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Randomised clinical trial: herbal extract HMPL-004 in active ulcerative colitis – a double-blind comparison with sustained release mesalazine

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SUMMARY

Background
Andrographis paniculata is an herbal mixture used to treat inflammatory diseases. An extract of the herb, HMPL-004, inhibits TNF-α and IL-1β, and prevents colitis in animal models.

Aim
To determine the efficacy and safety of HMPL-004 in patients with mild-to-moderate ulcerative colitis.

Methods
A randomised, double-blind, multicentre, 8-week parallel group study was conducted using HMPL-004 1200 mg/day compared with 4500 mg/day of slow release mesalazine (mesalamine) granules in patients with mild-to-moderately active ulcerative colitis. Disease activity was assessed at baseline and every 2 weeks for clinical response, and at baseline and 8 weeks by colonoscopy.

Results
One hundred and twenty patients at five centres in China were randomised and dosed. Clinical remission and response were seen in 21% and 76% of HMPL-004-treated patients, and 16% and 82% of mesalazine-treated patients. By colonoscopy, remission and response were seen in 28% and 74% of HMPL-004-treated patients and 24% and 71% of mesalazine-treated patients, respectively. There was no significant difference between the two treatment groups.

Conclusion
HMPL-004 may be an efficacious alternative to mesalazine in ulcerative colitis.

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INTRODUCTION

Ulcerative colitis (UC) is an idiopathic chronic inflammatory disease of the colon.[1, 2] The first line therapy for induction and maintenance of remission in patients with UC comprises drugs that contain 5-aminosalicylic acid, including oral and rectal mesalazine (mesalamine), sulfasalazine, balsalazide and olsalazine.[2–4] Approximately 50% of patients with UC are adequately treated with these medications.[5] Patients who fail first line therapy are treated with steroids,[6] azathioprine,[7] and the antitumour necrosis factor alpha (TNFα) agent infliximab.[8] These therapies have risks of infection and malignancy.[9] Novel medical therapies that can be administered orally and that are not immunosuppressive are needed.

Andrographis paniculata (AP) is a member of the plant family Acanthaceae. It has been widely used in Asian countries as well as in Sweden and Chile to treat a variety of inflammatory and infectious diseases, including a phase I study in China in UC.[10] There have been multiple randomised placebo-controlled clinical trials in which the herbal mixture was used to treat upper respiratory tract infections, which have shown statistically significant reductions in intensity and duration of symptoms in subjects treated with the botanical drug.[11, 12] The main known components of AP are diterpene lactones, composed of Andrographolide (AG) and its derivatives. HMPL-004 is an aqueous ethanol extract of the plant.

The purpose of the present pilot study was to determine if HMPL-004 given for 8 weeks at the dose recommended for the dietary supplement could, as does mesalazine, significantly decrease the activity of the disease and produce significant mucosal healing as compared with baseline. A parallel group was treated simultaneously with slow release mesalazine granules at the established therapeutic dose, to ensure that the population tested for response to HMPL-004 was similar to that responding to mesalazine.

MATERIALS AND METHODS

An 8 week randomised, double-blind, parallel-group study was conducted at five sites in Shanghai China between November 2005 and November 2006 in 120 patients, 60 patients/group. The protocol was approved by the institutional review board of each hospital, and the study was conducted with the approval of the State FDA (sFDA) in China. The sites are listed in the Appendix. All patients gave written informed consent. The clinical monitoring followed Good Clinical Practice (GCP) – International Committee on Harmonization (ICH) guidelines, and the study was monitored by Hutchison Medipharma Ltd. employees. Eligible patients were randomised (in a 1:1 ratio) to receive either HMPL-004 (Hutchison Medipharma Ltd., Shanghai, China) 400 mg t.d.s., 1200 mg/day or mesalazine SR Granules (Etiasa, Ethypharm Industries, France, same as Pentasa) 1500 mg t.d.s., 4500 mg/day in a blinded double-dummy fashion. Clinical symptoms were assessed using the Chinese Gastroenterological Association (CGA), 2001[13] Standard for Diagnosis of UC Symptom Score Paradigm (Table 1). Mucosal healing was evaluated by colonoscopy and histopathology by biopsy at baseline and at 8 weeks. Mucosal healing was scored using the CGA colonoscopy paradigm (Table 2) and histopathology was scored using the CGA histopathological paradigm (Table 3). Colonoscopy scores at baseline were compared with those obtained at the completion of the 8-week study.

There were two primary efficacy endpoints, both based on the clinical response. The 'general evaluation' was calculated by the percentage of the reduction of sum scores after completion of study treatment compared with the sum scores at the baseline.

$$\text{Percentage of sum score reduction} = \frac{\text{Sum before treatment - Sum after completion of treatment}}{\text{Sum before treatment}} \times 100\%$$

The 'clinical evaluation' was judged by the percentage of patients attaining remission, partial remission, or improvement at week 8. Remission meant all symptoms disappeared, partial remission meant reduction of 50% of symptoms, and improvement meant more than 25% reduction in symptoms.

Secondary endpoints were based on colonoscopy findings. The first was the percentage of patients showing remission (no inflammation), partial remission (inflammation reduced by two grades) or improvement (inflammation reduced by one grade) in the mucosal appearance, and the second was the percentage of patients who showed histological improvement on biopsy.

The criteria for eligibility included male or female patients, 18–65 years of age, with a diagnosis of mildly to moderately active UC confirmed by colonoscopy within 1 week of study entry. Mild-to-moderately active

Table 1 | Clinical symptom scores (Chinese Gastroenterologic Association, 2001[13])

	Scores			
Symptoms	Grade 0	Grade 1	Grade 2	Grade 3
Fever	≤37 °C	≤38 °C	38–39 °C	≥39 °C
Stool frequency	1–2/day	3/day	4–5/day	≥6/day
Stool property (consistency)	Shaped	Unshaped	Pasty soft	Watery
Stool blood	No	Streak blood	Obvious blood	Frank bleeding
Abdominal pain	No	Mild	Moderate	Severe
Mucous stool	No	Yes	NA	NA
Tenesmus	No	Yes		
Abdominal tension (distension)	No	Yes		

Table 2 | Colonoscopy finding scores[13]

Grade	Findings
0	Normal mucosa
1	Erythema, decreased vascular pattern
2	Marked erythema, oedema, granularity, friability, small ulcers
3	Rough granularity mucosal membrane, spontaneous bleeding, ulcerative lesions, mucosanguineous secretion (bloody mucus)
4	Obvious mucosal crypts, broad mucosal ulcers, large amount of secretion with mucus, blood and pus

UC was defined as chronic persistent or relapsing clinical symptoms of bloody stool, abdominal pain and distension. Patients were excluded from the study if they were pregnant or lactating, had stools positive for bacterial pathogens, renal or hepatic disease, a history of asthma, a bleeding or coagulation disorder, severe UC, or severe complications of UC, Crohn's disease, cancer, a history of allergy or hypersensitivity to aminosalicylates or any component of the HMPL-004 products, if they had received any medication for UC within 1 week of study, including sulfasalazine, mesalazine, steroids, and Chinese herbal medicines, or if they had participated in any clinical study within 3 months. During study participation, patients were prohibited from concomitant medications for UC.

Baseline evaluation included disease history, physical examination, complete blood count (CBC), serum chemistry, urinalysis, C-reactive protein (CRP) and disease assessment with colonoscopy and mucosal biopsy. Clinical symptom scores were assessed every 2 weeks during the 8 weeks of therapy. CBC was performed at 4 and 8 weeks. Colonoscopy with biopsy and CRP measurements were performed at baseline and week 8. Routine laboratory assessments and physical examination were repeated at the end of 8-week study assessment.

Analysis

The data were analysed by Department of Health Statistics, Second Military Medical University, Shanghai, China using SAS software Version 9.1.3 for safety and efficacy. The safety criteria are identical to those used by the United States FDA. The efficacy analysis was prespecified in the Statistical Analysis Plan prior to unblinding the study, and used the criteria specified by the Chinese Gastroenterological Association, 2001 for diagnosis of UC,[13] the Chinese Pharmaceutical and Technological Publishers Clinical Study Guideline for New Drugs,[14] and those used for a recent nationwide Chinese multicentre clinical trial of mesalazine for UC conducted by Fu-Lian.[15]

All analyses were conducted in the intent-to-treat (ITT) population. The ITT population included all patients who were randomised and took one or more doses of study medication. Patients whose treatment outcome was missing due to discontinuation of the study medication were considered not to have clinical, endoscopy or histological efficacy, from the time of the event onward. This was designed as an observational comparison, not as an inferential comparison. Thus, the change from baseline and end of study at week 8 was calculated within each treatment group by paired *t*-test. All statistical tests were two-sided with the significance level at 5%. No corrections for multiple comparisons were made. To allow comparison with the results of clinical trials run in the United States, the results were re-analysed using the Mayo scoring system commonly used in the United States and Europe, in a *post hoc* analysis, and those

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Table 3 | Scoring system of histopathological lesions[13]

Location and observation		Grade 0	1	2	3
Mucosa	Chronic inflammatory cells	None	A few	Middle	Large
	Neutrophils	None	A few	Middle	Large
	Eosinophils	None	A few	Middle	Large
Crypts	Neutrophils infiltrated in epithelium	None	A few	Middle	Large
	Inflammation	No	Yes		
	Abscesses	No	Yes		
	Epithelial hyperplasia	No	Yes		
Loss of goblet cells		No	Yes		
Surface	Erosion	No	Yes		
	Ulcers	No	Yes		
	Granulation tissue/hyperblastosis	No	Yes		

results are posted in the website accompanying this manuscript (Data S1).

The study was a pilot study. It was not powered to demonstrate non-inferiority. However, with the overall rate of clinical efficacy at week 8 of 82% for mesalazine and 76% for HMPL-004, a *post hoc* power calculation was performed to determine if we had a sufficient sample size to decide whether HMPL-004 was not inferior to mesalazine. If we assumed that there was a 5% difference in clinical efficacy rates between mesalazine and HMPL-004 (85% and 75% respectively), and set the non-interiority margin at 10%, then to establish non-inferiority between the two treatments for clinical efficacy at a two-sided upper 95% confidence interval, with 90% power, 1461 per treatment group would have been required. Therefore, non-inferiority was not assessed.

Study drugs

HMPL-004 is an extract of the plant AP harvested from Lijiang, Guangxi province, China. It was obtained from the ethanol/water (90/10 v/v) extracts of the AP leaves by extraction, evaporation, spray drying, homogenising/sieving, and packaging. The growing and harvesting of AP have been standardised in China under the supervision of Hutchison Medipharma, Ltd. A controlled plantation field that is certified by the China sFDA for Good Agricultural Practices is used to ensure the quality and consistency of the herbal raw material. The harvest is determined by plant maturation, which is confirmed by plant examination and testing for the marker compound, Andrographolide (AG) content in the plant specimens. The specific activity of the herbal preparation is set at >6% of a marker compound, AG, meaning that the release criteria required ≥6% AG. The two HMPL-004 lots used in this study contained 8–10% AG by weight. In the future, measurements of a biological marker (for instance demonstration of inhibitions IL-1β) could be included in the release criteria, but were not performed on the material used in the study.

The study material is water-soluble, formulated in single-dose level hard gelatin capsules each containing 200 mg *Andrographis paniculata* extract (APE), which was manufactured under current Good Manufacturing Practices (cGMP). Oral APE or Chuan Xin Lian/ChuanXinLian (CXL) is listed in the Chinese Pharmacopoeia at a recommended dose of 0.63–1.26 g/day. For the APE dietary supplements marketed in the U.S, a daily dose of 600–1200 mg is recommended, and the dose for the present study was 1200 mg/day, the equivalent of 20 mg/kg/day in a 60 kg person. Mesalazine SR granules were provided as 500 mg packets.

Pharmacokinetics

A clinical pharmacokinetics study was conducted in 16 healthy volunteers using Kang Jang tablets, a combination of standard extract of AP with *Eleutherococcus senticosus*. Four tablets of Kang Jang (4 × 5 mg of AG) were administered to each subject.

Andrographis paniculata extract was absorbed quickly into the circulation after oral administration of Kang Jang. The absorption half-life ($T_{1/2}$abs) was about 25 min. The maximal concentration as determined by the marker compound AG in the plasma was reached (T_{max}) at 1.4 h after administering Kang Jang. APE was

eliminated from the circulation with elimination half-lives ranging from 2 to 7 h. AG could no longer be detected in the blood at the eighth hour.[16] This is discussed in further detail in Data S1.

RESULTS

Characteristics and disposition of the patients

One hundred twenty patients were randomised to treatment and dosed (60 in each group). Eight to 18 patients were recruited at each centre, and at each centre, the patients were evenly distributed between the two treatment groups. The baseline characteristics were similar in the two treatment groups (Table 4). Although no other UC medications were allowed during study, about 50% of patients in each group had been on mesalazine at some time before the study, and about half of those had failed to respond satisfactorily to it on at least one occasion. In the group treated with HMPL-004, 20 of the sixty patients were newly diagnosed at the time of study, and 24/60 had suffered 1–4 relapses or flares. In the group treated with mesalazine, 24/60 were newly diagnosed and 21/60 had suffered 1–4 relapses. *Post hoc* analysis revealed that in both groups, there were more responding patients (remission and partial response) who had not received mesalazine previously, about 70%. The mean symptom scores of 6.7 and 6.3 in the two groups would be classified as mild-to-moderate disease. A summary of patient disposition is provided in Table 5. Clinical efficacy, adverse events and serious adverse events for the randomised population was collected at each visit (every 2 weeks); however, seven patients in the HMPL-004 group and five in the mesalazine group were lost to follow-up after randomisation, so the amount of drug taken (if any), and any adverse events experienced by them were not collected. Thus, the ITT population analysed for safety and efficacy in the initial analysis was 108 patients (HMPL-004 $N = 53$, mesalazine $N = 55$).

Table 4 | Baseline characteristics of patients with mildly to moderately active ulcerative colitis

	HMPL-004	Mesalazine
Gender		
Male, *n* (%)	31 (52)	27 (45)
Female, *n* (%)	29 (48)	33 (55)
Race		
Asian, *n* (%)	60 (100)	60 (100)
Mean age (years)	46	44
Disease extent at baseline	Not determined	Not determined
Current smokers, *n* (%)	7 (12)	6 (10)
Previous treatment		
5-Aminosalicylates, *n* (%)	29 (48)	30 (50)
Steroids, *n* (%)	2 (3)	3 (5)
Mean baseline clinical symptom score (points*)	6.7	6.3
Mean baseline colonoscopy findings score (points*)	2.3	2.3
Newly diagnosed	20/60	24/60
History of 1–4 relapses	24/60	21/60
History of 5–40 relapses	9/60	10/60

* Chinese Gastroentologic Association Ratings.[13]

Safety

The exposure duration to study medication was similar in both groups, with patients in the HMPL-004 group dosed for a mean of 54 days and those in the mesalazine group for a mean of 50 days. Thirteen per cent of patients in the HMPL-004 group and 27% of patients in the mesalazine group had at least one adverse event. A majority of adverse events were assessed as mild or moderate in severity and doubtfully related to the study medication. The incidence of the most common adverse events was similar in the two groups (Table 6). Seven patients were withdrawn from the study due to adverse events [2 patients (4%) in the HMPL-004 group and five patients (9%) in the mesalazine group]. Two patients had serious adverse events (4%) in the HMPL-004 group and none in the mesalazine group. The two serious adverse were worsening UC requiring hospitalisation for haematochezia in one patient and pregnancy in one

Table 5 | Patient disposition

	HMPL-004	Mesalazine
Randomised	60	60
Number assessed for safety at week 2 or greater, receiving at least one dose	53	55
Number completing treatment	49	47
Number discontinuing early	11	13
Reason for discontinuation		
Adverse events	2	5
Lack of efficacy	2	3
Lost to follow-up	4	5
Withdrawal of consent	3	0

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Table 6 | Adverse events

	HMPL-004	Mesalazine
Number assessed for safety	53	55
Mean number doses taken	510 packets 340 tablets	482 packets 314 tablets
No. patients with an adverse event	7 (13%)	15 (27%)
No. patients with adverse event related to study medication	2 (3%)	4 (7%)
No. patients with grade 3 adverse event	1	0
No. patients with a serious adverse event	2 (4%)	0
Adverse event leading to early discontinuation of study medication	2 (4%)	5 (9%)
Adverse events occurring in ≥10% in either group by MedDRA preferred term	0	0

patient (subsequently normal birth). No deaths occurred during the study. Table 7 lists the number of patients in each group with each type of adverse events.

Efficacy

Endpoints analysed included percentage reduction in the sum of the clinical symptom scores at weeks 2, 4, 6 and 8 as compared with baseline, and the number of patients having a complete or partial response or improvement at week 8. Additionally, efficacy was measured by comparison of endoscopic change at week 8 as compared with baseline, and histological efficacy at week 8 (Table 8) as compared with baseline.

Table 7 | Number of patients with adverse events

	HMPL-004	Mesalazine
Aphthous ulcer	1	
WBC decrease	1	1
Abdominal pain	1	1
Blood in stool	1	
Fever	1	1
Elevated glucose	1	
Rash	1	
Blood in urine	1	2
Elevated CRP	1	
Dry mouth		1
Oedema lower extremity		1
Cough, upper respiratory infection		2
Diarrhoea		2
Dizziness and nausea		1
WBC elevated in urine		1
Other (increased platelets, total bilirubin, joint pain		3

Symptom scores

As there was no 'carry forward' for missing data points, the number of patients evaluated at each time point for reduction of clinical symptom scores and clinical efficacy decreased from 53 and 55 (HMPL-004, mesalazine) at week 2, to 49 and 50 at week 8. Reduction in the mean clinical symptom scores for both treatment arms began as early as week 2, and reached values of 56% and 59% for HMPL-004 and mesalazine respectively by week 8 (Figure 1). The efficacy of the two treatments was not different in either group for reduction of clinical symptom scores from baseline at any time point.

Clinical efficacy

At week 8, 21% of patients treated with HMPL-004, and 16% of patients treated with mesalazine were in remission. An additional cohort of 36% in both groups was classified as being in partial remission. The overall efficacy evaluation includes all patients who had more than a 25% reduction in symptoms, and was 76% and 82% in each of the two groups respectively (Table 8). As compared with baseline, this was $P < 0.001$ for both groups.

Endoscopy and histology

The colonoscopy evaluation at week 8 was performed on 49 patients in the HMPL-004 group and 44 patients in the mesalazine group. In the group treated with HMPL-004, 15/53 (28% of patients in the ITT population) were in remission, meaning that no inflammation was present (mucosal healing), and in the mesalazine-treated group, 13/55 (24%) were in remission. Partial remission, meaning that the mucosal abnormalities had decreased by at least two grades, was seen in 19% and 18% of the patients in the two groups. The endoscopy efficacy rate in each group (complete or partial remission or improvement) was 74% and 71% respectively (Table 8). From a logistic regression, the covariant of centre effect was non-significant in colonoscopy score outcome, odds ratio 0.996 (0.97–1.03).

The histological efficacy assessment was restricted by the small number of patients in the two treatment groups who had pre- and post-treatment biopsies, (HMPL-004 $n = 19$; mesalazine $n = 15$). However, of the

Table 8 | Efficacy analysis, ITT population

Variable	HMPL-004	Mesalazine
Clinical efficacy at week 8	*N* = 53	*N* = 55
Remission	21% (11/53)	16% (9/55)
Partial remission	36% (19/53)	36% (20/55)
Improvement	19% (10/53)	29% (16/55)
No improvement or worsening	17% (9/53)	9% (5/55)
Missing	8% (4/53)	9% (5/55)
Overall efficacy (remission + partial remission + improvement)	76% (40/53)*	82% (45/55)*
Colonoscopy (Endoscopy) efficacy at week 8		
Remission	28% (15/53)	24% (13/55)
Partial remission	19% (10/53)	18% (10/55)
Improvement	26% (14/53)	29% (16/55)
No improvement or worsening	19% (10/53)	9% (5/55)
Missing	8% (4/53)	20% (11/55)
Overall efficacy (remission + partial remission + improvement)	74% (39/53)*	71% (39/55)*
Histological efficacy at week 8	*N* = 19	*N* = 15
Remission	0 (0%)	0 (0%)
Partial remission	0 (0%)	0 (0%)
Improvement	53% (10/19)*	40% (6/15)*
No improvement or worsening	47% (9/19)	60% (9/15)

* $P < 0.001$ at week 8 as compared with baseline. No significant difference in any parameter between the two treatment groups.

Criteria specified by CGA 2001,[13] Chinese Pharmaceutical and technological Publishers Clinical Study Guideline for New Drugs[14] and Fu-Lian.[15]

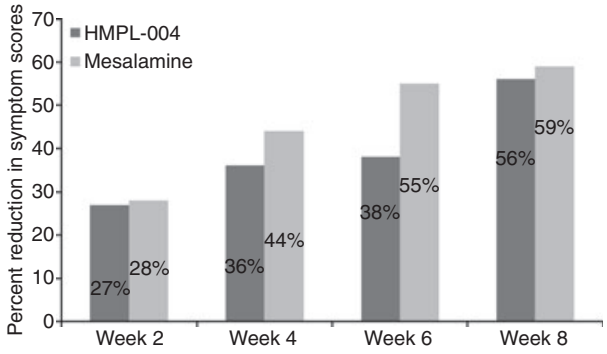

Figure 1 | General evaluation: Decrease in Symptom Scores with Time. Use of symptom scores to assess the time to response. The mean symptom score at baseline is subtracted from the score at each time point, and divided by the baseline score). The efficacy of the two treatments was not different in either group for reduction in clinical symptom scores at any time point, but paired *t*-test indicated $P < 0.001$ between baseline and week 8 score for both treated groups.

patients with biopsies available, 53% in the HMPL-004 group and 40% in the mesalazine group had a decrease in the degree of inflammation by at least 25% at week 8 of treatment. Of the patients who entered the study with CRP concentrations above the upper limit of the normal range, 12/15 patients (80%) in the HMPL-004 group, and 4/6 patients (66%) in the mesalazine group experienced normalisation of their CRP concentrations at week 8. In the HMPL-004 group, the mean CRP concentration decreased from 22 mg/dL at baseline to 7 mg/dL at week 8, and in the mesalazine group, the mean CRP concentration decreased from 25 mg/dL at baseline to 7 mg/dL at week 8 (*P* value <0.0001 for both comparisons).

DISCUSSION

When efficacy was measured by a decrease in symptom scores, number of patients achieving remission or partial remission, or by mucosal healing or improvement in

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inflammation seen by colonoscopy as defined by the Chinese Gastroenterological Association, patients' response to HMPL-004 and mesalazine was similar. Both drugs significantly improved the clinical severity of UC and eliminated inflammation assessed by colonoscopy in about 25% of patients. The distribution between the percentage of patients with remission, partial remission, or improvement was not different between patients treated with HMPL-004 or mesalazine in either clinical efficacy or by colonoscopy evaluation. These data suggest that HMPL-004 could serve either as a substitute for induction therapy with mesalazine, or be successfully used as induction therapy in those patients with a suboptimal response to mesalazine. It should be acknowledged that these data cannot be extrapolated to use of maintenance therapy with HMPL-004.

The adverse reactions observed with HMPL-004 were rare and were limited to allergic reactions such as urticaria. This study replicated the safety profile seen in other studies, with most of the adverse events related to the underlying disease. Rash was noted in one patient treated with HMPL-004. The worldwide safety data on HMPL-004 are extensive. Oral APE or Chuan Xin Lian/ChuanXinLian (CXL) was first listed in the Chinese Pharmacopoeia in 1977. The recommended dosage was 1500–2100 mg/day. Of the many published studies, the most readily accessible publications to the English speaking population are those reporting results of randomised controlled trials in upper respiratory tract infections.[11, 12]

In conclusion, in this Phase II study, HMPL-004 had efficacy similar to slow release mesalazine and was well tolerated in patients with mildly to moderately active UC.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. *Post hoc* analysis of efficacy data using Mayo Scoring System.

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APPENDIX

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