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Pain relief of foot blisters using COMPEED® hydrocolloid plasters: a randomized, open-labelled comparative superiority clinical investigation versus regular plasters

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Abstract

Introduction: Prolonged friction of the skin rubbing against another surface (such as a sock or footwear), is one of the most common minor dermatologic lesions, causing discomfort and pain. One treatment strategy consists in covering and protecting the blister with a plaster, in order to minimize pain and limit blister size and severity. COMPEED® hydrocolloid plasters for Blisters protect and cushion foot blisters, create the adequate environment for blisters healing and provide immediate pain and pressure relief. This clinical investigation aimed at evaluating the clinical performance of COMPEED® hydrocolloid plasters in providing pain and pressure relief in the population presenting with painful foot blisters after running or hiking.

Method: This was an interventional, subject-centered, longitudinal, randomized, open-labelled superiority study performed on a parallel-group cohort, including two subcohorts of specific interests. Included subjects were ≥ 14 years-old, presenting with at least one painful foot blister after participation in a sports event.

Results: From June 27th to October 2nd, 2021, 757 subjects were enrolled during 13 sports events, in France, of whom 752 (99.3%) were randomized. Among them, 551 subjects (73.2%) completed (partially or completely) the post-event ePRO questionnaire; and 516 subjects (93.6%) were included in the reference set: 368 subjects in the main cohort, 68 subjects in the paired group cohort and 80 subjects in the street shoes cohort. Results were overall comparable among cohorts. We described that 82.5% of subjects experienced instant pain relief after applying COMPEED® hydrocolloid plaster. Two days after COMPEED® hydrocolloid plaster application, 91.8% of subjects reported blister pain relief while 98.3% reported pain relief at the end of the study. Compared to COMPEED®, statistically significantly less subjects with regular plaster reported instant blister pain relief and pain relief over time ($p<.0001$). Likewise, compared to subjects in the COMPEED® group, statistically significantly less subjects ($p<.0001$) with regular plaster reported good pressure relief, adhesion and cushioning.

Conclusion: We demonstrated that COMPEED® hydrocolloid plasters provided pain relief instantly and over time of painful foot blisters after a sports event. Excepting the randomization, this investigation emulated real-life use of COMPEED® hydrocolloid plasters

Introduction

Prolonged friction of the skin rubbing against another surface (such as a sock or footwear), causes shear forces within the skin and erythema in and around the rubbing zone. The area encompassed by the erythema is commonly referred to as the 'hot-spot', due to the increased burning sensation [1]. Continuous shear further causes epidermal cells necrosis followed by accumulation of serum-like fluid, filling the intra-epidermal split and leading to formation of a blister [2]. Friction blisters are one of the most common minor dermatologic lesions of the human skin causing discomfort and pain, and may create entry portals for infections [3], which if aggravated, may trigger cellulitis or sepsis and even toxic shock. Among risk factors, affecting friction forces [1,2], intermediate levels of heat and moisture tend to trigger the development of blisters [2]. It is, therefore, not surprising that foot blister occurrence is particularly high in certain sports which place considerable performance demands on the feet. Estimates show that up to 39% of marathon runners, over 40% of soldiers in training, and over 50% of hikers are affected by this condition [4]. Blister severity varies from hot spot to intact blister (bubble filled with clear fluid), blood blister (bubble filled with blood), torn blister (blister not sealed by skin), bleeding blister, deroofed blister (blister upper skin or roof, rubbed off) [5,6].

Treatment of foot blisters aims at minimizing pain, limiting blister size and severity, preventing complications such as skin infections and optimizing return to full activities [7]. One of the most frequent treatment strategies consists of covering and protecting the blister with a plaster, in order to keep the blister roof intact [8]. The first hydrocolloid

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adhesive plasters were developed in the 80's and plaster composition has been optimized throughout the last decades. COMPEED® hydrocolloid plasters for Blisters are intended to be used for relieving blisters pain and discomfort and for creating the optimal environment for blisters healing. Hydrocolloid dressing applied on blisters acts as a second skin and protects from further skin shearing and rubbing, thus reducing associated pain. The goal of this clinical investigation was to evaluate the clinical performance of COMPEED® hydrocolloid plasters compared to regular non hydrocolloid plasters in providing pain relief, pressure relief in the population presenting with painful foot blisters after running or hiking.

Materials and Methods

Study Design and subjects

This was an interventional, subject-centered, longitudinal, randomized, open-labelled superiority study performed on a parallel-group cohort (herein referred to as main cohort), including two subcohorts of specific interests (paired group and street shoes cohorts, described below), conducted from June 2021 until October 2021 (date of last questionnaire completion of last included subject) and enrolling subjects during 13 sports events in France.

Eligible subjects were aged 14 years old or more at enrolment, presented with at least one painful foot blisters after participation at a sport event (running, trail-running, hiking). Subjects understood the full nature and purpose of the study, were willing to sign a written consent (or parent/legal representative consent as applicable) and were willing to complete the French questionnaire booklet. Finally, they had to be covered by healthcare insurance. Excluded from the investigation were: subjects presenting with any uncontrolled systemic disease (e.g. diabetes, cardiovascular disease, etc.) or with a contraindication/hypersensitivity/allergy to any component of any plaster.

The expected subject' study duration was up to 8 days (+ 2 extra days to allow questionnaire completion, i.e., ten days) post enrolment for self-completion of the electronic Patient Reported Outcome (ePRO) questionnaire) or until blister's complete healing, whichever came first. The end of the study was defined as the date of completion of the last expected ePRO questionnaire.

Investigational products

The COMPEED® hydrocolloid plasters for Blisters considered in this clinical investigation are medical devices, intended to be used for the protection, cushioning and ideally for healing of foot blisters. They are non-invasive and non-sterile dressings composed of: a semi-permeable membrane (polyurethane film) allowing the skin/wound to breathe and protecting it from external contaminants such as dirt and bacteria; a hydrocolloid adhesive, adhering to skin and providing wound micro-environment moisturizing capabilities that contributes to the healing process. Six hydrocolloid plasters from the COMPEED® range were used during the investigation differing mainly in size and shape, after subject randomisation (see below) according to the expected locations/sizes of blisters based on the participants' previous experience: COMPEED® Blister Small (herein referred to as Small), COMPEED® Blister Medium (Medium), COMPEED® Blister On Toes (On Toes), COMPEED® Blister Underfoot (Underfoot), COMPEED® Sports Heel Blister (Medium Extreme) COMPEED® Blister High Heel (High Heel). The chosen comparator was HANSAPLAST UNIVERSAL, a CE marked regular plaster, available in 4 different sizes (herein, the two smaller sizes grouped in "small" category and the two bigger ones in "big" category). The choice of such regular non hydrocolloid plasters has been driven by their wide availability and common use in the general European population to heal foot blisters.

Ethical aspects

The protocol was reviewed and approved by the French Ethics Committee (EC) Ouest IV, on May 6th, 2021, prior to inclusion of subjects. This clinical investigation was conducted in compliance with the latest version of the Declaration of Helsinki (October 2013), the international standard EN ISO 14155:2020 ('Clinical Investigation of medical devices for human subjects – Good Clinical Practice'), Regulation (EU) 2017/745 of 5 April 2017, MEDDEV 2.12/2 Post market clinical follow-up studies, for France, French Public Health Code. Written informed consent was obtained by subjects before start of any study-related procedure.

Study procedures

Subjects were made aware of the clinical investigation through an awareness campaign prior to each selected sports event. Any subjects presenting at least one painful blister at the end of the event and presenting to the study booth, was invited to participate in the clinical investigation. A dedicated trained study team, including a study nurse, explained the investigation, verified subject's investigation understanding and eligibility criteria and obtained each subject's informed consent to participate to the investigation. The study nurse also collected the variables of randomization (as described below) to randomize the subject. An inclusion package was provided to each randomized subject, including the plasters they could need over the eight-day study period as well as the identification card to access the dedicated and secured ePRO. The procedure to place the randomized plaster was explained by the study team to each randomized subject and a written procedure was also given in the inclusion package as a memory tip. Main cohort was composed of subjects who presented a painful foot blister after the event; randomisation was on parallel groups, so subjects were randomised either in COMPEED® group or regular plaster group. Paired group cohort was composed of subjects presenting with at least one painful blister per foot after the event. They were randomized using the same procedure at the difference that it was done on paired groups, i.e. each subject was his/her own control. Street shoes cohort was composed of subjects presenting at least one blister on the Achilles heel at the end of the event and who planned to regularly wear street shoes during the week that followed the event.

Subjects were asked to complete the ePRO questionnaires. In this questionnaire, each subject evaluated blister characteristics (e.g. location, size, severity), blister pain evaluation during follow-up, pressure relief, protection of blister and plaster adhesion. The subject also reported plaster changes and associated reasons and blister healing state.

Randomization

Randomization was performed after the sports event upon painful blister occurrence i.e. after having obtained the subject's informed consent, verified the eligibility criteria and collected the decisional tree data (blister on one or both feet, blister location, size, severity and use of street shoes in the days following the event by the site staff). In the main cohort, each subject applied on their painful blister a COMPEED® hydrocolloid plaster or a regular plaster depending on the randomization result. In the paired-groups cohort, each subject applied a COMPEED® hydrocolloid plaster on one foot and a regular plaster on the other foot depending on the randomization result. Both randomizations were done centrally using an interactive web response system (IWRS) and

consisted in a permuted block randomization with size block randomly assigned to 4 and 6. To preserve the blinded concealment principle, (a) the randomization lists was generated, loaded within the IWRS and only accessible by a study independent statistician and (b) the blocks sizes remained unknown to any operational stakeholders until the end of the recruitment period. Both randomization allocation ratios were 1:1.

An additional algorithm i.e. decisional tree, was added in order to determine which type of COMPEED® hydrocolloid plaster was required per blister type. This required the collection of:

- The presence or absence of at least one blister on each foot
- The foot location (i.e. left foot, right foot)
- The blister location (i.e. heel, underfoot, arch/top of foot, toe)
- The blister size (i.e. < 1 cm, 1 - 2 cm, > 2 cm)
- The blister severity (e.g. intact blister, blood blister, bleeding blister, torn blister, deroofed blister).

This decisional tree was integrated to the IWRS so that the location where the COMPEED® hydrocolloid plaster was to be applied as well as its type were provided at the time of the subject randomization. If there were several blisters, the subject was asked to select the most painful blister. However, the algorithm also took into account the intent of the subject to use street shoes within the week following the event (street shoes cohort).

Sports events characteristics

Subjects included in the study participated in sports events where circuit distances were between 1.4km and 220km, according to the event and could therefore last for several hours.

Primary outcome

Primary outcome was pain relief provided by COMPEED® hydrocolloid plaster, instantly and over time: description of the percentage of subjects presenting instant blister pain relief (defined as a reduction of at least 1 point in the pain evaluated using a numeric rating scale (NRS) ranging from 0 to 10 ('no pain at all' = 0, 'very mild pain' = 1 – 2, 'mild pain' = 3 – 4, 'moderate' pain = 5, 'severe pain' = 6 – 7, 'very severe pain' = 8 – 9, 'worst possible pain' = 10)), after the first COMPEED® hydrocolloid plaster application and after putting shoes on with respect to the worst pain experienced during or just after the sports event but prior to the first plaster application. And pain relief evolution over time, was defined as the mean change from baseline in pain as evaluated using a NRS, 5, 10, 30 min after shoes on; at Day 2 and at the study end (at Day 8 or full healing of the blister, whichever came first) with the baseline value defined as the worst pain experienced during the sports event or just after but prior to first COMPEED® hydrocolloid plaster application.

Secondary outcomes

Instant pain relief and pain relief evolution: comparison of the percentage of subjects presenting instant pain relief and pain relief evolution over time (as previously described), after the first plaster application (COMPEED® hydrocolloid plaster vs regular plaster) before and after putting shoes on, with respect to the worst pain experienced during or just after the event but prior to the first plaster application.

Pressure relief: as evaluated by subjects using a 7-point Likert scale (No /Little /Moderate /Fairly good /Good /Very good /Full), instantly post-event, at Day 2 and at study end, for COMPEED® hydrocolloid plaster and as compared to regular plaster.

Cushioning: as evaluated using a 7-point Likert scale (No /Little / Moderate /Fairly good /Good /Very good /Full) at Day 2 and at study end, for COMPEED® hydrocolloid plaster and as compared to regular plaster.

Adhesion: (plaster staying in place) as evaluated using a 7-point Likert scale (No /Little /Moderate /Fairly good /Good /Very good /Full) at Day 2 and at study end, for COMPEED® hydrocolloid plaster and as compared to regular plaster.

Time to Healing: was described only for subjects for whom the blister fully healed during the study and was defined as the date of blister's current healing state was 'fully healed' – Date of randomization. It was described for COMPEED® hydrocolloid plaster and as compared to regular plaster.

Global perception/satisfaction: subject's global impression of COMPEED® hydrocolloid plaster compared to regular plaster was rated using a 7-point Likert scale (1: 'no pain relief at all' and 7: 'complete pain relief); subject' overall satisfaction using a 7-point Likert scale (1: 'very unsatisfied' and 7: 'very satisfied'); subject's likeliness to recommend COMPEED® hydrocolloid plaster compared to regular plaster to family/ friends as evaluated post-event using a 5-point Likert scale (1: 'certainly not' and 5: 'absolutely') and subject's willingness to use the plaster again for blister treatment.

Medical Device Vigilance of COMPEED® hydrocolloid plasters: all adverse device effects related to each plaster type, anticipated or unanticipated.

Statistical analysis

Five analysis populations were defined:

- Enrolled set included all subjects who provided their information consent.
- Randomized set consisted of all subjects randomized in the investigation.
- Reference set consisted of all randomized with no missing data regarding the main study variables and having completed the event or having prematurely discontinued the event after having run/ walked on a distance considered to be significant with respect to the risk of blister occurrence (at least 1km). Demographics and baseline characteristics as well as all efficacy endpoints were analysed on the reference set.
- Safety set consisted of all randomized subjects having applied at least one of the study plasters. The safety data, including the analysis of adverse device effects with COMPEED® hydrocolloid plaster were described on the safety set.
- Per Protocol (PP) set included all subjects of the reference set free from major protocol deviation, which can bias the efficacy results. The primary endpoint was performed on the PP set as a sensitivity analysis.

All analysis were performed according to plaster brand, except for safety data which was described for each COMPEED® hydrocolloid plaster. All statistical analyses were performed using Statistical Analysis Systems (SAS®) release 9.4. Primary and secondary outcomes were described overall, for all COMPEED® hydrocolloid plaster. Comparison with all regular plasters were performed using a Chi-2 test or a Fisher

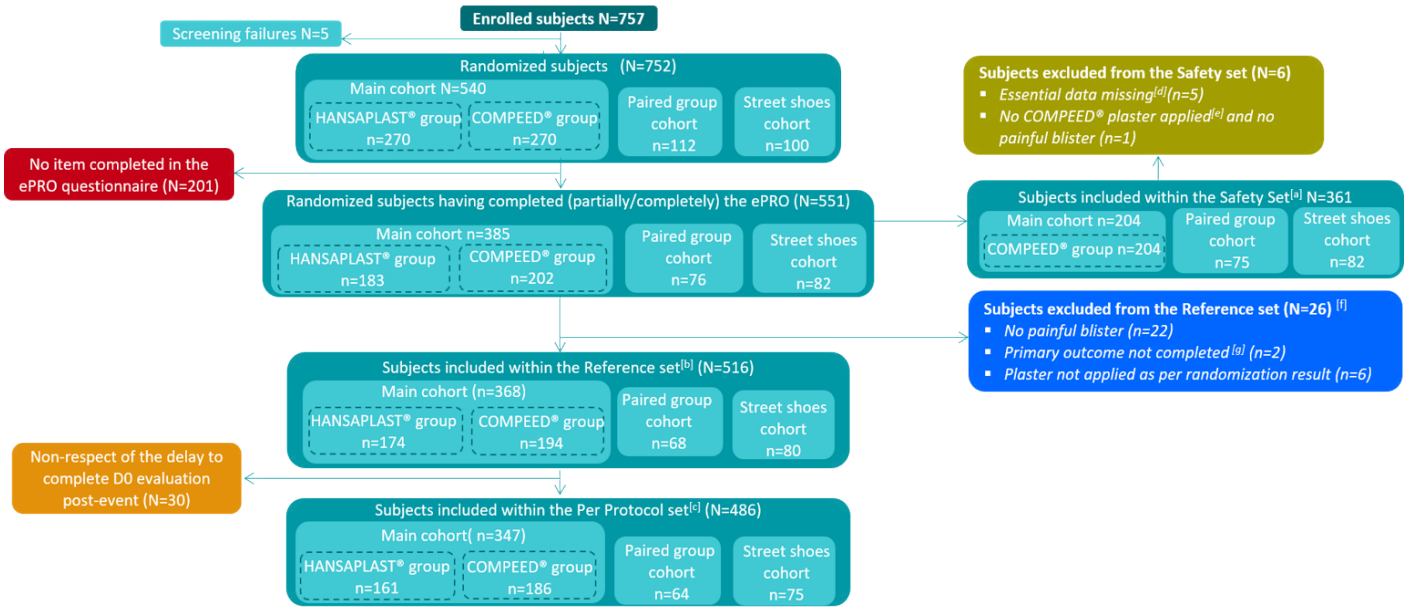

Figure 1. Study Flow chart

Flow chart of participants enrolled, randomized and included in the analysis sets of the study. (a) All randomized subjects having applied at least one COMPEED® plaster. (b) All randomized subjects for whom variables concerning the primary endpoint (plaster type, level of pain during/just after event and level of pain after plaster application and immediately after putting-on shoes) have been completed. (c) Subjects from the reference set free from any major protocol deviations. (d) At least one missing value for at least one of the following: (1) worst blister pain experienced during or just after the event, but prior to applying the first plaster and (2) level of blister pain AFTER putting on the shoes. (e) This subject did not apply the received plaster as per randomization result. (f) One subject had several reasons for not being included in the reference set. (g) This subject completed only demographics and baseline data on ePRO questionnaire

exact test. Secondary outcomes were compared between COMPEED® hydrocolloid plaster and the regular plaster using tests for parallel data or paired data, when applicable: Chi-2 test or Fisher exact test and T-test and paired T-test were used for ordinal and continuous data. The statistical significance level of the various two-sided tests performed was 5.0%.

Results

Subject's disposition and baseline characteristics

From June 27th to October 2nd, 2021, 757 subjects were enrolled during 13 sports events, in France, of whom 5 were considered as screen failures (0.6%) since no randomization data were reported, thus 752 (99.3%) were randomized (Figure 1). Among them, 551 subjects (73.2%) completed (partially or completely) the post-event ePRO questionnaire. Among the randomized subjects, 361 were included in the safety set (applied COMPEED® hydrocolloid plaster) and 516 subjects (93.6%) were included in the reference set: 368 subjects in the main cohort (194 in the COMPEED® group and 174 in the regular plaster group), 68 subjects in paired group cohort and 80 subjects in street shoes cohort (Figure 1). These 516 subjects applied 242 regular plasters and 342 COMPEED® hydrocolloid plaster, of which 74 (21.6%) COMPEED® Small, 67 (19.6%) COMPEED® Medium, 36 (10.5%) COMPEED® On Toes, 35 (10.2%) COMPEED® Underfoot, 50 (14.6%) COMPEED® Extreme and 80 (23.4%) COMPEED® High Heel. Among the 516 subjects of the reference set, 30 were excluded from the PP set as they did not complete the ePRO questionnaire within the required time window.

Since results were comparable among main cohort and subcohorts, we present hereinafter only results of the main cohort. Median age of the 368 subjects of the main cohort was 39.0 years old (ranging 14.0 to 70.0 years old) and 353 (95.9%) were aged between 18-60 years old; 211 subjects (57.3%) were male and 294 (80.1%) had normal weight (Table 1). Further, 319 out of the 368 subjects (87.1%) performed a physical activity at least 2-3 times/week; 187 (51.0%) did not have a sensitive skin as per their own evaluation and 284 (78.9%) had normal feet (as opposed to flat or hollow foot) (Table 1). Finally, 348 subjects (95.6%) reported no disease or chronic controlled condition.

Table 1. Subjects' baseline characteristics

		Main cohort - Reference Set (N=368)
Age (years)	Median	39.0
	Min; Max	14.0 ; 70.0
Age categories (years)	< 18 years	4 (1.1%)
	[18 - 60[years	353 (95.9%)
	≥ 60 years	11 (3.0%)
Gender	Female	154 (41.8%)
	Male	211 (57.3%)
	Does not want to reply	3 (0.8%)
Body mass index categories (kg/m²)*	< 18.5 'Underweight'	13 (3.5%)
	[18.5 ; 25['Normal weight'	294 (80.1%)
	[25 ; 30['Overweight'	53 (14.4%)
	≥ 30 'Obese'	7 (1.9%)
Level of physical activity**	Less than 1 time/month	2 (0.5%)
	2-3 times/month	2 (0.5%)
	1 time/week	43 (11.7%)
	2-3 times/week	185 (50.5%)
	Superior to 3 times/week	134 (36.6%)
Sensitive foot skin*	No	187 (51.0%)
	Yes	180 (49.0%)
Type of foot***	Flat foot (Fallen arch)	41 (11.4%)
	Normal foot	284 (78.9%)
	Hollow foot (High arch)	35 (9.7%)

Values are presented as median or numbers (%).* 1 missing value, ** 2 missing values, ***8 missing values.

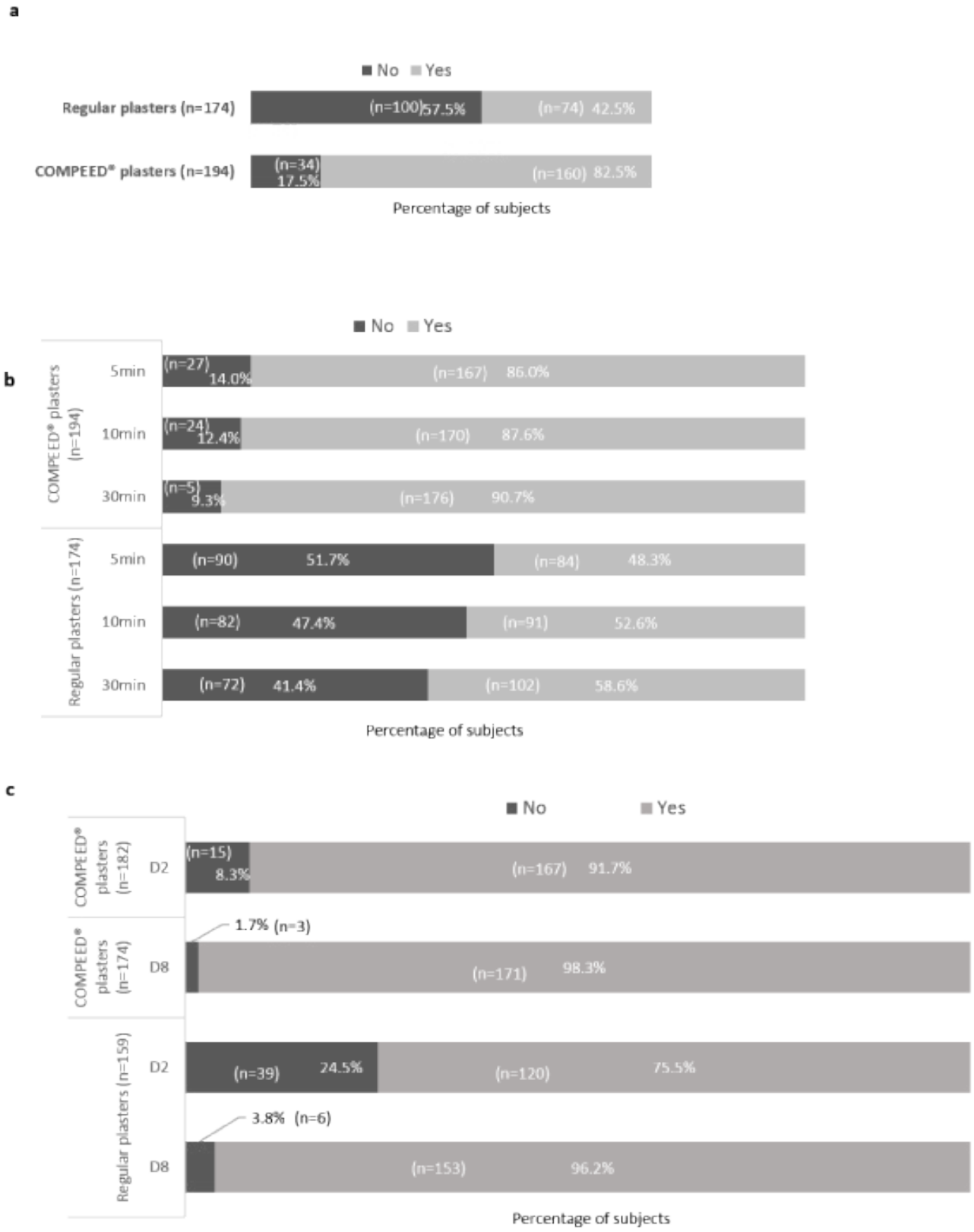

Figure 2. Blister pain relief provided according to plaster

(a) Instant pain relief, experienced immediately after putting on shoes (p value and difference (n) [95% CI]: p<.0001(39.9) [30.9 ; 49.0]) and (b) 5, 10 and 30min after having put on shoes (respectively, p<.0001 (37.8) [28.9 ; 46.7]; p<.0001 (35.0) [26.3 ; 43.8]; p<.0001 (32.1) [23.7 ; 40.5], and (c) pain relief evolution at Day 2 (12 missing values in Compeed® group and 15 in regular plaster group) (p<.0001 (16.3) [8.5 ; 24.1] and at the end of the study (20 missing values in Compeed® group and 15 in regular plaster group) (p=0.2493 (2.0) [-1.5 ; 5.6]). Instant blister pain relief was set to 'Yes' if the change of level of pain immediately after putting on shoes is ≤ -1 (i.e. reduction of at least 1 point in the pain evaluated using the NRS) and 'No' otherwise

Primary outcome - Pain relief experienced with COMPEED® hydrocolloid plaster

In order to assess instant blister pain relief, subjects attributed a score on their experienced blister pain using a NRS ranging from 0 to 10, during or right after the event but before first COMPEED® hydrocolloid plaster application vs. after the first plaster application and after putting on shoes. Among the 194 subjects of the main cohort having applied COMPEED® hydrocolloid plaster (COMPEED® group), 160 (82.5%) reported instant pain relief (Figure 2a). Blister pain relief was also evaluated over time by subjects after the first COMPEED® hydrocolloid plaster application right after putting on shoes but also 5, 10 and 30 min after putting on shoes, with respect to the worst pain experienced during or just after the event but prior to the first plaster application. Among 194 subjects in the COMPEED® group, 167 (86.0%) experienced blister pain relief 5 min after putting on shoes; 170 subjects (87.6%) 10 min after putting on shoes, and 176 subjects (90.7%) 30 min after putting on shoes (Figure 2b).

Pain relief evolution over time was further assessed after COMPEED® hydrocolloid plaster application and immediately after putting on shoes compared to Day 2 post-event and Day 8 (end of the study). Among 194 subjects in the COMPEED® group, 167 (91.7%) experienced blister pain relief at Day 2 after the sports event and 171 subjects (98.3%) at the end of study (Figure 2c). It is noteworthy, that these subjects reported that no painkilling treatment was used during the clinical investigation. Blister pain relief (instant and over time) was comparable among COMPEED® plaster types and among subjects of different age groups.

Secondary endpoints

Pain relief according to plaster brand

Among the subjects having applied regular plasters (regular plaster group), only 74 (42.5%) reported having experienced instant blister pain relief (during or right after the event but before first plaster application vs. after the first plaster application and after putting on shoes); a statistically significant difference (p<.0001) compared to COMPEED® hydrocolloid plaster, previously described (Figure 2a). Likewise, there were significantly less subjects in the regular plaster group having experienced blister pain relief at Day 2 (n=120; 75.5% vs. n=167; 91.7%, p<.0001). At the end of the study, subjects in the COMPEED® group and the regular plaster group who experienced blister pain relief, were comparable (n=171; 98.3% vs. n=153; 96.2%; p=0.2493), because their blister almost or completely healed (Figure 2c).

Pressure relief

Subjects reported on experiencing instant pressure relief and pressure relief evolution at Day 2 and at the end of the study. In the COMPEED® group, 126 subjects (65.3%) reported at least 'quite good' (cumulative results subjects answering 'quite good' and 'good' and 'very good') pressure relief instantly and immediately after putting on shoes. Over time, 145 subjects (79.7%) reported at least 'quite good' pressure relief at Day 2 and when asked at the end of the study, 158 subjects (92.4%) experienced at least 'quite good' overall pressure relief (Table 2).

Compared to the COMPEED® group, only 36 subjects in the regular plaster group (20.8%) reported at least 'quite good' pressure relief

Table 2. Pressure relief according to plaster brand

		COMPEED® plasters N = 194	Regular plasters N = 174	Total N = 368	P-value [a] Estimate of the between groups difference [95% IC]
Pressure relief instantly post-event [a]	**N**	193*	173*	366	
	Not good	67 (34.7%) [28.36;41.69]	137 (79.2%) [72.48;84.58]	204 (55.7%) [50.61;60.74]	
	Quite good	126 (65.3%) [58.31;71.64]	36 (20.8%) [15.42;27.52]	162 (44.3%) [39.26;49.39]	<.0001 44.5 [35.4 ; 53.5]
Pressure relief at Day 2	**N**	182**	157***	339	
	Not good	37 (20.3%) [15.12;26.82]	127 (80.9%) [73.96;86.29]	164 (48.4%) [43.11;53.69]	
	Good	145 (79.7%) [73.18;84.88]	30 (19.1%) [13.71;26.04]	175 (51.6%) [46.31;56.89]	<.0001 60.6 [52.1 ; 69.0]
Overall pressure relief at study end	**N**	171$	159£	330	
	Not good	13 (7.6%) [4.42;12.72]	116 (73.0%) [65.53;79.26]	129 (39.1%) [33.99;44.46]	
	Good	158 (92.4%) [87.28;95.58]	43 (27.0%) [20.74;34.47]	201 (60.9%) [55.54;66.01]	<.0001 65.4 [57.4 ; 73.3]

Values are presented as numbers (%) [95% IC].* 1 missing value, ** 12 missing values; ***17 missing values, $23 missing values, £15 missing values. [a] The pressure relief was considered as 'Quite Good' if the assessment of pressure relief is 'Good relief', 'Very good relief', 'Full relief' or 'Fairly good' and as 'Not good' otherwise. [b] The pressure relief will be considered as 'Good' if the assessment of pressure relief is 'Good relief', 'Very good relief' or 'Full relief' and as 'Not good' otherwise.

Table 3. Plaster adhesion

		COMPEED® plasters N = 194	Regular plasters N = 174	Total N = 368	P-value Estimate of the between groups difference [95% IC]
Good plaster adhesion at day 2 [a]	**N**	182*	157**	339	
	No	31 (17.0%) [12.25;23.23]	114 (72.6%) [65.12;78.98]	145 (42.8%) [37.62;48.09]	
	Yes	151 (83.0%) [76.77;87.75]	43 (27.4%) [21.02;34.88]	194 (57.2%) [51.91;62.38]	<.0001 55.6 [46.7 ; 64.4]
Good overall plaster adhesion end of study	**N**	171$	158£	329	
	No	38 (22.2%) [16.64;29.08]	105 (66.5%) [58.76;73.34]	143 (43.5%) [38.22;48.87]	
	Yes	133 (77.8%) [70.92;83.36]	53 (33.5%) [26.66;41.24]	186 (56.5%) [51.13;61.78]	<.0001 44.2 [34.6 ; 53.9]
Duration the plaster sticks to the skin (days) [b]	**N**	153***	168§	321	
	Median	4.00	1.00	2.00	<.0001 2.00 [1.66 ; 2.33]
	Min ; Max	1.0 ; 7.0	1.0 ; 6.0	1.0 ; 7.0	

Values are presented as numbers (%) [95% IC] or median.* 12 missing values; **17 missing values, $23 missing values, £15 missing values, *** 41 missing value, § 6 missing values. [a] A good plaster adhesion will be defined as an adhesion 'good', 'very good' or 'excellent (i.e. adhesion score = 5).

instantly and immediately after putting on shoes (p<.0001). Likewise, only 30 subjects (19.1%) reported at least 'quite good' pressure relief at Day 2 (p<.0001) and 43 subjects (27.0%) at the end of the study (p<.0001) (Table 2).

Plaster adhesion

At Day 2, COMPEED® hydrocolloid plaster adhesion was reported as at least 'good' by 151 subjects (83.0%) and overall, during the course of the study, by 133 subjects (77.8%) (Table 3).

Compared to COMPEED® group, only 43 subjects (27.4%) reported regular plaster adhesion as 'at least' good at Day 2 (p<.0001) and overall 53 subjects (33.5%) (p<.0001) (Table 3).

Subjects evaluated the duration of plaster adhesion on skin after application: Median duration of the plaster on skin was 4.00 days in the COMPEED® group as compared to median duration of regular plaster on skin was 1.00 day (p<.0001) (Table 3).

Cushioning

The cushioning effect of the plaster against rubbing/friction was assessed by subjects at Day 2 and overall, at the end of study. In the COMPEED® group, 127 subjects (70.2%) reported at least a 'good' cushioning effect of their plaster at Day 2 and 159 subjects (93.0%) at the end of the study (Table 4).

Compared to the COMPEED® group, only 22 subjects in the regular plaster group (13.9%) reported at least 'good' cushioning effect of their plaster at Day 2 (p<.0001) and 34 subjects (21.4%) at the end of the study (p<.0001) (Table 4).

Time to healing

Every day, starting Day 1 and up to Day 8, all subjects who changed their plaster, reported their blister's healing state. The number of subjects who changed their plaster from Day 1 to Day 8, were as follows: 17, 22, 39, 32, 54, 43, 30, 19 subjects respectively. The percentage of subjects reporting 'fully healed' blister day by day, from Day 1 and until Day 8 was 17.6%, 4.5%, 17.9%, 25.0%, 38.9%, 39.5%, 53.3% and 78.9% (Table 5a). Mean (± SD) time to healing for subjects for whom the studied blister fully healed during the study was 5.65 (± 1.77) days and 4.95 (± 1.90) days for the COMPEED® and regular plaster groups respectively (p=0.0274) (Table 5b).

Global Impression and satisfaction

Subjects assessed the ability of COMPEED® hydrocolloid plasters to generally relieve pain (n=163; 95.3%) and instantly relieve pain (n=140; 81.9%) as at least 'good'. Conversely, significantly less subjects assessed the ability of regular plasters to generally (n=45; 28.5%) or instantly (n=27; 17.1%) relieve pain (p<.0001) as at least 'good'. Significantly more subjects (n=164; 95.9%) were satisfied with the COMPEED®

Table 4. Cushioning against rubbing/friction according to plaster brand

		COMPEED® N = 194	Regular N = 174	Total N = 368	P-value Estimate of the between groups difference [95% IC]
Good cushioning effect of the plaster against rubbing/friction at Day 2 [a]	**N**	181*	158**	339	
	No	54 (29.8%) [23.65;36.89]	136 (86.1%) [79.71;90.66]	190 (56.0%) [50.72;61.23]	
	Yes	127 (70.2%) [63.11;76.35]	22 (13.9%) [9.34;20.29]	149 (44.0%) [38.77;49.28]	<.0001 56.2 [47.7 ; 64.8]
Good overall cushioning effect of the plaster against rubbing/friction end of study [a]	**N**	171$	159£	330	
	No	12 (7.0%) [3.98;12.02]	125 (78.6%) [71.55;84.28]	137 (41.5%) [36.33;46.90]	
	Yes	159 (93.0%) [87.98;96.02]	34 (21.4%) [15.72;28.45]	193 (58.5%) [53.10;63.67]	<.0001 71.6 [64.2 ; 79.0]

Values are presented as numbers (%) [95% IC].*13 missing values; **16 missing values, $23 missing values, £15 missing values. [a] The cushioning effect will be considered as 'good' if the cushioning effect is 'good', 'very good' or 'excellent' (i.e. score ≥ 5).

Table 5a. Blister healing state day by day upon COMPEED® hydrocolloid plaster for blisters change

		COMPEED® plasters N = 194
Blister's current healing state at day 1	N	17
	Not healed at all	1 (5.9%)
	Healing ongoing but no visible change since the last plaster change	3 (17.6%)
	Healing ongoing, the blister seems better compared to previous plaster change	10 (58.8%)
	Fully healed, I don't need to use a new plaster	3 (17.6%)
Blister's current healing state at day 2	N	22
	Not healed at all	0 (0.0%)
	Healing ongoing but no visible change since the last plaster change	8 (36.4%)
	Healing ongoing, the blister seems better compared to previous plaster change	13 (59.1%)
	Fully healed, I don't need to use a new plaster	1 (4.5%)
Blister's current healing state at day 3	N	39
	Not healed at all	0 (0.0%)
	Healing ongoing but no visible change since the last plaster change	8 (20.5%)
	Healing ongoing, the blister seems better compared to previous plaster change	24 (61.5%)
	Fully healed, I don't need to use a new plaster	7 (17.9%)
Blister's current healing state at day 4	N	32
	Not healed at all	1 (3.1%)
	Healing ongoing but no visible change since the last plaster change	2 (6.3%)
	Healing ongoing, the blister seems better compared to previous plaster change	21 (65.6%)
	Fully healed, I don't need to use a new plaster	8 (25.0%)

Blister's current healing state at day 5	N	54
	Not healed at all	0 (0.0%)
	Healing ongoing but no visible change since the last plaster change	6 (11.1%)
	Healing ongoing, the blister seems better compared to previous plaster change	27 (50.0%)
	Fully healed, I don't need to use a new plaster	21 (38.9%)
Blister's current healing state at day 6	N	43
	Not healed at all	2 (4.7%)
	Healing ongoing but no visible change since the last plaster change	3 (7.0%)
	Healing ongoing, the blister seems better compared to previous plaster change	21 (48.8%)
	Fully healed, I don't need to use a new plaster	17 (39.5%)
Blister's current healing state at day 7	N	30
	Not healed at all	2 (6.7%)
	Healing ongoing but no visible change since the last plaster change	1 (3.3%)
	Healing ongoing, the blister seems better compared to previous plaster change	11 (36.7%)
	Fully healed, I don't need to use a new plaster	16 (53.3%)
Blister's current healing state at day 8	N	19*
	Not healed at all	0 (0.0%)
	Healing ongoing but no visible change since the last plaster change	1 (5.3%)
	Healing ongoing, the blister seems better compared to previous plaster change	3 (15.8%)
	Fully healed, I don't need to use a new plaster	15 (78.9%)

Values are presented as numbers (%). * 1 missing value; N, subjects who changed their plaster on that day and included in the analysis.

Table 5b. Time to healing according to plaster brand

		COMPEED® plasters N = 194	Regular plasters N = 174	P-value Estimate of the between groups difference [95% IC]
Time to healing, only for subjects for whom the blister fully healed during the study (days)	N	88	108	
	Mean ± SD	5.65 ± 1.77	4.95 ± 1.90	0.0274 0.56 [0.06 ; 1.06]
	Median	6.00	5.00	
	Min ; Max	1.0 ; 8.0	1.0 ; 8.0	

Values are presented as mean (± SD).

hydrocolloid plaster used unlike the regular plaster (n=71; 44.9%) (p<.0001). All but one subject who used COMPEED® hydrocolloid plaster (n=169; 99.4%) reported they would probably or absolutely recommend the plaster to a member of family or to a friend unlike only 55 subjects (34.6%) who used regular plaster. Finally, at the end of the study, significantly more subjects (n=168; 98.8%) reported they would be willing to use COMPEED® hydrocolloid plaster again than a regular plaster (n=70; 44.0%) (p<.0001). These results were comparable among the different COMPEED® plaster types.

Adverse events & Adverse Device effects

Overall, during the clinical investigation, there were only 5 subjects with at least one adverse device effect (ADE) (1.4%) and a total of 8 ADEs within the 361 subjects of the safety set, concerning COMPEED® Underfoot, Medium Extreme and High Heel plaster types. Two (0.6%) application site pains with Underfoot and High Heel plasters, 1 (0.3%) application site swelling with High Heel plaster, 1 (0.3%) application site irritation with Medium plaster, 1 (0.3%) application site laceration with Medium Extreme plaster, 1 (0.3%) condition aggravated with High Heel plaster, 1 (0.3%) site infection with Underfoot plaster and 1 (0.3%) peripheral swelling with Underfoot plaster.

Discussion

This interventional, subject-centered, longitudinal, randomized, open-labelled clinical investigation demonstrated pain relief provided by COMPEED® hydrocolloid plasters, instantly and over time of painful foot blisters after a sports event. Even if it was subjective, self-assessment of pain (linked to the subject-centered design of the study) is the current clinical standard and was thus appropriate for pain relief evaluation during our clinical investigation. The pragmatic approach of our clinical investigation, conducted in real-life settings (except for the randomisation procedure) ensured external validity of our results and randomization process minimized selection bias. Despite subjects' relatively long follow-up duration (up to 10 days), the percentage of subjects who completed the ePRO questionnaire was significant (73.2%) and percentages of non-assessable subjects were in line with observed percentages in conventional clinical studies.

We described that 82.5% of subjects experienced instant pain relief after applying COMPEED® hydrocolloid plaster and immediately after putting on their shoes. Increasingly more subjects experienced pain relief 5min, 10min and 30min after putting on shoes (86.1%, 87.6% and 90.7% of subjects respectively). Two days after COMPEED® hydrocolloid plaster application, 91.8% of subjects reported blister pain relief while 98.3% reported pain relief at the end of the study. Compared to COMPEED®, statistically significantly less subjects with regular plaster reported instant blister pain relief and pain relief over time. Instant pressure relief was reported by 65.3% of subjects after COMPEED® hydrocolloid plaster application. Moreover, 2 days after the sports event, 90.1% of subjects reported pressure relief as at least 'quite good' and when asked at the end of the study, 96.5% of subjects reported at least 'quite good' pressure relief. COMPEED® hydrocolloid plaster adhesion was reported as at least 'good' by 83.0% at Day 2 and 77.8% of subjects, overall, during the course of the study. COMPEED® hydrocolloid plaster cushioning was reported as at least 'good' by 70.2% at Day 2 and 93.0% of subjects, overall, during the course of the study. Overall, compared to subjects in the COMPEED® group, statistically significantly less subjects (p<.0001) with regular plaster reported good pressure relief, adhesion and cushioning.

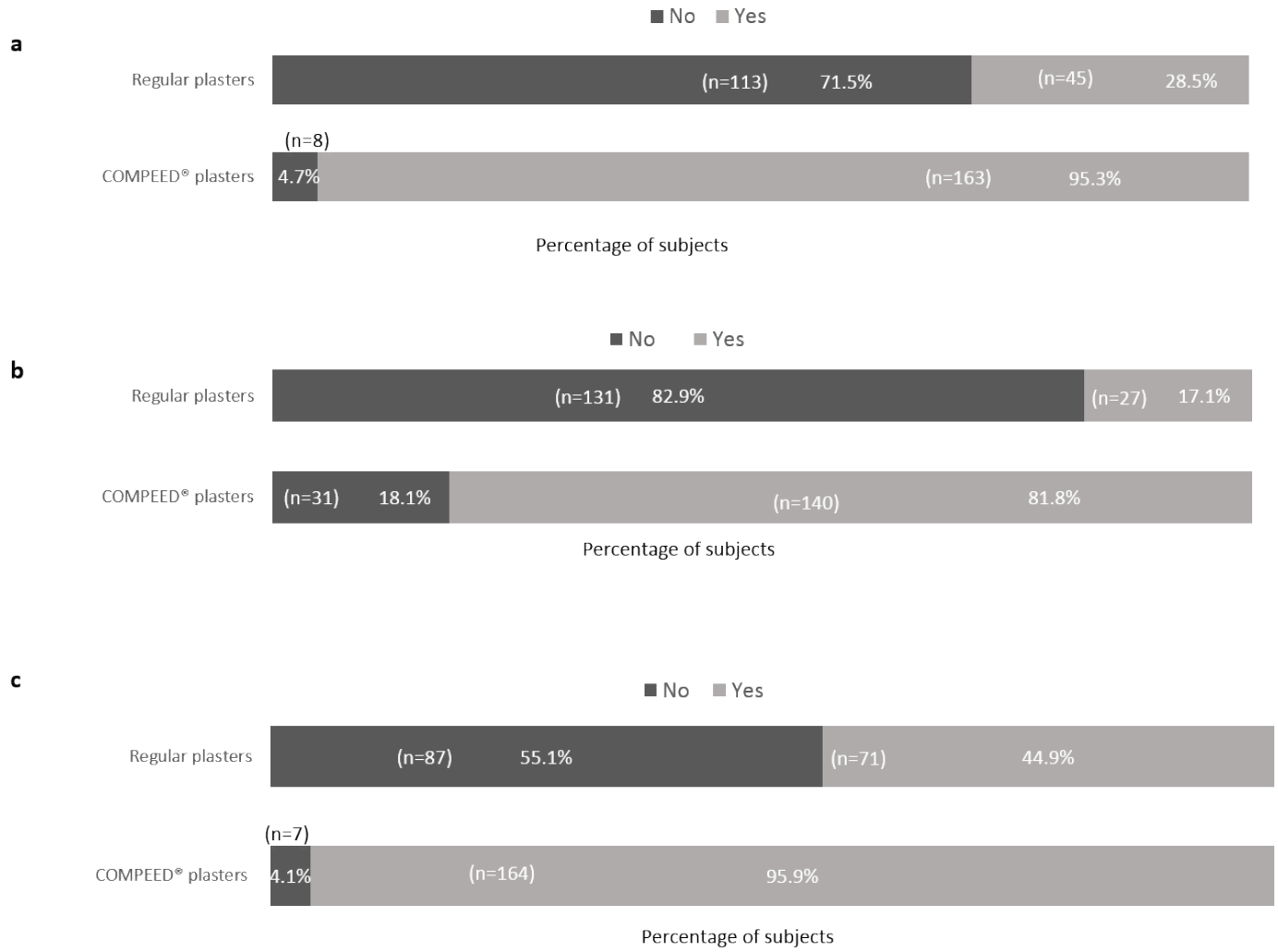

Figure 3. Global impression and satisfaction on efficacy of COMPEED® plaster versus regular plaster in relieving blister pain
(a) Global impression on general efficacy in relieving blister pain (p<.0001 (66.8) [59.1; 74.6]. (b) Global impression on instant efficacy in relieving instant pain (p<.0001 (64.7) [56.5; 72.9]. (c) Global satisfaction according to plaster brand (p<.0001 (51.0) [42.7; 59.3]. The good global impression was set to 'Yes' if the global impression was 'good pain relief', 'very good pain relief' or 'complete pain relief' (i.e. score ≥ 5). COMPEED® group: 23 values missing; regular plasters: 16 values missing

The assessment of time to healing was done only upon plaster change, so subjects who did not change their plaster on that day were not included in the analysis; it doesn't completely reflect a healing evolution. COMPEED® hydrocolloid plaster adhesion being excellent and plasters staying on skin for a median of 4 days, time to healing could not be precisely assessed for COMPEED® hydrocolloid plaster. Finally, in view of the small number of expected adverse device effects, our results demonstrated that COMPEED® hydrocolloid plaster presents an excellent safety profile.

Results of this clinical investigation are in line with the recently published prospective study by Artus-Arduise, *et al.* (4), showing superiority of COMPEED® plasters in terms of pain relief, adhesion, and cushioning as compared to regular plasters. To our knowledge, there are no other published reports on pain relief provided by hydrocolloid plasters. Overall, none of the results of our clinical investigation were contradictory and secondary outcomes were all in favour of COMPEED® hydrocolloid plaster for Blisters as compared to regular plasters.

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Conflicts of interest

JZB (Medical Operations Lead), PA (Scientific Affairs Assistant & Clinical Operations Assistant), TJ (Global Category Lead Wound Care) and CAA (Global Head of Medical Affairs) are employees at Laboratoire HRA Pharma (manufacturer of the COMPEED® brand of products). MK (Medical writer), VC (Head of Biometrics Department), CP (Chief Operating Officer & Head of Clinical Operations), SW (Head of Medical and Scientific Affairs Department), RG (Head of Business Operations) are employees at ICTA, the organization to which the study conception, operational set-up and conduct, analysis, article writing was subcontracted.

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