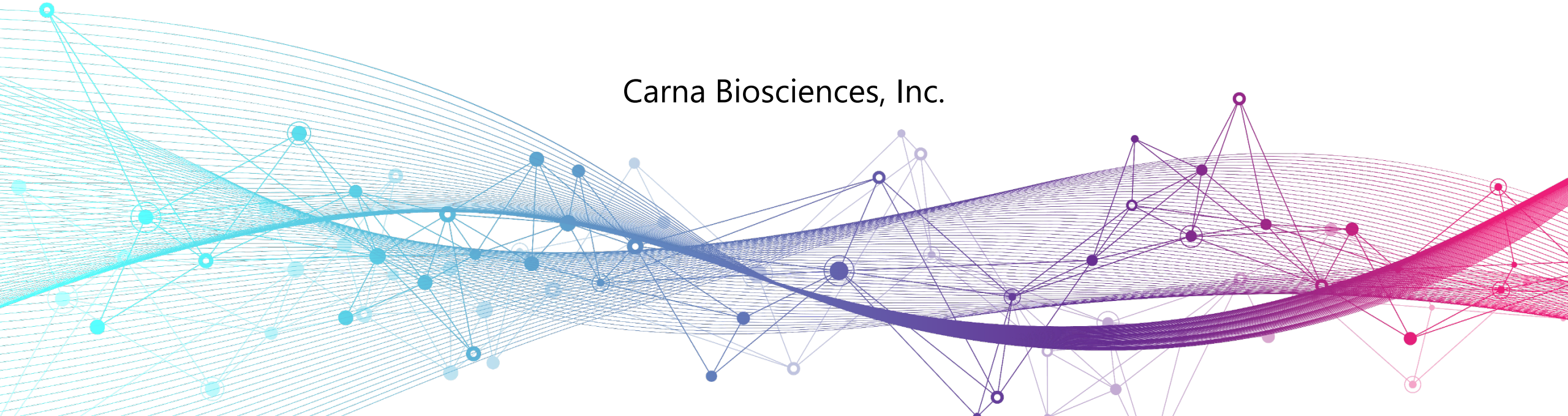
Financial Results
Q3 FY2023

(January to September 2023)

Carna Biosciences, Inc.



AGENDA

1 FY2023 Q3 Results

2 Updates on Pipelines in Clinical Development

3 Updates on Licensed Pipelines

4 Appendix

Q3 FY2023 Key Highlights

BTK inhibitor: AS-1763

- The first patient was dosed in Phase 1b study in the U.S in August 2023.
  Multi-center clinical study
  Principal Investigator : Dr. Nitin Jain, Department of Leukemia,
  University of Texas MD Anderson Cancer Center.

BTK inhibitor: sofnobrutinib (AS-0871)

- The final Clinical Study Report (CSR) for the Phase 1 MAD study has been finalized in November 2023.
- Demonstrated a favorable safety and tolerability profile as well as a promising pharmacokinetic (PK) and pharmacodynamic (PD) profile in the MAD study.

International Nonproprietary Name (INN) : sofnobrutinib, Code name : AS-0871
MAD : Multiple Ascending Dose

DGKα inhibitor: GS-9911 (Out-licensed to Gilead Sciences, Inc.)

- The Phase 1 study information has been published on ClinicalTrials.gov in October 2023.
- A patent application filed jointly with Gilead: Received a notice of allowance in the U.S. in July 2023.

Q3 FY2023 Key Highlights

STING inhibitor

- Fresh Tracks Therapeutics (FRTX), the licensee of STING inhibitor, announced that its Board of Directors has approved a plan of liquidation and dissolution of the company in September 2023.

ddSP

- Sales were JPY711 mn, 78% progress to FY plan of JPY902 mn.
- Sales of kinase protein were JPY448 mn, reached a record-high for Q3 YTD.

Others

- All the unexercised series 19th subscription rights to shares expired at the end of the exercise period in August 2023.

ddSP : Drug Discovery Support business

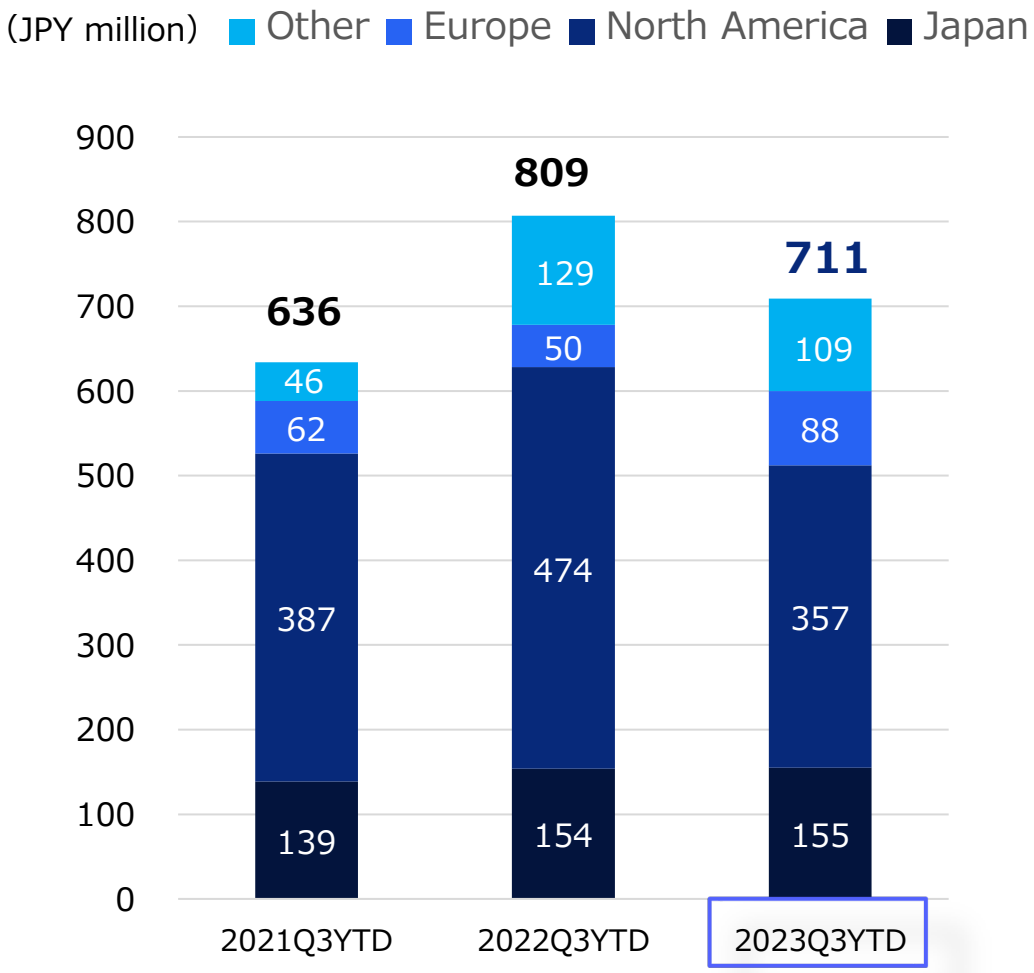
FY2023 Q3 YTD Results by Business Segment

(JPY million)	FY2022 Q3YTD Actual	**FY2023 Q3YTD Actual**	YoY Change	FY2023 Plan as of Feb 10	vs. FY Plan	
Total Sales	1,095	**711**	-384 -35.1%	902	78.8%	
ddSP business	809	**711**	-98 -12.1%	902	78.8%	• 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	-753	**-1,201**	-448	-1,890	—	
ddSP business	335	**218**	-117 -34.9%	221	98.8%	• 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	-1,089	**-1,420**	-331	-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	-735	**-1,203**	-467	-1,911	—	
Net Profit/Loss	-795	**-1,230**	-435	-1,936	—	
R&D Cost	1,267	**1,323**	+55	1,968		• Continued investment 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.
FRTX : Fresh Tracks Therapeutics, Inc.
Note : Rounded down to the nearest million yen

FY2023 Q3 YTD Drug Discovery Support Business Sales Trend

Drug Discovery Support Business Sales Trend by Region (Consolidated)



Japan

Increased 0.1% YoY

- While sales in 1H decreased due to a lack of large orders, the sales of profiling service were solid in Q3 and contributed to a marginal increase in sales YoY.

North America

Decreased 24.6% 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 74.4% YoY

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

Other

Decreased 15.2% 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 Sep.30, 2023	Change	Reason for changes
Current assets	4,104	4,050	-53	Cash and deposits +11
Cash and deposits	3,379	3,390	+11	Amount raised from exercised share options +1,349
Non-current assets	162	141	-20	
Total assets	4,266	4,192	-74	
Current liabilities	436	277	-159	Accounts payable -127 Current portion of long-term debt -32
Non-current liabilities	188	98	-89	Long term loans payable-89
Total liabilities	624	375	-248	
Total net assets	3,641	3,816	+174	Capital stock and capital surplus +1,388 Retained earnings -1,230
Total liabilities and net assets	4,266	4,192	-74	

Shareholders' equity ratio	85.0%	91.0%
BPS	255.0yen	222.61yen
PBR	2.0x	3.3 x
Share price of Carna	520yen	727yen

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

Financing

<Exercise of Subscription Rights to Shares for Q3 YTD FY2023>

	19th Subscription Rights to Shares	20th Subscription Rights to Shares	Total
Amount raised (JPY)	47mil.	1,302mil.	1,349mil.
No. of shares exercised (Shares)	50,000	2,836,500	2,886,500

<20th Subscription Rights to Shares >

	DEC. 2022	JAN.-APR.2023	Total
Amount raised (JPY)	300 mil.	1,302mil.	1,602mil.
No. of shares exercised (Shares)	550,000	2,836,500	3,386,500
No. of Exercised rights / No. of total rights issued	16.2 %	83.8%	100%

Cash and deposits as of the end of September 2023 : 3,390million 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. **sofnobrutinib (AS-0871)**
3. **monzosertib (AS-0141)**

International Nonproprietary Name (INN) : sofnobrutinib, Code name : AS-0871
International Nonproprietary Name (INN) : monzosertib, Code name : 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. Multi-center clinical study Principal Investigator：Dr. Nitin Jain, Department of Leukemia, University of Texas MD Anderson Cancer Center.
sofnobrutinib (AS-0871)	BTK	Immune-inflammatory diseases	• Phase 1 clinical trials (SAD study and MAD study) in healthy volunteers has been completed. • The Clinical Study Report (CSR) for the Phase 1 MAD study has been finalized in November 2023 . • Demonstrated a favorable safety and tolerability profile as well as a promising PK/PD profile in the MAD study.
monzosertib (AS-0141)	CDC7/ ASK	Cancer	• Phase 1 study in cancer patients is in progress in Japan. • Dose escalation part is on going. Clinical trial site : National Cancer Center Hospital and National Cancer Center Hospital East

SAD : Single Ascending Dose
MAD : Multiple Ascending Dose
BA : Bioavailability

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 Healthy Volunteers

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

Objectives of the study

A single dose of 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 clinically meaningful 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

Multi-center clinical study
Principal Investigator : Dr. Nitin Jain, Department of Leukemia, University of Texas MD Anderson Cancer Center.

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	• Opened 6 clinical sites. • First patient dosed in August. • Observed safety and tolerability at the first dose level. • Proceed to the next higher dose level in October.

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.

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)	P3
TT-01488	TransThera	P1
HMPL-760	HutchMed	P1

- FDA granted an accelerated approval to pirtobrutinib, the most advanced competitor to AS-1763, in the U.S early 2023.
- Focused differentiation strategy from pirtobrutinib 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.

Sofnobrutinib (AS-0871): Highlights

Ref. P.37-P.44

Mechanism/ Indication	Sofnobrutinib 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	Sofnobrutinib is designed to selectively inhibit BTK **to reduce a risk of potential side effects**.
Characteristics	Sofnobrutinib is a **non-covalent BTK inhibitor** that reversibly inhibits BTKs to reduce safety concerns associated with covalent inhibitors.

Sofnobrutinib (AS-0871): Results from the Phase I Clinical Trial (1)

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Objectives of Single Ascending Dose (SAD) study

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

A single dose of Sofnobrutinib was administered orally to healthy volunteers to evaluate:

- plasma concentration of sofnobrutinib
- 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 sofnobrutinib:

- plasma concentration of AS-0871 were increased in a dose dependent manner.
- no clinically meaningful 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 sofnobrutinib 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.

Sofnobrutinib (AS-0871): Results from the Phase I Clinical Trial (2)

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

Multiple Ascending Dose (MAD) study MAD part design

- Double blinded, placebo-controlled, randomized multiple ascending dose study in healthy volunteers
- 14-day multiple oral doses of sofnobrutinib tablets in 3 cohorts (50, 150 or 300 mg twice daily)
- The safety, tolerability, PK and PD were evaluated.

Result of MAD study MAD part

- Well tolerated with no dose-limiting adverse events (AEs): AEs were mostly mild.
- Favorable safety profile up to 300 mg twice daily
- Favorable PK profile: approximately dose proportional with increasing doses
- Robust PD effect was observed: over 90% inhibition for basophils activation on Day 14 at 150 and 300 mg BID doses.

These results from the Phase 1 studies of sofnobrutinib support to advance sofnobrutinib into Phase 2 clinical development for further investigations.

Sofnobrutinib: 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

- A significant number of patients having uncontrolled CSU by existing drugs.
- 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 sofnobrutinib (non-covalent BTK inhibitor) to provide clinical benefits by minimizing potential adverse events associated with covalent BTK inhibitors including remibrutinib.

Monzosertib (AS-0141): Highlights

Ref. 45-P.51

Mechanism/ Indication	Monzosertib is an **orally available** CDC7 kinase inhibitor targeting cancers.
To minimize a risk of side effects	Monzosertib is designed to selectively inhibit CDC7 kinase **to reduce a risk of potential side effects**.
Potentially effective for various cancers	Monzosertib exhibited **a potent anti-proliferative activity against a wide range of cancer cell lines in preclinical studies.**
Potential first-in-class molecule	Monzosertib has a potential to become a first-in-class drug as no CDC7 inhibitors have been approved.

Monzosertib (AS-0141): Phase 1 Clinical Trials

Ref. P.46

Clinical trial sites : National Cancer Center Hospital and National Cancer Center Hospital East

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 monzosertib.
Dosage	Oral administration, twice a day
Status	• Open-label Phase I study in patients with unresectable advanced, recurrent, or metastatic solid tumors in Japan • Dose Escalation on-going

Updates on Licensed Pipelines

1. **DGKα Inhibitor** (Gilead Sciences, Inc.)
2. **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)
Joint Research with Sumitomo Pharma	Kinase inhibitor (Psychiatric and neurological disorders)	JPY80M (including research milestone)	JPY10.6B	Undisclosed	Worldwide	Mar. 2018	

※Deleted the description on STING inhibitor from the list above due to the announcement of board approval of a plan of liquidation and dissolution by Fresh Tracks Therapeutics in September 2023.

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**
2. **Indication: Cancer (immunotherapy)**
   - GS-9911 was introduced by Gilead in its presentation "Oncology Deep Dive" held in April 2022. 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.
3. **The Phase 1 study information has been published on ClinicalTrials.gov in October 2023.**

Official Title	A Phase 1 Study to Evaluate the Safety and Tolerability of GS-9911 as Monotherapy and in Combination With an Anti-PD-1 Monoclonal Antibody in Adults With Advanced Solid Tumors
ClinicalTrials.gov ID	NCT06082960

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

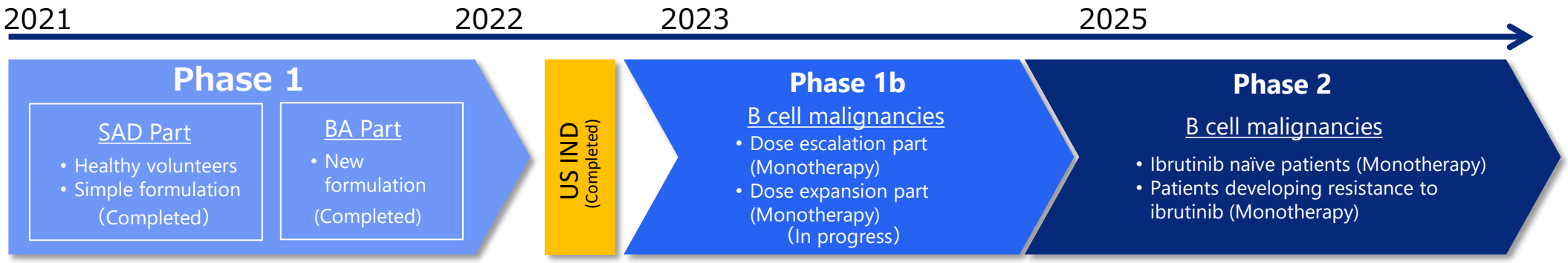
1. **Joint research to discover novel kinase inhibitors to treat psychiatric and neurological disorders.**
2. **The term of the joint research was extended in December 2021.**
3. **Joint research is ongoing to identify preclinical candidates.**

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

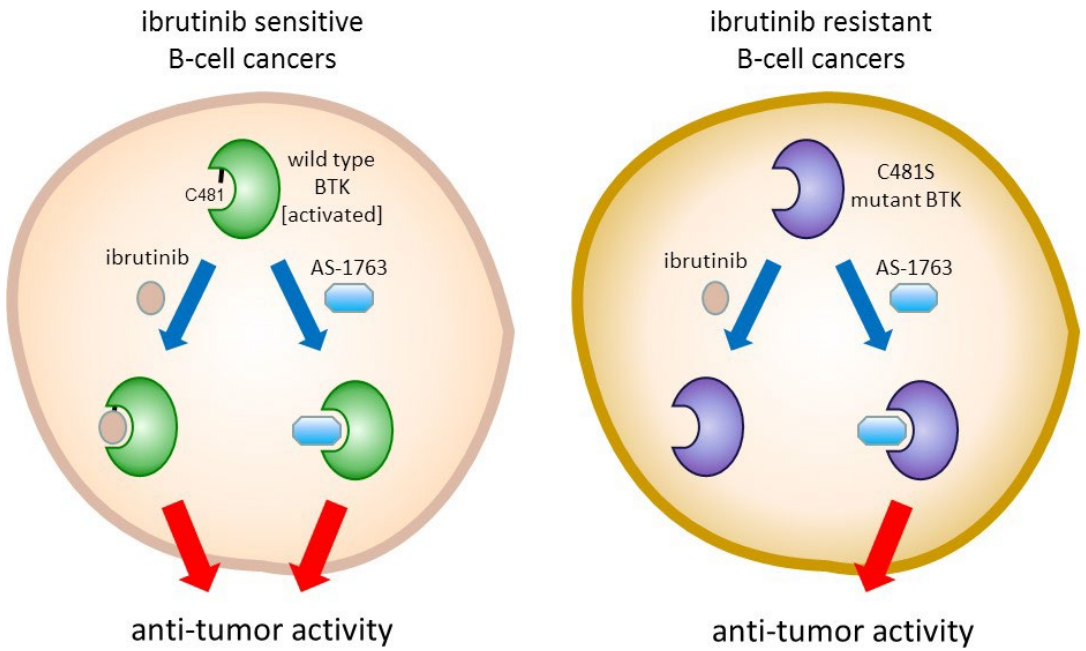
Completed

On-going

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

◆ 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

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◆ 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

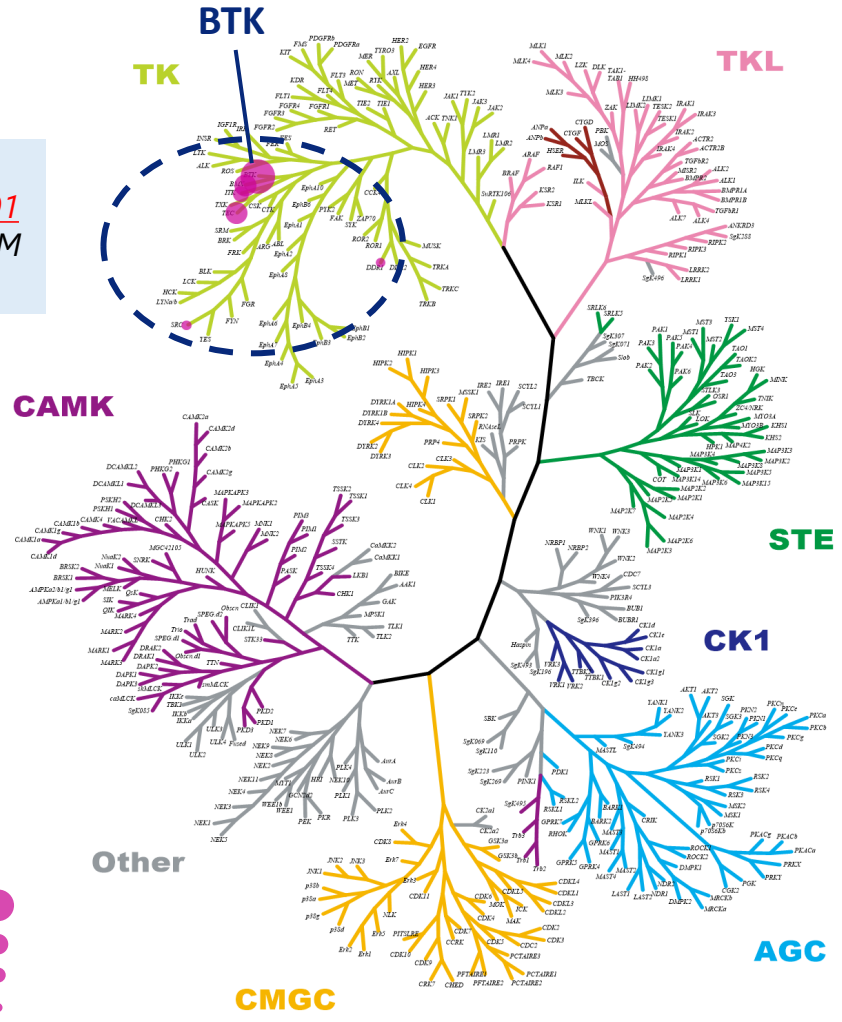
50-fold Stronger activity

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.

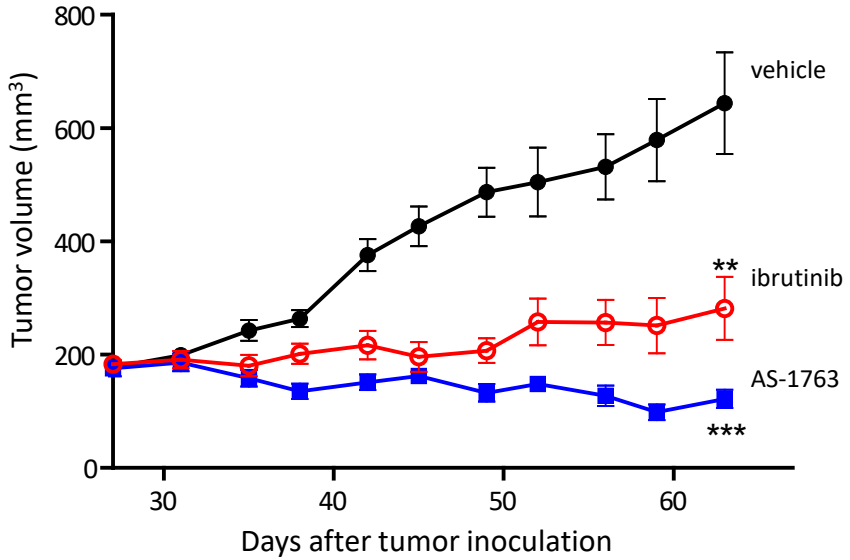
◆ Kinase selectivity profiling

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

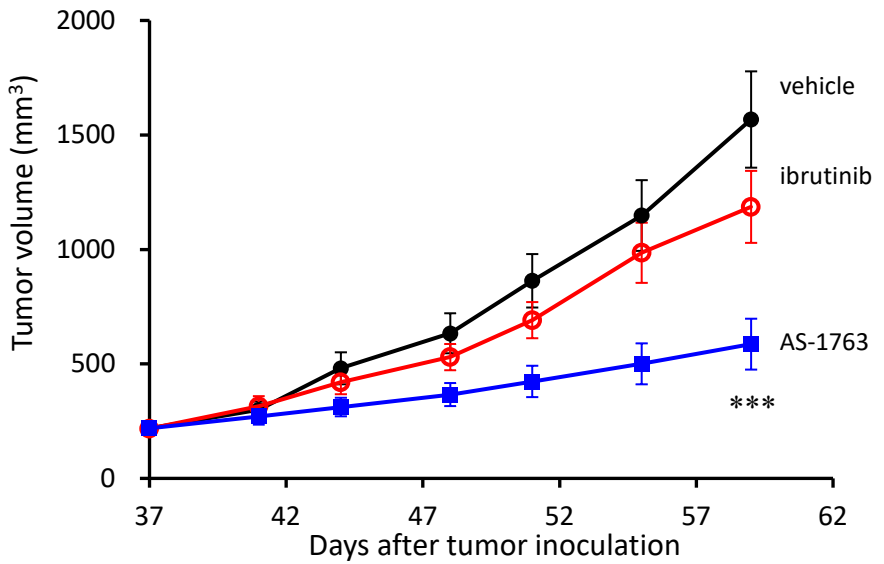
- **In vivo antitumor effects of AS-1763 on human B-cell non-Hodgkin lymphoma cell line, OCI-LY10 tumor xenograft mouse model (n=8-10)**



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

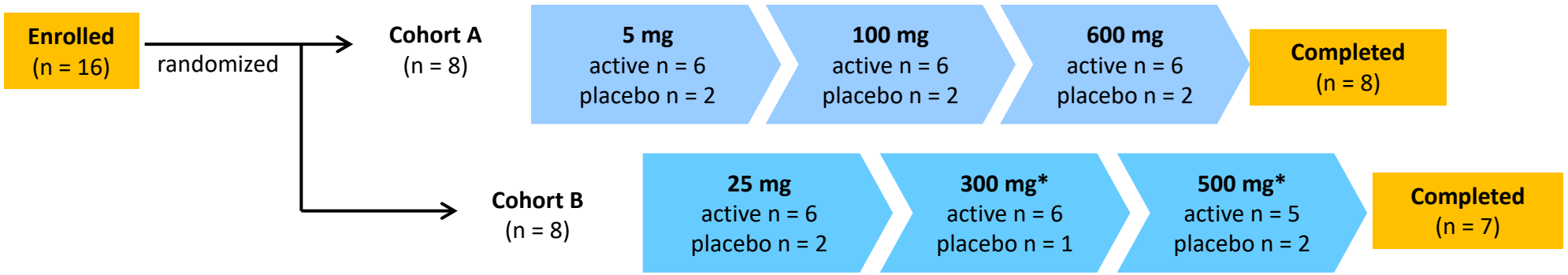
***: p<0.001

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

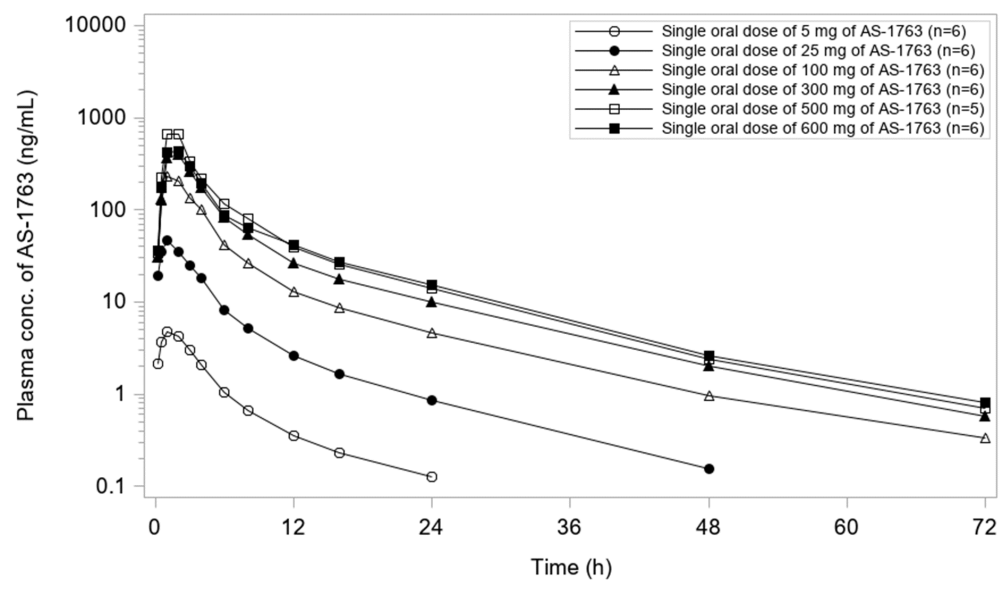
Safety and tolerability

- 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.

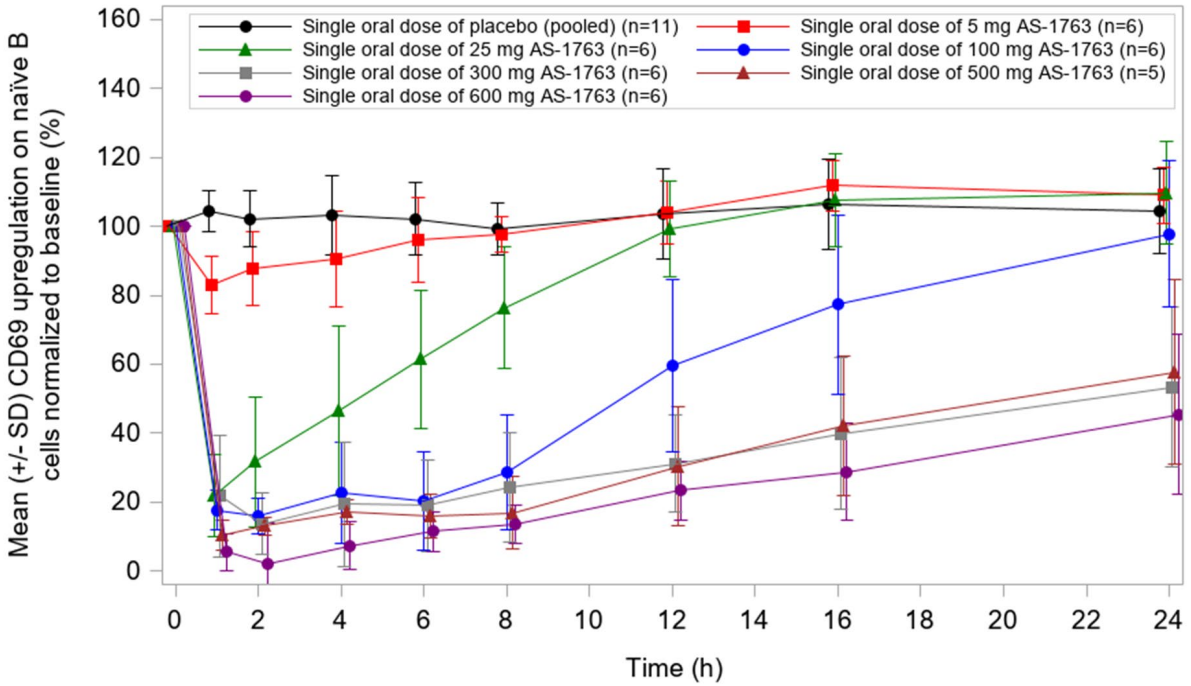
< Plasma concentration of a single oral dose of AS-1763 >



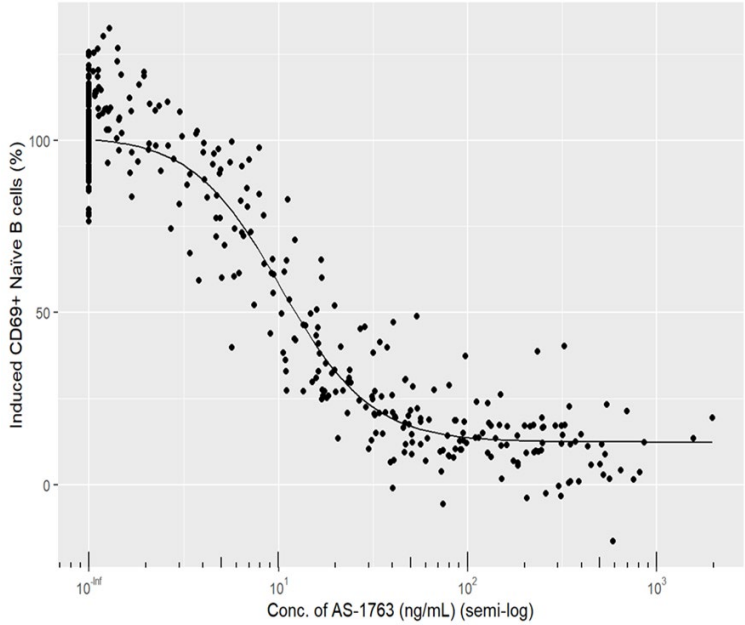
Pharmacodynamics of AS-1763

- 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 >



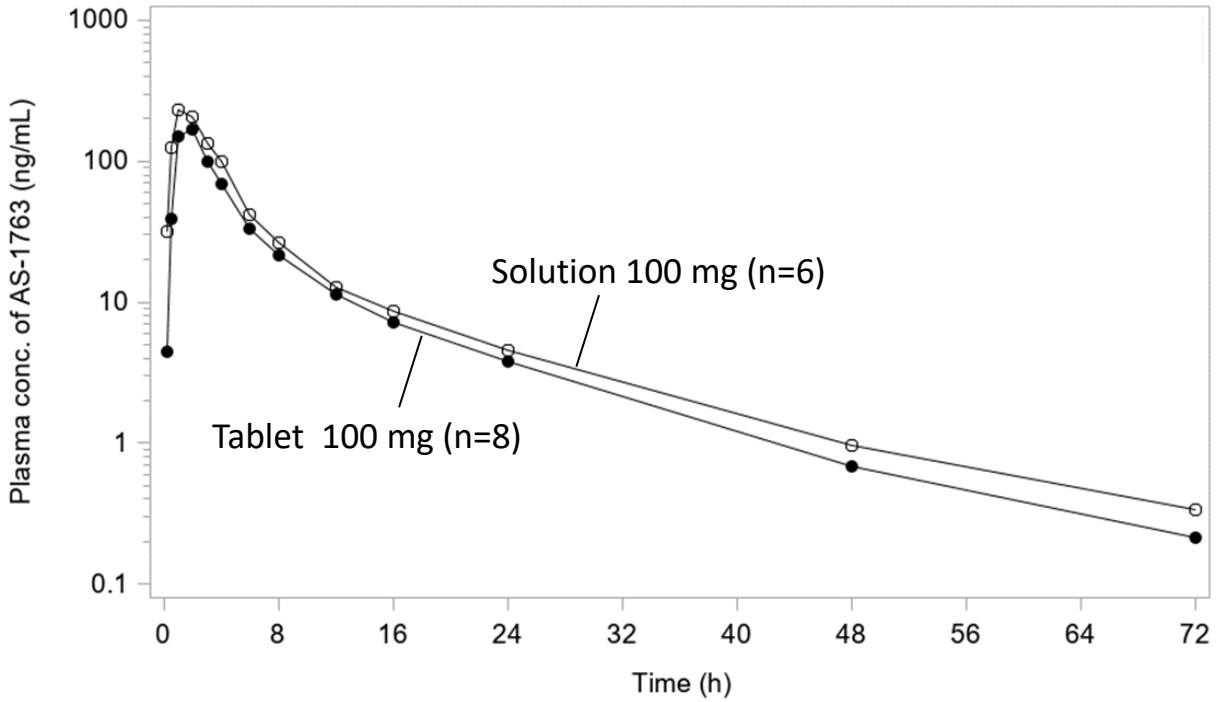
< PK/PD correlation analysis >



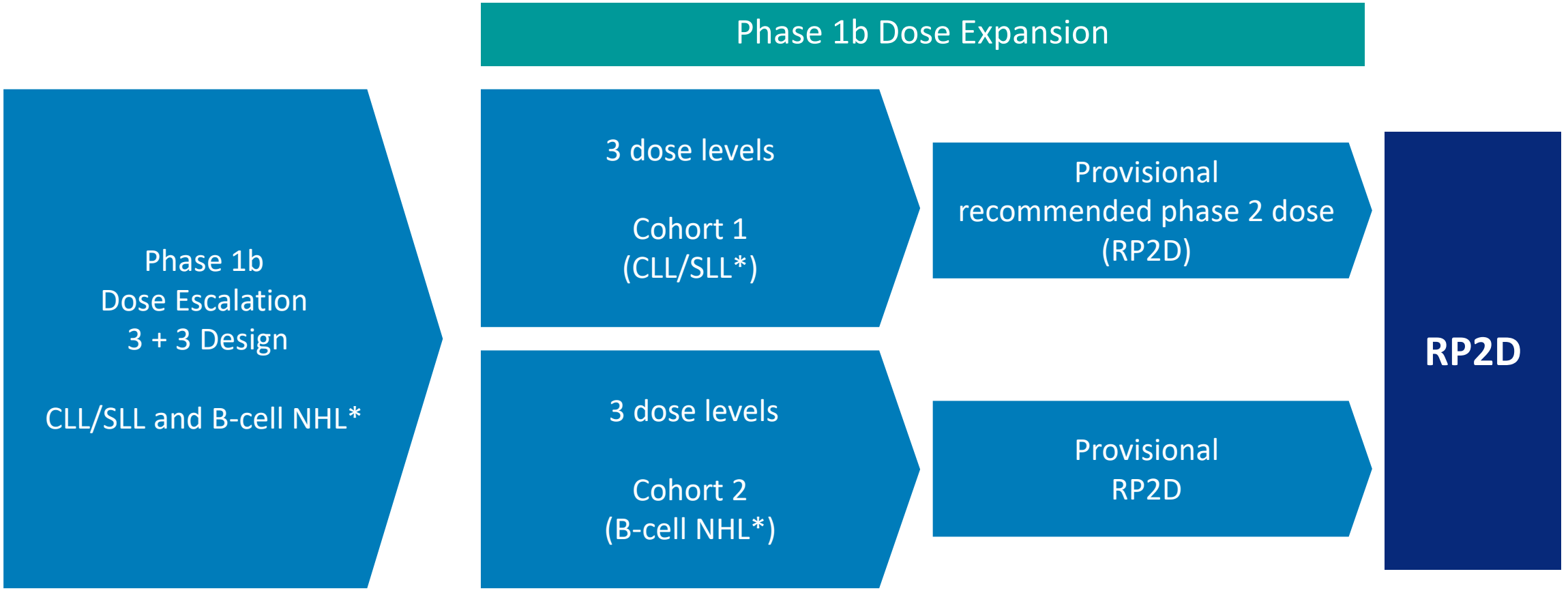
AS-1763: BA Part

- 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

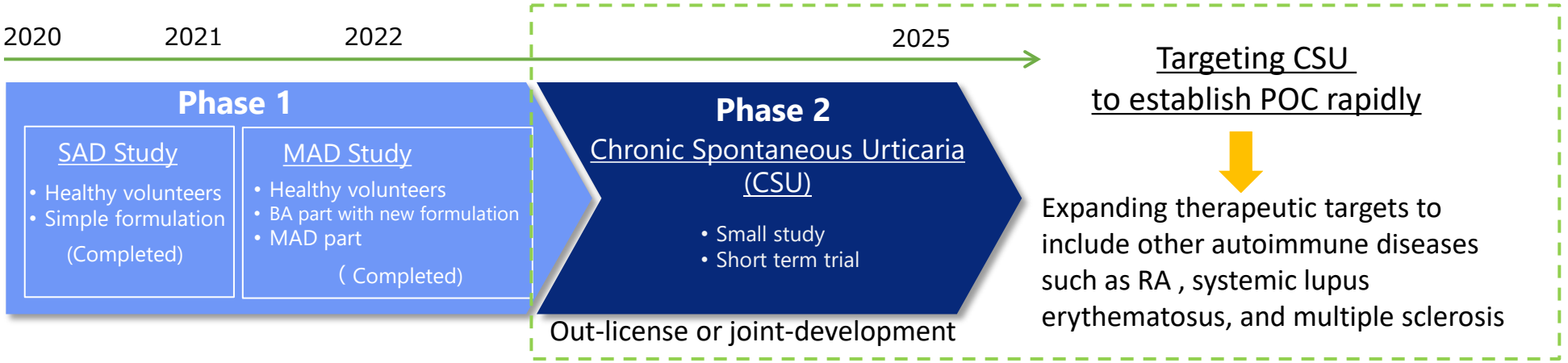
◆ **The first patient was dosed in August 2023.**

Sofnobrutinib (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
- Phase 1 MAD study was completed.
- Find a partner to conduct further development.



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

Sofnobrutinib (AS-0871): Phase 1 Clinical Trial in Progress

CARNA BIOSCIENCES

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 sofnobrutinib .

Completed

Sofnobrutinib (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

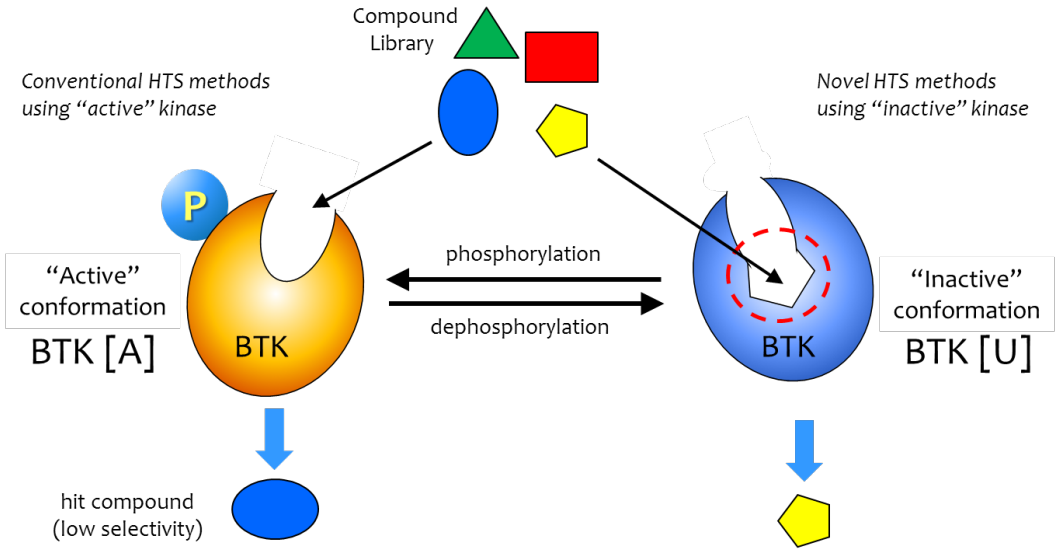
TR-FRET binding assay targeting unactivated form of Bruton's tyrosine kinase

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

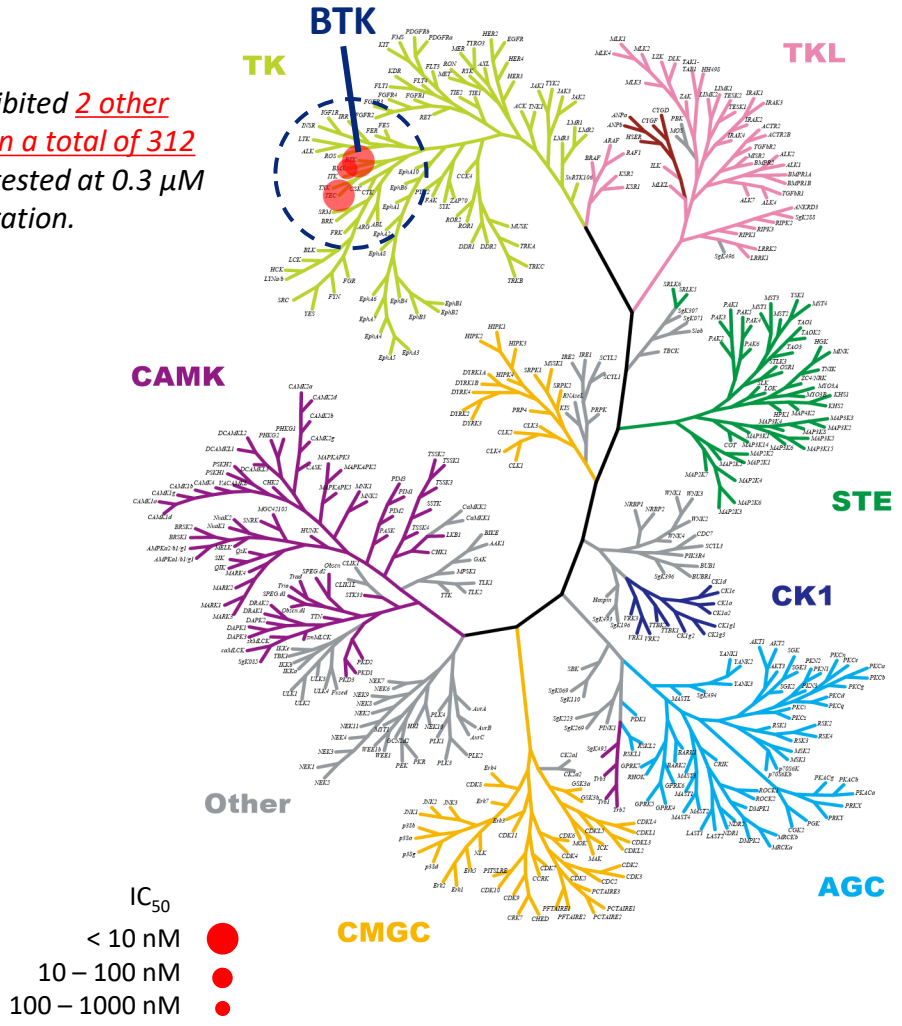


Bias classical ATP competitive inhibitors

	BTK IC_{50} (nM)	
	BTK[A]	BTK[U]
sofnobrutinib	3.4	0.3

Kinase Selectivity Profiling

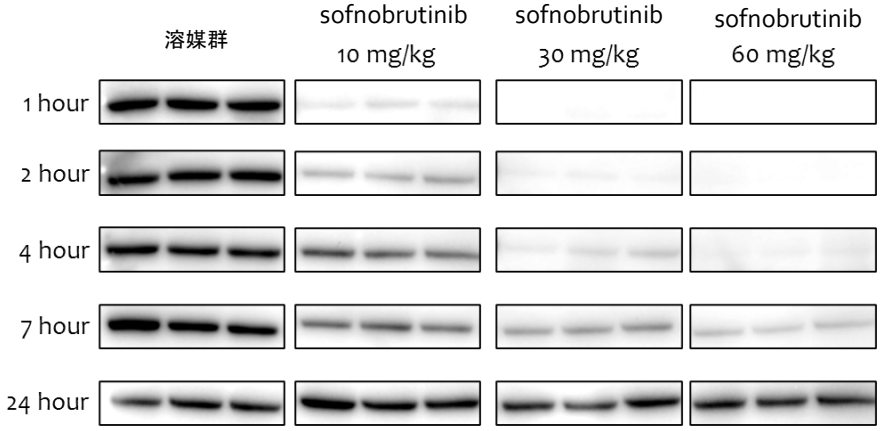
Only inhibited 2 other kinases in a total of 312 kinases tested at 0.3 μM concentration.

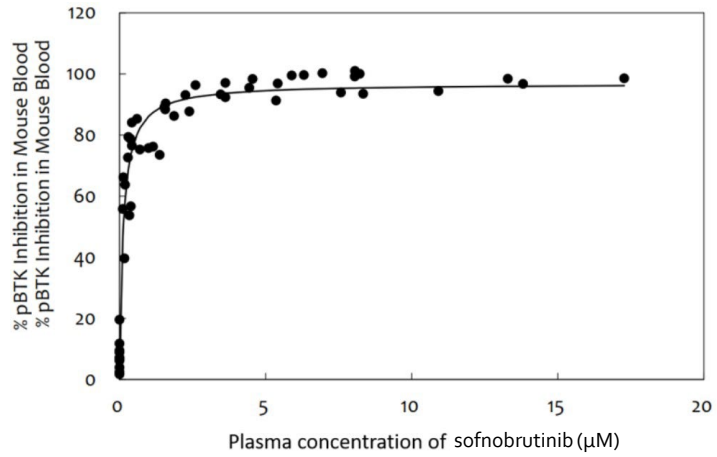


Sofnobrutinib (AS-0871): In Vivo Therapeutic Efficacy

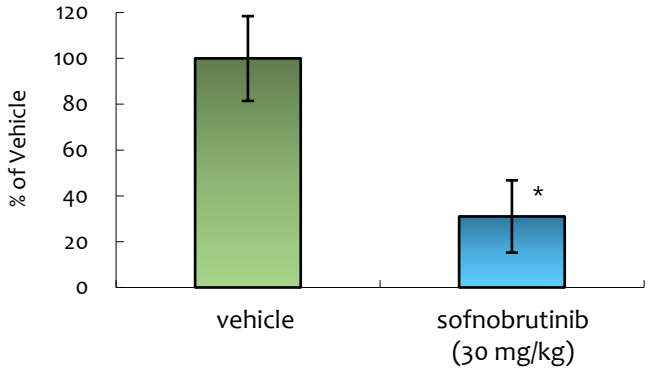
◆ PK/PD Study

Auto-phosphorylation status of BTK was measured following oral single administration of sofnobrutinib .

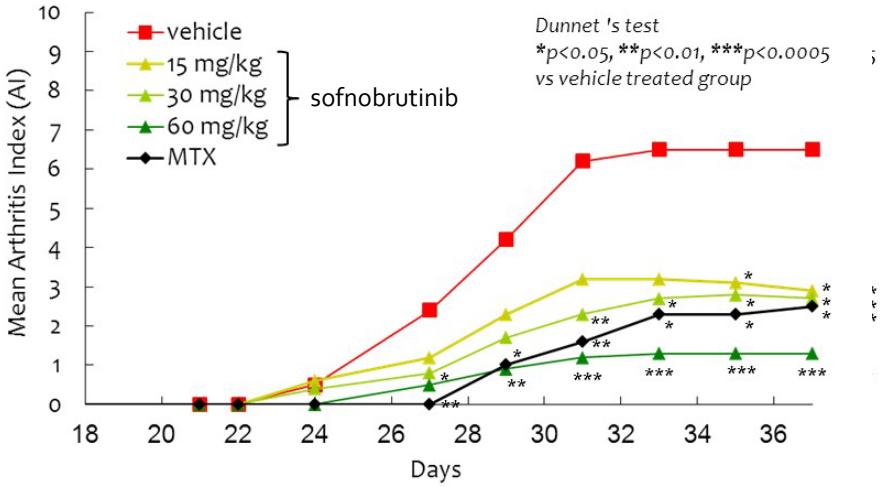




◆ Passive cutaneous anaphylaxis (PCA) mouse model (n=5)



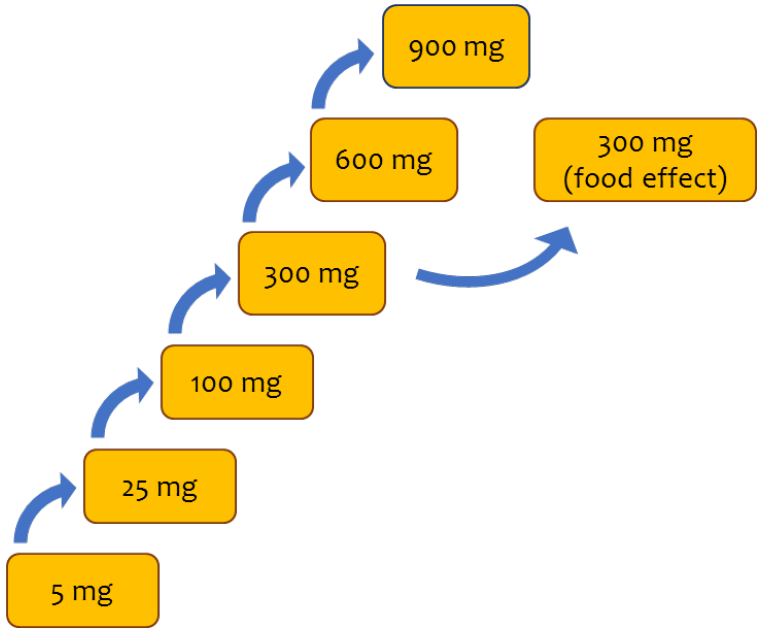
◆ Collagen-induced arthritis (CIA) mouse model (n=10)



Sofnobrutinib (AS-0871): FIH Study

SAD Part (Completed)

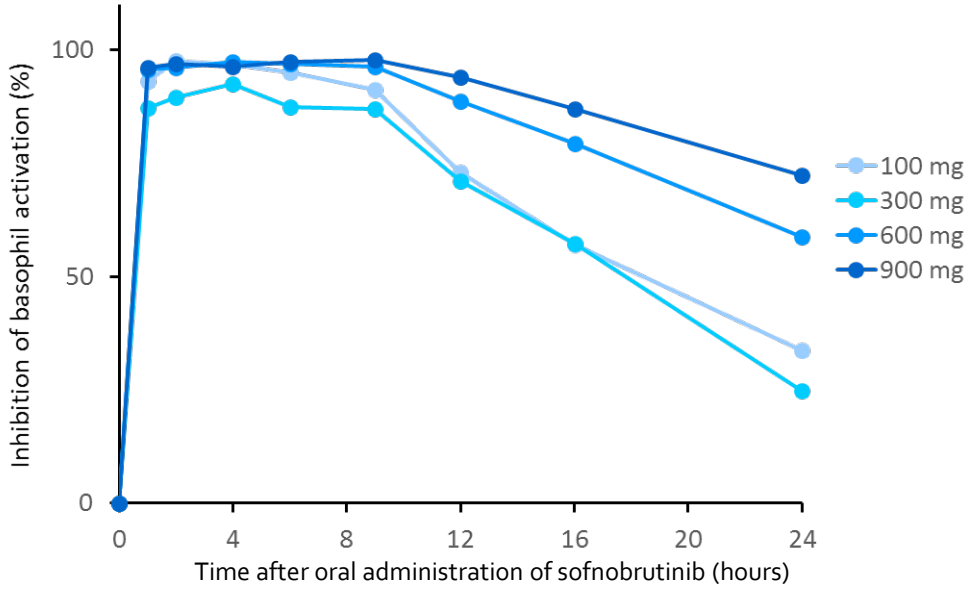
Step 1 Single Ascending Dose (SAD)	Step 2
• 6 dose levels (8 subjects/cohort) • Placebo controlled (6 active / 2 placebo) • Safety and tolerability • Pharmacokinetics and pharmacodynamics	• Food effect

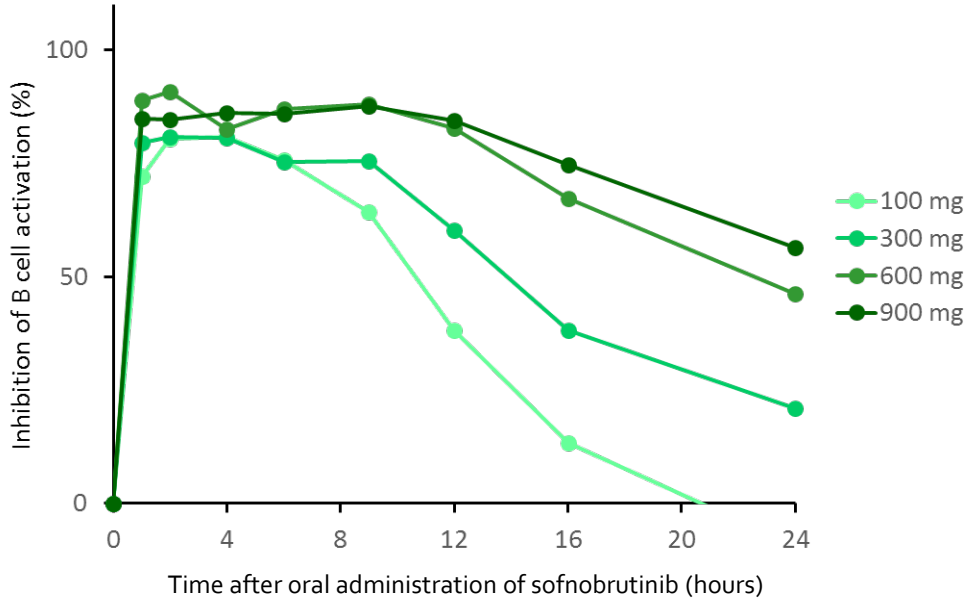


- Sofnobrutinib is well-tolerated without any safety concerns.
- Favorable pharmacokinetic profile.
- Blood samples to assess PD effects were analyzed for evaluation of the B-cell and basophil responses. Administration of sofnobrutinib at 100mg or above resulted in strong inhibition of B-cell and basophil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

Pharmacodynamics of sofnobrutinib (AS-0871)

- Pharmacodynamic study demonstrated that subjects who received sofnobrutinib 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 sofnobrutinib achieved therapeutic plasma levels needed to inhibit B cells and basophils activation, suggesting that sofnobrutinib has a potential to become a new treatment option for inflammatory diseases.

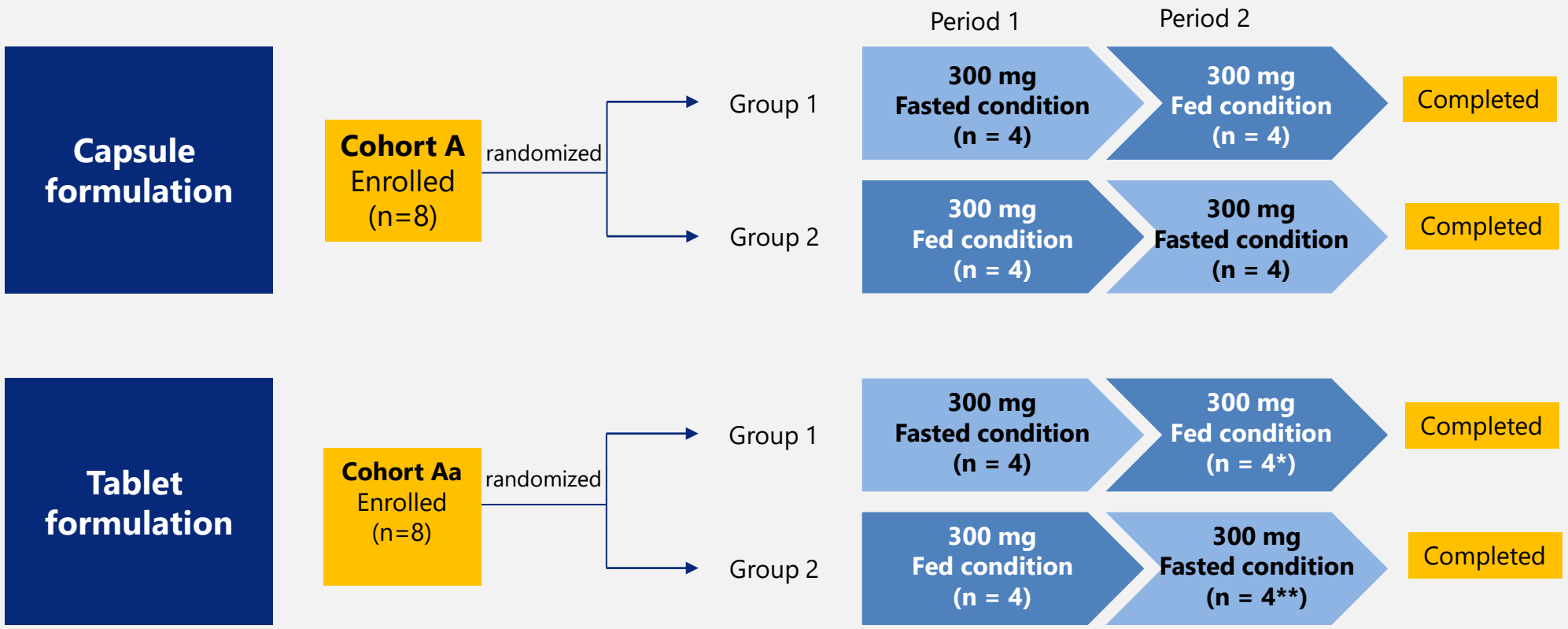




Sofnobrutinib (AS-0871): Phase 1 MAD Study BA part

Study Design of rBA/FE part

PK, safety, and tolerability after single-dose oral administration of sofnobrutinib, 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).

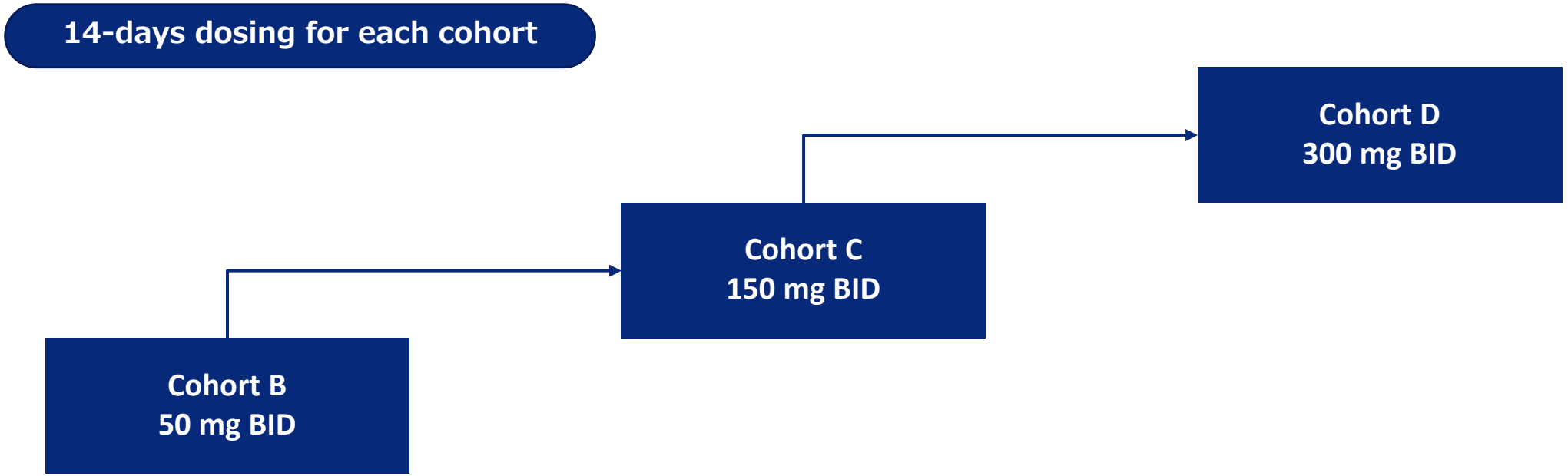


*One subject vomited after dosing (considered not related to study drug), excluded from the PK analysis.
**One subject withdrew from the study due to personal reasons before dosing.

Sofnobrutinib (AS-0871): Phase 1 MAD Study MAD part

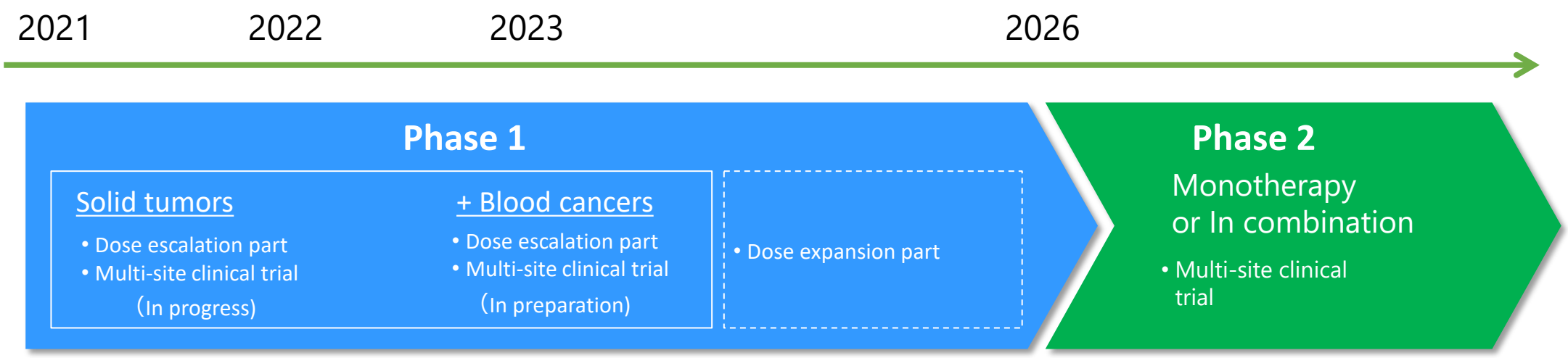
Study Design of MAD part

- In the MAD part, safety, tolerability, PK, and PD of 3 multiple ascending doses of sofnobrutinib, following 14-day multiple dose oral administration of sofnobrutinib, 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 final Clinical Study Report (CSR) for the Phase 1 MAD study has been finalized in November 2023.



Monzosertib (AS-0141): CDC7 Inhibitor

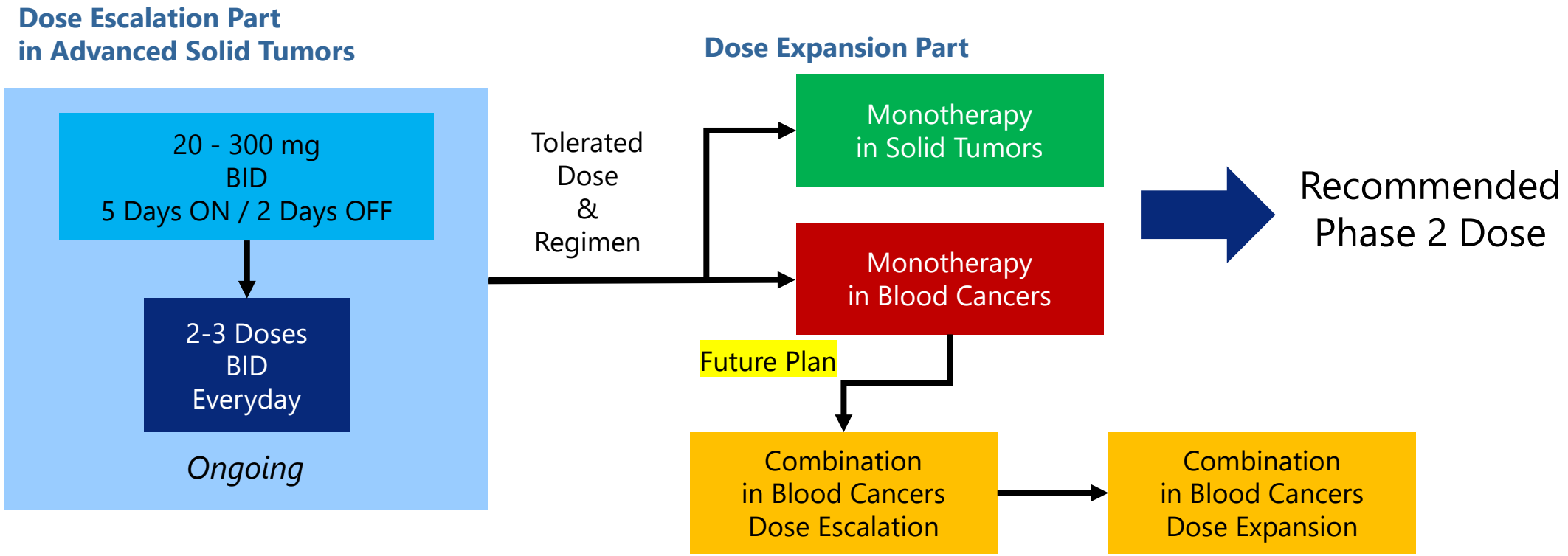
monzosertib：Targeting Cancer	
● Small molecule CDC7 inhibitor ● High kinase selectivity ● Potential First-in-class drug ● Orally available	● Potent anti-proliferative activity against various cancer cell lines ● Demonstrated strong anti-tumor activity in several human tumor xenograft models ● Conducting Phase 1 study in Japan targeting solid tumors ● Planning to expand to blood cancers as monotherapy or in combination with other drugs



Monzosertib (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 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.
- Pharmacodynamic effect of monzosertib was confirmed at 40 mg-80 mg BID and above.

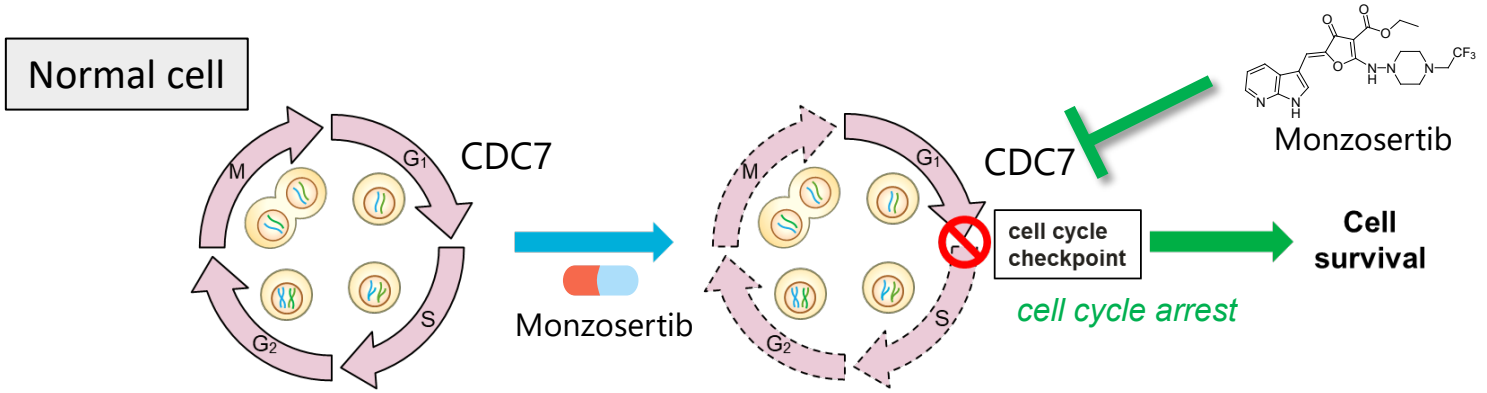


Monzosertib (AS-0141)

Potential Frist-in-class CDC7 Inhibitor Targeting Cancer

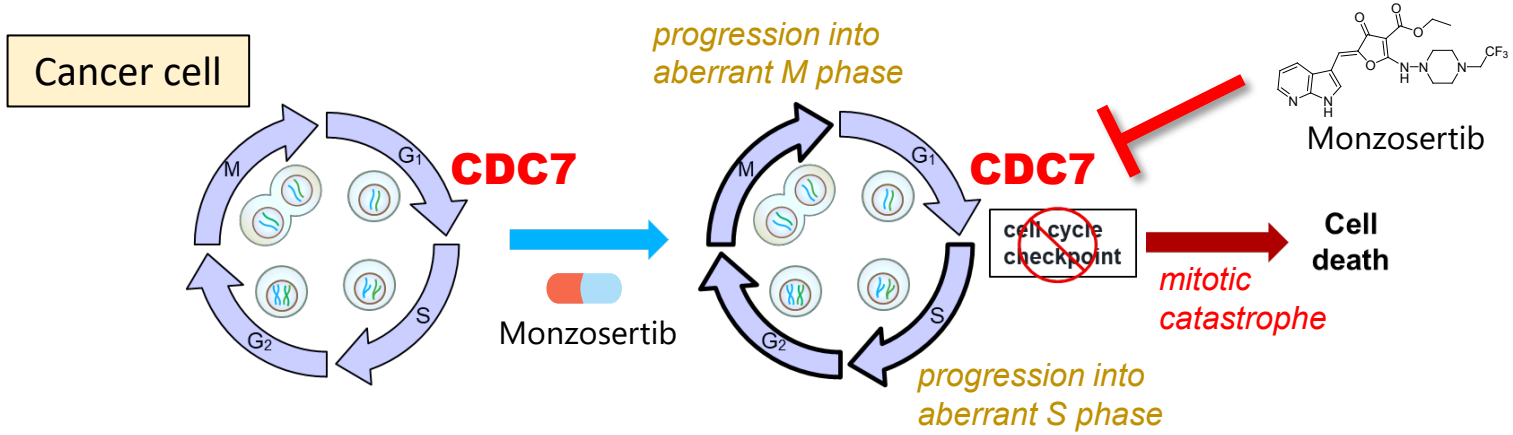
MoA of Monzosertib

◆ CDC7 (cell division cycle 7) is a serine/threonine kinase that facilitates DNA replication during DNA synthesis



Inhibition of CDC7 in normal cells does not cause cell death, only leads to cell cycle arrest at the DNA replication checkpoint

◆ Over expression of CDC7 has been reported to cause uncontrolled proliferation of many cancer types



Inhibition of CDC7 in cancer cells causes lethal S phase or M phase progression when the cancer cells have a defective cell cycle checkpoint

Monzosertib (AS-0141): Time-Dependent Inhibitor of CDC7

◆ Monzosertib 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

pubs.acs.org/jmc

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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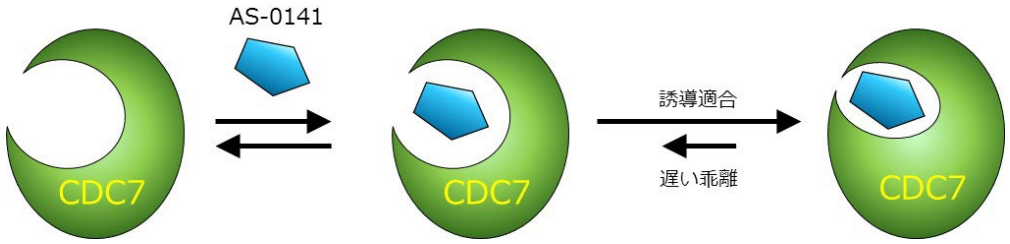
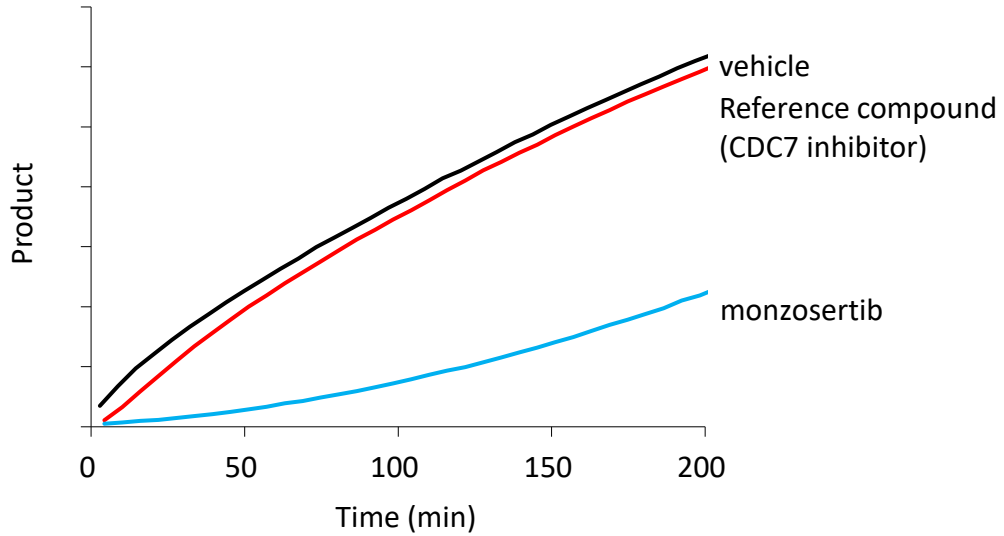


Inhibitory potency (IC50) for CDC7 in the presence of 1 mM ATP	
Without Preincubation	With Preincubation
503 nM	2.4 nM

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

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

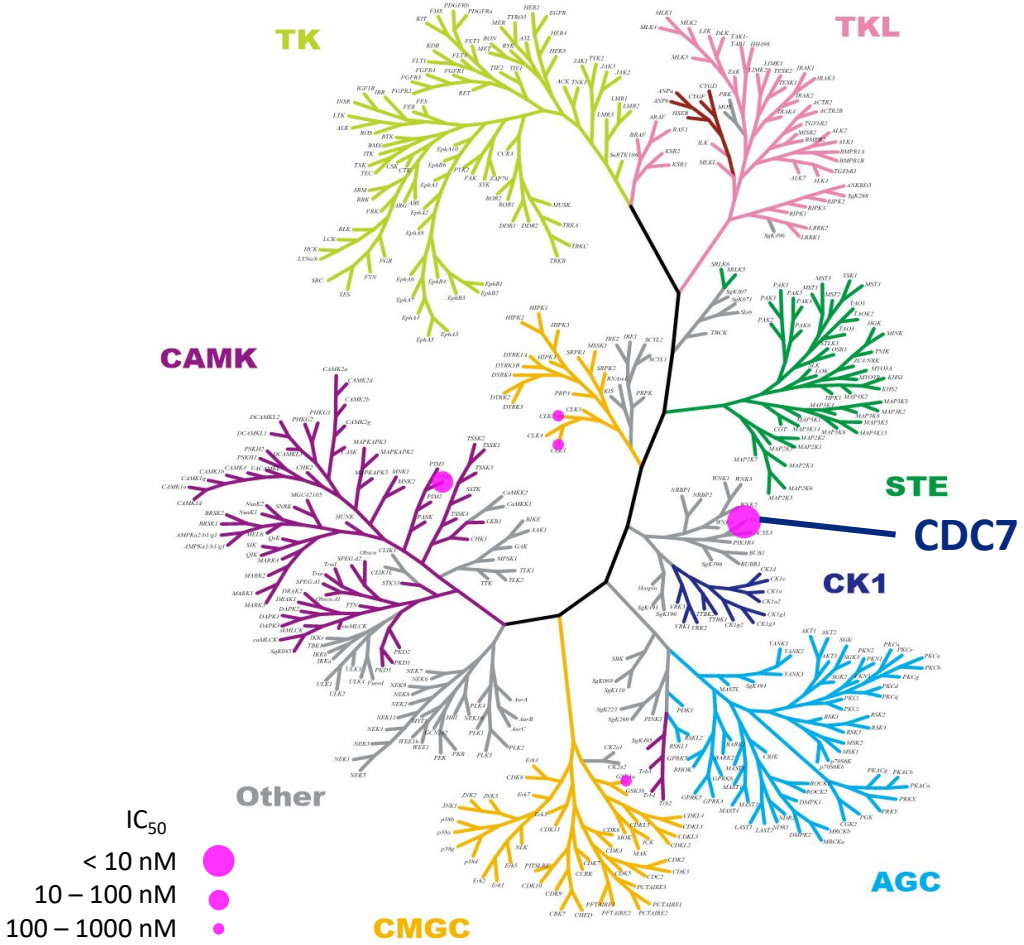
Rapid dilution assay for Cdc7 inhibitors. Recovery of enzymatic activity was monitored by formation of the phosphorylated product.



Monzosertib (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

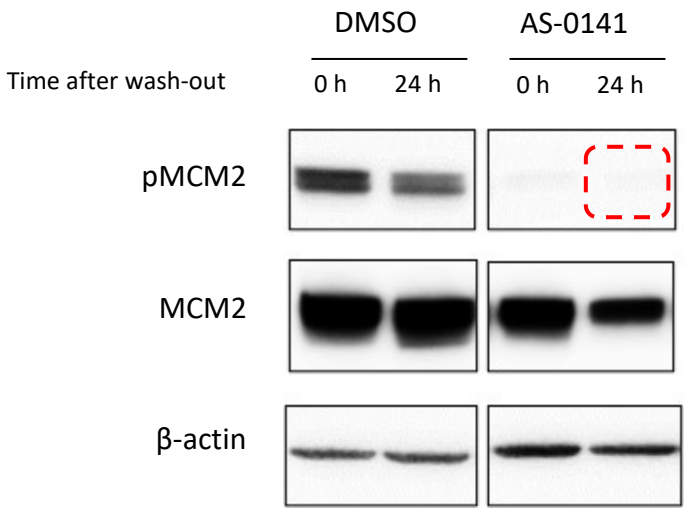
CDC7 is the only kinase that shows preincubation effect

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

Monzosertib (AS-0141): Strong Cellular Activity

◆ Prolonged inhibition in cells

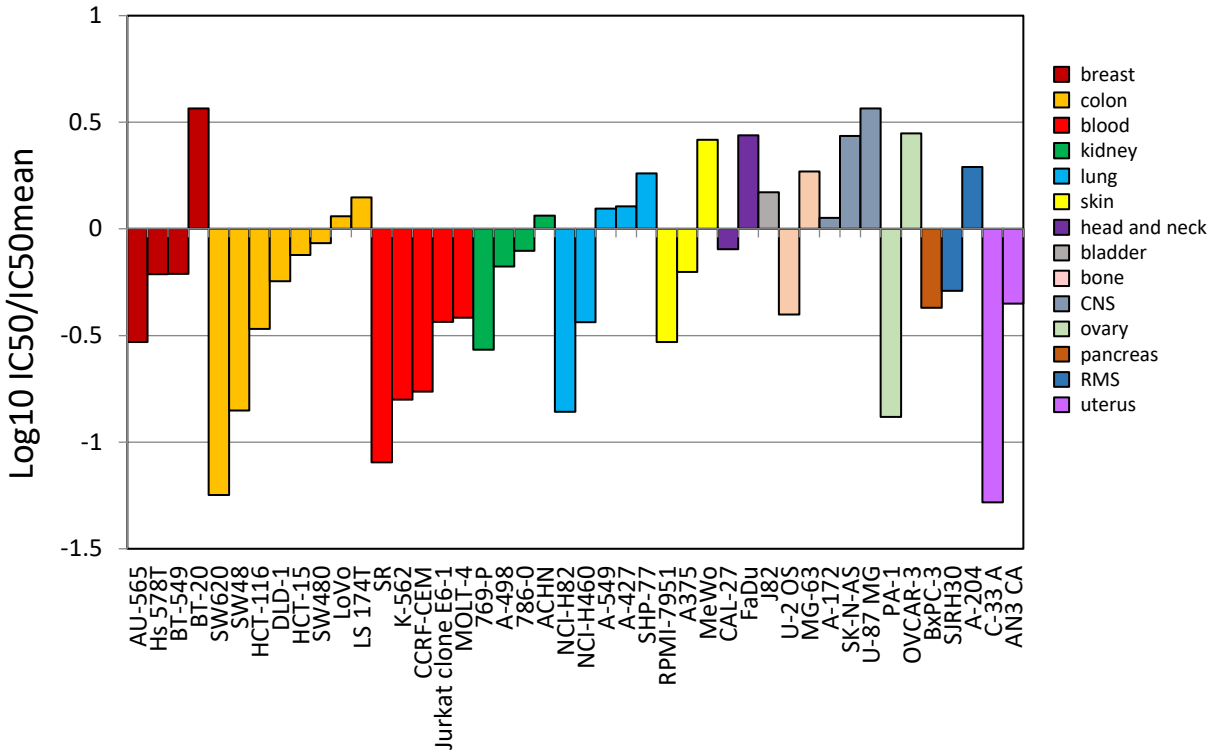
Human colon cancer cell line, Colo-205 cells were treated with DMSO control or monzosertib. After washout of the inhibitor, the cells were further incubated in the same media for 0 or 24 h and subjected to western blot analysis.



the inhibitory effect of monzosertib 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.

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

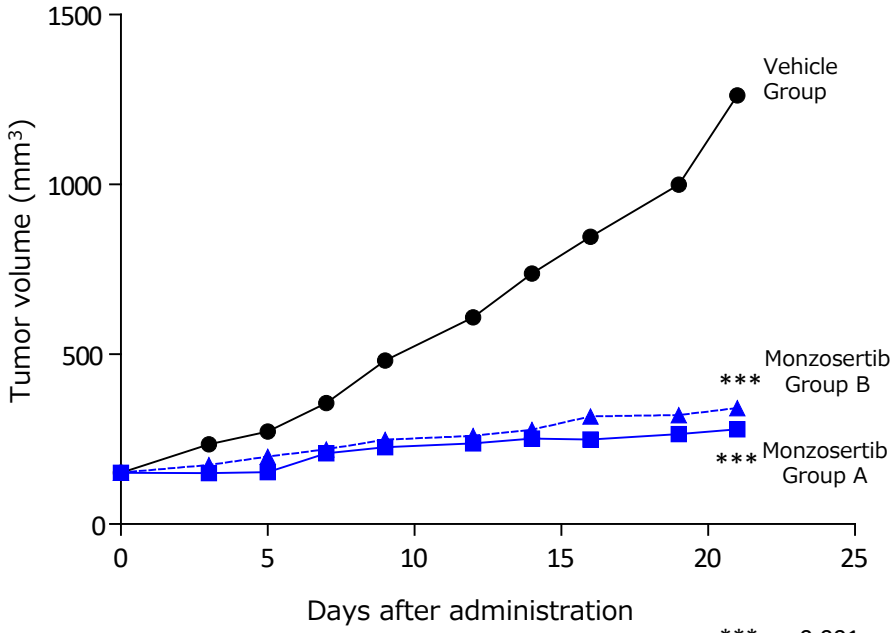


44 Cancer cell lines (Oncolines at NTRC)

Monzosertib (AS-0141): Robust In Vivo Antitumor

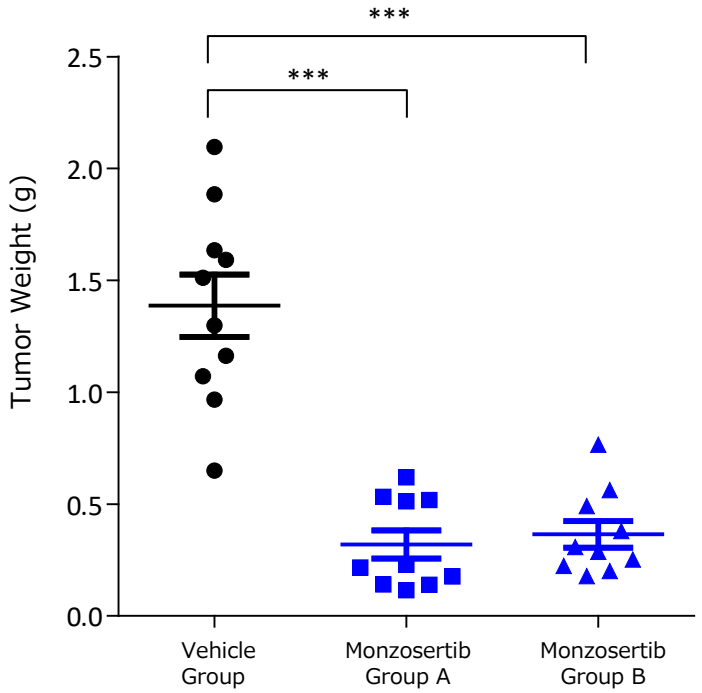
In vivo antitumor efficacy of monzosertib in a SW620 (human colon cancer) xenograft mouse model

Tumor Growth Curve (Mean, n = 10)



***: p<0.001

Final Tumor Weight of Each Mouse



***: p<0.001

Monzosertib group A: 60 mg/kg TID, 4d ON/2d OFF
Monzosertib 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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