International Journal of Research in Dermatology
*Bigge S et al. Int J Res Dermatol. 2026 Nov;12(6):688-695*
https://www.ijord.com

DOI: https://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20263681

**Review Article**

# Evidence and a proposed algorithm for periprocedural treatment sequencing in melasma

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**Received:** 10 September 2026
**Accepted:** 25 September 2026

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## ABSTRACT

Melasma treatment often combines photoprotection, topical depigmenting agents, oral tranexamic acid and procedures. Evidence for individual treatments is more developed than evidence for their order, spacing and periprocedural care. This narrative review examines the clinical literature relevant to a proposed sequence of tinted photoprotection, azelaic acid, and selected use of oral tranexamic acid, intradermal NCTF 135 HA and fractional 1064-nm picosecond laser. An existing reference collection was supplemented by targeted searches and source verification. Randomized trials support several medical components, whereas laser studies differ substantially in wavelength, optics and treatment schedules. A split-face trial found no additional clinical benefit from adding 755-nm picosecond laser to azelaic acid. Small studies of hyaluronic acid formulations use different products and delivery schedules, and do not establish the proposed pre-laser interval. We specify a candidate protocol, including a six-week medical lead-in, intradermal treatment fourteen days before laser, temporary interruption of azelaic acid and continued maintenance. The exact timing, laser settings and aftercare choices are identified as proposals for evaluation. No original patient observations or clinical outcomes are reported. The principal research questions are whether procedures add worthwhile benefit to medical treatment, whether intradermal NCTF adds further benefit, and whether any improvement persists after oral treatment stops. Controlled evaluation with standardized photographs, severity scores and complete adverse-event reporting is needed before the full sequence can be recommended as an established regimen.

**Keywords:** Melasma, Azelaic acid, Tranexamic acid, Picosecond laser, Hyaluronic acid, Photoprotection

## INTRODUCTION

Melasma frequently recurs despite an initial response to treatment. Its biology includes altered melanocyte activity, photoaging-associated dermal changes and hormonal and environmental influences. These features help explain why pigment clearance and durable disease control are different outcomes.[1–3] Photoprotection and topical treatment remain central to management; procedures require particular care when inflammation could worsen pigmentation.[4]

In combination treatment, the practical question is often when to introduce or interrupt a component. A clinician may wish to establish topical tolerance before laser, separate injections from energy delivery, or continue maintenance after oral treatment ends. Each decision has a rationale, but a plausible rationale does not establish an optimal interval. Adding a procedure also introduces cost, discomfort and pigmentary risk.[4]

We review the evidence relevant to a specified sequence of medical treatment, intradermal NCTF 135 HA and

fractional 1064-nm picosecond laser. The aim is to identify which decisions are supported directly and which require testing. A previous review by Bigge addressed low-dose oral tranexamic acid and thromboembolic risk assessment.[5] The present article concentrates on treatment sequencing, the additional value of procedures and the limits of transferring results between devices and injection methods.

## REVIEW APPROACH

This focused narrative review used an author-supplied collection of melasma publications, supplemented by targeted searches for PubMed-indexed reports and checks of publisher and manufacturer sources on 12 September 2026. Searches combined melasma with picosecond laser, hyaluronic acid or NCTF, azelaic acid, oral tranexamic acid and thromboembolism, or tinted photoprotection and iron oxide. Exact article titles and digital object identifiers were also checked. Manufacturer material was used to identify devices and delivery routes, not to establish clinical efficacy.

The present study prioritized randomized and comparative studies, systematic reviews and consensus reports relevant to the proposed components. Small uncontrolled reports were retained where direct combination evidence was sparse. Interpretation considered sample size, comparator, wavelength, optics, formulation, administration route, timing, follow-up and consistency of reporting. Findings from other laser indications or skin-quality studies were treated as indirect evidence. No quantitative pooling or formal certainty grading was performed. The search was selective and was not designed to produce a complete systematic-review study count. Table 1 summarizes the evidence most directly affecting sequencing decisions.

**Table 1: Evidence relevant to sequencing decisions.**

| Evidence | Main observation | Implication for the proposed sequence |
|---|---|---|
| **Photoprotection trials** | Visible-light protection improved selected outcomes; a later trial found no between-group mMASI difference.[8,9] | Supports sustained photoprotection; does not establish every tinted product as equivalent. |
| **Azelaic acid with or without laser** | In a 30-participant split-face trial, adding 755-nm laser did not improve clinical mMASI; four participants developed post-inflammatory hyperpigmentation.[12] | Reassess the medical response before adding a procedure. |
| **Fractional 1064-nm laser** | Small comparative and prospective studies used different optics and schedules.[20–22] | Does not determine the proposed two-session schedule or 225/250/275-mJ progression. |
| **NCTF with 755-nm laser** | Small randomized report used post-laser micropapular NCTF; recurrence significance is inconsistently reported.[27] | Does not establish benefit from pre-laser U225 delivery. |
| **Other hyaluronate combinations** | Uncontrolled 30-patient series used another product injected two weeks after laser.[28] | Product, route, ordering and incremental effect require separate evaluation. |
| **Postprocedural prevention** | Corticosteroid and cooling evidence comes from heterogeneous device settings.[33,34] | Does not establish the proposed methylprednisolone aceponate regimen or omission of cooling. |

Evidence is summarized qualitatively; these categories are not formal certainty grades. mMASI, modified Melasma Area and Severity Index; NCTF, NCTF 135 HA. Sources are cited within the table.

## ESTABLISHING MEDICAL TREATMENT BEFORE PROCEDURES

### *Photoprotection from the outset*

Broad-spectrum ultraviolet protection and protection against visible light address continuing exposure throughout treatment and maintenance. Iron oxides can provide visible-light attenuation that is not captured by the sun protection factor (SPF) alone.[6,7] In a randomized trial of 68 patients receiving hydroquinone, sunscreen with ultraviolet and visible-light protection produced greater improvement than ultraviolet-only sunscreen over eight weeks; 61 patients completed follow-up.[8]

The effect depends on the endpoint and formulation. In a later randomized study of 42 participants, both tinted and untinted sunscreens improved modified Melasma Area and Severity Index (mMASI) scores, without a significant difference between groups. Tinted sunscreen provided additional benefit in measures of color uniformity.[9] Thus, the proposal specifies daily tinted iron-oxide-containing SPF 50+ with adequate ultraviolet A protection, alongside reapplication and exposure reduction. It does

not assume that all tinted products perform identically or that sunscreen alone eliminates recurrence.

### *Azelaic acid and the decision to add laser*

Azelaic acid 20% is a topical option when sustained treatment is desired. Reviews support improvement in melasma, although comparisons with hydroquinone vary in outcome measures and trial quality.[10,11] Its inclusion in this sequence does not establish superiority over other accepted topical regimens. Local irritation is relevant because it can interfere with adherence and complicate assessment around a procedure.

Lai et al. provide a useful test of whether a procedure adds benefit. Thirty participants entered a randomized split-face trial of azelaic acid 20% twice daily, with three 755-nm picosecond treatments added to one side after a four-week topical lead-in. Twenty-seven completed follow-up. Both sides improved, but the laser-treated side showed no additional clinical mMASI benefit. Four participants developed post-inflammatory hyperpigmentation after laser; the investigators reduced subsequent energy settings.[12] This finding supports reassessing the medical response before committing to laser. It does not validate a six-week lead-in, a three-day pause, or a day-four restart.

### *Oral tranexamic acid in selected patients*

Oral tranexamic acid (TXA) 250 mg twice daily has placebo-controlled evidence for melasma. In the trial by Del Rosario et al., 44 patients were enrolled and 39 completed the study. At three months, mMASI decreased by 49% with TXA and 18% with placebo; some benefit was lost after treatment stopped.[13] Expert consensus describes this dose and recommends clinical thrombotic-risk assessment, baseline coagulation testing and further investigation according to risk.[14]

Risk assessment should address previous thrombosis, known thrombophilia, thrombotic family history, systemic estrogen exposure, smoking, immobility, planned surgery, renal disease, and pregnancy or breastfeeding. A normal coagulation screen cannot by itself establish eligibility. Off-label use, alternatives and remaining uncertainty should be discussed.[5,14] A melasma-specific matched cohort reported no increased thromboembolic risk after excluding major risk factors, whereas a broader TXA-exposure cohort reported an association with thromboembolism. Their populations and exposure definitions differ, limiting direct application to a 250-mg twice-daily melasma course.[15,16]

TXA is therefore conditional on individual assessment and reassessment, rather than an automatic requirement for anyone considering laser. The proposed stop at week sixteen is a schedule choice, not an established optimal duration. A detailed review of TXA pharmacology and risk stratification is available elsewhere.[5]

### *What fractional picosecond laser can add*

Picosecond-laser studies cannot be treated as a single interchangeable intervention. Wavelength, pulse duration, fractional optics, spot dimensions and session frequency vary considerably.[17] A randomized comparison favored nonfractional 1064-nm picosecond treatment over 755-nm picosecond laser or 2% hydroquinone, while a separate split-face trial found similar efficacy between 1064-nm picosecond and nanosecond treatment, with differences in tolerability.[18,19] Neither study defines settings for every fractional microlens array.

Evidence specific to fractional 1064-nm treatment includes a small randomized comparison with and without a microlens array and prospective studies using different numbers of sessions.[20–22] These reports justify investigating fractional delivery, but do not determine that two sessions, four weeks apart, are sufficient. Nor do they establish the proposed pulse-energy escalation or overlap for the platform described below.

Durability and pigmentary harm remain clinically relevant. In a split-face comparison of 755-nm picosecond laser with a diffractive lens array and 1064-nm Q-switched laser, 10 of 17 patients reported recurrence or exacerbation at two years.[23] A separate case series documented hypopigmentation after picosecond treatment.[24] Accordingly, short follow-up and a report of no adverse events in a small sample cannot establish long-term safety.

The proposed procedural sequence is intended for persistent melasma after an adequate medical trial and reassessment of diagnosis, adherence and irritation. Patients who improve satisfactorily with medical treatment have no demonstrated need to progress through every procedural step. Active inflammation, changing pigmentation or incomplete recovery should prompt reassessment before further exposure.[3,4]

### *Intradermal hyaluronic acid formulations*

#### *Direct evidence and differences in administration*

Microneedling-assisted topical therapy, intradermal injection and post-laser application expose tissue differently. A meta-analysis of microneedling as an adjunct to topical melasma therapies and a review of mesotherapy found heterogeneous agents and methods.[25,26] These findings cannot establish the efficacy of a particular injectable formulation at a specified depth.

The most directly relevant NCTF trial compared 755-nm alexandrite picosecond laser alone with laser plus NCTF 135 HA in 31 participants, allocated to groups of 12 and 19. The combination group showed greater reported pigmentation improvement, but the small sample, unequal groups and short follow-up restrict interpretation. NCTF was administered after laser using a micropapular technique. Reporting of recurrence also differs: the

abstract states statistical significance, whereas the main results give p=0.053.[27] We therefore regard this as preliminary support for further comparison, without adopting its recurrence claim as proof of prevention.

Zou et al reported a retrospective series of 30 women treated with fractional picosecond laser and a different sodium hyaluronate composite. Mean Melasma Area and Severity Index (MASI) decreased from 18.30 to 8.20, but there was no control group. The methods place injection two weeks after laser, and the reported primary assessment was four weeks after the final treatment.[28] This sequence and product differ from NCTF fourteen days before laser. A six-patient report of hyaluronic acid with antioxidant ingredients after a plateau in laser-toning response is also uncontrolled.[29] Finally, a randomized study of a hyaluronic acid micro-filler evaluated wrinkles and skin quality; it supplies indirect evidence rather than a melasma treatment comparison.[30]

### *Why the proposed interval remains a hypothesis*

The proposed fourteen-day pre-laser interval allows recovery from intradermal treatment before energy delivery. No retrieved comparative study established that this ordering is superior to post-laser injection, same-day treatment, or omitting the injectable. It also remains unknown whether any benefit would arise from hyaluronic acid, another ingredient, the injection process, or accompanying care. Terms such as dermal repair or priming describe a proposed rationale; they should not be used as measured outcomes without corresponding data.

The product and route require precise identification. NCTF 135 HA is an injectable formulation; manufacturer descriptions distinguish it from similarly named products intended for topical use. The U225 is an intradermal injector.[31,32] In the present proposal, product is delivered through the needle into the skin. This is intradermal injection, not topical application followed by microneedling. Melasma benefit from this exact product, route and schedule remains to be established.

## RECOVERY AND MAINTENANCE

Temporary interruption of an irritating topical agent is a practical choice around a procedure. The proposed three-day pre-laser pause and restart from day four are intended to permit recovery, with actual resumption dependent on intact, comfortable skin. Evidence from the azelaic-acid split-face trial does not establish those dates.[12]

Evidence for corticosteroid prophylaxis is indirect. A split-face trial after ablative fractional carbon dioxide resurfacing found less post-inflammatory hyperpigmentation with a short course of clobetasol than with petrolatum alone.[33] A network meta-analysis pooled preventive measures across different laser and energy-device settings, including corticosteroids and cooling.[34] These findings do not establish methylprednisolone aceponate for three days after this fractional picosecond protocol. Supportive care recommendations favor attention to barrier function and procedure-specific recovery.[35]

The proposed aftercare is once-daily methylprednisolone aceponate for three days, no routine cooling, and barrier products as needed. Comparative evidence for this exact regimen is lacking. Clinically indicated care takes priority, with changes and their reasons recorded.

Maintenance continues after the procedural phase because improvement does not remove the tendency to relapse.[2,3] Daily tinted photoprotection and azelaic acid 20% twice daily, as tolerated, form the proposed maintenance regimen. The duration of response after TXA cessation should be measured separately from the response while TXA is being taken. Persistent topical irritation requires adjustment rather than adherence to an inflexible dosing target.

### *A specified sequence for evaluation*

Table 2 sets out the candidate sequence. Day 0 denotes initiation of the proposed medical regimen; it is not a date inferred from a patient record. The medical lead-in is six weeks. Intradermal NCTF sessions are planned at weeks four and eight, followed by laser at weeks six and ten. The full combination is an investigational proposal. Evidence for photoprotection or TXA does not establish the necessity of its injectable or laser components.

Table 3 specifies the candidate procedural settings. The named laser platform has manufacturer-described 300-ps pulses, a 1064-nm wavelength option and a fractional handpiece.[36] The fixed fractional microlens array, 6-Hz repetition rate, painting application and approximately 40% overlap are the authors' proposed configuration. They are not comparative-study-derived optimal settings. The injector is specified as U225, with a nominal needle depth of 2 mm and 3 ml of NCTF 135 HA per session, subject to anatomical suitability and the applicable product instructions.

**Table 2: Candidate timeline for prospective evaluation.**

| Proposed time | Planned action | Condition for proceeding |
|---|---|---|
| **Day 0** | Start daily tinted iron-oxide SPF 50+, azelaic acid 20% twice daily and TXA 250 mg twice daily if eligible. | Confirm diagnosis, contraindications, topical tolerance and informed treatment choice. |
| **Days 28 and 56** | Intradermal NCTF 135 HA, 3 mL through the U225 at nominal 2-mm depth. | Investigational adjunct; assess anatomy, suitability and recovery before proceeding. |

Continued.

| Proposed time | Planned action | Condition for proceeding |
|---|---|---|
| **Days 39 and 67** | Pause azelaic acid three days before each planned laser. | Review any ongoing irritation. |
| **Days 42 and 70** | Fractional 1064-nm picosecond laser using the proposed configuration in Table 3. | Persistent indication and recovered skin; defer if the clinical situation has changed. |
| **First three days after each laser** | Methylprednisolone aceponate once daily; no routine cooling; barrier repair if needed. | Author-specified care; modify if clinically indicated and record the reason. |
| **Days 46 and 74** | Resume azelaic acid from the fourth day after laser. | Resume only when the skin is intact and comfortable; delay if recovery is incomplete. |
| **Day 112** | Planned TXA cessation, six weeks after the second laser. | Stop earlier for clinical reasons; document actual exposure and duration. |
| **Maintenance** | Continue tinted SPF 50+ daily and azelaic acid 20% twice daily as tolerated. | Record adherence, irritation and recurrence over follow-up. |

Source: the authors' proposed schedule, informed by the evidence discussed in the text. It is not an observed patient timeline or a validated optimum. Day 0 is medical treatment initiation. The alternative same-day NCTF-plus-laser approach, with azelaic acid restart no earlier than day seven, is outside this sequence and is also unvalidated. SPF, sun protection factor; TXA, tranexamic acid.

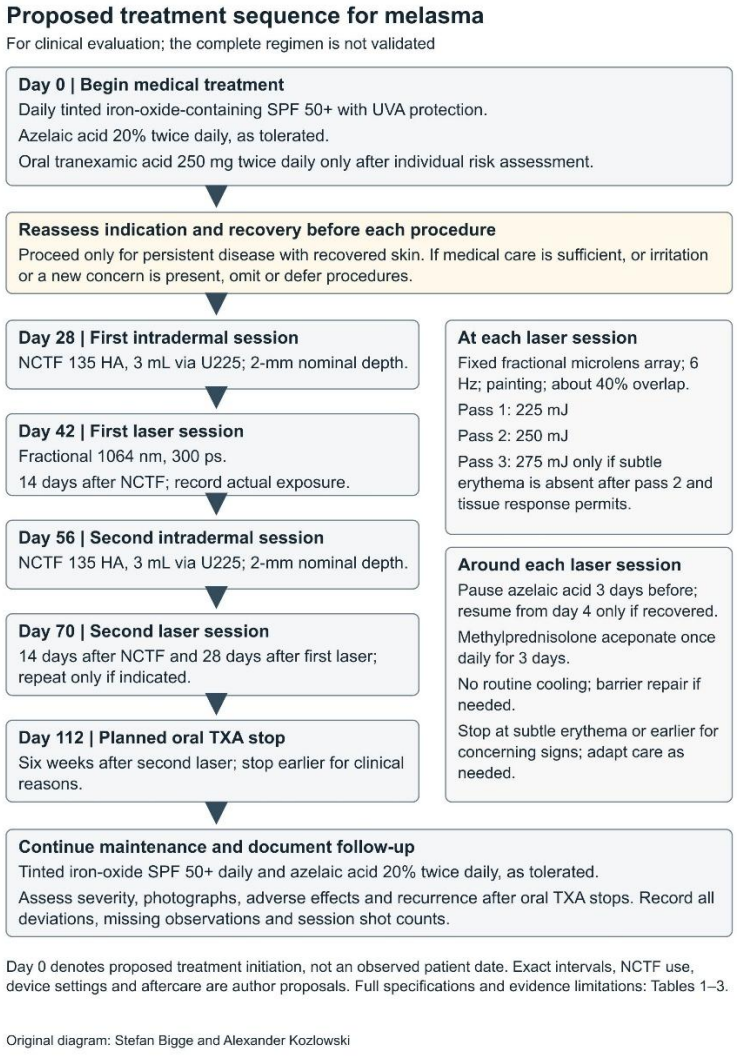



**Figure 1: Proposed sequence of medical treatment and procedures for melasma.**

Day 0 is initiation of the candidate medical regimen. Procedure dates depend on continuing indication and clinical recovery. The NCTF component, exact intervals, energy progression and aftercare choices require prospective evaluation. The diagram presents a proposal and contains no clinical results. Detailed settings and limitations are given in Tables 2 and 3. NCTF, NCTF 135 HA; SPF, sun protection factor; TXA, tranexamic acid; UVA, ultraviolet A. Original diagram by Stefan Bigge and Alexander Kozlowski; prepared with SVG and Sharp, with TIFF export using pillow.

**Table 3: Candidate procedural configuration and reporting requirements.**

| Item | Proposed specification | Interpretation or documentation |
|---|---|---|
| **Intradermal component** | NCTF 135 HA (FILLMED, Paris, France); 3 ml per session; U225 (Needle Concept, Biarritz, France); nominal 2-mm depth. | Product is injected through the needle. Record actual technique, depth, volume and treated area. |
| **Laser and optics** | Pico:premium (intros Medical Laser, Heilbad Heiligenstadt, Germany); 1064 nm; 300 ps; fixed fractional microlens array. | Confirm exact device and handpiece identifiers. Manufacturer specifications do not validate the proposed clinical settings.[36] |
| **Delivery** | 6 Hz; painting application; approximately 40% overlap. | Record actual coverage, passes and total shot count for each session. |
| **Energy progression** | First pass 225 mJ; second pass 250 mJ; conditional third pass 275 mJ. | Third pass only if subtle erythema is absent after pass two and tissue response is otherwise acceptable. Stop earlier if indicated. |
| **Endpoint** | Subtle erythema. | Document the response. Unexpected pain, marked erythema, whitening or epidermal injury prompt cessation and assessment. |
| **Units and transferability** | Displayed pulse energy in mJ. | Do not relabel as mJ/cm². Fluence and microbeam exposure require the relevant area and optical specifications. |

Source: the authors' proposed configuration; supporting device identification is cited. These specifications are candidates for evaluation and are not a claim of universal settings, manufacturer endorsement, or safety across skin phototypes. Brand names identify the intended configuration and do not imply superiority.

The proposed laser progression is 225 mJ for the first pass and 250 mJ for the second. A third pass at 275 mJ is conditional on absent subtle erythema after pass two and an otherwise acceptable tissue response. Treatment should stop earlier if the endpoint is reached or concerning signs appear. Marked erythema, whitening, blistering or unexpected pain should not be pursued as a target. Pulse energy must be recorded in mJ; conversion to fluence requires the relevant illuminated area and optical configuration. A displayed energy value alone does not establish exposure at each microbeam or permit transfer to another handpiece.

Figure 1 summarizes the sequence and decisions to defer treatment. Each actual session must retain its wavelength, handpiece, settings, passes, total shot count, treated area and endpoint. A change to 532 nm, a different device or another administration route is a different exposure that requires explicit reporting. The proposed sequence is sufficiently specified to support protocol development, but local device instructions, risk assessment and study governance remain necessary before prospective use.

## QUESTIONS FOR CLINICAL EVALUATION

A study should first establish whether the procedural sequence adds clinically worthwhile benefit to optimized medical treatment. The specific incremental effect of NCTF requires a comparator that receives the same medical treatment and laser without NCTF. A favorable outcome after the complete combination cannot isolate any one component.

A written protocol should define eligibility, recruitment, permissible treatment changes and a primary endpoint before data collection. A validated severity measure such as mMASI provides a stronger basis for assessment than satisfaction alone.[37] This study proposes assessments before medical treatment, immediately before each procedure, after the procedural phase and at prespecified follow-up after TXA cessation. Follow-up at six and twelve months after the second laser would assess durability; these are proposed assessment times, not outcomes reported here.

Photography should use consistent equipment, lighting, positioning and framing. Images should be obtained without makeup or freshly applied tinted sunscreen. Capture time should be recorded separately from satisfaction assessments and treatment time, particularly for photographs taken on a procedure day. Blinded assessment, where feasible, would reduce expectation bias. Clinically justified deviations, withdrawals, missing observations, lack of response and adverse effects should remain visible in the analysis, with denominators stated for each endpoint.

A prospective assignment to this sequence for evaluation can meet the definition of an interventional clinical trial even without a concurrent control group. The applicable ethics review and prospective registration should therefore be addressed before enrollment.[38] The publication of this review neither supplies that approval nor establishes clinical validation of the proposed combination.

### *Limitations*

This review uses a selective evidence base and does not provide pooled effect estimates or a formal certainty

assessment. Small samples, different optical systems, heterogeneous injection formulations and short follow-up limit transfer between studies. Manufacturer information identifies equipment and products but cannot resolve clinical effectiveness. The proposed timing and settings have not been validated as a complete sequence in a controlled study identified by this review.

## CONCLUSION

Photoprotection, topical treatment and selected use of oral TXA provide the medical basis for this proposal. The additional benefit of fractional picosecond laser depends on the comparator and treatment setting, while evidence for intradermal NCTF remains preliminary. The specified sequence makes its timing and procedural assumptions explicit. Its value should be tested through a defined comparison, complete documentation of actual exposures and follow-up after oral treatment ends.

### *Declaration*

Microsoft CoPilot as part of Microsoft Word was used for spelling control. The authors retain responsibility for the interpretation, accuracy and final approved text. No external sponsor supported this assistance.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: Not required*

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**Cite this article as:** Bigge S, Kozlowski A. Evidence and a proposed algorithm for periprocedural treatment sequencing in melasma. Int J Res Dermatol 2026;12:688-95.