Phase I/II Clinical Study on Tolerability and Bioavailability of Utidelone Capsule in Patients wth Advanced Solid Tumors

Study Number: BG02-2101

Version Number: V 4.0

Version Date: Jan-22-2024

Leading Site: National Cancer Center / Cancer Hospital, Chinese Academy of Medical Sciences

Principal Investigator: Binghe Xu

Sponsor: Chengdu Biostar Pharmaceuticals Co., Ltd.

Beijing Biostar Pharmaceuticals Co., Ltd.

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Study Title: Phase I/II Clinical Study on Tolerability and Bioavailability of Utidelone Capsule in Patients With Advanced Solid Tumors

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I have read this clinical Study protocol and agree to perform my duties in accordance with Chinese laws, the Declaration of Helsinki, and Chinese Good Clinical Practice (GCP), as well as this protocol.

This Study may only be conducted after approval by the Ethics Committee. During the implementation of this Study, I will strictly follow the requirements of this protocol. Any amendments to this protocol may only be implemented after re-approval or filing by the Ethics Committee, unless necessary measures must be taken to protect the safety, rights and interests of the participants.

I will keep this protocol and all relevant information confidential.

Name of Study Site: National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences

Principal Investigator (Print Name): Xu Binghe

（Signature）： Date：

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Sponsor：Chengdu Biostar Pharmaceuticals Co., Ltd.

Beijing Biostar Pharmaceuticals Co., Ltd.

Project Leader (Print Name): Li Tang

（Signature）： Date：

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1. Protocol Summary

1.1 Synopsis

Sponsor: Chengdu Biostar Pharmaceuticals Co., Ltd. Beijing Biostar Pharmaceuticals Co., Ltd.	Registration Classification: Chemical Drug Class 2.2
Investigational Drug Name: Utidelone Capsule	Active Ingredient: Utidelone
Study Name: Phase I/II Clinical Study on Tolerability and Bioavailability of Utidelone Capsule in Patients With Advanced Solid Tumors	
Protocol No., Version and Date BG02-2101 / V 4.0 / January 22, 2024	
Study Phase: Phase I/II	
Study Stages This Study consists of three parts. Part 1: Dose Escalation Study. Part 2: Pharmacokinetic Comparison and Food Effect Study. Part 3: Utidelone Capsule Combined with Capecitabine Expansion Study.	
Study Objectives Primary Objectives To evaluate the safety and tolerability of Utidelone Capsule in patients with advanced solid tumors, and to determine the Maximum Tolerated Dose (MTD) and Dose-Limiting Toxicity (DLT). To evaluate the Objective Response Rate (ORR) of Utidelone Capsule combined with capecitabine in patients with advanced metastatic breast cancer. Secondary Objectives 1. To evaluate the absolute bioavailability of Utidelone Capsule relative to Utidelone Injection; 2. To characterize the pharmacokinetic profile of Utidelone Capsule in patients with advanced solid tumors; 3. To preliminarily evaluate the efficacy and safety of Utidelone Capsule in patients with advanced solid tumors; 4. To recommend the dosage and regimen for subsequent clinical Studys; 5. To evaluate the efficacy (Progression-Free Survival, PFS), safety and pharmacokinetic characteristics of Utidelone Capsule combined with capecitabine in patients with advanced metastatic breast cancer.	
Overall Design Part 1 Dose Escalation Study: open-label, single-center design; Part 2 Pharmacokinetic Comparison and Food Effect Study: open-label, controlled, multi-center design; Part 3 Utidelone Capsule Combined with Capecitabine Expansion Study: open-label, single-arm, multi-center design.	
Control Selection Part 1 Dose Escalation Study: no control group. Part 2 Pharmacokinetic Comparison and Food Effect Study: Utidelone Injection as control in Cycle 0 and Cycle 1; administration after high-fat meal as control on Day 1 of Cycle 2. Part 3 Utidelone Capsule Combined with Capecitabine Expansion Study: no control group.	
Target Population Patients with advanced solid tumors who lack conventional effective treatment, have failed or relapsed after standard treatment.	
Sample Size Part 1 Dose Escalation Study: at least 3 dose groups planned, with an estimated enrollment of 14–26 participants.	

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1. Cohort 1: planned enrollment of 2 participants;
2. Other dose escalation cohorts adopt a 3+3 design, with 3–6 participants per cohort;

Part 2 Pharmacokinetic Comparison and Food Effect Study: including test and control groups, with a total planned enrollment of 18 participants.

Part 3 Utidelone Capsule Combined with Capecitabine Expansion Study: planned enrollment of 40 participants.

Study Duration

The Study is estimated to last 12 months.

Investigational Products

Three investigational products are used in this Study: Utidelone Capsule, Utidelone Injection and Capecitabine Tablet. All investigational products have passed inspection and meet the quality standards for clinical Study use.

Table 1 Information of Investigational Products

Product Name	Utidelone Capsule	Utidelone Injection	Capecitabine Tablet
Active Ingredient	Utidelone	Utidelone	Capecitabine
Trade Name	Not applicable	Utidelone	Xeloda
Specification	10 mg /capsule and 15 mg /capsule	5 mL: 50 mg/vial	0.5 g
Packaging Specification	20 capsules/box	1 vial/box	12 tablets/box
Manufacturer	Chengdu Huahao Zhongtian Pharmaceutical Co., Ltd.	Chengdu Huahao Zhongtian Pharmaceutical Co., Ltd.	Shanghai Roche Pharmaceuticals Ltd.
Shelf Life	3 years (tentative)	2 years	3 years
Storage Condition	Sealed at room temperature	Protected from light, sealed, stored at 2–8°C	Sealed at 25°C, acceptable between 15–30°C

Note: For details on content, batch number and production date, please refer to the drug inspection report.

Dosage and Administration Regimen

Part 1: Dose Escalation Study

The planned dose escalation regimen, administration cycle and frequency are shown in the table below. The dose escalation regimen, administration cycle and frequency will be adjusted in a timely manner based on the available safety data during the Study.

Table 2 Dose Escalation Regimen

Cohort	Cohort 1	Cohort 2	Cohort 3	Cohort 4	De-escalation Cohort 1
Dose (mg/m²/d)	50	75	75	85	65
Administration Route	QD	QD	QD	QD	QD
Administration Days	D1–D5	D1–D5	D1–D7	D1–D7	D1–D7
Cycle Length	21 days as one cycle				

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Investigational Drug Name: Utidelone Capsule	Active Ingredient: Utidelone

Total Dose per Cycle (mg/m²)	250	375	525	595	455
Escalation Ratio (based on total dose per cycle)	/	50%	40%	≈15%	/
Sample Size	2	3–6	3–6	3–6	3–6

This Study adopts a modified Fibonacci dose escalation design. Clinical studies have shown that Utidelone Injection at 40 mg/m²/d has good efficacy and tolerability. Considering that the oral bioavailability in animal studies is 55% of intravenous administration, the starting dose of the capsule is set at 50 mg/m²/d, enrolling 2 participants. Participants complete Cycle 1 treatment and evaluation; if no DLT is observed, escalation proceeds to the next cohort. Starting from Cohort 2, a traditional 3+3 design is adopted. Each cohort must have at least 3 participants who complete Cycle 1 treatment and evaluation and are evaluable for DLT assessment before dose escalation to the next cohort. A maximum of 2 participants may be under DLT observation at the same time. If 1 of the first 3 participants experiences DLT, an additional 3 participants are enrolled in the same cohort. If 2 participants experience DLT, dose escalation is terminated.

If Cohort 2 (75 mg/m²/d for 5 days) does not meet the escalation termination criteria, escalation proceeds to Cohort 3 (75 mg/m²/d for 7 days). If Cohort 3 meets the termination criteria, De-escalation Cohort 1 (65 mg/m²/d for 7 days) is established. If Cohort 3 does not meet the termination criteria, escalation proceeds to Cohort 4 (85 mg/m²/d for 7 days). Regardless of whether Cohort 4 meets the termination criteria, dose escalation will be terminated. During the Study, the dose of the cohort may be adjusted based on discussions between the sponsor and investigators.

Post-Treatment Period

Participants who complete Cycle 1 treatment and evaluation, without DLT observed, and for whom the investigator believes continued treatment is beneficial, may continue the same regimen voluntarily until disease progression, intolerable adverse events, participant withdrawal, or investigator decision to discontinue treatment.

Administration Regimen

All cohorts follow the Utidelone Injection instructions and adopt a once-daily (QD) oral regimen. Capsules are administered under fasting conditions with approximately 240 mL of warm water (fasting for 2 hours before and after administration). The regimen may be adjusted during the Study upon evaluation by the Safety Monitoring Committee (SMC) based on Study results.

Dose is calculated using the participant's body surface area (BSA) at screening. BSA is calculated using the Du Bois formula: BSA (m^2) = 0.0061 × height (cm) + 0.0128 × weight (kg) − 0.1529. Dose adjustment based on weight is not performed in subsequent cycles unless weight changes exceed 10% from baseline. Based on capsule specifications, calculated doses are rounded according to the rule: values ≤2.49 mg are rounded down to 0; values 2.50–4.99 mg are rounded up to 5 mg. Dose calculation and rounding results for each cohort are shown in Tables 3 and 4, with a permitted dose difference of ≤4% across all cohorts. (Capsule specifications: 15 mg and 10 mg)

Table 3 Part 1 and Part 2 Dose Rounding Scheme

Dose Group									
50 mg/m²/d		60 mg/m²/d		65 mg/m²/d		75 mg/m²/d		85 mg/m²/d	
BSA (m^2)	Dose (mg)	BSA (m^2)	Dose (mg)	BSA (m^2)	Dose (mg)	BSA (m^2)	Dose (mg)	BSA (m^2)	Dose (mg)
1.30-1.35	65	1.30-1.37	80	1.30-1.35	85	1.30	95	1.30-1.32	110
1.36-1.45	70	1.38-1.45	85	1.36-1.43	90	1.31-1.37	100	1.33-1.38	115
1.46-1.55	75	1.46-1.54	90	1.44-1.50	95	1.38-1.43	105	1.39-1.44	120
1.56-1.65	80	1.55-1.62	95	1.51-1.58	100	1.44-1.50	110	1.45-1.50	125
1.66-1.75	85	1.63-1.70	100	1.59-1.66	105	1.51-1.57	115	1.51-1.56	130
1.76-1.85	90	1.71-1.79	105	1.67-1.73	110	1.58-1.63	120	1.57-1.62	135

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1.86-1.95	95	1.80-1.87	110	1.74-1.81	115	1.64-1.70	125	1.63-1.68	140
1.96-2.05	100	1.88-1.95	115	1.82-1.89	120	1.71-1.77	130	1.69-1.74	145
2.06-2.15	105	1.96-2.04	120	1.90-1.96	125	1.78-1.83	135	1.75-1.80	150
2.16-2.25	110	2.05-2.12	125	1.97-2.04	130	1.84-1.90	140	1.81-1.86	155
2.26-2.35	115	2.13-2.20	130	2.05-2.12	135	1.91-1.97	145	1.87-1.92	160
2.36-2.45	120	2.21-2.29	135	2.13-2.19	140	1.98-2.03	150	1.93-1.98	165
2.46-2.50	125	2.30-2.37	140	2.20-2.27	145	2.04-2.10	155	1.99-2.04	170
		2.38-2.45	145	2.28-2.35	150	2.11-2.17	160	2.05-2.10	175
		2.46-2.50	150	2.36-2.43	155	2.18-2.23	165	2.11-2.16	180
				2.44-2.50	160	2.24-2.30	170	2.17-2.22	185
						2.31-2.37	175	2.23-2.28	190
						2.38-2.43	180	2.29-2.34	195
						2.44-2.50	185	2.35-2.40	200
								2.41-2.46	205
								2.47-2.50	210

Table 4 Part 1 and Part 2 Utidelone Capsule Allocation Scheme

Rounded Dose (mg)	Number of Capsules		Rounded Dose (mg)	Number of Capsules	
	15mg	10mg		15mg	10mg
30	**2**	**0**	200	**12**	**2**
35	**1**	**2**	205	**13**	**1**
40	**2**	**1**	210	**14**	**0**
45	**3**	**0**	215	**13**	**2**
50	**2**	**2**	220	**14**	**1**
55	**3**	**1**	225	**15**	**0**
60	**4**	**0**	230	**14**	**2**
65	**3**	**2**	235	**15**	**1**
70	**4**	**1**	240	**16**	**0**
75	**5**	**0**	245	**15**	**2**
80	**4**	**2**	250	**16**	**1**
85	**5**	**1**	255	**17**	**0**
90	**6**	**0**	260	**16**	**2**
95	**5**	**2**	265	**17**	**1**
100	**6**	**1**	270	**18**	**0**
105	**7**	**0**	275	**17**	**2**
110	**6**	**2**	280	**18**	**1**
115	**7**	**1**	285	**19**	**0**
120	**8**	**0**	290	**18**	**2**

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125	**7**	**2**	295	**19**	**1**
130	**8**	**1**	300	**20**	**0**
135	**9**	**0**	305	**19**	**2**
140	**8**	**2**	310	**20**	**1**
145	**9**	**1**	315	**21**	**0**
150	**10**	**0**	320	**20**	**2**
155	**9**	**2**	325	**21**	**1**
160	**10**	**1**	330	**22**	**0**
165	**11**	**0**	335	**21**	**2**
170	**10**	**2**	340	**22**	**1**
175	**11**	**1**	345	**23**	**0**
180	**12**	**0**	350	**22**	**2**
185	**11**	**2**	355	**23**	**1**
190	**12**	**1**	360	**24**	**0**
195	**13**	**0**			

Dose-Limiting Toxicity (DLT)

DLT is observed in Cycle 1 of Part 1 Dose Escalation Study. DLT is defined as any adverse event definitely or possibly related to the study drug occurring during the Study:

1. All ≥Grade 3 non-hematologic toxicities, excluding:

• Untreated or inadequately treated nausea, vomiting and diarrhea; any Grade 4 nausea, vomiting or diarrhea despite optimal treatment will be considered DLT; Grade 3 nausea, vomiting or diarrhea persisting >24 hours despite optimal treatment will be considered DLT;

• Alopecia;

• Grade 3 fatigue resolving within 7 days to ≤Grade 2;

• Clinically insignificant or easily reversible Grade 3 laboratory/metabolic abnormalities;

2. Any at least possibly related toxicity leading to treatment delay of ≥3 weeks.
3. Grade 4 neutropenia lasting ≥7 days.
4. Febrile neutropenia.
5. Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding.
6. Grade 4 anemia.

The above adverse events are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

No dose adjustment is allowed in Cycle 1. For non-DLT adverse events during administration, dosing may be paused as needed to ensure participant safety.

Maximum Tolerated Dose (MTD)

If only 1 of the first 3 participants in a cohort experiences DLT, 3 additional participants are enrolled in the same cohort. If no DLT occurs in the additional 3 participants, dose escalation proceeds. If 2 of the first 3 participants or 2 of 6 participants experience DLT, that dose is defined as the Maximum Administered Dose (MAD), and MTD is defined as the next lower dose level than MAD.

Dose Escalation Termination Criteria

Once MTD is determined, dose escalation is terminated. The sponsor and investigators may discuss whether to add an additional cohort between the DLT dose and the previous dose for DLT evaluation.

Part 2: Pharmacokinetic Comparison and Food Effect Study

Dosage

A: Utidelone Capsule, 60 mg/m²/d, rounded according to capsule specifications.

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Investigational Drug Name: Utidelone Capsule	Active Ingredient: Utidelone

B: Utidelone Injection, 30 mg/m²/d, dissolved in 250 mL normal saline and infused intravenously over 1.5 hours (±15 minutes).

Administration Regimen

Pharmacokinetic Comparison: 18 eligible participants are randomized 1:1 to either Group A-B or Group B-A. In Cycle 0, Group A-B receives oral Utidelone Capsule under fasting conditions; Group B-A receives intravenous Utidelone Injection. Both groups receive a single dose followed by a 7-day washout. On Day 8, Cycle 1 begins: Group A-B receives intravenous Utidelone Injection; Group B-A receives oral Utidelone Capsule under fasting conditions, once daily for 5 consecutive days, 21 days per cycle.

Food Effect: On Day 29, Cycle 2 begins. Both groups receive oral Utidelone Capsule after a high-fat meal on Day 1; Days 30–33, oral Utidelone Capsule under fasting conditions, once daily for 5 consecutive days, 21 days per cycle.

Table 5 Food Effect Administration Regimen

Group	Sequence	Cycle 0	Cycle 1	Cycle 2
A-B group	A-B	Utidelone Capsule (fasted)	Utidelone Injection	Utidelone Capsule (high-fat meal on Day 1)
B-A group	B-A	Utidelone Injection	Utidelone Capsule (fasted)	Utidelone Capsule (high-fat meal on Day 1)

Post-Treatment Period

Participants who complete Cycle 0, Cycle 1 and Cycle 2 treatment and evaluation, for whom the investigator believes continued treatment is beneficial, may continue the same regimen voluntarily. Participants previously on Utidelone Injection may switch to Utidelone Capsule in the post-treatment period until disease progression, intolerable adverse events, participant withdrawal, or investigator decision to discontinue treatment.

Administration Conditions

During Cycle 0 and Cycle 1, all patients receive premedication with diphenhydramine 40 mg IM/orally, dexamethasone 10 mg IV, and cimetidine 300–400 mg or ranitidine 50 mg IV 30–60 minutes before Utidelone Injection. Dexamethasone and diphenhydramine may be halved or omitted on subsequent days based on clinical judgment. Utidelone Capsule is administered under fasting conditions with approximately 240 mL warm water (fasting for 2 hours before and after administration).

During Cycle 2, participants receive Utidelone Capsule after a high-fat meal on Day 1 (meal completed within 30 minutes, administered 30–35 minutes post-meal; fasting for 2 hours after administration); Days 2–5, oral Utidelone Capsule under fasting conditions. No dietary restrictions in the post-treatment period.

Part 3: Utidelone Capsule Combined with Capecitabine Expansion Study

Dosage

Utidelone Capsule: 60 mg/m²/d, once daily under fasting conditions, Days 1–5 for 5 consecutive days, 21 days per cycle. Dosage may be adjusted based on SMC recommendations from Part 1 and Part 2 safety and efficacy data.

Capecitabine: 1000 mg/m² twice daily (total 2000 mg/m²), orally within 30 minutes after breakfast/dinner, Days 1–14 for 14 consecutive days, 21 days per cycle.

Administration Regimen

During the first three cycles (C1–C3), participants start breakfast approximately 30 minutes after Utidelone Capsule administration, then take capecitabine within 30 minutes after breakfast. On PK-intensive sampling days, capecitabine is administered 1 hour after Utidelone Capsule dosing. Meal, dosing and sampling times are recorded to the minute.

Dose is calculated using screening BSA via Du Bois formula. Dose adjustment based on weight is not performed unless weight changes exceed 10% from baseline. Dose rounding and allocation for Utidelone Capsule are shown in Table 6.

Table 6 Part 3 Utidelone Capsule Rounding and Allocation Scheme

Sponsor: Chengdu Biostar Pharmaceuticals Co., Ltd. Beijing Biostar Pharmaceuticals Co., Ltd.	Registration Classification: Chemical Drug Class 2.2
Investigational Drug Name: Utidelone Capsule	Active Ingredient: Utidelone

15mg UTD2 （Capsules）	10mgUTD2 （Capsules）	Rounded Dose （mg）	60 mg/m²/d	75% Dose 45 mg/m²/d	50% Dose 30 mg/m²/d
			BSA(m²)	BSA(m²)	BSA(m²)
2	1	40			1.17-1.66
4	0	60		1.17-1.55	1.67-2.33
4	2	80	1.17-1.49	1.56-1.99	2.34-2.49
6	1	100	1.50-1.83	2.00-2.44	
8	0	120	1.84-2.16	2.45-2.49	
8	2	140	2.17-2.49		

The above doses may be adjusted per the protocol based on the participant's adverse reactions. Participants shall continue treatment until disease progression, intolerable adverse events, voluntary withdrawal by the participant, or mandatory treatment discontinuation as determined by the investigator. In case of missed doses, the scheduled dosing time and reason for the missed dose shall be documented in detail. Participants shall resume dosing according to the protocol cycle thereafter, with no make-up doses or cycle adjustments.

Dose Adjustment

No dose adjustment is allowed in Part 1 Cycle 1 and Part 2 Cycle 0/1/2. Post-treatment and Part 3 may pause or reduce dose after toxicity resolves to ≤Grade 1 or baseline.

Inclusion Criteria

All inclusion criteria must be satisfied for enrollment:

1. Patients who have fully understood the objectives, content, process of the study and possible adverse events, voluntarily serves as a participant and signs the informed consent form.
2. Part 1 and Part 2: Patients with definitive histopathological diagnosis of advanced solid tumors. Part 3: Patients were diagnosed with advanced metastatic breast cancer by pathology and/or cytology.
3. Part 1 and Part 2: Male or female participants aged ≥18 and ≤65, Part 3: Male or female participants aged ≥18 and ≤70, with ECOG performance status scored 0-1.
4. Expected survival time ≥ 12 weeks;
5. At least one measurable lesion present according to RECIST 1.1 criteria.
6. Baseline routine blood tests within 1 week prior to enrollment is normal (not received blood transfusions or hematopoietic-stimulating factors within 14 days), with CTCAE grade ≤1 (based on normal values at each site's laboratory): a) Neutrophil count (ANC) ≥ 1.5 × 109/L; b) platelet count (PLT) ≥ 100 × 109/L; c) Hemoglobin ≥9.0 g/dL.
7. Liver and kidney function test results are normal within 1 week prior to enrollment, with CTCAE grade ≤1 (based on normal values at each site's laboratory): a) Total bilirubin (TBIL) ≤ 1.5× the upper limit of normal value (ULN); b) Serum Glutamic Pyruvic Transaminase/Alanine Aminotransferease (SGPT /ALT) ≤ 2.5× ULN (Part 3 allowed ≤5×ULN in patients with liver metastases); c) Serum Glutamic-oxaloacetic Transaminase/Aspartate Aminotransferase (SGOT /AST) ≤ 2.5× ULN (Part 3 allowed ≤5×ULN in patients with liver metastases); d) Creatinine clearance (Ccr) ≥60 ml/min.
8. Patients with no functional disorders of major organs.
9. Fertile males and females of childbearing potential must agree to use effective contraception (so do their partners, using hormonal or barrier contraception, or abstinence) during the study and within at least 6 months after the last dose. The blood or urine pregnancy test for female patients of childbearing potential prior to enrollment must be negative.
10. Part 3: breast cancer patients who had received ≤4 previous chemotherapy regimens (adjuvant chemotherapy/neoadjuvant chemotherapy was considered as one chemotherapy regimen);
11. Part 3: history of prior treatment with at least one anthracycline or one taxane as neoadjuvant/adjuvant or advance therapy or both.

Exclusion Criteria

Meeting any single exclusion criterion will result in exclusion:

1. Patients who have received non-investigational anti-tumor therapies (such as chemotherapy, radiotherapy, immunotherapy, biological therapy or traditional Chinese medicine treatment) within 4 weeks prior to study drug administration, except for the following:

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a. Nitrosoureas or mitomycin C: within 6 weeks prior to study drug administration;
b. Oral fluoropyrimidines and small molecule targeted agents: within 2 weeks or 5 half lives of the drug prior to study drug administration (whichever is longer);
c. Traditional Chinese medicine with anti tumor indications and endocrine therapy for breast cancer: within 2 weeks prior to study drug administration.

2. Participants with severe hypersensitivity to castor oil (this criteria is applicable to Part 2 of the study), and participants who had hypersensitivity reaction caused by previous anti-microtubule drugs.
3. Patients with uncontrollable brain metastases (brain metastatic lesion confirmed by examination within 2 months after radiotherapy or other localized treatment); patients with uncontrollable bone metastases (patients who have had fracture or have the risk of fracture in recent days, patients who need surgery or localized radiotherapy in recent days, patients with other critical conditions)
4. Patients with serious comorbidities, such as severe heart disease, cerebrovascular disease, uncontrolled diabetes, uncontrolled hypertension, severe infections, active peptic ulcers, etc.
5. Patients with mental illnesses which are hard to control, patients who lack legal capacity or have limited legal capacity.
6. Patients with gastrointestinal diseases such as esophageal obstruction, pyloric obstruction, intestinal obstruction, or who are post-operative of gastrointestinal resection, or who have difficulty in swallowing due to other factors, interfering with oral administration and absorption of the drug.
7. Patients with active hepatitis B infections.
8. Patients with peripheral neuropathy grade>1 within 4 weeks prior to enrollment (NCI CTCAE 5.0).
9. Patients who still experience ≥ Grade 2 acute toxicities caused by previous anti-tumor therapies (e.g. chemotherapy, radiotherapy, immunotherapy, biological therapy or TCM treatment) prior to enrollment (NCI-CTCAE 5.0, except alopecia).
10. Patients who have undergone any major surgery or have major trauma within 4 weeks prior to administration of the investigational product or are expected to undergo major surgery during the treatment.
11. Patients who have participated in another clinical study or have received other investigational treatments within 4 weeks prior to administration of the investigational product.
12. Patients who, in the opinion of the investigator, are not suitable to participate in this study.
13. Part 3: other malignant tumors within 5 years before enrollment, excluding cured cervical carcinoma in situ, skin basal cell carcinoma or skin squamous cell carcinoma, thyroid papillary carcinoma;
14. Part 3: previous or current capecitabine therapy (except if capecitabine was used in neoadjuvant/adjuvant therapy and progression occurred > 12 months after completion of treatment, inclusion was allowed);
15. Part 3: patients with previous fluorouracil medication history with severe allergy or known dihydropyrimidine dehydrogenase (DPD) deficiency;
16. Part 3: previous or current use of utidelone (including utidelone injection and utidelone capsule);
17. Part 3: pregnant or lactating patients;
18. Part 3: uncontrolled pleural effusion, pericardial effusion or ascites (drainage once a month or more);
19. Part 3: a history of immunodeficiency, including positive HIV antibody test, other acquired or congenital immunodeficiency diseases, or a history of organ transplantation.

Biological Sample Collection

Blood Sample Collection

The planned blood sampling time points are listed below. The sampling schedule may be adjusted in a timely manner based on available human pharmacokinetic data during the Study.

Part 1: Dose Escalation Study

Table 7 Blood Sampling Schedule – Dose Escalation Study

Sampling Time Point	Time Window	Visit	Volume						
		C1D1	C1D3	C1D4	C1D5 (5-day)	C1D5 (7-day)	C1D6 (7-day)	C1D7 (7-day)	

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0 h (within 60 min pre-dose)	–	1 tube	1 tube	1 tube	1 tube	1 tube	1 tube	1 tube	3 mL each
40 min post-dose	± 2 min	1 tube			1 tube		1 tube		3 mL each
1 h post-dose	± 2 min	1 tube			1 tube		1 tube		3 mL each
1.5 h post-dose	± 5 min	1 tube			1 tube		1 tube		3 mL each
2 h post-dose	± 5 min	1 tube			1 tube		1 tube		3 mL each
2.5 h post-dose	± 5 min	1 tube			1 tube		1 tube		3 mL each
4 h post-dose	± 5 min	1 tube			1 tube		1 tube		3 mL each
10 h post-dose	± 10 min	1 tube			1 tube		1 tube		3 mL each
24 h post-dose (pre-next dose)	± 20 min	1 tube			1 tube		1 tube		3 mL each
48 h post-dose	± 60 min				1 tube		1 tube		3 mL each
72 h post-dose	± 60 min				1 tube		1 tube		3 mL each
Total Samples		9	1	1	11	1	1	11	

Part 2: Pharmacokinetic Comparison and Food Effect Study

Table 8 Blood Sampling Schedule – PK Comparison and Food Effect Study

Sampling Time Point	Time Window	A-Group Visits	B-Group Visits	Volume									
		C0D1	C1D1	C1D3	C1D4	C1D5	C2D1	C0D1	C1D1	C1D3	C1D4	C1D5	C2D1	
0 h (within 60 min pre-dose)	–	1 tube	1 tube	1 tube	1 tube	1 tube	1 tube	1 tube	1 tube	1 tube	1 tube	1 tube	1 tube	3 mL each
Capsule Sampling														
40 min post-dose	± 2 min	1 tube					1 tube	1 tube					1 tube	3 mL each
1 h post-dose	± 2 min	1 tube					1 tube	1 tube					1 tube	3 mL each
1.5 h post-dose	± 5 min	1 tube					1 tube	1 tube					1 tube	3 mL each

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2 h post-dose	± 5 min	1 tube					1 tube	1 tube					1 tube	3 mL each
2.5 h post-dose	± 5 min	1 tube					1 tube	1 tube					1 tube	3 mL each
4 h post-dose	± 5 min	1 tube					1 tube	1 tube					1 tube	3 mL each
10 h post-dose	± 10 min	1 tube					1 tube	1 tube					1 tube	3 mL each
24 h post-dose (pre-next dose)	± 20 min	1 tube					1 tube	1 tube					1 tube	3 mL each
48 h post-dose	± 60 min	1 tube						1 tube					3 mL each	
72 h post-dose	± 60 min	1 tube						1 tube					3 mL each	
Injection Sampling														
45 min post-start	± 2 min		1 tube			1 tube							3 mL each	
0 h post-end	± 2 min		1 tube			1 tube							3 mL each	
0.5 h post-end	± 5 min		1 tube			1 tube							3 mL each	
1 h post-end	± 5 min		1 tube			1 tube							3 mL each	
4 h post-end	± 5 min		1 tube			1 tube							3 mL each	
10 h post-end	± 10 min		1 tube			1 tube							3 mL each	
24 h post-end (pre-next dose)	± 20 min		1 tube			1 tube							3 mL each	
48 h post-end	± 60 min				1 tube								3 mL each	

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72 h post-end	± 60 min				1 tube								3 mL each	
Total Samples		11	8	1	1	10	9	10	9	1	1	11	9	

Part 3: Utidelone Capsule + Capecitabine Expansion Study
Intensive blood sampling will be performed in 12 participants.

Table 9 Blood Sampling Schedule – Utidelone + Capecitabine Expansion Study

Sampling Time Point	Time Window	Visit	Volume					
		C1D1	C1D3	C1D4	C1D5	C2D1	C3D1	
0 h (within 60 min pre-dose)	–	1 tube	1 tube	1 tube	1 tube			3 mL each
40 min post-dose	± 2 min	1 tube			1 tube			3 mL each
1 h post-dose (blood draw first, then capecitabine)	± 2 min	1 tube			1 tube			3 mL each
1.5 h post-dose	± 5 min	1 tube			1 tube			3 mL each
2 h post-dose	± 5 min	1 tube			1 tube			3 mL each
2.5 h post-dose	± 5 min	1 tube			1 tube			3 mL each
3 h post-dose	± 5 min	1 tube			1 tube			3 mL each
4 h post-dose	± 5 min	1 tube			1 tube			3 mL each
4 h post-dose	± 60 min			1 tube		1 tube		3 mL each
7 h post-dose	± 5 min	1 tube			1 tube			3 mL each
24 h post-dose (pre-next dose)	± 20 min	1 tube			1 tube			3 mL each
48 h post-dose	± 60 min			1 tube				3 mL each
72 h post-dose	± 60 min			1 tube				3 mL each
Total Samples		9	1	1	11	1	1	

Note:
1. “Dose” refers to utidelone capsule administration.

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2. Blood samples collected at 0 h (within 60 min pre-dose), 40 min, 24 h, 48 h, 72 h post-dose, and at C2D1/C3D1 will only be analyzed for utidelone and its metabolites; capecitabine will not be assayed.

For the remaining participants, sparse blood sampling will be performed at the following time points:

- 4 h ± 60 min post-utidelone on C1D1
- 4 h ± 60 min post-utidelone on C2D1
- 4 h ± 60 min post-utidelone on C3D1

One tube (3 mL) per time point. Sparse samples will not be assayed for capecitabine.

Urine and Fecal Collection

Part 1: Dose Escalation Study

Urine and feces will not be collected.

Part 2: Pharmacokinetic Comparison and Food Effect Study

Urine: All urine will be collected in 9 intervals:

- Pre-dose: –2 to 0 h
- Post-dose: 0–4 h, 4–8 h, 8–12 h, 12–24 h, 24–48 h, 48–72 h, 72–96 h, 96–120 h

Feces: All feces will be collected whenever passed, starting from the first dose of Cycle 0 until 120 h post-dose. Each sample will be weighed and the time recorded.

Part 3: Utidelone Capsule + Capecitabine Expansion Study

Urine and feces will not be collected.

Bioanalysis

A liquid chromatography-tandem mass spectrometry (LC-MSn) method will be used to determine the concentrations of utidelone or capecitabine and their major metabolites (at least one metabolite) in plasma, urine, and feces. Other metabolites will be qualitatively detected. The specific metabolites to be analyzed will be adjusted and determined based on the Study results.

Evaluation Endpoints

Safety Evaluation Endpoints

Vital signs, physical examination, laboratory tests, Eastern Cooperative Oncology Group (ECOG) performance status, adverse events (AEs), and serious adverse events (SAEs). Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

Pharmacokinetic (PK) Evaluation Endpoints

F, Cmax, Tmax, AUC0-t, AUCinf, λz, t1/2, CL, Vd, etc.;
Cmax,ss, AUC0-t,ss, AUCinf,ss, AUC0-τ,ss, AUC_%Extrap, λz, T1/2z, CLss/F, Vz/F, Cmin,ss, Cav,ss, etc.

Efficacy Evaluation Endpoints (per RECIST 1.1)

Objective Response Rate (ORR), Progression-Free Survival (PFS), Disease Control Rate (DCR), Duration of Response (DoR).

Quantitative Pharmacology Research

PopPK and/or E-analyses will be performed using NONMEM (Version 7.3 or higher) and/or R (Version 4.0.5 or higher, http://www.r-project.org).

Statistical Analysis

The study population for analysis will include all enrolled participants who received at least one dose of the study drug. Descriptive statistics (e.g., mean, standard deviation, median, minimum, and maximum for continuous data; frequency and percentage for categorical data) will be used to summarize participant characteristics, compliance, efficacy, safety, and pharmacokinetic parameters. Data will be presented in tables and figures where appropriate.

Safety

Safety analysis will be performed in the safety set. All clinically and statistically observed safety parameters will be evaluated for safety and tolerability. Descriptive statistics will be applied to adverse events and laboratory parameters, and the incidence rates of adverse reactions will be calculated. Adverse events, including clinical observations and laboratory results, will be listed in frequency tables and summarized by organ system using

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MedDRA terminology. Key statistical parameters will include vital signs, electrocardiogram findings, and laboratory results.

Pharmacokinetic Characteristics

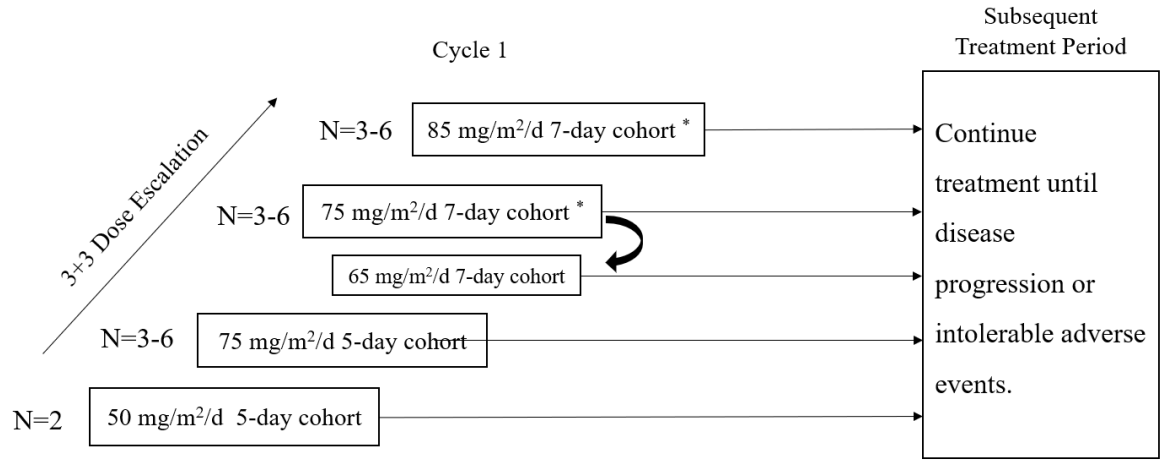
Drug concentrations and pharmacokinetic parameters will be summarized by dose level using descriptive statistics. Individual and mean concentration-time curves will be plotted based on measured data. Non-compartmental analysis (NCA) using WinNonlin software will be performed to estimate key pharmacokinetic parameters, fully characterizing the distribution and elimination of the drug in humans.

Efficacy

Objective Response Rate (ORR) and Disease Control Rate (DCR) will be summarized with frequencies and percentages, and 95% confidence intervals will be calculated. Median Progression-Free Survival (PFS) will be estimated using the Kaplan-Meier method, and survival curves will be plotted. Duration of Response (DoR) will be analyzed in the same manner as PFS.

1.2 Study Flow Chart

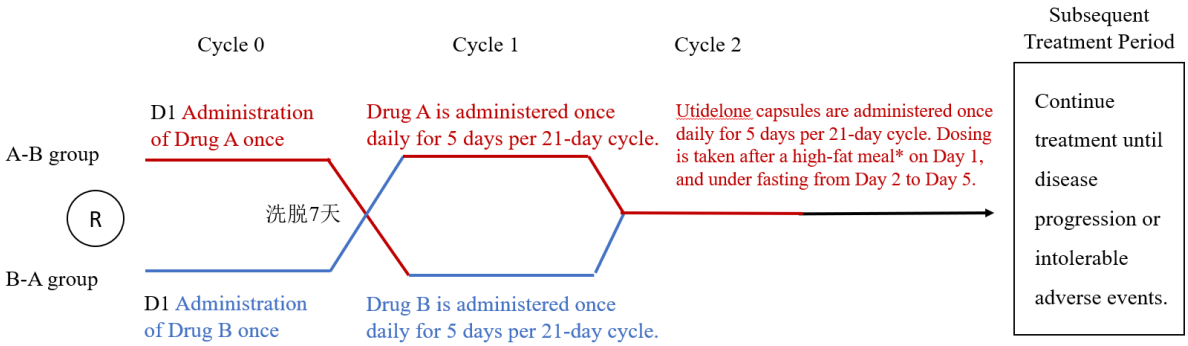
Part 1 Dose-Escalation Study



Utidelone capsules are administered once daily for 5 or 7 consecutive days per 21-day cycle.

*If the 75 mg/m²/d 7-day cohort meets the dose escalation stopping criteria, revert to the previous dose of 65 mg/m²/d for the 7-day cohort study.

Part 2 Pharmacokinetic Comparison and Food Effect Study



Drug A：Utidelone capsules, 60 mg/m² per day, administered once daily.

Drug B：Utidelone injection, 30 mg/m²/d, administered once daily with no restrictions on administration conditions.

*High-fat meal: In accordance with the standard high-fat meal at the study site.

Figure 1 Study Flow Chart

1.3 Schedule

Part 1 Dose-Escalation Study

Dose cohorts with 5 consecutive days of dosing per cycle:

Study Phase	Screening/Baseline		DLT Observation Period (Cycle 1)				Subsequent Treatment Period (≥ Cycle 2)	End of Treatment/Early Discontinuation	Safety Follow-up
Visit	**D-28~D-2**	**D-1**	**D1**	**D2-4**	**D5**	**D8±1**	**CnD1**		
Informed Consent	X								
Demographics[1]	X								
Medical and Personal History[2]	X								
ECOG[3]	X	X				X	X	X	
Vital Signs[4]	X	X				X	X	X	
Physical Examination[5]	X	X				X	X	X	
Complete Blood Count[6]	X	X				X	X	X	
Urinalysis[7]	X	X				X	X	X	
Blood Biochemistry[8]	X	X				X	X	X	
Stool Routine Test and Occult Blood[9]	X							X	
Pregnancy Test[10]	X								
Infectious Disease Screening[11]	X								
12-lead Electrocardiogram (ECG/EKG)[12]	X	X						X	
Imaging Examination[13]	X						X（±7 days）	X	
Study Drug Administration[14]			Dosing on Days 1 to 5 of each cycle, with a 21-day cycle.				X		
Blood Sample Collection[15]			X	X	X	X			
Adverse Events [18]			X						

Dose cohorts with 7 consecutive days of dosing per cycle:

Study Phase	Screening/Baseline		DLT Observation Period (Cycle 1)				Subsequent Treatment Period (≥ Cycle 2)	End of Treatment/Early Discontinuation	Safety Follow-up
Visit	**D-28~D-2**	**D-1**	**D1**	**D2-6**	**D7**	**D8±1**	**CnD1**		
Informed Consent	X								
Demographics[1]	X								
Medical and Personal History[2]	X								
ECOG[3]	X	X				X	X	X	
Vital Signs[4]	X	X				X	X	X	
Physical Examination[5]	X	X				X	X	X	
Complete Blood Count[6]	X	X				X	X	X	

Study Phase	Screening/Baseline		DLT Observation Period (Cycle 1)				Subsequent Treatment Period (≥ Cycle 2)	End of Treatment/Early Discontinuation	Safety Follow-up
Visit	D-28~D-2	D-1	D1	D2-6	D7	D8±1	CnD1		
Urinalysis[7]	X	X				X	X	X	
Blood Biochemistry[8]	X	X				X	X	X	
Stool Routine Test and Occult Blood[9]	X							X	
Pregnancy Test[10]	X								
Infectious Disease Screening[11]	X								
12-lead Electrocardiogram (ECG/EKG)[12]	X	X						X	
Imaging Examination[13]	X						X（±7 days）	X	
Study Drug Administration[14]			Dosing on Days 1 to 7 of each cycle, with a 21-day cycle.				X		
Blood Sample Collection[15]			X	X	X	X			
Adverse Events [18]			X						

Part 2 Pharmacokinetic Comparison and Food Effect Study

Study Phase	Screening/Baseline		Cycle 0		Cycle 1			Cycle 2			Subsequent Treatment Period (≥ Cycle 3)	End of Treatment /Early Discontinuation	Safety Follow-up
Visit	D-28~D-2	D-1	D1	D7	D1	D5	D8±1	D1±1	D5	D8±1	CnD1		
Informed Consent	X												
Demographics[1]	X												
Medical and Personal History[2]	X												
ECOG[3]	X	X		X				X			X	X	
Vital Signs[4]	X	X		X				X			X	X	
Physical Examination[5]	X	X		X				X			X	X	
Complete Blood Count[6]	X	X		X			X	X		X	X	X	
Urinalysis[7]	X	X		X				X			X	X	
Blood Biochemistry[8]	X	X		X				X			X	X	
Stool Routine Test and Occult Blood[9]	X											X	

Study Phase	**Screening/Baseline**		**Cycle 0**		**Cycle 1**			**Cycle 2**			**Subsequent Treatment Period (≥ Cycle 3)**	**End of Treatment /Early Discontinuation**	**Safety Follow-up**
Visit	**D-28~D-2**	**D-1**	**D1**	**D7**	**D1**	**D5**	**D8±1**	**D1±1**	**D5**	**D8±1**	**CnD1**		
Pregnancy Test[10]	X												
Infectious Disease Screening[11]	X												
12-lead Electrocardiogram (ECG/EKG)[12]	X	X										X	
Imaging Examination[13]	X										X（±7 days）	X	
Randomization		X											
Study Drug Administration[14]			X		X————X			X————X			X		
High-Fat Meal								X					
Blood Sample Collection[15]			X		X	X		X					
Urine Sample Collection[16]			X										
Stool Sample Collection[17]			X										
Adverse Events[18]			X										

Part 3 Expansion Study of Utidelone Capsules Combined with Capecitabine

Study Phase	**Screening/Baseline**	**Treatment Period**						**End of Treatment/Early Discontinuation**	**Follow-up**
		Cycle 1		**Cycle 2**		**Cycle 3+**			
Visit	**D-28~D-1**	**D1**	**D15±1**	**D1**	**D15±1**	**D1**	**D15±1**		
Informed Consent	X								
Demographics[1]	X								
Medical and Personal History[2]	X								
ECOG[3]	X	X		X		X		X	
Vital Signs[4]	X	X		X		X		X	
Physical Examination[5]	X	X		X		X		X	
Complete Blood Count[6]	X	X	X	X	X	X	X	X	
Urinalysis[7]	X	X		X		X		X	
Blood Biochemistry[8]	X					X (every 2 cycle)		X	
Stool Routine Test and Occult Blood[9]	X							X	
Pregnancy Test[10]	X								
Infectious Disease Screening[11]	X					X (every 2 cycle)		X	
12-lead Electrocardiogram (ECG/EKG)[12]	X					X[13]		X	X
Imaging Examination[13]		Dosing on Days 1 to 5 of each cycle, with a 21-day cycle.							
Capecitabine Administration[20]		Dosing on Days 1 to 14 of each cycle, with a 21-day cycle.							
Blood Sample Collection[15]		X		X		X			
Adverse Events [18]		X							

Study Phase	Screening/Baseline	Treatment Period						End of Treatment/Early Discontinuation	Follow-up
		Cycle 1		Cycle 2		Cycle 3+			
Visit	**D-28~D-1**	**D1**	**D15±1**	**D1**	**D15±1**	**D1**	**D15±1**		
Concomitant Medications/Treatments[21]	X	X							
Efficacy Follow-up[22]		X							
Survival Follow-up[23]		X							

Note: All scheduled assessments must be completed prior to study drug administration. The visit window for the post-treatment phase of Part 1/2 and for all CnD1 (n≥2) visits in Part 3 is ±3 days.

1. Demographic Information: Date of birth, gender, height, weight, occupation, ethnicity, marital status, etc.; assessed at screening/baseline.
2. Personal and Medical History: History of alcohol abuse, drug abuse, allergies, smoking history, hepatitis B/C/HIV/syphilis infection, prior medical history, and current illnesses with treatment history; assessed at screening/baseline.
3. ECOG Performance Status: Assessed at screening/baseline (Day -1); on C1D8 and all CnD1 (n≥2) visits in Part 1; on C2D1 and all CnD1 (n≥3) visits in Part 2; on all CnD1 visits during treatment in Part 3; and at the end of treatment or early withdrawal.
4. Vital Signs: Body temperature, respiratory rate, pulse, sitting blood pressure; assessed at screening/baseline (Day -1); on the day prior to dosing in each subsequent cycle; on C1D8 in Part 1; on all CnD1 visits during treatment in Part 3; and at the end of treatment or early withdrawal.
5. Physical Examination: General appearance, skin/mucous membranes, lymph nodes, head and neck, chest, abdomen, spine/extremities, and other systems. Height is generally only measured at baseline; weight is measured at every physical exam. Assessed at screening/baseline (Day -1); on the day prior to dosing in each subsequent cycle; on C1D8 in Part 1; on all CnD1 visits during treatment in Part 3; and at the end of treatment or early withdrawal.
6. Complete Blood Count (CBC): White blood cell count, neutrophil count, lymphocyte count, red blood cell count, hemoglobin, platelet count; assessed at screening/baseline (Day -1); on C1D8 in Part 1; on C0D7, C1D8, C2D1, and C2D8 in Part 2; on Day 1 of each cycle during the post-treatment phase; on CnD1 and CnD15 during treatment in Part 3; and at the end of treatment or early withdrawal. If the screening/baseline assessment is within 3 days of Day -1 (Day 1 for Part 3), the Day -1 assessment may be omitted. If early withdrawal occurs within 3 days of the previous assessment, repeat testing is not required.
7. Urinalysis: Urine red blood cells, white blood cells, glucose, and protein; assessed at screening/baseline (Day -1); on C1D8 in Part 1; on C0D7 and C2D1 in Part 2; on Day 1 of each cycle during the post-treatment phase; starting from Cycle 3, on Day 1 of every other cycle during treatment in Part 3; and at the end of treatment or early withdrawal. If the screening/baseline assessment is within 3 days of Day -1 (Day 1 for Part 3), the Day -1 assessment may be omitted. If early withdrawal occurs within 3 days of the previous assessment, repeat testing is not required.
8. Serum Biochemistry: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, indirect bilirubin, total protein, albumin, creatine kinase (CK), creatinine, blood urea nitrogen (BUN), uric acid, glucose, potassium, sodium, chloride, calcium; assessed at screening/baseline (Day -1); on C1D8 in Part 1; on C0D7 and C2D1 in Part 2; on Day 1 of each cycle during the post-treatment phase; on all CnD1 visits during treatment in Part 3; and at the end of treatment or early withdrawal. If the screening/baseline assessment is

within 3 days of Day -1 (Day 1 for Part 3), the Day -1 assessment may be omitted. If early withdrawal occurs within 3 days of the previous assessment, repeat testing is not required.

9. Routine Stool Test and Occult Blood: Stool red blood cells, stool white blood cells, and stool occult blood; assessed at screening/baseline, and at the end of treatment or early withdrawal. If early withdrawal occurs within 3 days of the last examination, repeat testing is not required.
10. Pregnancy Test: Serum or urine beta-human chorionic gonadotropin (β-HCG); for females of childbearing potential only; assessed at screening/baseline.
11. Infectious Disease Screening: Hepatitis B serology panel; HIV antibody testing is also required for Part 3; assessed at screening/baseline.
12. 12-Lead Electrocardiogram (ECG) : Rhythm, heart rate, PR interval, QRS interval, QT interval, QTcB, QTcF, and interpretation; assessed at screening/baseline, Day –1, and starting from Cycle 3, Day 1 of every other cycle in Part 3. If a cardiac or neurological adverse event (e.g., syncope, dizziness, seizure, stroke) occurs or QTc > 500 ms, repeat ECG three times at intervals of at least 5 minutes; echocardiography may be performed if clinically indicated. If screening/baseline is within 7 days of Day –1, Day –1 ECG may be omitted. If early withdrawal occurs within 7 days of the last examination, repeat testing is not required.
13. Imaging: At screening, head/neck, chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) must be performed. Bone scan may be done if bone metastasis is suspected during the Study. Additional sites may be imaged per clinical judgment. Post-treatment imaging: at least CT/MRI of relevant lesions; Cycles 1–6: every 2 cycles; Cycles 7–18: every 3 cycles; after Cycle 18: every 4 cycles; window ±7 days. Part 3: Cycles 1–6: every 2 cycles; after Cycle 7: every 3 cycles; window ±7 days. Screening imaging done within 28 days prior to enrollment does not need to be repeated. If early withdrawal occurs within 4 weeks of the last imaging, repeat imaging is not required. Assessed at screening/baseline, post-treatment, Part 3, and at the end of treatment or early withdrawal.
14. Administration: Dosing on Day 1 must follow completion of all scheduled visit assessments. Part 1 (5-day cohort): once daily, fasting, Days 1–5; 21-day cycle. Part 1 (7-day cohort): once daily, fasting, Days 1–7; 21-day cycle. Part 2: Cycle 0: single dose; Cycle 1: once daily, fasting, Days 8–12; Cycle 2: Day 1 after high-fat meal, Days 2–5 fasting; 21-day cycle. Post-treatment: once daily, fasting, Days 1–5; 21-day cycle.
15. Blood Sample Collection: Part 1: Intensive sampling at first and last dose of each cycle during DLT observation until 72 hours post-last dose; pre-dose (0 h) on Days 3–4 (5-day cohort) or Days 3–6 (7-day cohort); see sampling schedule. Part 2: Intensive sampling on Cycle 0 Day 1 and Cycle 2 Day 1 for both arms; intensive sampling on Cycle 1 Day 1 and Day 5 until 72 hours post-last dose; pre-dose (0 h) on Days 3–4; see sampling schedule. Part 3: Intensive sampling in 12 participants during Cycle 1; sparse sampling in Cycles 2–3; all other participants sparse sampling in Cycles 1–3; see sampling schedule.
16. Urine Collection – Part 2, Cycle 0: All urine collected in nine intervals: –2–0 h pre-dose, 0–4 h, 4–8 h, 8–12 h, 12–24 h, 24–48 h, 48–72 h, 72–96 h, 96–120 h post-first dose.
17. Fecal Collection – Part 2, Cycle 0: All feces collected from first dose until 120 h post-dose; each sample weighed and time recorded.
18. Adverse Events (AEs) : Closely observe and record all AEs from first study treatment until 28 days after last dose, including clinical symptoms, vital sign abnormalities, and laboratory abnormalities. All ongoing AEs at safety follow-up will be followed until resolution, stabilization, return to Grade ≤1, or reasonable explanation (e.g., loss to follow-up, death, new anti-tumor therapy, unrelated), whichever comes first. Record AE grade, causality, concomitant medications/treatments, and unscheduled tests.
19. Utidelone Capsule Dosing: 60 mg/m² once daily, fasting, Days 1–5; 21-day cycle. Dose adjustments per Safety Monitoring Committee (SMC) recommendation based on Part 1/2 safety/efficacy data.
20. Capecitabine Dosing: 1000 mg/m² twice daily (2000 mg/m²/day), 30 minutes after meals, Days 1–14; 21-day cycle.
21. Concomitant Medications/Treatments: Record all medications within 28 days pre-enrollment and during the Study. After Study discontinuation, only document medications/treatments for new or ongoing treatment-related AEs.

22. Efficacy Follow-Up – Part 3: Participants withdrawn for non-progression/non-death reasons: imaging every 2 cycles (6 weeks) until Cycle 6, then every 3 cycles (9 weeks), until progression, new anti-tumor therapy, or death. Record dates, imaging results, and anti-tumor therapy.
23. Survival Follow-Up – Part 3: Every 3 months via telephone/clinic contact after safety/efficacy follow-up (whichever later), until death, loss to follow-up, or end of data collection. Record survival status, death date/cause, and post-Study anti-tumor therapy.

List of Abbreviations

Abbreviation	Full English Name
AE	Adverse Event
ALT	Alanine Amiotransferase
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
$AUC_{_\%Extrap}$	$100\times（AUC_{inf}\text{-}AUC_{0\text{-}t} / AUC_{inf}）$
AUC_{inf}	Area Under Curve（$_{inf}$）
$AUC_{0\text{-}t}$	Area Under Curve（0-t）
BMI	Body Mass Index
BPKCS	Blood Pharmacokinetics Concentration Set
CAP	Capecitabinen
Ccr	Creatinine Clearance
C_{max}	Maximum Concentration
C_{min}	Minimum Concentration
CI	Confidence Interval
CL	Clearance
CR	Complete Remission
CTCAE	Common Terminology Criteria for Adverse Event
CV	Coefficient of Variation
CV%-GM	The Geometric Coefficient of Variation
DLT	Dose Limiting Toxicity
DLTS	DLT Analysis Set
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	E- Case Report Form
EDC	Electronic Data Capture System
E-R	Exposure-Response
FAS	Full Analysis Set
FPKCS	Feces Pharmacokinetics Concentration Set
GCP	Good Clinical Practice
Geo_Mean	The Geometric Mean
GLP	Good Laboratory Practice
h	Hour
HIV	Human Immunodeficiency Virus
ICH	International Conference On Harmonization
IEC	Independent Ethics Committee
LC-MS/MS	Liquid Chromatography - Mass Chromatography
MAD	Maximum Administration Dose
MDR	Multidrug Resistance

Abbreviation	Full English Name
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximal Tolerable Dose
NMPA	National Medical Products Administration
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progress Free Survival
PK	Pharmacokinetic(s)
PKCS	Pharmacokinetics Concentration Set
PKPS	Pharmacokinetics Parameter Set
PLT	Platelet Count
PN	Peripheral Neuropathy
PopPK	Population Pharmacokinetic
PPS	Per Protocol Set
PR	Partial Remission
SAE	Serious Adverse Event
SD	Stable Disease
SMC	Safety Monitoring Committee
SMO	Site Management Organization
SOC/PT	System Organ Class/ Preferred Term
SOP	Standard Operating Procedure
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total Bilirubin
$t_{½}$	Apparent Terminal Half-Life
T_{max}	Time to Reach C_{max}
ULN	Upper Limits of Normal
UPKCS	Urinary Pharmacokinetics Concentration Set
UTD1	Utidelone
Vd	Apparent Volume Of Distribution
λz	Lambda z

2. Study Background

2.1 Study Rationale

According to the latest data released by the World Health Organization (WHO), there were 19.29 million newly diagnosed cancer cases globally in 2020, with nearly 10 million cancer-related deaths. China currently reports the largest number of new cancer cases worldwide each year, and cancer has become a prevalent and serious disease threatening human health. Since early diagnosis and treatment of cancer remain suboptimal, most patients experience tumor recurrence or systemic metastasis after surgery or radiotherapy and thus require systemic therapy. At present, chemotherapy remains the mainstay of systemic treatment, especially for patients with advanced cancer. Therefore, the development of safe and effective chemotherapeutic agents continues to be a key focus of anti-cancer research across the globe.

A wide variety of anti-cancer drugs are available clinically. Agents that promote tubulin polymerization and inhibit mitosis represent an important class of chemotherapeutics, with paclitaxel as the representative drug. Since its launch, paclitaxel has been one of the most widely used broad-spectrum anti-tumor agents. However, paclitaxel and its analogs have notable limitations, including limited raw material supply (mainly extracted from yew trees) that causes resource damage, frequent development of drug resistance, and inherent resistance in certain tumor types. These challenges have driven researchers to explore novel compounds with similar mechanisms of action but distinct chemical structures to overcome the drawbacks of paclitaxel. Epothilones were subsequently discovered; they share the same pharmacological mechanism as paclitaxel but possess a completely different molecular structure, offering new perspectives to address the indusStudy production issues and drug resistance associated with paclitaxel.

Utidelone Injection (brand name: Youtidì) is a novel epothilone derivative independently developed by Beijing Huahao Zhongtian Biopharmaceutical Co., Ltd. Produced from myxobacteria with proprietary intellectual property rights and manufactured via biofermentation technology, utidelone is a Class 1 innovative anti-tumor drug in China. Approved for marketing in 2021, utidelone injection in combination with capecitabine is indicated for the treatment of patients with advanced metastatic breast cancer who have disease progression or recurrence after prior chemotherapy with taxanes and anthracyclines. The successful launch and

commercialization of utidelone injection further validate the clinical value of epothilone-class anti-tumor agents.

Currently, no oral formulations of tubulin inhibitors have been approved in China, the United States or Australia. Among several oral paclitaxel preparations, only Liporaxel has obtained marketing approval in South Korea, while tesetaxel and Oraxol were successively rejected by the U.S. Food and Drug Administration (FDA) due to safety concerns. This highlights a substantial unmet clinical need for oral tubulin inhibitors. In completed clinical studies, utidelone has demonstrated a better safety profile compared with taxanes. In pharmaceutical development, multiple technologies including sustained/controlled release formulations and solid dispersions have been adopted to effectively address the poor water solubility of utidelone, laying a solid foundation for the development of its oral dosage form. Preclinical animal studies have shown that the oral capsule formulation achieves a bioavailability of over 55% in beagle dogs. While maintaining comparable peak plasma concentration (Cmax) and overall systemic exposure (AUC) to the injection, the oral capsule can significantly improve patient medication adherence and clinical convenience.

Accordingly, we intend to develop utidelone capsules, and apply quantitative pharmacology to bridge the efficacy and safety profiles of the injection formulation. This Phase I/II Study is conducted in patients with advanced solid tumors to conduct an initial evaluation of the tolerability, safety, pharmacokinetic profiles and efficacy of utidelone capsules. The results will serve as critical evidence to support subsequent clinical development and guide future research strategies.

Developed by Beijing Huahao Zhongtian Biopharmaceutical Co., Ltd., utidelone capsule is classified as Class 2.2 chemical drug. It obtained the clinical Study approval from the National Medical Products Administration (NMPA) of China on December 8, 2022, and the present Phase I/II clinical Study is hereby initiated.

2.2 Investigational Drug Information

2.2.1 Basic Information of Investigational and Control Drugs

2.2.1.1 Name, Molecular Formula and Molecular Weight

1. Generic Name: Utidelone Capsules; Utidelone Injection

English Name: Utidelone

Pinyin: you ti de long

Active Ingredient: Utidelone

IUPAC Name: 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methylthiazol-4-yl)vinyl]oxacyclohexadec-13-ene-2,6-dione

Molecular Formula: $C_{27}H_{41}NO_5S$

Molecular Weight: 491.68

2. Generic Name: Capecitabine Tablets

English Name: Capecitabine Tablets

Pinyin: Kapeitabin Pian

Active Ingredient: Capecitabine

2.2.1.2 Dosage Form and Strength

Utidelone Capsules: 10 mg per capsule and 15 mg per capsule

Utidelone Injection: 5 mL: 50 mg

Capecitabine Tablets: 0.5 g per tablet, 12 tablets per box

2.2.2 Preclinical Research Data 错误!未找到引用源。

2.2.2.1Mechanism of Action

The mechanism of action of utidelone capsules is consistent with that of Utidelone Injection (UTD1). The molecular target of UTD1 is tubulin. It primarily binds directly to the β-tubulin subunit of microtubules, promotes tubulin polymerization, arrests cells at the mitotic phase of cell division, and ultimately induces cell death. In vitro, UTD1 promotes tubulin polymerization not only in drug-sensitive tumor cells but also in multidrug-resistant (MDR) tumor cells. In contrast, paclitaxel exerts negligible tubulin polymerization effect on MDR tumor cells. This difference explains the distinct activities of UTD1 and paclitaxel against MDR cells from the perspective of mechanism of action.

2.2.2.2 Pharmacodynamics

Utidelone capsule is a modified new drug derived from UTD1. Relevant pharmacodynamic data are cited from the regulatory submission dossiers of UTD1. UTD1 exhibits potent cytotoxic activity against twelve human tumor cell lines, including MCF-7 (breast cancer), NCI/ADR-Res (MDR breast cancer), LS1034 (MDR colon cancer), HCT-15 (MDR colon cancer), PC-3 (prostate cancer), HepG2 (liver cancer), NCI-H460 (non-small cell lung cancer), SF-268 (glioma), HL-60 (promyelocytic leukemia), HL60/MX2 (MDR subline of HL-60), CCRF-CEM (T-cell leukemia) and CEM/C2 (MDR subline of CCRF-CEM). In vivo anti-tumor activity of UTD1 was observed in multiple human tumor xenograft models in nude mice, including A549 (lung cancer), HepG2 (liver cancer), HCT-15 (colon cancer), Bcap-37 (breast cancer) and PC-3 (prostate cancer). The dosing regimen was twice daily intravenous administration for 10 consecutive days at three dose levels: 2.5, 1.0 and 0.4 mg/kg/day. Combination regimens also demonstrated synergistic anti-tumor effects: low-dose UTD1 plus gemcitabine for A549 lung cancer, low-dose UTD1 plus cisplatin (DDP) for HepG2 liver cancer, and ultra-low-dose UTD1 (0.16 mg/kg/day) plus 5-fluorouracil (5-Fu) for HCT-15 colon cancer.

2.2.2.3 Pharmacokinetics

As a modified new drug with reformulated dosage form and altered route of administration based on UTD1, utidelone capsules were tested for pharmacokinetics in a single animal species in accordance with relevant technical guidelines for nonclinical safety evaluation. Results from in vitro liver microsome metabolic stability studies and solubility tests indicated that maintaining the structural integrity of the formulation is critical for accurate assessment of drug absorption. Therefore, beagle dogs were selected as the animal model for pharmacokinetic studies of utidelone capsules. Meanwhile, oral pharmacokinetic studies were conducted in rats to evaluate gastrointestinal adverse reactions under high systemic exposure, with utidelone injection (UTD1) serving as the control in all studies.

After oral administration in beagle dogs, utidelone was rapidly absorbed, with the mean peak plasma concentration time (Tmax) ranging from 0.63 to 1.25 hours. Plasma drug concentrations declined rapidly thereafter, dropping to near or below the lower limit of quantification (LLOQ) at 24 hours post-dose, and the mean elimination half-life was approximately 1.96 to 3.22 hours. Systemic exposure parameters including peak plasma concentration (Cmax) and area under the plasma concentration-time curve from time zero to the last measurable time point (AUC_{0-t})

increased in a generally dose-dependent manner. A crossover study was performed to calculate the absolute bioavailability of utidelone capsules. In beagle dogs administered 1 mg/kg utidelone injection intravenously, the mean $AUC_{0-48}h$ was 3122.74 h·ng/mL. For the same dose given orally as capsules, the mean $AUC_{0-48}h$ was 1729.73 h·ng/mL, corresponding to an absolute bioavailability (F%) of 55.39%. Utidelone undergoes extensive metabolism in humans. The major metabolite, seco-UTD1, is generated via lactone hydrolysis by esterase and exhibits nearly no cytotoxic activity. Oxidation mediated by CYP3A4 represents the primary metabolic pathway. Up to 30 metabolites of utidelone were detected in rat urine and feces, and no single metabolite accounted for more than 6% of the administered dose. Utidelone showed wide tissue distribution in rats. The parent drug was detected in all examined tissues, with concentrations in most tissues and organs higher than those in plasma. The tissue half-life was markedly longer than the plasma half-life. Repeated oral administration for 3 consecutive days in rats did not induce or inhibit total cytochrome P450 enzyme activity. In vitro, the plasma protein binding rate of utidelone in both canine and human plasma was higher than 95%.

2.2.2.4 Toxicology

Prior to the clinical Study application for utidelone capsules, acute toxicity studies in rats and repeated-dose toxicity studies in rats and beagle dogs were conducted in compliance with ICH M3 and relevant technical guidelines for nonclinical safety evaluation of reformulated drugs and drugs with changed administration routes. Relevant preclinical toxicology data of UTD1 were also referenced.

In mice, single intravenous doses of utidelone ranging from 78.6 to 300 mg/m² resulted in animal death, which occurred 6 to 10 days after dosing. The median lethal dose (LD_{50}) of single intravenous utidelone in mice was approximately 134 mg/m².

In rats given single oral doses of utidelone from 90 mg/m² to 360 mg/m², no moribundity or death was observed, and no abnormal clinical signs were noted. Transient body weight loss, retarded weight gain and decreased food consumption were observed in the 360 mg/m² group, while no abnormal findings were identified upon clinical observation and gross anatomical examination.

In beagle dogs, single intravenous doses above 150 mg/m² produced overt toxicity, including severe gastrointestinal toxicity and post-dose death.

In SD rats, utidelone was administered orally once daily for 5 consecutive days followed by a 16-day recovery period. Utidelone injection given intravenously over the same cycle was set as the

control. Death occurred in animals receiving intravenous utidelone injection at 5 mg/kg with no preceding abnormal clinical manifestations. No death or moribundity was observed in other oral and intravenous groups. Common adverse reactions included decreased food intake, slow body weight gain and loose stools. No remarkable abnormalities were found in blood cell counts, coagulation function, serum biochemistry or gross pathology.

In beagle dogs, utidelone was administered orally once daily for 5 consecutive days followed by a 16-day recovery period, and intravenous utidelone injection at 0.6 mg/kg with the same dosing cycle served as control. One death was reported on Day 8 after the first oral dose at 1.8 mg/kg. Gross examination revealed blackened duodenal mucosa, whereas no corresponding microscopic lesions were observed. No death or moribundity occurred in other groups. Other adverse reactions included soft/loose stools, vomiting, decreased spontaneous activity, general weakness, reduced body weight and food intake, which generally resolved around 10 days after dosing. Changes in white blood cell counts and differential counts, reticulocyte count (Retic) and fibrinogen (FIB) were detected in both intravenous and oral groups. All parameters including clinical observations remained normal in the oral groups at doses of 0.3 mg/kg, 0.6 mg/kg and 1.2 mg/kg.

2.2.2.5 Genotoxicity

Genotoxicity and other safety tests for utidelone capsules were conducted with reference to the submission data of UTD1. The results were all negative in the Ames test for microbial mutagenicity, mammalian cell chromosome aberration assay, rodent micronucleus test, hemolysis test, vascular and muscle irritation test, active systemic anaphylaxis test in guinea pigs, and passive cutaneous anaphylaxis test in rats.

2.2.3 Clinical Pharmacology Studies

2.2.3.1 Phase I Clinical Study of Single-dose Utidelone Injection

The Phase I clinical Study of utidelone (UTD1) injection was initiated at the Cancer Hospital, Chinese Academy of Medical Sciences in October 2007. This study aimed to evaluate the tolerability of single and multiple-cycle administration of UTD1 in humans, investigate its pharmacokinetics across different dose levels, and conduct a preliminary assessment of anti-tumor efficacy.

The treatment regimen consisted of a 3-hour intravenous infusion administered once every 3 weeks, with each cycle lasting 3 weeks. A total of 21 patients with advanced metastatic solid

tumors who met the eligibility criteria completed at least one cycle of the dose-escalation tolerability Study across six dose levels ranging from 25 mg/m² to 225 mg/m². No patients withdrew from the study due to protocol violations or deviations, and all were included in the safety analysis.

Among the 21 participants, 16 were female and 5 were male. Primary tumor types included breast cancer (10 cases), non-small cell lung cancer (4 cases), and malignant melanoma (2 cases). One case each was diagnosed with sigmoid colon cancer, submandibular gland carcinoma of the floor of mouth, primitive neuroectodermal tumor, scapular small cell carcinoma and phyllodes sarcoma. All patients had stage IV recurrent disease, except for two patients (Participant No.12 and No.14) with stage IIIb disease.

Common adverse events (AEs) were transient, manageable mild to moderate gastrointestinal reactions (anorexia, nausea, vomiting and diarrhea), peripheral neuropathy (paresthesia, numbness and pain in hands and feet), myalgia, arthralgia, fatigue, alopecia, dizziness and insomnia. Grade 1 transient leukopenia was observed in 19% of patients. The most frequent laboratory abnormalities included decreased lymphocyte percentage and elevated gamma-glutamyl transferase (GGT).

In the 170 mg/m² dose group (3 participants), predominant AEs of Grade 2 severity included anorexia, generalized myalgia and numbness of extremities. In the 225 mg/m² dose group (4 participants), 2 patients developed Grade 3 ataxia, and one of them also experienced Grade 3 memory impairment, which resolved spontaneously. No severe myelosuppression or drug-related serious adverse events (SAEs) were reported, and no deaths occurred during the Study. A clear dose-response relationship was observed, with adverse events becoming more severe as the dose increased.

Eighteen out of 21 participants (85.7%) completed 2 to 6 treatment cycles (maximum 6 cycles as specified in the protocol) and were evaluable for efficacy. Of these, 8 patients (44.4%) achieved stable disease (SD) and 10 patients (55.6%) had progressive disease (PD). The remaining 3 female patients received only one cycle of treatment and were not evaluable for efficacy. The recommended Phase II dose for this regimen was determined as 170 mg/m².

2.2.3.2 Phase I Pharmacokinetics of Single-dose Utidelone Injection

The pharmacokinetics of UTD1 following single 3-hour intravenous infusion at six dose levels from 25 mg/m² to 225 mg/m² exhibited linear characteristics. The corresponding peak plasma

concentration (Cmax) values were 639 ng/mL, 1743 ng/mL, 1963 ng/mL, 2737 ng/mL, 2617 ng/mL and 2612 ng/mL; the area under the concentration-time curve (AUC) values were 2205 ng·h/mL, 4782 ng·h/mL, 6468 ng·h/mL, 9451 ng·h/mL, 13186 ng·h/mL and 14125 ng·h/mL, respectively.

Cmax was reached at the end of the 3-hour infusion. The mean plasma elimination half-life ($t_{1/2}$) was approximately 15 hours post-infusion. Only a small fraction of the parent drug was excreted in urine. UTD1 was primarily metabolized via cytochrome P450-mediated oxidation to multiple oxidative metabolites. A known chemical degradation product, UTD1-seco, was detected in plasma, with a molar recovery rate of 1.1% in urine. This metabolite showed no evident cytotoxicity against multiple human tumor cell lines in vitro. At the maximum tolerated dose (MTD) for single intravenous infusion, the mean clearance (CL) was 0.43 L/h and the volume of distribution (Vd) was 10.2 L.

2.2.3.3 Phase Ib Clinical Study of Repeated-dose Utidelone Injection

This was a single-center, open-label, uncontrolled Phase Ib dose-escalation and tolerability Study of repeated administration, conducted at the Cancer Hospital, Chinese Academy of Medical Sciences. Each dose group enrolled 3 to 6 participants. The starting dose was set at 35 mg/m²/day, equivalent to one-fifth of the single-dose MTD (170 mg/m²). The regimen was a 1.5-hour intravenous infusion once daily for 5 consecutive days (Days 1–5), with each treatment cycle consisting of 21 days.

Fifteen patients with advanced metastatic solid tumors who met the inclusion criteria received UTD1 across three dose levels: 35 mg/m²/day, 40 mg/m²/day and 45 mg/m²/day. All enrolled patients were assessable for safety, and no patients withdrew due to protocol violations.

In the 45 mg/m²/day group (6 patients), 2 cases developed Grade 3 numbness of hands and feet. Grade 3 peripheral neuropathy was therefore defined as the dose-limiting toxicity (DLT), and the DLT dose was identified as 45 mg/m²/day. Laboratory abnormalities included one case of Grade 3 neutropenia, and one case of Grade 3 thrombocytopenia combined with Grade 2 neutropenia.

Common adverse events included transient, manageable mild to moderate peripheral neuropathy (paresthesia and numbness), gastrointestinal reactions (anorexia, diarrhea and vomiting), myalgia, arthralgia, alopecia, fatigue, dizziness and insomnia. Mild transient leukopenia or neutropenia was also observed in some patients. Adverse events showed a distinct dose-response relationship, with severity increasing along with dose escalation. No drug-related SAEs occurred. The

recommended clinical MTD was determined as 40 mg/m²/day.

Thirteen of the 15 participants (86.7%) completed at least two treatment cycles and were evaluable for efficacy; the other 2 patients received only one cycle and were excluded from efficacy assessment. Among the 13 evaluable patients, 3 achieved partial response (PR), 3 had progressive disease (PD), and the remaining 7 had stable disease (SD). Two PR cases were observed after 2 cycles of treatment, and one case after 4 cycles. These patients received initial doses of 40 mg/m²/day and 45 mg/m²/day. The median number of treatment cycles was 4 (maximum 6 cycles per protocol).

2.2.3.4 Phase Ib Pharmacokinetics of Repeated-dose Utidelone Injection

In this Study, the study drug was administered once daily for 5 consecutive days via 1.5-hour constant-rate intravenous infusion using a pump at a concentration of 0.5 mg/mL. A total of 12 participants were enrolled across three dose groups: 35 mg/m²/day (3 participants), 40 mg/m²/day (3 participants), and 45 mg/m²/day (6 participants).

Blood samples were collected at pre-dose, 0 min, 15 min, 1 h, 4 h, 10 h and 24 h after dosing on Day 1; pre-dose, 0 min, 15 min, 1 h, 4 h, 10 h, 24 h and 48 h after dosing on Day 5; and post-dose on Day 2, Day 3 and Day 4.

The mean time to peak concentration (Tmax) of parent UTD1 in plasma was 1.5 h after dosing on both Day 1 and Day 5. The elimination half-life ($t_{1/2}$) for the 35, 40 and 45 mg/m²/day groups was 8.2±1.2 h and 8.5±1.7 h, 8.6±0.1 h and 8.2±1.1 h, 6.5±0.2 h and 9.6±1.6 h on Day 1 and Day 5, respectively.

The corresponding AUC_{0-24} values were 5515.2±1110.9 ng·h/mL and 4280.6±2142.0 ng·h/mL, 4178.3±1008.5 ng·h/mL and 4547.4±1628.1 ng·h/mL, 3455.0±1651.4 ng·h/mL and 4946.1±591.4 ng·h/mL. No statistically significant difference was found between Day 1 and Day 5 values, indicating no plasma accumulation of UTD1 following 5 consecutive days of administration across the three tested doses.

Plasma clearance (CL) on Day 1 and Day 5 was 6.1±1.2 L/h/m² and 8.4±3.4 L/h/m², 9.2±2.7 L/h/m² and 8.9±3.9 L/h/m², 14.0±5.1 L/h/m² and 8.4±0.8 L/h/m² for the three dose groups. The observed apparent volume of distribution (Vz_obs) was 71.4±14.4 L/m² and 108.2±57.3 L/m², 114.0±35.2 L/m² and 109.1±62.6 L/m², 131.3±47.4 L/m² and 117.7±27.5 L/m², respectively.

None of the pharmacokinetic parameters showed statistically significant differences between the first and final dosing days, demonstrating that repeated administration did not alter the metabolic disposition of UTD1 in vivo.

2.2.3.5 Phase II Clinical Study of Utidelone Injection Combined with Capecitabine

This was a multicenter, open-label, uncontrolled Phase I/II Study evaluating continuous administration of utidelone (UTD1) in combination with capecitabine for patients with metastatic or locally advanced breast cancer who had disease progression following prior anthracycline and taxane therapy. The Study consisted of two phases.

The first phase was a dose-finding study conducted at the Cancer Hospital, Chinese Academy of Medical Sciences. UTD1 (administered on Days 1–5, with a 21-day cycle) was combined with capecitabine (2000 mg/m²/day twice daily for 14 consecutive days) across three dose cohorts. Three patients were enrolled in the 25 mg/m²/day group, four in the 30 mg/m²/day group, and five in the 35 mg/m²/day group. Treatment tolerability and synergistic anti-tumor activity were assessed, and preliminary pharmacokinetic analysis of the combination was performed during the first cycle to determine the recommended UTD1 dose for the second phase.

Based on the results of the first phase, the combination regimen for the second phase was defined as UTD1 30 mg/m²/day (Days 1–5) plus capecitabine 2000 mg/m²/day (Days 1–14), with each cycle lasting 21 days. Enrollment continued until a total of 21 additional patients were recruited across three study centers for preliminary efficacy and safety evaluation. Each patient received treatment for a maximum of 6 cycles, or discontinued treatment upon disease progression or intolerable toxicity.

Efficacy

A total of 33 eligible patients with stage IV metastatic breast cancer were treated across both phases, including 25 patients in the 30 mg/m² group, 3 in the 25 mg/m² group and 5 in the 35 mg/m² group. One patient in the 30 mg/m² group from the second phase withdrew before

completing one cycle, leaving 32 patients evaluable for efficacy. Among them, 1 patient achieved complete response (CR), 13 partial response (PR), 15 stable disease (SD), and 3 progressive disease (PD). The overall response rate (ORR) was 42.4% (FAS, 95% CI: 26.6, 60.9), with a median time to response of 6 weeks. The median number of treatment cycles was 6 (maximum 6 cycles per protocol). With follow-up cut-off on February 28, 2014, the median duration of response was 9 months, and the median progression-free survival (PFS) was 7.9 months (FAS, 95% CI: 6.1, 9.8).

Safety

No deaths occurred during the Study, and no serious adverse events (SAEs) were reported. Peripheral numbness (peripheral neuropathy) and hand-foot syndrome (palmar-plantar erythrodysesthesia) were the most common adverse events, graded Grade 1 to 3 per NCI CTC Version 3.0 and deemed related to the study drugs. A total of 11 cases of Grade 3 peripheral numbness and hand-foot syndrome were reported, all of which resolved to Grade 0–1 within 1 to 2 weeks without intervention. Other common toxicities were typical for cytotoxic agents, including gastrointestinal reactions (diarrhea, vomiting), myalgia, arthralgia, fatigue, asthenia and alopecia. Most events were Grade 1 or 2 and easily manageable. Additional Grade 3 adverse events included one case of diarrhea, one case of dizziness, two cases of myalgia/arthralgia, and three cases of hematologic toxicity (two cases of neutropenia were judged unrelated to the study drugs). Hepatotoxicity was not a major concern for this

2.2.3.6 Phase II Combination Pharmacokinetics of Utidelone Injection plus Capecitabine

The dosing regimen in the first phase of this Study was once daily for 5 consecutive days. UTD1 was administered via 1.5-hour constant-rate intravenous infusion at a concentration of 0.5 mg/mL. A total of 12 patients were assigned to three dose groups: 3 patients in the 25 mg/m²/day group, 4 in the 30 mg/m²/day group, and 5 in the 35 mg/m²/day group.

Blood samples were collected pre-dose, at 0 min, 5 min, 30 min, 1 h, 4 h, 12 h and 24 h post-dose on Day 1; pre-dose, at 0 min, 15 min, 1 h, 4 h, 10 h and 24 h post-dose on Day 5; as well as prior to and at the end of infusion on Day 2, Day 3 and Day 4. Capecitabine was administered orally twice daily for 14 consecutive days.

The mean time to peak plasma concentration (Tmax) of parent UTD1 was 1.5 hours on both Day

1 and Day 5. For the 25, 30 and 35 mg/m²/day groups, the elimination half-life ($t_{1/2}$) was 7.48 h, 9.55 h, 8.66 h on Day 1 and 14.07 h, 10.43 h, 10.67 h on Day 5, respectively. The corresponding AUC_{0-24} values were 1908.28, 2513.33, 2986.22 ng·h/mL on Day 1 and 1640.95, 2675.88, 5379.29 ng·h/mL on Day 5. The Cmax values were 699.09, 1045.33, 1022.18 ng/mL on Day 1 and 446.83, 807.50, 1154.81 ng/mL on Day 5. No statistically significant differences were observed between Day 1 and Day 5 parameters.

The pharmacokinetic profile of UTD1 after 5 consecutive days of combination therapy was consistent with that of monotherapy, showing approximately linear kinetics. Coadministration with capecitabine did not alter the metabolic disposition of UTD1, and no drug accumulation was detected in plasma.

2.2.3.7 Phase II Clinical Study of Single-agent Utidelone Injection

This was a multicenter, open-label, uncontrolled Phase II Study of single-agent UTD1 in patients with metastatic breast cancer who failed prior anthracycline and taxane treatment, designed in two stages.

Efficacy

In the first stage, two UTD1 regimens were evaluated in parallel: single high-dose administration (170 mg/m²) and repeated daily administration (40 mg/m² for 5 consecutive days). Patients were randomized to the two groups across five study centers. Fourteen patients completed treatment in the 170 mg/m² group, and 15 in the 40 mg/m² group. In the 170 mg/m² group, 5 patients withdrew before completing 2 cycles; among the remaining 9 evaluable patients, 3 achieved SD and 6 had PD. In the 40 mg/m² group, 2 patients discontinued treatment early; of the 13 evaluable patients, 1 achieved CR, 3 PR, 5 SD and 4 PD.

Based on the first-stage results, the repeated 40 mg/m² regimen was selected for further enrollment, reaching a total of approximately 60 planned patients. Ultimately, 70 eligible patients with metastatic breast cancer were enrolled (including the 15 patients from the first stage). Seven patients withdrew prior to completing 2 cycles, leaving 63 evaluable patients. Among them, 1 achieved CR, 19 PR, 25 SD and 18 PD. The ORR was 28.57% (FAS, 95% CI: 18.4, 40.6), and the clinical benefit rate was 66%. The median PFS was 4.57 months (FAS, 95% CI: 2.87, 6.53), and the median overall survival (OS) was 17.5 months (FAS, 95% CI: 13.5, [incomplete]). The median number of treatment cycles was 4 (maximum 6 cycles per protocol). A total of 8 study centers participated in this Study.

Safety

No deaths occurred during the study. Two SAEs were reported. The first case occurred in a patient from the 170 mg/m² group in the first stage at Tianjin Medical University Cancer Institute & Hospital, who was hospitalized due to fever after the first cycle; the investigator assessed the event as possibly unrelated to UTD1. The second case was a patient from the 40 mg/m² group in the second stage at Jiangsu Cancer Hospital, who developed Grade 3 peripheral neuropathy after the first cycle and required hospitalization. The symptom resolved within 2 weeks, and the patient withdrew from the Study.

Peripheral numbness was a common adverse event, graded Grade 1 to 3 per NCI CTC Version 3.0 and considered study drug-related, with spontaneous resolution in most cases. Among the 70 patients in the 40 mg/m² group, 6 developed Grade 3 peripheral neuropathy. Other common adverse events were typical for cytotoxic chemotherapy, including gastrointestinal toxicity (diarrhea, vomiting), myalgia, arthralgia, fatigue, asthenia and alopecia, mostly Grade 1 or 2 and well manageable. One patient experienced Grade 3 diarrhea. No severe myelosuppression was observed. Seven patients (10%) discontinued treatment early due to intolerable toxicity.

2.2.3.8 Phase III Clinical Study of Utidelone Injection Combined with Capecitabine

This multicenter, randomized, controlled Phase III Study adopted a 2:1 enrollment ratio for the investigational combination arm (utidelone plus capecitabine) versus the monotherapy arm (capecitabine). The study aimed to compare the clinical efficacy and safety of utidelone combined with capecitabine versus single-agent capecitabine in patients with advanced breast cancer who experienced recurrence or drug resistance after prior treatment with anthracyclines and taxanes.

Efficacy

As of the data cutoff date (September 15, 2016), tumor assessments for the full analysis set (FAS) were performed by the Independent Radiology Review Committee (IRRC). In the combination group, 214 patients (79.3%) experienced disease progression or death, with a median progression-free survival (PFS) of 8.44 months (95% CI: 7.89, 9.49%). In the capecitabine (CAP) monotherapy group, 115 patients (85.2%) had disease progression or death, with a median PFS of 4.14 months (95% CI: 3.09, 5.09%). The difference in median PFS between the two groups was statistically significant (Log-rank $P < 0.001$). The combination regimen reduced the risk of disease progression or death by 53%, with a hazard ratio (HR) of 0.47 (95% CI: 0.37, 0.59), demonstrating a substantial delay in tumor progression.

The confirmed objective response rate (ORR) was 45.6% (123 responders, 95% CI: 39.5%, 51.7%) in the combination group, versus 23.7% (95% CI: 16.8%, 31.8%) in the control group. The between-group difference in ORR was 21.9% (95% CI: 11.4%, 32.0%), reaching statistical significance ($P < 0.001$), with an HR of 0.22 (95% CI: 0.11, 0.32%).

The clinical benefit rate (defined as complete response [CR], partial response [PR] or stable disease [SD] lasting no less than 6 months) was 60% (162 patients) in the combination group and 33.3% (45 patients) in the control group. The absolute difference was 26.7% (95% CI: 16.3%, 36.6%), with a statistically significant difference ($P < 0.0001$).

Consistent results were observed when the same statistical analyses were repeated based on investigator assessments and the per-protocol set (PPS).

As of December 15, 2018, a total of 313 deaths were recorded in the FAS. There were 203 deaths (75.2%) in the combination group and 110 deaths (81.5%) in the CAP monotherapy group. The median overall survival (OS) was 19.81 months (95% CI: 17.02, 21.59) for the combination group and 15.97 months (95% CI: 14.26, 18.53) for the control group. The difference was statistically significant (Log-rank $P = 0.014$). The combination therapy reduced the risk of death by 25%, with an HR of 0.75 (95% CI: 0.59, 0.94).

Analyses based on the PPS yielded similar outcomes. The median OS was 20.90 months (95% CI: 17.81, 22.74) in the combination group and 15.74 months (95% CI: 14.19, 19.29) in the monotherapy group. The between-group difference was statistically significant (Log-rank $P = 0.0032$). The combination regimen reduced the risk of death by 31%, with an HR of 0.69 (95% CI: 0.54, 0.89).

Safety Results

Adverse Reactions

In this Phase III Study for advanced metastatic breast cancer, the most frequently reported treatment-emergent adverse events (TEAEs) in the combination group versus the CAP monotherapy group were as follows: peripheral sensory neuropathy [228 cases (85.4%) vs 12 cases (9.2%)], decreased white blood cell count [136 cases (50.9%) vs 61 cases (46.9%)], decreased neutrophil count [112 cases (41.9%) vs 46 cases (35.4%)], hand-foot syndrome [98 cases (36.7%) vs 52 cases (40.0%)], and elevated bilirubin [44 cases (16.5%) vs 37 cases (28.5%)].

Grade ≥3 TEAEs occurred in 145 patients (54.3%) in the combination group, including 139 cases

(52.0%) of Grade 3 events and 6 cases (2.3%) of Grade 4 or 5 events. In the CAP monotherapy group, Grade ≥3 TEAEs were reported in 46 patients (35.4%), consisting of 38 Grade 3 cases (29.2%) and 8 Grade 4 or 5 cases (6.2%).

Serious adverse events (SAEs) occurred in 19 patients (7.1%) in the combination group and 14 patients (10.8%) in the CAP group, with a slightly higher incidence in the monotherapy arm. Apart from peripheral neuropathy (25.1% vs 0.8%) and diarrhea (7.5% vs 2.3%), the incidence of other adverse events was comparable between the two groups.

Grade 3 peripheral neuropathy was common in the combination group, while no Grade 4 cases were reported. Among patients with peripheral neuropathy, 64 cases (95.5%) resolved to Grade 1 or better, with a median resolution time of 3.1 weeks.

Adverse Events of Special Interest

Adverse events of special interest included peripheral neuropathy, myelosuppression and liver function-related events.

Grade 3 peripheral neuropathy was reported in 67 patients (25.1%) in the combination group, with no Grade 4 cases. A total of 64 out of 67 patients (95.5%) achieved resolution, with a median resolution time of 3.29 weeks. Only 1 patient (0.8%) in the CAP group developed Grade ≥3 peripheral neuropathy, which resolved with a median resolution time of 0.71 weeks.

Grade 3 hand-foot syndrome occurred in 19 patients (7.1%) in the combination group and 10 patients (7.7%) in the CAP group. Grade 3 myelosuppression was seen in 44 patients (16.5%) and 20 patients (15.4%) respectively. Grade 3 liver function-related adverse events were reported in 5 patients (1.9%) in the combination group and 6 patients (4.6%) in the CAP group.

These data indicated that utidelone presents no obvious hepatotoxicity, representing another safety advantage of the agent.

Mortality, Serious Adverse Events and Other Notable Events

By the data cutoff on September 15, 2016, a total of 178 deaths were documented. Most deaths (173 cases) occurred more than 30 days after treatment discontinuation, and only 5 deaths happened during the treatment period (from the first dose to 30 days after the last dose), including 3 deaths due to malignant tumor and 2 deaths related to adverse events.

In the combination group, 19 patients (7.1%) experienced at least one SAE, among whom 11 patients (4.1%) had treatment-related SAEs. In the CAP group, 14 patients (10.8%) reported at least one SAE, including 9 patients (6.9%) with treatment-related SAEs.

The most common TEAEs in the combination group were peripheral sensory neuropathy (228 cases, 85.4%), decreased white blood cell count (136 cases, 50.9%), decreased neutrophil count (112 cases, 41.9%) and hand-foot syndrome (98 cases, 36.7%).

The most common TEAEs in the CAP group were decreased white blood cell count (61 cases, 46.9%), decreased neutrophil count (46 cases, 35.4%), hand-foot syndrome (52 cases, 40.0%) and elevated blood bilirubin (37 cases, 28.5%).

2.2.3.9 Phase II Clinical Study of Utidelone Injection for Advanced Non-Small Cell Lung Cancer

Utidelone injection demonstrated favorable efficacy in patients with advanced or metastatic non-small cell lung cancer (NSCLC) who failed to respond to or could not tolerate second-line standard platinum-based chemotherapy.

All 26 enrolled patients received at least one dose of the study drug. The median number of treatment cycles was 3, and some patients completed more than 12 cycles. A total of 21 patients were evaluable for efficacy: 4 achieved PR, 13 achieved SD and 4 had PD. The ORR was 19.0% (95% CI: 5.4%–41.9%), and the disease control rate (DCR) was 81.0% (95% CI: 58.1%–94.6%). The median PFS was 4.37 months (95% CI: 2.50–5.29). The median OS was not reached, and the 12-month OS rate was 69.0%.

Safety

TEAEs related to utidelone occurred in all 26 patients. Severe TEAEs were reported in 10 patients (38.5%), among which 9 cases were judged related to utidelone. Dose reduction due to TEAEs was implemented in 8 patients (30.8%), treatment interruption in 8 patients (30.8%), and permanent treatment discontinuation in 2 patients (7.7%). SAEs occurred in 4 patients (15.4%), including 1 case related to utidelone. No deaths caused by TEAEs were observed.

2.2.4 Development Status of Similar Drugs

UTD1 targets tubulin. One of its mechanisms of action is to bind directly to the β-tubulin subunit of microtubules, promote tubulin polymerization, arrest cells at the mitotic phase of cell division, and ultimately induce cell death. Ixabepilone shares an identical mechanism of action with UTD1, and both are epothilone analogs.

Ixabepilone for injection (brand name: Ixempra), an anti-cancer drug developed by Bristol-Myers Squibb, was approved by the U.S. Food and Drug Administration (FDA) in October 2007. It is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients resistant to anthracyclines, taxanes and capecitabine (Xeloda). It is also approved for combination use with capecitabine in patients with metastatic or locally advanced breast cancer who have developed resistance to anthracyclines and taxanes, or who are taxane-resistant and have contraindications to further anthracycline therapy.

Ixabepilone is a semi-synthetic analog of natural epothilone B. Bristol-Myers Squibb conducted two large multinational, multicenter Phase II/III clinical Studys to support the new drug application of Ixempra.

The first study was a multicenter, open-label, uncontrolled Phase II Study (CA163081) of single-agent Ixempra. A total of 126 patients with metastatic or locally advanced breast cancer previously treated with anthracyclines, taxanes and capecitabine received Ixempra at a dose of 40 mg/m² once every 3 weeks. Tumor response was assessed via CT scans every 2 cycles (6 weeks). The confirmed objective response rate (ORR) was 12%. The median time to response was 2 cycles, the median duration of response was 6.3 months, the median progression-free survival (PFS) was 3.2 months, and the median overall survival (OS) was 9.0 months. Another supportive Study (CA163009) evaluated the efficacy of Ixempra in patients with metastatic breast cancer who experienced disease progression or resistance after prior taxane therapy. Partial response (PR) was achieved in 6 out of 49 patients (12%), with a median PFS of 2.2 months and a median OS of 7.9 months.

The second large multinational, multicenter Phase III Study (CA163046) enrolled 369 patients receiving combination therapy of Ixempra plus capecitabine and 368 patients receiving single-agent capecitabine, with PFS as the primary endpoint. The results demonstrated that compared with capecitabine monotherapy, the combination regimen significantly prolonged PFS in patients previously treated with anthracyclines and taxanes. The median PFS was 5.85 months in the combination group versus 4.17 months in the capecitabine group. The ORR was 34.7% in the combination group and 14.3% in the monotherapy group. The median number of treatment cycles was 5 for combination therapy and 4 for capecitabine monotherapy. The median OS was 12.9 months in the combination group and 11.1 months in the control group, and the difference was not statistically significant.

Ixempra was associated with severe toxicities. Myelosuppression was the predominant hematologic toxicity. The incidence of Grade 3/4 neutropenia reached 68% in the combination group, compared with 11% in the capecitabine group, and neutropenia showed a dose-dependent increase. The major non-hematologic toxicities related to Ixempra were peripheral neuropathy and hand-foot syndrome (palmar-plantar erythrodysesthesia). Peripheral neuropathy is a class-specific adverse reaction of microtubule stabilizers. Grade ≥3 peripheral neuropathy (classified as serious adverse events or disability) occurred in 23% of patients in the combination group, while no such cases were reported in the capecitabine monotherapy group.

The peripheral neuropathy induced by Ixempra combined with capecitabine was predominantly reversible sensory neurotoxicity. The majority of patients with severe (Grade 3/4) neuropathy recovered to Grade 1 or better, with a mean recovery period of 6 weeks. No exposure-response correlation was observed for the onset of initial neuropathy. Hand-foot syndrome was the main non-hematologic toxicity associated with capecitabine, which was commonly seen in both treatment groups. The overall incidence was slightly higher in the combination group (64% vs 62%). The rates of Grade ≥3 hand-foot syndrome were comparable between the two groups (18% vs 17%), indicating that Ixempra did not exacerbate capecitabine-induced hand-foot syndrome or diarrhea. A total of 12 patients in the combination group died of treatment-related toxicities, all attributable to complications of neutropenia, whereas 2 deaths related to study drug toxicity occurred in the capecitabine group.

Another large multinational Phase III Study (CA163048) was conducted across 199 study centers in 29 countries. It enrolled 595 patients with metastatic or locally advanced breast cancer receiving Ixempra plus capecitabine and 603 patients receiving capecitabine monotherapy; all participants had prior exposure to anthracyclines or taxanes. The primary endpoint was OS. During the follow-up period, 430 deaths (71%) occurred in the combination group and 450 deaths (75%) in the control group. No significant difference was observed in median OS (16.5 months vs 15.6 months; HR=0.9, 95% CI: 0.78–1.03; *P*=0.1162). Among 79% of evaluable patients, the combination therapy significantly prolonged median PFS (6.24 months vs 4.4 months; HR=0.79, 95% CI: 0.69–0.90; *P*=0.0005).

Severe toxicities were also observed in this Study. For hematologic adverse reactions, the incidences of Grade 3 and Grade 4 neutropenia were 39% and 41% in the combination group, versus 6% and 3% in the capecitabine group. Grade 3 and Grade 4 leukopenia occurred in 48% and 15% of combination group patients, compared with 5% and 2% in the control group. The

rate of Grade 3/4 thrombocytopenia was 6% in the combination group and 3% in the monotherapy group.

Peripheral neuropathy remained the main non-hematologic toxicity of Ixempra. Grade 3 peripheral neuropathy was reported in 24% of combination group patients and Grade 4 in 1%, while the incidence of Grade 3 neuropathy was only 1% in the capecitabine group. Among 120 patients with Grade 3/4 peripheral neuropathy in the combination group, symptoms resolved to Grade 1 or better, with a median recovery time of 6.2 weeks. The incidence of Grade ≥3 hand-foot syndrome related to capecitabine was similar between the two groups (21% in the combination group vs 20% in the control group).

2.3 Risk-Benefit Assessment

2.3.1 Known Potential Risks

Based on nonclinical pharmacology and toxicology findings as well as clinical Study data of utidelone injection, utidelone capsules are expected to demonstrate favorable safety and tolerability. Investigators will closely monitor all study participants throughout the Study. Any adverse events (AEs) or adverse drug reactions (ADRs) will be evaluated promptly, and appropriate therapeutic interventions will be administered in a timely manner.

Combining completed clinical data of utidelone injection and relevant toxicology results, the AEs potentially related to the study drug are summarized as follows: peripheral sensory neurotoxicity, gastrointestinal toxicity, myelosuppression, liver function impairment, myalgia and arthralgia, fatigue, asthenia and alopecia.

In addition, blood samples will be collected from participants for pharmacokinetic (PK) analysis and laboratory safety tests during the study. Transient discomforts such as pain and bruising may occur after venipuncture. To mitigate relevant risks, blood collection will only be performed by fully qualified study personnel in strict compliance with standard safety protocols, so as to avoid potential hazards to study participants.

If any new medical condition, disease or adverse event occurs, investigators will immediately assess whether the participant shall continue participation or withdraw from the Study prematurely, and provide corresponding medical treatment as needed.

2.3.1.1 Direct Risks

No clinical data are currently available for utidelone capsules. Utidelone injection has completed all clinical development and obtained marketing approval in March 2021. Common adverse reactions stated in the approved prescribing information [2] of utidelone injection are listed below:

1. General disorders and administration site conditions: fatigue, alopecia
2. Psychiatric disorders: insomnia
3. Musculoskeletal and connective tissue disorders: myalgia and arthralgia
4. Gastrointestinal disorders: nausea, diarrhea, vomiting, etc.
5. Metabolism and nutrition disorders: decreased appetite
6. Nervous system disorders: peripheral neuropathy, dizziness, neuralgia, memory impairment, etc.
7. Hepatobiliary disorders: elevated alanine transaminase (ALT), aspartate transaminase (AST) and gamma-glutamyl transferase (GGT)
8. Laboratory abnormalities: decreased neutrophil count, decreased white blood cell count, decreased hemoglobin and decreased platelet count

2.3.1.2 Long-term Risks

There is no clinical data for utidelone capsules to date. Long-term risks indicated in the prescribing information of utidelone injection include peripheral neuropathy, hematologic toxicity and hepatotoxicity.

2.3.2 Known Potential Benefits

This Study is conducted in patients with advanced solid tumors. Enrolled participants may obtain clinical benefits including delayed disease progression. Meanwhile, the Study data will provide valuable evidence to support the research and marketing approval of the study drug.

2.3.2.1 Direct Potential Benefits

Conducted in patients with advanced solid tumors, this Study is expected to bring clinical benefits to participants and slow down disease progression.

2.3.2.2 Long-term Potential Benefits

Data from this Study will support the further development of utidelone capsules. The oral formulation is expected to become a new therapeutic option for various solid tumors, which will benefit patients with recurrent or metastatic solid tumors in the future.

2.3.3 Assessment of Potential Risks and Benefits

Multiple measures will be implemented to minimize risks for Study participants, including strict adherence to inclusion and exclusion criteria and rigorous clinical examinations. The main potential risks consist of drug-related adverse events and procedural injuries during the Study.

All study sites are equipped with emergency medical devices and rescue medications. Investigators will conduct continuous and close observation of participants and actively monitor the occurrence of adverse events. Any adverse event will be managed timely, and relevant participants will be followed up until full recovery or condition stabilization.

Optimized testing and analytical methods will be adopted to reduce the volume of biological samples (blood, urine and feces) collected, so as to further lower the risks for participants.

Clinical results of utidelone injection have proven that both monotherapy and combination therapy with capecitabine yield superior efficacy compared with single-agent capecitabine and the combination of ixabepilone plus capecitabine. It is anticipated that participants will achieve the goal of delayed disease progression through this Study.

In conclusion, the benefits of participation in this Study outweigh the potential risks.

2.4 Rationale for the Study

Available clinical data from the current study demonstrate that utidelone capsules exhibit favorable safety and tolerability at the dose levels of 50 mg/m²/day and 75 mg/m²/day administered for 5 consecutive days. No dose-limiting toxicity (DLT) has been observed so far, and all adverse events (AEs) are predictable and clinically manageable. Similar to utidelone injection, the predominant AEs are common chemotherapy-related reactions including peripheral neurotoxicity, gastrointestinal toxicity and hematologic toxicity. The vast majority of reported AEs are mild to moderate and well controlled clinically. None of the AEs led to treatment interruption, dose modification or permanent discontinuation. No clinically significant abnormalities or trends were identified in other laboratory tests, vital signs and physical examinations. Following joint discussion between the Sponsor and investigators, further evaluation of the safety and tolerability of utidelone capsules at 75 mg/m²/day for 7 consecutive days is approved.

A multicenter, dose-escalation Study of utidelone capsules in patients with advanced solid tumors is ongoing across 3 study sites in the United States, which was initiated in May 2023. The primary

objective is to assess the safety and tolerability of utidelone capsules, and determine the maximum tolerated dose (MTD) and DLT in the US population. Secondary objectives include characterization of the pharmacokinetic profile, preliminary evaluation of efficacy and safety, and determination of the recommended dose and regimen for subsequent clinical Studys. As of January 22, 2024, a total of 10 participants have been enrolled. No DLT was detected in the dose cohorts of 25 mg/m²/day, 50 mg/m²/day and 75 mg/m²/day administered for 5 consecutive days. One case of Grade 3 diarrhea, defined as DLT, was reported among 3 participants in the 100 mg/m²/day cohort with 5 consecutive days of dosing. Other major AEs were Grade 1–2 events, including gastrointestinal toxicity, hematologic toxicity, peripheral neurotoxicity and alopecia.

Based on the above findings and considering potential safety risks at higher dose levels, the Sponsor and investigators have reached a consensus to remove Cohort 5 and Re-escalation Cohort 2 from the Part 1 dose-escalation phase. The dose of Cohort 4 was revised from 100 mg/m²/day for 7 consecutive days to 85 mg/m²/day for 7 consecutive days. The dose of Re-escalation Cohort 1 was adjusted from 70 mg/m²/day for 7 consecutive days to 65 mg/m²/day for 7 consecutive days.

An expansion phase (Part 3) is added to evaluate the efficacy, safety and pharmacokinetics of utidelone capsules in combination with capecitabine in patients with advanced metastatic breast cancer. Given the satisfactory safety and tolerability without DLT in the Part 1 cohort of 75 mg/m²/day for 5 days, a moderately reduced dose is selected for combination therapy. The dose of utidelone capsules is set at 60 mg/m²/day, administered orally once daily under fasting conditions for 5 consecutive days (Days 1–5), with each treatment cycle lasting 21 days. The dose and regimen may be adjusted by the Safety Monitoring Committee (SMC) based on accumulated safety and efficacy data from Part 1 and Part 2.

As a widely used antimetabolite anti-tumor agent, capecitabine has well-established safety and efficacy at its standard clinical dose. Referencing the regimen of utidelone injection combined with capecitabine, capecitabine is administered at 1000 mg/m² twice daily (total daily dose: 2000 mg/m²). This Study will assess the efficacy, safety and pharmacokinetic characteristics of the combination of utidelone capsules plus capecitabine.

3. Study Objectives

3.1 Primary Objectives

To evaluate the safety and tolerability of utidelone capsules in patients with advanced solid tumors, and determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT).

Endpoint(s): Maximum tolerated dose (MTD), dose-limiting toxicity (DLT).

To evaluate the objective response rate (ORR) of utidelone capsules combined with capecitabine in patients with advanced metastatic breast cancer.

Endpoint(s): Objective response rate (ORR) assessed per RECIST 1.1 criteria.

3.2 Secondary Objectives

1. To evaluate the absolute bioavailability of utidelone capsules relative to utidelone injection.

Endpoint(s): Absolute bioavailability (F).

2. To characterize the pharmacokinetic profiles of utidelone capsules in patients with advanced solid tumors.

Endpoint(s):

- Cmax, Tmax, AUC_{0-t}, AUCinf, λz, $t_{1/2}$, CL, Vd, etc.
- Cmax,ss, $AUC_{0-t,ss}$, AUCinf,ss, $AUC_{0-\tau,ss}$, AUC_%Extrap, λz, $T_{1/2}z$, CLss/F, Vz/F, Cmin,ss, Cav,ss, etc.

3. To preliminarily evaluate the efficacy and safety of utidelone capsules in patients with advanced solid tumors.

Endpoint(s):

- Efficacy endpoint (per RECIST 1.1): Objective response rate (ORR).
- Safety endpoints: Vital signs, physical examination, laboratory tests, electrocardiogram (ECG), ECOG performance status score, adverse events (AEs) and serious adverse events (SAEs).

4. To recommend the dose and administration regimen for subsequent clinical Studys.

5. To evaluate the efficacy, safety and pharmacokinetic profiles of utidelone capsules in combination with capecitabine in patients with advanced metastatic breast cancer.

Endpoint(s):

- Progression-free survival (PFS): Assessed per RECIST 1.1 criteria.
- Disease control rate (DCR): Assessed per RECIST 1.1 criteria.
- Duration of response (DoR): Assessed per RECIST 1.1 criteria.
- Safety endpoints: Vital signs, physical examination, laboratory tests, ECOG performance status score, adverse events (AEs) and serious adverse events (SAEs). AEs are graded according to NCI-CTCAE Version 5.0.

4. Study Design

4.1 Overall Design

4.1.1 Study Phase

This is a Phase I/II clinical Study.

4.1.2 Study Type and Design

In strict compliance with the Good Clinical Practice for Drug Clinical Studys [3], Guidelines for the Management of Phase I Drug Clinical Studys (Study) [4], Technical Guidelines for Clinical Pharmacokinetic Studies of Chemical Drugs [5] and other relevant regulations issued by the National Medical Products Administration (NMPA), this Study is designed to evaluate the tolerability, safety, pharmacokinetic profiles and efficacy of utidelone capsules in patients with advanced solid tumors.

4.1.3 Study Duration

The total study duration shall not exceed 12 months.

4.1.4 Measures to Minimize Bias

4.1.4.1 Randomization

Part 1: Dose-escalation Study

No randomization will be performed. During screening, each participant will be identified by a screening number formatted as S + study number + site number + 3-digit serial number. The study number for Part 1 is 1, e.g., S11001.

Eligible participants will be enrolled on Study Day -1 and assigned enrollment numbers in ascending order of screening numbers. Participants will be grouped by dose level, and enrollment numbers will be coded as study number + cohort number + 2-digit serial number. The enrollment

numbers for Cohort 1 are 1101, 1102…; for Cohort 2: 1201, 1202…; for Cohort 3: 1301, 1302…, and so forth.

Part 2: Pharmacokinetic Comparison and Food Effect Study

The randomization scheme will be developed by statisticians. A block randomization schedule (including random numbers and group assignments) will be generated using the PLAN procedure of SAS 9.4 or higher version. The generated randomization schedule is reproducible, and the set random seed parameters shall be properly retained.

During screening, each participant will be assigned a screening number formatted as S + study number + site number + 3-digit serial number. The study number for Part 2 is 2, e.g., S21001. Eligible participants will be randomized on Study Day -1 to different administration sequence groups and assigned random numbers formatted as study number + group number + 2-digit serial number. Random numbers for Group A-B are 2101, 2102…; for Group B-A: 2201, 2202….

Supplemental participants will be recruited to replace those who discontinue the Study due to non-drug-related toxicities prior to Study completion (e.g., missed follow-up visits, incorrect study drug supply, medical conditions preventing oral administration, rapid disease progression, etc.). New random/enrollment numbers will be assigned to supplemental participants in sequence.

For participants who withdraw from the Study for any reason:

- Those who have not received any study drug may be re-screened and re-enrolled if eligible, and will be assigned new random/enrollment numbers.
- Those who have received study drug and withdraw due to reasons other than treatment failure shall retain their original random/enrollment numbers and are not allowed to re-participate in the Study.
- Those who withdraw due to treatment failure shall retain their original random/enrollment numbers. After a 3-month washout period, they may be re-enrolled into a higher-dose cohort upon re-obtaining informed consent if they still meet all inclusion and exclusion criteria, and will be assigned new enrollment numbers. Each participant may participate in a maximum of 2 dose cohorts.

Part 3: Expansion Study of Utidelone Capsules Combined with Capecitabine

No randomization will be performed. During screening, each participant will be identified by a screening number formatted as S + study number + site number + 3-digit serial number. Site numbers are coded from 1 to 99 in the order of site activation, and the study number for Part 3 is

3, e.g., S31001 … S399001.

Eligible participants will receive enrollment numbers in ascending order of screening numbers. Enrollment numbers are formatted as study number + site number + 3-digit serial number, with site numbers ranging from 1 to 99. Enrollment numbers for Site 1 are 31001, 31002…; for Site 99: 399001, 399002…, and so forth.

4.1.4.2 Control

No control group will be set in Part 1 (Dose-escalation Study). In Part 2 (Pharmacokinetic Comparison and Food Effect Study), utidelone injection will serve as the control in Cycle 0 and Cycle 1, and administration under high-fat meal conditions will be used as the control on Day 1 of Cycle 2. No control group will be established in Part 3 (Expansion Study of utidelone capsules combined with capecitabine).

4.1.4.3 Blinding

This is an open-label Study. No blinding will be applied to clinical investigators, project managers, clinical monitors, bioanalysts, data management staff and statistical analysts.

4.1.5 Study Population

Patients with advanced solid tumors who have no standard effective treatment options, or experienced treatment failure or disease recurrence after standard therapies.

4.1.6 Sample Size

Part 1 (Dose-escalation Study): At least 3 dose cohorts are planned, with a total enrollment of 14 to 26 participants.

Part 2 (Pharmacokinetic Comparison and Food Effect Study): Including the test group and control group, a total of 18 participants will be enrolled.

Part 3 (Expansion Study of utidelone capsules combined with capecitabine): A total of 40 participants are planned for enrollment.

4.1.7 Interim Analysis

No interim analysis is planned for this Study.

4.2 Rationale for Dose Selection

4.2.1 Dose Determination for Part 1 Dose-escalation Study

1) Selection of Starting Dose

According to the approved prescribing information of utidelone injection, the recommended dose for combination therapy is 30 mg/m²/day (40 mg/m²/day for monotherapy), administered once daily for 5 consecutive days with a 21-day treatment cycle. The absolute bioavailability of utidelone capsules is estimated to be approximately 55%. In consideration of ethical requirements and drug safety for the dose-escalation Study, 50 mg/m²/day is selected as the starting dose for utidelone capsules.

2) Dose-escalation Regimen

A modified Fibonacci dose-escalation design is adopted in this Study. Clinical studies have demonstrated favorable efficacy and tolerability for utidelone injection at the clinical dose of 30–40 mg/m²/day. Taking the oral bioavailability into account, only 2 participants will be enrolled in the starting dose cohort of utidelone capsules at 50 mg/m²/day. Participants shall complete treatment and assessments of Cycle 1 and be eligible for DLT evaluation. If no DLT is observed, dose escalation will proceed to the next cohort. The conventional 3+3 design will be applied for dose escalation starting from the second cohort.

All subsequent cohorts follow the 3+3 design, with 3 to 6 participants planned per cohort. Dose escalation to the next level is permitted only after no less than 3 participants complete Cycle 1 treatment and assessments for DLT evaluation with no DLT reported. A maximum of 2 participants may be under DLT observation concurrently.

- If 1 out of the initial 3 participants develops DLT, an additional 3 participants will be enrolled in the same cohort.
- If 2 participants develop DLT in total within one cohort, dose escalation will be terminated.
- If 2 out of the initial 3 participants develop DLT, dose escalation will be terminated immediately.

Upon completion of tolerability assessment for the current cohort, the Safety Monitoring Committee (SMC) will review study data and decide whether to adjust the dose for the subsequent cohort.

Considering treatment adherence for 7-day oral administration and previous study findings:

- If the 75 mg/m²/day cohort with 5-day dosing (Cohort 2) does not meet the dose-escalation termination criteria, dose will be escalated to Cohort 3: 75 mg/m²/day administered for 7 consecutive days.

- If Cohort 3 meets the termination criteria, Re-escalation Cohort 1 will be set at 65 mg/m²/day for 7 consecutive days.
- If Cohort 3 does not meet the termination criteria, dose will be escalated to Cohort 4: 85 mg/m²/day for 7 consecutive days.

Dose escalation will be terminated regardless of whether Cohort 4 meets the termination criteria. Doses of individual cohorts may be adjusted during the Study based on discussions between the Sponsor and investigators.

Subsequent Treatment Phase

Participants who complete Cycle 1 treatment and assessments, and are deemed to benefit from continued treatment at the same dose by the investigator, may voluntarily enter the subsequent treatment phase. They will receive utidelone capsules at the same dose and frequency on a 21-day cycle until disease progression, intolerable adverse events, voluntary withdrawal, or treatment discontinuation as decided by the investigator.

Detailed dose-escalation regimen is presented in Table 2. The dose-escalation scheme, treatment cycle and dosing frequency will be adjusted timely based on accumulated human pharmacokinetic and safety data during the Study.

Table 2 Dose-escalation Regimen

Cohort	Cohort 1	Cohort 2	Cohort 3	Cohort 4	De-escalation Cohort 1
Dose (mg/m²/d)	50	75	75	85	65
Administration Route	QD	QD	QD	QD	QD
Administration Days	D1–D5	D1–D5	D1–D7	D1–D7	D1–D7
Cycle Length	21 days as one cycle				
Total Dose per Cycle (mg/m²)	250	375	525	595	455
Escalation Ratio (based on total dose per cycle)	/	50%	40%	≈15%	/
Sample Size	2	3–6	3–6	3–6	3–6

All cohorts adopt once-daily (QD) dosing in accordance with the prescribing information of utidelone injection. Study drugs shall be administered under fasting conditions: 2 hours of fasting

before dosing and 2 hours of fasting after dosing. The dosing method may be adjusted by the SMC based on Study results.

3) Dose-Limiting Toxicity (DLT)

DLT will be assessed throughout Cycle 1 in Part 1. DLT is defined as any adverse event definitely or possibly related to the study drug occurring during the observation period, as listed below:

1. All Grade ≥3 non-hematologic toxicities, excluding the following conditions:
   - Untreated or inadequately treated nausea, vomiting and diarrhea. Grade 4 nausea, vomiting or diarrhea despite optimal supportive treatment, and Grade 3 nausea, vomiting or diarrhea persisting for more than 24 hours after optimal treatment will be defined as DLT.
   - Alopecia.
   - Grade 3 fatigue that resolves to Grade ≤2 within 7 days.
   - Grade 3 laboratory or metabolic abnormalities deemed clinically insignificant or easily reversible.
2. Any toxicity at least possibly related to the study drug leading to treatment delay of 3 weeks or longer.
3. Grade 4 neutropenia lasting for 7 days or longer.
4. Febrile neutropenia.
5. Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia accompanied by bleeding.
6. Grade 4 anemia.

All adverse events are graded per NCI-CTCAE Version 5.0. No dose adjustment is allowed during Cycle 1. For adverse events other than DLT, investigators may pause dosing as needed to ensure participant safety.

4) Maximum Tolerated Dose (MTD)

- If only 1 out of the initial 3 participants in a cohort develops DLT, an additional 3 participants will be enrolled in the same cohort. If no additional DLT occurs, dose escalation will proceed to the next level.

- If 2 participants develop DLT among the initial 3 participants, or 2 participants develop DLT among a total of 6 participants in one cohort, the current dose will be defined as the MTD.

Dose-escalation Termination Criteria and Dose Adjustment

Once a cohort is confirmed as the MTD, dose escalation will be terminated. The Sponsor and investigators will discuss whether to add an intermediate dose level between the MTD cohort and the prior cohort for further DLT evaluation.

No dose adjustment is permitted during Cycle 1 of Part 1, as well as Cycle 0, Cycle 1 and Cycle 2 of Part 2. In the subsequent treatment phase and Part 3, dosing may be temporarily interrupted based on individual participant conditions. Treatment may be resumed or the dose may be reduced after toxicities resolve to meet the inclusion criteria.

4.2.2 Dose Determination for Part 2 Pharmacokinetic Comparison and Food Effect Study

According to the approved prescribing information, the recommended dose of utidelone injection is 30 mg/m²/day for combination therapy and 40 mg/m²/day for monotherapy. Satisfactory efficacy and safety have been demonstrated for utidelone injection at 30 mg/m²/day. Preclinical studies in Beagle dogs showed that the bioavailability of utidelone capsules was approximately 55%. To ensure clinical benefits for participants and based on an assumed bioavailability of 50%, 60 mg/m²/day of utidelone capsules was selected as the dose equivalent to 30 mg/m²/day of utidelone injection.

4.3 Study Groups

Part 1 (Dose-escalation Study): All dose cohorts are treatment groups.

Part 2 (Pharmacokinetic Comparison and Food Effect Study): Cycle 0 and Cycle 1 consist of two arms: utidelone capsules and utidelone injection, both administered under fasting conditions. On Day 1 of Cycle 2, all participants receive the study drug after a high-fat meal.

Part 3 (Expansion Study of utidelone capsules combined with capecitabine): Only one treatment group is designed, with no control group.

4.4 Dosing Regimen

Part 1: Dose-escalation Study

For cohorts with 5 consecutive days of once-daily dosing per cycle: each treatment cycle lasts 21 days.

For cohorts with 7 consecutive days of once-daily dosing per cycle: each treatment cycle lasts 21 days.

See Section 4.2.1 for detailed dose specifications for Part 1.

Dose calculation is based on the body surface area (BSA) measured during the screening period. BSA is calculated using the Xu Wensheng formula:

BSA (m^2) = 0.0061 × Height (cm) + 0.0128 × Body weight (kg) − 0.1529

Dose will not be recalculated in subsequent cycles unless the participant's body weight changes by more than 10% relative to baseline.

In accordance with the capsule strength specification, the calculated dose is rounded as follows: values of 2.49 mg or less are rounded down to 0 mg; values ranging from 2.50 mg to 4.99 mg are rounded up to 5 mg. The calculation methods and results for each cohort are presented in Table 3 and Table 4. A dose deviation within 4% is acceptable for all cohorts.

Table 3 Part 1 and Part 2 Dose Rounding Scheme

Dose Group									
50 mg/m²/d		50 mg/m²/d		50 mg/m²/d		50 mg/m²/d		50 mg/m²/d	
BSA (m^2)	BSA (m^2)	BSA (m^2)	BSA (m^2)	BSA (m^2)	BSA (m^2)	BSA (m^2)	BSA (m^2)	BSA (m^2)	BSA (m^2)
1.30-1.35	65	1.30-1.37	80	1.30-1.35	85	1.30	95	1.30-1.32	110
1.36-1.45	70	1.38-1.45	85	1.36-1.43	90	1.31-1.37	100	1.33-1.38	115
1.46-1.55	75	1.46-1.54	90	1.44-1.50	95	1.38-1.43	105	1.39-1.44	120
1.56-1.65	80	1.55-1.62	95	1.51-1.58	100	1.44-1.50	110	1.45-1.50	125
1.66-1.75	85	1.63-1.70	100	1.59-1.66	105	1.51-1.57	115	1.51-1.56	130
1.76-1.85	90	1.71-1.79	105	1.67-1.73	110	1.58-1.63	120	1.57-1.62	135
1.86-1.95	95	1.80-1.87	110	1.74-1.81	115	1.64-1.70	125	1.63-1.68	140
1.96-2.05	100	1.88-1.95	115	1.82-1.89	120	1.71-1.77	130	1.69-1.74	145
2.06-2.15	105	1.96-2.04	120	1.90-1.96	125	1.78-1.83	135	1.75-1.80	150
2.16-2.25	110	2.05-2.12	125	1.97-2.04	130	1.84-1.90	140	1.81-1.86	155
2.26-2.35	115	2.13-2.20	130	2.05-2.12	135	1.91-1.97	145	1.87-1.92	160
2.36-2.45	120	2.21-2.29	135	2.13-2.19	140	1.98-2.03	150	1.93-1.98	165
2.46-2.50	125	2.30-2.37	140	2.20-2.27	145	2.04-2.10	155	1.99-2.04	170
		2.38-2.45	145	2.28-2.35	150	2.11-2.17	160	2.05-2.10	175
		2.46-2.50	150	2.36-2.43	155	2.18-2.23	165	2.11-2.16	180
				2.44-2.50	160	2.24-2.30	170	2.17-2.22	185
						2.31-2.37	175	2.23-2.28	190
						2.38-2.43	180	2.29-2.34	195

2.44-2.50	185	2.35-2.40	200
		2.41-2.46	205
		2.47-2.50	210

Table 4 Part 1 and Part 2 Utidelone Capsule Allocation Scheme

Rounded Dose (mg)	Number of Capsules		Rounded Dose (mg)	Number of Capsules	
	15mg	10mg		15mg	10mg
30	**2**	**0**	200	**12**	**2**
35	**1**	**2**	205	**13**	**1**
40	**2**	**1**	210	**14**	**0**
45	**3**	**0**	215	**13**	**2**
50	**2**	**2**	220	**14**	**1**
55	**3**	**1**	225	**15**	**0**
60	**4**	**0**	230	**14**	**2**
65	**3**	**2**	235	**15**	**1**
70	**4**	**1**	240	**16**	**0**
75	**5**	**0**	245	**15**	**2**
80	**4**	**2**	250	**16**	**1**
85	**5**	**1**	255	**17**	**0**
90	**6**	**0**	260	**16**	**2**
95	**5**	**2**	265	**17**	**1**
100	**6**	**1**	270	**18**	**0**
105	**7**	**0**	275	**17**	**2**
110	**6**	**2**	280	**18**	**1**
115	**7**	**1**	285	**19**	**0**
120	**8**	**0**	290	**18**	**2**
125	**7**	**2**	295	**19**	**1**
130	**8**	**1**	300	**20**	**0**
135	**9**	**0**	305	**19**	**2**
140	**8**	**2**	310	**20**	**1**
145	**9**	**1**	315	**21**	**0**
150	**10**	**0**	320	**20**	**2**
155	**9**	**2**	325	**21**	**1**
160	**10**	**1**	330	**22**	**0**
165	**11**	**0**	335	**21**	**2**
170	**10**	**2**	340	**22**	**1**
175	**11**	**1**	345	**23**	**0**
180	**12**	**0**	350	**22**	**2**
185	**11**	**2**	355	**23**	**1**
190	**12**	**1**	360	**24**	**0**
195	**13**	**0**			

Cycle 1 is designated for DLT assessment in cohorts receiving 5 consecutive days of dosing per cycle, and for tolerability evaluation in cohorts receiving 7 consecutive days of dosing per cycle. Under the supervision of investigators at the study site, participants shall take the study drug orally at room temperature under fasting conditions, with approximately 240 mL of warm water. The oral cavity and drug containers will be checked after administration to confirm complete drug intake. Starting from Cycle 2 and throughout subsequent treatment cycles, tumor efficacy assessments will be performed. Participants may take the study drug either at the study site or at home as instructed by investigators.

Part 2: Pharmacokinetic Comparison and Food Effect Study

Doses

- Drug A: Utidelone capsules, 60 mg/m²/day. The calculated dose shall be rounded in accordance with capsule specifications (see Table 3 and Table 4).
- Drug B: Utidelone injection, 30 mg/m²/day. Utidelone injection at 30 mg/m²/day shall be diluted in 250 mL normal saline and administered via intravenous infusion over 1.5 hours (infusion duration may be shortened by up to 5 minutes or prolonged by up to 15 minutes).

Dosing Regimen

Pharmacokinetic Comparison

A total of 18 eligible participants will be randomized at a 1:1 ratio into two administration sequence groups (Group A-B and Group B-A).

In Cycle 0: The 9 participants in Group A-B will receive oral utidelone capsules under fasting conditions; the 9 participants in Group B-A will receive intravenous infusion of utidelone injection. All participants will receive a single dose, followed by a 7-day washout period.

Cycle 1 will start on Day 8. Participants in Group A-B will receive intravenous utidelone injection, while those in Group B-A will take oral utidelone capsules under fasting conditions. Dosing will be administered once daily for 5 consecutive days, followed by a 16-day treatment-free observation period.

Food Effect Assessment

Cycle 2 will start on Day 29. All participants will take oral utidelone capsules after a high-fat meal on Day 29. From Day 30 to Day 33, the drug will be administered orally under fasting conditions. Dosing will be given once daily for 5 consecutive days, followed by a 16-day treatment-free observation period.

Table 5 Food Effect Administration Regimen

Group	Sequence	Cycle 0	Cycle 1	Cycle 2
A-B group	A-B	Utidelone Capsule (fasted)	Utidelone Injection	Utidelone Capsule (high-fat meal on Day 1)
B-A group	B-A	Utidelone Injection	Utidelone Capsule (fasted)	Utidelone Capsule (high-fat meal on Day 1)

Subsequent Treatment Phase

After completing treatment and assessments of Cycle 0, Cycle 1 and Cycle 2, participants may continue treatment at the original dose on a voluntary basis if the investigator determines that continued administration will bring clinical benefits. Participants receiving utidelone injection may switch to utidelone capsules during this phase. Treatment will continue until disease progression, occurrence of intolerable adverse events, voluntary withdrawal by the participant, or treatment discontinuation as decided by the investigator.

Administration Conditions

During Cycle 0 and Cycle 1, all patients will receive premedication 30 to 60 minutes prior to utidelone injection: 40 mg diphenhydramine via intramuscular injection or oral administration, plus 10 mg dexamethasone and 300–400 mg cimetidine (or 50 mg ranitidine) by intravenous injection. On the following dosing day, the doses of dexamethasone and diphenhydramine may be halved or omitted based on the patient's clinical status.

Utidelone capsules shall be administered under fasting conditions: participants shall fast for 2 hours before dosing and 1 hour after dosing, and take the drug with approximately 240 mL of warm water.

No specific dietary restrictions are required during the subsequent treatment phase.

Part 3: Expansion Study of Utidelone Capsules Combined with Capecitabine

Doses

- Utidelone capsules: 60 mg/m²/day, administered orally once daily under fasting conditions on Days 1 to 5 of each 21-day treatment cycle. The dose and regimen may be adjusted by the Safety Monitoring Committee (SMC) based on accumulated safety and efficacy data from Part 1 and Part 2.
- Capecitabine: 1000 mg/m² twice daily (total daily dose: 2000 mg/m²), taken orally within 30 minutes after meals in the morning and evening on Days 1 to 14 of each 21-day treatment cycle.

Dosing Regimen

For the first three cycles (Cycle 1 to Cycle 3), participants shall have breakfast approximately 30 minutes after taking utidelone capsules, and take capecitabine tablets within 30 minutes after the meal. On days with intensive pharmacokinetic (PK) sampling, capecitabine shall be administered after the blood collection at the 1-hour time point post utidelone dosing. The time of meals, drug administration and blood sampling shall be recorded precisely to the minute.

Doses are calculated based on the body surface area (BSA) measured during the screening period. BSA is calculated using the Xu Wensheng formula:

BSA (m²) = 0.0061 × Height (cm) + 0.0128 × Body weight (kg) − 0.1529

Doses will not be recalculated in subsequent cycles unless the participant's body weight changes by more than 10% compared with the baseline value. The rounding rules and dosage allocation for the original and adjusted doses of utidelone capsules shall follow the specifications in Table 6.

Table 6 Part 3 Utidelone Capsule Rounding and Allocation Scheme

15mg UTD2 （Capsules）	10mgUTD2 （Capsules）	Rounded Dose （mg）	60 mg/m²/d	75% Dose 45 mg/m²/d	50% Dose 30 mg/m²/d
			BSA(m²)	BSA(m²)	BSA(m²)
2	1	40			1.17-1.66
4	0	60		1.17-1.55	1.67-2.33
4	2	80	1.17-1.49	1.56-1.99	2.34-2.49
6	1	100	1.50-1.83	2.00-2.44	
8	0	120	1.84-2.16	2.45-2.49	
8	2	140	2.17-2.49		

Dose adjustments for the above medications may be performed in accordance with the protocol based on adverse events observed in participants (see Section 6.5 Dose Adjustment). Participants will continue treatment until disease progression, intolerable adverse events, voluntary withdrawal, or treatment discontinuation as determined by the investigator.

In case of a missed dose, the scheduled dosing time and reason for the missed dose shall be documented in detail. Participants shall resume dosing per the original cycle schedule thereafter. No make-up dose will be administered, and no treatment cycle will be modified.

5. Patient Population

5.1 Inclusion Criteria (All criteria must be met for enrollment)

1) Patients who have fully understood the objectives, content, process of the study and possible adverse events, voluntarily serves as a participant and signs the informed consent form.

2) Part 1 and Part 2: Patients with definitive histopathological diagnosis of advanced solid tumors. Part 3: Patients were diagnosed with advanced metastatic breast cancer by pathology and/or cytology.

3) Part 1 and Part 2: Male or female participants aged ≥18 and ≤65, Part 3: Male or female participants aged ≥18 and ≤70, with ECOG performance status scored 0-1.

4) Expected survival time ≥ 12 weeks;

5) At least one measurable lesion present according to RECIST 1.1 criteria.

6) Baseline routine blood tests within 1 week prior to enrollment is normal (not received blood transfusions or hematopoietic-stimulating factors within 14 days), with CTCAE grade ≤1 (based on normal values at each site's laboratory): a) Neutrophil count (ANC) ≥ 1.5 × 109/L; b) platelet count (PLT) ≥ 100 × 109/L; c) Hemoglobin ≥9.0 g/dL.

7) Liver and kidney function test results are normal within 1 week prior to enrollment, with CTCAE grade ≤1 (based on normal values at each site's laboratory): a) Total bilirubin (TBIL) ≤ 1.5× the upper limit of normal value (ULN); b) Serum Glutamic Pyruvic Transaminase/Alanine Aminotransferease (SGPT /ALT) ≤ 2.5× ULN (Part 3 allowed ≤5×ULN in patients with liver metastases); c) Serum Glutamic-oxaloacetic Transaminase/Aspartate Aminotransferase (SGOT /AST) ≤ 2.5× ULN (Part 3 allowed ≤5×ULN in patients with liver metastases); d) Creatinine clearance (Ccr) ≥60 ml/min.

8) Patients with no functional disorders of major organs.

9) Fertile males and females of childbearing potential must agree to use effective contraception (so do their partners, using hormonal or barrier contraception, or abstinence) during the study and within at least 6 months after the last dose. The blood or urine pregnancy test for female patients

of childbearing potential prior to enrollment must be negative.

10) Part 3: breast cancer patients who had received ≤4 previous chemotherapy regimens (adjuvant chemotherapy/neoadjuvant chemotherapy was considered as one chemotherapy regimen);

11) Part 3: history of prior treatment with at least one anthracycline or one taxane as neoadjuvant/adjuvant or advance therapy or both.

5.2 Exclusion Criteria (Participants will be excluded if any criterion is met)

1) Patients who have received non-investigational anti-tumor therapies (such as chemotherapy, radiotherapy, immunotherapy, biological therapy or traditional Chinese medicine treatment) within 4 weeks prior to study drug administration, except for the following:

a. Nitrosoureas or mitomycin C: within 6 weeks prior to study drug administration;

b. Oral fluoropyrimidines and small molecule targeted agents: within 2 weeks or 5 half lives of the drug prior to study drug administration (whichever is longer);

c. Traditional Chinese medicine with anti tumor indications and endocrine therapy for breast cancer: within 2 weeks prior to study drug administration.

2) Participants with severe hypersensitivity to castor oil (this criteria is applicable to Part 2 of the study), and participants who had hypersensitivity reaction caused by previous anti-microtubule drugs.

3) Patients with uncontrollable brain metastases (brain metastatic lesion confirmed by examination within 2 months after radiotherapy or other localized treatment); patients with uncontrollable bone metastases (patients who have had fracture or have the risk of fracture in recent days, patients who need surgery or localized radiotherapy in recent days, patients with other critical conditions)

4) Patients with serious comorbidities, such as severe heart disease, cerebrovascular disease, uncontrolled diabetes, uncontrolled hypertension, severe infections, active peptic ulcers, etc.

5) Patients with mental illnesses which are hard to control, patients who lack legal capacity or have limited legal capacity.

6) Patients with gastrointestinal diseases such as esophageal obstruction, pyloric obstruction, intestinal obstruction, or who are post-operative of gastrointestinal resection, or who have

difficulty in swallowing due to other factors, interfering with oral administration and absorption of the drug.

7) Patients with active hepatitis B infections.

8) Patients with peripheral neuropathy grade>1 within 4 weeks prior to enrollment (NCI CTCAE 5.0).

9) Patients who still experience ≥ Grade 2 acute toxicities caused by previous anti-tumor therapies (e.g. chemotherapy, radiotherapy, immunotherapy, biological therapy or TCM treatment) prior to enrollment (NCI-CTCAE 5.0, except alopecia).

10) Patients who have undergone any major surgery or have major trauma within 4 weeks prior to administration of the investigational product or are expected to undergo major surgery during the treatment.

11) Patients who have participated in another clinical study or have received other investigational treatments within 4 weeks prior to administration of the investigational product.

12) Patients who, in the opinion of the investigator, are not suitable to participate in this study.

13) Part 3: other malignant tumors within 5 years before enrollment, excluding cured cervical carcinoma in situ, skin basal cell carcinoma or skin squamous cell carcinoma, thyroid papillary carcinoma;

14) Part 3: previous or current capecitabine therapy (except if capecitabine was used in neoadjuvant/adjuvant therapy and progression occurred > 12 months after completion of treatment, inclusion was allowed);

15) Part 3: patients with previous fluorouracil medication history with severe allergy or known dihydropyrimidine dehydrogenase (DPD) deficiency;

16) Part 3: previous or current use of utidelone (including utidelone injection and utidelone capsule);

17) Part 3: pregnant or lactating patients;

18) Part 3: uncontrolled pleural effusion, pericardial effusion or ascites (drainage once a month or more);

19) Part 3: a history of immunodeficiency, including positive HIV antibody test, other acquired or congenital immunodeficiency diseases, or a history of organ transplantation.

6. Study Interventions

6.1 Investigational Product Information

Three investigational products are used in this Study: utidelone capsules, utidelone injection and capecitabine tablets. All products have been tested and comply with the quality standards for clinical Study drugs. For detailed information, see Table 1 Investigational Product Information.

Table 1 Information of Investigational Products

Product Name	Utidelone Capsule	Utidelone Injection	Capecitabine Tablet
Active Ingredient	Utidelone	Utidelone	Capecitabine
Trade Name	Not applicable	Utidelone	Xeloda
Specification	10 mg /capsule and 15 mg /capsule	5 mL: 50 mg/vial	0.5 g
Packaging Specification	20 capsules/box	1 vial/box	12 tablets/box
Manufacturer	Chengdu Huahao Zhongtian Pharmaceutical Co., Ltd.	Chengdu Huahao Zhongtian Pharmaceutical Co., Ltd.	Shanghai Roche Pharmaceuticals Ltd.
Shelf Life	3 years (tentative)	2 years	3 years
Storage Condition	Sealed at room temperature	Protected from light, sealed, stored at 2–8°C	Sealed at 25°C, acceptable between 15–30°C

Note: For details on content, batch number and production date, please refer to the drug inspection report.

6.2 Packaging and Labelling of Investigational Products

Utidelone capsules (investigational drug) and utidelone injection (Utidi, comparator drug) are randomly sampled by the Sponsor from commercial-scale production lines operated in compliance with Good Manufacturing Practice (GMP), and all batches have passed quality inspection.

Both utidelone injection and utidelone capsules are packaged specifically for clinical Studys and labelled in accordance with Good Clinical Practice (GCP) requirements. The outer package labels include drug number, clinical Study protocol number, name of investigational product, indications, dosage and administration, package specification, batch number, manufacturing date/expiry date, storage conditions, manufacturer and supplier. The statement "For Clinical Research Use Only" is clearly marked on all labels.

6.3 Supply, Receipt, Dispensing, Storage and Destruction of Investigational Products

The Sponsor shall supply each study site with sufficient qualified investigational products together with official drug inspection reports to meet Study demands. All investigational products shall be stored and transported under specified storage conditions.

The Sponsor is responsible for the delivery and handover of investigational products. All products are uniformly coded by the Sponsor and delivered to each study site together with the corresponding drug codes. Transportation shall be undertaken by qualified institutions, with continuous temperature monitoring and complete records throughout the transit process.

Upon receipt of investigational products, the study site shall verify relevant information immediately. The products can only be signed for acceptance after compliance confirmation, and relevant handover documents shall be completed. The study site shall properly store all investigational products (including retained samples), and shall not transfer any investigational products to non-Study participants or third parties. Each participant shall be assigned one unique drug number only. Timely records shall be kept for drug administration, collection of used packaging, and recovery of residual or unused investigational products. Upon Study completion, the study site shall return all residual investigational products and used packaging to the Sponsor for final disposal.

Investigational products shall be stored in a dedicated locked cabinet and managed by designated personnel at each study site. The site drug manager is responsible for drug dispensing. On the dosing day of each cycle, the investigator issues prescriptions based on each participant’s enrollment/randomization information and prescribed dose. In accordance with the dose rounding criteria in Table 3 and the dosage allocation scheme for utidelone capsules in Table 4, the drug manager dispenses the investigational products to study staff. Study staff shall deliver the drugs to participants and supervise drug administration.

6.4 Concomitant Therapy and Concomitant Medications

In this Study, prescription drugs are defined as medications that can only be prescribed by authorized and qualified physicians. The investigator shall fully document all non-investigational products (including concomitant prescription drugs, over-the-counter drugs and dietary supplements) and non-drug therapies (such as physical therapy, tuina, massage and acupuncture) used by participants after randomization and throughout the Study period.

6.4.1 Permitted Medications During the Study

For the management of concomitant diseases, existing therapies may be continued or appropriate new treatments may be administered. Investigators shall evaluate the potential impacts of such medications on the efficacy and safety assessment of the investigational product. If permitted for

use, the regimen (medications, dosage and administration) shall remain unchanged throughout the study. Participants must inform the investigator if any new non-investigational drug is initiated or the dose of any concomitant medication is adjusted during the Study.

All concomitant medications used to manage adverse events or acute illnesses during the Study shall be documented in detail.

Medications permitted for concomitant use as needed during the study are specified as follows:

a) Close monitoring and active symptomatic treatment shall be implemented upon the occurrence of adverse reactions. All concurrent medications shall be recorded and explained in the Case Report Form (CRF).

b) Antiemetics may be administered for chemotherapy-induced vomiting.

c) Neurotrophic agents such as cobamamide and B vitamins may be used for neurotoxicity.

d) Effective analgesic therapy or analgesics shall be given when pain impairs the participant's quality of life.

e) Symptomatic medications may be prescribed for constipation, diarrhea and other related symptoms.

f) In the event of severe myelosuppression (Grade 3 or 4 toxicity) induced by the investigational product, leukocyte-stimulating agents such as granulocyte colony-stimulating factor (G-CSF) may be administered.

g) Bisphosphonates are allowed for participants with bone metastases.

6.4.2 Medications to Be Used with Caution During the Study

Utidelone is mainly metabolized via hepatic cytochrome P450 enzymes. Therefore, medications metabolized by cytochrome P450 enzymes shall be used with caution on a case-by-case basis.

In Part 3, dose reduction of anticoagulants including phenytoin and coumarin derivatives may be required when co-administered with capecitabine. Refer to the prescribing information of capecitabine for details.

6.4.3 Prohibited Medications During the Study

The following medications are prohibited throughout the treatment period:

a) Strong CYP3A4 inhibitors are prohibited to avoid potential variability in drug metabolism. Strong CYP3A4 inhibitors refer to agents that increase the area under the curve (AUC) of sensitive substrates for specific metabolic pathways by ≥5-fold, including cobicistat, clarithromycin, darunavir, ritonavir, ceritinib, grapefruit juice and grapefruit-containing products.

b) Moderate CYP3A4 inhibitors such as aprepitant, ciprofloxacin and verapamil are prohibited to avoid potential variability in drug metabolism.

c) Strong and moderate CYP3A4 inducers such as enzalutamide, apalutamide, St. John's wort and telotristat are prohibited to avoid potential variability in drug metabolism.

d) Antacids (including acid suppressants, proton pump inhibitors and H2 receptor antagonists) are prohibited during treatment with utidelone capsules, so as to prevent potential impacts of altered gastric acid on drug metabolism of the oral formulation.

e) Other anti-tumor agents are prohibited.

f) Prophylactic adjuvant medications related to anti-tumor therapy are prohibited.

No non-investigational products are allowed during the Study, except for those specified above or those used for managing adverse events and acute illnesses. If a participant requires non-investigational products during the Study (including the washout period), the investigator will decide whether the participant may continue participation, based on the potential impacts of such medications on the tolerability, efficacy and pharmacokinetic profiles of utidelone capsules. The assessment shall take the following factors into consideration:

1. Potential drug-drug interactions between the non-investigational product and the study drug;

2. Pharmacological effects and elimination half-life of the non-investigational product.

6.4.4 Post-Study Treatment

All participants will receive treatment in accordance with current standard medical practice in China after completion or premature discontinuation of the Study.

6.5 Dose Adjustment

No dose adjustment is permitted during Cycle 1 of Part 1, as well as Cycle 0, Cycle 1 and Cycle 2 of Part 2. During the subsequent treatment phase and Part 3, dosing may be interrupted based

on the participant's condition. Treatment may be resumed or continued at a reduced dose after toxicities resolve to Grade ≤ 1 or return to baseline.

6.5.1 Interruption and Dose Adjustment Regimen for Utidelone Capsules

In the event of adverse events during the study, investigators shall provide prompt symptomatic management and fully document all concomitant treatments and medications in medical records and the Case Report Form (CRF). If dosing is delayed, subsequent visits and administrations shall be rescheduled accordingly. The duration of subsequent cycles and visit intervals will be recalculated as 21±3 days starting from the resumption of dosing.

Investigators shall implement dosing interruption or dose reduction in accordance with the criteria below based on the participant's condition and adverse events. Prior to resuming treatment or administering a reduced dose of utidelone capsules, all treatment-related adverse events must resolve to Grade ≤ 1 or baseline. For Grade 3 alopecia, fatigue and other adverse events judged by investigators to pose no safety risks, resolution to Grade ≤ 2 is acceptable. No dose reduction is required for the first occurrence of such events.

Treatment with utidelone capsules may be delayed for a maximum of 4 weeks. If adverse events fail to resolve to the resumption criteria within 4 weeks, study treatment shall be permanently discontinued.

If adverse events resolve, the investigator may evaluate and approve continued treatment with the participant's consent for clinical benefit.

- Participants who cannot tolerate combination therapy due to severe hand-foot syndrome may switch to single-agent utidelone capsules.
- Participants who cannot tolerate combination therapy due to severe peripheral neuropathy may switch to single-agent capecitabine.

The dose adjustment criteria for utidelone capsules are presented in Table 10 below.

Table 10 Dose Adjustment Regimen for Utidelone Capsules

Adverse Event (NCI CTCAE Version 5.0)	**Dose Adjustment for Utidelone Capsules**
Major non-hematologic toxicities: Peripheral neuropathy, diarrhea Grade 2 Grade 3 diarrhea/vomiting resolving to Grade 2 or lower within ≤7 days after supportive care	1st occurrence: Interrupt dosing; resume at the original dose upon recovery. 2nd occurrence: Interrupt dosing; resume at **75% of the starting dose (one dose level reduction)** upon recovery. 3rd occurrence: Interrupt dosing; resume at **50% of the starting dose (two dose levels reduction)** upon recovery. 4th occurrence: Permanently discontinue the drug.

Adverse Event (NCI CTCAE Version 5.0)	**Dose Adjustment for Utidelone Capsules**
Grade 3	1st occurrence: Interrupt dosing; resume at **75% of the starting dose (one dose level reduction)** upon recovery. 2nd occurrence: Interrupt dosing; resume at **50% of the starting dose (two dose levels reduction)** upon recovery. 3rd occurrence: Permanently discontinue the drug.
Grade 4	Permanently discontinue the drug.
Other non-hematologic toxicities Grade 2	Interrupt dosing; resume at the original dose upon recovery.
Grade 3	1st occurrence: Interrupt dosing; resume at **75% of the starting dose (one dose level reduction)** upon recovery. 2nd occurrence: Interrupt dosing; resume at **50% of the starting dose (two dose levels reduction)** upon recovery. 3rd occurrence: Permanently discontinue the drug.
Grade 4	1st occurrence: Interrupt dosing; resume at **50% of the starting dose (two dose levels reduction)** upon recovery. 2nd occurrence: Permanently discontinue the drug.
Major hematologic toxicities Grade 3 thrombocytopenia with bleeding or requiring platelet transfusion	Interrupt dosing until platelet count ≥ 90×10^9/L. Recovery within ≤7 days: Resume at the original dose. Recovery over 7 days: Resume at **75% of the starting dose (one dose level reduction)**.
Grade 4 thrombocytopenia	Interrupt dosing until platelet count ≥ 90×10^9/L; resume at **75% of the starting dose (one dose level reduction)** upon recovery.
Grade 3 neutropenia	Interrupt dosing until neutrophil count ≥ 1.5×10^9/L. Recovery within ≤7 days: Resume at the original dose. Recovery over 7 days: Resume at **75% of the starting dose (one dose level reduction)**.
Grade 4 neutropenia or febrile neutropenia	Interrupt dosing until neutrophil count ≥ 1.5×10^9/L; resume at **75% of the starting dose (one dose level reduction)** upon recovery.
Other hematologic toxicities Grade 2	Interrupt dosing; resume at the original dose upon recovery.
Grade 3	1st occurrence: Interrupt dosing; resume at **75% of the starting dose (one dose level reduction)** upon recovery. 2nd occurrence: Interrupt dosing; resume at **50% of the starting dose (two dose levels reduction)** upon recovery. 3rd occurrence: Permanently discontinue the drug.
Grade 4	1st occurrence: Interrupt dosing; resume at **50% of the starting dose (two dose levels reduction)** upon recovery. 2nd occurrence: Permanently discontinue the drug.

Notes:

1. Following each dose interruption, all treatment-related adverse events must resolve to Grade ≤ 1 or return to baseline. For Grade 3 alopecia, fatigue and other adverse events deemed by the investigator to pose no safety risks, resolution to Grade ≤ 2 is acceptable.

2. If adverse events resolve, the investigator may evaluate and approve continued treatment with the participant's consent for the participant's clinical benefit.

6.5.2 Interruption and Dose Adjustment Regimen for Capecitabine

No dose adjustment is recommended for Grade 1 adverse events associated with capecitabine. Treatment with capecitabine shall be interrupted for Grade 2 or Grade 3 adverse events, unless the investigator determines that there is no potential safety risk. Once the adverse event resolves or improves to Grade 1, treatment may be resumed at the original dose or a reduced dose as specified in the table.

For Grade 4 adverse events, treatment shall be discontinued or interrupted. After the adverse event resolves or improves to Grade 1, treatment may be restarted at 50% of the original dose. The rules for dose interruption and reduction of capecitabine shall comply with its prescribing information. Once the dose of capecitabine is reduced, no subsequent dose escalation is allowed. Missed doses of capecitabine shall not be supplemented.

The dose adjustment criteria for capecitabine are presented in Table 11 below.

Table 11 Dose Adjustment Regimen for Capecitabine

NCIC Toxicity Grade*	**Management During Treatment**	**Dose for Next Cycle (% of Starting Dose)**
Grade 1	Continue the original dose	100%
Grade 2		
1st occurrence	Interrupt dosing until toxicity resolves to Grade 0–1	100%
2nd occurrence	Interrupt dosing until toxicity resolves to Grade 0–1	75%
3rd occurrence	Interrupt dosing until toxicity resolves to Grade 0–1	50%
4th occurrence	Permanently discontinue treatment	NA
Grade 3		
1st occurrence	Interrupt dosing until toxicity resolves to Grade 0–1	75%
2nd occurrence	Interrupt dosing until toxicity resolves to Grade 0–1	50%

NCIC Toxicity Grade*	Management During Treatment	Dose for Next Cycle (% of Starting Dose)
3rd occurrence	Permanently discontinue treatment	NA
Grade 4		
1st occurrence	Permanently discontinue treatment; OR If the physician deems continued treatment to be in the patient's best interest, interrupt dosing and resume after toxicity resolves to Grade 0–1	50%
2nd occurrence	Permanently discontinue treatment	NA

* Except for hand-foot syndrome and hyperbilirubinemia, toxicity is graded according to the Common Toxicity Criteria established by the National Cancer Institute of Canada Clinical Studys Group (NCIC CTG).

7. Discontinuation/Withdrawal Criteria and Management Principles

7.1 Discontinuation Criteria

Discontinuation refers to the termination of investigational product administration by the investigator when a participant develops conditions that preclude continued study drug intake during the Study.

- The participant experiences a Serious Adverse Event (SAE) and is no longer suitable for continued treatment with the investigational product.
- The investigator determines that stopping the investigational product is in the participant's best interest from a medical ethics perspective.
- Poor participant compliance:

a) The participant fails to use the investigational product or undergo examinations in accordance with the protocol.

b) The participant takes other medications or consumes food that may affect the assessment of safety, efficacy and pharmacokinetic outcomes.

c) The participant engages in other behaviors that may interfere with Study results.

Discontinuation of investigational product administration does not equal Study withdrawal. The participant shall complete all subsequent Study procedures as specified in the protocol,

including safety assessments, efficacy evaluations, pharmacokinetic assessments, adverse event follow-up and post-drug discontinuation follow-up.

If clinically significant changes (including but not limited to deviations from baseline) are observed from drug discontinuation until the end of follow-up, the investigator shall decide whether to adjust the participant's management. Any newly identified clinically relevant findings during this period shall be reported as Adverse Events (AEs).

7.2 Management

Both discontinuation and withdrawal are defined as study drop-outs. The following data (but not limited thereto) shall be collected to the fullest extent possible when a participant discontinues or withdraws from the Study:

- Date and reason for discontinuation/withdrawal.
- End-of-study assessments: vital signs, physical examination, electrocardiography, laboratory tests, efficacy evaluation and pharmacokinetic assessment, as well as adverse event follow-up.
- Follow-up assessment: adverse events that have not resolved to Grade 1 within 28 days after study exit.

Common reasons for participant discontinuation/withdrawal:

- The participant fails to meet inclusion criteria or meets exclusion criteria (newly identified or previously undetected), making continued investigational product administration inappropriate.
- Errors occur in the dosage or administration method of the investigational product, or the participant shows poor compliance.
- Adverse events occur, and continued treatment is no longer in the participant's best interest.
- Disease progression necessitates discontinuation of the investigational product.
- Voluntary withdrawal by the participant (for reasons other than those listed above).
- Loss to follow-up.
- Other conditions preventing further participation in the Study.

8. Study Procedures and Endpoints

8.1 Study Parts

This study consists of three parts. Part 1 is a dose-escalation Study to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of utidelone capsules. Part 2 is a pharmacokinetic comparison and food effect Study, aiming to evaluate the absolute bioavailability of utidelone capsules relative to utidelone injection, as well as the impact of food on the pharmacokinetic parameters of utidelone capsules. Part 3 is an expansion Study of utidelone capsules combined with capecitabine, to assess the efficacy and safety of this combination regimen in patients with advanced metastatic breast cancer.

Part 1: Dose-escalation Study

This Study includes three phases: screening period, Cycle 1 and subsequent treatment phase.

Cohorts with 5 consecutive days of dosing per cycle

After screening, eligible participants will be assigned Study numbers on Study Day -1, receive the investigational product and start the 21-day dosing and observation period. Cycle 1 commences on Study Day 1, with dosing administered from Day 1 to Day 5. Biological samples are collected from Day 1 to Day 8, and DLT is monitored throughout Day 1 to Day 21. The subsequent treatment phase starts on Study Day 22.

If no DLT is observed in Cohort 1, dose escalation will proceed directly to the next cohort. If one participant develops DLT, the conventional 3+3 design will be adopted for subsequent dose escalation starting from this cohort. All other cohorts follow the 3+3 design, with a maximum of 2 participants under DLT observation concurrently. If DLT occurs in 1 out of the initial 3 participants, an additional 3 participants shall be enrolled in the same cohort.

Cohorts with 7 consecutive days of dosing per cycle

After screening, eligible participants will be assigned Study numbers on Study Day -1, receive the investigational product and enter the 21-day dosing and observation period. Cycle 1 starts on Study Day 1, with dosing given from Day 1 to Day 7. Biological samples are collected from Day 1 to Day 10. The subsequent treatment phase begins on Study Day 22.

Part 2: Pharmacokinetic Comparison and Food Effect Study

This part will be initiated after sufficient data are available to estimate the capsule dose yielding exposure equivalent to 30 mg/m²/day of utidelone injection, and the safety and tolerability of this

dose are confirmed by preliminary results. It comprises five phases: screening period, Cycle 0, Cycle 1, Cycle 2 and subsequent treatment phase.

Upon completion of screening, eligible participants will be randomized and assigned random numbers on Study Day -1 before entering Cycle 0. Dosing is performed on Study Day 1, and biological samples are collected from Day 1 to Day 2, followed by a 7-day washout period.

Cycle 1 starts on Study Day 8. Dosing is administered from Day 8 to Day 12, and biological samples are collected from Day 8 to Day 13.

Cycle 2 commences on Study Day 29. Dosing is given from Day 29 to Day 33, and biological samples are collected from Day 29 to Day 34. The subsequent treatment phase starts on Study Day 50.

Part 3: Expansion Study of Utidelone Capsules Combined with Capecitabine

This expansion Study is divided into three phases: screening period, treatment period and follow-up period.

After screening, eligible participants will be assigned Study numbers, complete pre-dosing visits and receive treatment on Study Day 1 to enter the treatment period. Treatment will continue until disease progression or intolerable toxicity occurs.

For participants withdrawn from the Study due to reasons other than progressive disease (PD) or death, efficacy follow-up shall be continued. Starting from the last tumor imaging assessment during the study, tumor imaging examinations will be performed every 2 cycles (6 weeks) as specified in the protocol. After Cycle 7, assessments will be conducted every 3 cycles (9 weeks), until the participant develops PD, initiates other anti-tumor therapies or dies (whichever comes first).

All surviving participants who complete safety follow-up and efficacy follow-up (the later one prevails) shall receive survival follow-up.

For detailed Study procedures, see Figure 1 Study Flowchart.

8.2 Study Flow

8.2.1 Screening Period (Study Day -28 to Day -1)

Screening assessments are performed from Study Day -28 to Day -1. Only participants who meet all inclusion criteria and do not have any exclusion criteria are eligible for enrollment.

Study Day -28 to Day -2

Participants with basic profiles complying with Study requirements will be recruited for screening. All participants must sign a written informed consent form voluntarily prior to screening. Assessments to be completed in this period include:

Demographic information, personal medical history, disease-related information, height, weight, ECOG performance status, vital signs, physical examination, 12-lead electrocardiogram (ECG), blood biochemistry, complete blood count (CBC), urinalysis, urine pregnancy test (for females of childbearing potential only), stool routine and occult blood test, infectious disease screening, and imaging examinations. Infectious disease test results obtained within the past 3 months are acceptable for screening.

Study Day -1

Eligible participants shall arrive at the study site on Study Day -1 (one day prior to the first dose). Investigators will conduct re-assessments as needed, including body weight measurement, ECOG score, vital signs, physical examination, blood biochemistry, CBC, urinalysis, stool routine and occult blood test, and 12-lead ECG.

Investigators will re-verify the inclusion and exclusion criteria, and assign randomization numbers or enrollment numbers to qualified participants. Participants will be admitted to the study site and receive health education regarding Study regulations and management requirements. Restrictions during on-site stay include: unauthorised ward access is prohibited; outside food is not allowed; smoking, alcohol consumption, physical exercise and strenuous activities are forbidden. Meanwhile, adverse events, concomitant medications and non-drug therapies will be monitored and documented.

8.2.2 Observation Period

Dosing and treatment will be administered, along with vital signs monitoring, laboratory tests and imaging examinations, in accordance with the Study flow chart and schedule.

8.2.3 Subsequent Treatment Phase

Required assessments and procedures in this phase are listed below:

- Body weight measurement: performed on Day 1 of each treatment cycle
- ECOG performance status: assessed on Day 1 of each treatment cycle
- Vital signs and physical examination: performed on Day 1 of each treatment cycle

- Drug dispensing: Once daily dosing for 5 consecutive days per 21-day cycle; for cohorts with 7-day dosing schedule, once daily dosing for 7 consecutive days per 21-day cycle
- Laboratory tests (blood biochemistry, CBC, urinalysis): performed on Day 1 of each treatment cycle
- Imaging examinations:

At minimum, CT or MRI scans of relevant lesion sites are required, with an allowable time window of ±7 days.

Within the first 6 cycles (including Cycle 1 and Cycle 2), imaging assessments are conducted at the end of every 2 cycles. From Cycle 7 to Cycle 18, assessments are performed at the end of every 3 cycles. After Cycle 18, assessments are carried out at the end of every 4 cycles.

- Monitoring and documentation of adverse events, concomitant medications and non-drug therapies.

8.2.4 Follow-up Period

Prior to discharge from the study site, investigators will provide health education and instruct participants to contact medical staff promptly if any discomfort occurs during follow-up.

Safety follow-up will cover all adverse events occurring within 28 days after the last dose. Any ongoing adverse events at the time of safety follow-up shall be followed up until resolution, stabilization, improvement to Grade ≤1, or reasonable explanation (including loss to follow-up, death, initiation of new anti-tumor therapy, or confirmation of irrelevance to the study drug or Study procedures). Clinical data collection will be terminated upon the first occurrence of the above situations.

All adverse events, concomitant medications/therapies and unscheduled examinations during this period shall be documented in detail.

8.2.5 Unscheduled Visits

If additional follow-up is required or a participant withdraws from the Study ahead of schedule, investigators shall record all interventions and corresponding results, including laboratory test findings.

8.3 Clinical Examinations

All clinical assessments will be performed at the time points specified in the Study flow chart. All tests listed

in Table 12 are sampled and analyzed by the local study site. Unscheduled clinical examinations may be conducted at any time for participant safety.

Table 12 List of Clinical Examinations

Category	Items
Demographic Information	Date of birth, Gender, Height, Weight, Body Mass Index (BMI), Occupation, Ethnicity, Marital status
Personal History	History of alcohol abuse, Drug abuse history, Smoking history, Allergic history
Medical History	Past medical history; Current illnesses and related treatments (including cardiovascular and cerebrovascular diseases, hematologic and lymphatic diseases, urinary system diseases, digestive system diseases, neurological diseases, respiratory diseases, immune system disorders, mental disorders, metabolic and skeletal disorders)
Infectious Disease Screening	Hepatitis B serology; HIV antibody test (required for Part 3); Screening for Hepatitis C, HIV and syphilis
Urine Pregnancy Test	Urinary beta-human chorionic gonadotropin (β-HCG) (for females of childbearing potential only)
Vital Signs	Body temperature, Respiratory rate, Pulse, Sitting blood pressure
Physical Examination	General condition, Skin and mucous membranes, Lymph nodes, Head and neck, Chest, Abdomen, Spine and extremities, Other body parts
Complete Blood Count (CBC)	White blood cell count, Neutrophil count, Lymphocyte count, Red blood cell count, Hemoglobin, Platelet count
Urinalysis	Urinary red blood cells, Urinary white blood cells, Urine glucose, Urine protein
Blood Biochemistry	Alanine transaminase (ALT), Aspartate transaminase (AST), Gamma-glutamyl transferase (GGT), Alkaline phosphatase (ALP), Total bilirubin, Direct bilirubin, Indirect bilirubin, Total protein, Albumin, Creatine kinase, Creatinine, Uric acid, Blood glucose, Urea, Serum potassium, Sodium, Chloride, Calcium
Stool Routine & Occult Blood	Fecal red blood cells, Fecal white blood cells, Fecal occult blood
12-lead ECG	Rhythm, Heart rate, PR interval, QRS interval, QT interval, QTcB interval, QTcF interval

8.4 Safety Assessment

Adverse Event (AE)

- Endpoint: Any adverse events occurring during the Study, including clinical symptoms, abnormal vital signs and abnormal laboratory findings.

- Assessment Timing: Participants shall be observed and questioned about participantive discomfort throughout the Study. Potential adverse reactions and adverse events shall be closely monitored. All identified AEs shall be followed up until final outcome is confirmed.

8.5 Pharmacokinetic (PK) Blood Sample Collection

8.5.1 Rationale for PK Blood Sampling Time Points

In accordance with the Technical Guidelines for Clinical Pharmacokinetic Studies of Chemical Drugs [5], a complete plasma concentration-time curve shall cover sampling points across all phases post-dose, including the absorption phase, vicinity of peak concentration and elimination phase.

Generally, a minimum of 2 to 3 sampling points are required for the absorption phase, at least 3 points around the peak concentration, and 3 to 5 points for the elimination phase. The total number of sampling points shall be no less than 11 to 12. Sampling shall last for 3 to 5 elimination half-lives, or continue until the plasma drug concentration declines to 1/10 ~ 1/20 of the maximum plasma concentration (Cmax).

This is the first-in-human Study of utidelone capsules, and no relevant human pharmacokinetic data are available. Therefore, the sampling schedule is designed based on non-clinical study data and pharmacokinetic results of utidelone injection.

Blood Sampling Time Points

The scheduled sampling time points are specified below. Adjustments to sampling time points will be made in a timely manner based on accumulated human pharmacokinetic data during the Study. Biological samples shall be collected within the permitted time windows, and any deviation from the specified time ranges must be documented.

Sampling time points for the dose-escalation Study are shown in Table 7, and those for the pharmacokinetic comparison and food effect Study are presented in Table 8. Intensive sampling will be performed in 12 participants enrolled in the expansion Study of utidelone capsules combined with capecitabine, with corresponding time points listed in Table 9.

Sparse sampling will be conducted in the remaining participants as follows:

- Cycle 1 Day 1: 4 h ± 60 min after administration of utidelone capsules
- Cycle 2 Day 1: 4 h ± 60 min after administration of utidelone capsules
- Cycle 3 Day 1: 4 h ± 60 min after administration of utidelone capsules

One tube of blood (3 mL per tube) will be collected at each time point. Capecitabine will not be assayed for sparse sampling samples.

8.5.2 Collection of Pharmacokinetic (PK) Blood Samples

Venous blood shall be collected from the upper limbs of participants, with approximately 3 mL obtained at each time point. Appropriate venipuncture techniques shall be adopted to minimize discomfort to participants. Blood samples shall be collected strictly per the scheduled time points specified in this section. Prior to each sampling, discard the normal saline used for locking the indwelling catheter. PK blood samples shall not be drawn from the arm receiving intravenous infusion of utidelone injection.

After centrifugation, separate the supernatant plasma and aliquot it into two cryotubes (one for analysis and one for backup). Store the samples in a refrigerator prior to transportation. Any abnormalities occurring during sample processing, such as hemolysis and spillage, shall be documented.

8.5.3 Pharmacokinetic (PK) Endpoints

Plasma concentration data will be used to calculate key pharmacokinetic parameters to fully characterize the absorption, distribution, metabolism and excretion profiles of the study drug in humans. The parameters include absolute bioavailability (F), maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), area under the plasma concentration-time curve from time zero to the last measurable concentration (AUC0−t), area under the plasma concentration-time curve extrapolated to infinity (AUCinf), terminal elimination rate constant (λz), terminal elimination half-life (t1/2), clearance (CL) and volume of distribution (Vd).

Steady-state parameters include steady-state maximum plasma concentration (Cmax,ss), steady-state area under the curve from time zero to the last measurable concentration (AUC0−t,ss), steady-state area under the curve extrapolated to infinity (AUCinf,ss), steady-state area under the curve over one dosing interval (AUC0−τ,ss), percentage of AUC extrapolation (AUC%Extrap), terminal elimination rate constant (λz), terminal elimination half-life (T1/2z), apparent steady-state clearance (CLss/F), apparent volume of distribution at steady

state (Vz/F), steady-state minimum plasma concentration (Cmin,ss) and steady-state average plasma concentration (Cav,ss).

8.6 Collection of Urine and Fecal Biological Samples

8.6.1 Rationale for Sampling Time Points of Urine and Fecal Samples

The sampling schedule for utidelone capsules in this Study is formulated based on non-clinical research data and relevant data of utidelone injection.

Part 1 Dose-escalation Study

No urine or fecal samples will be collected.

Part 2 Pharmacokinetic Comparison and Food Effect Study

- Urine samples: All urine will be collected during 9 time intervals in Cycle 0: -2–0 h prior to the first dose, and 0–4 h, 4–8 h, 8–12 h, 12–24 h, 24–48 h, 48–72 h, 72–96 h, 96–120 h after dosing initiation.
- Fecal samples: Feces will be collected whenever defecation occurs within 120 hours after dosing initiation in Cycle 0. The weight and defecation time shall be recorded for each sample.

8.6.2 Collection of Urine and Fecal Samples

Urine Samples

Participants shall empty their bladders before dosing. Urine samples shall be collected according to the scheduled time points specified herein, and the bladder shall be emptied at the start of each collection interval.

After collection and thorough mixing of urine from each interval, record the total urine volume. Aliquot no more than approximately 20 mL of urine into two cryotubes (one for analysis and one for backup), and store the tubes in a refrigerator pending transportation. Any abnormalities during sample handling, such as anuria and sample spillage, shall be documented.

Fecal Samples

Participants shall defecate completely before dosing. Fecal samples shall be collected in accordance with the specified time points. For each defecation event, record the total fecal weight

and collection time, then freeze the samples immediately and store them in a refrigerator before transportation. Any abnormalities during handling, such as no defecation and sample loss, shall be documented.

For detailed procedures for biological sample collection and processing, refer to the Biological Sample Collection Manual.

8.6.3 Evaluation Indices for Urine and Fecal Samples

· Amount of drug excreted in urine: Calculated as the product of drug concentration in urine and total urine volume for each time interval.

· Cumulative urinary excretion rate: Ratio of cumulative urinary drug excretion to the administered dose.

· Amount of drug excreted in feces: Calculated as the product of drug concentration in feces and total fecal weight for each time interval.

· Cumulative fecal excretion rate: Ratio of cumulative fecal drug excretion to the administered dose.

8.7 Efficacy Assessment

Objective Response Rate (ORR)

Assessed per RECIST 1.1 criteria. It is defined as the proportion of participants achieving best overall response of Complete Response (CR) plus Partial Response (PR) among all enrolled participants. Participants must have measurable tumor lesions at baseline. Tumor responses are categorized as Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD) in accordance with RECIST 1.1. All initial CR or PR findings must be confirmed by a repeat assessment after no less than 4 weeks.

Progression-Free Survival (PFS)

Assessed per RECIST 1.1 criteria. It refers to the time from enrollment to the first radiologically confirmed disease progression or death from any cause. For participants without PD or death by the study cut-off date, or those who receive other anti-tumor therapies, the last efficacy assessment prior to the cut-off date or the initiation of alternative anti-tumor treatment (whichever occurs earlier) will be taken as the censoring time.

Disease Control Rate (DCR)

Assessed per RECIST 1.1 criteria. It is defined as the proportion of participants achieving best overall response of CR plus PR plus SD among all enrolled participants.

Duration of Response (DoR)

Assessed per RECIST 1.1 criteria. It is calculated from the first documentation of CR or PR (whichever occurs earlier) until the observation of PD or death. Duration of response is only calculated for participants whose best overall response is CR or PR.

9. Safety Monitoring

9.1 Safety Monitoring

9.1.1 Definition of Adverse Events

An Adverse Event (AE) refers to any untoward medical occurrence following administration of the investigational product to a participant, which may present as signs, symptoms, illnesses or abnormal laboratory findings, regardless of causal relationship with the investigational product. Accordingly, an AE is any unfavorable and/or unintended sign, symptom or disease temporally associated with the use of the investigational product, whether or not considered related to the study drug.

The following occurrences are excluded from AE classification: pre-existing illnesses, symptoms, signs or laboratory abnormalities identified prior to or at screening without subsequent worsening; events definitively attributable to underlying disease progression; events clearly resulting from lack of therapeutic efficacy.

9.1.2 Documentation of Adverse Events

All adverse events occurring from initiation of study treatment through 28 days after the last study drug administration shall be collected and documented in this study. During the study, the following information shall be truthfully recorded for each adverse event: event name, onset date/time, severity, duration, causal relationship to the investigational product (assessed exclusively by trained, qualified investigative physicians), interventions implemented and clinical outcome. All adverse events emerging during the study must be documented irrespective of relatedness to the investigational product. Every adverse event shall be followed up until satisfactory resolution whenever feasible.

Medical conditions present at screening serve as baseline findings and are not reported as adverse

events unless such conditions deteriorate, in which case the deterioration shall be recorded as an adverse event. Changes in adverse event severity shall be documented to allow calculation of duration at each toxicity grade. For intermittent adverse events, each episode's onset and duration shall be recorded separately.

9.1.3 Onset Date and Time

The onset date of an adverse event is defined as the date when the first sign or symptom is initially observed. For clinically significant abnormal laboratory or instrumental findings, onset corresponds to the specimen collection or examination date. When an adverse event progresses to a serious adverse event (SAE), the date when the event is upgraded to SAE status is documented as the SAE onset date.

9.1.4 Severity Grading Criteria for Adverse Events

Adverse event severity shall be graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 5.0). Adverse events not specified in NCI-CTCAE v5.0 shall be graded in accordance with Table 13.

Table 13 Severity Classification Criteria for Adverse Events

Grade	Severity Description
Grade I	Mild; asymptomatic or mild clinical manifestations; clinical or laboratory abnormalities only; no therapeutic intervention required.
Grade II	Moderate; minimal, local or non-invasive treatment indicated; limitation in age-appropriate instrumental activities of daily living (IADL). IADL includes meal preparation, grocery shopping, telephone communication, etc.
Grade III	Severe or medically significant but not immediately life-threatening; hospitalization or prolonged hospitalization required; permanent disability; limitation in self-care activities of daily living (ADL). ADL refers to bathing, dressing/undressing, feeding, toileting and medication administration, excluding bedridden status.
Grade IV	Life-threatening; urgent medical intervention mandatory.
Grade V	Death attributable to the adverse event.

9.1.5 Causality Assessment Criteria between AEs and Investigational Product

Based on the causality assessment criteria, the correlation between an adverse event and the investigational product is classified into five categories: Definitely Related, Probably Related, Possibly Unrelated, Definitely Unrelated, and Unassessable.

9.1.6 Management and Follow-up of Adverse Events

All adverse events shall be managed in accordance with unified guidance specified in NCI-CTCAE Version 5.0.

Regardless of causal relatedness to the investigational product, regular monitoring shall be implemented where feasible, and necessary symptomatic treatments shall be provided during follow-up to minimize participant harm and fully safeguard participant safety.

Upon study completion or early participant withdrawal, AEs must be followed up until any of the following endpoints is achieved:

- The event resolves or stabilizes;
- The event improves to Grade 1 or baseline level (if baseline data is available);
- The event can be attributed to concomitant medications or factors irrelevant to study procedures; or further relevant information is unlikely to be obtained (e.g., participants or clinicians decline further information provision, or participants are lost to follow-up despite exhaustive follow-up attempts).

9.1.7 Potentially Expected Adverse Reactions and Management during Study

Based on non-clinical data and historical clinical study findings of utidelone injection, the primary anticipated adverse reactions of the investigational product include peripheral neuropathy (PN) and musculoskeletal pain. All relevant AEs shall be managed per routine clinical practice.

Peripheral Neuropathy

Patients commonly present with paresthesia such as numbness and pain in distal extremities (sensory neuropathy) or limb muscular atrophy and weakness (motor neuropathy). Investigators shall obtain detailed history regarding the nature, distribution and progression of paresthesia, confirm whether sensory disturbance conforms to peripheral nerve innervation and whether limb pain features neuropathic characteristics, with focused physical examination on limb sensory function and tendon reflexes. Required physical assessments include:

① Sensory examination: Carefully screen for diminished vibration, pain, tactile, temperature sensation or hyperalgesia at distal extremities;

② Motor examination: Evaluate weakness and atrophy of small intrinsic muscles in hands or feet;

③ Tendon reflex examination: Reduced or absent tendon reflexes, most prominently Achilles reflex, constitute a key diagnostic sign of PN.

9.1.8 Unexpected Beneficial Events

Any investigational product overdose, underdose or secondary new-onset malignancy identified during the study shall be promptly reported to the Sponsor and Principal Investigator.

9.2 Serious Adverse Events (SAEs)

9.2.1 Definition of Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence following investigational product administration resulting in death, life-threatening condition, permanent or substantial disability/incapacity, inpatient hospitalization or prolonged hospitalization, congenital anomaly/birth defect, or other medically important events.

Disease progression clearly attributable to the underlying indication is not classified as an AE; accordingly, events related to disease progression (including progression-associated death) are excluded from AE documentation and SAE reporting. However, all unexpected deaths or deaths with indeterminate association to disease progression shall be reported as SAE.

Per appropriate medical judgment, other medically significant events that do not immediately result in death, life threat or hospitalization may still qualify as SAE if intervention (medical or surgical) is required to prevent any of the above serious outcomes. Examples include allergic bronchospasm, hematologic disorders or seizures requiring intensive outpatient/home management without formal hospitalization or substance dependence/abuse. For reporting purposes, any suspected transmission of infectious pathogens via the investigational product is also deemed a serious adverse reaction and participant to expedited SAE reporting as specified herein.

The following admissions do not qualify as SAE:

- Admission to rehabilitation facilities or nursing homes;
- Routine emergency department visits without inpatient admission;

- Same-day outpatient surgery.

Hospitalization or prolonged stay unrelated to an adverse event alone does not constitute an SAE, including but not limited to:

- Admission for pre-existing disease without new-onset AE or disease exacerbation (e.g., workup for persistent baseline laboratory abnormalities);
- Administrative admission for routine annual physical examination;
- Protocol-mandated hospitalization required per study design;
- Elective admission for pre-planned non-AE related procedures (e.g., elective cosmetic surgery);
- Pre-scheduled therapeutic or surgical interventions documented in protocol and/or participant baseline records;
- Elective admission solely to facilitate study drug administration or study procedures (e.g., overnight admission for intravenous dosing);
- Hospitalization exclusively for blood product transfusion.

Nevertheless, all unanticipated admissions or unplanned prolongation of pre-scheduled hospitalization triggered by adverse drug effects must be documented and reported as SAE.

Diagnostic or therapeutic invasive/non-invasive procedures themselves are not reported as AEs; only the underlying medical condition prompting such procedures shall be documented when it satisfies the AE definition.

9.2.2 Documentation and Reporting of SAEs

Immediately upon becoming aware of an SAE, the investigator shall notify the Sponsor without delay; fatal events shall also be reported to the Institutional Review Board (IRB)/Ethics Committee of the study site concurrently. The investigator shall subsequently submit detailed follow-up reports in a timely manner. For fatal cases, additional required documents such as autopsy reports and final medical summaries shall be provided. All SAE initial and follow-up reports must include the participant's unique identification code.

9.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)

9.3.1 Documentation of SUSARs

Individual case safety reports (ICSRs) for SUSARs shall be prepared in compliance with ICH Guideline E2B(R3): Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports. All relevant medical terms shall be coded using the ICH M1: Medical Dictionary for Regulatory Activities (MedDRA).

9.3.2 Reporting of SUSARs

Upon receipt of any safety information from any source during the study, the Sponsor shall promptly conduct an assessment covering severity, causal relationship to the investigational product and expectedness of the event. If a case is confirmed as a SUSAR, expedited reporting to the National Medical Products Administration (NMPA) shall be performed within the timelines specified below based on SUSAR category:

a) For fatal or life-threatening SUSARs: the Sponsor shall submit the expedited report as soon as possible and no later than 7 calendar days from the day of first awareness (defined as Day 0), with supplementary follow-up information submitted within the subsequent 8 calendar days.

b) For non-fatal, non-life-threatening SUSARs: the Sponsor shall submit the expedited report as soon as possible and no later than 15 calendar days after first awareness.

Following the initial SUSAR submission, ongoing follow-up shall be performed, and any new findings or revisions to prior reports shall be submitted via follow-up reports within 15 calendar days of obtaining such new information.

The Sponsor shall forward copies of all SUSAR reports to the relevant investigators and health authorities; the investigators are responsible for subsequent submission to the Ethics Committee.

10. Biological Sample Management and Analysis

Refer to the Biological Sample Management Manual.

11. Statistical Considerations

11.1 Determination of Sample Size

This is a Phase I/I clinical study of utidelone capsules consisting of repeated-dose tolerability assessment, pharmacokinetic comparison and food-effect evaluations. Approximately 72–84 participants are planned for enrollment in total. The sample size of this study complies with the requirements specified in the NMPA Technical Guidelines for Single and Multiple-Dose Escalation Pharmacokinetic Clinical Studies of Innovative Chemical Drugs (2021)[9] and

Technical Guidelines for Clinical Studys of Anticancer Drugs (2012). No statistical power calculation or formal sample size quantification was performed.

11.2 Analysis Populations

Full Analysis Set (FAS)

The FAS comprises all enrolled participants who received at least one dose of the investigational product. Analyses will be performed according to the treatment assigned at enrollment following the intention-to-treat (ITT) principle.

Per Protocol Set (PPS)

Also defined as the efficacy analysis set. The PPS includes all enrolled participants who received no less than 2 cycles of investigational product, had measurable lesions per RECIST 1.1 at baseline, possessed at least one post-dose evaluable efficacy assessment, and had no major protocol deviations that could interfere with efficacy endpoint evaluation.

Safety Set (SS)

The SS consists of all participants administered at least one dose of investigational product with available post-dose safety data. Safety analyses will be based on actual treatment received.

DLT Analysis Set (DLTS)

All enrolled participants satisfying either of the following two criteria are included in DLTS, which is used exclusively for safety evaluation of Part 1 Cycle 1:

1. Participants complete Part 1 Cycle 1 treatment and corresponding follow-up assessments with treatment compliance ≥80% of the planned dosage;
2. Participants discontinue or interrupt Part 1 Cycle 1 treatment due to investigational product-related adverse events, irrespective of full completion of all Cycle 1 follow-up or compliance <80%.

Blood Pharmacokinetics Concentration Set (BPKCS)

All enrolled participants receiving ≥1 dose of investigational product and with at least one valid post-dose plasma concentration measurement. Participants may be excluded from plasma concentration analysis if:

a) Factors substantially interfering with PK quantification occur during the study;

b) Pre-dose concentration exceeds 5% of the observed Cmax.

Urinary Pharmacokinetics Concentration Set (UPKCS)

All enrolled participants receiving ≥1 dose of investigational product and with at least one valid post-dose urinary drug concentration measurement. Exclusion criterion:

a) Occurrence of factors markedly affecting urinary PK assay during the study.

Feces Pharmacokinetics Concentration Set (FPKCS)

All enrolled participants receiving ≥1 dose of investigational product and with at least one valid post-dose fecal drug concentration measurement. Exclusion criterion:

a) Occurrence of factors markedly affecting fecal PK assay during the study.

Pharmacokinetics Parameter Set (PKPS)

All enrolled participants receiving ≥1 dose of investigational product and with calculable valid PK parameters. Participants may be excluded from PK parameter analysis under the following circumstances:

a) Protocol violations affecting parameter estimation, such as erroneous blood sampling timing, prohibited concomitant medication or off-protocol food intake;

b) Pre-dose concentration above 5% of Cmax;

c) Loss or non-reportability of ≥3 consecutive samples in absorption or elimination phase (absorption-related parameters including Cmax and Tmax will still be calculated if absorption profile is adequately characterized);

d) The first post-dose measured concentration equals Cmax with no early samples collected within 5–15 min post-dosing;

e) Extremely low drug exposure (AUC0−t less than 5% of the geometric mean AUC0−t of other participants within the same dose cohort);

f) Vomiting occurs within twice the median Tmax after drug administration;

g) Errors in pre-analytical processing, shipment or storage compromising sample quantification results after collection but prior to bioanalysis.

Population Assignment for Analyses

DLTS will be used for tolerability assessment; SS for safety evaluation; FAS and PPS for efficacy analyses; corresponding PK datasets for pharmacokinetic analyses; FAS for compliance and baseline characteristic analyses.

11.3 Statistical Analyses

11.3.1 General Methodology

Pharmacokinetic parameters will be estimated via non-compartmental analysis using Phoenix WinNonLin software (Pharsight Corporation, Version 8.2 or higher). All other statistical analyses will be performed using SAS software (Version 9.4 or higher).

11.3.2 Demographic and Baseline Analyses

Participant distribution, demographic characteristics and other baseline features will be summarized by dose cohort/sequence based on the Full Analysis Set (FAS). Baseline comparability across cohorts will be evaluated descriptively.

11.3.3 Safety Analyses

Safety and tolerability analyses will be conducted on the Safety Set (SS). Adverse events (AEs) will be coded and summarized by System Organ Class (SOC) and Preferred Term (PT) per MedDRA dictionary. The number, number of occurrences and percentage of participants with all AEs, investigational product-related AEs, all serious adverse events (SAEs), and investigational product-related SAEs will be presented stratified by study formulation and dose level.

11.3.4 Pharmacokinetic Statistical Analyses

Rules for Below the Limit of Quantification (BLQ) concentrations

For concentration values below the lower limit of quantification (BLQ): BLQ results obtained prior to Cmax will be assigned a value of zero; BLQ results after Cmax will be treated as missing data.

For concentration summary tables: scheduled nominal sampling times will be used regardless of actual sampled clock time deviations.

For PK parameter calculation: if actual sampling times deviate from scheduled times but remain within pre-specified allowable windows, nominal scheduled times will be retained for computation; for samples collected outside permitted time windows, actual recorded sampling times will be applied for parameter estimation.

Concentration–Time Data Analysis

Plasma, urine and fecal concentrations of utidelone, capecitabine and at least one primary metabolite will be summarized by formulation and dose using the Blood PK Concentration Set (BPKCS), Urinary PK Concentration Set (UPKCS) and Fecal PK Concentration Set (FPKCS).

Summary statistics include number of participants (N), arithmetic mean, standard deviation (SD), coefficient of variation (CV), minimum (Min), median, maximum (Max), geometric mean (Geo_Mean) and geometric coefficient of variation (CV%-GM) at each nominal time point. Individual and mean concentration-time profiles will be plotted on linear and semi-logarithmic scales.

PK Parameter Analysis

Key pharmacokinetic parameters will be summarized by formulation and dose on the Pharmacokinetic Parameter Set (PKPS) using N, Mean, SD, CV, Min, Median, Max, Geo_Mean and CV%-GM. A power model will be applied on PKPS to assess dose proportionality between administered dose and systemic exposure metrics (AUC, Cmax) following single-dose administration.

11.3.5 Efficacy Analysis

Objective Response Rate (ORR) and Disease Control Rate (DCR) will be summarized with frequency counts and percentages, together with corresponding 95% confidence intervals. Median Progression-Free Survival (PFS) will be estimated via the Kaplan-Meier method, with corresponding survival curves plotted; Duration of Response (DoR) will be analyzed using the identical approach as PFS.

11.4 Quantitative Pharmacology Analysis

Population pharmacokinetic (PopPK) and/or Exposure-Response (E-R) analyses will be performed using NONMEM (Version 7.3 or higher) and/or R software (Version 4.0.5 or higher, http://www.r-project.org).

12. Ethical Requirements and Informed Consent

12.1 Ethical Requirements

This study shall be conducted in compliance with the Declaration of Helsinki, China’s Good Clinical Practice (GCP) and relevant domestic regulatory requirements. The study protocol must obtain approval from the Ethics Committee prior to study initiation. Any subsequent protocol amendments implemented during the study shall be participant to additional Ethics Committee approval or filing. Investigators are obligated to submit periodic progress reports to the Ethics Committee per its requirements and notify the Ethics Committee upon study completion.

12.2 Informed Consent

The informed consent process commences prior to a participant's enrollment and continues throughout their entire study participation. The informed consent form must receive prior Ethics Committee approval. Investigators shall conduct informed consent discussions and obtain written signed consent from each participant to safeguard participants' legitimate rights and interests. If the consent document is revised mid-study, the updated version shall be approved by the Ethics Committee before re-obtaining written consent from relevant participants.

Investigators will fully explain study details and answer all inquiries raised by participants in an easily understandable manner, covering study objectives, study procedures, potential risks and participants' legal rights. Participants shall be afforded sufficient time to review the written consent document and ask questions before signature, and may consult their family members or legal representatives or conduct independent deliberation prior to making the enrollment decision. All participants must be explicitly informed of their voluntary participation right and the entitlement to withdraw from the study at any time without adverse repercussions. A copy of the signed informed consent form will be provided to the participant for personal retention.

The informed consent procedure must be completed before any study-related procedures are performed on the participant. The consent process (including execution date) shall be documented in source documents, and the originally signed informed consent form shall be properly archived.

12.3 Confidentiality and Privacy

Participant privacy shall be strictly protected by participating investigators and their study staff. All study-related procedures shall be conducted in a private setting to the greatest extent feasible. Participants' contact information is retained locally at each investigative site solely for internal use during the study.

No personal identifiers or contact details will be incorporated into study datasets. Participants' clinical information and bioanalytical results will be identified exclusively via unique randomization/enrollment numbers.

13. Quality Assurance for Clinical Study Conduct

13.1 Monitoring

In accordance with standard operating procedures (SOPs), monitors will verify study compliance with the latest approved protocol/protocol amendments, Chinese GCP and applicable local

regulations. Monitoring activities cover study conduct as well as the collection, processing, analysis, storage and reporting of study data and biological samples.

14. Data Handling and Record Retention

14.1Responsibilities for Data Collection and Management

Investigators are responsible for data collection and shall guarantee the accuracy, completeness, legibility and timeliness of all reported data. Source documents shall be kept neat and legible to enable unambiguous data identification.

Clinical and laboratory data will be captured via an Electronic Data Capture (EDC) system complying with prevailing regulatory requirements and relevant guidelines. Data entered into electronic Case Report Forms (eCRFs) must be sourced from and consistent with source documentation.

Data managers will develop a Data Management Plan to govern the full data management lifecycle, specifying timelines, deliverables and methodologies for all data management activities.

Based on the study protocol and source medical records/paper CRFs, data managers will build and validate the eCRF system. Validation items include page layout, scheduled visit configuration, sequence of data entry forms within each visit and ordering of individual data fields, alongside verification of role-based access rights for different system users. Leveraging EDC system functionality and project-specific requirements, data managers configure and test programmed edit checks to enable automatic system validation and real-time query generation during data entry. In addition to system-generated queries, manual data review will be performed by data managers to issue manual queries for identified discrepancies.

The EDC system enforces dual control via user role and access privilege management. All prospective EDC users shall complete an account application form; following review and approval by the project manager, the system administrator will create dedicated accounts for investigators, monitors and data managers with tiered access permissions. Access applications from the data management lead are approved by the project manager, while applications from other data management personnel are authorized by the data management lead.

Per GCP and protocol requirements, investigators shall capture participant data and complete eCRFs accurately, promptly, comprehensively and in compliance with the eCRF completion guidance issued by data management. Monitors access the EDC to cross-check eCRF entries against source data and raise online queries as needed. Investigators or Clinical Research

Coordinators (CRCs) resolve queries online in real time, or download query logs for offline resolution followed by CRC entry of responses into the EDC. Data managers and monitors review query resolutions and may re-issue follow-up queries until the dataset is fully cleaned.

External data are managed per pre-defined external data transfer agreements. Medical history and adverse events are coded using the MedDRA dictionary.

Upon completion of data cleaning, the Principal Investigator, Sponsor, statistician and data manager jointly review and confirm database integrity prior to database lock performed by the data manager. Post-lock, raw datasets are extracted and provided to the statistical team for analysis; locked data cannot be further edited. Any post-lock identified errors will be rectified within statistical programming code upon confirmation. Database unlocking after final lock requires documented approval signatures from both the investigator and Sponsor and can only be performed with substantiated justifications.

After study completion, data managers generate a PDF copy of each participant's finalized eCRF for archiving on optical disc, compile a final data management report based on actual study execution, export secured backup datasets, and decommission the EDC system.

14.2 Retention of Study Documentation

The Investigator shall retain all study documents, including source documents such as inpatient medical records for study participants, informed consent forms and investigational product dispensing records. All paper and electronic documents generated at investigative sites and testing laboratories shall be properly archived for timely traceability and retained for a minimum of 5 years after study completion OR 5 years following marketing approval of utidelone capsules, whichever is longer.

All study documents are the proprietary property of the Sponsor. Without prior written approval from the Sponsor, the Investigator shall not damage any site documents. Written consent from the Sponsor is mandatory should the Investigator intend to transfer study documents to a third party or relocate archives. Except for inspections conducted by the National Medical Products Administration (NMPA), monitoring and audit activities authorized by the Sponsor, no study documents may be disclosed to any third party in any form without the Sponsor's written permission.

15. Management of Unexpected Occurrences During Study Conduct

15.1 Suspension / Termination of the Study

15.1.1 Temporary Suspension of Study

Study suspension refers to the temporary halt of study activities rather than full study discontinuation, implemented primarily to protect participant rights and safety, secure study quality and prevent unnecessary economic losses. All relevant study parties shall be notified of suspension in writing; the Investigator shall contact affected participants to adjust scheduled visit timelines. Study resumption is permitted only after identified issues are fully resolved and all requirements of the Sponsor and Ethics Committee are satisfied.

The study shall be temporarily suspended if any of the following occurs:

1. Participants are experiencing or at risk of unexpected, study-related substantial physical harm with an unfavourable benefit-risk profile;
2. Quality defects of the investigational product that compromise participant safety are identified;
3. Regulatory authorities order suspension due to failure to timely submit SUSARs, DSURs or other critical safety risk reports within required statutory timelines;
4. The Sponsor requests suspension while ensuring full protection of participant rights and safety;
5. Other circumstances posing substantial safety risks to participants, including:

a) Review of serious, unexpected and related AEs necessitates potential protocol amendments;

b) Severe protocol non-compliance requiring consideration of protocol revision.

15.1.2 Early Termination of Study

Study termination denotes complete permanent discontinuation of all study activities prior to scheduled protocol completion, intended to safeguard participant interests, ensure study quality and avoid unnecessary financial losses. All involved parties shall receive formal written notification of early termination.

Full study termination shall be implemented under the following conditions:

1. The Sponsor requests termination with adequate protection of participant safety and rights (e.g., due to funding or administrative reasons);
2. The primary study endpoint has been definitively achieved;
3. The study is confirmed to lack clinical efficacy;

4. Critical flaws in the study protocol or substantial implementation deviations preclude achievement of study objectives;

5. The NMPA or Ethics Committee mandates termination based on determination that continued study conduct would pose substantial health hazards to participants or conflict with public interests;

6. Other legitimate reasons attributable to the Sponsor.

15.2 Protocol Deviations

All specifications stipulated in the study protocol shall be strictly followed. A protocol deviation is defined as any non-compliance with the clinical study protocol, GCP or requirements specified in operation manuals. Non-compliance may originate from participants, investigators or site staff. Corrective actions shall be formulated and implemented promptly for identified protocol deviations.

Investigators and monitors shall remain vigilant for protocol deviations and report them as soon as identified. All protocol deviations must be documented in source documents and reported to the Ethics Committee and the Sponsor.

16. Protocol Amendments

No party other than the Sponsor is authorized to revise the protocol. Any necessary protocol modifications shall be issued in the form of a formal protocol amendment. Following signature approval by the Sponsor and Principal Investigator, the amendment shall be submitted to the Ethics Committee for approval or filing as required.

17. Clinical Study Reports

Upon study completion, all relevant parties shall prepare corresponding study deliverables based on study findings, including assay validation reports, bioanalytical reports, data management and statistical analysis reports. The final clinical study report will be compiled based on the above documents.

18. Policy on Study Result Disclosure and Conflict of Interest

Investigators and all other study participants (including Ethics Committee members) shall maintain strict confidentiality for all study-related information, including but not limited to the study protocol and Investigator’s Brochure. All study documents and study results are the proprietary property of the Sponsor. Without prior written consent from the Sponsor, investigators

shall not publish or disclose study results in any format independently. Any manuscripts, abstracts or posters intended for academic presentation or journal submission shall be submitted to the Sponsor for review and approval prior to public release.

This study will be registered on the clinical study registry platforms of Chinadrugstudys.org.cn and ClinicalStudys.gov with study results submitted accordingly, and every reasonable effort will be made to publish study findings in peer-reviewed journals.

19. References

[1] Investigator's Brochure of Utidelone Injection.

[2] Approved Prescribing Information for Utidelone Injection.

[3] NMPA. Good Clinical Practice for Pharmaceutical Clinical Studys. 2020.

[4] NMPA. Guidelines for the Management of Phase I Clinical Studys (Study Version). 2011.

[5] NMPA. Technical Guidelines for Clinical Pharmacokinetic Studies of Chemical Drugs. 2005.

[6] NMPA. Technical Guidelines for Human Bioequivalence Studies of Generic Chemical Drugs with Pharmacokinetic Parameters as Endpoints. 2016.

[7] NMPA. Chinese Pharmacopoeia – Guidelines for Validation of Quantitative Bioanalytical Methods. 2020.

[8] NMPA. Guidelines for Laboratory Management of Biological Sample Analysis in Drug Clinical Studys (Study Version). 2011.

[9] NMPA. Technical Guidelines for Single and Multiple Ascending Dose Pharmacokinetic Clinical Studys of Innovative Chemical Drugs. 2021.

[10] NMPA. Technical Guidelines for Clinical Studys of Anticancer Drugs. 2012.

Appendix 1 Contraceptive Measures and Contraception Requirements

1 Background

No clinical data are available regarding the use of the investigational product in pregnant women.

Women with confirmed or suspected pregnancy are excluded from enrollment in this study. If the investigational product is administered during pregnancy or a participant becomes pregnant throughout the study, the participant shall be informed of potential fetal risks.

Pregnancy must be ruled out prior to the first dose of investigational product. Effective contraception shall be maintained throughout treatment and for 3 months following the last study drug administration. Additional contraception is not required for participants who have undergone bilateral tubal ligation, or have an inserted TCu380A intrauterine device (IUD) or LNg 20 intrauterine system (IUS).

2 Definition of Women of Childbearing Potential and Contraception Requirements for Participants (and Their Partners)

Non-childbearing-potential females: Females aged over 54 years with ≥12 consecutive months of spontaneous amenorrhea, or females of any age status post hysterectomy, bilateral oophorectomy, or medically confirmed ovarian failure.

Women of childbearing potential (WOCBP): Females aged ≤54 years without prior hysterectomy or bilateral oophorectomy and without medically proven ovarian failure (including females with amenorrhea of any duration).

WOCBP must yield a negative urine pregnancy test at screening and a negative serum pregnancy test at Visit Day −1.

WOCBP must agree to refrain from oocyte donation from screening through 3 months after the final investigational product dose. Male participants must agree to refrain from sperm donation over the identical period.

All participants must adhere to one of the following contraceptive regimens from screening until 3 months after the last study drug dose:

1. Complete continuous abstinence; periodic rhythm-based abstinence (calendar, ovulation, symptothermal, post-ovulation methods) is not acceptable.
2. Consistent and correct use of one of the following validated contraceptive options:
    - Female partner with bilateral tubal sterilization

- Female partner fitted with an intrauterine device (IUD) with annual failure rate <1%
- Vaginal contraceptive ring used by female partner
- Barrier contraception for female partner: cervical cap or diaphragm with spermicide
- Levonorgestrel subdermal implant for female partner
- Transdermal contraceptive patch for female partner
- Progestogen injectable for female partner
- Oral contraceptives (combined hormonal pills or progestogen-only pills) for female partner
- Consistent correct condom use by male partner
- Male partner with prior bilateral vasectomy

3 Procedures Upon Suspected or Confirmed Pregnancy

Any confirmed or suspected pregnancy in a participant or the participant's partner occurring during treatment or within 3 months after the last investigational product dose must be promptly reported to the investigator. Female participants shall immediately discontinue study drug upon confirmation of pregnancy.

Appendix 2 Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Zubrod-ECOG-WHO (ZPS, 5-grade scale): Developed by the Eastern Cooperative Oncology Group (ECOG, USA) in 1982. The scale covers six grades ranging from 0 to 5, with Grade 0 indicating full wellness and Grade 5 representing death.

Table 1 ECOG Performance Status Criteria (Zubrod-ECOG-WHO, ZPS)

Grade	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

Appendix 3 Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1)

1 Definitions

At baseline, tumor lesions/lymph nodes are categorized as measurable or non-measurable as specified below.

1.1 Measurable Lesions

Malignant tumor lesions: A lesion is measurable if at least one dimension meets or exceeds the lower quantification limit of the detection modality; the longest diameter will be recorded as the primary measurement:

- ≥10 mm by computed tomography (CT; slice thickness ≤5 mm);
- ≥10 mm by clinical caliper measurement (lesions not amenable to accurate caliper measurement are classified as non-measurable);
- ≥20 mm by chest radiography.

Malignant lymph nodes: For CT assessment (recommended slice thickness ≤5 mm), a lymph node is considered pathologically enlarged and measurable when its short-axis diameter is ≥15 mm. Only the short-axis is measured and followed at baseline and all subsequent assessments. Additional guidance on lymph node measurement is provided in annotations under Baseline Documentation of Target and Non-Target Lesions.

1.2 Non-Measurable Lesions

All remaining lesions, including small lesions (longest diameter ＜10 mm or pathological lymph nodes with short axis ≥10 mm and ＜15 mm) and intrinsically non-measurable disease. Intrinsically non-measurable findings consist of clinically documented leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, cutaneous or pulmonary lymphangitic involvement, and bulky abdominal masses/organomegaly not quantifiable via reproducible imaging.

2 Standardized Measurement Methodology

2.1 Lesion Measurement

Clinical measurements are obtained with calipers and documented in metric units. All baseline assessments shall be performed as close to treatment initiation as feasible and no earlier than 4 weeks prior to the first study dose.

2.2 Measurement Techniques

When assessing the same lesion, identical imaging modalities and measurement techniques shall be applied at baseline and all follow-up visits. Lesions must be evaluated by imaging whenever feasible rather than clinical examination alone, except for superficial lesions that can only be assessed clinically without available imaging.

Clinical measurement of lesions: Caliper-based clinical measurement is only acceptable for superficial lesions ≤10 mm (e.g., subcutaneous nodules). Color photography with a size reference scale is recommended to document cutaneous lesions. As specified above, if a lesion is amenable to both clinical and imaging assessment, imaging is preferred given superior objectivity and feasibility for post-hoc endpoint review.

(1) Chest radiograph vs. chest CT: CT is prioritized over plain chest radiography for lesion measurement due to higher sensitivity for identifying new lesions, especially for key efficacy endpoints. Well-demarcated parenchymal pulmonary lesions may alternatively be assessed via chest X-ray.

(2) CT and MRI: CT represents the most robust and reproducible modality for tumor response evaluation per current standards. Per guideline criteria, measurable lesions assessed by CT require slice thickness ≤5 mm; for CT scans with slice thickness exceeding 5 mm, the minimum diameter for a measurable lesion is twice the slice thickness (refer to Appendix 2). MRI may be utilized under selected circumstances such as whole-body imaging.

(3) Ultrasonography: Ultrasound is not permitted for quantitative lesion sizing due to poor inter-visit reproducibility and operator-dependent variability, precluding consistent serial measurements. Any new lesion detected incidentally on ultrasound must be confirmed by CT or MRI; MRI may substitute CT to avoid ionizing radiation exposure when clinically indicated.

(4) Endoscopy and laparoscopy: These modalities are not recommended for routine solid tumor response assessment, but may be used to histologically confirm pathologic complete response or recurrent disease following surgical resection.

(5) Tumor biomarkers: Tumor markers alone cannot define solid tumor treatment response. For patients with baseline elevated tumor markers used to confirm complete response, marker assays must be standardized. Given disease-specificity of biomarkers, assay methodology shall be documented alongside baseline testing for each indication. Specific published criteria govern serial CA125 monitoring for ovarian cancer recurrence and PSA testing for prostate cancer recurrence; the Gynecologic Cancer Intergroup has established CA125 response criteria initially validated for ovarian cancer studys.

(6) Cytology and histopathology: These assays may be applied on a case-by-case basis to differentiate partial versus complete response, e.g., distinguishing benign residual lesions from malignant tissue in germ cell tumors where benign residual masses are common. For treatment-related effusions with known severe adverse risk associated with taxane chemotherapy or anti-angiogenic agents, new or worsening effusions occurring during therapy require cytologic confirmation of malignant cell origin irrespective of target lesion response status, to correctly classify overall disease as responding, stable or progressive.

3 Assessment of Tumor Response

3.1 Assessment of All Tumor Sites and Measurable Lesions

Baseline assessment of overall tumor burden across all malignant lesions is required to establish a reference for subsequent measurements for objective response evaluation and future progressive disease determination. For studys with objective response as the primary efficacy endpoint, only participants with measurable lesions at baseline are eligible for enrollment, where measurable disease is defined as the presence of at least one measurable lesion. For studys designed with disease progression (time-to-progression or progression status at fixed time points) as the primary endpoint, the eligibility criteria shall explicitly specify whether enrollment is restricted to patients with measurable lesions or also permits entry of patients without measurable lesions.

3.2 Baseline Documentation of Target and Non-Target Lesions

If more than one measurable lesion is identified at baseline, a maximum of five lesions overall (no more than two per organ site) shall be documented and designated as target lesions to represent all involved organs (i.e., patients with one or two affected organs may have up to two or four target lesions selected for baseline measurement, respectively).

Target lesions are selected according to size (longest diameter), representative of all involved organs, and must allow reproducible serial measurement. Where the largest lesion is not amenable to consistent repeat measurement, the largest alternative reproducible lesion may be selected instead.

Lymph nodes require special consideration given their physiological visibility on imaging even in the absence of metastatic infiltration. Pathological lymph nodes qualifying as measurable or target lesions must meet the following criterion: short-axis diameter ≥15 mm by CT; only the short-axis is recorded at baseline. Radiologists routinely utilize short-axis dimension to identify metastatic nodal involvement. Nodal size is derived from two orthogonal imaging dimensions (axial plane for CT; axial, sagittal or coronal plane for MRI), with the smaller value defined as the short axis. For illustration, an abdominal node measuring 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant measurable lesion, with 20 mm recorded as the nodal measurement. Nodes measuring ≥10 mm but ＜15 mm in short axis cannot be selected as target lesions; nodes with short axis ＜10 mm are classified as non-pathologic and require no documentation or follow-up.

The sum of diameters of all target lesions (longest diameter for non-nodal lesions, short-axis diameter for nodal lesions) is calculated and recorded as the baseline sum of diameters, serving as the baseline reference for overall disease burden. Only nodal short-axis measurements are incorporated into the summed total for lymphatic target lesions as specified above.

All remaining lesions including pathological lymph nodes are classified as non-target lesions; formal dimensional measurement is not required but presence must be documented at baseline as “present”, “absent”, or in rare cases “unequivocal progressive disease”. Extensive disseminated non-target disease may be annotated under the corresponding affected organ (e.g., bulky pelvic lymphadenopathy or extensive hepatic metastases).

3.3 Response Assessment Criteria

3.3.1 Response Evaluation for Target Lesions

Complete Response (CR)

Disappearance of all target lesions; short-axis diameter of all pathological lymph nodes (target or non-target) reduced to ＜10 mm.

Partial Response (PR)

At least a 30% decrease in the sum of diameters of target lesions relative to baseline sum of diameters.

Progressive Disease (PD)

At least a 20% increase in the sum of diameters of target lesions relative to the nadir sum (including nadir equal to baseline), accompanied by an absolute increase of ≥5 mm in the summed diameter.

Note: Appearance of any new lesion also constitutes PD.

Stable Disease (SD)

Neither sufficient shrinkage to meet PR criteria nor sufficient increase to satisfy PD criteria, referenced to the nadir sum of target lesion diameters.

3.3.2 Evaluation of Non-Target Lesions

Even if some non-target lesions are technically measurable, only qualitative assessment is required at scheduled study time points rather than formal dimensional measurement.

Complete Response (CR)

Resolution of all non-target lesions plus normalization of all tumor marker levels; all lymph nodes revert to non-pathologic size (short axis ＜10 mm).

Non-CR/Non-PD

Persistence of ≥1 non-target lesion and/or sustained elevation of tumor markers above upper limit of normal.

Progressive Disease (PD)

Unequivocal progression of existing non-target lesions.

Note: Appearance of any new malignant lesion is also defined as PD.

3.3.3 New Lesions

Emergence of any new malignant lesion confirms progressive disease, making standardized identification of new lesions critical. No dedicated radiographic thresholds exist to define new lesions; findings must be unequivocally malignant and cannot be attributed to variations in scanning technique, changes in imaging modality, or benign etiology (e.g., apparent new bone lesions may represent healing or previously occult pre-existing lesions). This principle is especially critical when target lesions demonstrate PR or CR. For example, necrosis within a pre-existing hepatic lesion may appear as a “new cystic lesion” on CT and does not qualify as true new disease.

Lesions identified at follow-up in an anatomical site free of disease on baseline scans are regarded as new lesions and indicative of progressive disease. A typical scenario involves patients with known visceral malignancies who undergo brain CT or MRI during follow-up to screen for metastatic spread; any newly detected brain metastasis counts as progressive disease regardless of whether baseline brain imaging was performed.

When a suspected new lesion is too small for definitive identification yet highly suggestive of de novo malignancy, its final response classification shall be deferred to subsequent treatment cycles and follow-up assessments. Progressive disease is confirmed if repeat imaging unequivocally verifies a true new lesion relative to baseline scans.

When FDG-PET is incorporated for exploratory response assessment, combined interpretation of FDG-PET and correlative CT is recommended to adjudicate progressive disease, especially when new malignant lesions are highly suspected. New lesions identified on FDG-PET are defined per the following algorithm:

a) Baseline FDG-PET negative with follow-up FDG-PET positive: Progressive disease is confirmed due to new lesion formation.

b) No baseline FDG-PET performed but follow-up FDG-PET positive:

- Progressive disease is confirmed when the PET-positive lesion is corroborated by concurrent CT.

- If CT fails to verify the PET-positive lesion, definitive confirmation is deferred to the next scheduled CT scan (the date of the abnormal FDG-PET acquisition is recorded as the progressive disease onset date).

- If the PET-positive finding corresponds to a pre-existing lesion identified on CT without anatomical progression on structural imaging, progressive disease is not established.

3.4 Assessment of Best Overall Response

Best Overall Response (BOR) is defined as the optimal disease response documented from initiation to completion of study treatment after comprehensive integration of all available assessment data. In some instances, a definitive response can only be confirmed after treatment discontinuation; accordingly, study protocols shall pre-specify whether post-treatment follow-up assessments are included for BOR determination. Protocols must also define how initiation of subsequent anti-tumor therapy impacts BOR endpoints prior to the start of such subsequent treatment. BOR is determined collectively based on findings from target lesions, non-target lesions and emergence of new lesions, with quantitative metrics specified per study design requirements. Notably, in single-arm non-randomized studys with response as the primary endpoint, documented CR or PR constitutes the patient's Best Overall Response.

3.4.1 Per-Time-Point Response Determination

Response evaluation is conducted at pre-defined scheduled assessment visits per study protocol. Table 1 below summarizes the composite overall response adjudication rules at each assessment timepoint for participants with measurable baseline disease.

Table 1 Per-Time-Point Response: Patients with Target plus Non-Target Lesions

Target Lesions	**Non-Target Lesions**	**New Lesion**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD

Target Lesions	Non-Target Lesions	New Lesion	Overall Response
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: CR = Complete Response; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease; NE = Not Evaluable.

Table 2 Per-Time-Point Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesion	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Note: CR = Complete Response; PD = Progressive Disease; NE = Not Evaluable.

3.4.2 Assessment of Resolved Lesions and Non-Measurable Disease

A patient is classified as not evaluable at a given time point if no imaging or measurable data are available for that visit. If only a subset of lesions is assessed at a scheduled evaluation, the time point is generally deemed nonevaluable unless compelling evidence confirms that disappearance of unassessed lesions would not alter the assigned response status. This exception applies most commonly in cases of progressive disease.

For example: a patient with three measurable target lesions summing to 50 mm at baseline; only two lesions are assessable at follow-up with a total sum increased to 80 mm. The patient is adjudged to have progressive disease regardless of disappearance of the third unevaluated lesion.

3.4.3 Best Overall Response Across All Assessment Time Points

Best Overall Response (BOR) is determined based on all available evaluable data collected from the participant throughout the study.

Scenario 1: No mandatory confirmation visit required for CR/PR adjudication for BOR**

BOR is defined as the optimal response observed across all scheduled assessments. For instance, a participant achieving Stable Disease (SD) at Visit 1, Partial Response (PR) at Visit 2, and Progressive Disease (PD) at the final visit will have PR documented as BOR.

Where SD constitutes the best observed response, the duration of SD must meet the minimum predefined follow-up period from baseline.

If SD fails to persist for the required minimum duration and no superior response is documented at subsequent visits, the participant's BOR is assigned per later assessments. Example: SD at the first assessment followed by PD at the second visit with insufficient SD duration results in PD as BOR. Participants with initial SD but lost to follow-up before completing the minimum required stable period are classified as Not Evaluable (NE).

Scenario 2: Mandatory confirmatory assessment required to verify CR/PR for BOR**

Complete Response (CR) or PR is only confirmed when corresponding response criteria are re-satisfied at a subsequent confirmatory time point (typically ≥4 weeks later). BOR assignment under this rule is outlined in Table 3.

Table 3 Best Overall Response When Confirmation of CR and PR Is Required

Overall Response at Initial Timepoint	**Overall Response at Subsequent Timepoint**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD if minimum SD duration criteria are satisfied; otherwise PD
CR	PD	SD if minimum SD duration criteria are satisfied; otherwise PD
CR	NE	SD if minimum SD duration criteria are satisfied; otherwise NE

Overall Response at Initial Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD if minimum SD duration criteria are satisfied; otherwise PD
PR	NE	SD if minimum SD duration criteria are satisfied; otherwise NE
NE	NE	NE

[a] Footnote: If complete response is documented at the initial assessment followed by disease recurrence at a subsequent visit, the case shall be rated as progressive disease at this later timepoint even if the recurrent lesion burden meets partial response criteria versus baseline (due to disease relapse following prior complete remission).

Best overall response is contingent upon whether the pre-specified minimum duration for stable disease is fulfilled. In certain scenarios, an initial CR assignment may be revised to PR when follow-up imaging identifies residual small lesions that were undetected previously. Under such circumstances, the original CR designation shall be amended to PR, and partial response will be recorded as the participant's final best overall response.

3.4.4 Special Notes for Response Assessment

When lymph nodes are designated as target lesions and subsequently shrink to normal size (<10 mm), their measured dimensions shall still be documented on imaging reports. These measurements are retained even after normalization of nodal size, and response calculations shall be based on actual dimensional changes to avoid overestimation of therapeutic benefit. As noted previously, this means patients achieving Complete Response (CR) may not have a total summed diameter of zero recorded on Case Report Forms (CRFs).

Repeated Not Evaluable (NE) assessments at scheduled visits may complicate adjudication of Best Overall Response (BOR) in studys with response-driven endpoints. The study's Statistical Analysis Plan shall predefine rules for handling missing or unevaluable data when assigning

objective response or progressive disease status. For example, it is clinically reasonable to classify a sequential response pattern of PR-NE-PR as a confirmed partial response in most study designs.

Patients requiring treatment discontinuation due to symptomatic clinical deterioration without objective radiologic evidence of progressive disease at the corresponding timepoint shall be documented as having “symptomatic deterioration”. Post-discontinuation objective confirmation of progressive disease should still be pursued whenever feasible. Symptomatic deterioration is not an objective response category and solely serves as a reason for premature treatment cessation; final objective response classification for such patients remains governed by target and non-target lesion assessments listed in Tables 1, 2 and 3.

Definitions for early progression, early death and non-evaluable status are study-specific and must be predefined in the study protocol at an early planning stage according to treatment duration and cycle schedule.

Distinction between residual viable tumor and benign post-treatment tissue can be diagnostically challenging. When CR confirmation relies on imaging findings suggestive of residual abnormality, fine-needle aspiration biopsy is recommended prior to final CR adjudication. Residual lesions deemed abnormal by conventional imaging but characterized as fibrosis or scar tissue on FDG-PET may support upgrading response to CR in a manner analogous to histopathologic verification. Use of FDG-PET for this purpose must be prespecified in the study protocol and substantiated by disease-specific published clinical literature. Nevertheless, limitations in spatial resolution and diagnostic sensitivity of FDG-PET and biopsy carry inherent risks of false-positive CR determinations.

For equivocal suspicious findings suggestive of possible progression (e.g., tiny indeterminate new lesions, cystic or necrotic change within pre-existing lesions), study treatment may continue until the next scheduled assessment visit. If progressive disease is formally confirmed at the subsequent timepoint, the date of initial suspicion shall be recorded as the official progression date.

3.5 Frequency of Tumor Assessments

Imaging reassessment schedules are determined per protocol specifications, tumor histology and intended treatment duration. For Phase II studys with unknown anti-tumor activity, follow-up evaluations approximately every 6–8 weeks per treatment cycle represent standard practice; adjustment of assessment intervals is permitted for disease-specific clinical scenarios. The

protocol shall explicitly define baseline organs requiring screening (typically sites with high metastatic propensity) and the periodicity of repeat evaluations. All target and non-target lesions are generally assessed at each scheduled visit; selected non-target organ evaluations may be omitted at follow-up. For instance, repeat bone scintigraphy is only indicated to confirm complete response of osseous target lesions or when new bone metastasis is clinically suspected.

Post-treatment surveillance imaging is dictated by study primary objectives: response-focused studys require follow-up only for response confirmation, whereas endpoint-driven studys measuring time-to-event outcomes (e.g., progression-free survival, disease-free survival) mandate regular scheduled reassessments per protocol. Randomized controlled studys shall adhere to fixed predefined evaluation timetables (e.g., every 6–8 weeks during active treatment or every 3–4 months post-discontinuation), with no rescheduling permitted for treatment delays, drug holidays or other protocol deviations that could unbalance study arms.

3.6. Definition of Duration Endpoints

3.6.1 Confirmation Requirements

For single-arm non-randomized studys with objective response as the primary endpoint, confirmation of Partial Response (PR) or Complete Response (CR) is required to rule out measurement error and enable consistent historical study cross-study comparison (refer to publications by Bogaerts et al.). Confirmatory repeat assessment is not mandatory for all other study designs, including randomized Phase II/III studys and studys utilizing stable disease or progression as primary endpoints, where formal response validation is unnecessary for result interpretation. Elimination of mandatory response confirmation heightens the importance of bias mitigation strategies, particularly in open-label non-blinded studys.

Stable Disease (SD) classification must satisfy predefined minimum duration criteria: the assessment interval between baseline and confirmatory SD evaluation shall comply with protocol-specified minimum intervals (typically no less than 6–8 weeks).

3.6.2 Overall Response Duration

Overall Response Duration: Time from the initial assessment date meeting formal CR/PR criteria (first documented response) to the first confirmed objective progression or disease relapse, referenced against the nadir summed target lesion diameter recorded throughout the study.

Complete Response Duration: Time from initial CR confirmation to the first objectively verified disease relapse.

3.6.3 Stable Disease Duration

Stable Disease Duration is defined from the treatment initiation date (randomization date for randomized studys) to the first assessment satisfying progressive disease criteria, calculated against the nadir summed target lesion diameter (or baseline sum when nadir equals baseline measurement).

Clinically meaningful minimum SD duration varies substantially across tumor types and individual study designs. If minimum SD duration constitutes a key study endpoint for a subset of enrolled participants, the protocol shall clearly stipulate two alternative prespecified minimum interval thresholds for SD adjudication.

Note: Calculated response duration, stable disease duration and progression-free survival are impacted by post-baseline imaging follow-up frequency. Standardization of surveillance schedules falls outside the scope of RECIST guidance; final follow-up timelines are customized per disease subtype, disease stage, treatment regimen and institutional SOPs. Such variability in measurement precision must be accounted for when conducting cross-study comparative analyses.

Appendix 4 Formula for Calculation of Creatinine Clearance

Creatinine Clearance Calculation Equation (Cockcroft-Gault Formula) Serum

Creatinine Concentration (mg/dL):

$$\text{Male creatinine clearance (mL/min)} = \frac{(140\text{-Age}) \times \text{Weight}}{72 \times \text{serum creatinine}}$$

$$\text{Female creatinine clearance (mL/min)} = \frac{0.85 \times (140 - \text{Age}) \times \text{Weight}}{72 \times \text{serum creatinine}}$$

Serum creatinine concentration (μmol/L):

$$\text{Male creatinine clearance (mL/min)} = \frac{(140\text{-Age}) \times \text{Weight}}{0.818 \times \text{serum creatinine}}$$

$$\text{Female creatinine clearance (mL/min)} = \frac{0.85 \times (140 - \text{Age}) \times \text{Weight}}{0.818 \times \text{serum creatinine}}$$

Note: age is in years and weight is in kg.