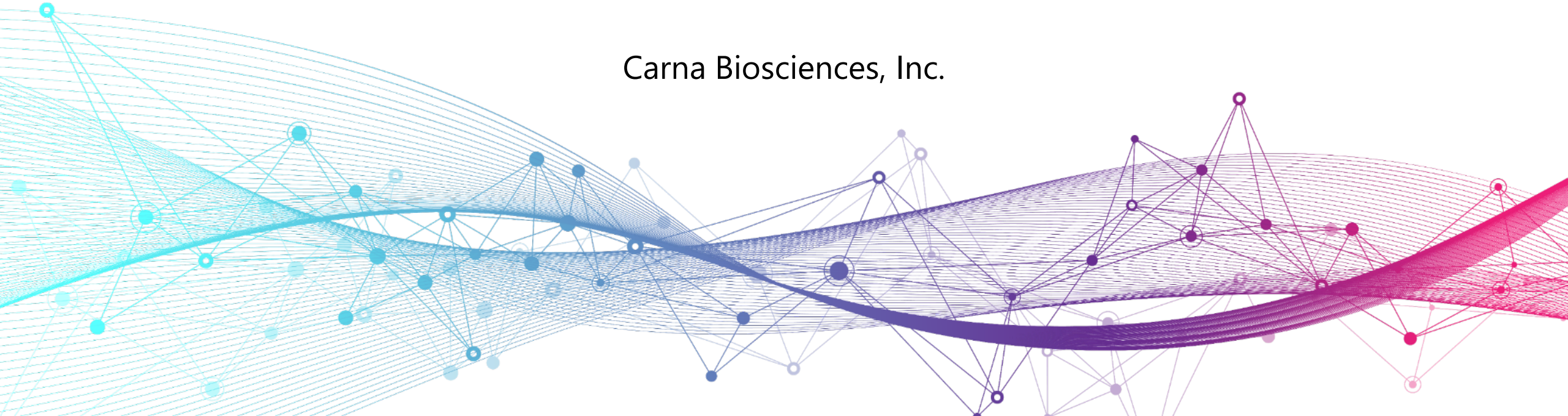
Financial Results
Q1 FY2024

(January to March 2024)

Carna Biosciences, Inc.



AGENDA

1. FY2024 Q1 Key Highlights
2. Updates on Pipelines in Clinical Development
3. Updates on Licensed Pipelines
4. Drug Discovery Support Business
5. FY2024 Q1 Results
6. Appendix

FY2024 Q1 Key Highlights

BTK inhibitor AS-1763

- Phase 1b study is ongoing in the U.S.

  Multi-center clinical study
  Study Lead : Prof. Nitin Jain, MD, Department of Leukemia,
  University of Texas MD Anderson Cancer Center.

- Safe and well tolerated at the first three dose levels and moved to the dose level 4 in March 2024.

CDC7 inhibitor monzosertib (AS-0141)

- Phase 1 study in cancer patients is in progress in Japan.

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

- Presented new preclinical data on monzosertib at AACR in April 2024.

  The preclinical data demonstrates the antitumor efficacy of monzosertib alone against human AML cell lines.
  Monzosertib also demonstrated strong synergistic effects in combination with current therapies in AML models.

AACR: American Association for Cancer Research

FY2024 Q1 Key Highlights

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

- Phase 1 study in patients with solid tumor is ongoing.
- The patent filed jointly with Gilead was granted in China.

STING Antagonist

- The patent was granted in the U.S. in January 2024.
- The license agreement between Carna and Fresh Tracks Therapeutics (FRTX) was terminated in March 2024 as the Board of Directors of FRTX approved a plan of liquidation and dissolution of the company.

FY2024 Q1 Key Highlights

Drug Discovery Support Business

- Presented the development progress of next generation profiling system with BioPhase 8800 at SLAS2024 in February 2024.
- Planning to start a cutting edge profiling service employing BioPhase8800 in May 2024.

New profiling system
This system consists of combination with Sciex BioPhase8800 and the robot arm which we originally installed.

- Carna and Carterra jointly presented new data investigating kinase-compound interactions at SLAS2024 in February 2024.
- Published a paper on a joint research with Japanese Foundation for Cancer Research at npj Precision Oncology.

SLAS : Society for Laboratory Automation and Screening

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 1b clinical trial is ongoing in the U.S. The first patient was dosed in August 2023. Safe and well tolerated at the first three dose levels and moved to the dose level 4 in March 2024. Multi-center clinical study Study Lead ：Prof. Nitin Jain, MD, Department of Leukemia, University of Texas MD Anderson Cancer Center.
sofnobrutinib (AS-0871)	BTK	Immune-inflammatory diseases	• Completed Phase 1 clinical trials in healthy volunteers in the Netherlands. Demonstrated a favorable safety and tolerability profile as well as a promising PK/PD profile in the study. These results supported to advance sofnobrutinib into Phase 2 clinical development for further investigations in November 2023. • Focusing on the partnering activities.
monzosertib (AS-0141)	CDC7/ ASK	Cancer	• Dose escalation part of Phase 1 study in cancer patients is ongoing in Japan. Clinical trial site : National Cancer Center Hospital and National Cancer Center Hospital East

AS-1763: Highlights

Refer to P.41-P.48 for more information

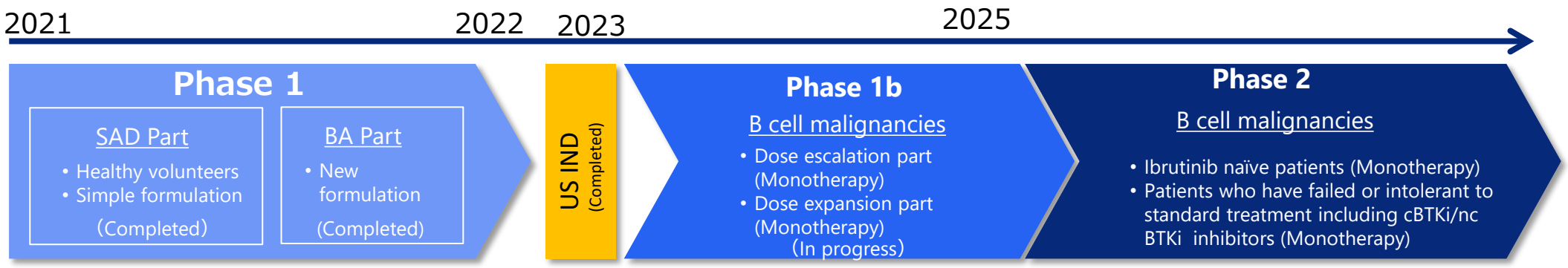
Mechanism/ Indication	**Orally available** small molecule inhibitor of Bruton's Tyrosine Kinase (BTK) targeting B-cell malignancies
To overcome drug resistance	AS-1763 is a **non-covalent inhibitor** that reversibly inhibits BTK, **having a potential to be effective for patients who have developed resistance to the existing BTK inhibitors**.
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: Next Generation BTK Inhibitor

AS-1763 : Targeting Blood Cancer

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

- Active against covalent/non-covalent BTK inhibitor-resistant mutations found in patients (C481x, T474x, T316A, L528x)
- 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.
cBTKi: covalent BTK inhibitor
ncBTKi: noncovalent BTK inhibitor

AS-1763: Ph I 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: Ph I Clinical Trial in Healthy Volunteers

Ref. P.44-P.47

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 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.48

Multi-center clinical study
Study Lead：Prof. Nitin Jain, MD, Department of Leukemia, University of Texas MD Anderson Cancer Center.

Clinical trails in progress	Phase 1b dose escalation part was initiated in the U.S.
Indication	Patients with CLL(Chronic Lymphocytic Leukemia), SLL(Small Lymphocytic Leukemia), and B-cell NHL(B-cell non-Hodgkin Lymphoma).
Status	• Opened 9 clinical sites. • Safe and well tolerated at the first three dose levels. • Moved to the dose level 4 in March 2024.

BTK Inhibitors in clinical development

Competitors: other non-covalent BTK inhibitors in clinical development

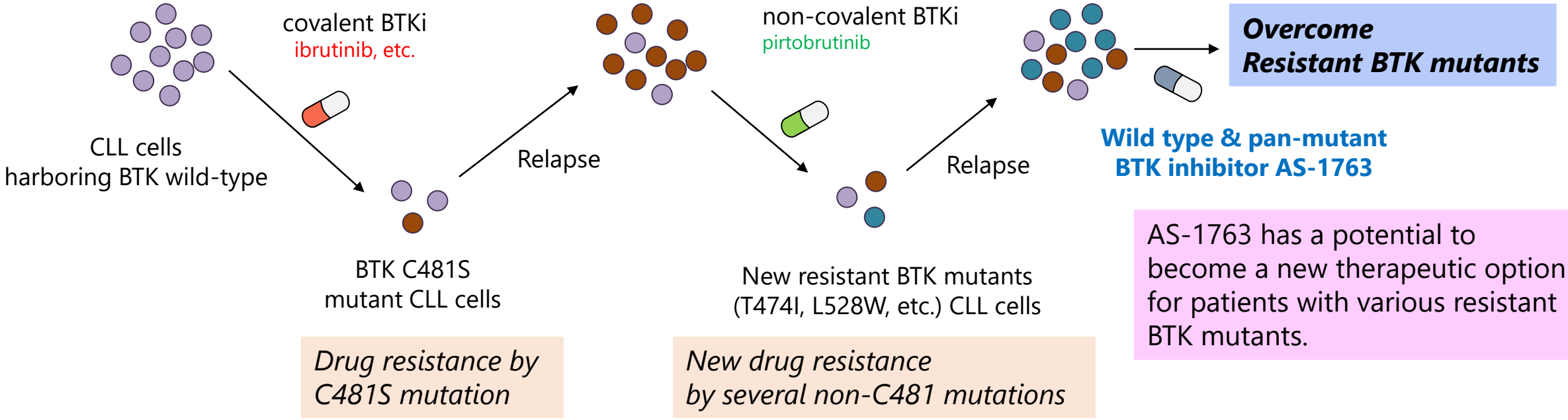
Compound	Company	Development Phase
pirtobrutinib (LOXO-305)	Lilly (Loxo)	Approved/P3
nemtabrutinib (ARQ 531)	Merck (ArQule)	P3
TT-01488	TransThera	P1
HMPL-760	HutchMed	P1

- 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.
**Poster presentation at ASH 2024

AS-1763: Wild-type & Pan-mutant BTK Inhibitor

- Covalent BTK inhibitors have been widely appreciated as a promising targeted therapy for patients with B-cell malignancies.
- However, patients are reported to develop resistance during the treatment due to substitution of cysteine residue at 481 position with serine (C481S mutation) in BTK, which reduces the efficacy of the covalent BTK inhibitors.
- In addition, the emergence of other types of resistance mutations to non-covalent BTK inhibitor, pirtobrutinib approved in 2023, has been reported.
- AS-1763 potently inhibited both wild type and those mutant BTKs, strongly suggesting that AS-1763 will be a new therapeutic option for treating patients with B-cell malignancies both having wild type and resistance mutations in BTK.



AS-1763 has a potential to become a new therapeutic option for patients with various resistant BTK mutants.

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

Present

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

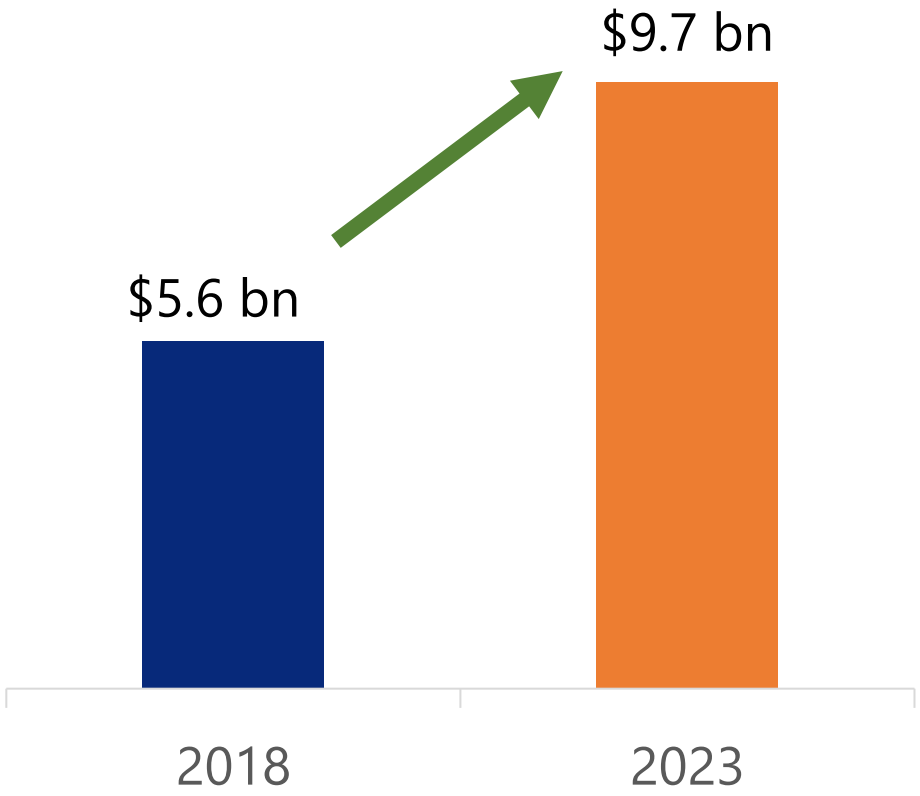
Opportunity

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 for Blood Cancer



BTK Inhibitors WW sales
(1st generation/covalent type)

The sales growth of first-generation BTK inhibitors has slowed due to potential side effects and drug-resistance by C481S mutation.

Next generation BTK inhibitors including AS-1763 are under development to overcome side effects and drug-resistance.

Global BTK inhibitors market size is still expanding significantly and expected to reach > $22Bn by 2030!

https://www.insightaceanalytic.com

Sofnobrutinib (AS-0871): Highlights

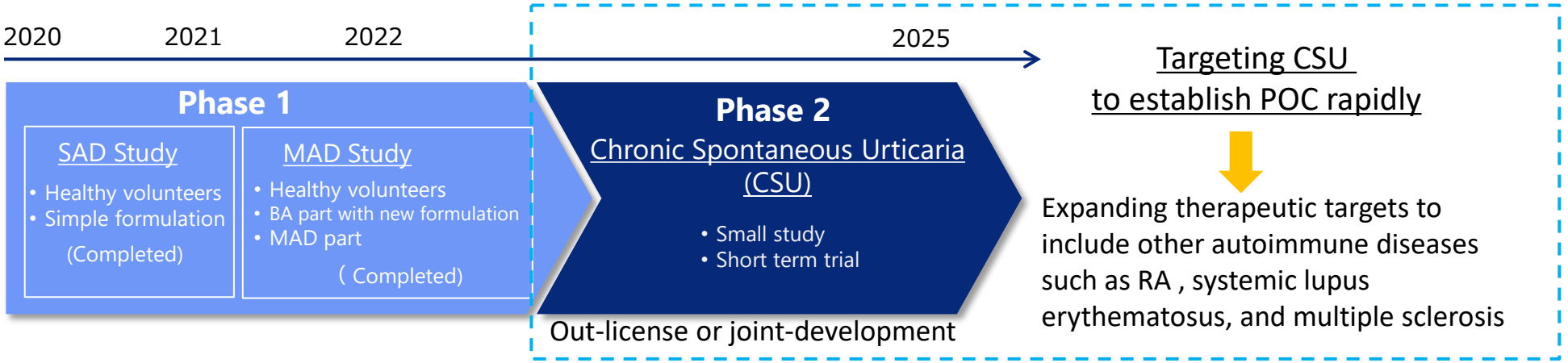
Ref. P.49-P.54

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): Non-covalent BTK Inhibitor

Sofnobrutinib (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

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 sofnobrutinib .

Completed

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

Objectives of Single Ascending Dose (SAD) study

Ref. P.51-P.53

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.54

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 is 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

The Phase III trials met the primary endpoints and showed rapid symptom control in CSU, supporting the potential of BTK inhibitors as a new treatment option for those uncontrolled by first-line H1-antihistamines.*

＊https://www.novartis.com/news

Opportunity

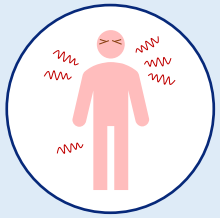
- Approval of new treatment options may trigger the expansion of CSU market.
- We plan to pursue the clinical implications of sofnobrutinib (non-covalent BTK inhibitor) to provide clinical benefits by minimizing potential adverse events associated with covalent BTK inhibitors including remibrutinib.

Chronic Spontaneous Urticaria (CSU)

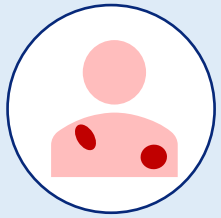
CSU is a debilitating disease of chronic itch, hives and angioedema, lasting six weeks or more.

Symptoms

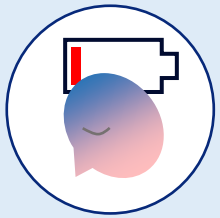
There is no specific external trigger for CSU, but the autoimmune system may play a role.



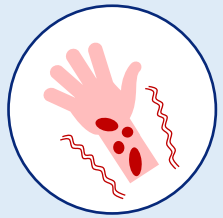
Spontaneously present & re-occur



Red swollen hives



Lack of Energy
Depression/Anxiety
Chronic (Lasting for at least six weeks)



Itch

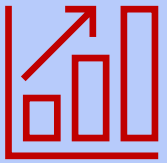
Number of Patients

2.8 million

diagnosed prevalent cases in major seven markets

- ✓ Approximately 1% of the population worldwide is affected.
- ✓ Approximately 50% of CSU patients don't respond to H1-antihistamine.
- ✓ Curative treatment is not available.
- ✓ High socio-economic costs for patients with high disease activity.

Market Size



$1,315 million

in 2021 in seven major markets

- ✓ The market size of CSU in major seven countries is expected to reach $7,664 mn by 2032 growing at a CAGR of 14.96% from 2019.

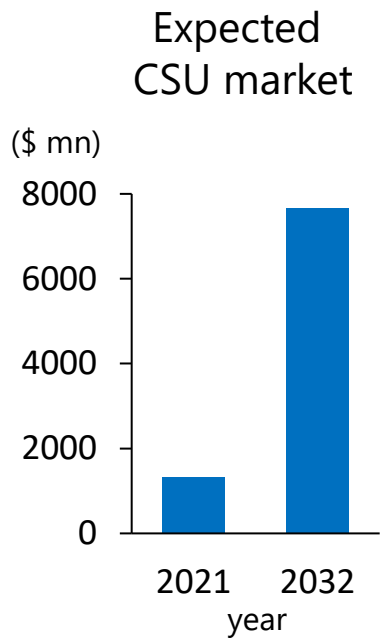
https://www.delveinsight.com/

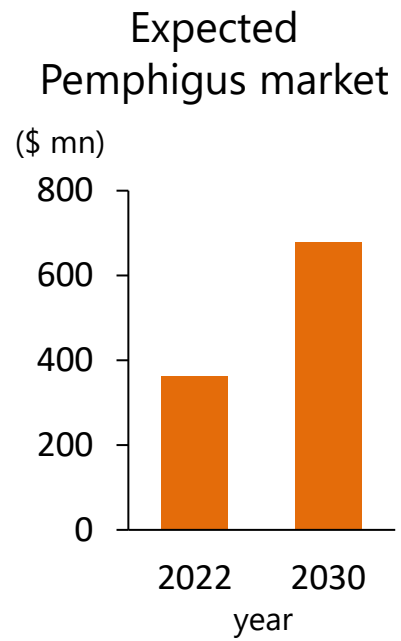
Potential Market Size for Sofnobrutinib

Initial focus

Diseases	Number of patients
CSU	• Diagnosed prevalent cases : 2.8 mn* • WW population affected: 76 mn
Pemphigus	• Diagnosed prevalent cases : 40,000*

*in major 7 markets





Other potential therapeutic area

Diseases	Number of patients	Market size in value
Systemic lupus erythematosus (SLE)	Global SLE prevalence is estimated to be 15.87 to 108.92 per 100,000 people	expected to reach $3,517 mn by 2030
Multiple sclerosis (MS)	In 2016, an estimated 2.2 million people worldwide had MS, corresponding to a prevalence of 30.1 cases per 100,000 population	expected to reach $34 bn by 2031
Rheumatoid arthritis (RA)	18 million people worldwide were living with RA	expected to reach $70 bn by 2030

https://www.delveinsight.com/
https://www.databridgemarketresearch.com/
https://ard.bmj.com/
https://straitsresearch.com/
https://www.skyquestt.com/
https://www.who.int/
Ann Rheum Dis 2023;82:351–356
Lancet Neurol 2019 ; 18: 269–85

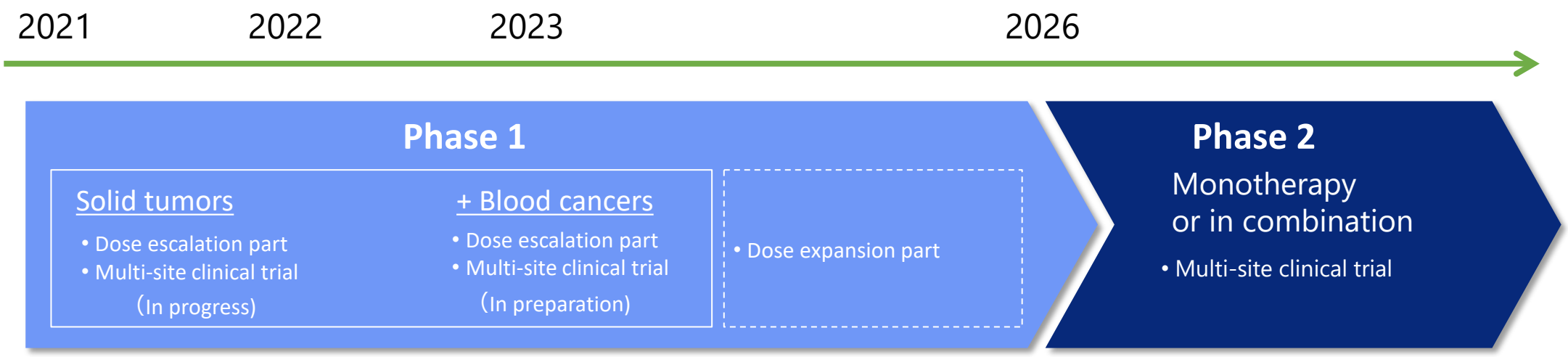
Monzosertib (AS-0141): Highlights

Ref. P.55-P.59

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): CDC7 Inhibitor

Monzosertib (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 and blood cancers



Monzosertib (AS-0141): Phase 1 Clinical Trials

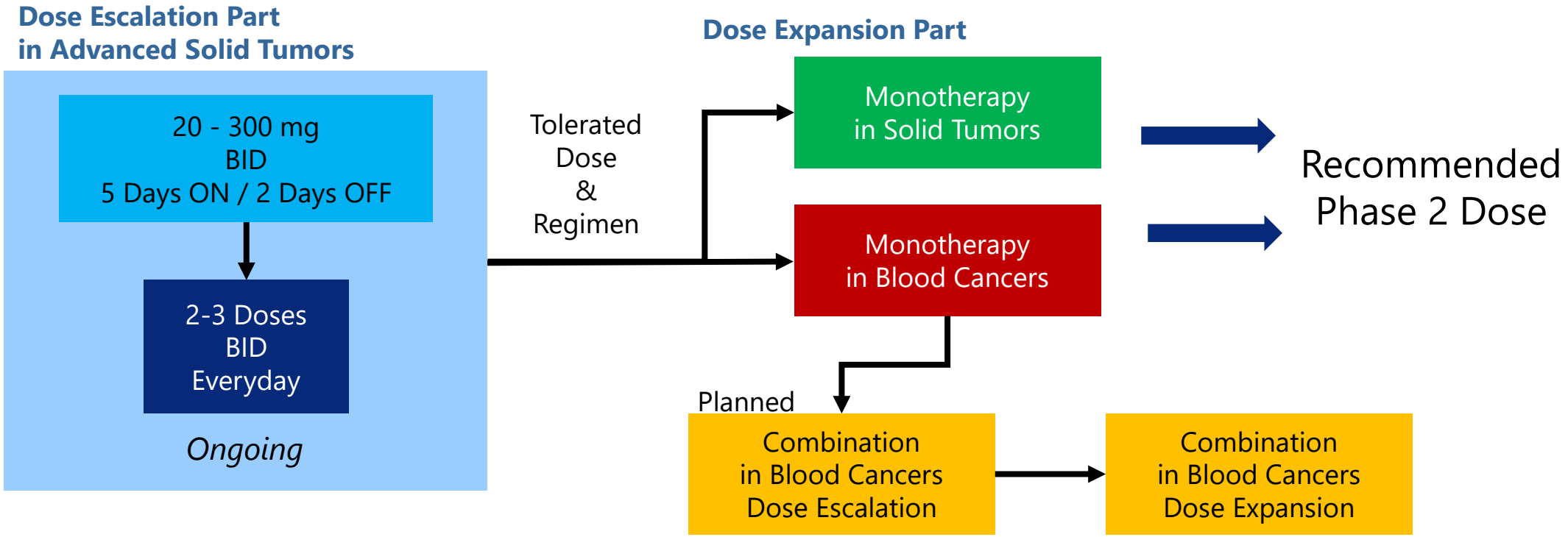
Clinical trial sites : National Cancer Center Hospital and National Cancer Center Hospital East

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	• Treating patients at doses up to 300 mg BID (5d on/2d off). • 80 mg BID (5d on/2d off) was well-tolerated and safe. • Switched to a continuous dosing schedule (without drug holiday) to maximize efficacy, and confirmed tolerability at the first dose level. • Expanded the target indications to blood cancers to exploratorily investigate the efficacy.

Monzosertib (AS-0141): Phase 1 Clinical Trial

Phase 1 study targeting cancer patients

- The Phase 1 study in patients with advanced, metastatic, relapsed or refractory malignancies. The protocol has been changed to include patients with blood cancers.
- 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.



Updates on Licensed Pipelines

1. **DGKα Inhibitor** (Gilead Sciences, Inc.)
2. **Joint Research with Sumitomo Pharma**

Out-licensed Programs

Program/ Partner	Compound (Target)	Status	Upfront payment	Total milestone payments expected	Royalty	Region	Contract date	Milestones received
DGKα inhibitor Gilead Sciences (Out-license)	GS-9911 (Immuno-oncology)	Phase 1	$20M	$450M	Undisclosed	Worldwide	Jun. 2019	Received milestones twice, totaling $15M
Joint Research with Sumitomo Pharma	Kinase inhibitor (Psychiatric and neurological disorders)	Late discovery	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

2. Indication: Cancer (immunotherapy)

- At JP Morgan Annual Healthcare Conference held in January 2024, Gilead introduced DGKα as next generation target in oncology and presented GS-9911 as the DGKα inhibitor in Phase 1 trials.

3. The Phase 1 study in patients with solid tumors is ongoing.

Refer Gilead's website for details of the study.
https://www.gileadclinicaltrials.com/study?nctid=NCT06082960

Joint Research with Sumitomo Pharma

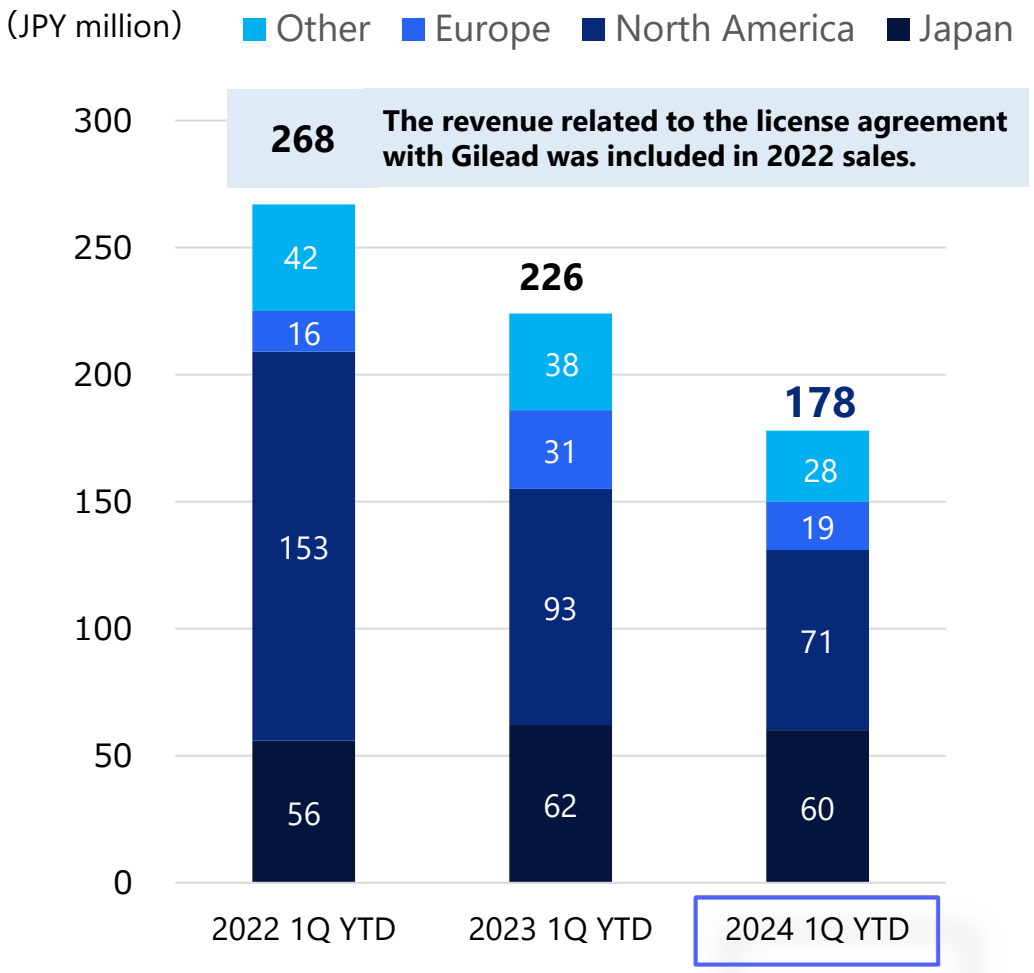
Partner	Sumitomo Pharma Co., Ltd. Joint Research Agreement in March 2018 (worldwide rights)
Deal size	• Upfront payment + Research milestone JPY80 million • Maximum of JPY10.6 billion potential milestone payments upon achievement of certain development and commercial milestones
Royalties	• Royalties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

Drug Discovery Support (ddSP) Business

FY2024 Q1 YTD Drug Discovery Support Business Sales Trend

Drug Discovery Support Business Sales Trend by Region (Consolidated)



The revenue related to the license agreement with Gilead was included in 2022 sales.

Japan

Decreased 3.0% YoY

- Though the sales of proteins to distributors were weak, sales to pharmaceutical companies were robust.
- Overall sales remained at the same level YoY.

North America

Decreased 23.1% YoY

- Sales decreased YoY. Accompanied with our major customers' projects progress, the needs of kinase protein declined.
- Sales of profiling services to AI-driven drug discovery companies remained strong.

Europe

Decreased 38.1% YoY

- Overall sales declined YoY due to the progress of research of our major customers.

Other

Decreased 26.9% YoY

- The economic recession and the possibility of restraint of trade with Chinese biotech companies by the U.S. government had negative impacts on Chinese market and decreased demand from CROs.

Profiling Services

- Conventionally, capillary electrophoresis has been known as highly reliable method for measuring kinase protein activity without using radioisotopes.
- Perkin Elmer (renamed Revvity in 2023)'s EZ Reader which equipped electrophoresis system on microchip with 12 capillaries has been a de facto standard for measuring kinase activity, was announced its discontinuation including supply of consumables and the support as of the end of this year. This boosts high demand for a substitute system with the same data quality.
- We have been providing high quality profiling services with EZ Reader.
- To continue offering profiling services, we challenged and succeeded in developing our original substitute system. The new system consists of combination with Sciex BioPhase8800 of 8 capillary electrophoresis, and the robot arm with stacker which we originally installed by combining stand alone machines.

Carna will continue reliable profiling services with this original system and aim to acquire even more customers.

Biotinylated Protein Kinases

- The demand for high throughput screening systems for small molecule compounds which bind to kinase proteins is increasing.
- Carterra (U.S) developed a new innovative high throughput system, LSA^{XT}, which enabled small molecule screening and characterization in addition to antibody.
- Carna and Carterra collaborated to preliminary develop the assay with this new screening system in combination with Carna's single site biotinylated kinase proteins and Carterra's HT-SPR LSA^{XT} instrument.
- This collaboration successfully proved this new system screen about hundreds kinases and compound binding event just in 3 days.

Our biotinylated kinase protein sales is expected to be expand with the permeation of Carterra LSA^{XT}.

FY2024 Q1 Results

FY2024 Q1 Results by Business Segment

(JPY million)	Q1FY2023 Actual	**Q1FY2024 Actual**	YoY Change	FY2024 Plan	
Total Sales	226	**180**	-46 -20.3%	925	
ddSP business	226	**180**	-46 -20.3%	925	• Overall sales declined due to weaker than expected overseas sales while sales in Japan remained solid.
ddRD business	—	**—**	—	—	
Total Operating Profit/Loss	-505	**-416**	89	-2,201	• Operating loss decreased YoY mainly due to the decrease in R&D cost.
ddSP business	64	**1**	-62 -97.7%	229	• Operating profit declined YoY due to the decrease in sales.
ddRD business	-570	**-417**	152	-2,431	• Operating loss decreased YoY due to the decrease in R&D cost.
Ordinary Loss	-513	**-394**	118	-2,208	
Net Loss	-519	**-398**	120	-2,225	• Net loss decreased YoY mainly due to the decrease in R&D cost.
R&D cost	535	**377**	-157	2,309	• Continued investment in the clinical-stage programs. • Clinical trial cost and manufacturing cost of investigational new drugs of sofnobrutinib (AS-0871) were recorded in 2023.

Business plan for FY2024 dose 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

Consolidated Balance Sheet

(JPN million)	As of Dec. 31,2023	As of Mar. 31,2024	Change	Reason for changes
Current assets	4,191	3,743	-447	Cash and deposits +270 Accounts receivable-trade -703
Cash and deposits	2,889	**3,159**	+270	Received a milestone payment of $5 million from Gilead.
Non-current Assets	158	150	-7	
Total assets	4,349	3,894	-455	
Current liabilities	375	273	-102	Accounts payable -52
Non-current liabilities	96	102	+6	Long term loans payable -4
Total liabilities	472	376	-96	
Total net assets	3,877	3,517	-359	Retained earnings -398
Total liabilities and net assets	4,349	3,894	-455	

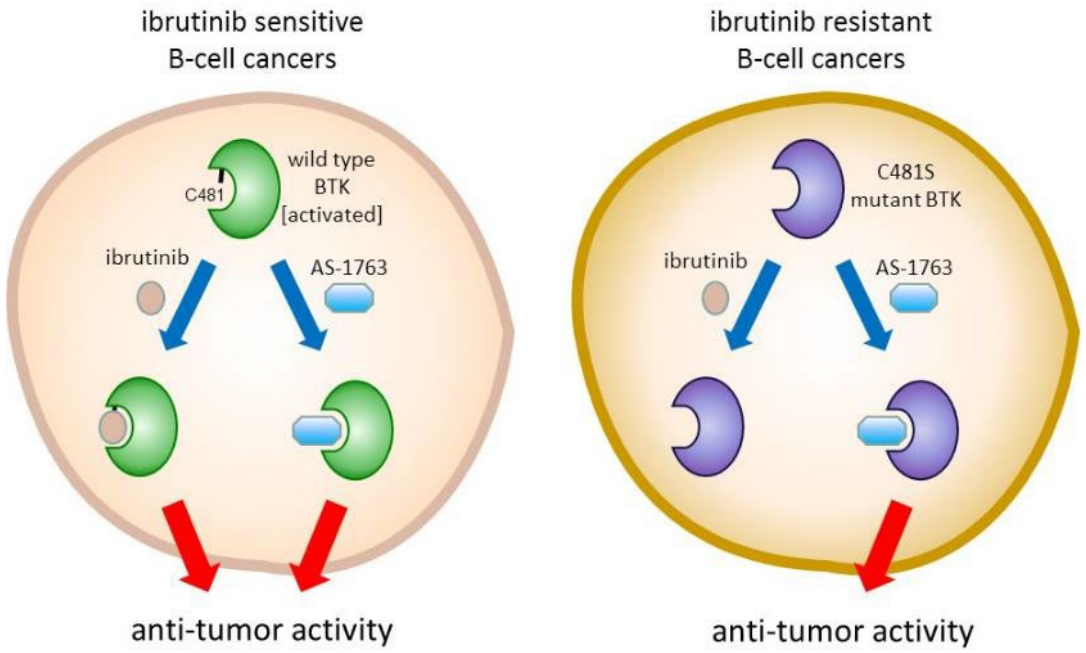
Shareholders' equity ratio	89.1%	90.3%
BPS	226.16yen	205.19yen
PBR(株価純資産倍率)	2.3x	2.3x
Share price of Carna	522yen	479yen

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

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

Appendix

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

◆ 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

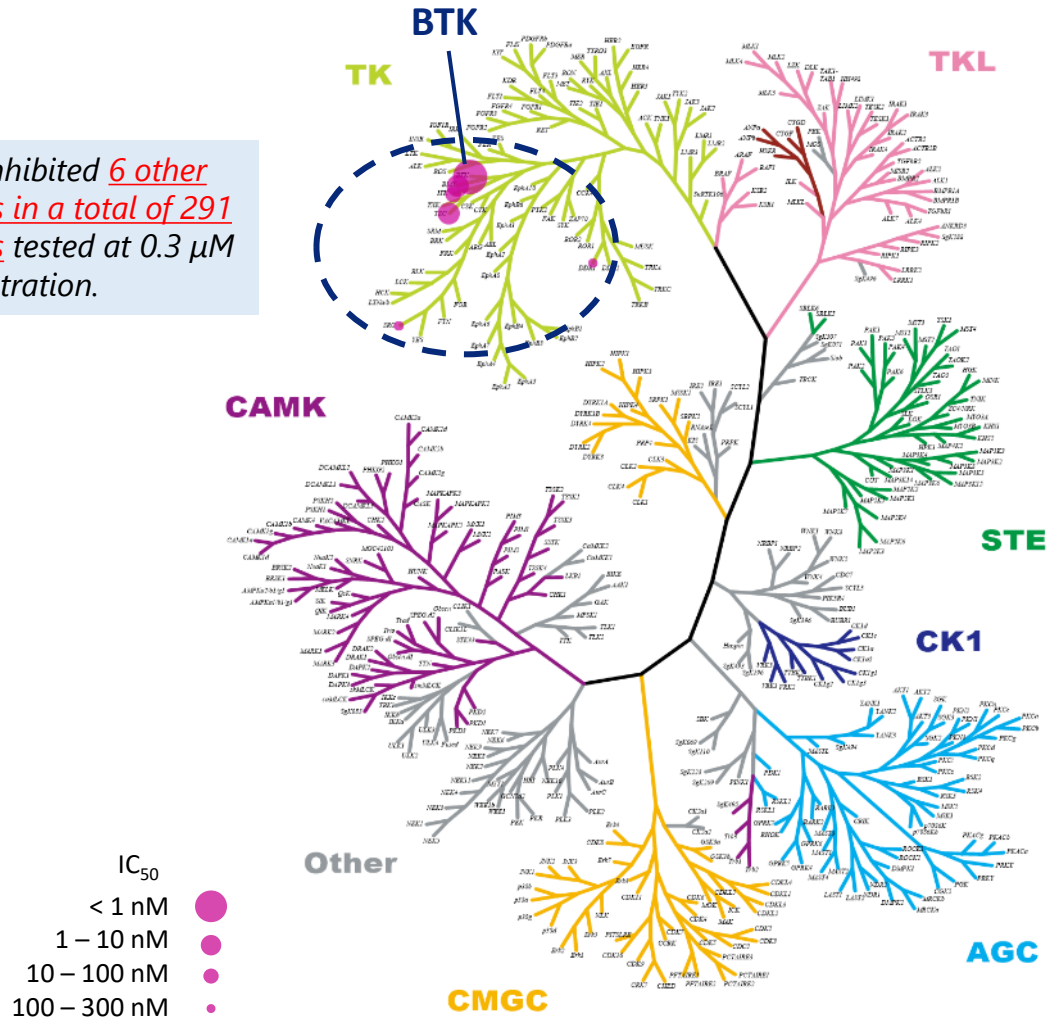
50-fold Stronger activity

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.

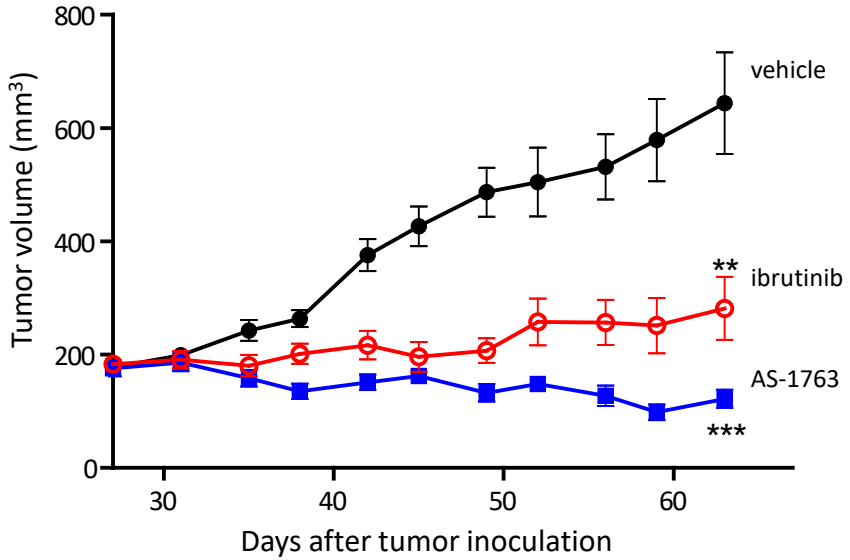
◆ Kinase selectivity profiling

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

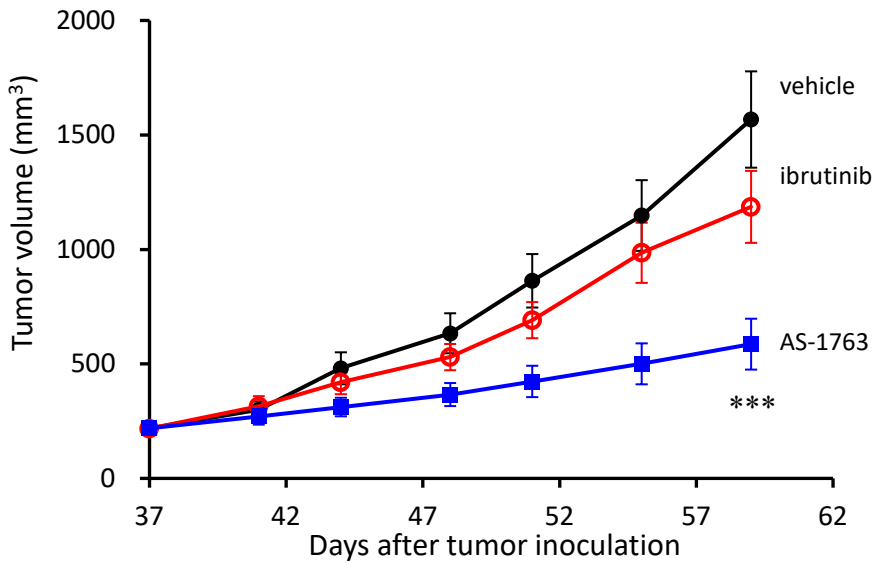
- **In vivo antitumor effects of AS-1763 on human B-cell non-Hodgkin lymphoma cell line, OCI-LY10 tumor xenograft mouse model (n=8-10)**



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

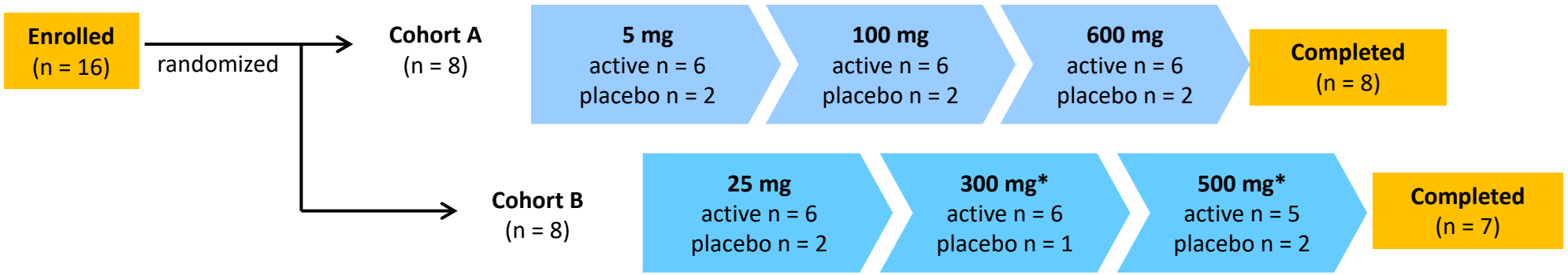
***: p<0.001

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

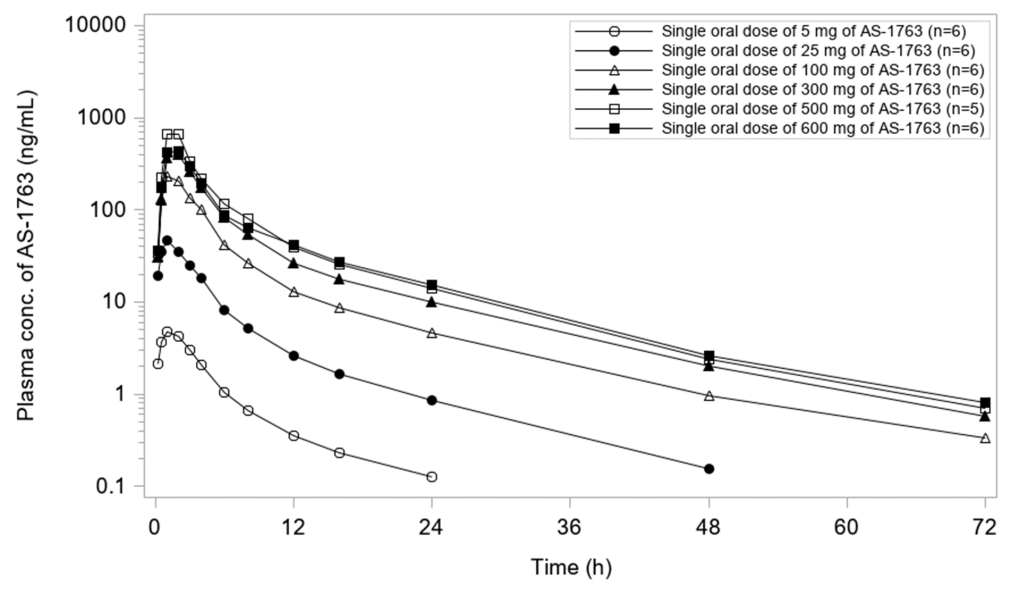
Safety and tolerability

- 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.

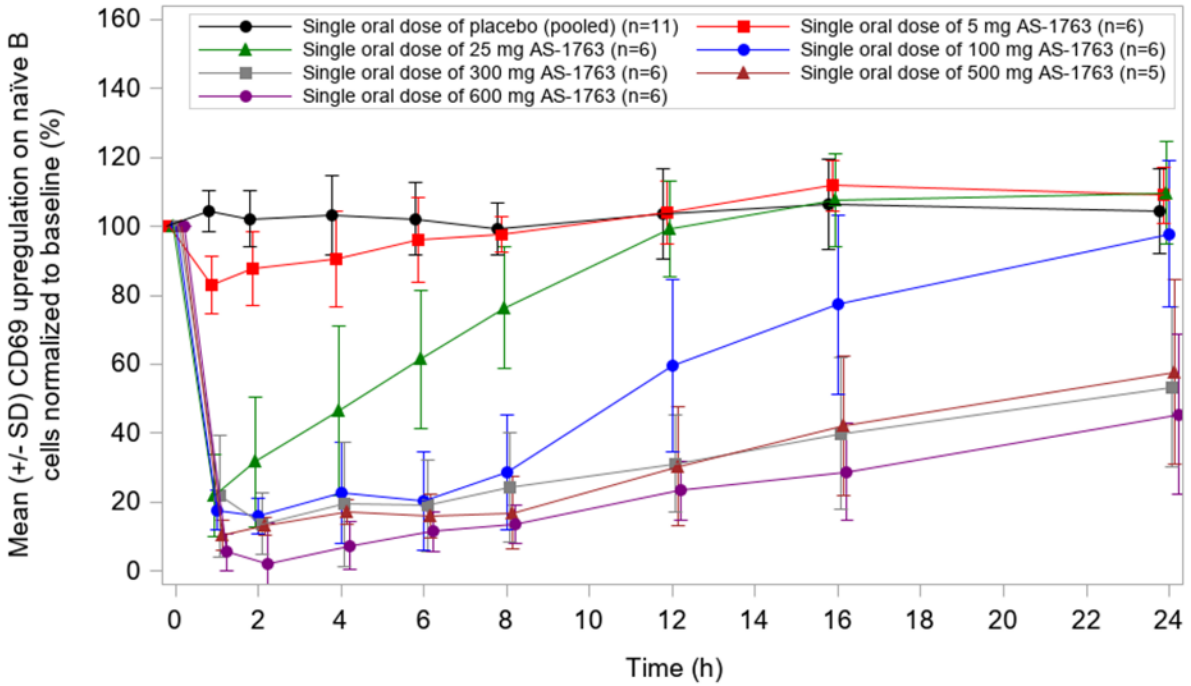
< Plasma concentration of a single oral dose of AS-1763 >



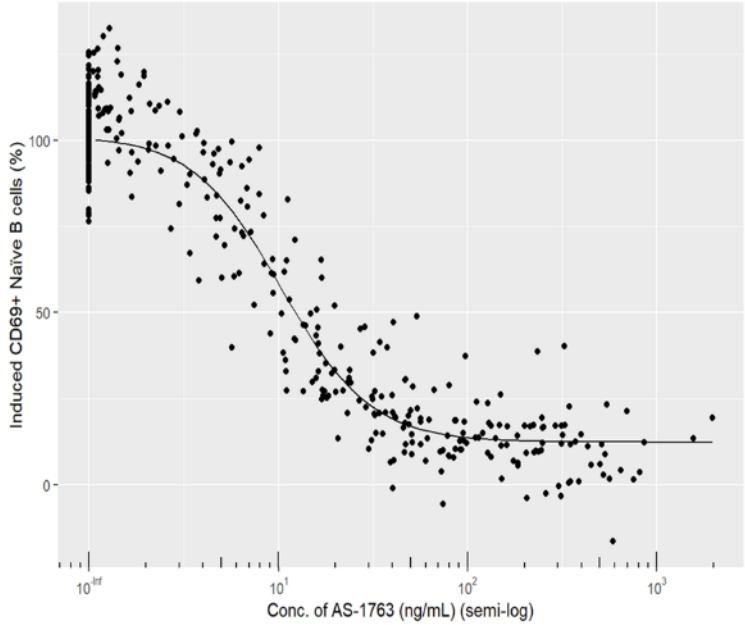
Pharmacodynamics of AS-1763

- 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 >



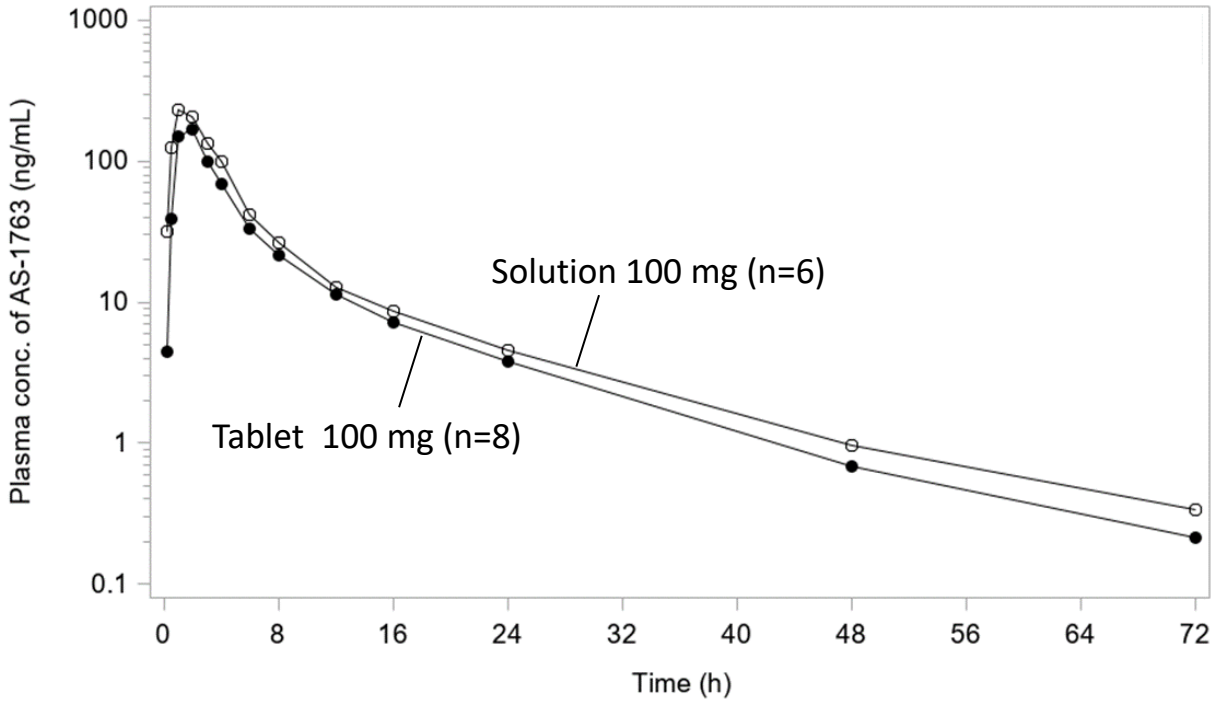
< PK/PD correlation analysis >



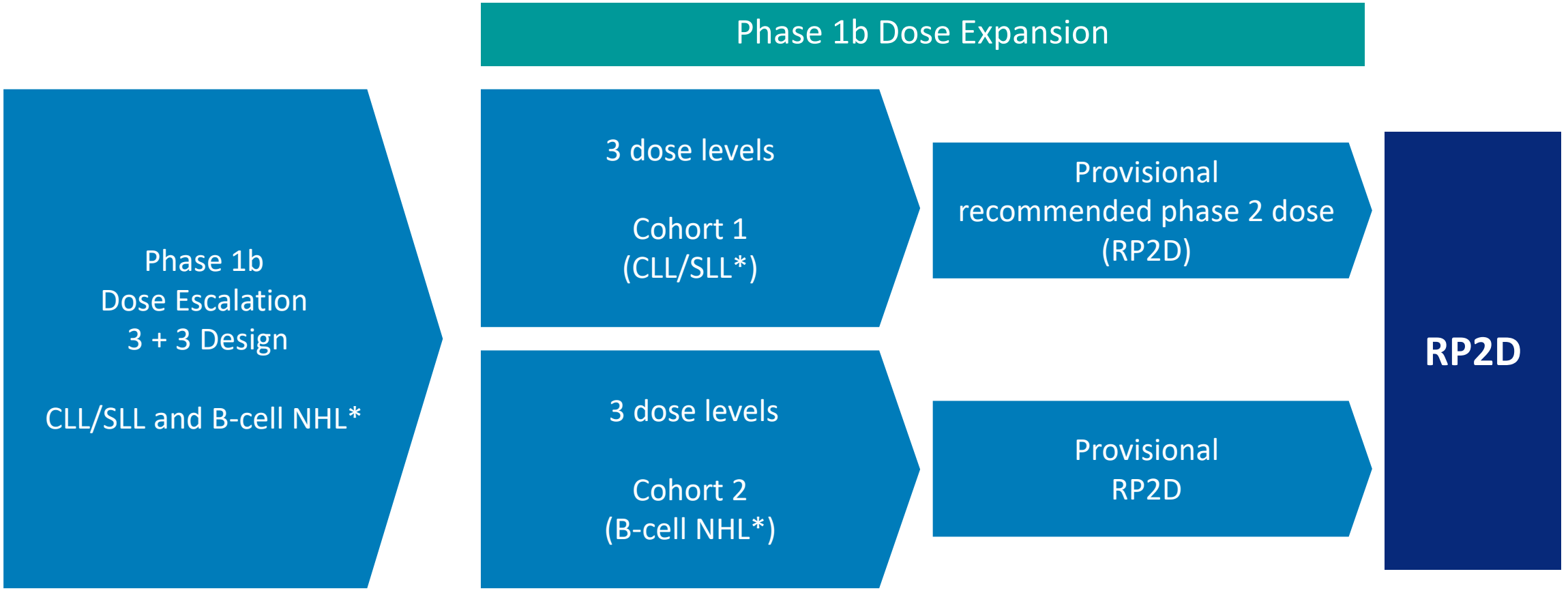
AS-1763: BA Part

- 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)

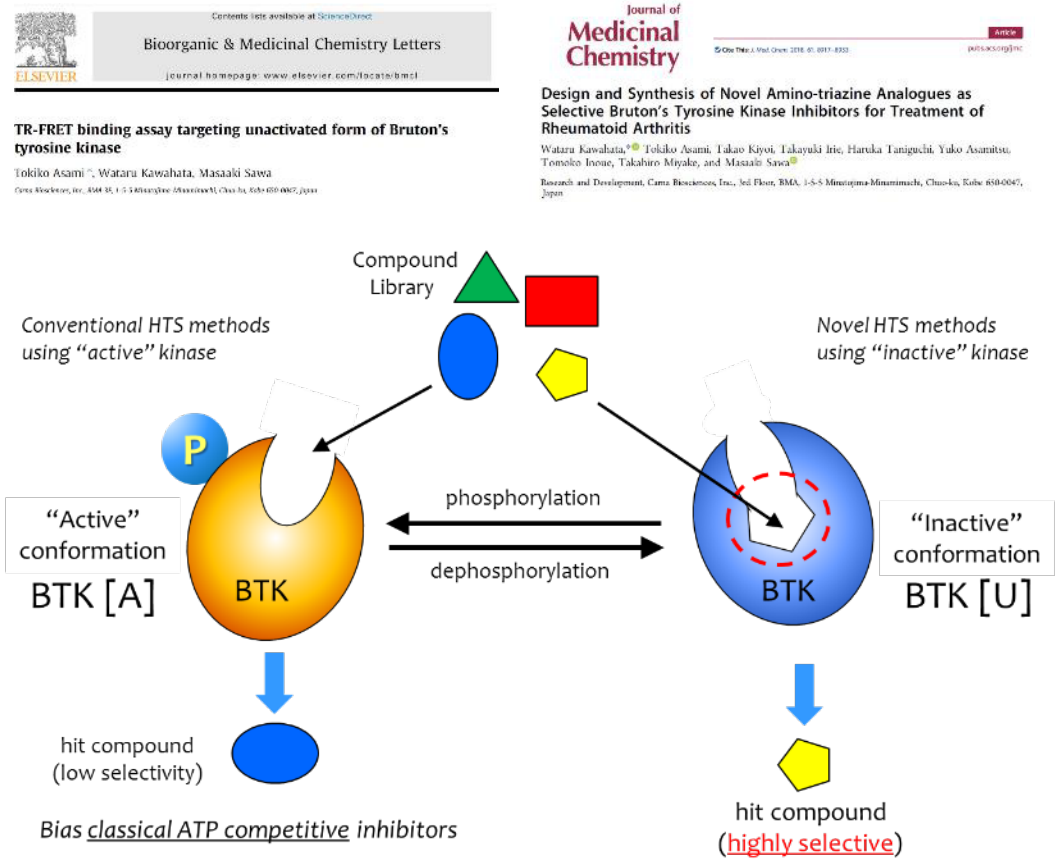


*Previously treated patients

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

Sofnobrutinib (AS-0871): Excellent Kinase Selectivity

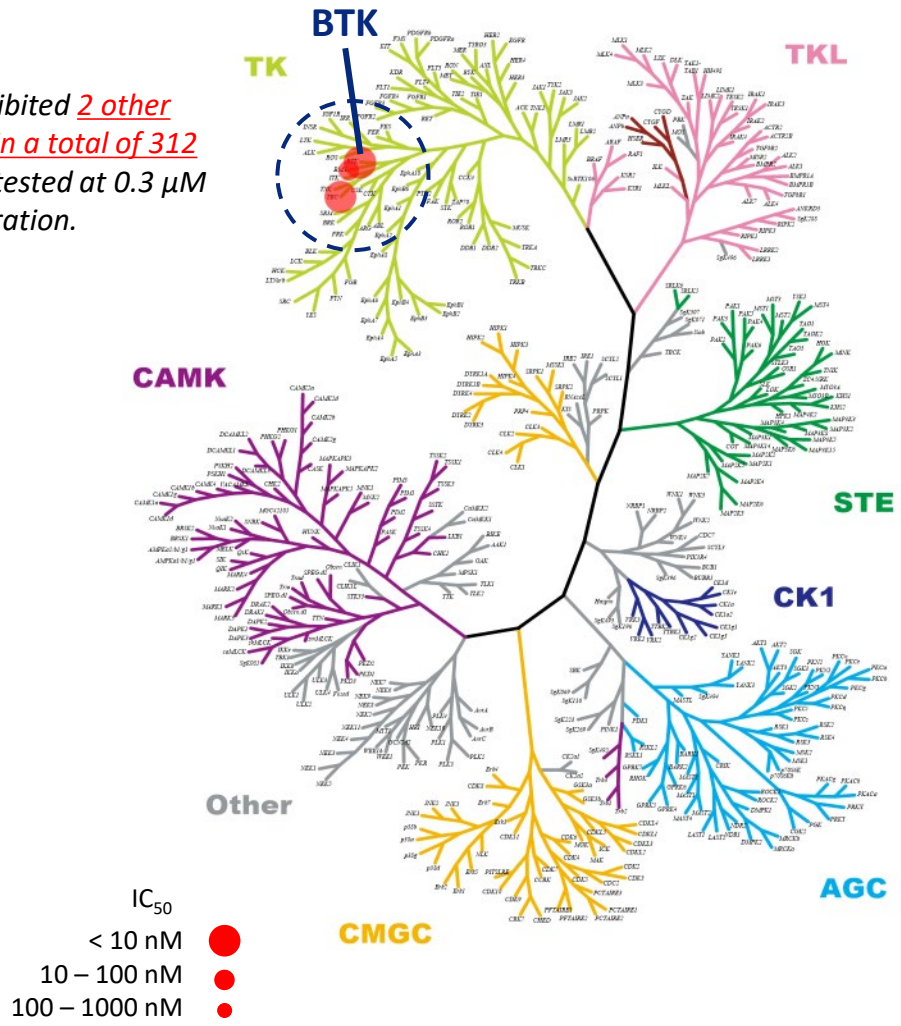
◆ Targeting Inactive Conformation of BTK



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

◆ Kinase Selectivity Profiling

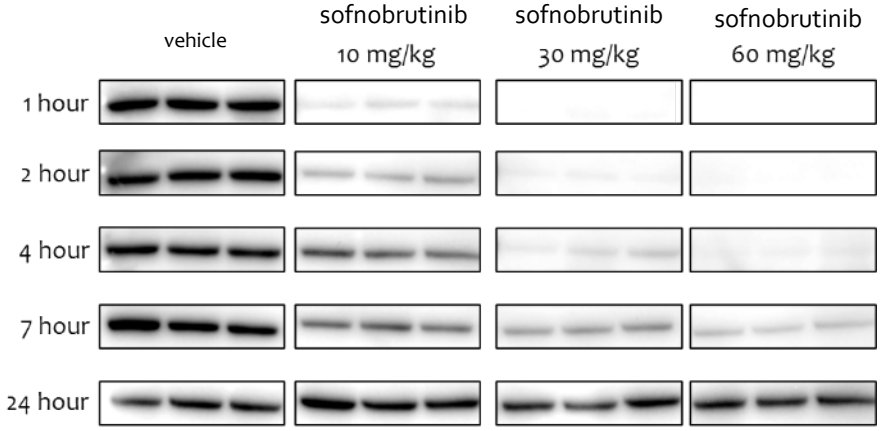
Only inhibited 2 other kinases in a total of 312 kinases tested at 0.3 μM concentration.

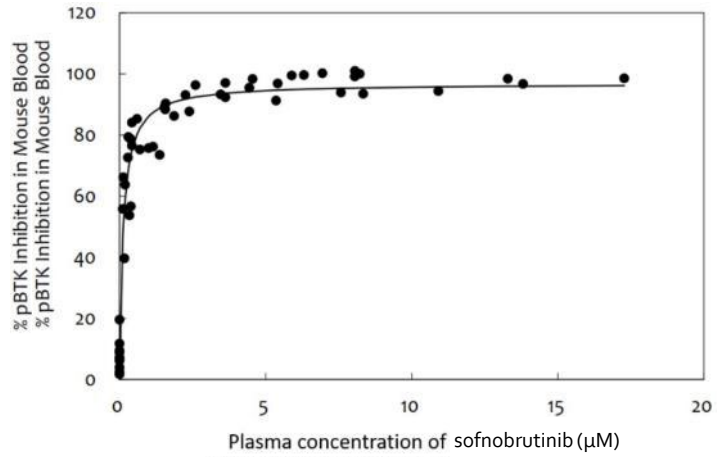


Sofnobrutinib (AS-0871): In Vivo Therapeutic Efficacy

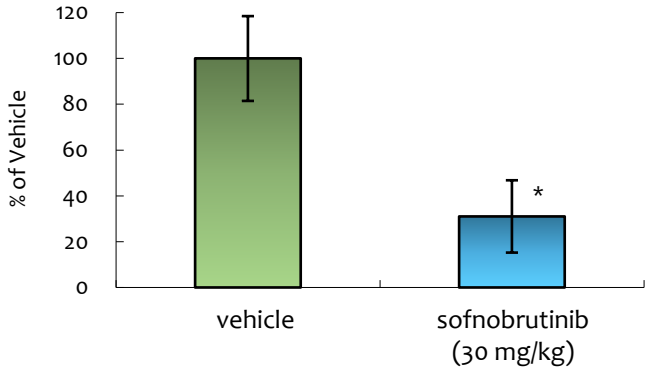
◆ PK/PD Study

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

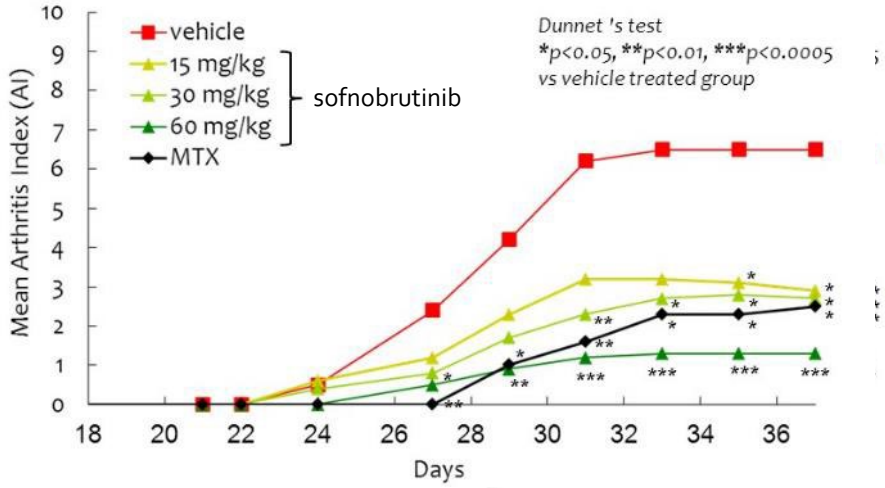




◆ Passive cutaneous anaphylaxis (PCA) mouse model (n=5)



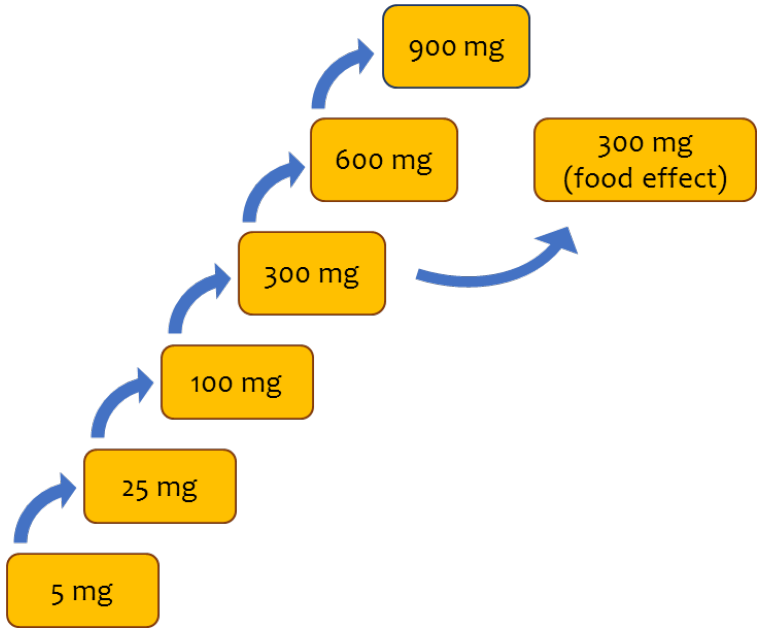
◆ Collagen-induced arthritis (CIA) mouse model (n=10)



Sofnobrutinib (AS-0871): FIH Study

SAD Part (Completed)

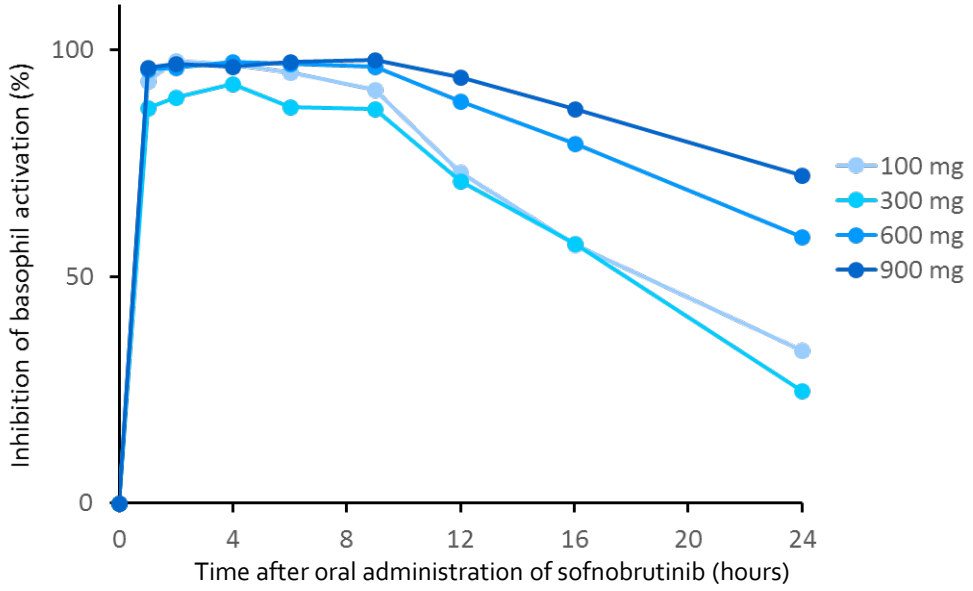
Step 1 Single Ascending Dose (SAD)	Step 2
• 6 dose levels (8 subjects/cohort) • Placebo controlled (6 active / 2 placebo) • Safety and tolerability • Pharmacokinetics and pharmacodynamics	• Food effect

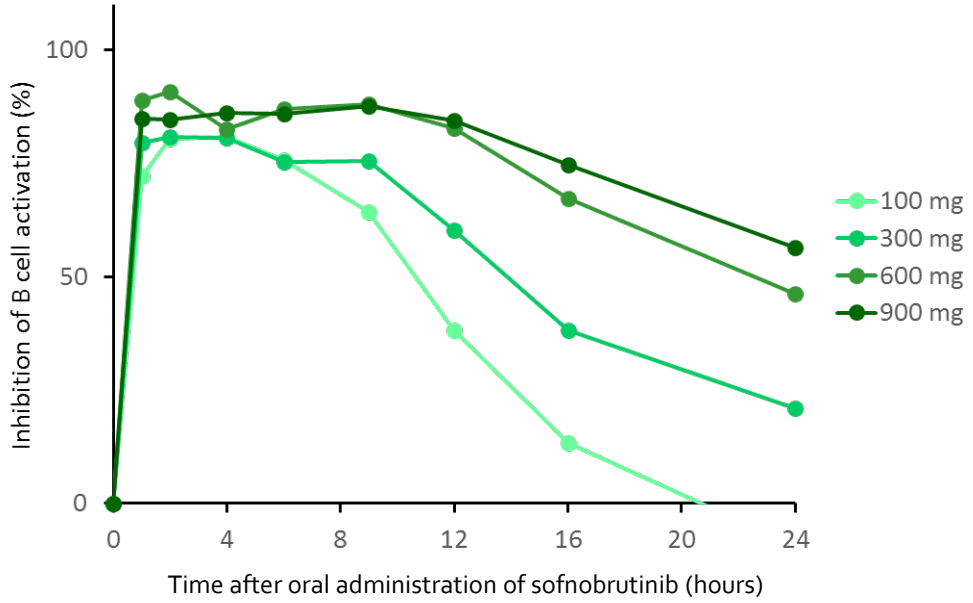


- Sofnobrutinib is well-tolerated without any safety concerns.
- Favorable pharmacokinetic profile.
- Blood samples to assess PD effects were analyzed for evaluation of the B-cell and basophil responses. Administration of sofnobrutinib at 100mg or above resulted in strong inhibition of B-cell and basophil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

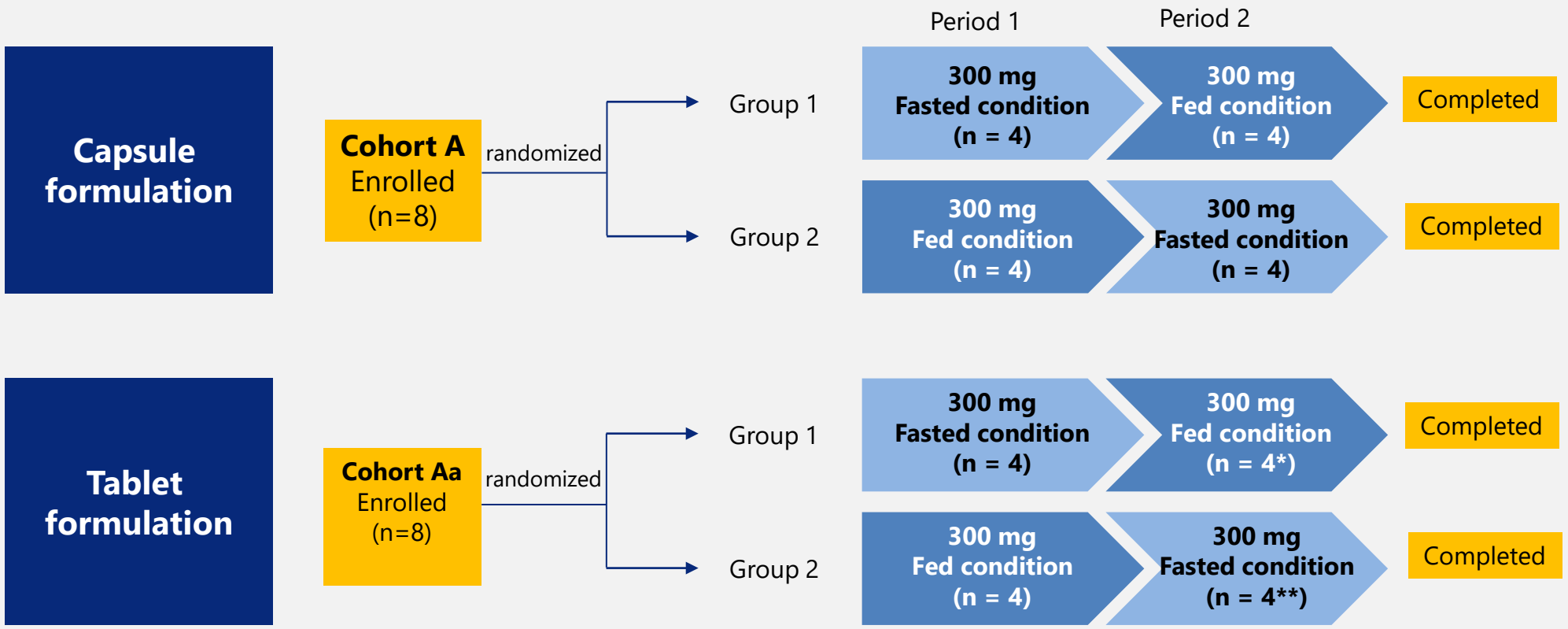




Sofnobrutinib (AS-0871): Phase 1 MAD Study BA part

Study Design of rBA/FE part

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

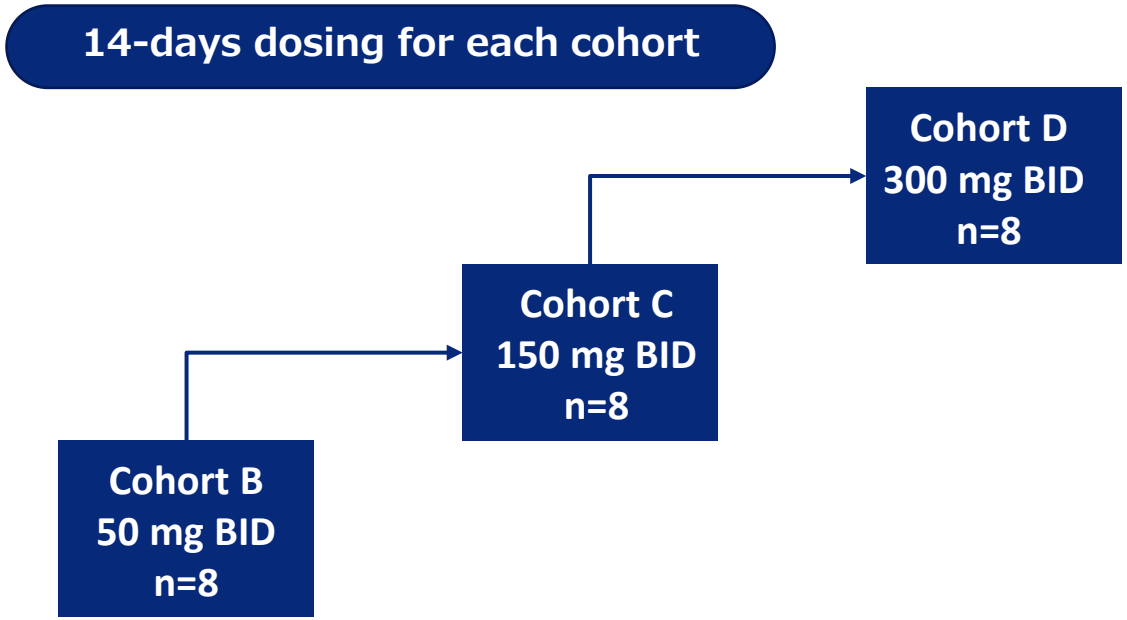


*One subject vomited after dosing (considered not related to study drug), excluded from the PK analysis.
**One subject withdrew from the study due to personal reasons before dosing.

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.

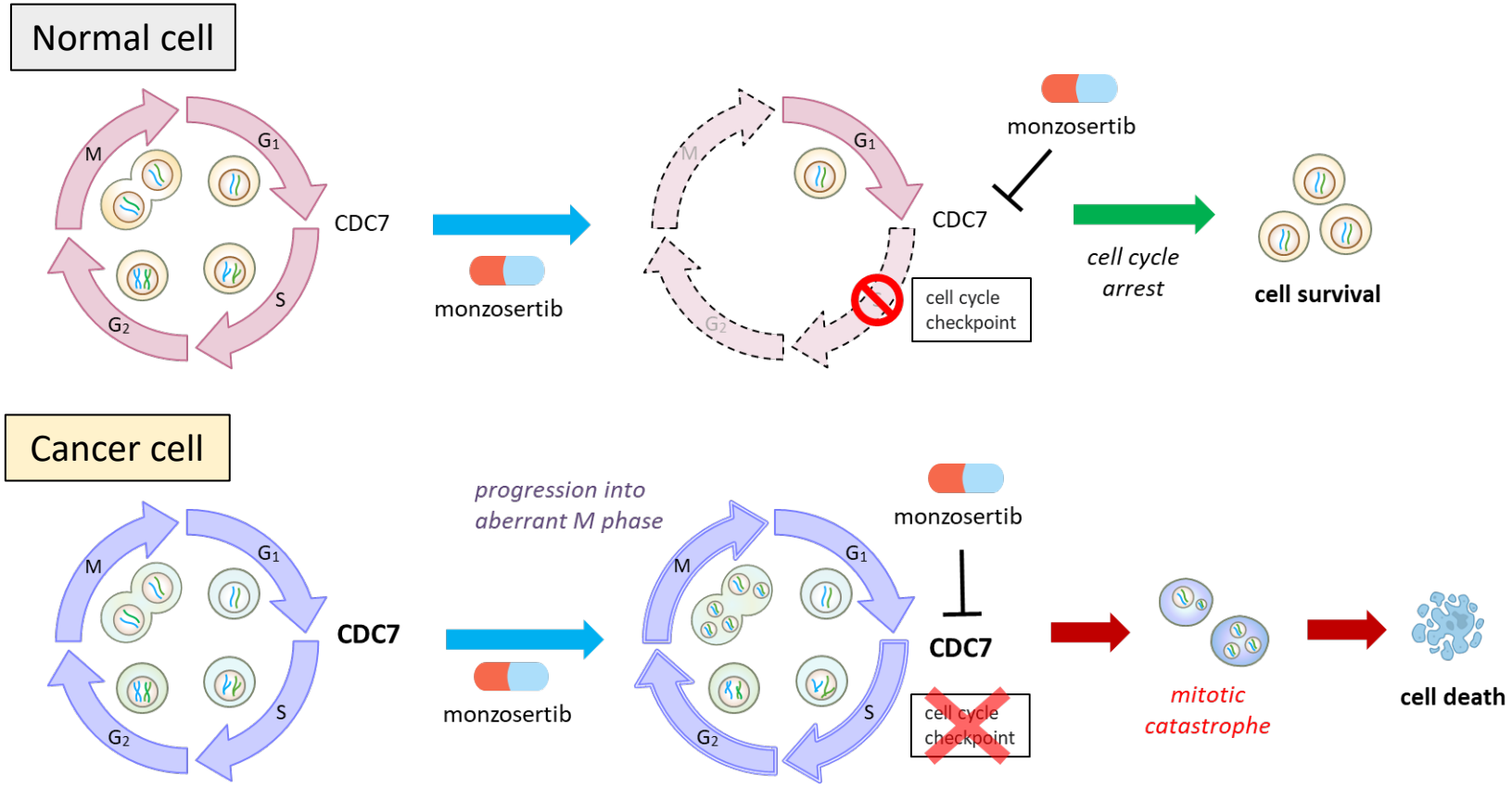


- Well tolerated with no dose-limiting AEs.
- Favorable safety profile up to 300 mg BID.
- The exposure levels increased dose-dependently, and favorable PK profile with tablet formulation was confirmed.
- Achieved almost complete inhibition of basophil activation (PD marker) at 150 mg and 300 mg BID at a steady state

monzosertib (AS-0141)

CDC7 Kinase Inhibitor: MoA of monzosertib

- CDC7 (cell division cycle 7) is a serine/threonine kinase that facilitates DNA replication during DNA synthesis
- Over expression of CDC7 has been reported to cause uncontrolled proliferation of many cancer types



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

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)

European Journal of Medicinal Chemistry

Research paper

Discovery of novel furanone derivatives as potent Cdc7 kinase inhibitors

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

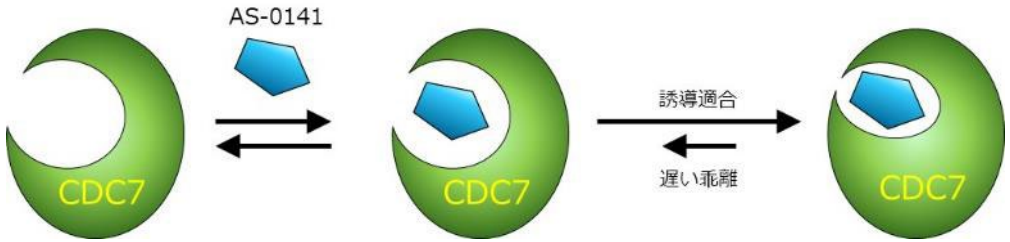
Journal of Medicinal Chemistry

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 Read Online

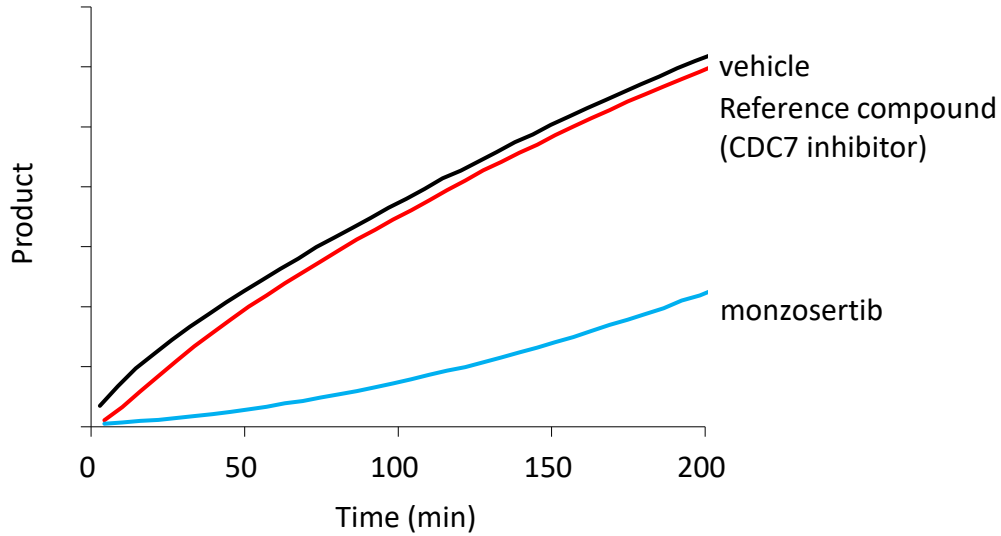


Inhibitory potency (IC50) for CDC7 in the presence of 1 mM ATP	
Without Preincubation	With Preincubation
503 nM	2.4 nM

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

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

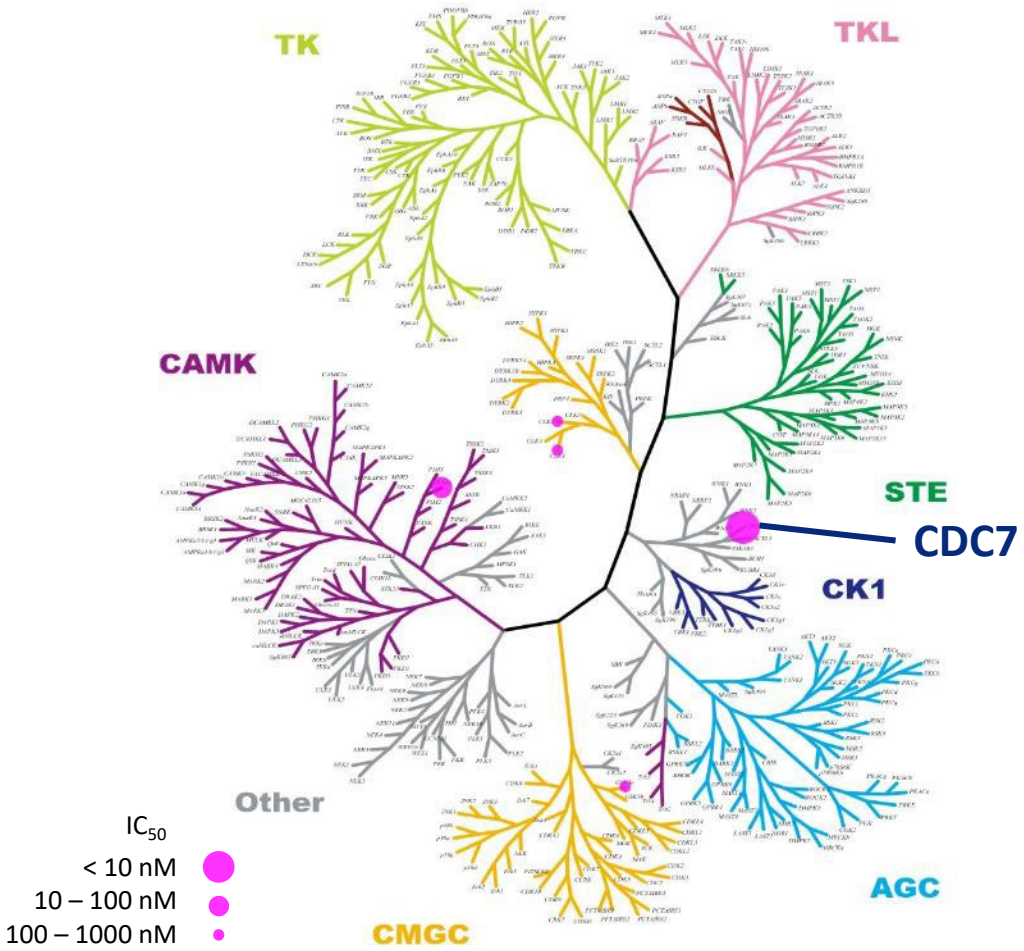
Rapid dilution assay for Cdc7 inhibitors. Recovery of enzymatic activity was monitored by formation of the phosphorylated product.



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

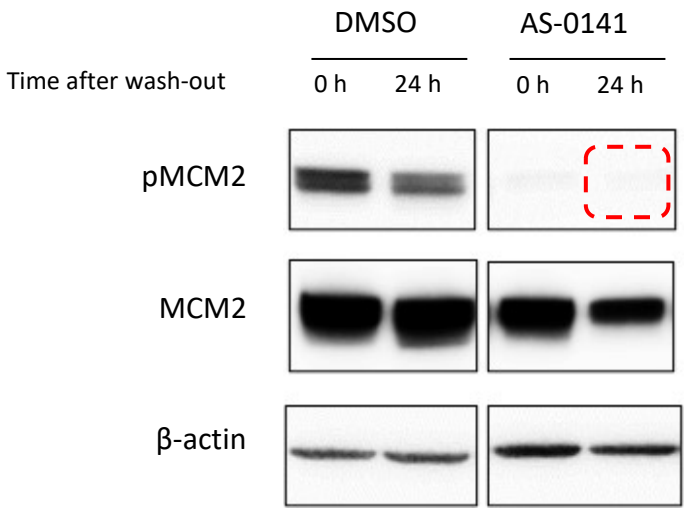
CDC7 is the only kinase that shows preincubation effect

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

Monzosertib (AS-0141): Strong Cellular Activity

◆ Prolonged inhibition in cells

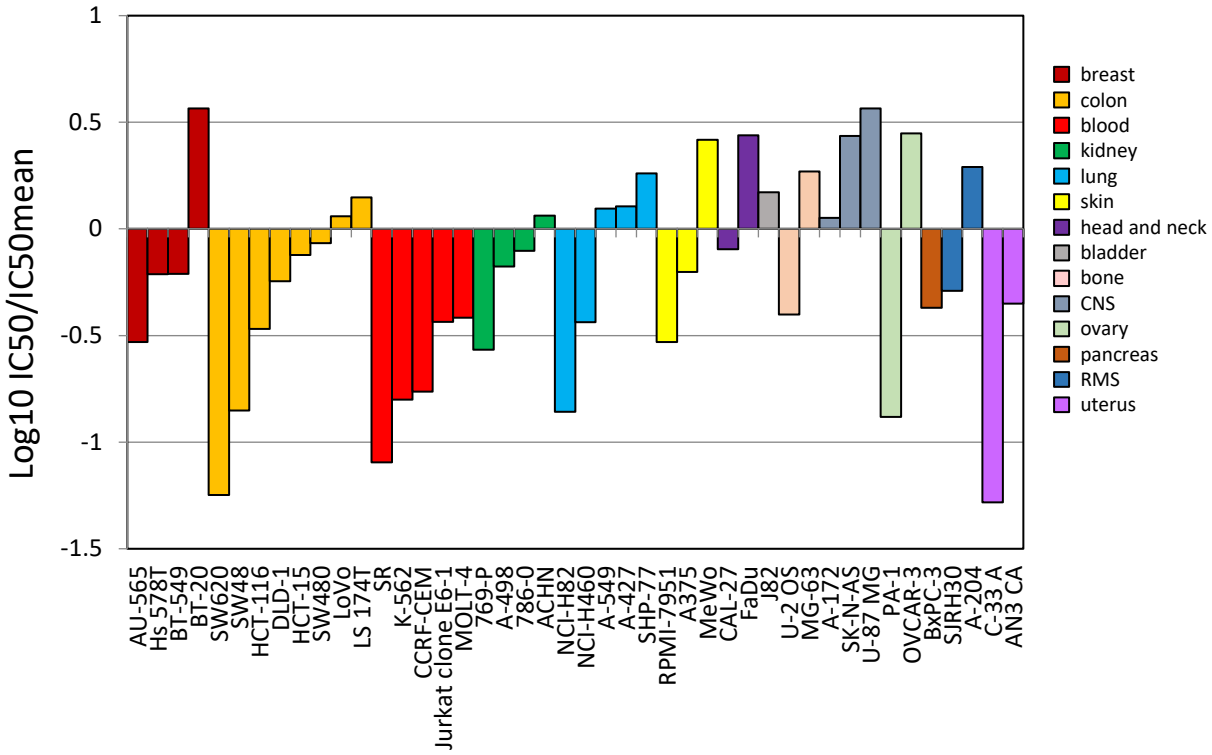
Human colon cancer cell line, Colo-205 cells were treated with DMSO control or monzosertib. After washout of the inhibitor, the cells were further incubated in the same media for 0 or 24 h and subjected to western blot analysis.



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

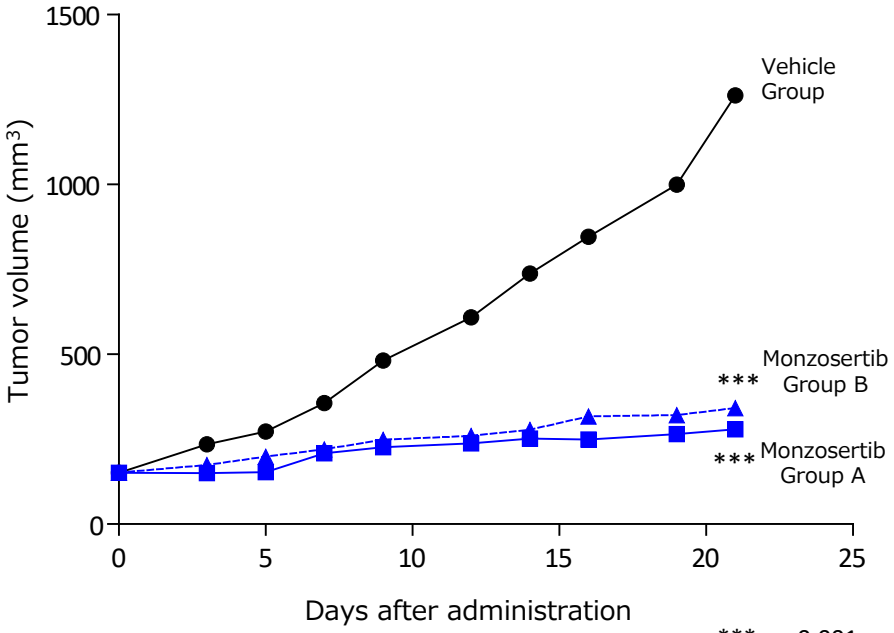


44 Cancer cell lines (Oncolines at NTRC)

Monzosertib (AS-0141): Robust In Vivo Antitumor

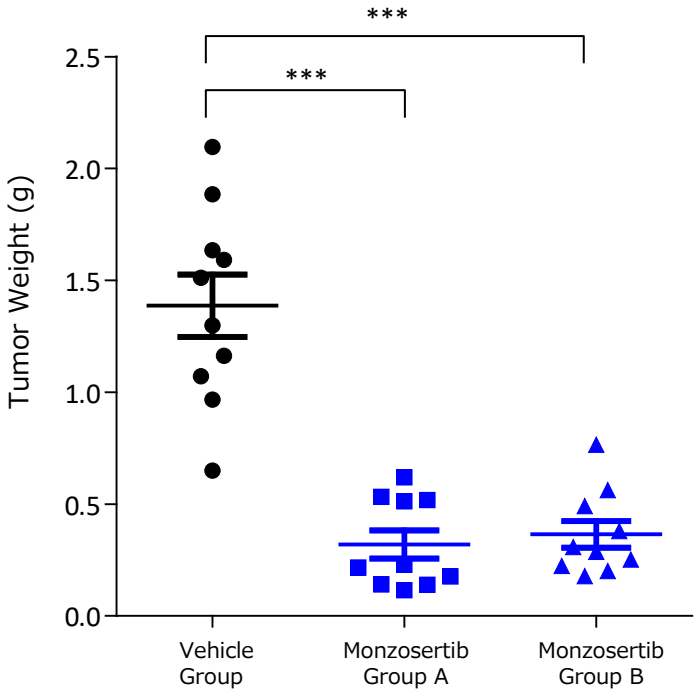
In vivo antitumor efficacy of monzosertib in a SW620 (human colon cancer) xenograft mouse model

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

BMA3F 1-5-5 Minatojia-Minaimachi,

Chuo-ku, Kobe 650-0047

https://www.carnabio.com/

ir-team@carnabio.com