Assessing the technical and programmatic feasibility of a microarray patch for intradermal delivery of primaquine to treat *P. vivax*

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**OBJECTIVE**

Assess the technical and programmatic feasibility of a microarray patch for sustained, intradermal delivery of primaquine (PQ) to treat *Plasmodium (P.) vivax* malaria.

**METHODS**

We conducted a landscape analysis to assess the potential for using microarray patch technology for delivery of PQ and to inform the development of target product profile characteristics. We reviewed publicly available literature on PQ delivery challenges and alternative delivery technologies and evaluated the chemical properties of PQ using the Embase database.

**RESULTS**

**Primaquine delivery challenges**

Primaquine (PQ), in combination with either chloroquine or artemisinin-based combination therapy, is the only drug currently recommended for radical cure of *P. vivax* malaria (Figure 1). However, the standard formulation of oral PQ has several side effects that prevent wide use: it can cause acute hemolytic toxicity in individuals with glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency; has a bitter taste that makes oral delivery difficult, particularly for children; and can cause gastrointestinal side effects that can result in poor patient adherence to the extended drug regimen (7–14 days).

**Microarray patch delivery technology**

Microarray patches (MAPs) are an intradermal delivery technology that consists of an array of micron-scale (11 mm long) projections (Figure 2). Upon application to the skin (like a bandage) the projections painlessly penetrate the skin and release a dry active pharmaceutical ingredient (API) formulation. Queen’s University Belfast (QUB) has developed a unique hydrogel MAP design that employs a cross-linked polymer system to provide sustained drug release from a lyophilized reservoir.1 Hydrogel MAPs swell upon contact with the skin’s interstitial fluid to act as a conduit for drug release from the reservoir via diffusion (Figure 3). The rate of API diffusion from the backing is controlled by the density of the cross-linked polymers, enabling sustained release. The hydrogel MAP projections themselves do not dissolve. Upon removal from the skin, the projections are soft and swollen, so the MAP cannot be reapplied and does not pose a sharps injury risk during disposal.

**Value proposition of a hydrogel microarray patch for primaquine delivery**

A hydrogel MAP that provides sustained release of PQ transdermally has the potential to reduce side effects related to this drug by excluding gastric absorption and by potentially reducing the dose amount required to ensure sustained systemic levels adequate to kill parasites or prevent infection. Reduced side effects could increase adherence. Should serious side effects occur, such as dark urine and other signs of hemolysis, a MAP could be removed to immediately stop drug delivery. In addition, a patch could be of particular value for young children, in whom *P. vivax* can cause severe disease, and for whom oral tablet regimens are not ideal. A PQ MAP has the potential to enable expanded use, safety, and adherence to drug therapy for radical cure of *P. vivax*.

**Target product profile**

We developed a target product profile to specify key attributes to guide PATH and QUB’s product development program for a hydrogel PQ MAP (Table 1).

**REFERENCES**


**JOIN A ROUNDTABLE DISCUSSION**

PATH is assessing the technical and programmatic feasibility of a microarray patch for intradermal delivery of primaquine to treat *P. vivax* malaria. Join one of our focus groups for discussion and input on the target product profile.

- **Tuesday, November 7 @ 12:30–1:30 pm**
  - Hilton Baltimore, Holiday Ballroom 2 (East Building, 2nd floor)

- **Wednesday, November 8 @ 12:30–1:30 pm**
  - Hilton Baltimore, Holiday Ballroom 2 (East Building, 2nd floor)

Please contact Sarah McGray (smcgray@path.org) for more details.

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**TABLE 1.** Target product profile (TPP) attributes for a primaquine (PQ) microarray patch (MAP).

<table>
<thead>
<tr>
<th>ATTRIBUTES</th>
<th>MINIMAL TARGET</th>
<th>OPTIMAL TARGET</th>
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<tbody>
<tr>
<td><strong>INDICATION</strong></td>
<td>The primary indication of a PQ MAP is to achieve radical cure of <em>P. vivax</em> malaria when delivered concurrently with chloroquine or ACT. Testing for G6PD deficiency is recommended for radical cure regimens. It is anticipated that point-of-care G6PD testing would be required prior to administration of a PQ MAP (same as requirement for PQ oral tablets) but recognized this is not always followed in clinical practice. In the event of any AE related to primaquine, the MAP could be removed to immediately stop drug delivery.</td>
<td>Future indications for a PQ MAP could include use as a single drug for primary prevention of <em>P. vivax</em> or <em>P. ovale</em> malaria.</td>
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<td><strong>DOSE</strong></td>
<td>PQ MAP delivers a sustained, uniform, clinically effective dose comparable to the dose delivered by oral PQ tablets to achieve systemic blood concentration levels required for radical cure of <em>P. vivax</em> malaria. According to WHO guidelines, standard primaquine therapy for radical cure of <em>P. vivax</em> malaria in adults and children 16 months with normal levels of G6PD activity is 15 mg primaquine diphosphate/day for 14 days.</td>
<td>PQ MAP delivers a sustained, uniform, clinically effective dose that is less than the dose delivered by oral PQ tablets to achieve systemic blood concentration levels required for radical cure of <em>P. vivax</em> according to WHO guidelines. The dose required for a PQ MAP is currently unknown and will be determined through pharmacokinetic studies.</td>
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<tr>
<td><strong>WEAR TIME AND FREQUENCY OF ADMINISTRATION</strong></td>
<td>PQ MAP is applied once and worn continuously for 3 days, then removed and replaced with a new PQ MAP every 3 days to complete the 14-day treatment regimen required for radical cure of <em>P. vivax</em> malaria.</td>
<td>A single PQ MAP can be worn for the complete treatment duration, and cumulative dose can be achieved in 144 days.</td>
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<td><strong>INTENDED USE CASE</strong></td>
<td>Passive case detection: For treating patients identified in clinic settings who are positive for <em>P. vivax</em>.</td>
<td>Active case detection: For treating cases identified during screening for asymptomatic individuals positive for <em>P. vivax</em>. Mass drug administration: Community-wide administration to clear parasite reservoirs in the population.</td>
</tr>
<tr>
<td><strong>SAFETY AND ADVERSE EVENTS</strong></td>
<td>Safety profile of PQ MAP is equivalent to that of oral PQ tablets. Reactions at the site of application, such as redness, tenderness, or swelling, are mild and acceptable to patients and providers.</td>
<td>Safety profile of PQ MAP is improved compared to that of oral PQ tablets. No reactions observed at the site of application.</td>
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