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Sublingual Minoxidil for the Treatment of Male and Female Pattern Hair Loss: a randomized, double-blind, placebo-controlled, phase 1B clinical trial

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Conflict of interest: RS: Director and Founder Samson Medical Pty Ltd and holds the patent for the use of sublingual minoxidil and low dose oral minoxidil for promoting hair growth and treatment of hair loss or excessive hair shedding. Pharmaceutical advisory board Eli Lily, Pfizer, Leo Pharmaceutical. Speaker bureau Abbvie, Novartis. Principal investigator in clinical trials for Amgen, Novartis, Arcutis, Aerotech, Merck and Co, Celgene, Coherus Bioscience, Janssen, Regeneron, MedImmune, Glaxo Smith Kline, Samson Clinical, Boehringer Ingelheim, Oncobiologics, Roche, Ascend, Demira, Astra Zeneca, Akesobio, Reistone, UCB, Sanofi, Connect, Arena, Sun Pharma, Bristol Myer Squibb, Galderma.

No conflict of interests has been identified for the remaining authors.

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Key Words: androgenic, androgenetic, alopecia, minoxidil, baldness, hair

Abbreviations:

AGA - androgenetic alopecia
BP - Blood Pressure
SULT – sulfotransferase
SULT1A1 - thermostable phenol sulfotransferase
SULT2A1 - dehydroepiandrosterone sulfotransferase
SUR2 - sulfonylurea receptor 2
K_{ATP} channels – ATP-sensitive potassium (KATP) channels
ML – minoxidil lotion
SM - sublingual minoxidil
OM – oral minoxidil

Minoxidil is an approved medication for severe hypertension androgenetic alopecia[1]. Oral minoxidil (OM) is potent vasodilator used to treat hypertension. It is a pro-drug, activated by hepatic dehydroepiandosterone sulfotransferase (SULT2A1) to minoxidil sulfate.[2] OM doses of 2.5mg and 5mg produce peak plasma concentrations of 16.8 and 37.2ng/mL within 30mins post-dose.[3] Side-effects include hypertrichosis, lower limb oedema, postural hypotension and tachycardia. Minoxidil lotion (ML) is approved for the treatment of hairloss. It is also a pro-drug converted in hair bulbs by thermostable phenol sulfotransferase (SULT1A1) to minoxidil sulfate. There is considerable inter-subject variability in levels of both hepatic SULT2A1 and follicular SULT1A1. Low SULT1A1 predicts weak hair regrowth with both ML and OM.[4,5] Weak hair growth due to low follicular SULT1A1 can be overcome with OM through dose escalation, but cannot be overcome with ML due to low solubility and saturation absorption kinetics.[6]

As sublingual dosing bypasses hepatic first-pass metabolism, sublingual minoxidil (SM) would be anticipated to increase follicular minoxidil sulfate bioavailability and consequently hair growth[7]. As hepatic sulfation of minoxidil enhances the haemodynamic effect, SM would also be anticipated to reduce haemodynamic side effects and consequently improve safety.

To investigate SM as an alternative to OM, we conducted a prospective, randomised placebo-controlled, double-blinded dose escalation phase 1B clinical trial (HREC approval number 2017-09-669; ANZCTR number: ACTRN12618000606280). Forty men with Hamilton Norwood stages III vertex to V or women with Sinclair stages 2-5 hair loss, aged 30-65 years, were enrolled and completed the core study receiving either SM 0.45mg daily or placebo for 24 weeks. Twelve participants rolled into a 24-week open-label extension study and received SM 1.35mg or 4.05mg daily. Co-primary end-points were macrophotography and terminal hair count on phototrichogram.

Macrophotographs were scored using a 7-point scale. At 24 weeks, 9 patients (45%) receiving 0.45mg SM had improved frontal hair density and 11 patients (55%) showed vertex improvement. One out of 6 patients (17%) treated with 1.35mg SM had improved frontal and 3 out of 6 (50%) had an improved vertex hair density. Four of 6 patients (67%) treated with 4.05mg dose showed improvement in both frontal and vertex hair density (Figure 1).
Phototrichograms demonstrated a mean increase in terminal hair count/cm^2 of 4 for the frontal and 9 for the vertex scalp with the 0.45mg dose. The 1.35 mg dose produced a mean increased terminal hair count/cm^2 of 10 and 26 and 4.05mg SM produced a mean increase terminal hair count/cm^2 of 38 and 88 for the frontal and vertex scalp respectively. (Figure 2). Compared to placebo, the difference in mean hair count o achieved statistical significance for both the frontal and vertex scalp at all doses except the 0.45mg dose over the vertex.

Failure to achieve statistical significance at the 0.45 mg dose on the vertex scalp is attributed to a solitary patient in the placebo group whose vertex scalp hair density unexpectedly increased by76 hair per cm^2.

Mean peak minoxidil plasma concentration following the initial sublingual dose was at 1.62ng/mL (range 0.3- 5.3ng/ml), 30 minutes post-dose. Minoxidil was undetectable in plasma after 24 hours. This is more than an order of magnitude below the plasma concentration threshold (20 ng/ml) for development of any haemodynamic effects.[8] No significant change in BP was detected in the placebo or treatment arms.

In conclusion, SM produced a dose-dependent increase in mean terminal hair count on the frontal and vertex scalp and improvement in hair density. Further studies with larger patient cohorts are warranted to determine the optimal dose of SM and comparing the relative efficacy of OM and SM as well as the pharmacokinetics of SM.

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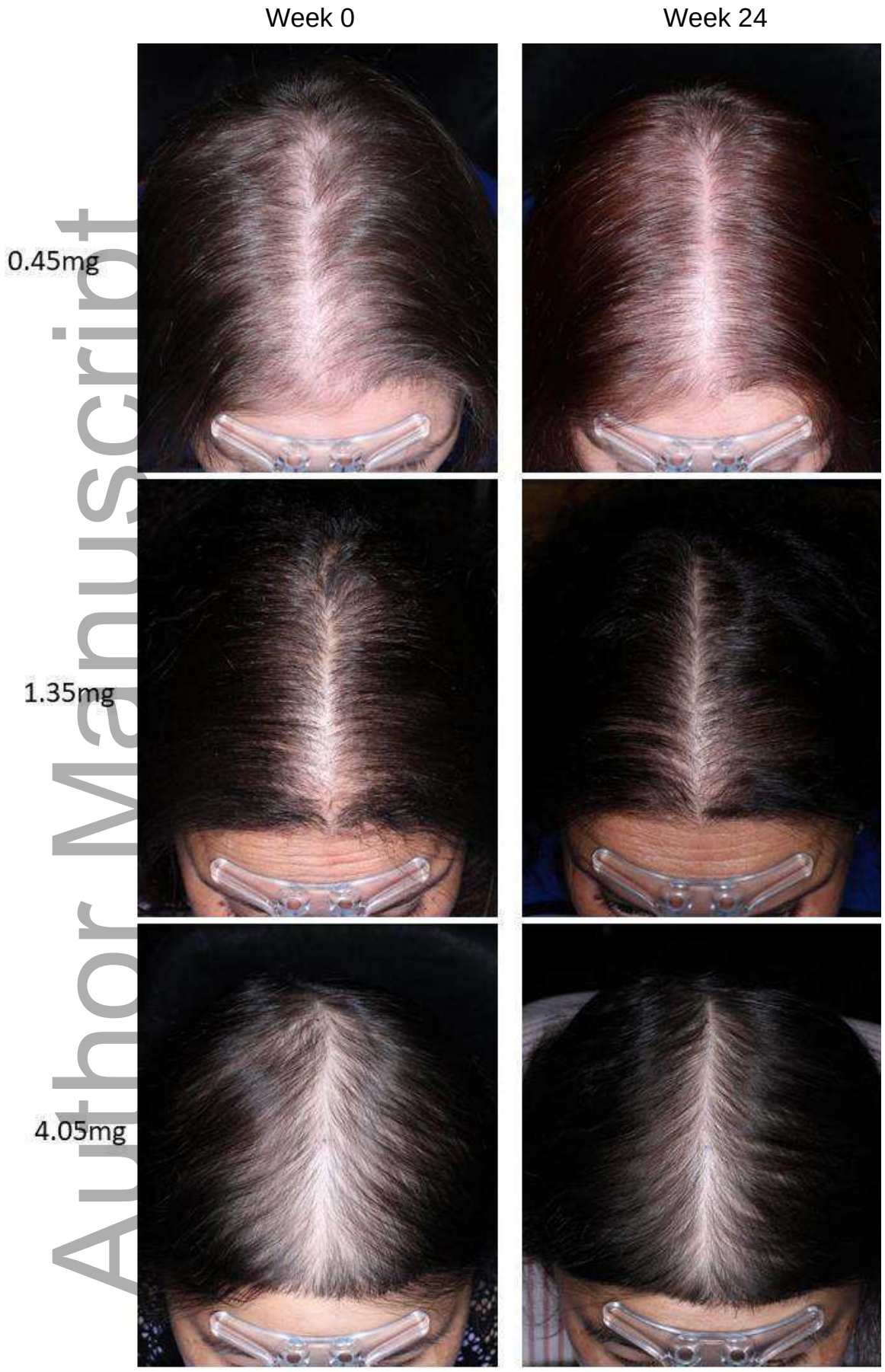

Figure 1. Representative global photographs of the frontal scalp of patients in each arm at Week 0 and Week 24.

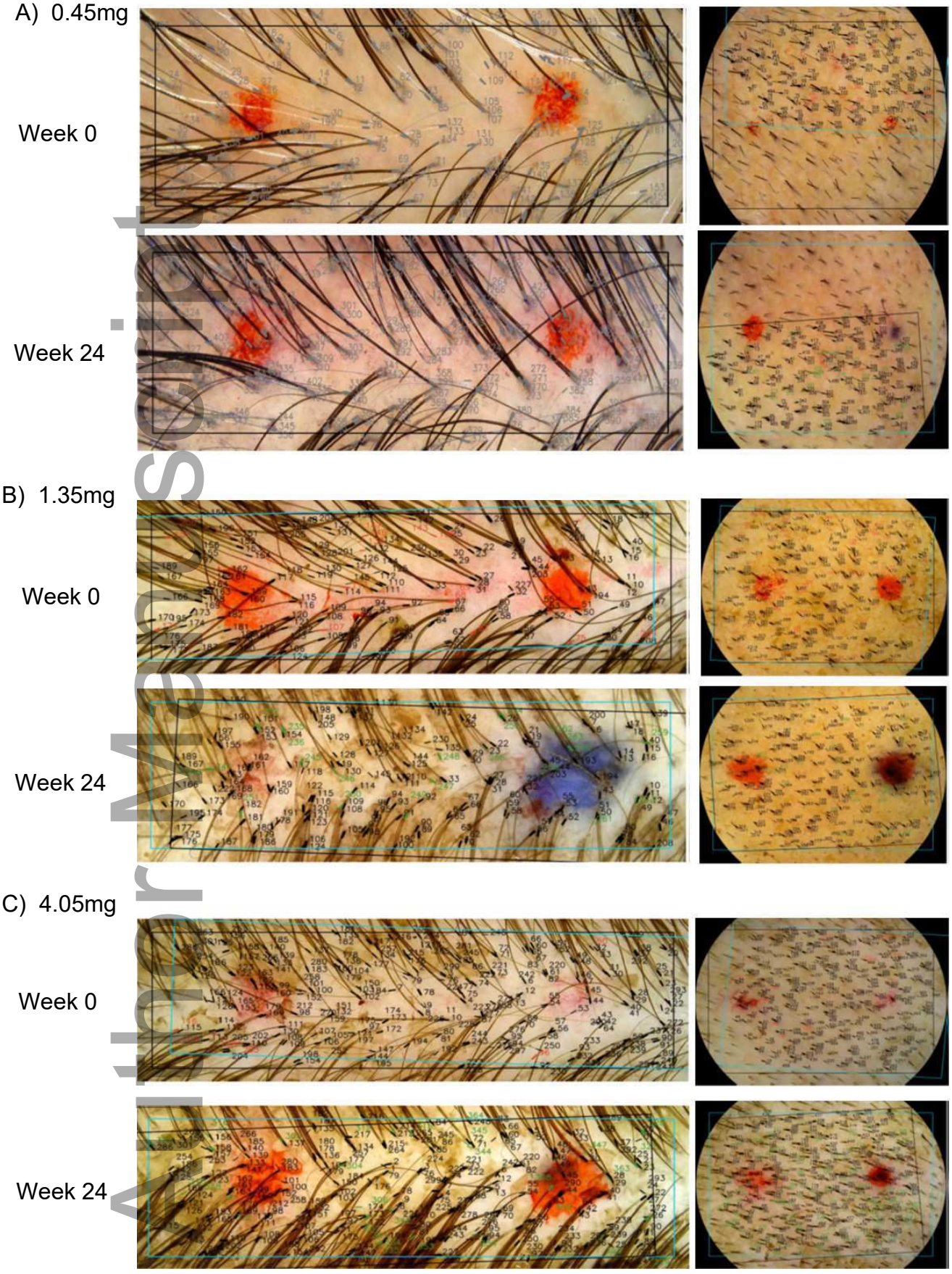

Figure 2. Representative phototrichograms of frontal and vertex macrophotographs of patients on sublingual minoxidil A) 0.45mg arm B) 1.35mg arm and C) 4.05mg arm at Week 0 and Week 24.