*These results are supplied for informational purposes only.*
*Prescribing decisions should be made based on the approved package insert in the country of prescription.*

| | |
|---|---|
| Sponsor / Company: Sanofi<br>Drug substance(s): Ketoprofen | Study Identifiers: NCT00799838<br>Study code: KETOP_L_03102 |
| Title of the study: Local, Phase IV, multicenter, double-blind, randomized, parallel, with two treatment arms, placebo-controlled study to evaluate the reduction of inflammatory symptoms in the treatment of bacterial pharyngitis with ketoprofen and amoxicillin in pediatric patients | |
| Study center(s): 6 active sites in Brazil | |
| Study period:<br>Date first patient enrolled: 17/Nov/2008<br>Date last patient completed: 21/Jun/2013 | |
| Phase of development: Phase 4 | |

Objectives:

Primary:

- To evaluate the reduction* of inflammatory signs and symptoms (hyperemia, edema and pain) after 24 hours of treatment with ketoprofen when associated with amoxicillin.

Secondary:

- To evaluate the reduction* of inflammatory signs and symptoms (hyperemia, edema and pain) after 72 hours of treatment with ketoprofen (active or placebo) when associated with amoxicillin.

- Usage of rescue medication (paracetamol) for fever or sore throat after randomization, during the period of ketoprofen treatment (active or placebo).

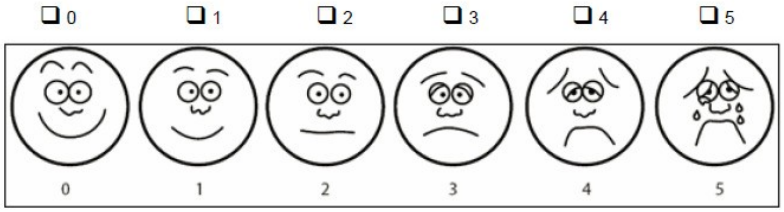
- Safety (adverse events [AE] occurrence).

* It is considered as a reduction of inflammatory signs and symptoms when there is an improvement in at least 2 of the 3 signs/symptoms evaluated: hyperemia, edema, and pain.

For hyperemia and edema, the improvement consists in a reduction of at least 1 cross (+) in a 4-cross scale (+, ++, +++, ++++), according to the clinical assessment.

For pain, the improvement consists in a decrease of at least 1 level in the Wong-Baker Faces Pain Rating Scale (shown below), according to patient's evaluation.

Wong-Baker Faces Pain Rating Scale:




0= no pain; 1-2=mild; 3=moderate; 4=intense; 5=intolerable

Methodology:

Phase IV, multicenter, double-blind, randomized (1:1), parallel, placebo-controlled study, with 2 treatment arms (Test and Control).

It was planned to randomize 210 patients divided into 2 treatment groups (105 patients per arm):

- Test Group: active ketoprofen drops for 3 days + amoxicillin suspension for 10 days.

- Control Group: placebo ketoprofen drops for 3 days + amoxicillin suspension for 10 days.

Both, active and placebo of ketoprofen, were stored in an identical, indistinguishable bottle, with exactly the same size and shape, and with a content of identical color, appearance, and flavor.

Throughout the treatment, the use of paracetamol was allowed as rescue medication in therapeutic doses defined according to the labeling, in case of axillary temperature >37.8°C and/or presence of sore throat.

The study was comprised of 4 visits:

- Screening and randomization visit (baseline visit - Visit V0)

- Visit V1 (D1): 24 to 36 hours after the initiation of treatment

- Visit V2: D3 ±1 day

- Visit V3: D10 ±1 day

During the study period, a diary should be fulfilled by the patient's legal representative with the following information: dose and time of study treatment administration, AEs, use of rescue medication (paracetamol), and (if applicable) usage of other medications (dose, time of administration, and the reason for use).

At the Visits V1, V2, and V3, a physical examination should be performed, checking rescue medication usage, AE occurrence, clinical evaluation, verifying the diary card information, adherence to the study treatment, and the application of Wong-Baker Faces Pain Rating Scale for pain evaluation.

| | |
|---|---|
| Number of patients: | Planned: 210 (105 per treatment arm) |
| | Randomized: 106 (51 Test Group / 55 Control Group) |
| | Treated: 106 |
| Evaluated: | |
| | Efficacy: 104 |
| | Safety: 106 |

| |
|---|
| Diagnosis and criteria for inclusion:<br><br>Children aged 4-11 years old with acute bacterial pharyngotonsillitis (Quick Test positive for *Streptococcus pyogenes*) and indication for treatment with amoxicillin according to labeling and physician's clinical evaluation, and presence of pain (for swallowing) evaluated by Wong-Baker Faces Pain Rating Scale with at least grade 3. The presence of at least 2 clinical signs of acute bacterial pharyngitis mentioned below and without the use of any analgesic or antiinflammatory medication (except paracetamol) in the previous 12 hours of patient inclusion:<br><br>• Hyperemia and edema assessed by the Investigator with at least 2 out of 4 crosses (++/4+);<br><br>• Tonsils with erythema and pus, or erythema and white exudate;<br><br>• Cervical adenomegaly, with or without pain;<br><br>• Presence of fever in the previous 48 hours of patient inclusion. |
| Study treatments<br><br>Investigational medicinal product(s): Ketoprofen active or placebo<br><br>Formulation: Oral solution 20 mg/mL<br><br>Route(s) of administration: Oral<br><br>Dose regimen: 1 drop/Kg for children aged between 4 to 6 years old or 25 drops for children from 7 to 11 years old, administered 3 times a day (TID) for 3 days. |
| Investigational medicinal product(s): Amoxicillin<br><br>Formulation: Suspension 125 mg/5 mL<br><br>Route(s) of administration: Oral<br><br>Dose regimen: 20-40 mg/Kg/day, administered TID for 10 days |
| Duration of treatment: 3 days of treatment with ketoprofen (9 doses) and 10 days with amoxicillin<br><br>Duration of observation: 10 ±1 day |

Criteria for evaluation:

Efficacy:

Primary Efficacy

Proportion of patients with reduction* of inflammatory signs and symptoms (hyperemia, edema, and pain) after 24 hours of treatment (Visit V1).

Secondary Efficacy

Proportion of patients with reduction* of inflammatory signs and symptoms (hyperemia, edema, and pain) after 72 hours of treatment (Visit V2).

Proportion of patients with reduction* of inflammatory signs and symptoms (hyperemia, edema, and pain) after 24 hours of treatment (Visit V1) with no use of rescue medication during treatment period with ketoprofen (active or placebo).

Proportion of patients with reduction* of inflammatory signs and symptoms (hyperemia, edema, and pain) after 72 hours of treatment (Visit V2) with no use of rescue medication during treatment period with ketoprofen (active or placebo).

Proportion of patients who used rescue medication after randomization, during the period of ketoprofen treatment (active or placebo).

* It was considered as a reduction of inflammatory signs and symptoms when there was an improvement in at least 2 of the 3 signs/symptoms evaluated: hyperemia, edema, and pain.

Safety: Proportion of patients who experienced AEs and number of AEs: any; related to the study treatment, serious, or leading to death and/or leading to study/treatment withdrawal, by treatment group.

Proportion of patients presenting any new feature in the physical examination, along the study visits, by treatment group.

Statistical methods: All randomized patients who had used at least 1 dose of the study drugs (ketoprofen or amoxicillin) were considered in the Intent-to-treat (ITT) population. From this total, the patients with available information for primary efficacy evaluation were considered in the Modified Intent-to-Treat (m-ITT) population.

The safety analyses were conducted based on the ITT population and the efficacy analysis based on the m-ITT population.

As the study was prematurely terminated due to low recruitment, all analyses were performed using descriptive statistics.

Summary: The study was prematurely terminated on 30-Aug-2013 due to recruitment challenges. Over approximately 5 years and many attempts to increase enrollment as new sites opening and patient referral tactics, there were 106 patients randomized from a total of 210 planned (105 per treatment arm).

Although the study was prematurely terminated, this report shows the planned efficacy and safety analysis with only descriptive results.

Population characteristics:

Patients disposition

Between 17-Nov-2008 and 12-Jun-2013, 111 patients were enrolled to the study. From this total, 106 patients attended the Visit V0 and were randomized to the study treatments: 51 (48.1%) to the Test Group and 55 (51.9%) to the Control Group (Table 1).

The Table 1 shows the total number of patients screened, the total randomized, and the number of patients assessed at each study visits (V0, V1, V2 and V3), as well as the reason for premature discontinuation. From the 106 randomized patients, a total of 6 (5.7%) did not complete the study for any reason, 3 patients in the Test Group and 3 patients in the Control Group. The main reasons for that were: the occurrence of AEs for 4 patients, withdrawal of consent for 1 patient, and other reasons (did not attend the visit V2 at the scheduled date) for 1 patient.

From the 106 patients randomized to the study, 2 patients from the Test Group did not attend the Visit V1. The reasons for that were the occurrence of an AE leading to study withdrawal and the usage of not allowed medication. A total of 104 patients attended Visit V1; 49 (47.1%) from the Test Group and 55 (52.9%) from the Control Group (Table 1).

From the 104 patients who attended the Visit V1, 3 patients did not attend the Visit V2: 1 patient from the Test Group withdrew consent at V1; 1 patient of the Control Group observed an AE which led to study withdrawal at V1; and 1 patient from the Control Group did not attend the Visit V2 as scheduled. A total of 101 patients attended the Visit V2; 48 (47.1%) from the Test Group and 53 (52.9%) from the Control Group (Table 1).

From the 101 patients who attended the Visit V2, 1 patient from the Control Group observed an AE which led to study withdrawal at V2. A total of 100 patients attended the Visit V3; 48 (48.0%) from the Test Group and 52 (52.0%) from the Control Group (Table 1).

Table 1. Number of patients by study visits

| | Total | Test Group | Control Group |
|---|---|---|---|
| Screened | 111 | | |
| Quick-test negative for S. pyogenes | 5 | | |
| Visit V0 (randomized) – ITT Population | 106 (100%) | 51 (48.1%) | 55 (51.9%) |
| Adverse event leading to the study withdrawal* | | 2 | - |
| Visit V1 – mITT Population | 104 (100%) | 49 (47.1%) | 55 (52.9%) |
| Consent withdrawal | | 1 | - |
| Adverse event leading to the study withdrawal | | - | 1 |
| Other: not attended the visit V2 as scheduled | | - | 1 |
| Visit V2 | 101 (100%) | 48 (47.5%) | 53 (52.5%) |
| Adverse event leading to the study withdrawal | | - | 1 |
| Visit V3 | 100 (100%) | 48 (48.0%) | 52 (52.0%) |

* The patient used a not allowed medication due to the Adverse Event

Study Population

From all the randomized patients, a total of 106 (51 in the Test Group and 55 in the Control Group), were considered as ITT Population. Of these, a total of 104 patients (49 in the Test Group and 55 in the Control Group) were considered in the m-ITT Population.

Demographic data

The age of the randomized patient at enrollment ranged from 4 to 11 years for both groups, with a mean age of 6.9 (Standard Deviation [SD]=2.3) years for Test Group and 7.5 (SD=2.2) years for the Control Group. In both groups, most of children were girls (52.9% in the Test Group and 54.6% in the Control Group). Most of children were Caucasian (41 patients [80.4%] in Test Group and 48 [87.3%] in the Control Group). Their weight at enrollment ranged from 13 to 58 Kg with a mean of 24.1 Kg (SD=8.1) for the Test Group, and between 15 and 67 Kg with a mean of 26.6 Kg (SD=10.7) for the Control Group.

Baseline data

According to the Wong-Baker Faces Pain Rating Scale, the mean and SD at Visit V0 for pain was 3.9 (SD=0.7) and 4.0 (SD=0.6) for Test and Control Groups, respectively, and ranged between grades 3 and 5 for both groups.

In Table 2, the presence of signs according to clinical evaluation at Visit V0 is shown for both groups. For almost all patients from both groups, hyperemia and edema were observed at inclusion.

Table 2. Clinical evaluation at Visit V0

| Signs | Test Group (N=51) | Control Group (N=55) |
|---|---|---|
| Hyperemia | 50 (98.0%) | 55 (100%) |
| Edema | 50 (98.0%) | 54 (98.2%) |
| Erythema and pus | 26 (51.0%) | 30 (54.6%) |
| Erythema and white exudate | 26 (51.0%) | 25 (45.5%) |
| Adenomegaly | 36 (70.6%) | 30 (54.6%) |
| Fever | 10 (19.6%) | 13 (23.6%) |
| Dysphagia | 47 (92.2%) | 54 (98.2%) |

Efficacy results:

Although the study was prematurely terminated, the results of primary and secondary endpoints are presented below in a descriptive manner.

Primary

The proportion of patients with reduction of inflammatory signs and symptoms for Test and Control Groups at Visit V1 were 81.6% and 76.4%, respectively (Table 3).

Table 3. Reduction of inflammatory sign and symptoms at Visit V1 - mITT Population

| Reduction of inflammatory sign and symptoms | Test Group (N=49) | Control Group (N=55) |
|---|---|---|
| Yes | 40 (81.6%) | 42 (76.4%) |
| No | 9 (18.4%) | 13 (23.6%) |

Secondary

1. The proportion of patients with reduction of inflammatory signs and symptoms for Test and Control Groups at Visit V2 were 98.0% and 96.4%, respectively (Table 4).

Table 4. Reduction of inflammatory sign and symptoms at Visit V2 - mITT Population

| Reduction of inflammatory sign and symptoms | Test Group (N=49) | Control Group (N=55) |
|---|---|---|
| Yes | 48 (98.0%) | 53 (96.4%) |
| Visit V2 not performed | 1 (2.0%) | 2 (3.6%) |

2. The proportion of patients with reduction of inflammatory signs and symptoms without the use of rescue medication during treatment period with ketoprofen (active or placebo) for Test and Control Groups respectively were 59.2% and 49.1% at Visit V1 (Table 5), and 91.8% and 78.2% at Visit V2 (Table 6).

Table 5. Reduction of inflammatory signs and symptoms without use of rescue medication at Visit V1 - mITT Population

| Reduction of inflammatory signs and symptoms without use of rescue medication (V1) | Test Group (N=49) | Control Group (N=55) |
|---|---|---|
| Yes | 29 (59.2%) | 27 (49.1%) |
| No | 20 (40.8%) | 28 (50.9%) |

Table 6. Reduction of inflammatory signs and symptoms without use of rescue medication at Visit V2 - mITT Population

| Reduction of inflammatory signs and symptoms without use of rescue medication (V2) | Test Group (N=49) | Control Group (N=55) |
|---|---|---|
| Yes | 45 (91.8%) | 43 (78.2%) |
| No | 3 (6.1%) | 10 (18.2%) |
| Visit V2 not performed | 1 (2.0%) | 2 (3.6%) |

3. The proportion of patients who used rescue medication after randomization during the period of ketoprofen treatment (active or placebo) was 30.6% for Test Group and 43.6% for Control Group until Visit V1 (Table 7), and 36.7% for Test Group and 61.8% for Control Group until Visit V2 (Table 8).

Table 7. Use of rescue medication until Visit V1 - mITT Population

| Use of rescue medication (until V1) | Test Group (N=49) | Control Group (N=55) |
|---|---|---|
| Yes | 15 (30.6%) | 24 (43.6%) |
| No | 34 (69.4%) | 31 (56.4%) |

Table 8. Use of rescue medication until Visit V2 - mITT Population

| Use of rescue medication (until V2) | Test Group (N=49) | Control Group (N=55) |
|---|---|---|
| Yes | 18 (36.7%) | 34 (61.8%) |
| No | 30 (61.2%) | 19 (34,5%) |
| Visit V2 not performed | 1 (2.0%) | 2 (3.6%) |

Safety results:

Of the 51 patients randomized to the Test Group, 9 patients (17.6%) reported at least 1 AE during the study period, with a total of 20 events. Of the 55 patients randomized to the Control Group, 5 patients (9.1%) reported an AE during the study period, with a total of 10 events. For both groups, none of the events were considered serious (Table 9).

In the Test Group, 3/51 patients (5.9%) had a total of 4 AEs considered as related to the study medication according to the investigators (Table 9):

- 1/51 (2.0%) patient had diarrhea, considered as related to ketoprofen (active or placebo) and amoxicillin;

- 1/51 (2.0%) patient had oral candidiasis considered as related to amoxicillin;and,

- 1/51 (2.0%) patient had cutaneous rash and itch, considered as related to ketoprofen (active or placebo).

These events led to the patients' study withdrawal.

In the Control Group, 3/55 patients (5.5%) had a total of 6 AEs considered as related to the study medication, all of them related to amoxicillin according to the investigators (Table 9):

- 1/55 (1.8%) patient had cutaneous allergy in thorax; this event led to patient's study withdrawal.

- 1/55 (1.8%) patient presented itch, labial edema, facial hyperemia, and cutaneous rash; these events led to patient's study withdrawal.

- 1/55 (1.8%) patient had headache.

One patient in the Test Group withdrew from the study due to an AE (sore throat worsened), considered as unrelated to the study treatment. Due to this event, benzidamide, a prohibited medication, was administered to the patient.

A total of 3 patients were withdrawn from the study due to an AE considered as related to study treatment: 1/51 (2.0%) patient in the Test Group and 2/55 (3.6%) patients in the Control Group (Table 9).

Table 9. Adverse Events Summary

| Adverse Event | Test Group | | Control Group | |
|---|---|---|---|---|
| | Patients N=51 (%) | Nº of Events | Patients N=55 (%) | Nº of Events |
| Any | 9 (17.6) | 20 | 5 (9.1) | 10 |
| Related to, according to the investigator | | | | |
| Ketoprofen | 1 (2.0) | 2 | - | - |
| Amoxicillin | 1 (2.0) | 1 | 3 (5.5) | 6 |
| Ketoprofen + amoxicillin | 1 (2.0) | 1 | - | - |
| Serious | - | - | - | - |
| Serious and related to study medication | - | - | - | - |
| Causing death | - | - | - | - |
| Related and causing death | - | - | - | - |
| Leading to study withdrawal | 2 (3.9)[1] | 3 | 2 (3.6)[2] | 5 |
| Related and leading to study withdrawal: ketoprofen | 1 (2.0)[3] | 2 | - | - |
| Related and leading to study withdrawal: amoxicillin | - | - | 2 (3.6) | 5 |

[1] cutaneous rash + itch; sore throat worsened; [2] cutaneous allergy in thorax; itch + labial edema + facial hyperemia + cutaneous rash; [3] cutaneous rash + itch

A list of all AEs by study groups according to the diagnosis reported by the investigator in the CRF and according to the MedDRA dictionary is provided in Table 10. The classification by MedDRA was done after the database lock as it was not planned in the protocol.

Most of the AEs were classified as related to the System Organ Class (SOC) of "Skin and subcutaneous tissue disorders". In the Test Group, most of the events were related to the SOC "Gastrointestinal disorders and General disorders".

Table 10. List of Adverse events and MedDRA (PT and SOC)

| | | | | Total | | Test Group | | Control Group | |
|---|---|---|---|---|---|---|---|---|---|
| Group | Adverse event | Preferred Term (PT) | System Organ Class (1º) | nº AEs | % | nº AEs | % | nº AEs | % |
| Test | Cutaneous rash | Mucocutaneous rash | Skin and subcutaneous tissue disorders | 7 | 23.3% | 4 | 13.3% | 3 | 10.0% |
| Test | Itch | Pruritus | | | | | | | |
| Test | Cutaneous rash | Mucocutaneous rash | | | | | | | |
| Test | Angular cheilittes | Cheilitis | | | | | | | |
| Control | Itch | Pruritus | | | | | | | |
| Control | Cutaneous rash | Mucocutaneous rash | | | | | | | |
| Control | Cutaneous rash | Mucocutaneous rash | | | | | | | |
| Test | Diarrhea | Diarrhoea | Gastrointestinal disorders | 6 | 20.0% | 6 | 20.0% | - | - |
| Test | Diarrhea | Diarrhoea | | | | | | | |
| Test | Worsening sore throat | Oropharyngeal pain worsened | | | | | | | |
| Test | Vomiting | Vomiting | | | | | | | |
| Test | Sore throat | Oropharyngeal pain | | | | | | | |
| Test | Vomiting | Vomiting | | | | | | | |
| Test | Fever | Pyrexia | General disorders and administration site conditions | 4 | 13.3% | 4 | 13.3% | - | - |
| Test | Fever | Pyrexia | | | | | | | |
| Test | Fever | Pyrexia | | | | | | | |
| Test | Body pain | Pain | | | | | | | |
| Test | Headache | Headache | Nervous system disorders | 3 | 10.0% | 1 | 3.3% | 2 | 6.7% |
| Control | Headache | Headache | | | | | | | |
| Control | CEPHALEIA | Headache | | | | | | | |
| Control | Labial edema | Localised oedema | Cardiac disorders | 2 | 6.7% | - | - | 2 | 6.7% |
| Control | Facial hyperemia | Localised oedema | | | | | | | |
| Test | Oral candidiasis | Oral candidiasis | Infections and infestations | 2 | 6.7% | 1 | 3.3% | 1 | 3.3% |
| Control | Varicella | Varicella | | | | | | | |
| Test | Leg pain | Pain in extremity | Musculoskeletal and connective tissue disorders | 2 | 6.7% | 2 | 6.7% | - | - |
| Test | Back pain | Back pain | | | | | | | |
| Test | Burn in left leg | Thermal burn | Injury, poisoning and procedural complications | 2 | 6.7% | 2 | 6.7% | - | - |
| Test | Insect bite | Arthropod bite | | | | | | | |
| Control | Conjunctivitis | Conjunctivitis | Eye disorders | 1 | 3.3% | - | - | 1 | 3.3% |
| Control | Cutaneous drug allergy in thorax | Mucocutaneous drug hypersensitivity in thorax | Immune system disorders | 1 | 3.3% | - | - | 1 | 3.3% |
| | | | Total | 30 | 100% | 20 | 67% | 10 | 33% |

Changes in the physical examination at Visit V1 were reported for 7 patients (13.7%) in the Test Group and for 9 patients (16.4%) in the Control Group. At visit V2, changes were reported for 3 patients (5.9%) in the Test Group and 5 patients (9.1%) in the Control Group. At visit V3, changes were also reported for 3 patients (5.9%) in the Test Group and 2 patients (3.6%) in the Control Group. For all visits, most of the changes were related to lymph node.

Issue date: 06-Feb-2014