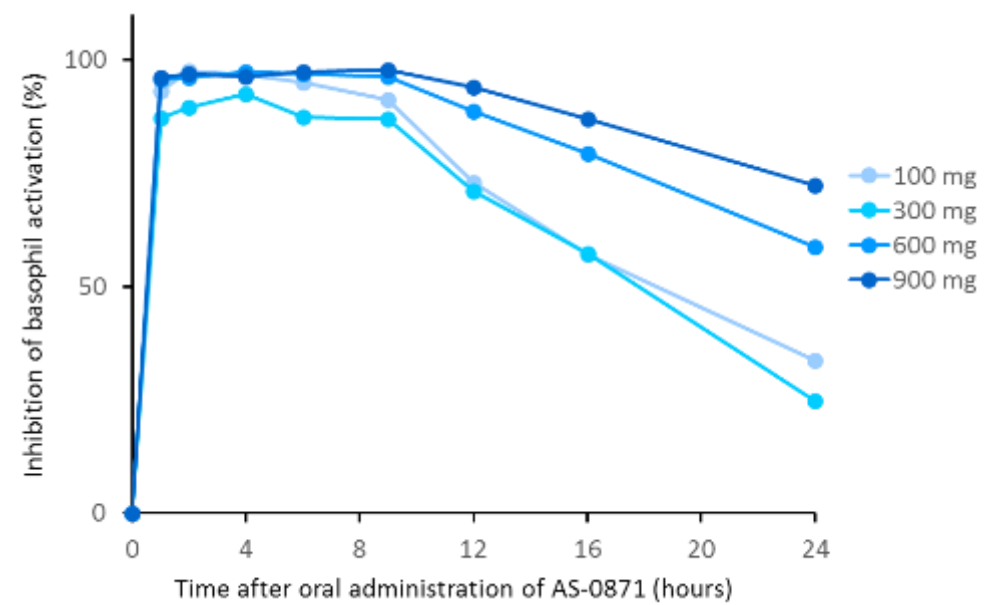
Step 1 Single Ascending Dose (SAD)	Step 2
<ul style="list-style-type: none"><li>• 6 dose levels (8 subjects/cohort)</li><li>• Placebo controlled (6 active / 2 placebo)</li><li>• Safety and tolerability</li><li>• Pharmacokinetics and pharmacodynamics</li></ul>	<ul style="list-style-type: none"><li>• Food effect</li></ul>



- AS-0871 is well-tolerated without any safety concerns.
- Favorable pharmacokinetic profile.
- Blood samples to assess PD effects were analyzed for evaluation of the B-cell and basophil responses. Administration of AS-0871 at 100mg or above resulted in strong inhibition of B-cell and basophil activation.
- Switching to a new formulation in the MAD study.



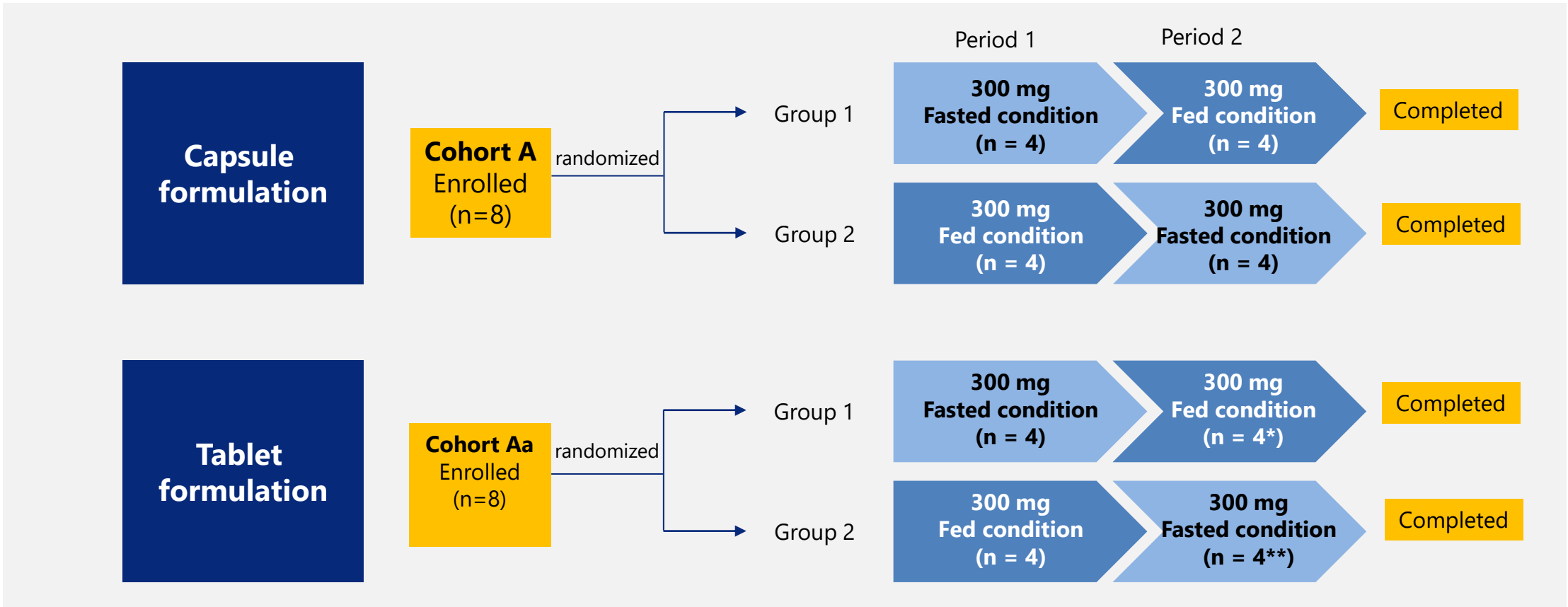
- Pharmacodynamic study demonstrated that subjects who received AS-0871 showed dose proportional inhibitions in basophil and B-cell activations, and significant and sustained inhibitory effects were observed at 100 mg and above.
- Oral administration of AS-0871 achieved therapeutic plasma levels needed to inhibit B cells and basophils activation, suggesting that AS-0871 has a potential to become a new treatment option for inflammatory diseases.





## Study Design of rBA/FE part

PK, safety, and tolerability after single-dose oral administration of AS-0871, formulated as capsules or tablets, were evaluated under fasted and fed conditions in an open-label, randomized, 2-period crossover design. Eight healthy subjects (Cohort A or Cohort Aa) were randomized to either Group 1 or Group 2 (4 subjects per group).



\*One subject vomited after dosing (considered not related to study drug), excluded from the PK analysis.

\*\*One subject withdrew from the study due to personal reasons before dosing.

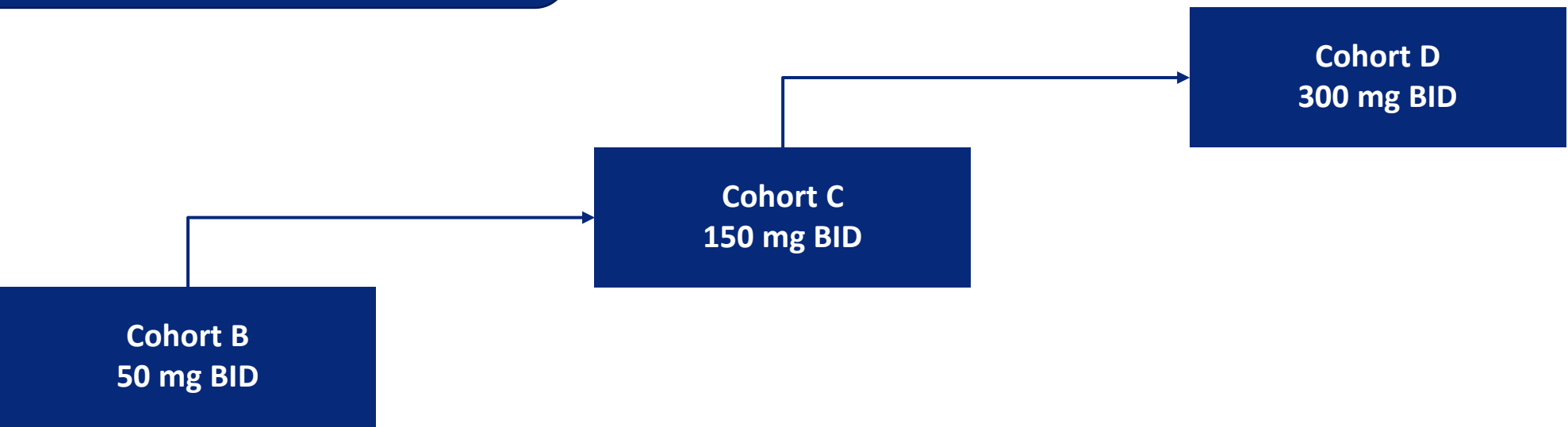




## Study Design of MAD part

- In the MAD part, safety, tolerability, PK, and PD of 3 multiple ascending doses of AS-0871, following 14-day multiple dose oral administration of AS-0871, will be investigated using a double blind, placebo-controlled, randomized design in 3 cohorts of 8 healthy subjects each.
- ◆ Dosing was completed as planned.
- ◆ The top-line results are expected in Q3 2023, after unblinding.

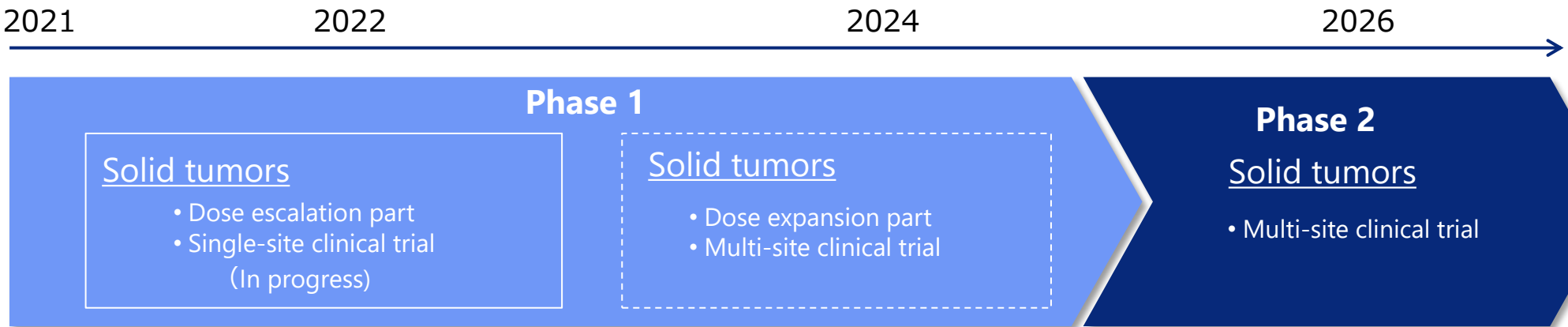
**14-days dosing for each cohort**





## AS-0141 : Targeting Cancer

- Small molecule CDC7 inhibitor
- High kinase selectivity
- Potential First-in-class drug
- Orally available
- Potent anti-proliferative activity against various cancer cell lines
- Demonstrated strong anti-tumor activity in several human tumor xenograft models
- Conducting Phase 1 study in Japan targeting solid tumors



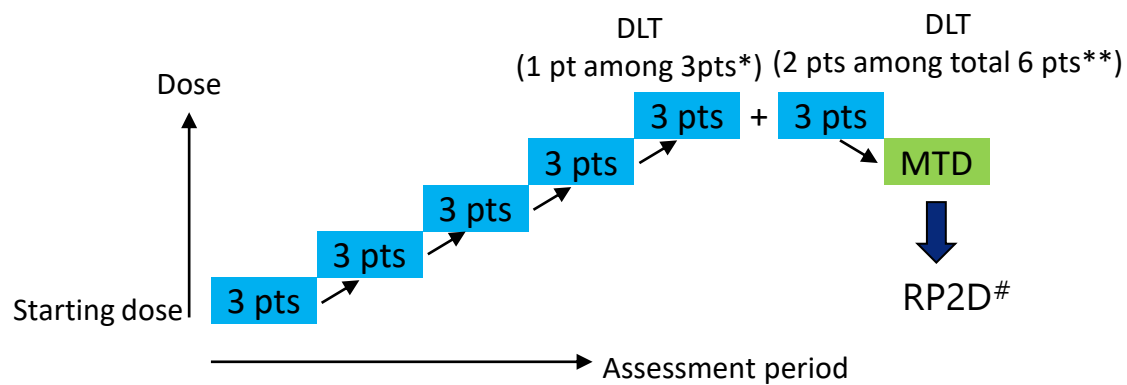


# AS-0141: Phase 1 Clinical Trial

## Phase 1 study targeting cancer patients

- Phase 1 study in patients with unresectable, advanced, recurrent, or metastatic solid tumors was initiated in Japan in H1 2021.
- The study consists of two parts, a dose escalation and an expansion.
- The primary objective is to assess safety, tolerability, maximum tolerated dose(MTD), preliminary anti-tumor activity, and PK / PD as well as to determine RP2D.
- The dose escalation part employs accelerated titration design.
  - One patient is treated per cohort unless a Grade  $\geq 2$  AE occurs during dose limiting toxicity (DLT) assessment period.
  - Switch to 3+3 dose escalation design when any Grade  $\geq 2$  AEs are observed during DLT assessment period.

### Standard 3+3 Dose Escalation part (Image)

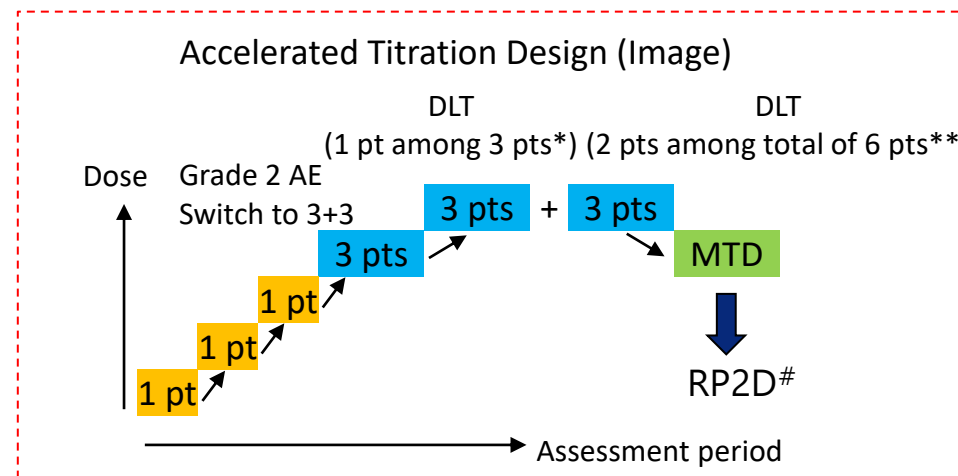


\* No more patients will be added to this cohort if 2 pts among 3 pts experience DLT.

\*\* If only 1 pt experiences a DLT among 6 pts, 3+3 design will be continued with higher dose levels.

# Recommended dose level will be determined at MTD or lower dose level.

### AS-0141



pt/pts: patient(s)



- Favorable pharmacokinetic profile at dosages of 20 mg BID to 300 mg BID.
- The study was switched to 3+3 design as one Grade 2 AE was observed in Cohort 6 (300 mg BID).
- After switching to 3+3 design, 2 patients among 3 patients experienced dose-limiting toxicities (DLTs). The MTD is considered at the dose lower than 300 mg BID as 2/3 patients experienced DLTs.
- Additional patients are being enrolled at 150 mg BID to determine MTD and recommended dose level.

## ◆ Ongoing Phase 1 Dose escalation part

Cohort	Dose level (5d on/2d off)	Status	
1	20 mg BID	N=1	No G2 AE/No DLT
2	40 mg BID	N=1	No G2 AE/No DLT
3	80 mg BID	N=1	No G2 AE/No DLT
4	150 mg BID	N=1	No G2 AE/No DLT
5	250 mg BID	N=1	No G2 AE/No DLT
6	300 mg BID (switched to 3+3 design)	N=3	DLT (2/3 pts)



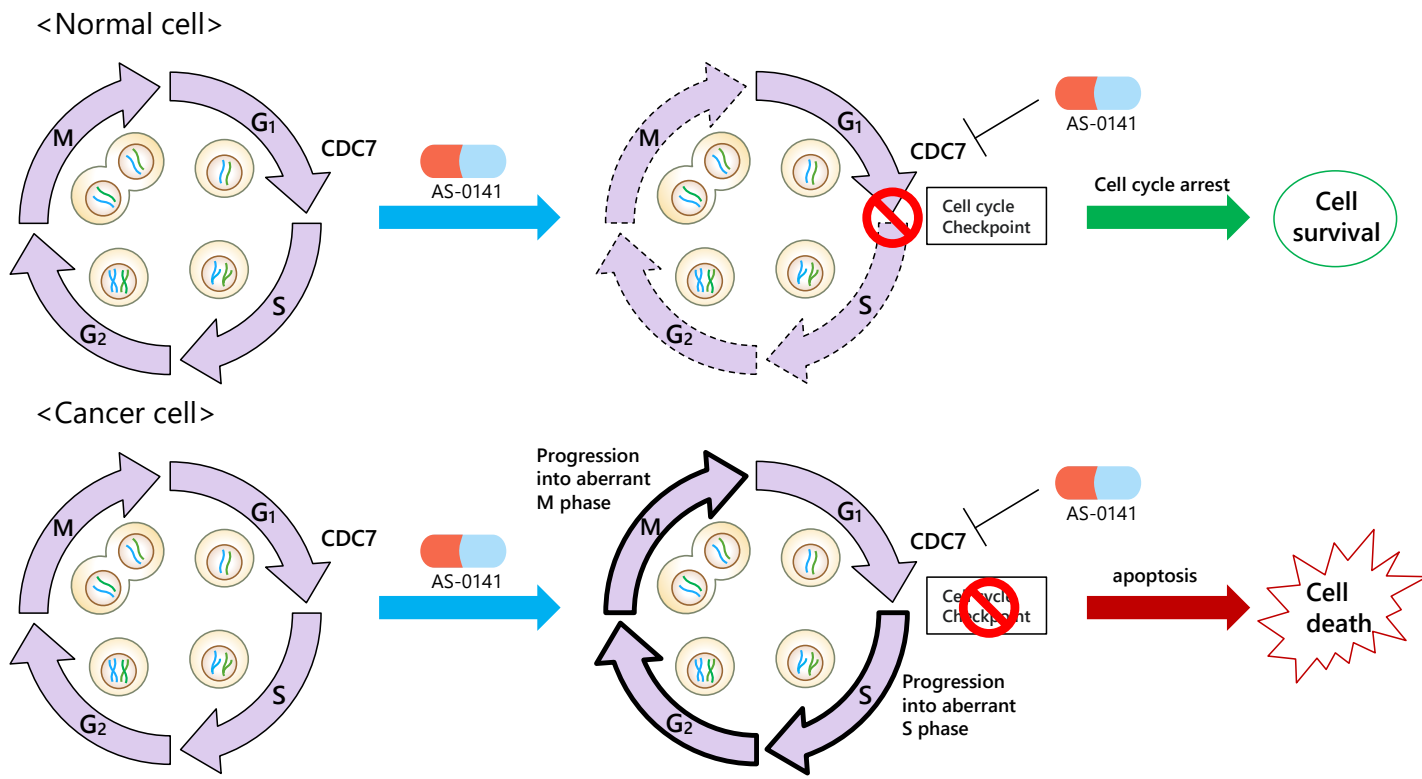
4	150 mg BID (3+3 design)		
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\*BID: Twice a day, 5d on/2d off: 5 days medication followed by 2 days drug holiday



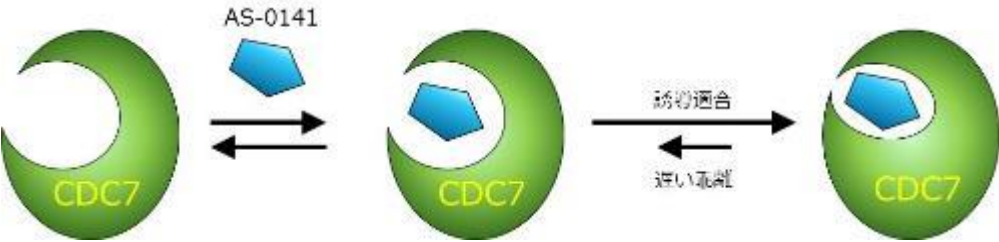
## CDC7 kinase inhibitor

CDC7 (cell division cycle 7) is a serine-threonine kinase that plays a critical role in DNA synthesis and is required for the activation of DNA replication origins throughout the S phase of the cell cycle. Inhibition of CDC7 in cancer cells causes lethal S phase or M phase progression, whereas normal cells survive, most likely through induction of cell cycle arrest at the DNA replication checkpoint. It has been reported in the literature that CDC7 is overexpressed in many cancers. Therefore, CDC7 is an attractive target for cancer drug development.





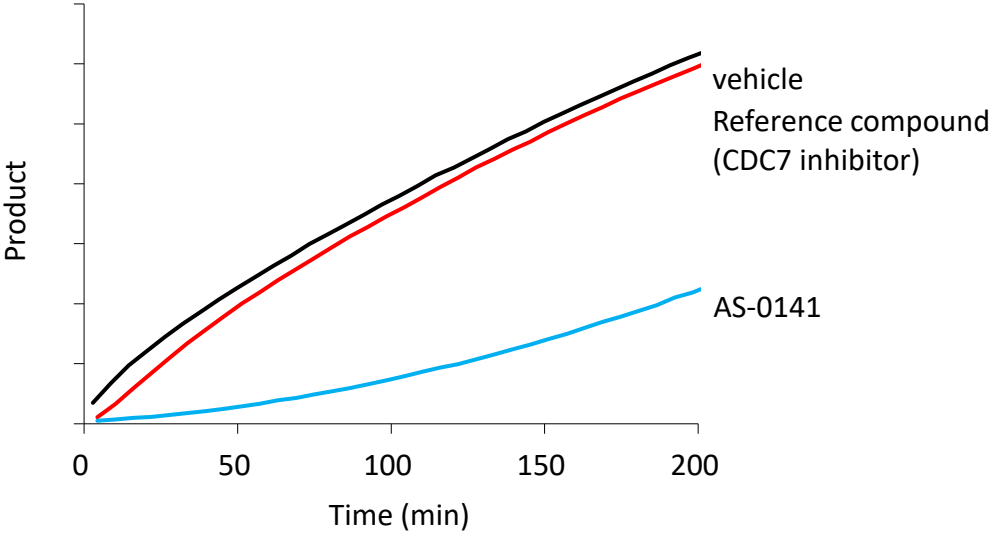
◆ AS-0141 has a unique inhibitory mechanism for CDC7 kinase (time-dependent inhibition)



Inhibitory potency (IC50) for CDC7 in the presence of 1 mM ATP	
Without Preincubation	With Preincubation
503 nM	2.4 nM

◆ AS-0141 inhibits CDC7 in a reversible fashion but has a very slow off-rate

Rapid dilution assay for Cdc7 inhibitors. Recovery of enzymatic activity was monitored by formation of the phosphorylated product.

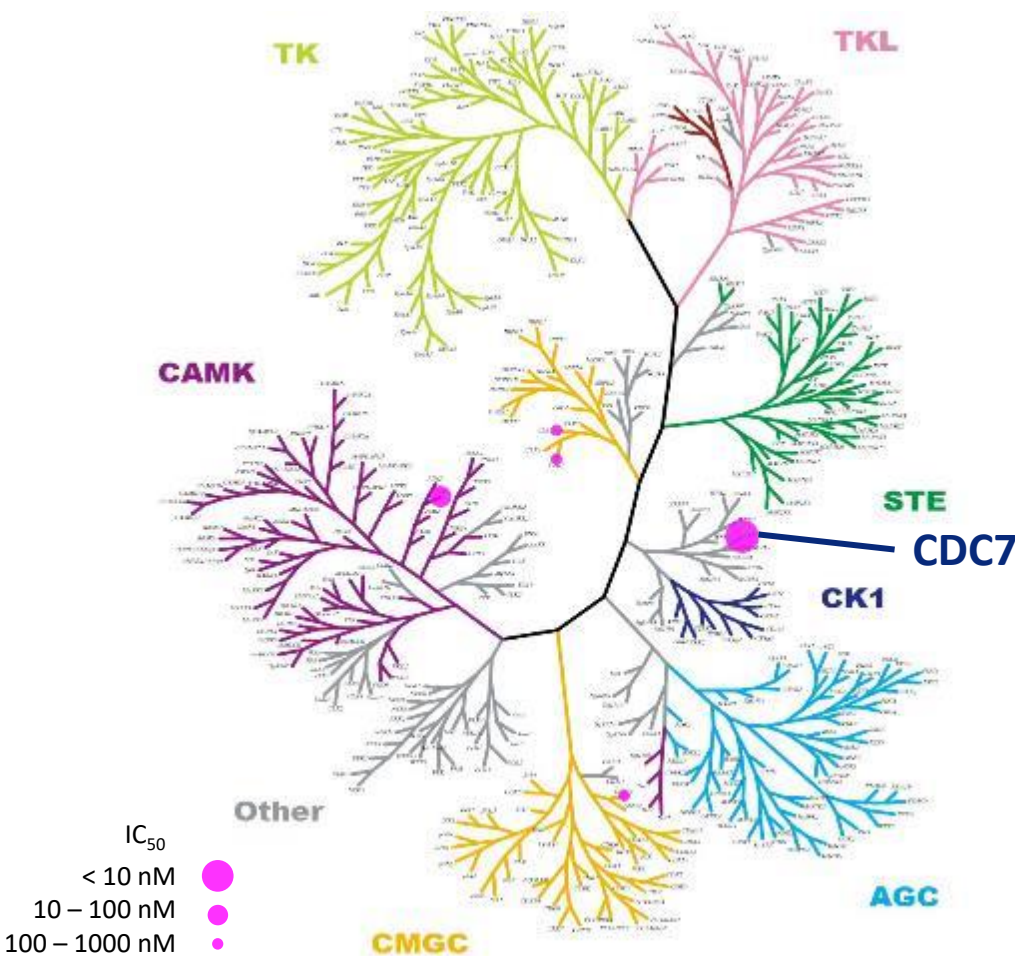


J Med Chem. 2021 Oct 14;64(19):14153-14164.



## ◆ Kinase Selectivity Profiling

In the presence of 1 mM ATP with preincubation



## ◆ IC50 values of hit kinases (at 1 mM ATP)

	IC <sub>50</sub> (nM)	
	Preincubation	
	-	+
CDC7	503	2.4
PIM1	30	34
CLK1	212	206
CLK2	270	227
GSK3α	189	251

CDC7 is the only kinase that shows preincubation effect

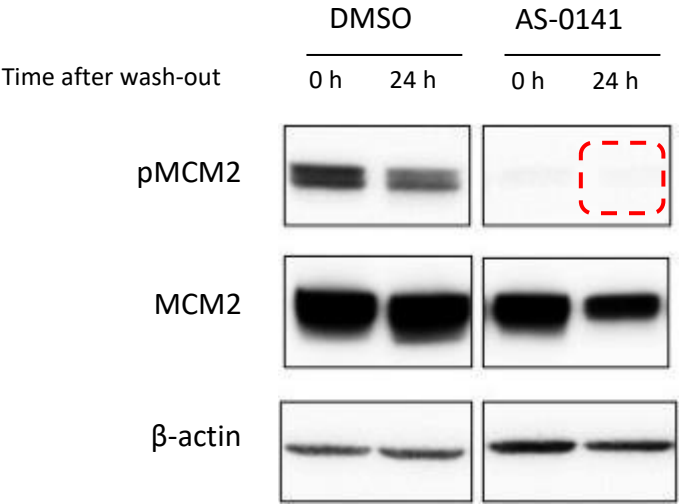




# AS-0141: Strong Cellular Activity

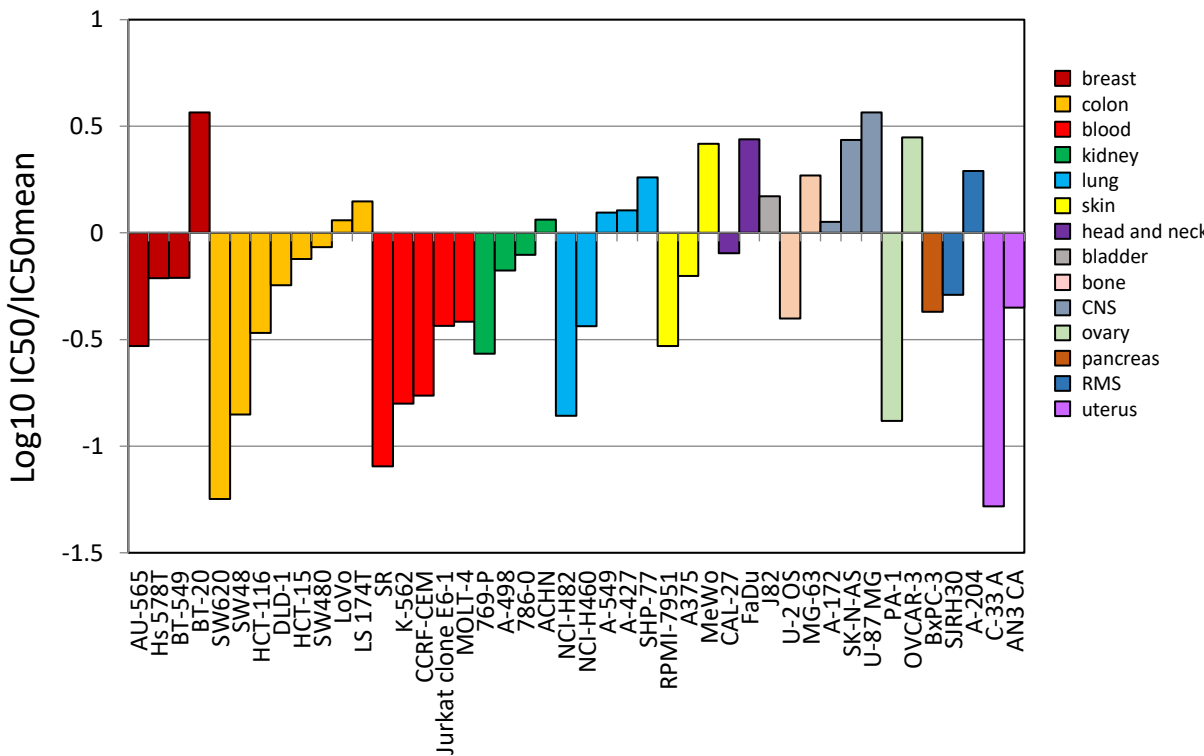
## ◆ Prolonged inhibition in cells

Human colon cancer cell line, Colo-205 cells were treated with DMSO control or AS-0141. After washout of the inhibitor, the cells were further incubated in the same media for 0 or 24 h and subjected to western blot analysis.



the inhibitory effect of AS-014 on the phosphorylation of MCM2 in cells continued up to 24 h after washing out

## ◆ AS-0141 potently inhibited growth in a wide range of tumor cell lines, including solid and hematological tumors

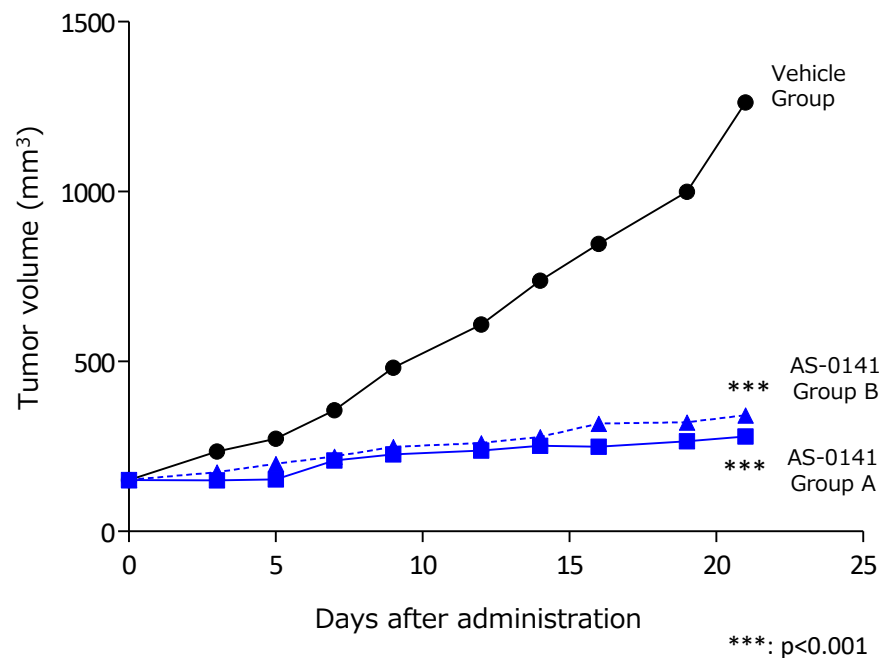


44 Cancer cell lines (Oncolines at NTRC)

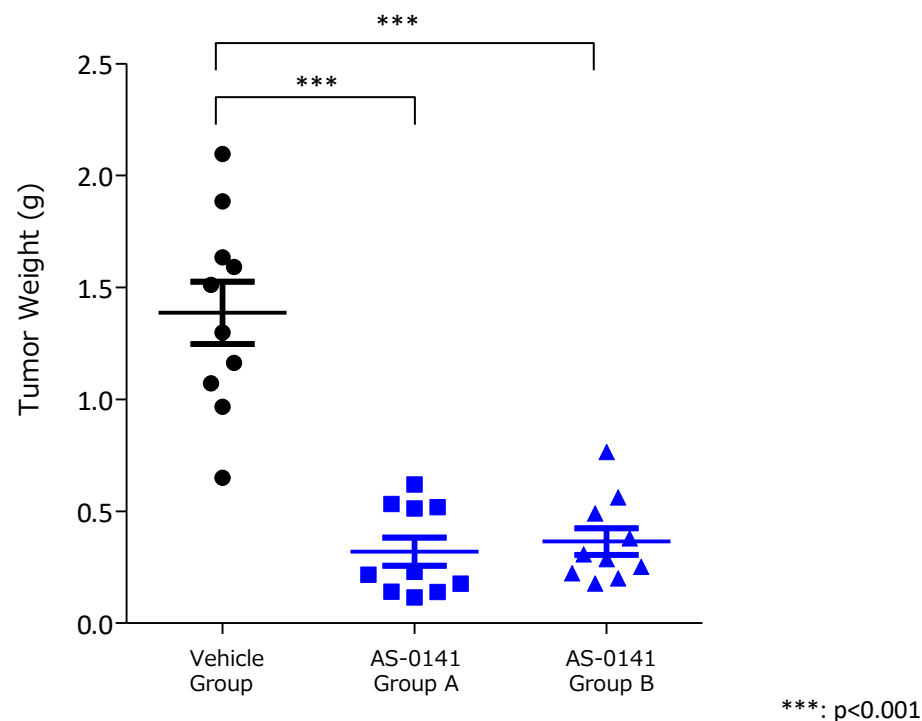


## In vivo antitumor efficacy of AS-0141 in a SW620 (human colon cancer) xenograft mouse model

Tumor Growth Curve (Mean, n = 10)



Final Tumor Weight of Each Mouse



AS-0141 group A: 60 mg/kg TID, 4d ON/2d OFF  
AS-0141 group B: 120 mg/kg QD



“Carna” is a goddess of Roman mythology who takes care of human health, protecting the human heart and other organs as well as everyday life, and is said to be the root for the word “cardiac.”

The word “biosciences” is derived from the words 'biology' and 'life sciences.'

Carna Biosciences has created contemporary Carna goddess with protein kinase.

## **Carna Biosciences, Inc.**

### **Corporate Planning**

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Chuo-ku, Kobe 650-0047

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