DEVELOPMENT OF A TOPICAL HEDGEHOG INHIBITOR FOR PREVENTION OF NEW SURGICALLY ELIGIBLE BASAL CELL CARCINOMAS IN PATIENTS WITH GORLIN SYNDROME: PHASE 3 TRIAL

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ABSTRACT

Identification of PTCH1 gene mutations in the Gorlin syndrome two decades ago led to the development of small molecule Hedgehog (HH) inhibitors that replace the function of the mutant gene. These drugs have remarkable oral efficacy against advanced BCCs and off-label vs. the multiple BCCs in patients with Gorlin syndrome. Unfortunately, on target, extra-cutaneous adverse effects cause patients to stop these drugs, after which BCCs in complete clinical and histologic remission generally recur. Therefore, PellePharm is developing a small molecule HH inhibitor for topical use. Our goal is to develop a drug that produces skin concentrations high enough to inhibit HH signaling but not so high that circulating levels produce the unwanted adverse effects.

We have incorporated the cyclopamine derivative patidegib into a gel that in two Phase 2 trials has demonstrated efficacy potential vs. BCCs - complete response (12 of 45 tumors in patidegib topical gel arms vs. 0 of 16 in vehicle) and fewer new BCCs (3 out of 12 subjects in patidegib topical gel arms vs. 3 out of 5 in vehicle; ITT one-sided P=0.05); with none of the significant oral HH inhibitor class adverse events observed. Very low to undetectable systemic exposure of the drug has been observed - circulating levels 500-1000x lower than those when patidegib is administered orally. These data suggest that the benefit-risk of patidegib topical gel in patients with Gorlin syndrome is positive. Therefore, we have initiated a Phase 3 Trial in North America and Europe with the aim of enrolling 150 Gorlin subjects randomized 1:1 for application of active vs. placebo gel to the face for a year, testing prevention of the development of new surgically eligible BCCs (ClinicalTrials.gov Identifier: NCT03703310).

Patients interested in participating and clinicians interested in more details can contact us at clinical@pellepharm.com.

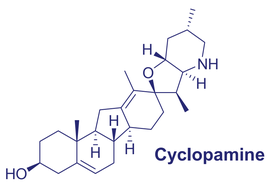
The Major Remaining Problem for Drug Rx of Non-Advanced BCCs

How to Reduce AEs so that patients can continue to use these HH inhibitors? We're Dermatologists Dummy -> Well Duh ->

Apply the HH inhibitor TOPICALLY!

PELLEPHARM'S PROGRESS

1. Outlicensed Patidegib (Infinity) – a cyclopamine derivative.



Cyclopamine

2. Hired MedPharm -> formulate the gel.

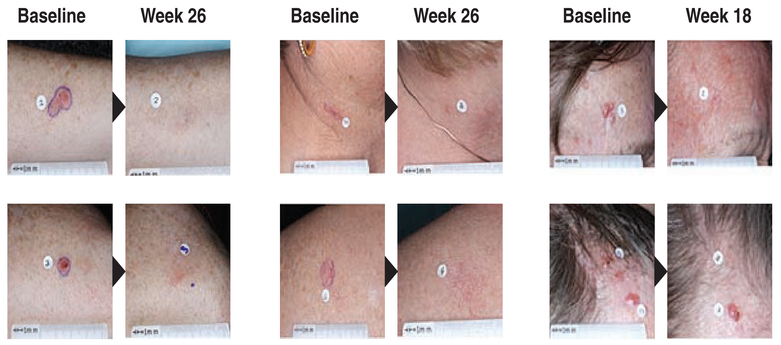
3. Preclinical safety studies in minipigs, etc.

4. Maximal use study: apply 2/day to face and trunk in healthy volunteers.

5. Phase 2 POC Trial: adult Gorlin patients randomized 1:1 for 6 months of 2x/day application of 0%, 2%, or 4% gel to the face and neck.

6. Phase 2 Trial in Gorlin Patients 6m bid to face and neck -> shrinks existing BCCs and reduces number of new BCCs at treated sites.

Complete clearing of BCCs only in 2% and 4% groups; none in vehicle group

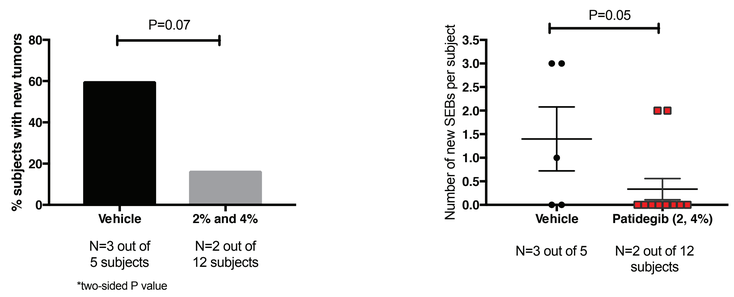


- Complete response.
- No irritation or itch.

- Complete response.
- No irritation or itch.

- Complete and partial responses.

Fewer NEW Surgically Eligible BCCs Seen in Patidegib-Treated Pts



- 16% of drug treated patients developed new tumors (SEB after wk2) vs. 60% of vehicle patients.
- 0.4 new tumors in drug treated vs 1.4 new tumors in vehicle patients.

7. Blood levels 500-1000x lower than when given orally/no hair loss, taste loss, muscle cramps thus far.

CONCLUSION FROM PHASE 2A TRIAL IN GORLIN SYNDROME

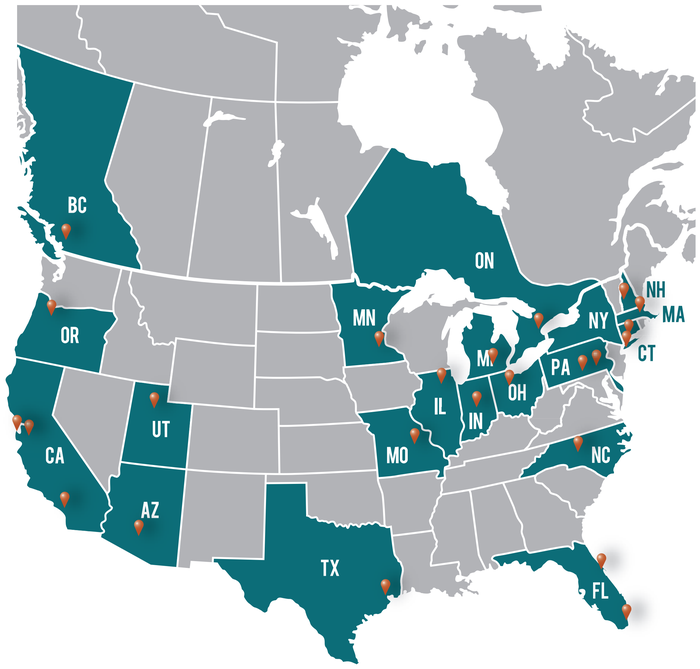
Proof of concept achieved:

- Patidegib reduces existing BCC diameter compared with vehicle.
- Tumors with CR seen only in patidegib treated subjects.
- Correlation of tumor response and biomarker reduction.
- Trend towards fewer new facial BCCs in drug treated subjects.
- Strong safety thus far.

PHASE 3 TRIAL

Primary End Point – Reduction in the Number of New Surgically Eligible BCCs.

First sites now open in USA and EUROPE



Thanks for Discussing the Possibility of their Becoming a Subject in Our Trial With Your Patients with Gorlin Syndrome!!

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More Details

Clinicaltrials.gov/NCT03703310
EudraCT Number 2018-001462-42

Study Sites: **www.gorlinstudy.com**
Contact us: **clinical@pellepharm.com**