Clinical trial results:
An antimicrobial cream for the treatment of impetigo

Summary

EudraCT number	2008-000036-41
Trial protocol	GB
Global end of trial date	27 February 2019

Results information

Result version number	v1 (current)
This version publication date	12 March 2021
First version publication date	12 March 2021

Trial information

Trial identification

Sponsor protocol code	IPTG-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dermal Laboratories Limited
Sponsor organisation address	Tatmore Place, Gosmore, Hitchin, United Kingdom, SG4 7QR
Public contact	Sue Dean, Dermal Laboratories Ltd, 44 01462 458866, clinical@dermal.co.uk
Scientific contact	Sue Dean, Dermal Laboratories Ltd, 44 01462 458866, clinical@dermal.co.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2019
Global end of trial reached?	Yes
Global end of trial date	27 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was:
• to determine whether IPTG Cream is efficacious in the treatment of primary non-bullous impetigo, using a non-inferiority study design based on the treatment effect of Fucidin Cream from a previous placebo-controlled study.

Protection of trial subjects:

Once a potential patient was identified for the study, a Patient Information Sheet was provided to the patient and/or their parent/guardian to read through before considering participation in the study, and to keep for review during the study. In addition to the normal style and format used for adults, child-friendly versions specifically tailored for 6 to 7 years, 8 to 10 years, and 11 to 15 years, were used. For children below the age of 6 years, the study was explained to the child patient verbally, using language suitable for their capacity of understanding.

Once the potential participant fully confirmed their understanding of the requirements for the study and their questions or queries regarding the trial were satisfactorily answered and they agreed to participate, written, signed, fully informed consent was then taken. All patients aged 16 years and above signed an Informed Consent Form prior to their involvement in the study. For patients less than 16 years, their parent/guardian signed an Informed Consent Form to confirm that they were volunteering their fully informed consent for their child to enter the study. Those patients under 16 years of age, deemed capable of giving their assent to take part in the study, were also asked to sign an Assent Form.

Background therapy:

Patients were instructed to gently cleanse the affected areas before the initial application, as long as this did not cause discomfort and then to apply enough of the cream provided (either IPTG or Fucidin) to gently rub into the impetigo affected area(s) and immediately surrounding skin, three times daily for the full 7 day treatment period (21 treatments in all) following the instructions provided in the Product Information Leaflet within the Treatment Diary.

Patients were instructed not to cover their impetigo lesions with dressings, bandages and/or nappies etc. while treating these areas.

Evidence for comparator:

Fucidin Cream was a suitable comparator because, despite recent concerns about emerging bacterial resistance, it was, at the time the study was designed and implemented, the standard first line treatment in this indication as recommended by NICE and its effectiveness has been demonstrated in a number of good quality published studies, including the key placebo controlled study used for the determination of the non-inferiority margin for the primary efficacy objective (Koning et al, 2002). In addition, Fucidin is a white cream formulation which enables the study to be designed as a double-blind comparison.

Actual start date of recruitment	16 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 273
Worldwide total number of subjects	273
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	10
Children (2-11 years)	148
Adolescents (12-17 years)	14
Adults (18-64 years)	87
From 65 to 84 years	12
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Recruitment was opportunistic, involving patients presenting for treatment at 28 GP centres across the UK.

Pre-assignment

Screening details:

276 potential participants were consented and screened, of whom 3 were found to be ineligible. The remaining 273 patients were randomised. Six patients were excluded from the full ITT analysis set.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Fucidin group

Arm description:

Patients allocated to receive fucidin cream.

Arm type	Active comparator
Investigational medicinal product name	Fucidin cream (2% fusidic acid)
Investigational medicinal product code	PL 00043/0065
Other name	Fucidic acid cream 20 mg/g
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

Fucidin cream, topically applied three times daily, for 7 days.
Enough fucidin cream to gently rub into the impetigo affected areas and immediate surrounding skin.

Arm title	IPTG group

Arm description:

Patients allocated to receive IPTG cream.

Arm type	Experimental
Investigational medicinal product name	IPTG cream
Investigational medicinal product code	
Other name	IPTG cream: Chlorhexidine dihydrochloride 0.1% w/w Benzalkonium chloride 0.1% w/w Isopropyl Myristate 10% w/w Liquid paraffin 10% w/w
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

IPTG Cream, topically applied three times daily, for 7 days.
Enough IPTG Cream to gently rub into the impetigo affected areas and immediate surrounding skin.

Number of subjects in period 1	Fucidin group	IPTG group
Started	137	136
Completed	112	106
Not completed	25	30
Randomised twice in error	1	-
Not invited back to V3	1	1
Disallowed medication to prevent recurrence	2	1
Adverse event, non-fatal	2	1
Serious breach	2	3
Impetigo disease progression	6	9
Used disallowed emollient on impetigo	2	2
No longer willing/able to attend	4	6
Lost to follow-up	4	5
Disallowed medication for a different condition	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Fucidin group
Reporting group description:	
Patients allocated to receive fucidin cream.	
Reporting group title	IPTG group
Reporting group description:	
Patients allocated to receive IPTG cream.	

Reporting group values	Fucidin group	IPTG group	Total
Number of subjects	137	136	273
Age categorical Units: Subjects			
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	4	6	10
Children (2-11 years)	76	72	148
Adolescents (12-17 years)	7	7	14
Adults (18-64 years)	43	44	87
From 65-84 years	5	7	12
85 years and over	2	0	2
Gender categorical Units: Subjects			
Female	85	74	159
Male	52	62	114

End points

End points reporting groups

Reporting group title	Fucidin group
Reporting group description:	
Patients allocated to receive fucidin cream.	
Reporting group title	IPTG group
Reporting group description:	
Patients allocated to receive IPTG cream.	

Primary: Clinical response at end of treatment (EOT)

End point title	Clinical response at end of treatment (EOT)

End point description:

The Primary Efficacy Parameter was the clinical response, i.e. success or failure, at the EOT visit, after the end of the seven-day treatment period.
As defined by Oranje et al. (2007):
Clinical success at EOT was defined as:
• a total absence of treated lesions, or
• the treated lesions have become dry without crusts, with or without erythema, compared with appearance at baseline, or
• the lesions show improvement (defined as a decrease in the size of the affected area, number of lesions, or both) so that no further antimicrobial/antibacterial therapy is deemed necessary by the Investigator.
Clinical failure at EOT was defined as:
• deterioration of condition, or
• insufficient improvement (i.e. lesions remain crusted and / or have exudate leaving a yellow or honey coloured crust, or the lesion area(s) has increased from baseline, with or without an increase in the number of lesions), so that additional antimicrobial/antibacterial therapy is required.

End point type	Primary

End point timeframe:

Clinical response was assessed at the EOT visit (Day 8). A clinical response of 'clinical failure' prior to the EOT visit was carried forward to that visit.

End point values	Fucidin group	IPTG group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115[1]	116[2]		
Units: Number of patients	97	87		

Notes:

[1] - Per Protocol Analysis Set

[2] - Per Protocol Analysis Set

Statistical analyses

Statistical analysis title	Difference in success: Fucidin - IPTG

Statistical analysis description:

A one sided 2.5% significance level (Type I Error rate) was used in this non-inferiority study design, corresponding to the use of a 95% confidence interval for the difference in percentage of patients with clinical response of success between the two treatments, where the upper bound of the interval for the difference (Fucidin-IPTG) was of interest.

Comparison groups	Fucidin group v IPTG group

Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Mean difference (final values)
Point estimate	9.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	19.6

Notes:

[3] - 75% of patients treated with IPTG cream were classed as clinical success compared to 84% of patients treated with Fucidin. This is a difference of 9.4%. The M1 non-inferiority margin for the primary objective is 16 percentage points. Since the upper bound of the two-sided 95% confidence interval for the difference in percentage of patients with clinical response of success between the two treatments (Fucidin-IPTG) was more than 16 percentage points, the primary objective was not met.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From consent through to follow-up visit.	
Adverse event reporting additional description:	
Safety results are reported using the Safety Analysis Set and according to the actual study treatment received rather than the randomised treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups	
Reporting group title	Fucidin group
Reporting group description:	
Safety results are reported using the Safety Analysis Set and according to the actual study treatment received rather than the randomised treatment.	
Reporting group title	IPTG group
Reporting group description:	
Safety results are reported using the Safety Analysis Set and according to the actual study treatment received rather than the randomised treatment.	

Serious adverse events	Fucidin group	IPTG group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 136 (0.00%)	0 / 137 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Fucidin group	IPTG group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 136 (22.79%)	49 / 137 (35.77%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Condition aggravated			
subjects affected / exposed	6 / 136 (4.41%)	4 / 137 (2.92%)	
occurrences (all)	6	4	
Pain			
subjects affected / exposed	0 / 136 (0.00%)	2 / 137 (1.46%)	
occurrences (all)	0	3	
Feeling hot			
subjects affected / exposed	1 / 136 (0.74%)	2 / 137 (1.46%)	
occurrences (all)	1	2	
Pyrexia			
subjects affected / exposed	1 / 136 (0.74%)	2 / 137 (1.46%)	
occurrences (all)	1	2	
Application site erythema			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Application site pain			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Application site pruritus			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
application site redness			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Inflammation			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Swelling			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Perineal pain			

subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 136 (0.74%)	3 / 137 (2.19%)	
occurrences (all)	1	3	
Oropharyngeal pain			
subjects affected / exposed	1 / 136 (0.74%)	4 / 137 (2.92%)	
occurrences (all)	1	4	
Asthma			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
cough			
subjects affected / exposed	1 / 136 (0.74%)	1 / 137 (0.73%)	
occurrences (all)	1	1	
Nasal discomfort			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	2	
Rhinalgia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Intraocular pressure increased			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Skin injury			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	

Nervous system disorders			
Headache			
subjects affected / exposed	5 / 136 (3.68%)	6 / 137 (4.38%)	
occurrences (all)	5	6	
Paraesthesia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Lymphadenopathy			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Ocular hyperaemia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 136 (0.00%)	2 / 137 (1.46%)	
occurrences (all)	0	2	
Teething			
subjects affected / exposed	1 / 136 (0.74%)	2 / 137 (1.46%)	
occurrences (all)	1	2	
Vomiting			
subjects affected / exposed	2 / 136 (1.47%)	1 / 137 (0.73%)	
occurrences (all)	2	1	
Abdominal discomfort			

subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Cheilitis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 136 (0.74%)	1 / 137 (0.73%)	
occurrences (all)	1	1	
Irritable bowel syndrome			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 136 (0.74%)	4 / 137 (2.92%)	
occurrences (all)	2	5	
Rash			
subjects affected / exposed	0 / 136 (0.00%)	2 / 137 (1.46%)	
occurrences (all)	0	2	
Dry skin			
subjects affected / exposed	0 / 136 (0.00%)	6 / 137 (4.38%)	
occurrences (all)	0	6	
Eczema			
subjects affected / exposed	2 / 136 (1.47%)	1 / 137 (0.73%)	
occurrences (all)	2	1	
Skin lesion			
subjects affected / exposed	2 / 136 (1.47%)	0 / 137 (0.00%)	
occurrences (all)	2	0	
Dermatitis allergic			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	

Rash erythematous			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Skin haemorrhage			
subjects affected / exposed	1 / 136 (0.74%)	1 / 137 (0.73%)	
occurrences (all)	1	1	
Skin irritation			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Skin reaction			
subjects affected / exposed	1 / 136 (0.74%)	1 / 137 (0.73%)	
occurrences (all)	1	1	
Skin swelling			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal discomfort			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Osteitis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 136 (1.47%)	3 / 137 (2.19%)	
occurrences (all)	2	3	
Body tinea			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Ear lobe infection			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Folliculitis			

subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Impetigo			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Omphalitis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Tinea pedis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 137 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 136 (0.74%)	1 / 137 (0.73%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	
Varicella			
subjects affected / exposed	0 / 136 (0.00%)	1 / 137 (0.73%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2018	This amendment allowed for: • the implementation of a new recruitment strategy which included the ability of investigators to recruit patients not registered with their practice in order to address the recruitment challenges posed by the opportunistic nature of impetigo patients. However, no patients were actually recruited who were not registered at the Investigator site practice and therefore this part of the amendment has no implications for the interpretation of the study. • Investigators to delegate roles, specifically including the EOT and Follow-Up clinical assessments, to be performed by qualified Nurse Practitioners who were considered by the Investigator to be suitably experienced. Note that the Nurse Practitioners were not permitted to conduct patient eligibility or safety assessments. • minor changes to facilitate study management at the investigative sites. This amendment was managed by, and documented within, the company's Study Amendment control procedure, and REC, MHRA and HRA approval gained before implementation. There were no changes to the inclusion/exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported