Background:

- Sarilumab (Kevzara®) is an interleukin-6 antagonist approved for the treatment of rheumatoid arthritis. Due to similarities in the clinical presentation of CAR-T cytokine release syndrome and the hyperinflammatory state of severe COVID-19, interest in tocilizumab and other IL-6 antagonists (sarilumab) for severe COVID-19 developed early in the pandemic. Sarilumab has been studied less extensively compared to tocilizumab with only a few case series and prospective observational cohorts, and randomized controlled trials published to date. While both drugs are IL-6 receptor antagonists, there may be differences between tocilizumab and sarilumab in receptor binding or lung concentrations.
- Although preliminary studies suggest the use of sarilumab is safe, literature to date has yet to establish clinical efficacy in patients with severe or critical COVID-19. Additional data from randomized controlled trials in adults are lacking.

Data Summary:

- Randomized Controlled Trials:
  - To date, there is only one large, randomized, placebo-controlled trial investigating sarilumab against severe or critical COVID-19 which failed to improve outcomes in patients requiring respiratory support (i.e. supplemental oxygen, high flow nasal cannula, invasive or non-invasive mechanical ventilation). These findings are inconsistent with the REMAP-CAP trial where survival benefit was observed among 48 critically ill patients treated with sarilumab.
  - Sarilumab is currently under investigation in 4 clinical trials to address the potential benefit of early treatment in mild-to-moderate COVID-19 patients as well as those with severe or critical disease. Two clinical trials have been terminated early due to change in clinical conditions, recruitment issues, and futility. Results of 3 completed randomized controlled trials of sarilumab have not been made available raising the concern for publication bias.

- Systematic Review and Meta-Analysis:
  - Although an overall survival benefit was seen with tocilizumab in the large WHO-REACT meta-analysis, statistical significance was not observed in severe or critically ill patients treated with sarilumab, regardless of level of respiratory support at baseline or glucocorticoid use.
  - No conclusions can be made from other published meta-analyses since few sarilumab-treated patients were included. Overall, there is insufficient evidence for the efficacy of other IL-6 antagonists (i.e. siltuximab or sarilumab) in COVID-19.

- Prospective Observational Cohorts:
  - Preliminary data from one small prospective study suggested sarilumab may lead to positive clinical outcomes including mortality in patients with severe COVID-19. However, a subsequent prospective open-label study failed to observe overall clinical improvement and mortality in severe COVID-19.

- Ongoing Clinical Trials:

<table>
<thead>
<tr>
<th>STUDY</th>
<th>SAMPLE SIZE (estimated)</th>
<th>STUDY DESIGN/STATUS</th>
<th>INCLUSION</th>
<th>TREATMENT VS COMPARATOR</th>
<th>PRIMARY OUTCOME</th>
</tr>
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<tbody>
<tr>
<td>NCT04399801</td>
<td>50</td>
<td>Phase 2, randomized, open label</td>
<td>Active, not recruiting</td>
<td>Adults ≥18 years with confirmed COVID-19 and O2 SAT ≤ 94% with or without supplemental oxygen, or requiring ≥ 2L oxygen to maintain O2 Sat &gt; 94%</td>
<td>Sarilumab 400 mg SUBQ x1 plus SOC vs SOC alone</td>
</tr>
<tr>
<td>NCT04260733</td>
<td>229</td>
<td>Phase 2/3, Bayesian, randomized, open-label</td>
<td>Active, not recruiting</td>
<td>Adults ≥18 years with moderate COVID-19 (non-ICU level care) and severe COVID-19 requiring ICU admission</td>
<td>Sarilumab 400 mg IV as 1-hour infusion vs SOC</td>
</tr>
<tr>
<td>NCT04260629</td>
<td>40</td>
<td>Phase 1, open-label, single group</td>
<td>Recruiting</td>
<td>Adults ≥18 years with confirmed COVID-19 and worsening of respiratory function (VM ≥ 8L/min) and D-Dimer &gt; 1500 ng/ml</td>
<td>Sarilumab in combination with chloroquine 500 mg PO BID or hydroxychloroquine 400 mg BID, followed by 200 mg PO BID</td>
</tr>
<tr>
<td>NCT04061527</td>
<td>60</td>
<td>Phase 2, open-label, dose-escalation</td>
<td>Recruiting</td>
<td>Adults ≥18 years with severe COVID-19</td>
<td>Sarilumab 200 mg IV day 1; 200 mg Q24h x2 doses (n=6). If tolerated, remaining patients will receive 400 mg IV once followed by 200 mg 24 hours later</td>
</tr>
</tbody>
</table>

Guideline Recommendations:

- **WHO:** We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe or critical COVID-19 infection. Corticosteroids have previously been strongly recommended in patients with severe and critical COVID-19, and we recommend patients meeting these severity criteria now receive both corticosteroids and IL-6 receptor blockers (Last updated July 6, 2021).
- **NIH guidelines:** Use as an alternative if tocilizumab is not available or not feasible to use (BII). (Last updated August 25, 2021).
  - **Rationale:** Even though the REMAP-CAP trial supports that sarilumab and tocilizumab have similar efficacy in the treatment of hospitalized patients with COVID-19, the Panel recommends sarilumab only when tocilizumab is not available or is not feasible to use (BII).
  - The evidence for the efficacy of tocilizumab is more extensive than that for sarilumab, and currently, sarilumab is only approved as a subcutaneous (SQ) injection in the United States.
  - The guidelines recommend IV sarilumab, in addition to corticosteroids, for patients who are recently hospitalized (i.e., within 3 days of hospital admission) with elevated markers of inflammation and rapidly increasing oxygen needs requiring invasive mechanical ventilation or high-flow oxygen or for hospitalized patients within 24 hours of ICU admission who require invasive mechanical ventilation or ECMO.
- **NICE guidelines:** Consider sarilumab for adults in hospital with COVID-19 only if tocilizumab cannot be used or is unavailable. The recommended dosage for sarilumab is a single dose of 400 mg by intravenous infusion. Use the same eligibility criteria as those for tocilizumab (Last updated August 10, 2021):
  - They have or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids, have not had another interleukin-6 inhibitor during this admission, and there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by sarilumab AND
  - Need supplemental oxygen and have a C-reactive protein level of 75 mg/L or more OR are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.

Recommendations:

- At this time, there is insufficient evidence to support the use of sarilumab (SUBQ or IV) as a treatment option for COVID-19 outside of clinical trials. Use in COVID-19 is NOT recommended by the Sutter Health COVID-19 Clinical Advisory Group.
- Given recent guideline support, it is reasonable to consider sarilumab in patients who meet tocilizumab criteria and restrictions previously outlined in Sutter Health Tocilizumab Guidance, if tocilizumab and baricitinib become completely unavailable.
- In addition, Sarilumab is currently only FDA approved for the subcutaneous route and compatibility, storage, and stability data of premixed syringes used to compound infusions intended for intravenous administration is lacking.
### Study Design

**Lesure, Mar 2021**

- Global, multicenter, randomized, double-blind, placebo-controlled trial among 416 hospitalized adults requiring oxygen supplementation or ICU care across 45 hospitals in Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russia, and Spain between March 28 and July 3, 2020.
- Randomized to sarilumab 200 mg IV (n=159); sarilumab 400 mg IV (n=173) or placebo (n=84).
- A second dose could be administered within 24-48 hours of the first dose at the discretion of the attending physician.

**Gordon, January 2021 (REMAP-CAP)**

- Open-label, randomized, adaptive trial of 803 adult ICU patients.
- Randomized to tocilizumab (n=353; 8 mg/kg, max 800 mg) or sarilumab (n=48; 400 mg IV once) in NS 100 ml infused over 1 hour or standard of care (n=402).
- A second dose of tocilizumab could be given 12-24 hours at discretion of physician (29%).

### Results

#### Primary outcome: No statistically significant difference

- No difference in time to improvement of two or more points on a seven-point clinical assessment scale was observed in sarilumab 200 mg or 400 mg dose groups compared to placebo (p-values = 0.96 and 0.34, respectively).
- No differences were observed in progression over time between patients with severe and critical disease.

#### Secondary outcome: No statistically significant differences

- No significant differences were observed in the overall proportions of patients alive at day 29 (200 mg: 90% (143/159); 400 mg: 92% (n=159/173), PBO: 92% (77/84)) or between patients with severe and critical disease.
- Authors report a trend toward 9% improvement in survival was seen in patients who received non-invasive or invasive mechanical ventilation or ECMO at baseline but was not statistically significant (8.3%, [95% CI: -7.7-25.5]; p=0.25). Confidence interval was wide indicating low certainty of evidence.
- No significant differences were seen in either dose group compared to placebo other secondary endpoints in the intent-to-treat analysis including:
  - Patients alive at 60 days
  - Time to resolution of fever and/or improvement in oxygenation
  - Patients alive off supplemental oxygen at day 29
  - Ventilator-free days at day 28
  - Patients in need of ICU care
  - Hospital length of stay
  - Patients discharged due to recovery

#### Serious Adverse effects:

- Rates of invasive bacterial or fungal infection, LFT elevation, grade ≥2 hypersensitivity or infusion reaction, and grade 4 neutropenia were numerically higher in the high dose sarilumab group but not significantly different between groups.
- Overall, 11% (44/416) of patients died due to a treatment-emergent adverse event, with similar rates between treatment groups (placebo [11%]; sarilumab 200 mg [11%], sarilumab 400 mg [10%]).

### Conclusions

- Sarilumab 200 mg or 400 mg was not associated with improved clinical outcomes or survival in severe or critically ill adults with COVID-19 compared to placebo.
- No new safety signals for sarilumab were observed in these patients with COVID-19.
- Study limitations:
  - Ordinal clinical status scale based on intensity of respiratory support may not be sufficient to measure treatment effects.
  - Variable geographic location, areas of pandemic surge, viral mutations, and usual care across study sites.
  - Glucocorticoids not yet standard of care and administered concomitantly in less than 50% of patients.
  - Possible unmeasured confounding variables.

<table>
<thead>
<tr>
<th>Study</th>
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<tbody>
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<td>Lesure, Mar 2021</td>
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<td>Primary outcome: No statistically significant difference  - No difference in time to improvement of two or more points on a seven-point clinical assessment scale was observed in sarilumab 200 mg or 400 mg dose groups compared to placebo (p-values = 0.96 and 0.34, respectively).  - No differences were observed in progression over time between patients with severe and critical disease. Secondary outcome: No statistically significant differences  - No significant differences were observed in the overall proportions of patients alive at day 29 (200 mg: 90% (143/159); 400 mg: 92% (n=159/173), PBO: 92% (77/84)) or between patients with severe and critical disease.  - Authors report a trend toward 9% improvement in survival was seen in patients who received non-invasive or invasive mechanical ventilation or ECMO at baseline but was not statistically significant (8.3%, [95% CI: -7.7-25.5]; p=0.25). Confidence interval was wide indicating low certainty of evidence.  - No significant differences were seen in either dose group compared to placebo other secondary endpoints in the intent-to-treat analysis including:  - Patients alive at 60 days  - Time to resolution of fever and/or improvement in oxygenation  - Patients alive off supplemental oxygen at day 29  - Ventilator-free days at day 28  - Patients in need of ICU care  - Hospital length of stay  - Patients discharged due to recovery.</td>
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<td>Primary outcome: Respiratory and cardiovascular support-free days up to day 21  - Median organ-support free days with sarilumab (11 [0-16]; OR 1.76; [95% CI: 1.17-2.91]) compared to control (0; IQR 1-15). Probability of superiority over control 99.5%.  - Hospital mortality was lower for sarilumab compared to control (22.2% (10/45) vs 35.8% (142/397); aOR 2.01; [95% CI: 1.18-4.71]).  - Treatment effect was greater with corticosteroids vs. any intervention alone. Secondary outcome:  - 90 Day Survival: sarilumab (1.82; [95% CI: 1.22-3.38]), Control 1.</td>
<td>In critically ill COVID-19 adult patients requiring respiratory or cardiovascular support, treatment with sarilumab improved clinical outcomes, including survival. Similar effects were seen in all CRP subgroups. Greatest benefit seen using both IL-6 receptor antagonists.</td>
</tr>
</tbody>
</table>
### Study Design and Results

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<tbody>
<tr>
<td>Included</td>
<td>Critically ill adults ≥18 years admitted to the ICU with suspected or confirmed COVID</td>
<td></td>
<td>and corticosteroids in critically ill population (vs. monotherapy)</td>
</tr>
</tbody>
</table>
| | Respiratory or cardiovascular support
| | Exclusion
| | Presumption of imminent death
| | Prior participation in REMAP-CAP within 90 days
| | Admitted to ICU >24 hours earlier
| | Known immune suppression
| | Enrolled in another trial
<p>| | Additional exclusion criteria specific to immune modulation therapy |
| | Time to ICU Discharge: sarilumab (95% CI: 1.64; [1.24-2.19]), Control 1 (OR 1.00; [0.74-1.35]) |
| | Time to Hospital Discharge: sarilumab (95% CI: 1.60; [1.17-2.40]), Control 1 (OR 1.00; [0.76-1.32]) |
| Serious Adverse effects: | | | |
| | Sarilumab (n=0) |
| Patient selection: | Mean age 63.4, male (81%), white (74%), median BMI 29.2, median APACHE II 10 |
| | All patients received respiratory support (high-flow oxygen, non-invasive (35%), non-invasive mechanical ventilation (17%); 8 patients received vasopressors |
| | Median Time to enrollment from hospital admission (1.4 days), from ICU admission (16 hours) |
| | Median CRP 136 mcg/ml (105-204), D-Dimer 828 ng/ml, PaO2/FiO2 126 mmHg (99-157) |
| | Analyses of 27 randomized controlled trials encompassing 10,930 patients treated with tocilizumab between February 26, 2020 and January 14, 2021. Nine studies were published and the remaining 18 were unpublished or reported as pre-prints |
| | IL-6 antagonists assessed: tocilizumab (19 trials; n=8048), sarilumab (9 trials; n=2826), siltuximab (1 trial; n=149) |
| | Risk of bias was assessed to be low in 22 of the trials |
| Sarilumab studies assessed: | [95% CI: 0.86-1.36] p=0.25; (I^2=0%) |
| | No difference in mortality was seen for those not receiving corticosteroids at baseline (OR 1.18; [95% CI: 0.88-1.58]) compared to patients receiving corticosteroids at randomization (OR 0.92; [95% CI: 0.61-1.38]) |
| | No statistical difference was seen for patients receiving oxygen flow rates ≤ 15 L/min (OR 0.96; [95% CI: 0.60-1.35]), noninvasive ventilation (OR 1.20; [95% CI: 0.78-1.84]), IMV or ECMO at baseline (OR 1.05; [95% CI: 0.74-1.50]) |
| | No statistical difference was seen for patients receiving cardiovascular support at baseline (OR 0.14; [95% CI: 0.00-5.95]) |
| | Age, sex, and baseline CRP also did not affect outcome |
| Primary outcome: No statistically significant difference | | | |
| | Unlike tocilizumab, sarilumab was NOT associated with lower 28-day mortality (26% vs 25%; OR 1.08; [95% CI: 0.86-1.38]) |
| | No heterogeneity was observed among studies for any clinical or safety outcome |
| Secondary outcome: No statistically significant difference | | | |
| | Unlike tocilizumab, among patients not requiring IMV at randomization (24 trials), sarilumab was NOT associated with reduced progression to IMV or ECMO or death (OR 1.00; [95% CI: 0.74-1.35]; (I^2=0%)) |
| | No significant difference was seen among patients receiving corticosteroids, cardiovascular support, lower oxygen rates, noninvasive ventilation, or invasive ventilation or ECMO at baseline |
| | Age, sex, and baseline CRP also did not affect outcome |
| Adverse events: No statistically significant difference | | | |
| | No difference in secondary infection (OR 1.03; [95% CI: 0.80-1.32]; (I^2=0%)) or adverse events compared to usual care or placebo were observed |
| Systematic Review and Meta-Analyses | | | |
| WHO (REACT Work Group), July 2021 | | | |
| LOE 1b, n = 10,930 | | | |
| (sarilumab n = 2826) | | | |
| Global, prospective meta-analysis of 27 randomized controlled trials encompassing 10,930 patients treated with tocilizumab between February 26, 2020 and January 14, 2021. Nine studies were published and the remaining 18 were unpublished or reported as pre-prints |
| Concomitant glucocorticoids (sarilumab 35%; (890/3136); tocilizumab 66% [5317/8134]), IMV (sarilumab 31% [873/3136]; tocilizumab 15% (1211/8134)), oxygen flow rate ≤ 15 L/min (sarilumab 43% [1214/2826]; tocilizumab 40% [3223/8050]), anticoagulants (sarilumab 9% (266/2826); tocilizumab 46% [3860/8050]) | | | |
| FMCP Team September 2021 | | |</p>
<table>
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<th>Study</th>
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| Pinzon, June 2021 | LOE 1b, n = 3303 (sarilumab n = 28) | Systematic review and meta-analysis of 18 non-randomized studies encompassing 3303 patients (sarilumab = 1 prospective cohort) | **Efficacy outcomes:**  
- Pooled analysis of IL-6 inhibitors revealed a lower risk of mortality (22.35% vs 37.72%; RR = 0.61, [95% CI: 0.49–0.76]; p<0.00001; I²=58%). In the prospective study, sarilumab treatment group had a longer median time to death than the control group (19 days [IQR 13–26] vs 4 days [IQR 3–4]; p = 0.006). But no mortality reduction was observed (p=0.42)  
- Pooled data showed similar risk of mechanical ventilation between IL-6 inhibitors and control (14.75% vs 19.55%; RR = 0.68, [95% CI: 0.32–1.45]; I²=5%) | **Confidence intervals of some outcomes were wide making certainty of evidence low** |
| Khan, Jan 2021 | LOE 1b, n = 22,058 (sarilumab = 389) | Qualitative synthesis of 71 studies evaluating all immunomodulators in COVID-19 patients (sarilumab = 4 prospective and 1 adaptive RCT). Quantitative synthesis of 57 studies Overall, studies were primarily retrospective (n=42), followed by non-randomized prospective studies (n=23), and 6 randomized controlled trials. Quality of studies included were primarily fair (52%) or good (32%), 15% were poor | **Efficacy outcomes:**  
- Sarilumab was associated with increased survival from the only RCT (REMAP-CAP), reduced hospitalization and improved ordinal outcomes  
- However, in a prospective, non-randomized study, significance was not observed with respect to mortality and ordinal outcomes  
- The combined case fatality rates across the five included studies was 11% (43/389) for sarilumab, while in the only study reporting control mortality data the CFR was 35.8% (142/397) | **There is insufficient evidence to demonstrate efficacy of sarilumab in COVID-19** |
| Gremise, June 2020 | LOE 3, n = 53 | Single-center, prospective, non-randomized, observational study of 53 hospitalized adults with severe COVID-19 treated with sarilumab in an Italian hospital between March 23 and April 4th, 2020  
Protocol recommended sarilumab 400 mg IV (n=53). A second dose of sarilumab could be given at discretion of physician (n=26; 13 non-ICU, 13 ICU)  
Included  
- Hospitalized adults ≥18 years with confirmed COVID  
- Interstitial pneumonia on CXR or CT AND PaO2/FiO2 < 300 and rapid worsening of respiratory condition or need for ICU admission  
Exclusion  
- Septic state  
- ANC < 1500 or AST/ALT > 5 x ULN  
- Diverticulitis/diverticulosis  
- Pregnancy | **Clinical outcome:**  
- Overall mortality rate was 5.7% after sarilumab administration (Medical ward n=1 (2.5%); ICU n=2 (14.2%))  
- At 19 days median follow-up, 89.7% of medical inpatients significantly improved (46.1% after 24 h, 61.5% after 3 days), 70.6% were discharged from the hospital and 85.7% no longer needed oxygen therapy  
- Among ICU patients, 64.2% were discharged from ICU to the ward and 35.8% were still alive at the last follow-up  
**Serious Adverse effects:**  
- No serious adverse effects or secondary bacterial infections were observed during the follow-up period. Mild neutropenia was noted in 2 patients after the first dose of sarilumab  
Patient selection:  
- Median age (66 years), male (88%), overweight/obese (62.3%), comorbidities (64.2%)  
- All patients received lopinavir/ritonavir or darunavir/ritonavir, hydroxychloroquine, azithromycin, and heparin/subQ for VTE prophylaxis. If admitted to ICU, intensivist may use corticosteroids  
- Most patients were treated on medical wards (n=39) and 14 required ICU admission (4 required intubation) at baseline. Of those treated on medical ward, 7 (17.9%) progressed requiring ICU admission, of whom 4 (57.1%) were readmitted to the ward after 5-8 days, and 2 died in the ICU  
- Patients treated in the ICU were significantly older (75 vs 64 years; p=0.01) and had lower PaO2/FiO2 ratios (101 (89-141) vs 167.5 (125.4-226.5); p=0.007) | Sarilumab may improve clinical outcomes in patients with severe COVID-19 without safety concerns |
| Della Torre, June 2020 | LOE 3, n = 56 | Single-center, prospective, open-label, observational study of 56 hospitalized adults with severe COVID-19 treated with sarilumab in an Italian hospital between March 2nd and April 14th, 2020  
**Clinical outcome:**  
- At day 28 of follow-up, 60% of patients treated with sarilumab experienced clinical improvement compared to 64% of controls (p=0.99). Time to clinical improvement was not different (18 vs 19 days; p=0.89)  
- No difference in mortality was observed between groups (7% vs 18%; p=0.42)  
**Safety outcomes:**  
- Not analyzed | **Although sarilumab was associated with faster recovery in those with minor lung consolidation, overall clinical improvement and mortality in non-mechanically ventilated patients was not significantly different** |
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<tbody>
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<td>Protocol recommended sarilumab 400 mg IV (n=28) in 100 ml NS infused over 1 hour plus SOC vs SOC alone (n=28)</td>
<td>Included ▪ Hospitalized adults ≥18 years with confirmed COVID Bilateral pneumonia on CXR or CT ▪ O2SAT ≤ 92% on RA or PaO2/FIO2 &lt; 300 on supplemental oxygen AND elevated LDH plus at least one of the following: CRP ≥ 100 mg/L, IL-6 ≥ 40 pg/mL, or ferritin ≥ 900 ng/mL Exclusion ▪ Hospitalization &gt; 14 days ▪ Mechanical ventilation ▪ Concomitant/previous immunosuppressants ▪ Uncontrolled systemic infection ▪ Diverticulitis/diverticulosis ▪ ANC &lt; 1500, AST/ALT &gt; 5x ULN ▪ Pregnancy</td>
<td>• Median time to death was shorter in patients treated with sarilumab (19 vs 4 days; p=0.006) ▪ No difference in mechanical ventilation (21% vs 25%; p=0.99) or time to mechanical ventilation (5 vs 3 days; p=0.52) were observed ▪ Median time to clinical improvement in patients with minor lung consolidation was shorter in sarilumab treated patients (10 vs 24 days; p=0.01) ▪ Time to discharge and number of patients alive at discharge were not different</td>
<td>Ventilated patients with severe COVID-19 was not different compared to controls ▪ Small, single-center, non-randomized study ▪ Use of glucocorticoids not yet standard of care ▪ Comparator group tended to have higher PaO2/FIO2 levels at baseline compared to those treated with sarilumab ▪ Patients who responded to sarilumab had less severe lung consolidation on imaging and PaO2/FIO2 levels &gt; 100 ▪ Results not generalizable to patients who require MV at baseline</td>
</tr>
</tbody>
</table>

### References

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