A randomized, open-label, parallel-group multicentre study on the efficacy and tolerability of a non-medicated, patented gel for the relief of teething symptoms in infants

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Oral gels, Paediatric dentistry, Teething, Tooth eruption, Teething remedies.

ABSTRACT
Aim Gels containing high molecular weight hyaluronic acid (HMWHA) proved to be well tolerated and effective in providing pain relief in inflammatory conditions of the oral cavity. The purpose of this study was to evaluate the efficacy and safety of a novel HMWHA-based oral gel formulation in comparison with a standard anaesthetic gel in relieving teething pain in infants.

Materials and methods Fifty-four infants, aged 3 to 36 months, were enrolled in this randomized, controlled, open-label, parallel-group, multicentre study. Children with acute episodes of teething received a 7-day treatment with either HMWHA gel (test group) or a standard anaesthetic gel (control group). Swelling, redness and pain were evaluated at baseline (T0) and 3 (T1), 7 (T2) and 14 days (T3) after treatment, while symptoms were recorded by parents on a daily basis.

Results In the test group a significant pain reduction at both T1 and T2 was recorded. The ratio of children with no symptoms of swelling, redness and pain at T2 was higher in the test group than in the control group: 65.4% vs. 30.8% at T1, 80.8% vs. 19.2% at T2 and 88.5% vs. 34.6% at T3, respectively. No safety concerns were identified during the study or the follow-up period.

Conclusion The novel gel containing HMWHA proved to be an effective and safe alternative to the anaesthetic gel in the relief of teething symptoms in infants.

Introduction
Dealing with teething symptoms is still a challenge for clinicians and parents. Teething usually begins at the age of 4-8 months and continues until 36 months of age. Tooth eruption can cause pain, restlessness, increased biting, drooling, gum-rubbing, sucking, irritability, facial rash, ear rubbing, decreased appetite for solid foods and mild temperature rise (1,2). These symptoms usually begin about three to five days before the tooth shows, and they disappear as soon as the tooth breaks the skin.

Topical anaesthetics are generally used for the relief of the symptoms associated with gingival inflammatory conditions or gums trauma in infants, but they can cause serious toxicity, side effects as allergic skin reaction, fatigue and even death.

The majority of studies of infant teething have been retrospective, small, or conducted on institutionalized infants (2).

In 2003, 8576 adverse reactions to local/topical anaesthetics were reported to the American Association of Poison Control Centres, and in 67% of cases the children were less than six years of age (3).

A commercially available high molecular weight hyaluronic acid (HMWHA) mouth gel has gained increasing acceptance among dentists in the last 15 years due to its ability to protect the oral mucosa and reduce swelling, pain and bleeding in various inflammatory conditions of the mouth. Several clinical trials have demonstrated its ability to restore the periodontal tissue/fluid balance, together with accelerated healing and repair properties (i.e. soreness, redness and gingival swelling) (4-9). A pilot study conducted on 18 infants analysed its use in the topical treatment of teething pain in infants (10). Following
the experience of this pilot study, a medical device in the form of gel having a novel, proprietary formulation containing 0.54% HMWHA was specifically designed for relieving teething symptoms in babies. The gel creates a protective layer on the gingival tissue and maintains compatibility with the mouth environment. Furthermore, the gel is color-free and does not contain preservatives, alcohol, or flavours. This gel is a medical device classified in IIa risk class, according to European regulations, and was designed to protect inflamed areas against noxious agents due to its film-forming properties, and therefore to reduce pain. As a secondary action, the specific ability of hyaluronic acid to normalise the tissue/water balance can contribute in reducing oedema.

The purpose of this clinical study was to evaluate the efficacy and safety of this HMWHA gel in the topical treatment of teething symptoms in infants, and to compare it with a gingival gel containing a local anaesthetic.

Materials and methods
The study included 54 infants aged between 3 and 36 months recruited at two private dental clinics, Societatea Civila Medicala Dr. Rosu and Cabinet Medical Individual Stomarox (Timisoara, Romania), by investigators coordinated by Professor Serban Rosu. All the investigators were specialists with more than 10 years of experience in pediatric dentistry.

Parents or legal representatives gave their informed consent for the infant’s participation in the study. Selection criteria were children presenting an acute episode of teething diagnosed by the presence of at least three of the following clinical symptoms: pain, swelling, gingival rush, hyper-salivation, redness or abnormal tooth depth characteristic of an unerupted tooth. Additionally, absence of subcutaneous mucosal laceration was required for inclusion. Exclusion criteria were: hospitalization; history of severe renal insufficiency, cardiac dysfunction, or liver pathology; topical lidocaine and/or topical non-steroidal anti-inflammatory drugs (NSAIDs) administration one day before or systemic NSAIDs within 3 days or the use of inflammatory drugs (NSAIDs) administration one day before or systemic NSAIDs within 3 days or the use of inflammatory drugs (NSAIDs) administration one day before or systemic NSAIDs within 3 days or the use of

Following a randomization list, infants were assigned to either the two groups and used the product for seven days.

Ethical approval
The present randomized, open-label, parallel-group multicentre study was conducted in accordance with the ethical standards and principles of the current version of the Helsinki Declaration and Good Clinical Practice (GCP). The study protocol was approved by the National Competent Authority (Ministry of Health) and Ethics Committee (Romania).

Sample size
Sample size of the present trial was based on a pilot study (10), in which a similar formulation of HMWHA gel was used for treating teething symptoms. The number of patients necessary to detect a statistically significant difference between the two groups, with 80% power and a confidence level of 99% (alpha=0.01, 0.05/5, considering multiple testing) was 24 subjects per group. Considering it realistic to have a dropout rate of about 10%, 54 subjects were enrolled.

Treatment
Infants were randomly allocated to two groups. Group A: patients treated with the HMWHA study gel (Gengigel® Teething, Ricerfarma, Italy) containing 0.54% Hyaluronic Acid; Group B: patients treated with a standard anaesthetic drug (Calgel®, GlaxoSmithKline Pharmaceuticals S.A, Poland) containing cetlypyridinium chloride and lidocaine hydrochloride. During the 7 days of treatment, parents were instructed to soothe the affected teeth by gently massaging the surface around the teeth and applying locally a small amount of gel, up to a maximum of 6 times per day for Group A and 4 times per day for Group B. Parents were also instructed not to use toothbrushes, cold tethers, or other devices to relieve their children’s teething pain. Parents were also instructed to record symptoms on a daily diary card.

Assessments
The investigators examined each child at baseline (T0), three (T1) and seven days (T2) after the first administration of the treatment, and seven days after the last administration (day 14, T3). During the study period, the investigators did not discuss with the parents or the children about the symptoms in order to avoid influencing subjective evaluation. Before the start of the trial, to increase the inter observer agreement and to avoid bias due to the subjective evaluation of symptoms, the investigator and the co-investigators performed a pre-trial training in a sub-group of children; each investigator separately examined a child in the same visit and the two scores were collected. Later, the two investigators compared and analysed the data, evidencing and discussing the discrepancies.

The following parameters were evaluated: intensity of swelling, intensity of redness, salivation and intensity of pain. Swelling, redness and pain were assessed by the investigator and scored, using a 3-point Verbal Rating Scale (VRS): Absent = 0; Moderate = 1; Intense = 2. Another three-point scale (Poor = 0; Normal = 1; Intense = 2) was used to evaluate salivation.

Collecting and evaluating symptoms like pain is very difficult in infants because non-verbal language is their unique communication; in the present trial the children’s parents were reminded of the importance of evaluating pain strictly according to the general behavior of their
child, like facial expression, movements and crying.

According to the investigator’s instructions, parents recorded all the changes in their children's behavior and mouth spasm in the patient's diaries, together with the daily frequencies of administration of the product as well as other symptoms noticed during the trial, such as daily sleep quality, or concomitant medications. Daily sleep quality is considered a performance indicator, as patients with symptoms related to teething sleep worse than usual. For each symptom, its duration was calculated from baseline to the day when the symptom disappeared. The tolerability of the two products administered was assessed by the parents according to investigator’s indications. Parents were asked to report any changes in their children health condition. All the adverse events reported by parents were evaluated by the investigator in order to decide if they were related or not to the products.

Only one parent for each child was asked to keep the diary and, during the study period, the children did not attend nurseries.

Statistical analysis
Descriptive statistics were used to summarize the data. A chi-square test or Fisher’s exact test was used to compare categorical variables and t-test was utilized for comparing continuous variables. Changes in the primary performance parameters (pain, redness and swelling) between T0 (baseline) and T1 (day 3), and T0 and T2 (day 7 of treatment) were assessed as score differences. Similarly, changes in the secondary performance parameters (crying and mouth spasm intensity) between T0 and T1 and T0 and T2 of treatment, and between T2 and T3 (14 days follow-up) were assessed as score differences. These changes were compared between treatment groups by the Wilcoxon Signed Rank Test. Investigator’s global assessment of performance, and safety scores between groups, were compared using the Wilcoxon-Mann-Whitney Test. The same test was used to compare the scores between treatment groups at each time-point. Statistical significance level was set at p<0.01 to adjust for multiple primary endpoints.

Results
In the present trial, 54 Caucasian children, 29 females (53.70%), were enrolled. Subjects’ age ranged between 3 and 36 months and the mean age was 17.0 months. The children had a mean weight of 10.7 kg and a mean height of 81.5 cm. Each group included 27 children. Two patients, one for each treatment group, withdrew after T1 and then they had no available data for following visits. No statistically significant differences were found between the groups in any of the demographic or baseline characteristics (p>0.05) (Table 1).

Primary endpoints assessed at baseline (pain, redness and swelling) had similar scores between groups (Figure 1). In terms of pain intensity evaluation, the number of children with intense pain decreased from baseline to T2 in the test group (from 59.3% to 0%) (Figure 1A). The number of children with intense pain in the control group increased at T1 and decreased thereafter (Figure 1A). After 7 days of treatment (T2), the ratio of patients with no pain was higher in the test group than in the control group (88.5% vs. 34.6%). The mean pain scores decreased significantly between T0 and the subsequent time points (Day 3 and Day 7) in the test group, while in the control group the decrease was significant only from baseline to T2 (Table 2). The improvement in the test group was significantly greater than in controls at both T1 and T2 (Tables 2 and 3).

With regards to swelling, the number of children with intense swelling decreased progressively from baseline to T2 in the test group. In the control group, the number raised at T1 and then decreased (Figure 1B). The number of subjects with no swelling was higher in the test group (65.4%) compared with the control group (30.8%) (Figure 1B). After the administration of the HMWHA gel, the mean swelling scores in the test group were not statistically significantly improved at T1, while a statistically significant improvement was observed at T2 (p<0.0001) (Table 2). In the control group, the score increased at T1 and then decreased; the improvement was statistically significant at T2 (p<0.01) (Table 2). The improvement in the test group was greater at both time points than in the control group, although the difference was statistically significant at T2 only (p<0.01) (Table 2, 3).

The number of children with intense redness decreased from visit to visit in the test group; in the control group, the number increased at T1 and then decreased (Figure 1C). The percentage of children without redness was higher in the test group (21 of 26 patients, 80.8%), compared with the control group at T2 (5 of 26 patients, 19.2%) (Figure 1C). The mean changes in redness between T0 and T1 and between T0 and T2 showed a significant improvement in the test group, while a significant decrease was noticed only at T2 in the control group (Table 2). Both at T1 and T2, the improvement was better in the test group than in the control group (Table 2, 3).

The main symptoms daily recorded by parents in the diary were consistent with those observed by the investigators. Times to recovery from pain (Log-rank test p=0.0017), swelling (Log-rank test p=0.0307) and redness (Log-rank test p<0.0001) were shorter for the test group than the control group; median times were 6 vs. 9 days (Figure 2A); 7 vs. 9 days (Figure 2B) and 5 vs. 10 days (Figure 2C), respectively. The number of days when children stopped crying did not show any difference between the two groups (Log-rank test p=0.1810), with respective median times of 3 and 4 days (data not shown).
Mouth spasm score, a secondary outcome, decreased in both groups, but this was significant only in the test group (at T2, Table 4). After this time, this symptom disappeared in both groups and no additional changes were observed during the following week (Table 4). Also the sleep quality, evaluated as secondary outcome, was better in the test group than in the control group at T1 (p=0.0171) and T2 (p=0.0016) (Figure 3).

At the beginning of the trial, at T0 most children had abundant salivation. In the test group (Figure 4A), salivation decreased day by day more than in the control group (Figure 4B). The difference between the two groups was statistically significant at T2 (p<0.01).

Regarding the global performance assessment, the values reported by investigators were better in the test group than in the control group. In fact, in the test group the performance was rated as "good" in 4 patients and as "very good" in 15 patients, i.e. 73.1% of patients had a globally good performance (Figure 5A). In the standard drug group, the performance was rated as "good" for 1 patient and "very good" for 2 patients (globally, 11.5%) (Figure 5B). The difference between the two groups was

<table>
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<tr>
<th>Symptom</th>
<th>Period</th>
<th>Treatment group</th>
<th>N</th>
<th>Mean score (SD) at Day 0</th>
<th>Difference [Score at Day # - Score at baseline]</th>
<th>Within group</th>
<th>Between groups</th>
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<td></td>
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<td>99% CI</td>
<td>p-value</td>
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<td>0.26</td>
<td>-0.06</td>
<td>0.58</td>
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<td>Test</td>
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<td>0.37</td>
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<td>-1.61</td>
<td>-1.01</td>
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<td></td>
<td></td>
<td>Control</td>
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<td>-0.65</td>
<td>-1.14</td>
<td>-0.17</td>
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<tr>
<td>Redness</td>
<td>T0 – T1</td>
<td>Test</td>
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<td>1.63 (0.56)</td>
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<td>-0.82</td>
<td>-0.07</td>
</tr>
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<td></td>
<td></td>
<td>Control</td>
<td>27</td>
<td>1.63 (0.49)</td>
<td>0.07</td>
<td>-0.22</td>
<td>0.37</td>
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<tr>
<td></td>
<td>T0 – T2</td>
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<td>-1.82</td>
<td>-1.18</td>
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<tr>
<td></td>
<td></td>
<td>Control</td>
<td>26</td>
<td>1.63 (0.49)</td>
<td>-0.62</td>
<td>-1.00</td>
<td>-0.23</td>
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</tbody>
</table>

Table 2 Mean Changes in pain, swelling and redness score
1 Wilcoxon Signed Rank Sum Test
2 Wilcoxon-Mann-Whitney Test
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Statistically significant (p<0.0001).

In the present trial, the relationship between the number of daily applications and the pain intensity was also evaluated. The results showed that in the test group, the number of doses continuously decreased day after day and clearly related to the assessed level pain, in contrast to the control group (Figure 6).

Safety and concomitant medication

Two patients, one of the test group and one of the control group, experienced fever. This mild adverse event appeared to be related to teething, not to the treatment and disappeared completely in few days after NSAIDs administration. Both patients were dropped from the study.

### Table 3

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Period</th>
<th>Treatment group</th>
<th>N</th>
<th>Mean score (SD)</th>
<th>Within group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0</td>
<td>Test</td>
<td>27</td>
<td>1.59 (0.50)</td>
<td>p=0.2849</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>27</td>
<td>1.44 (0.51)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>T1</td>
<td>Test</td>
<td>27</td>
<td>1.18 (0.62)</td>
<td>p=0.0018</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>27</td>
<td>1.7 (0.47)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>Test</td>
<td>26</td>
<td>0.10 (0.33)</td>
<td>p&lt;0.0001</td>
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<tr>
<td></td>
<td></td>
<td>Control</td>
<td>26</td>
<td>0.86 (0.73)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Mean pain, redness, and swelling scores at each examination by treatment group

1 Wilcoxon-Mann-Whitney Test

### Table 4

<table>
<thead>
<tr>
<th>Period</th>
<th>Group</th>
<th>N</th>
<th>Mean score (SD) at reference day (Day 1 or Day 7)</th>
<th>Difference [Score at Day # - Score at reference day]</th>
<th>Within group</th>
<th>Between groups</th>
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<td></td>
<td></td>
<td></td>
<td>Mean (99% CI)</td>
<td>Mean (99% CI)</td>
<td>p=1.0000</td>
<td>p=0.1648</td>
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<td>T0 – T1</td>
<td>Treatment</td>
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<td>0.30 (0.47)</td>
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<td>-0.27</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>27</td>
<td>0.19 (0.48)</td>
<td>0.15</td>
<td>-0.14</td>
<td>0.43</td>
</tr>
<tr>
<td>T0 – T2</td>
<td>Treatment</td>
<td>26</td>
<td>0.30 (0.47)</td>
<td>-0.31</td>
<td>-0.56</td>
<td>-0.05</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>26</td>
<td>0.19 (0.48)</td>
<td>-0.15</td>
<td>-0.41</td>
<td>0.10</td>
</tr>
<tr>
<td>T2 – T3</td>
<td>Treatment</td>
<td>26</td>
<td>0.00 (0.00)</td>
<td>0.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>26</td>
<td>0.04 (0.20)</td>
<td>-0.04</td>
<td>-0.15</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Table 4 Mean changes in mouth spasm score as assessed by subjects’ parents

1 Wilcoxon Signed Rank Sum Test

2 Wilcoxon-Mann-Whitney Test
For most children involved in the trial, the investigator’s global assessment of tolerability was good and no difference was seen between the two groups. In the test group, 20 out of 26 parents (76.9%) reported good tolerability and 4 a satisfactory evaluation (Figure 7A). In the control group, for 19 out of 26 patients (73.1%) the tolerability was good, and for five it was satisfactory (Figure 7B). Four patients, two in each group, appeared to dislike the product administration, and were uncooperative. Consequently, their tolerability was rated as poor (Figure 7), even though no side effects nor safety problems were reported.

**Discussion**

Symptoms related to teething are known to be generally self-extinguishing. The physicians often underestimate both relative restlessness and pain, even if the symptoms are extremely worrisome for parents. The situation is confirmed by the wide use of anaesthetics and NSAIDs (either topical or systemic). These products with pharmacological activity are readily absorbed by the oral mucosa and give to the child a rapid, albeit short-lived, relief. However, these drugs should be reserved for the most severe cases and used under medical supervision, due to the risk of adverse events, which can be serious, although rare.

Coating gels have been used for 15 years for various disorders in the oral cavity and have become more and more common in adults. Most of the gels are self-prescribed and some of them contain glycopolymers with high molecular weight hyaluronic acid. Due to their effectiveness, ease of use and patient satisfaction, these products gained the interest of many dentists, periodontists and dental hygienists.

Hyaluronic acid (HA) is a polysaccharide present in the oral mucosa. It plays an important role in epithelial protection and in maintaining intercellular exchange and water balance. Preclinical studies have shown its
effects in the treatment of pathological conditions of the oral cavity, evidencing some anti-inflammatory, healing and anti-oedematous actions (11-16). Several studies reported the clinical utility of HA in many oral disorders such as gingivitis and gingival trauma (7-9), which are conditions similar to teething. In such cases, a protective gel must also provide enough adhesion and a sufficient barrier and residence time on the mucosa to be effective, and baby gums are not an optimal environment. Moreover, utmost safety is essential for babies.

This study showed that the symptoms of teething decreased shortly after the beginning of treatment with the HMWHA-based oral coating gel. The decrease continued until the symptoms were almost eliminated after 7 days of treatment. The relief of teething symptoms was less pronounced with the standard anaesthetic drug used in this study, and few patients still exhibited some symptoms at T2. This trend was common to all the parameters monitored, namely pain, swelling, redness, crying and mouth spasm, and is confirmed by the analysis of time to disappearance.

The described findings exceeded our expectations to some extent, as we did not anticipate the device to have a stronger effect on pain than an anaesthetic. The mechanism of action of the anaesthetic gel used in this study is well known; it contains two active ingredients: lidocaine hydrochloride and cetylpyridinium chloride. Lidocaine hydrochloride (0.33% w/w) is a local anaesthetic that works by temporarily blocking the pathway of pain signals along the nerves. Cetylpyridinium chloride (0.10% w/w) is a mild antiseptic that kills a variety of bacteria and fungi that can infect sore or broken skin in the mouth. In contrast to anaesthetics, filming agents cannot block the pathway of pain signals along nerves. HA has no pharmacological effect but, due to its rheological properties, it acts on rebalancing tissue fluid distribution and on reducing local oedema. Gum swelling results from inflammation, and is responsible for the throbbing sensation and most of the pain; its reduction can therefore help to reduce pain.

Two children, one in each group, were excluded from the final analysis due to mild fever. These events were not related to the treatments. The global tolerability evaluation was assessed predominantly as ‘good’ or ‘very good’ by physicians and parents, with no differences between the two groups, apart from two children per group who disliked the application of gels. However, a larger number of patients would be required to perform an accurate safety assessment.

The major weakness of this trial was the lack of quantitative outcomes and subjective measurement of pain reported by parents. To avoid this potential bias, investigators performed a pre-trial training in a sub-group of children affected by teething in order to increase the inter observer agreement. In addition, parents were reminded of evaluating pain strictly according to the children non-verbal language expressed by facial expression, crying, and similar activities, as suggested by international guidelines (17). Unfortunately, the direct use of structured scale like FLACC was not applicable in this trial.

Figure 2 Time for pain (A), swelling (B) and redness (C) symptoms to disappear in the test group (Study device) and the control group (Standard drug)
due to level of pain characterizing the teething, that is totally different to that experienced by children during surgery (18). Further paediatric trials are advisable in view of the relatively small number of children involved in the present study. Nevertheless, the availability of a gel with clinically proven efficacy, whose mode of action is based on physical rather than pharmacological properties, provides a considerable advantage in terms of safety. Furthermore, the tested HMWHA device was designed for babies, and thus exhibits increased safety characteristics (i.e., no alcohol, no preservatives, no artificial colors and no added flavors).

**Conclusion**

Based on the 54 cases of the children enrolled in this clinical trial, it was proved that teething-related symptoms were reduced more rapidly and efficiently.
using a newly developed gel based on high molecular weight hyaluronic acid than a standard anaesthetic drug, and no safety issues occurred using this device on infants. Therefore, this patented, non-medicated gel can be considered helpful to both parents and physicians in safely managing the irritation and pain resulting from tooth eruption in infants.

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SR and RO, have no financial interest or direct association with the Sponsor, FM was employed at Latis Srl Contract Research Organization and performed the statistical analysis of the study, AR was employed at Opera CRO and did the clinical site management of the study.

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