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TRIALS IN PROGRESS

ASCEND: a randomised, double-blinded, placebo-controlled, phase II study of gemcitabine and nab-paclitaxel with LSTA1 in untreated metastatic pancreatic adenocarcinoma. An Australasian Gastro-Intestinal Trials Group (AGITG) trial☆

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Background: The dense stroma of pancreatic ductal adenocarcinoma (PDAC) is thought to impede tumour drug delivery. LSTA1, a novel cyclic tumour-penetrating peptide internalising arginylglycylaspartic acid, promotes tumour-specific drug delivery. In the phase Ib setting, LSTA1 3.2 mg/kg with gemcitabine and nab-paclitaxel showed a 92% disease control rate at 16 weeks and was well tolerated.

Methods/design: This is a multicentre, phase II, double-blinded, placebo-controlled, randomised trial evaluating the activity and safety of LSTA1 in combination with gemcitabine and nab-paclitaxel in untreated advanced PDAC. Initially, participants were randomised 2 : 1 to receive gemcitabine 1000 mg/m^2, nab-paclitaxel 125 mg/m^2 and LSTA1 3.2 mg/kg or placebo. The trial design was updated in a protocol amendment (v4.0) to include a second placebo-controlled cohort which receives a second dose of LSTA1/placebo 4 h following chemotherapy. Treatment is administered on days 1, 8, and 15 of each 28-day cycle until progression (progressive disease). The sample size is 155 based on a clinically worthwhile increase in 6-month progression-free survival (PFS) of 16%-63% with 80% power and 95% confidence to exclude the null hypothesis. The recruitment period is 22 months and follow-up 18 months. Study endpoints are: (1) PFS; (2) objective response rate (RECIST 1.1), safety (Common Terminology Criteria for Adverse Events v5.0), overall survival, participant-reported outcomes; (3) predictive/prognostic biomarkers via archival tissue, and to assess whether a second dose of LSTA1 warrants further evaluation.

Key words: iRGD, pancreatic ductal adenocarcinoma, pancreatic carcinoma, LSTA1, chemotherapy

DESCRIPTION OF PROTOCOL

Background

Standard first-line chemotherapy for metastatic pancreatic ductal adenocarcinoma (PDAC) with FOLFIRINOX (5-fluorouracil, irinotecan, oxaliplatin, and leucovorin), or gemcitabine and nab-paclitaxel is associated with modest response rates and improvement in overall survival (OS) of 34.1% and 11 months, and 23% and 8.5 months, respectively.[1,2] The dense stroma of PDAC is thought to interfere with chemotherapy delivery and contribute to the low chemotherapy response rates observed.[3] LSTA1

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☆Note: Related research article: Dean A, Gill S, McGregor M, Broadbridge V, Jarvelainen HA, Price TJ. 1528P Phase I trial of the first-in-class agent CEND-1 in combination with gemcitabine and nab-paclitaxel in patients with metastatic pancreatic cancer. *Ann Oncol.* 2020;31:S941.

GRAPHICAL ABSTRACT

Specifications table	
Subject area	**Medicine and Dentistry**
More specific subject area	*Medical Oncology*
Name of your trial in progress	*ASCEND: a randomised, double-blinded, placebo-controlled, phase II study of gemcitabine and nab-paclitaxel with LSTA1 in untreated metastatic pancreatic adenocarcinoma. An Australasian Gastro-Intestinal Trials Group (AGITG) trial*
Trial design	Randomised, double-blinded, placebo-controlled, phase II study with 2 : 1 randomisation in two cohorts, and stratification by age (<65 versus >65 years), ECOG (0 versus 1), presence of liver metastasis (yes versus no), and sites. *Eligible population:* Adults with histologically proven metastatic pancreatic ductal adenocarcinoma suitable for first-line gemcitabine and nab-paclitaxel chemotherapy. *Endpoints:* - *Primary endpoint: PFS* - *Secondary endpoints: OTRR, OS, safety, quality of life* - *Exploratory: translational biomarkers* *Cohort A (65 intervention, 30 control arm):* - *Intervention arm treatment:* nab-paclitaxel (125 mg/m^2) + LSTA1 (3.2 mg/kg) + gemcitabine (1000 mg/m^2) on days 1, 8, and 15 of 28-day cycle. - *Control arm treatment:* nab-paclitaxel (125 mg/m^2) + placebo + gemcitabine (1000 mg/m^2) on days 1, 8, and 15 of 28-day cycle. *Cohort B (40 intervention, 20 control arm):* - *Intervention arm treatment:* nab-paclitaxel (125 mg/m^2) + LSTA1 (3.2 mg/kg) + gemcitabine (1000 mg/m^2) + LSTA1 (3.2 mg/kg) on days 1, 8, and 15 of 28-day cycle. - *Control arm treatment:* nab-paclitaxel (125 mg/m^2) + placebo + gemcitabine (1000 mg/m^2) + placebo on days 1, 8, and 15 of 28-day cycle. Treatment will continue until PD, unacceptable toxicity, or other discontinuation criterion is met. *Statistical methods:* Cohort A requires a sample size of 90 (2 : 1 randomisation) based on expected control arm 6-month PFS of 47% and clinically worthwhile increase in 6-month PFS of 16%-63% for the intervention arm. This will have 80% power with 95% confidence to exclude the null hypothesis. A total of 95 participants are allocated to cohort A to allow for attrition of 5 participants. Cohort B is an exploratory cohort of 60 participants. The Kaplan–Meier method will be used to calculate the PFS.
Trial registration	Australia New Zealand Clinical Trials Registry: ACTRN12621001290886. Registration date: 24 September 2021.
Ethics	This study will be conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP), the NHMRC National Statement on Ethical Conduct in Human Research, and other relevant ethical and regulatory directives within each country the research operates. Written informed consent is prerequisite to participant enrolment. The trial was approved by the Sydney Local Health District (SLHD) Ethics Review Committee (Royal Prince Alfred Hospital Zone). Ethics was approved on 1 July 2021 (2021/ETH00985). All participants must provide written informed consent to the study procedures before enrolment into study. Consent will be obtained by delegated site investigators.
Value of the trial in progress	The ASCEND study addresses this issue of treatment resistance and aims to improve outcomes to existing standard-of-care chemotherapy. This is the first phase II study to evaluate the efficacy of iRGD peptides in combination with chemotherapy in PDAC. This study will collect data on PROs including disease- and neuropathy-specific symptoms and assess the feasibility of ePRO tools to improve future trial designs.

ECOG, Eastern Cooperative Oncology Group; ePRO, electronic patient-reported outcomes; iRGD, internalising arginylglycylaspartic acid; OS, overall survival; OTRR, objective tumour response rate; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PROs, participant-reported outcomes.

(previously known as CEND-1) is a novel cyclic tumour-penetrating peptide internalising arginylglycylaspartic acid (iRGD) which may overcome poor drug delivery by activation of a complex trans-tissue active transport pathway, providing an opportunity to overcome this mechanism of resistance in PDAC. The iRGD motif mediates binding of LSTA1 to αvB3/5-integrins on tumour vascular endothelium, with subsequent protease cleavage of LSTA1 yielding a linear peptide fragment that activates neuropilin-1, leading to an increased tumour permeability and tumour penetration of co-administered anticancer agents.[4,5]

METHODS

Objective

The aim of the ASCEND study is to investigate the activity, safety, and tolerability of LSTA1 in combination with first-line gemcitabine and nab-paclitaxel in people with previously untreated metastatic PDAC. The results of this study will inform future comparative phase III randomised controlled trials, with the aim of improving response rate and survival of first-line systemic therapy for PDAC.

Trial design

ASCEND is a randomised, double-blinded, placebo-controlled, multicentre, phase II study to assess the effect of adding LSTA1 to standard-of-care chemotherapy with gemcitabine and nab-paclitaxel. A protocol amendment was approved on 30 November 2022, adding a second placebo-controlled cohort evaluating a second dose of LSTA1. The trial will take place in hospitals in Australia and New Zealand (see Table 1).

In the initial trial design, participants were randomised 2 : 1 in favour of the intervention arm. The intervention arm received gemcitabine (1000 mg/m^2), nab-paclitaxel (125 mg/m^2) plus LSTA1 (3.2 mg/kg) on days 1, 8, and 15 of 28-day cycle. The placebo arm received gemcitabine (1000 mg/m^2), nab-paclitaxel (125 mg/m^2) plus placebo.

The revised trial design involves two placebo-controlled cohorts randomised 1 : 1 to cohort A or B and

Table 1. ASCEND participating centres

Site	Location	Principal investigator
Frankston Hospital	VIC, Australia	Zee Wan Wong
Calvary Mater Newcastle	NSW, Australia	Fiona Day
Newcastle Private Hospital	NSW, Australia	James Lynam
Lake Macquarie Private Hospital	NSW, Australia	Stephen Ackland
Royal Brisbane & Women's Hospital	QLD, Australia	Matthew Burge
St John of God, Subiaco	WA, Australia	Andrew Dean
The Alfred Hospital	VIC, Australia	Sanjeev Gill
Epworth Healthcare	VIC, Australia	Ross Jennens
Border Medical Oncology Research Unit	NSW, Australia	Chris Steer
Warringal Private Hospital	VIC, Australia	Niall Tebbutt
The Queen Elizabeth Hospital	SA, Australia	Timothy Price
Monash Health	VIC, Australia	Marion Harris
Fiona Stanley Hospital	WA, Australia	Chris Lomma
Flinders Medical Centre	SA, Australia	Chris Karapetis
Sunshine Coast University Hospital	QLD, Australia	Alexandra Franscesconi
Northern Health	VIC, Australia	Belinda Lee
Chris O'Brien Lifehouse	NSW, Australia	Sara Wahlroos
St George Hospital	NSW, Australia	Katrin Sjoquist
Launceston General Hospital	TAS, Australia	Shamsudheen Padinharakam
ICON Cancer Centre Wesley	QLD, Australia	David Grimes
Auckland Hospital	New Zealand	Jane So
Waikato Hospital	New Zealand	Michael Jameson
Dunedin Hospital	New Zealand	Christopher Jackson
Nepean Hospital	NSW, Australia	Jenny Shannon
Royal Darwin Hospital	NT, Australia	Timothy Price

randomised again 2 : 1 (intervention : placebo) within each cohort. The intervention arm in cohort A will receive the treatment outlined in the initial trial design. Cohort B will receive an additional dose of 3.2 mg/kg of LSTA1/placebo ~4 h after gemcitabine.

The sample size has been increased to a total of 155 participants: 95 in cohort A, 60 in cohort B. Recruitment duration has been increased to 22 months and follow-up remains 18 months. Recruitment commenced on 13 April 2022. One hundred and twelve of 155 participants from 23/28 sites have been recruited as of 30 June 2023.

Study endpoints and objectives

The primary endpoint is progression-free survival (PFS) in each arm defined as the time from randomisation to first evidence of progressive disease (PD), the occurrence of new disease, or death from any cause. PD will be assessed using RECIST v1.1 criteria.[6]

Secondary endpoints are objective tumour response rate assessed by RECIST v1.1, safety [adverse events (AEs)] [National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 (NCI CTCAE)], OS defined as the time from randomisation to death from any cause, and participant-reported outcomes (PROs). PROs will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life of Cancer Patients (QLQ-C30) and Pancreatic Cancer (QLQ-PAN26) tools[7,8] and a question on neuropathy from the EORTC item bank. The EORTC QLQ-30 is a well-validated tool widely used to assess quality-of-life outcomes in cancer participants.[9] The EORTC QLQ-PAN26 is a tool for assessing quality of life in pancreatic cancer participants.[8,10]

The exploratory objectives of the study are to investigate potential prognostic and/or predictive biomarkers, to explore the activity of a second dose of LSTA1 ~4 h after chemotherapy, and to evaluate the feasibility and acceptability of assessing PROs electronically in this population.

Study population

- Histologically confirmed PDAC or poorly differentiated pancreatic carcinoma
- No prior treatment in metastatic setting
- Participants aged ≥18 years
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Other main inclusion criteria include:

1. Measurable disease by RECIST 1.1
2. Archival tumour tissue available for tertiary correlative studies (fine needle aspirates or brushings are not acceptable)
3. No prior chemotherapy or investigational anticancer therapy for metastatic pancreatic adenocarcinoma. Prior treatments with curative intent or for locally advanced disease allowed if last dose was >6 months ago
4. Creatinine clearance ≥50 ml/min (by Cockcroft-Gault equation)
5. Adequate haematological function:
   a. Platelets $\geq 100 \times 10^9$/l
   b. Absolute neutrophil count $\geq 1.5 \times 10^9$/l
   c. Haemoglobin ≥90 g/l
6. Adequate hepatic function:
   a. Bilirubin <1.5 × ULN (upper limit of normal)
   b. Aspartate aminotransferase or alanine aminotransferase ≤5 × ULN

Main exclusion criteria include:

1. Pancreatic neuroendocrine tumours.
2. Uncontrolled metastatic disease in the central nervous system (CNS). Participants with known CNS metastases are eligible if the metastases have been treated with surgery and/or radiotherapy, and the participant is on a stable dose of steroids for 2 weeks before randomisation without neurological deterioration.

3. Prior radiotherapy or major surgery within 14 days of starting treatment.
4. Significant active infection, including chronic active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV). Participants with known hepatitis B/C or HIV infection will be allowed if evidence of viral suppression has been documented and the participant remains on anti-viral therapy.
5. Life expectancy $<$3 months.

The full inclusion and exclusion criteria are detailed in the full study protocol.

Study procedures

Consent and randomisation. Participants will be provided with a trial and site-specific Participant Information and Consent Form, opportunity to ask questions, and sufficient time for reflection and consultation before being consented by the site investigator. Participants will be encouraged to continue in the trial even if withdrawn from randomised treatment allocation to enable intention-to-treat analyses.

Randomisation will be carried out by sites online via the ASCEND clinical data system (Medidata RTSM) via minimisation with stratification by age ($<$65 or $\geq$65 years), ECOG (0 or 1), and presence of liver metastasis (yes or no).

Treatment. The intervention arm of cohort A will receive nab-paclitaxel 125 mg/m^2, LSTA1 3.2 mg/kg, and gemcitabine 1000 mg/m^2 on days 1, 8, and 15 of each 28-day cycle. The intervention arm of cohort B will receive intravenous (i.v.) nab-paclitaxel 125 mg/m^2, i.v. LSTA1 3.2 mg/kg, and i.v. gemcitabine 1000 mg/m^2 and a second dose of LSTA1 3.2 mg/kg on days 1, 8, and 15 of each 28-day cycle. Cohort A and B control arms will receive the same chemotherapy as the respective intervention arms but LSTA1 will be replaced by matching placebo.

Treatment will continue until PD, unacceptable toxicity, or other criterion for discontinuation is met, e.g. participant withdrawal of consent. Supportive medication will be given as per local protocol and should include anti-emetics and steroids pre-chemotherapy. Concomitant use of investigational medicinal products, anticancer treatments, and warfarin are prohibited. Supportive care, including antibiotics for infections, and blood products are permitted.

Chemotherapy dose reductions for AEs are allowed using the levels defined in the full protocol. There will be no dose modifications for LSTA1. Participants and sites are encouraged to continue treatment as per protocol schedule. Reasons for any missed or discontinued doses must be recorded in the case report form (CRF).

Treatment following discontinuation of study treatment is at the discretion of the participant's clinician.

Assessments. Baseline assessment of participants consists of clinical examination, haematological, creatinine and serum electrolytes, liver function, and tumour markers (CA19.9 and carcinoembryonic antigen), computed tomography (CT) of chest, abdomen, and pelvis, and PROs. Clinical evaluation, haematology, biochemistry, liver function, tumour markers, and safety assessments occur at day 1 of every cycle. PRO assessment will take place every 8 weeks until PD. PRO assessment will be completed electronically unless the participant does not have access to an electronic device. ePRO feasibility assessment will take place at week 16 or at progression if this occurs sooner. CT of chest, abdomen, and pelvis will be carried out every 8 weeks until PD or commencement of a new anticancer therapy. See Table 2.

Data entry and management. All data will be recorded on to electronic CRFs (eCRFs). The coded data will be stored in highly secure databases that meet national and international standards for data protection and privacy. Trial documentation at Australian sites will be kept in a secure location and held for at least 15 years after the end of the trial. International sites will follow local regulatory requirements.

Blinding/unblinding. Participants, investigators, and staff involved in the outcome assessment and data analysis will be blinded. Site pharmacists are not blinded but will not participate in assessment or data analysis. Emergency unblinding is allowed for medical emergency, where knowledge of the participant's group assignment could impact the participant's treatment. It is the responsibility of the investigator to determine whether emergency unblinding is warranted. Unblinding can be carried out through the unblinding phone number recorded on the protocol. The date and reason for unblinding must be recorded.

Translational research

Availability of formalin-fixed paraffin-embedded tissue for translational research is mandatory for this study. Optional consent will be sought for use of tissue (obtained where clinically indicated during or after treatment) for translational research. Tissue samples will be bio-banked and used for exploratory studies to identify potential biomarkers that are prognostic and/or predictive of clinical endpoints: response to treatment, safety, survival, and resistance to study treatment.

Statistical considerations

The median PFS in the control group is expected to be 5.5 months, corresponding to a 6-month PFS of 47%. A 16% increase the PFS rate in the experimental arm would be a clinically worthwhile difference which equates to a 6-month PFS rate of 63%. Based on Fleming's single-arm phase II design, a sample size of 65 participants in the combination gemcitabine nab-paclitaxel with LSTA1 will have at least 80% power with 95% confidence to exclude an uninteresting 6-month PFS rate of 47% in favour of a 63% rate which would warrant further investigation. Cohort A will comprise 95 participants (30 placebo). Cohort B will be an exploratory cohort comprising 60 participants (20 placebo). The total

Table 2. SPIRIT flow chart

	Study period						
	Enrolment	Allocation	Post-allocation				Follow-up
Timepoint	≤7 days before randomisation	0	Every 4 weeks	Every 8 weeks	Other	Safety follow-up (30 days from end of treatment)	Every 8 weeks from last CT
Enrolment							
Eligibility screen	X						
Informed consent	X (up to 28 days before randomisation)						
Medical history	X						
Clinical evaluation	X		X			X	X
Allocation		X					
Interventions							
Arm A			X				
Arm B			X				
Assessments							
Blood tests (haematology, biochemistry, CA19.9, CEA)	X		X			X	X (until PD)
Urine pregnancy test			As indicated				
Serious adverse events assessment			X			X	X (until PD)
CT chest, abdomen, pelvis	X (up to 21 days before randomisation)			X			X (until PD or new treatment)
PRO	X	X		X			X (until PD)
ePRO feasibility					X (at week 16 or PD)		
Survival status							X

CEA, carcinoembryonic antigen; CT, computed tomography; ePRO, electronic patient-reported outcomes; PD, progressive disease; PROs, participant-reported outcomes.

sample size of 155 participants includes 5 additional participants to account for attrition.

Estimates of PFS at 6 months and the corresponding 95% confidence interval will be calculated using the Kaplan–Meier method. A formal interim futility analysis will be carried out and reviewed by the Australasian Gastro-Intestinal Trials Group (AGITG)'s Independent Data Monitoring Committee (IDMC) after 30 participants on the experimental arm have been followed up for 6 months.

The EORTC QLQ-C30 will be scored according to the scoring manual using all available data.[11] Missing items will be imputed using the scale mean, if >50% of the scale has been completed, as per the scoring manual. If <50% of a scale has been completed, it will be set to missing. Mean and range scale scores will be calculated for each analysis group and plotted for each time point, by analysis group. This study is insufficiently powered for statistical comparisons of PROs, hence analyses will be of descriptive nature and will be detailed in a separate statistical analysis plan.

Safety

All events will have the severity graded according to the toxicity grading scale within the CTCAE v5.0. AEs will be recorded from the first exposure to investigational product until 30 days following the last treatment dose. Serious adverse events (SAEs) will be reported as per Good Clinical Practice (GCP) guidelines and applicable regulations.

The investigator is responsible for ensuring all AEs observed by the investigator or reported by the trial participants are documented in eCRFs. The sponsor is responsible for the medical review of all SAEs and for their notification to the appropriate ethics committees and local authorities.

The IDMC will meet 6-monthly to assess participant safety and trial progress and provide recommendations to the trial management committee (TMC) about continuation and/or modification of the trial. The IDMC consists of a statistician, medical oncologists, and is chaired by a radiation oncologist. The IDMC is provided by the sponsor, AGITG, but is independent of the ASCEND study.

Data monitoring and sharing

Data will be monitored remotely by Clinical Trials operational staff from the National Health and Medical Research Council Clinical Trials Centre (NHMRC CTC) or their delegates. This will include centralised review of CRFs and other study documents for protocol compliance, data accuracy, and completeness.

A clinical study report with summary and interpretation of relevant data will be compiled and provided to the funder, Lisata Therapeutics. A manuscript will be drafted by a writing committee appointed by the AGITG TMC with the intent to submit for publication in a peer-reviewed journal.

The study chairs, TMC along with the relevant NHMRC CTC and AGITG staff will review all requests for data sharing and/or transfer of trial data.

The ASCEND study may be subject to auditing by representatives of institutions such as the NHMRC CTC, Lisata Therapeutics, and regulatory bodies, and as required by law.

Protocol validation

In the phase Ib CEND-1-001 study, LSTA1 was administered in combination with nab-paclitaxel and gemcitabine in participants with previously untreated metastatic PDAC.[12] Escalating doses of single-agent, single-dose LSTA1 were administered initially with safety monitoring. There were no dose-limiting toxicities reported during the study. The overall safety profile was comparable to the published studies of nab-paclitaxel and gemcitabine in metastatic pancreatic cancer.[12] The response rates for participants treated with LSTA1 1.6 mg/kg and LSTA1 3.2 mg/kg in combination with nab-paclitaxel and gemcitabine were 50% and 61.5%, respectively. The disease control rates were 64.3% and 92.3% for participants who received LSTA1 doses of 1.6 mg/kg and 3.2 mg/kg, respectively. 3.2 mg/kg was therefore chosen as the dose for phase II testing. Pharmacokinetic analyses and whole-body imaging in preclinical studies indicate that LSTA1 is highly tumour specific and LSTA1 did not accumulate in healthy tissues. The half-life of LSTA1 in humans was also assessed to be 1-2 h. Hence in the updated protocol, an exploratory cohort examining the effect of two doses of LSTA1 3.2 mg/kg separated by 4 h was added.

CRediT AUTHOR STATEMENT

JL: writing—original draft, writing—review and editing, visualisation; AD: supervision, resources, writing—review and editing; TP: supervision, writing—review and editing; KS: investigation, resources, writing—review and editing, supervision; VG: methodology, writing—review and editing; JM: supervision, project administration, writing—review and editing; FD: supervision, project administration, writing—review and editing; SY: methodology, writing—review and editing; KW: methodology, writing—review and editing; CJ: supervision, project administration, writing—review and editing; SP: supervision, project administration, writing—review and editing; BL: supervision, project administration, writing—review and editing; MB: supervision, project administration, writing—review and editing; DS: writing—review and editing; CK: resources, supervision, project administration, writing—review and editing, LC: writing—review and editing; ZWW: resources, writing—review and editing; RJ: resources, writing—review and editing; CL: resources, writing—review and editing; AF: resources, writing—review and editing; SA: resources, writing—review and editing; JL: resources, writing—review and editing; SW: resources, writing—review and editing; JS: resources, writing—review and editing; MJ: resources, writing—review and editing; NT: resources, writing—review and editing; SG: resources, writing—review and editing; DG: resources, writing—review and editing; CS: resources, writing—review and editing; MH: supervision, resources, writing—review and editing.

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FUNDING

Lisata Therapeutics provided the funding for the trial and LSTA1 drug (no grant number). Lisata Therapeutics led the update of the study design and does not have a role in trial management, data analysis, or interpretation.

DISCLOSURE

CL is employed by South Metropolitan Health Services South Australia, and is the primary investigator for the NAPOLI 3 trial which has received research funding. All other authors have declared no conflicts of interest.

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