Effect of a far-infrared emitting patch on local skin perfusion, microcirculation, and oxygenation

PFR181

Sebastiaan JW van Kraaij, MD[1,2]; Michael R Hamblin, PhD[3]; Gisele Pickering, MD, PhD[4]; Bill Giannokopoulos, PharmMBA[5]; Hayet Kechemir, MD[6]; Iva Igracki-Turudic, MD[7]; Robert Rissmann, PhD[1,8]; Pim Gal, MD, PhD[9]

[1]Centre for Human Drug Research, Leiden, The Netherlands; [2]Leiden University Medical Centre, Leiden, The Netherlands; [3]Laser Research Centre, Faculty of Health Science, University of Johannesburg, Doornfontein 2028, Johannesburg, South Africa; [4]Clinical Investigation Center CIC Inserm 1405; University Hospital Clermont-Ferrand, Clermont-Ferrand France; [5]Sanofi, CHC Science Hub, Athens Greece; [6]Sanofi, Research & Development, Chilly-Mazarin, France; [7]Sanofi, CHC Science Hub, Frankfurt, Germany; [8]Leiden Academic Centre for Drug Research, Leiden, The Netherlands; [9]Logex Healthcare Analytics, Amsterdam, The Netherlands

INTRODUCTION

- The electromagnetic spectrum of Far infrared radiation (FIR) with wavelengths ranging from 750 nm–100 µm has been the subject of investigation for health benefits when delivered through various powered or non-powered modalities.
- Clinical and preclinical evidence showed that, FIR therapy can exert therapeutic benefits on cardiovascular and endothelial function[1,2] and acute and chronic pain conditions such as musculoskeletal pain.[3,4]
- The mechanism of action (MoA) is believed to exert improving vascular function by increasing nitric oxide (NO) bioavailability and reducing oxidative stress[5,6] and by improving mitochondrial function in *ex-vivo*.[7,8]
- FIR may heat skin to exert an effect; however, FIR modalities that do not heat skin seem to exert beneficial effects as well.
- The FIR patch is a drug-free thin medical device containing titanium dioxide (TiO_2) dispersed in an adhesive layer. It absorbs body heat and re-emits in the form of FIR reducing the chances of skin heat, while improving local skin microcirculation, oxygenation, and mitochondrial function.

OBJECTIVE

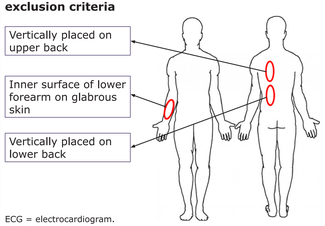
- To elucidate the possible mechanisms of action of FIR re-emitted by the FIR patch by evaluating the local effects of this patch on local perfusion, skin temperature and tissue oxygen consumption.

METHODS

Study design and subject selection

- The prospective, open-label, parallel designed study randomized each subject (N=20) to receive three FIR patches (target treatment group).
- Contralateral untreated areas served as control for treated areas in the same subject (**Figure 1**).

Figure 1. Study design - Application of the FIR patch on each subject- inclusion and exclusion criteria



Adults (male and female): ≥18 – <55 years

Inclusion criteria

No significant abnormal findings in:

- Medical history
- Physical examination
- 12-lead ECG
- Alcohol breathalyser
- Clinical laboratory tests

Exclusion criteria

- Pregnant/nursing women
- Any medication (except paracetamol/ acetaminophen up to 4g/day)
- Body modifications/impediments on treatment location

ECG = electrocardiogram.

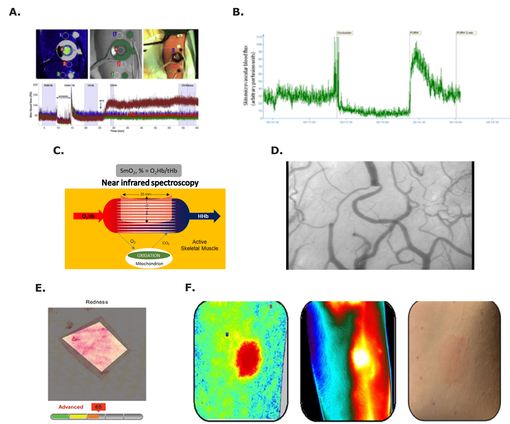
Study endpoints

- Primary endpoints: baseline perfusion increase during treatment on the upper back.
- Secondary endpoint: change in baseline perfusion, oxygen consumption and temperature of treated versus untreated areas.
- Safety: adverse event/concomitant medication/vital signs monitoring.

Outcome assessment techniques

- Imaging of local microcirculation was conducted at regular intervals on treated areas through 'windows' in the patches which were closed between measurements, and on control areas.
- Measurements were conducted in temperature-controlled rooms (20-24°C) at the Centre for Human Drug Research (CHDR).
- Skin perfusion was measured with laser speckle contrast imaging (LSCI) combined with local thermal hyperaemia (LTH) (**Figure 2A**) and post-occlusive hyperaemia (PORH) challenges to quantify microcirculatory response to heat and ischemia (**Figure 2B**).
- Near infrared spectroscopy (NIRS) combined with arterial and venous occlusion challenges was conducted to quantify oxygen consumption and blood flow (**Figure 2C**).
- Sidestream dark-field microscopy (SDFM) to quantify blood vessel morphological characteristics and perfusion in tape-stripped skin (**Figure 2D**), multispectral imaging (MSI) to quantify skin colour and texture (**Figure 2E**) and thermography to assess changes in skin temperature on treated and non-treated sites (**Figure 2F**).

Figure 2. Techniques used for assessments
(A) LSCI with LTH; (B) LSCI with PORH; (C) NIRS; (D) SDFM; (E) MSI; (F) Thermography



LSCI = laser speckle contrast imaging; LTH = local thermal hyperemia; MSI = multispectral imaging; NIRS = near infrared spectroscopy; PORH = post-occlusive reactive hyperemia; SDFM = side-stream darkfield microscopy.

Statistical analysis

- To detect significant treatment effects on pharmacodynamic endpoints a mixed model analysis of covariance (ANCOVA) was used for the analysis with three contrasts, namely patch vs no-patch over two days, at Day 1 only and at Day 2 only.
- All other endpoints were to be interpreted in an exploratory way if the primary endpoint did not achieve statistical significance (hierarchical procedure).

RESULTS

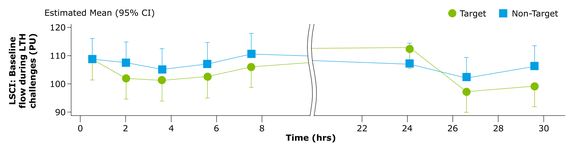
Subject disposition

- A total of 20 subjects (male [70%], mean age [SD]: 25.2 [7.3]) received the study treatment with the median treatment exposure of 1874.5 minutes on the left side and 1875 minutes on the right side.

Pharmacodynamic assessments

- Baseline blood flow measured before initiating LTH during the treatment on the upper back was not statistically different between treated and non-treated areas (least squares means [LSMs] difference [95% CI]: -3.06 PU [-6.55, 0.44]) (**Figure 3**).

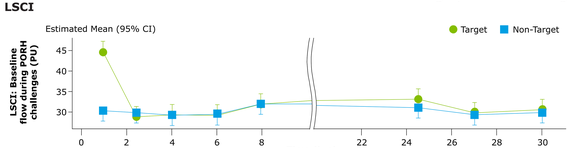
Figure 3. LSMs of absolute baseline blood flow before LTH challenges, measured using LSCI



CI = confidence interval; hrs = hours; LSCI = laser speckle contrast imaging; LSMs = least squares means; LTH = local thermal hyperemia; PU = perfusion units.

- Baseline perfusion of the forearm was significantly increased in the treated area compared to the non-treated area at Day 1 (LSMs difference [95%CI]: 2.625 PU [0.973, 4.278]) (**Figure 4**). Peak blood flow after PORH was not significantly different between treated and non-treated areas (LSMs: 6.61 vs 5.66, LSMs difference [95% CI]: 0.94 PU [-1.42, 3.30]).

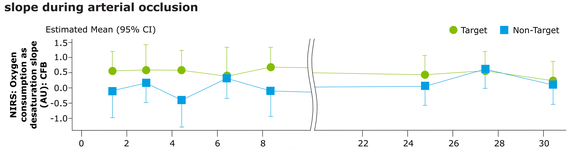
Figure 4. LSMs of absolute baseline blood flow before PORH challenges, measured using LSCI



CI = confidence interval; hrs = hours; LSCI = laser speckle contrast imaging; LSMs = least squares means; PORH = post-occlusive reactive hyperemia; PU = perfusion units.

- Oxygen consumption was higher in treated areas when compared to non-treated areas (LSMs difference: 0.42 AU [95% CI: 0.04, 0.81]) (**Figure 5**).

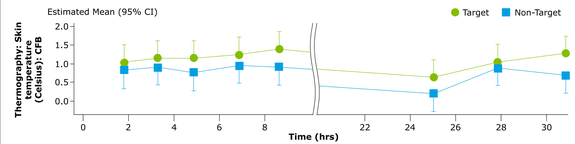
Figure 5. LSMs of CFB in oxygen consumption, measured with NIRS as desaturation slope during arterial occlusion



AU = arbitrary units; CFB = change from baseline; CI = confidence interval; hrs = hours; LSCI = laser speckle contrast imaging; LSMs = least squares means; NIRS = near-infrared spectroscopy.

- There were no clear differences between treated and non-treated sites in SDFM and MSI.
- Skin temperature was higher in treated areas (+1.11°C) vs non-treated areas (+0.76°C) (LSMs: 0.35 [95% CI: 0.15, 0.56]). This difference was significant on both Day 1 (LSMs difference: 0.326 [95% CI: 0.113, 0.540]) and Day 2 (LSMs difference: 0.399 [95% CI: 0.173, 0.626]) (**Figure 6**).

Figure 6. LSMs of CFB of absolute skin temperature in Celsius measured using thermography



CFB = change from baseline; CI = confidence interval; hrs = hours; LSMs = least squares means.

Safety assessments

- No serious adverse events (SAEs) nor treatment discontinuations occurred. Only one possibly treatment related AE (Eczema) was observed which was resolved within one day.
- Vital signs showed no significant out-of-range values during study treatment.

DISCUSSION

- FIR patch application resulted in a local increase in dermal blood flow (~30 minutes post administration of treatment and returned to baseline after 2 hours), increased oxygen consumption and increased skin temperature although the primary endpoint was not met. It showed an excellent safety and tolerability profile.
- The vascular response was short-lived as opposed to the longer-lasting increase in skin temperature, suggesting a non-thermal effect of the FIR patch immediately post application, possibly due to the induction of buffering mechanisms in the skin.
- An increase in skin temperature by the FIR patch possibly contributes to the measured increase in oxygen consumption and increase in flow.[9]

CONCLUSION

- Overall, the first primary endpoint in the pharmacodynamic confirmatory analysis, defined as increase in basal blood flow measured during LTH challenges, did not achieve statistical significance. However, increases in flow, oxygen consumption and temperature were measured on secondary endpoints.
- The treatment with FIR patch was found to be safe with beneficial effects on skin microcirculation and also oxygen consumption. Further research is needed to have more clarity on the efficacy data of the treatment.

DISCLOSURES

- **SJK, RR, PG**: No conflict of interest; **MRH**: MRH declares the following potential conflicts of interest. Scientific Advisory Boards: Transdermal Cap Inc, Cleveland, OH; Hologenix Inc. Santa Monica, CA; Vielight, Toronto, Canada; JOOVV Inc, Minneapolis-St. Paul MN; Consulting; USHIO Corp, Japan; Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany. Stockholding: Niraxx Light Therapeutics, Inc, Irvine CA; JelikaLite Corp, New York NY; **GP**: has received consultancy fees from Grunenthal, Mylan, MundiPharma and Sanofi; **BG, HK** and **IIT** are Sanofi employees and may hold shares and/or stock options in the company.

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