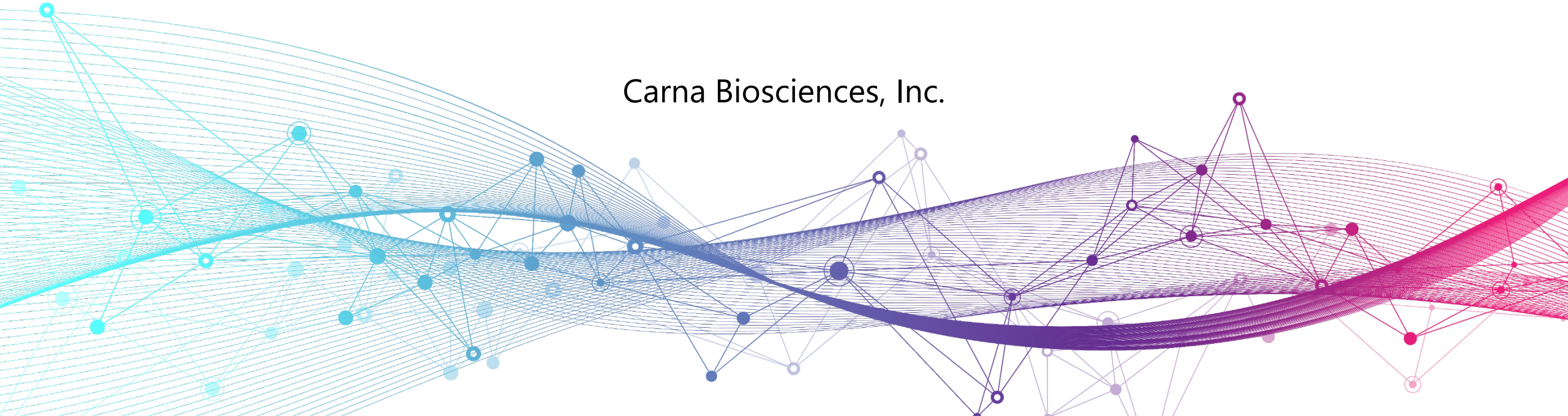
Financial Results
Q2 FY2023

(April to June 2023)

Carna Biosciences, Inc.



AGENDA

1. FY2023 Q2 Results
2. Updates on Pipelines in Clinical Development
3. Updates on Licensed Pipelines
4. Appendix

Q2 FY2023 Key Highlights

ddRD business

- BTK inhibitor AS-1763: The first patient was dosed in Phase 1b study in August 2023.
- A patent application filed jointly with Gilead: Received a notice of allowance in the U.S. in July 2023.

ddSP business

- Sales were JPY500 mn, 55% progress to FY plan of JPY902 mn.
- Sales of kinase protein were JPY324 mn, reached a record-high for H1.

Company-wide

- The exercise of series 20th Subscription rights to shares was completed in April 2023.
- All the unexercised series 19th subscription rights to shares expired at the end of the exercise period in August 2023.

ddRD: Drug Discovery R&D business
ddSP: Drug Discovery Support business

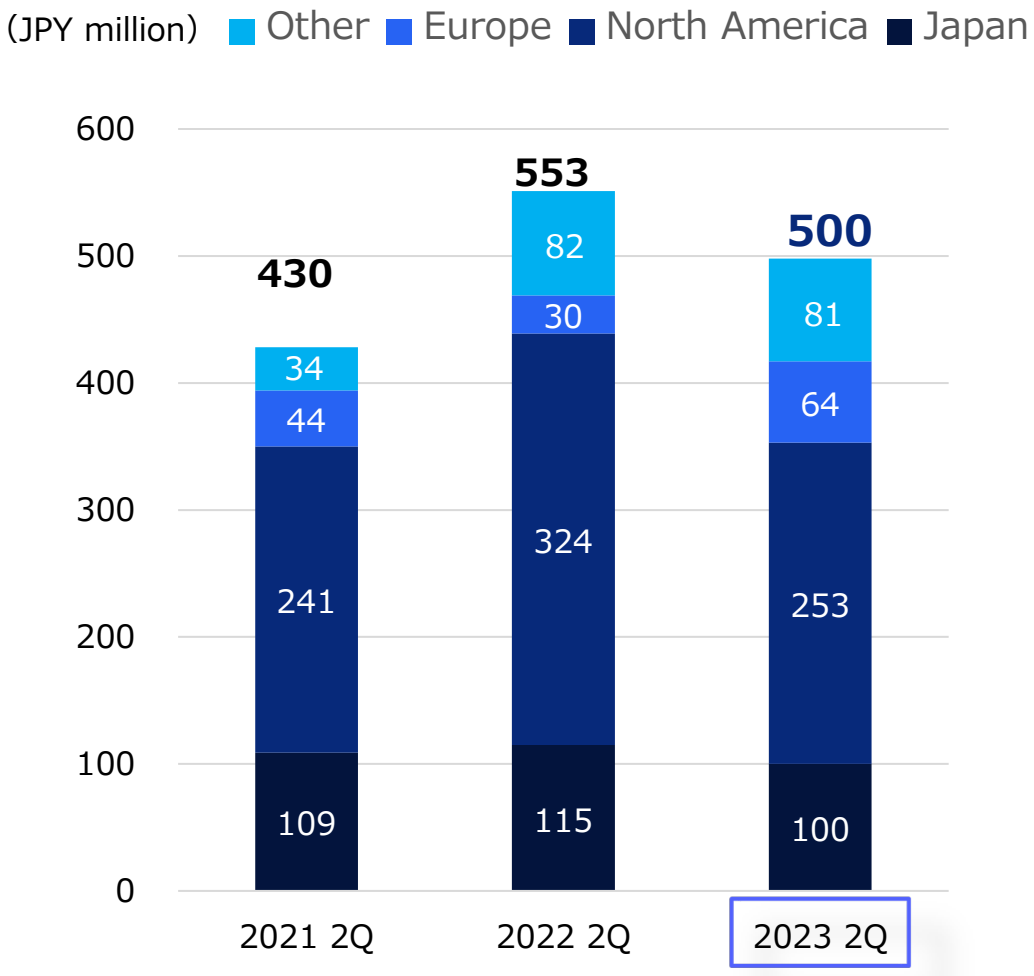
FY2023 Q2 Results by Business Segment

(JPY million)	Q2FY2022 Actual	**Q2FY2023 Actual**	YoY Change	FY2023 Plan as of Feb 10	vs. FY Plan	
Total Sales	839	**500**	-338 -40.4%	902	55.5%	
ddSP business	553	**500**	-52 -9.6%	902	55.5%	• Sales were on track to achieve FY plan. • While sales of kinase proteins were solid, overall sales declined YoY as revenue related to the license agreement with Gilead contributed to FY2022 sales.
ddRD business	286	**—**	-286	—	–	• Received an upfront payment from FRTX and a milestone payment from BioNova in FY2022.
Total Operating Profit/Loss	-312	**-863**	-551	-1,890	—	
ddSP business	235	**169**	-65 -28.0%	221	76.6%	• Strong sales of highly profitable protein accelerated the operating profit growth toward FY plan achievement. • Operating profit declined YoY due to a decrease in sales.
ddRD business	-547	**-1,033**	-485	-2,111	—	• Received an upfront payment and a milestone payment in 2022. • Operating loss increased YoY due to the increase in R&D expenses.
Ordinary Profit/Loss	-306	**-868**	-561	-1,911	—	
Net Profit/Loss	-359	**-885**	-526	-1,936	—	
R&D Cost	745	**959**	+213	1,968		• Invested in the programs in clinical trials.

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 Q2 Drug Discovery Support Business Sales Trend

Drug Discovery Support Business Sales Trend by Region (Consolidated)



Japan

Decreased 12.9% YoY

- Sales of kinase proteins and profiling service both decreased due to a lack of large orders.

North America

Decreased 21.8% YoY

- Sales of kinase proteins increased significantly.
- Demand from biotech companies including AI-driven drug discovery companies remained strong.
- Overall sales declined YoY as sales from Gilead contributed to FY2022 sales.

Europe

Increased 110.0% YoY

- Thanks to the continuous order from AI-driven drug discovery companies, sales of kinase proteins were very strong.

Other

Decreased 1.3% 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 Jun.30, 2023	Change	Reason for changes
Current assets	4,104	4,407	+303	Cash and deposits +305
Cash and deposits	3,379	3,684	+305	Amount raised from exercised share options +1,274
Non-current assets	162	157	(4)	
Total assets	4,266	4,565	+298	
Current liabilities	436	325	(111)	Accounts payable -97 Current portion of long-term debt -14
Non-current liabilities	188	128	(60)	Long term loans payable-59
Total liabilities	624	453	(171)	
Total net assets	3,641	4,111	+469	Capital stock and capital surplus +1,340 Retained earnings -885
Total liabilities and net assets	4,266	4,565	+298	

Shareholders' equity ratio	85.0%	89.9%
BPS	255.0yen	240.06yen
PBR	2.0x	3.0 x
Share price of Carna	520yen	716yen

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

Financing

<20th Subscription Rights to Shares >

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

Cash and deposits as of the end of June 2023 : 3,684million 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

Pipelines in Clinical Development

Compound	Target	Indication	Status
AS-1763	BTK	Blood Cancer	• Phase 1 SAD and BA part in healthy volunteers were completed in the Netherlands. • In August 2023, the first patient was dosed in Phase 1b study in the U.S.
AS-0871	BTK	Immune-inflammatory diseases	• Phase 1 study in healthy volunteers is in progress in the Netherlands. • SAD study and BA part of MAD study were completed. • Dosing in MAD part of MAD study has been completed. • Top-line results will be available in Q3 2023 (the CSR expected in Q4 2023).
AS-0141	CDC7/ ASK	Cancer	• Phase 1 study in cancer patients is in progress in Japan. • Dose escalation part is on going.

CSR: Clinical Study Report

AS-1763: Highlights

Refer to P.27-P.36 for more information

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.**

AS-1763: Ph I Clinical Trial in Health Volunteers

Ref. P.28, P.32-P.35

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.

AS-1763: Phase 1b Clinical Trial

Ref. P.36

Clinical trails in progress	Phase 1b study in the U.S.: Open and enrolling.
Indication	Patients with CLL(Chronic Lymphocytic Leukemia), SLL(Small Lymphocytic Leukemia), and B-cell NHL(B-cell non-Hodgkin Lymphoma).
Status	**The dose-escalation ongoing; The first patient was dosed with AS-1763 in August 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 inhibitors 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 inhibitors

↓

- Next generation **non-covalent BTK inhibitors** including AS-1763 are expected to be promising therapeutic options for the patients who have developed resistance to covalent BTK inhibitors. Our goal is to take a certain share of this potential large market, making AS-1763 a blockbuster drug.
- We regained the development and commercialization rights in Greater China from BioNova, aiming to partner with major pharmaceutical companies for global license.

BTK Inhibitors in clinical development

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 an 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.

AS-0871: Highlights

Ref. P.37-P.44

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 inhibits BTKs to reduce safety concerns associated with covalent inhibitors.

AS-0871: Ph I Clinical Trial in Health Volunteers

Ref. P.38, P.41-P.43

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.

AS-0871: Updates on Phase 1 Study

Ref. P.44

Status

Dosing in MAD part of MAD study was completed as planned.
Top-line results will be available in Q3 2023 (the CSR expected in Q4 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 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 potential large market

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

Competitors

Compound	Company	Development Phase
Remibrutinib (LOU064)	Novartis	P3

Novartis announced a positive Ph 2b result that remibrutinib rapidly and effectively improved the symptoms of patients whose CSU was inadequately controlled. *

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

Opportunity

- Approval of new treatment options may trigger the expansion of CSU market.
- We plan to pursue the clinical implications of AS-0871 (non-covalent BTK inhibitor) to provide clinical benefits by minimizing potential adverse events associated with covalent BTK inhibitors including remibrutinib.

AS-0141: Highlights

Ref. 45-P.52

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 a first-in-class drug as no CDC7 inhibitors have been approved.

AS-0141: Phase 1 Clinical Trials

Ref. P.46-P.47

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 lower dose levels to evaluate safety and tolerability and to determine MTD as well as recommended dose level and administration for the expansion part.

Updates on Licensed Pipelines

1. **DGKα 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
DGKα inhibitor Gilead Sciences (Out-license)	GS-9911 (Immuno-oncology)	$20M	$450M	Undisclosed	Worldwide	Jun. 2019	$10M (Dec. 2021)
STING inhibitor 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	

DGKα Inhibitor

Partner

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 DGKα inhibitor: GS-9911

- GS-9911, as well as its target kinase, was introduced for the first time 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.

STING Inhibitor

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

Deal size	• Upfront payment $2 million • Maximum of $258 million potential milestone payments upon achievement of certain development and commercial milestones
Royalties	• Tiered royalty payments ranging up to 10% of net sales

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.**

Joint Research with Sumitomo Pharma

Partner	Sumitomo Pharma Co., Ltd. Joint Research Agreement in March 2018 (worldwide rights)
Deal size	• Upfront payment + Research milestone JPY80 million • Maximum of JPY10.6 billion potential milestone payments upon achievement of certain development and commercial milestones
Royalties	• Royalties on future net sales

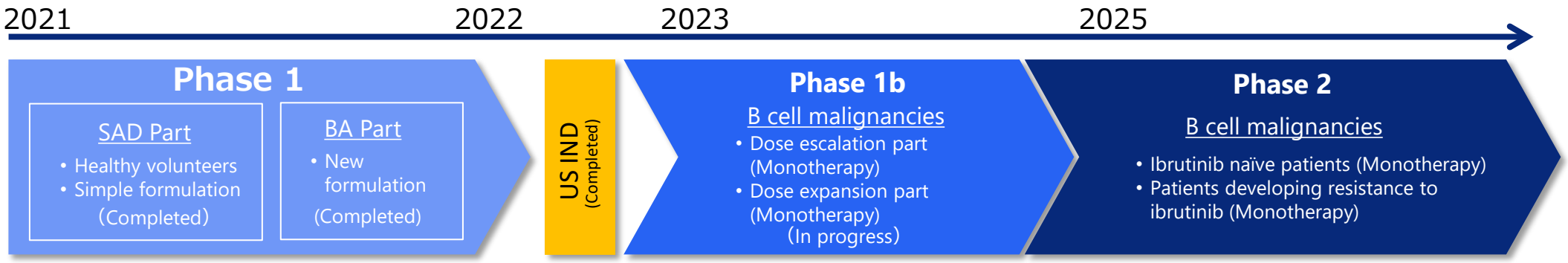
1. **Joint research to discover novel kinase inhibitors to treat psychiatric and neurological disorders.**
2. **The term of the joint research was extended in December 2021.**
3. **Joint research is ongoing to identify preclinical candidates.**

Appendix

AS-1763: Next Generation BTK Inhibitor

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
- The first patient was dosed in August 2023 in Ph 1b study in the U.S.



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

Phase 1 in the Netherlands
(Healthy volunteers)

Completed

SAD Part

Evaluated the safety, tolerability and PK using simple formulation

- Completed dosing in SAD part
- Favorable Pharmacokinetic Profile
- Safe and well-tolerated
- Promising Pharmacodynamic effects

BA Part

Evaluated relative bioavailability using new formulation

- Pre-IND meeting
- IND submission

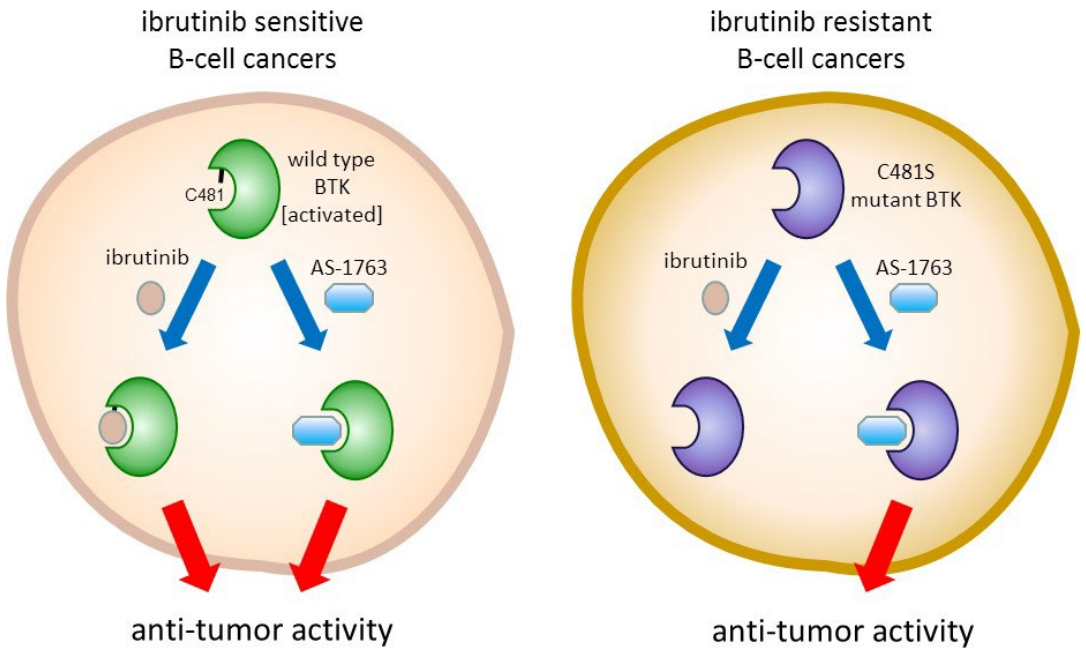
Completed

Phase 1b in the U.S.
(Patients with CLL/SLL/B-cell NHL)

On-going

◆ The first patient was dosed in Phase 1b study in August 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_{50} values of AS-1763 against wild-type and C481S-mutant BTK**

	IC_{50} (nM)	
	BTK[A]	BTK^{C481S}
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

CARNA BIOSCIENCES

◆ In vitro pharmacological activities of AS-1763

	IC_{50} (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

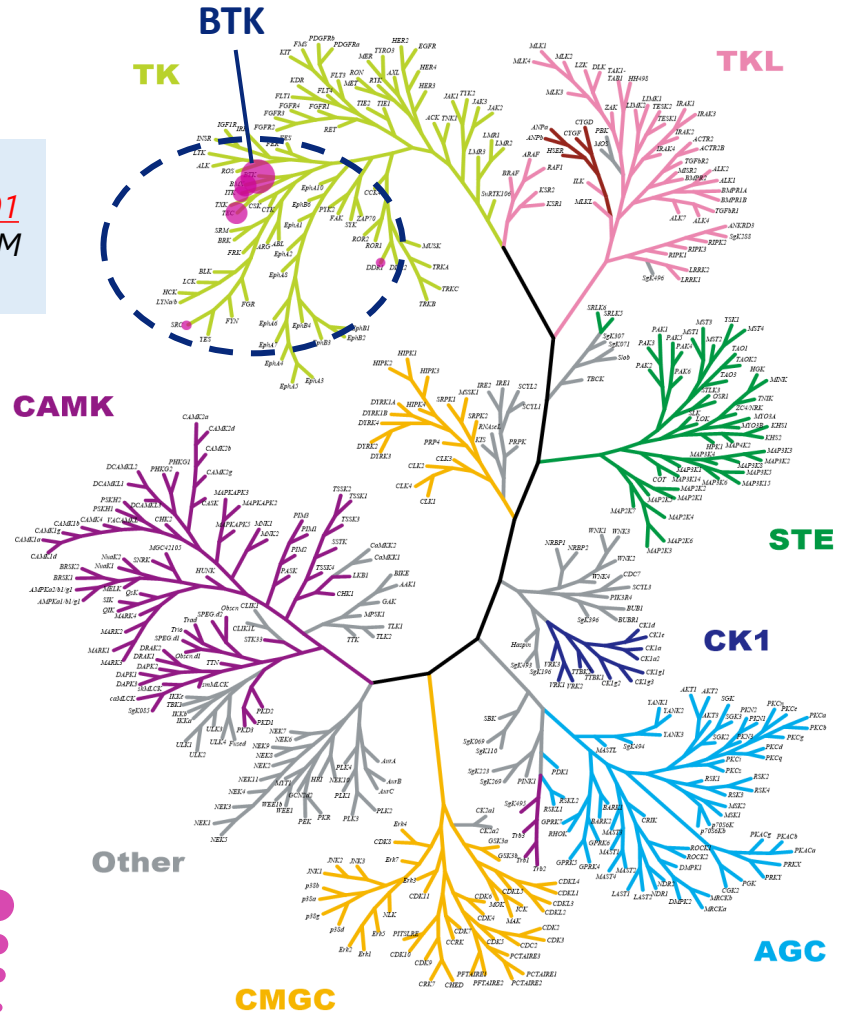
50-fold Stronger activity

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.

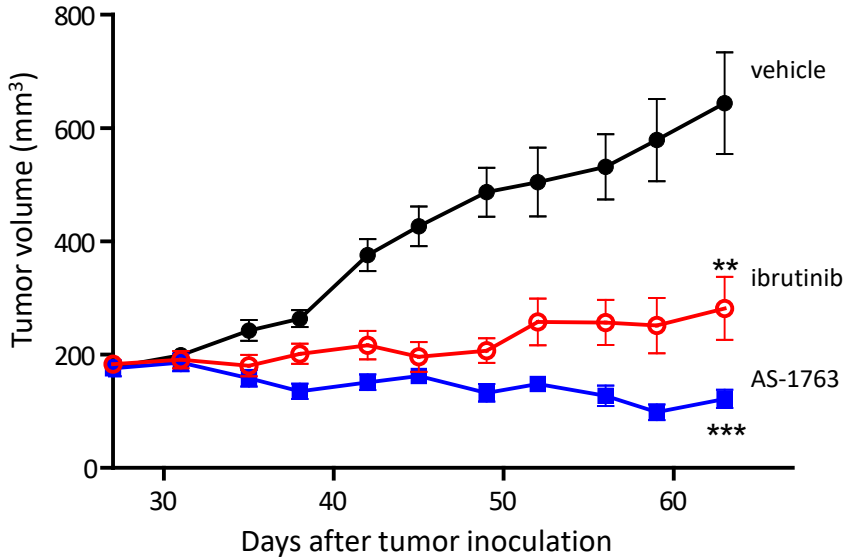
◆ Kinase selectivity profiling

Only inhibited 6 other kinases in a total of 291 kinases tested at 0.3 μM concentration.



AS-1763: In Vivo Antitumor Effect against BTK^{C481S} Mutant

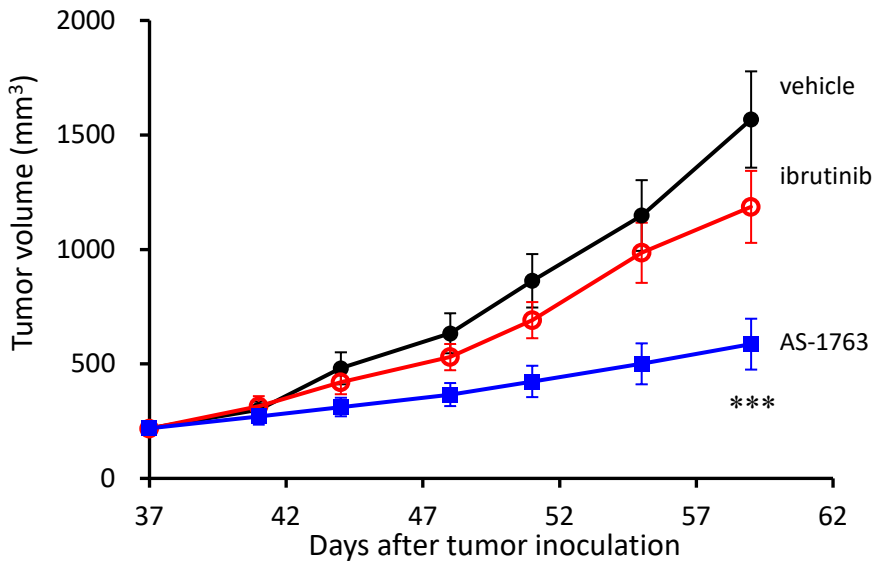
- **In vivo antitumor effects of AS-1763 on human B-cell non-Hodgkin lymphoma cell line, OCI-LY10 tumor xenograft mouse model (n=8-10)**



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 BTKC481S knock-in OCI-LY10 tumor xenograft mouse model (n=11)**



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

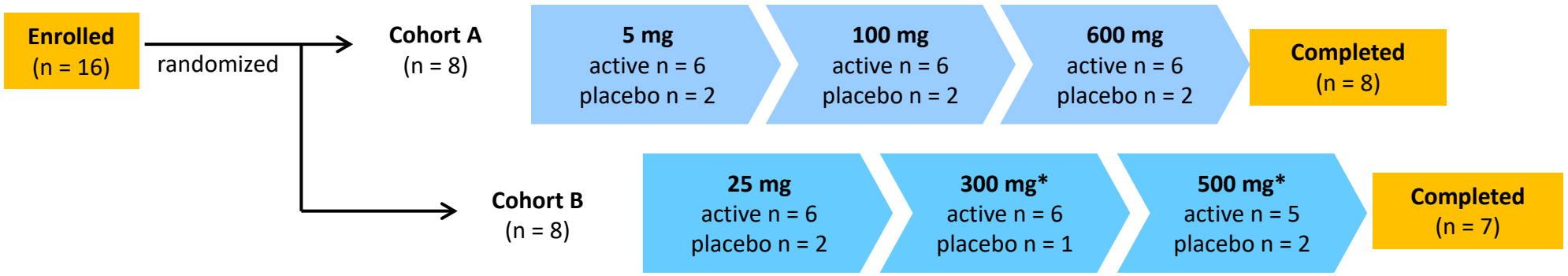
***: p<0.001

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

AS-1763: FIH Phase 1 Clinical Trial in Healthy Volunteers

Study Design

Step 1 Single Ascending Dose (SAD) Part	Step 2 Relative Bioavailability (BA) Part
• Double-blind, placebo-controlled, randomized FIH study • Simple formulation (solution) • 6 dose levels (8 subjects/cohort A, 8 subjects/cohort B) • 6 active / 2 placebo for each dose level • Safety and tolerability • Pharmacokinetics and pharmacodynamics (PD; CD69 upregulation on naïve B cells)	• Open label study • Another cohort of 8 subjects • The subjects were dosed with a single dose of AS-1763 100-mg tablet, and relative bioavailability with simple formulation was evaluated



*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.

AS-1763: SAD Part

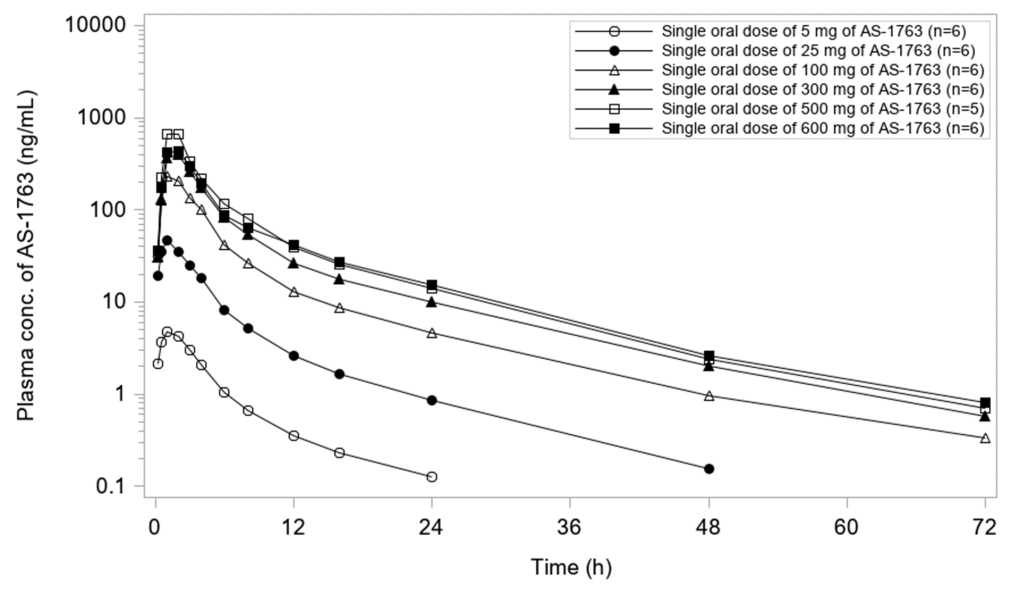
Safety and tolerability

- 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 tmax between 0.5 and 1.5 hours; mean t1/2 between 8.4 and 12.1 hours).
- Mean AS-1763 exposures generally increased with dose up to 500 mg.

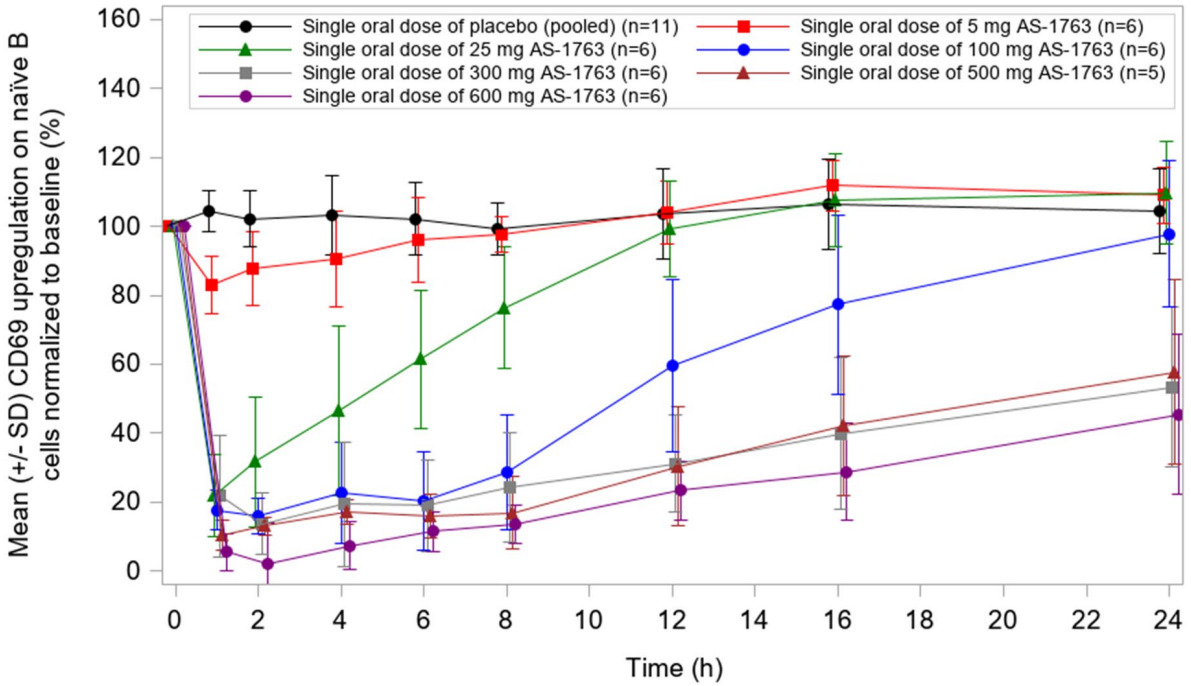
< Plasma concentration of a single oral dose of AS-1763 >



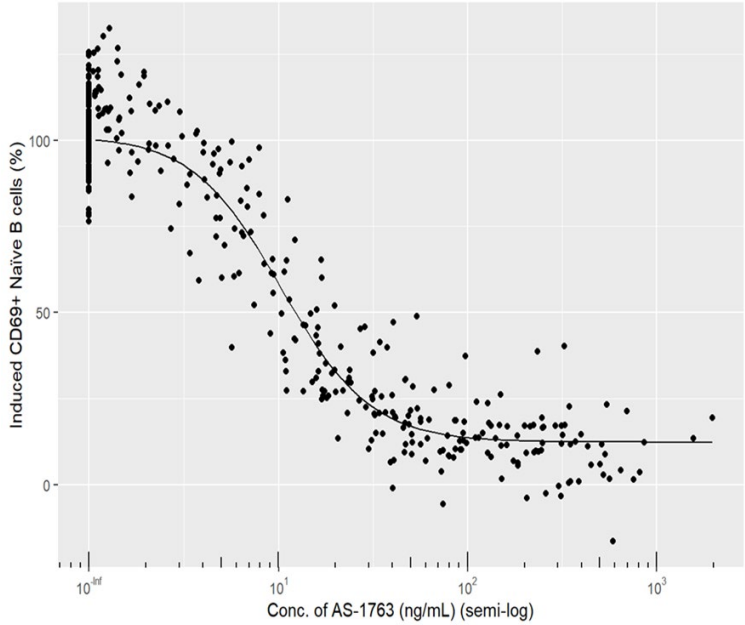
Pharmacodynamics of AS-1763

- Inhibition of B cell CD69 upregulation was observed for 5 mg onwards.
- Maximum inhibition (arbitrarily defined as ≥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 IC50 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 >



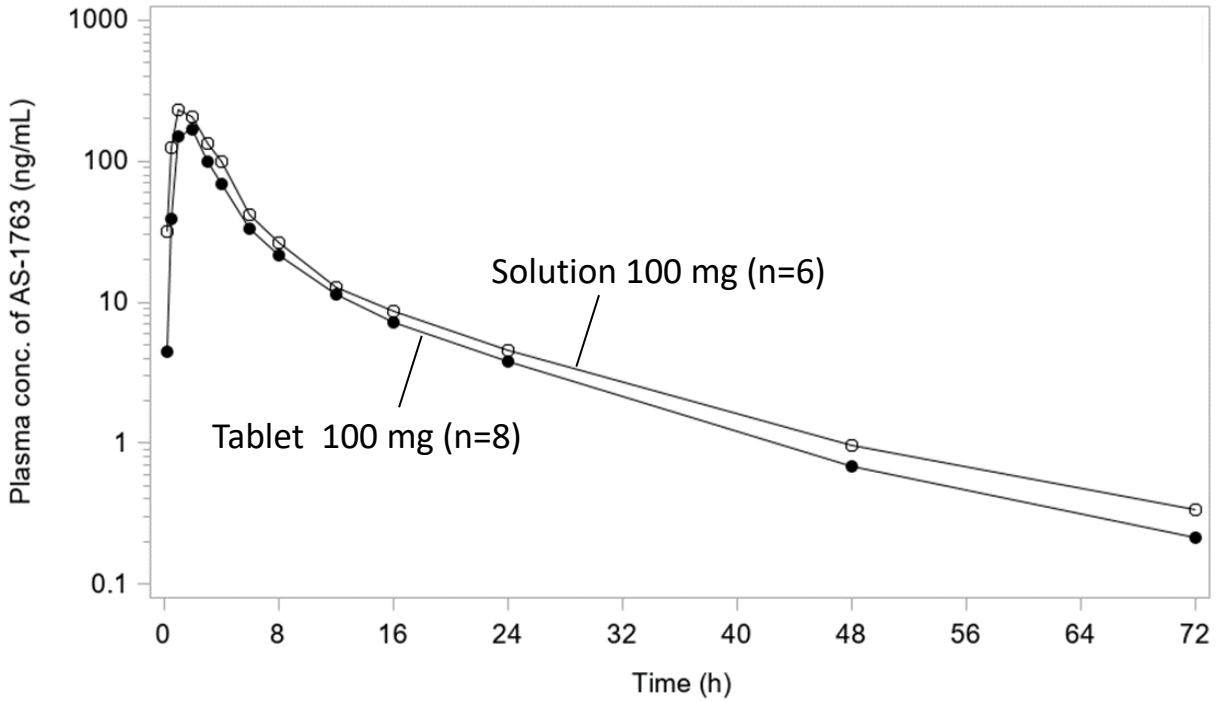
< PK/PD correlation analysis >



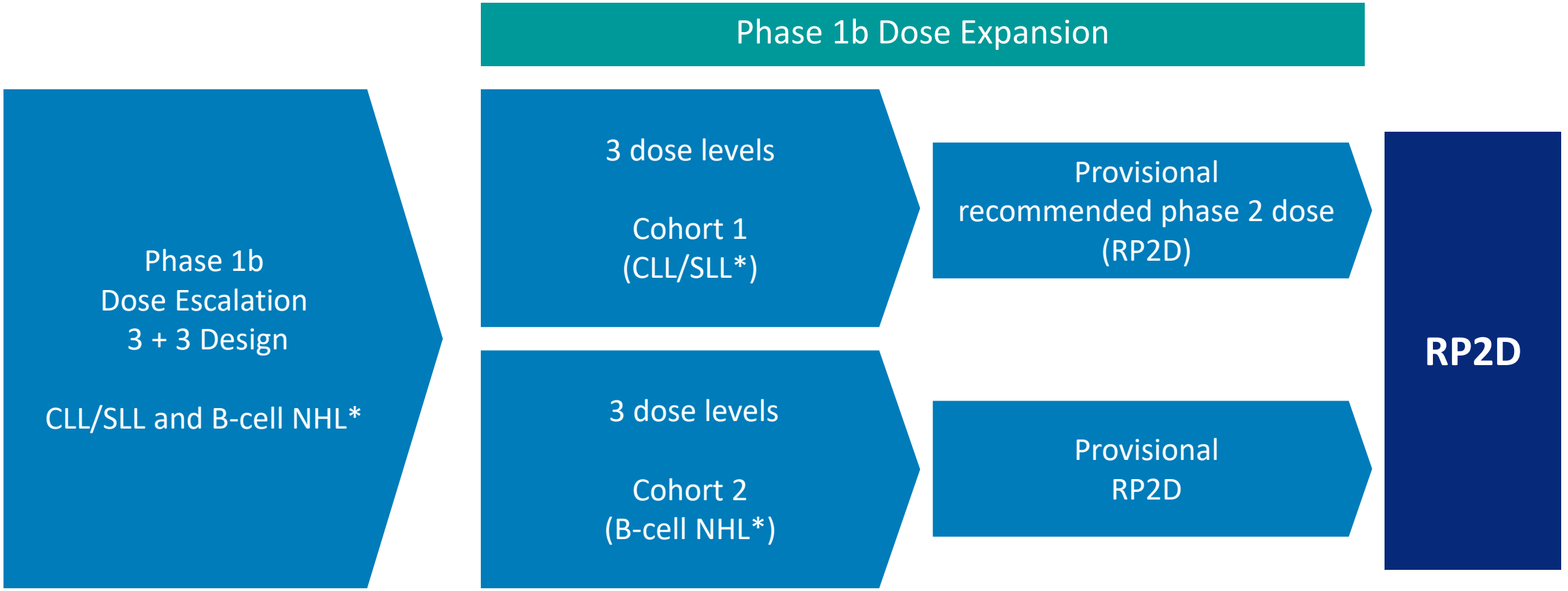
AS-1763: BA Part

- In the BA part, 100 mg tablet and the solution showed almost 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

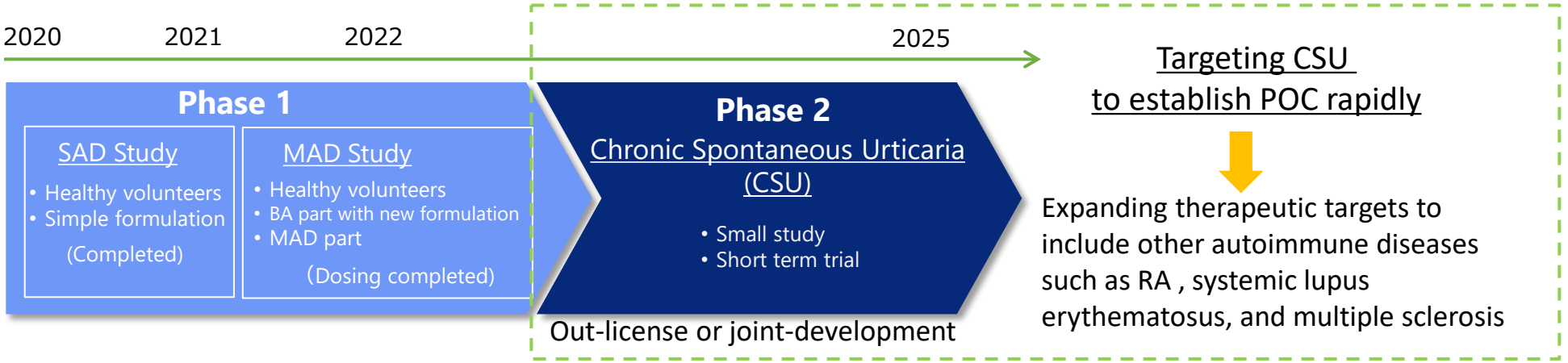
◆ **The first patient was dosed in August 2023.**

AS-0871: Non-covalent BTK Inhibitor

AS-0871 : Targeting Immune-inflammatory diseases

- Small molecule BTK inhibitor
- Non-covalent/reversible
- High kinase selectivity
- Orally available

- Demonstrated significant efficacies in arthritis models
- Showed efficacy in systemic lupus erythematosus model
- Dosing in Phase 1 MAD study was completed.
- Find a partner to conduct further development after completing Ph 1 study



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

AS-0871: Phase 1 Clinical Trial in Progress

Phase 1 in the Netherlands
SAD study (Healthy volunteers)

Completed

- 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

AS-0871: Excellent Kinase Selectivity

Targeting Inactive Conformation of BTK


Contents lists available at ScienceDirect
Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com/locate/bmcl

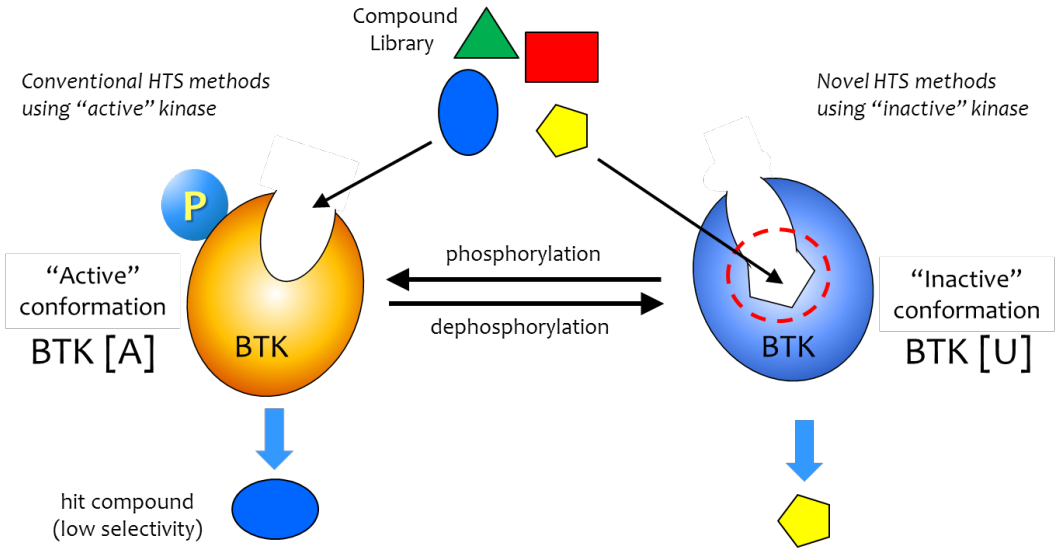
TR-FRET binding assay targeting unactivated form of Bruton's tyrosine kinase

Tokiko Asami *, Wataru Kawahata, Masaaki Sawa
Carna Biosciences, Inc., BMA 3F, 1-5-5 Minatojima-Minamimachi, Chuo-ku, Kobe 650-0047, Japan


Journal of Medicinal Chemistry
Article
pubs.acs.org/jmc

Design and Synthesis of Novel Amino-triazine Analogues as Selective Bruton's Tyrosine Kinase Inhibitors for Treatment of Rheumatoid Arthritis

Wataru Kawahata,* Tokiko Asami, Takao Kiyoi, Takayuki Irie, Haruka Taniguchi, Yuko Asamitsu, Tomoko Inoue, Takahiro Miyake, and Masaaki Sawa
Research and Development, Carna Biosciences, Inc., 3rd Floor, BMA, 1-5-5 Minatojima-Minamimachi, Chuo-ku, Kobe 650-0047, Japan

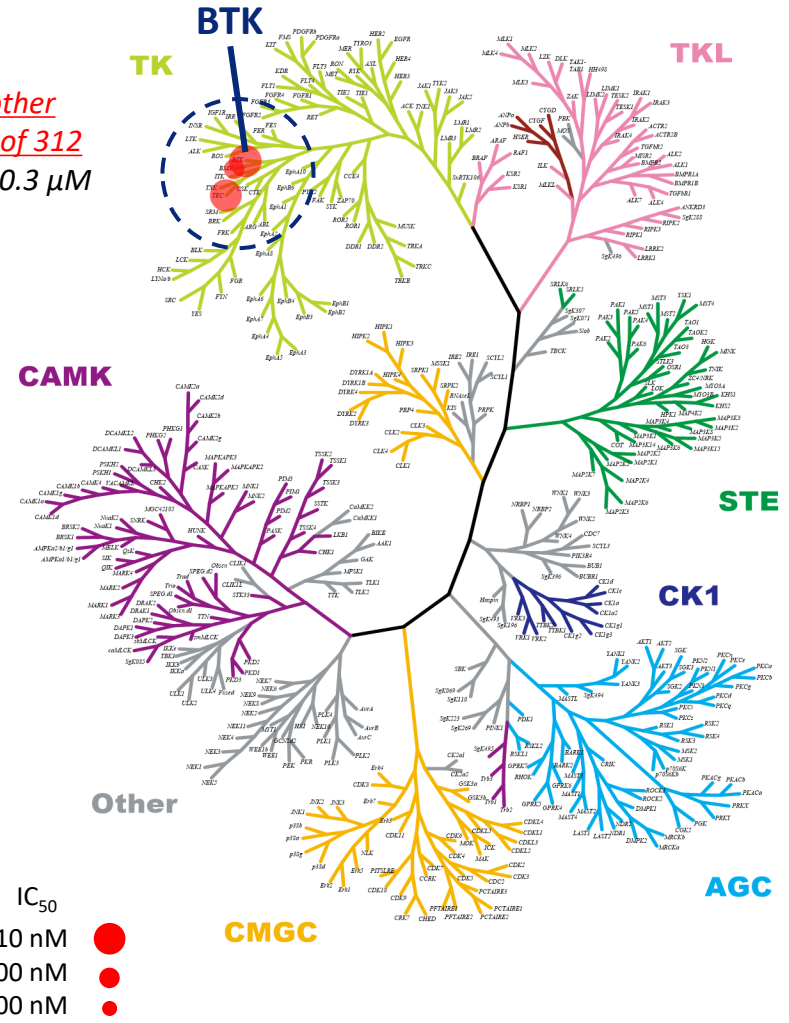


Bias classical ATP competitive inhibitors

	BTK IC_{50} (nM)	
	BTK[A]	BTK[U]
AS-0871	3.4	0.3

Kinase Selectivity Profiling

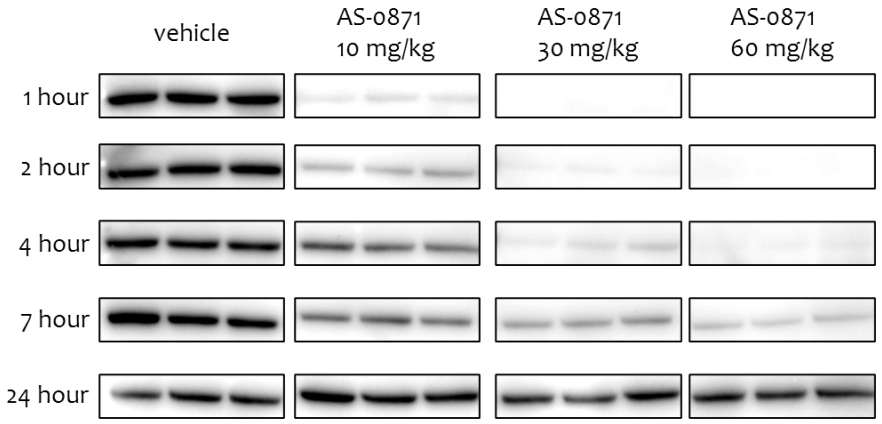
Only inhibited 2 other kinases in a total of 312 kinases tested at 0.3 μM concentration.

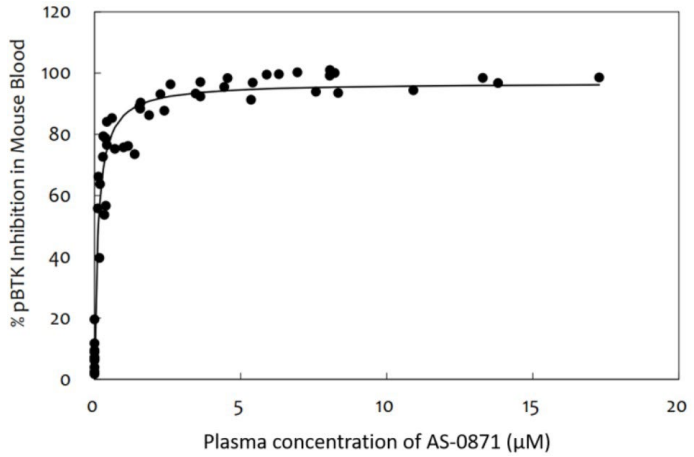


AS-0871: In Vivo Therapeutic Efficacy

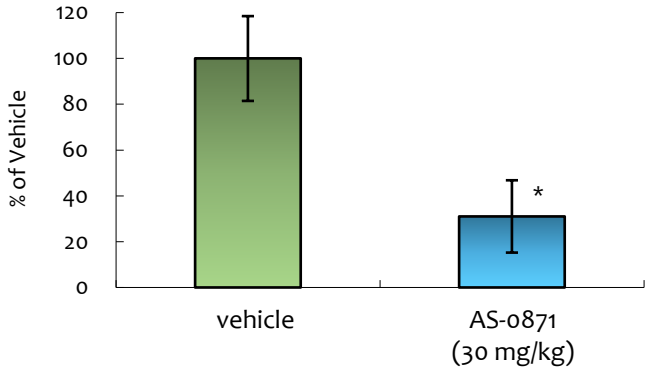
◆ PK/PD Study

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

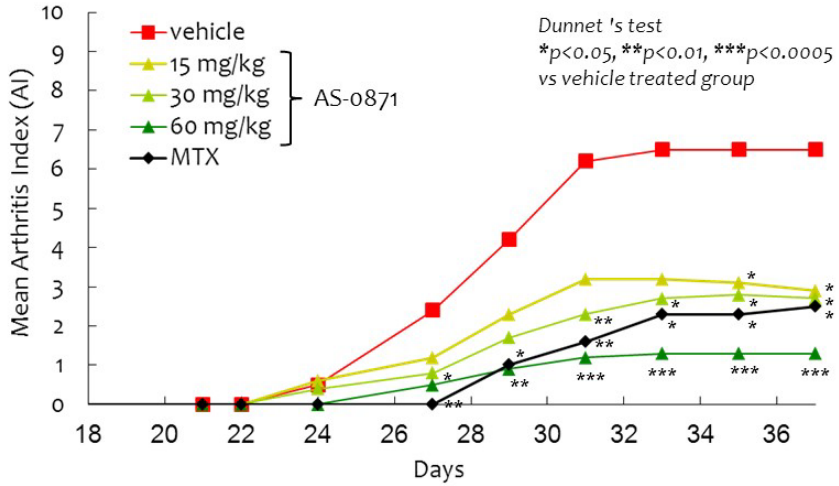




◆ Passive cutaneous anaphylaxis (PCA) mouse model (n=5)



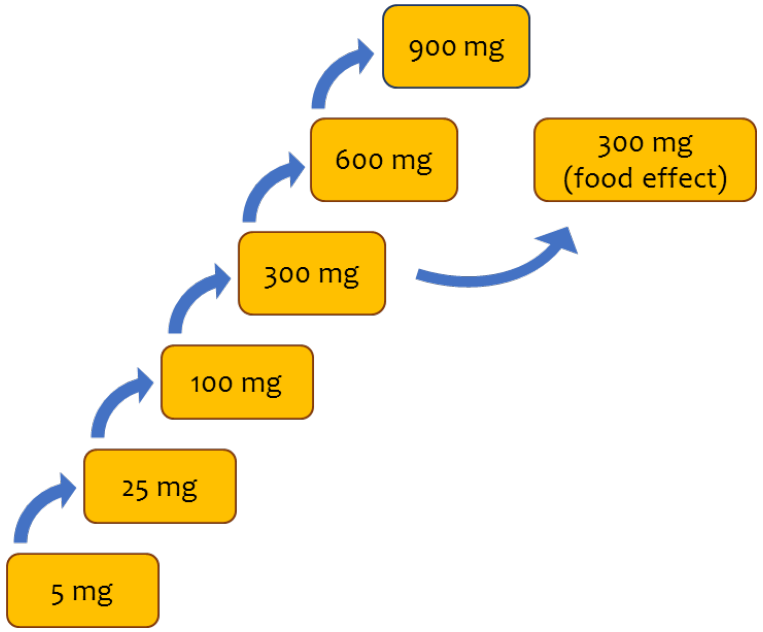
◆ Collagen-induced arthritis (CIA) mouse model (n=10)



AS-0871: FIH Study

SAD Part (Completed)

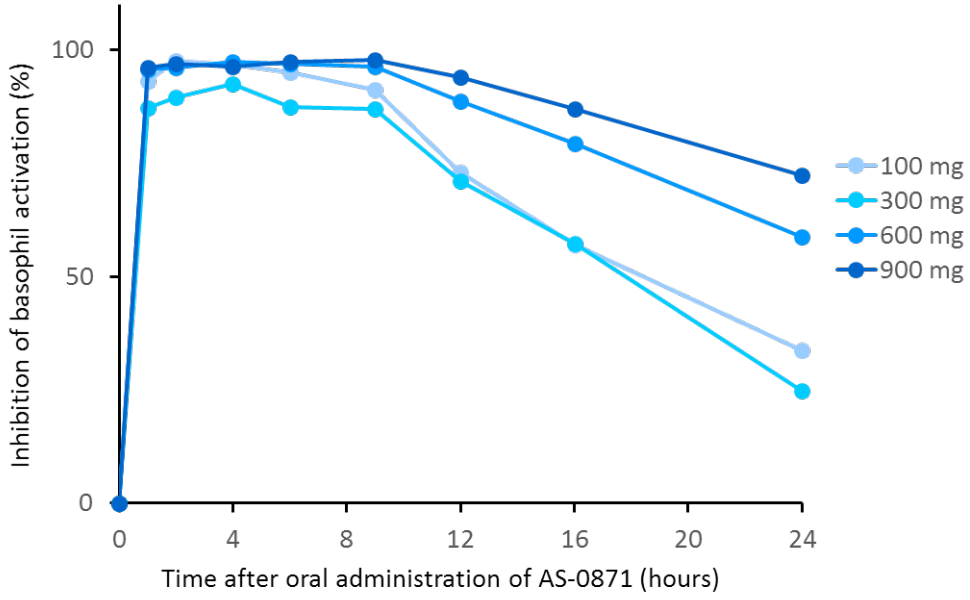
Step 1 Single Ascending Dose (SAD)	Step 2
• 6 dose levels (8 subjects/cohort) • Placebo controlled (6 active / 2 placebo) • Safety and tolerability • Pharmacokinetics and pharmacodynamics	• Food effect

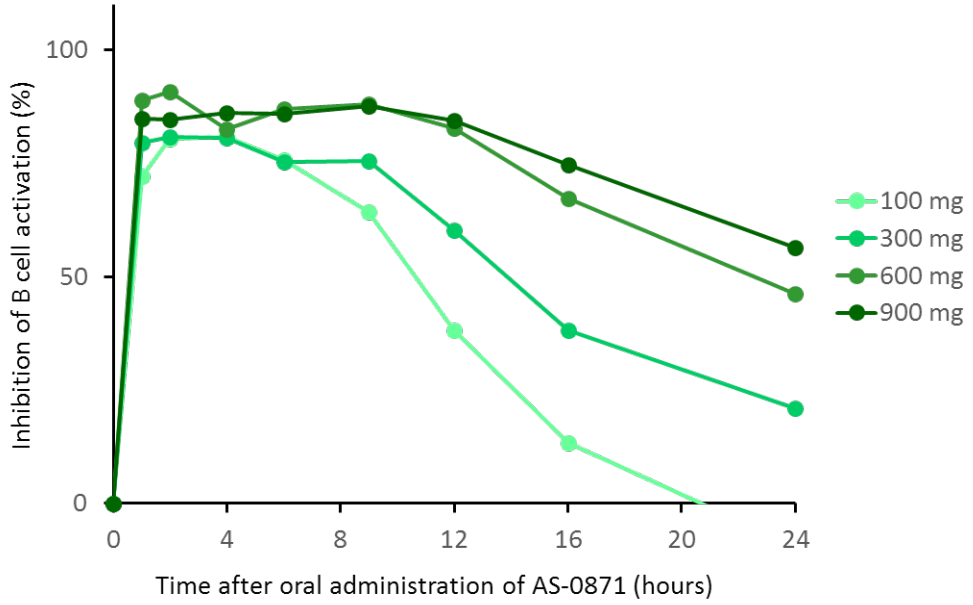


- AS-0871 is well-tolerated without any safety concerns.
- Favorable pharmacokinetic profile.
- Blood samples to assess PD effects were analyzed for evaluation of the B-cell and basophil responses. Administration of AS-0871 at 100mg or above resulted in strong inhibition of B-cell and basophil activation.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

Pharmacodynamics of AS-0871

- 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.

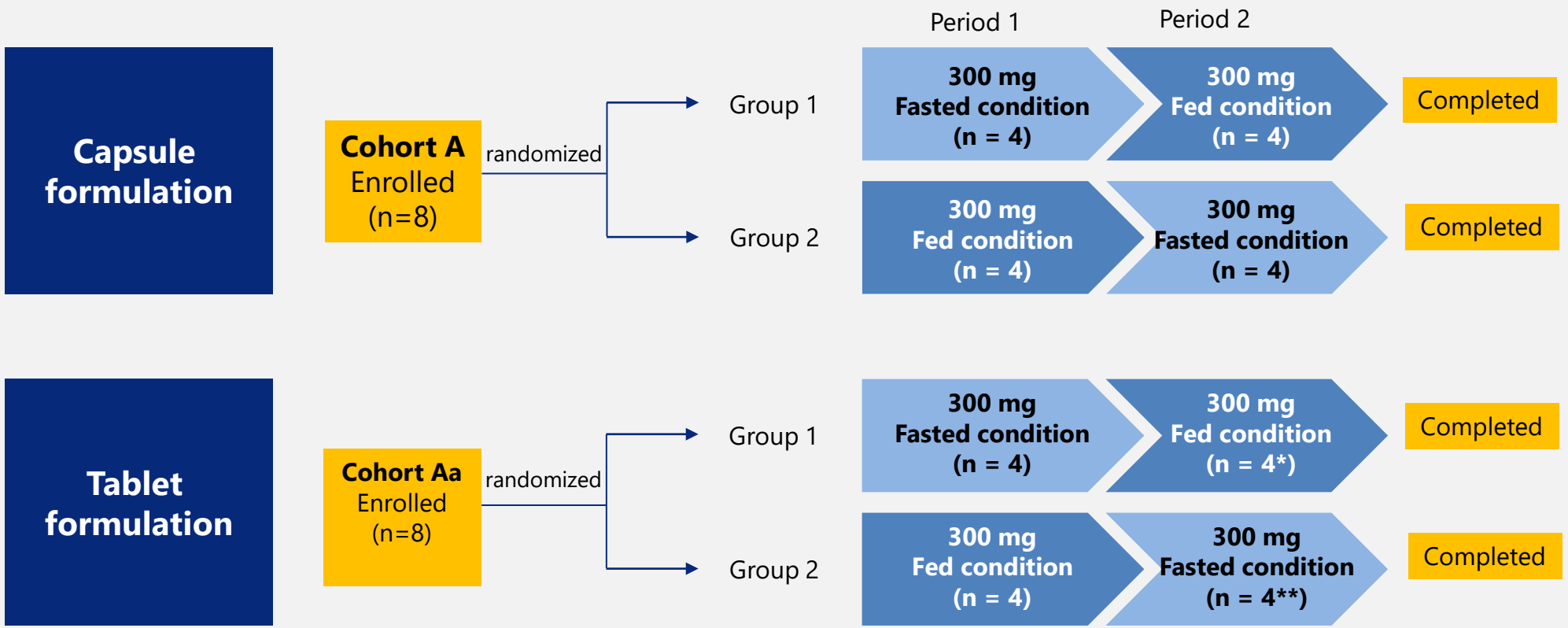




AS-0871: Phase 1 MAD Study BA part

Study Design of rBA/FE part

PK, safety, and tolerability after single-dose oral administration of AS-0871, formulated as capsules or tablets, were be 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).

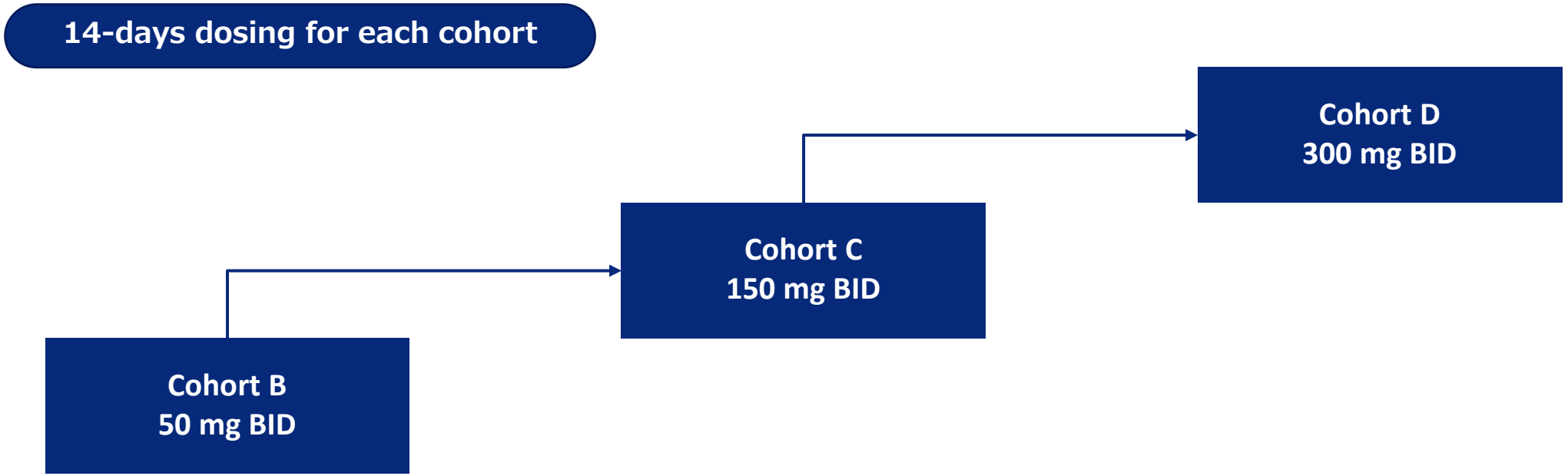


*One subject vomited after dosing (considered not related to study drug), excluded from the PK analysis.
**One subject withdrew from the study due to personal reasons before dosing.

AS-0871: Phase 1 MAD Study MAD part

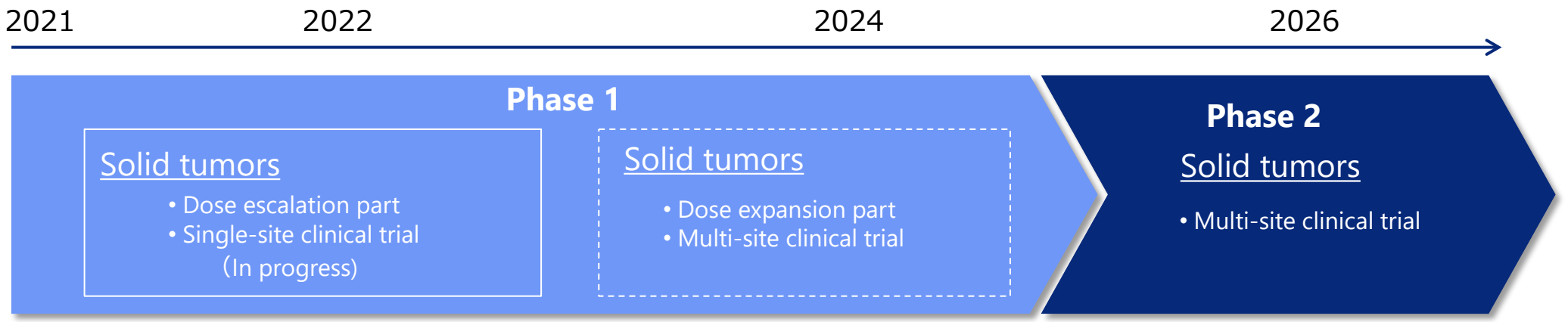
Study Design of MAD part

- 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.
- Top-line results will be available in Q3 2023 (the CSR expected in Q4 2023).



AS-0141: CDC7 Inhibitor

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

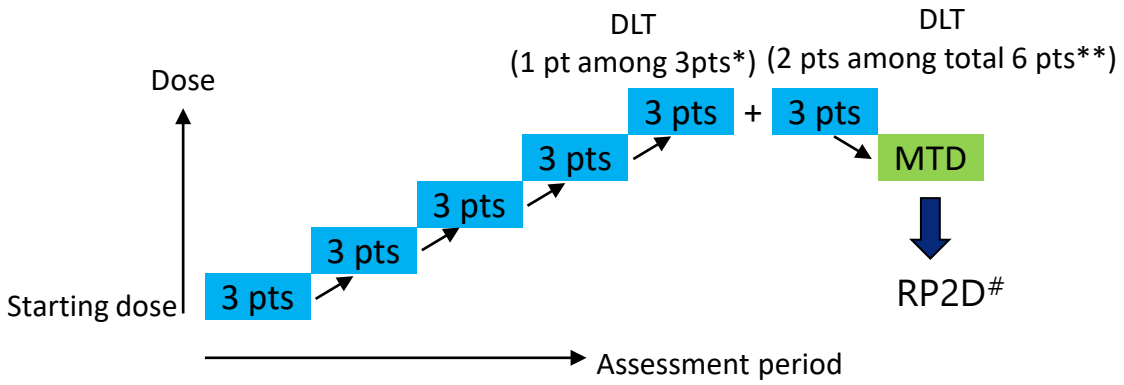


AS-0141: Phase 1 Clinical Trial

Phase 1 study targeting cancer patients

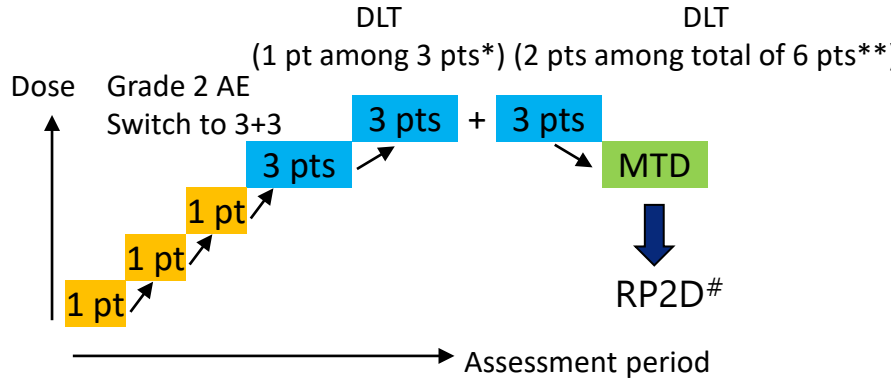
- Phase 1 study in patients with unresectable, advanced, recurrent, or metastatic solid tumors was initiated in Japan in H1 2021.
- The study consists of two parts, a dose escalation and an expansion.
- The primary objective is to assess safety, tolerability, maximum tolerated dose(MTD), preliminary 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 ≥ 2 AE occurs during dose limiting toxicity (DLT) assessment period.
  - Switch to 3+3 dose escalation design when any Grade ≥ 2 AEs are observed during DLT assessment period.

Standard 3+3 Dose Escalation part (Image)



AS-0141

Accelerated Titration Design (Image)

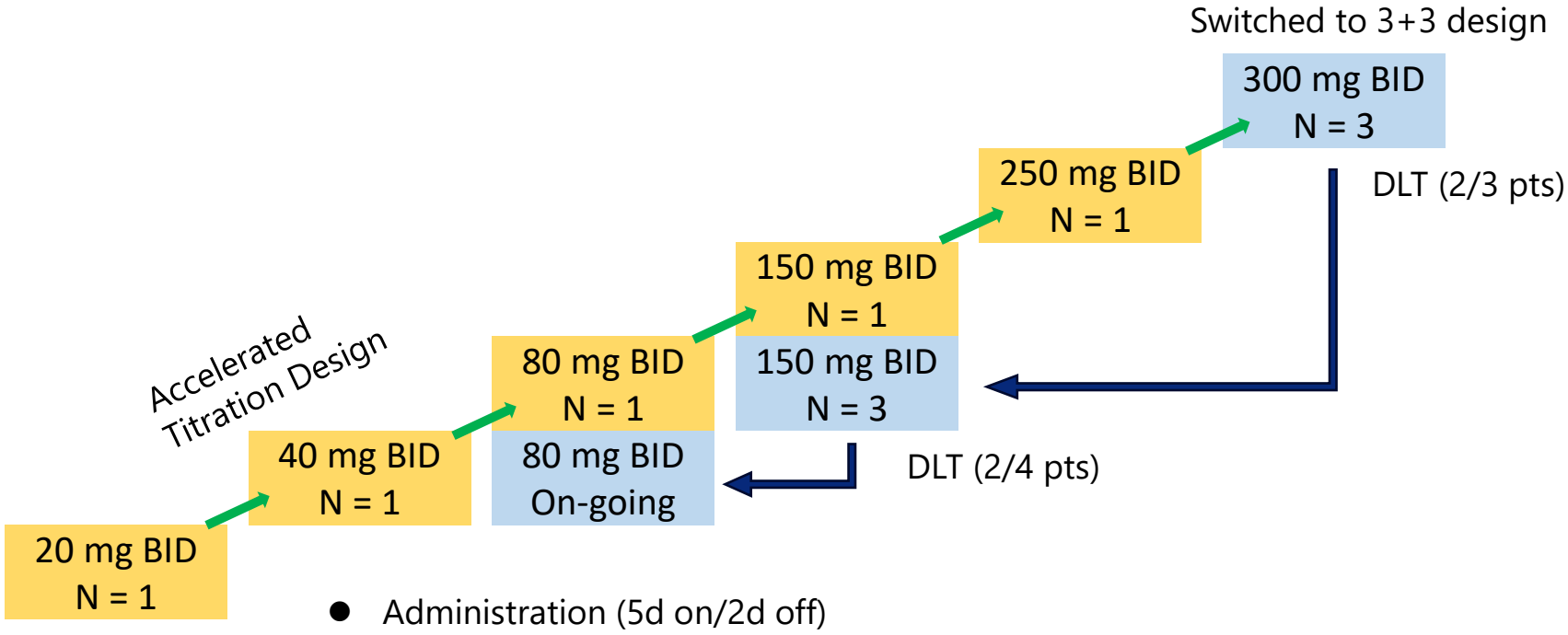


* No more patients will be added to this cohort if 2 pts among 3 pts experience DLT.
** If only 1 pt experiences a DLT among 6 pts, 3+3 design will be continued with higher dose levels.
# Recommended dose level will be determined at MTD or lower dose level.

pt/pts: patient(s)

AS-0141: Phase 1 Clinical Trial in Progress

- 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.
- Additional patients were enrolled at 150 mg BID and 2 out of 4 patients experienced DLTs.
- Additional patients are being enrolled at 80 mg BID.
- Pharmacodynamic effect of AS-0141 was confirmed at 40 mg-80 mg BID and above.

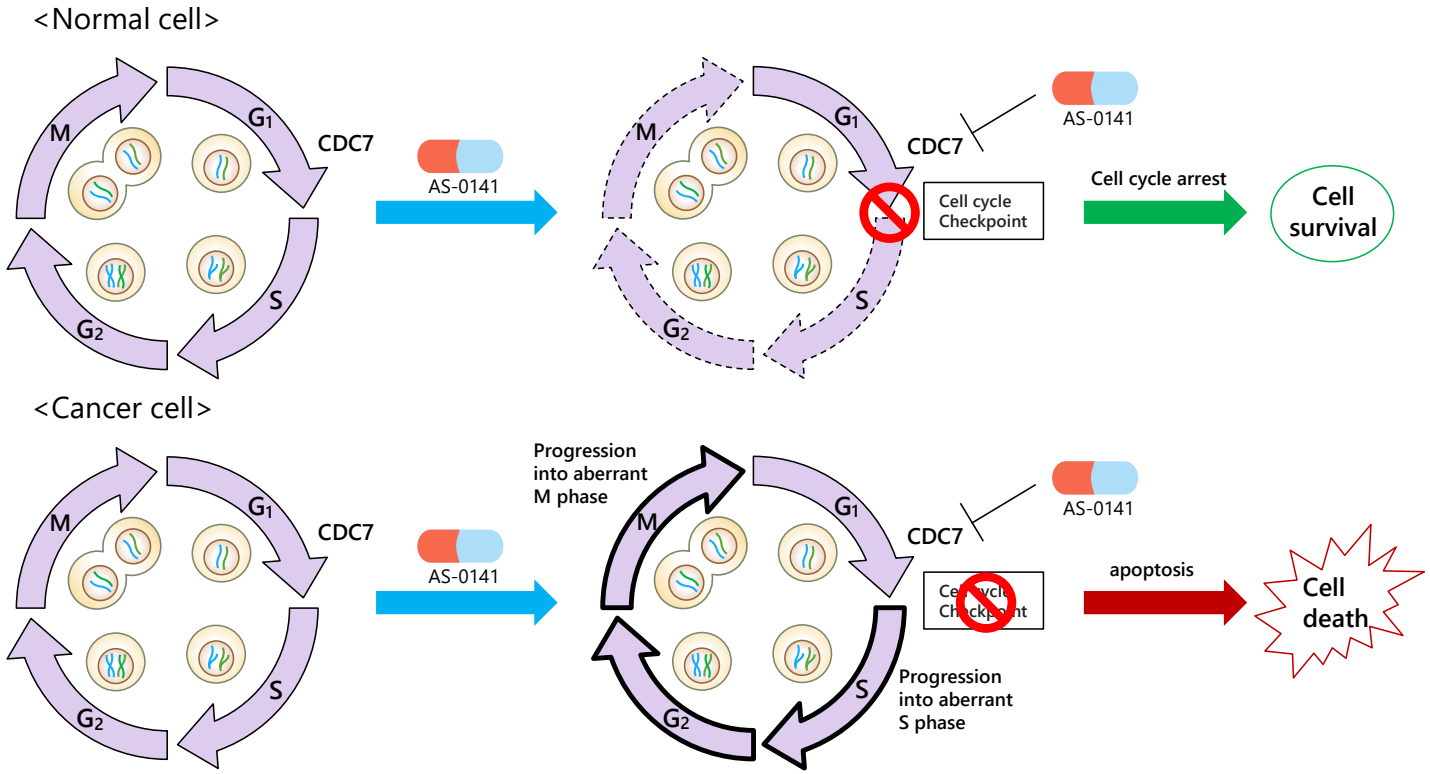


*BID: Twice a day, 5d on/2d off: 5 days medication followed by 2 days drug holiday

AS-0141: Highly Selective CDC Inhibitor

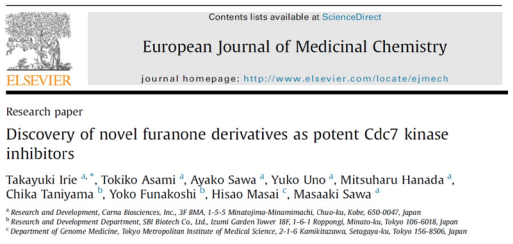
CDC7 kinase inhibitor

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: Time-Dependent Inhibitor of CDC7

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


Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

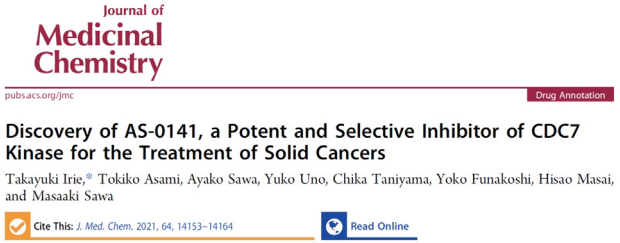
journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Discovery of novel furanone derivatives as potent Cdc7 kinase inhibitors

Takayuki Irie [a,*], Tokiko Asami [a], Ayako Sawa [a], Yuko Uno [a], Mitsuharu Hanada [a], Chika Taniyama [b], Yoko Funakoshi [b], Hisao Masai [c], Masaaki Sawa [a]

[a] Research and Development, Carna Biosciences, Inc., 3F BMA, 1-5-5 Minatojima-Minamimachi, Chuo-ku, Kobe, 650-0047, Japan
[b] Research and Development Department, SBI Biotech Co., Ltd., Izumi Garden Tower 18F, 1-6-1 Roppongi, Minato-ku, Tokyo 106-6018, Japan
[c] Department of Genome Medicine, Tokyo Metropolitan Institute of Medical Science, 2-1-6 Kamikitazawa, Setagaya-ku, Tokyo 156-8506, Japan


Journal of Medicinal Chemistry

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Drug Annotation

Discovery of AS-0141, a Potent and Selective Inhibitor of CDC7 Kinase for the Treatment of Solid Cancers

Takayuki Irie,* Tokiko Asami, Ayako Sawa, Yuko Uno, Chika Taniyama, Yoko Funakoshi, Hisao Masai, and Masaaki Sawa

Cite This: J. Med. Chem. 2021, 64, 14153−14164

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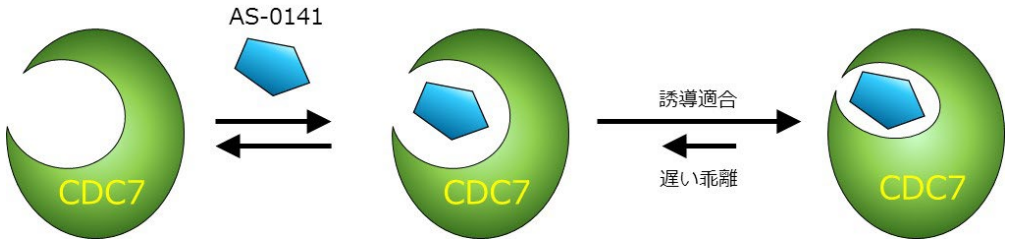
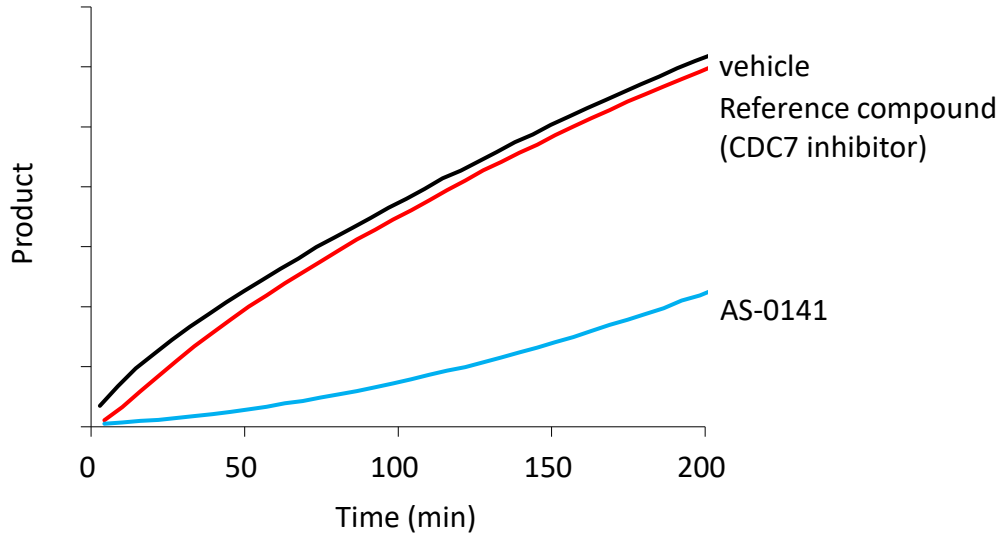


Inhibitory potency (IC50) for CDC7 in the presence of 1 mM ATP	
Without Preincubation	With Preincubation
503 nM	2.4 nM

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

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

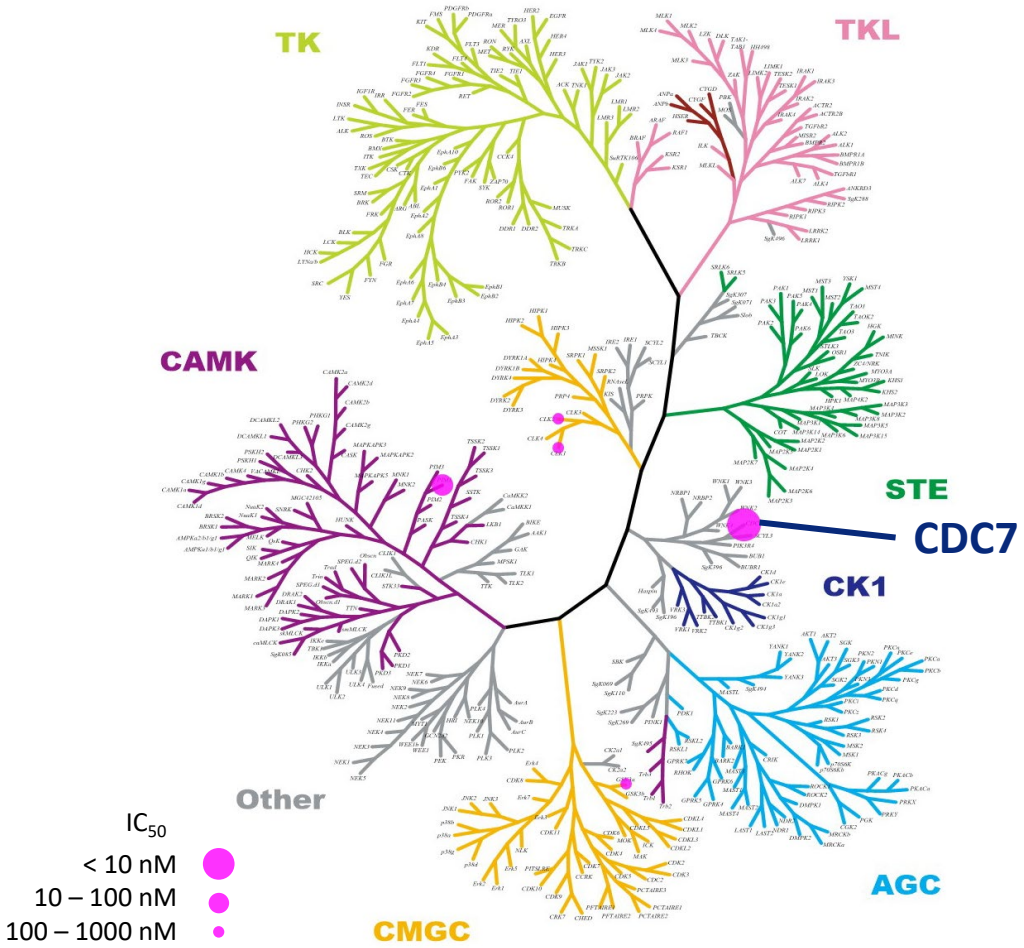
Rapid dilution assay for Cdc7 inhibitors. Recovery of enzymatic activity was monitored by formation of the phosphorylated product.



AS-0141: High Kinase Selectivity

◆ Kinase Selectivity Profiling

In the presence of 1 mM ATP with preincubation



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

	IC_{50} (nM)	
	Preincubation	
	-	+
CDC7	503 (210-fold)	2.4
PIM1	30	34
CLK1	212	206
CLK2	270	227
GSK3α	189	251

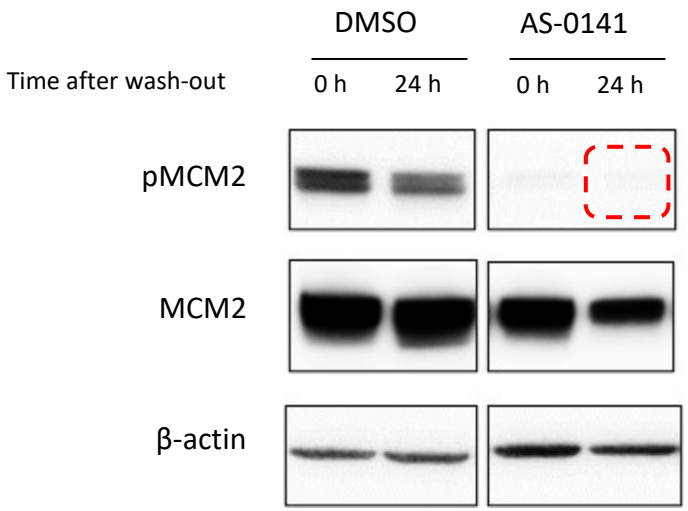
CDC7 is the only kinase that shows preincubation effect

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

AS-0141: Strong Cellular Activity

◆ Prolonged inhibition in cells

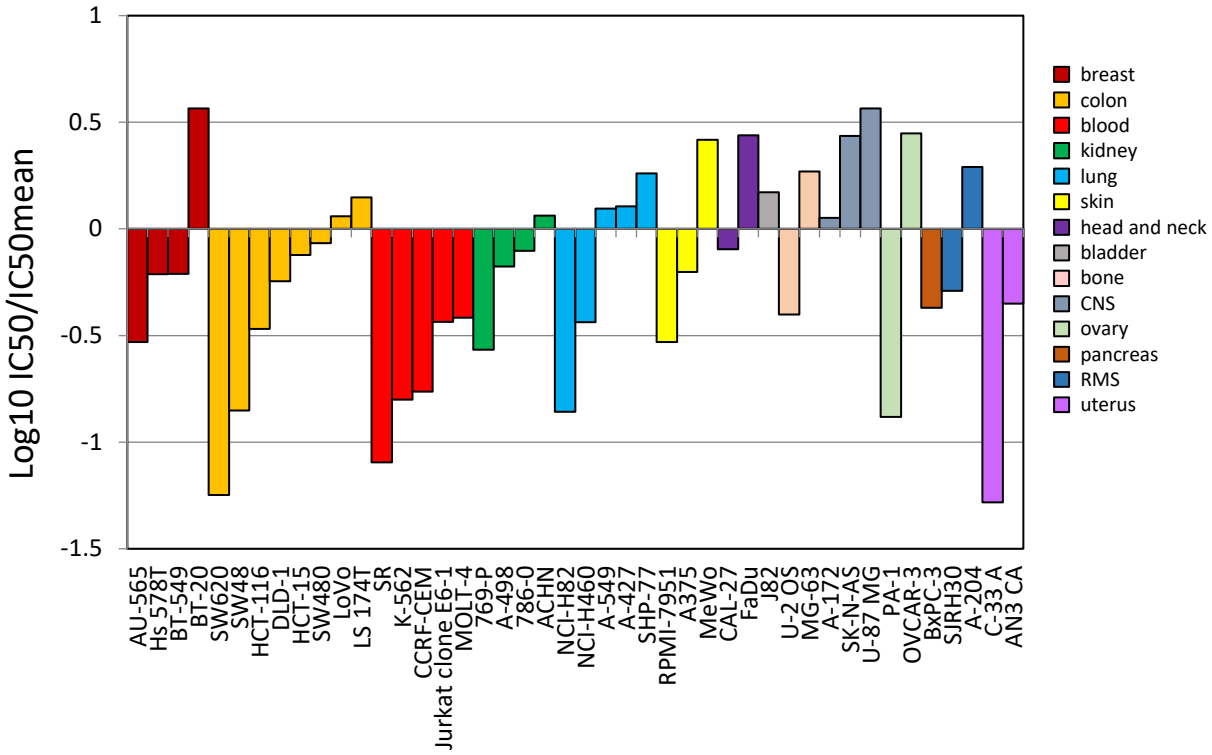
Human colon cancer cell line, Colo-205 cells were treated with DMSO control or AS-0141. After washout of the inhibitor, the cells were further incubated in the same media for 0 or 24 h and subjected to western blot analysis.



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

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

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

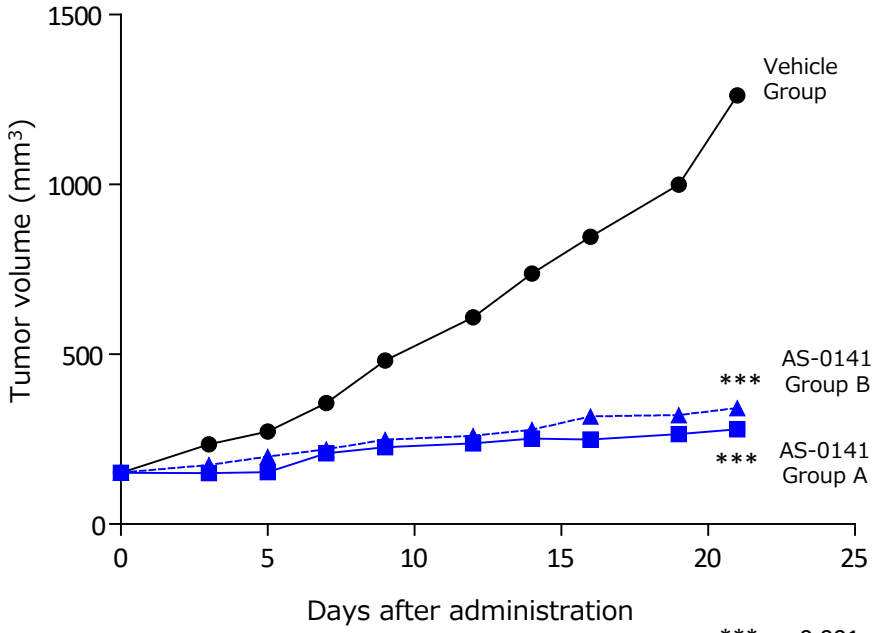


44 Cancer cell lines (Oncolines at NTRC)

AS-0141: Robust In Vivo Antitumor

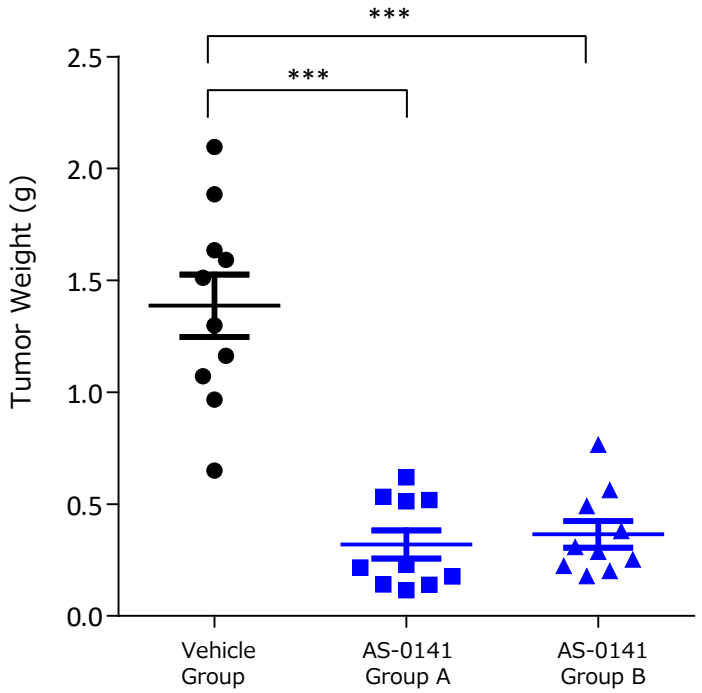
In vivo antitumor efficacy of AS-0141 in a SW620 (human colon cancer) xenograft mouse model

Tumor Growth Curve (Mean, n = 10)



***: p<0.001

Final Tumor Weight of Each Mouse



***: p<0.001

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

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

"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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