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Efficacy and Safety of a Novel Gummy Formulation for the Management of Cough in Adults: Double Blind, Randomized, Placebo-Controlled Trial

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Abstract: The cough is one of the most common medical complaints affecting the general population. It is well known that persisting cough negatively affects subjects' quality of life (QoL) and sleep quality. The aim of the current double blind, randomized, placebo-controlled, pilot study was to assess the effectiveness of a novel medical device in gummy format in reducing cough and improving QoL in adult subjects with acute persisting cough. Forty subjects were enrolled and randomized into two arms according to the treatment. Both the investigational product (IP) and placebo were administered orally, three times per day for 10 consecutive days. Cough symptoms and severity were measured by the Cough Clinical Score (CCS) consisting of a 6-point Likert scale, Leicester Cough Questionnaire (LCQ) and cough severity visual analogue scale (VAS). QoL was rated using the SF-36 (short form) questionnaire. Significant improvements were seen both in the daytime and nighttime cough score after 5 days and at the end of treatment in the IP group but not in those subjects taking the placebo. QoL and sleep disturbances were ameliorated significantly in the IP group only. In conclusion, IP was found safe, well-tolerated and effective in the management of persisting cough in adults.

Keywords: cough; common cold; medical device; honey; *Pelargonium sidoides*

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1. Introduction

The cough is a vital protective and defensive reflex that the body uses to remove mucus and irritants from the lower airways. On the other hand, excessive or pathologic coughing is among the most common complaints affecting the general population including both adults and children, and it usually represents one of the most frequent reasons for seeking medical consultation. It affects negatively people's quality of life, causing distress and sleep disruption. In fact, coughing often becomes worse at night because the laying position causes mucus to stagnate in the throat.

Upper respiratory tract infections, also known as the common cold, and acute bronchitis are the most common causes of acute cough in adults. These conditions are characterised by acute inflammation of the mucosa associated with oedema and increased secretions and mucus production. Although the majority of acute respiratory tract infections are caused by viruses and are self-limited, a persisting cough may lead to further irritation of the oropharyngeal mucosa making it more sensitive to local irritants and starting a vicious cycle able to damage the tissue itself [1]. Moreover, inhalation of foreign irritants can trigger the sensory nerves in the upper airways and lungs causing the cough reflex.

Generally, in adults and older children, a common cold tends to last about one week while a cough may persist for up to three weeks or longer [2]. On the contrary, a chronic

cough may represent a key symptom of more severe conditions such as chronic obstructive pulmonary disease (COPD) or extra-pulmonary disease such as gastroesophageal reflux disease (GERD) [3]. A recent online survey found that a cough outlasted other cold symptoms in 69% of the survey respondents [4]. Adults in the United States have an average of two to three colds per year, and this number is even higher in children [5]. According to a recent survey carried out in Italy on 1251 subjects, 18.4% of respondents reported more than three episodes of cough/year with a duration ranging 10–30 days in about 20% of subjects and longer than 30 days in 7% of subjects [6]. Interestingly, 23% of subjects declared using domestic remedies for cough relief while almost 21% ask for advice from the pharmacist, or the doctor (33.4%), primarily the general practitioner [6].

Pelargonium sidoides, also known as African geranium, is native to South Africa and its root extract has been traditionally used to treat URTI when antibiotic use is unnecessary [7], due to its clinical effectiveness and margin of safety in different target populations including children [8,9] and teenagers [10]. A variety of potential mechanisms have been identified which provide a rational basis for its use, including moderate antagonistic effects against both viruses and bacteria. In fact, *P. sidoides* extract may interfere with the invasion and adherence of several pathogen microorganisms such as group-A streptococci (i.e., *S. pyogenes*) to human host cells [8,11], potentially preventing bacterial superinfection [12–14]. Other hypotheses include similar effects on viral adherence [15–17]. *Pelargonium sidoides* root extract interferes with the replication of several respiratory viruses such as seasonal influenza virus, human coronavirus, parainfluenza virus, and coxsackievirus, mainly acting indirectly by inhibition of virus attachment to the host cells and spreading whilst no direct virucidal effect is reported [18]. The extract exhibits mucolytic properties and improves cilia function in vitro, thus favouring the clearance of excess mucous and bacteria from the upper airways [19]. Moreover, *P. sidoides* extract is able to boost the immune response to infection through the improvement of the innate immune defence, enhancement of macrophages phagocytic activity, and a positive effect on NK cells activity and oxidative burst was also shown [14].

Empirical evidence supports the use of herbal and plant-derived substances for the relief of cough and congestion of the pharyngeal mucosa and upper respiratory tract as well as airway hyper-responsiveness. In particular, *Malva sylvestris* is traditionally used mainly for its soothing, calming, expectorant, anti-inflammatory, and antispasmodic effects due to the high content of compounds such as mucilage, high molecular weight polysaccharides, and flavonoids [20]. Mucilage has been used effectively for years particularly due to its soothing action which is able to reduce the irritation of the upper respiratory epithelium and for its mucoadhesive properties, which lead to the formation of a protective layer avoiding the contact of the host tissue with exogenous irritants and pathogens [21].

Honey is an ancient remedy to calm cough; the World Health Organization (WHO) has classified honey as an effective remedy (demulcent) for the treatment of cough (WHO monograph 2001) promoting the hydration of excess mucus facilitating its clearance, calming local irritation by covering the throat epithelium and soothes the pain caused by a persisting cough. A recent meta-analysis [22] confirmed the effectiveness of honey for cough relief and improvement of symptoms of upper respiratory tract infections compared to the usual care and antibiotics.

The aim of the current pilot clinical investigation was to assess the effectiveness and safety of a new drug-free product formulated in gummy containing *Pelargonium sidoides* root extract, *Malva sylvestris* mucilage and acacia honey in an adult population diagnosed with acute cough.

2. Materials and Methods

This randomized, double blind, placebo-controlled study was approved by the Institutional Ethics Committee of the Rajalakshmi Hospital, Bangalore, India. The trial was registered prospectively in CTRI with registered number CTRI/2020/09/027838. The study

was conducted in accordance with the ethical principles of the Declaration of Helsinki, ICH-GCP guidelines and ISO 14155.

Forty (40) subjects were enrolled after signing the informed consent form. They were randomly allocated to one of the study arms equally using a blocked randomisation method. The randomisation list was computer-generated (1998-2022 Random.org, Dublin, Ireland).

Inclusion and exclusion criteria are listed in Table 1.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria
Signed written informed consent; adult subjects (males and females) 18–65 years of age (both inclusive); acute cough (at least 7 days up to 3 weeks, not treated with any antitussive product); Cough Clinical Score = 3 at baseline.
Exclusion Criteria
Persisting cough lasting more than 3 weeks; respiratory diseases such as TB, COPD or asthma, pulmonary fibrosis, lung cancer; co-morbid conditions (such as diabetes, immunodeficiency, HIV, HPV) and/or deteriorating health status; concomitant therapy with ACE inhibitors; pregnant and lactating women; history of drug or alcohol abuse; smokers; subjects on hormone replacement therapy or chemotherapy or radiotherapy; subjects participating in any other studies or participated in any clinical trial 3 months prior to start of this trial; known hypersensitivity to, or intolerance to the study products or their formulation excipients.

The investigational product (ImmunoWay™ Cough Relief from International Health Science Srl, Italy) is a medical device (class IIa) formulated in gum Arabic-based gummies containing acacia honey in combination with *Pelargonium sidoides* root extract and *Malva sylvestris*.

The characteristics of active product and placebo including appearance, dimension, colour and texture were the same. Primary and secondary packaging were identical for both treatments in order to guarantee the blindness. Moreover, the study investigator, the research staff and participants remained blind to the treatment allocation.

All subjects were asked to take 1 gummy 3 times a day (morning, afternoon and at night before sleeping) for 10 consecutive days.

The primary outcome was to assess an improvement of 2 scores in Cough Clinical Score in 25% of subjects at the end of treatment with investigational product (IP). The clinical effectiveness of the investigational product compared to the placebo in improving daytime and nighttime cough was assessed by using Cough Clinical Score (CCS) consisting of a 6-point Likert scale ranging from 0 (absence of cough) to 5 (disturbing cough) [23].

Secondary outcomes were the change in the Leicester Cough Questionnaire (LCQ), which is a validated tool evaluating the health status and quality of life of subjects with a cough over a period of 24 h. Such a questionnaire includes 19 items grouped in 3 domains, i.e., physical, psychological and social ones. Each item is ranked on a 7-points Likert scale from 1 (severe condition) to 7 (good condition); mean scores are calculated for each domain, and their sum is the overall score ranging from 3 to 21. Therefore, higher scores are indicative of a healthy status.

VAS was used as a tool to assess the cough severity daily ranging from 0 cm (no cough) to 10 cm (very severe cough).

Moreover, the improvement of sleep quality as a consequence of the reduction of night cough, and quality of life were assessed by using the SF-36 (short form) questionnaire.

Finally, the safety and tolerability of the 10-day treatment were assessed by monitoring all adverse events throughout the study period, laboratory testing (haematology and biochemistry), physical examination and vital signs at the end of the study.

2.1. Determination of Sample Size

For the sample size calculation, type I error of 0.05 (two-tailed z-test) and power greater than 80% were considered. Assuming a Cough Clinical Score of 3 in both study

arms at screening, and an average change of 2 scores in 25% of patients with the active product, a sample size of 36 patients was considered enough to reject the null hypothesis (no difference between groups). Thus, considering a 10% dropout rate, a total of 40 subjects were recruited.

2.2. Statistical and Analytical Plans

Continuous variables were reported as mean ± standard deviation (SD), median and interquartile (IQR) range. Comparison of continuous variables was performed by analysis of variance (ANOVA) or Mann–Whitney test. Comparison of paired measurements was carried out by using Wilcoxon signed-rank sum test. A *p*-value lower than 0.05 was considered statistically significant.

All statistical analyses were performed using SAS 9.4 (GK Analytics, Hyderabad, India).

3. Results

Forty-two (42) subjects with acute cough were screened and 2 subjects were considered screen failures. A total of 40 subjects were recruited and randomly allocated in the 2 study arms: 20 subjects were treated with the investigational product and 20 subjects were treated with the placebo (Figure 1).

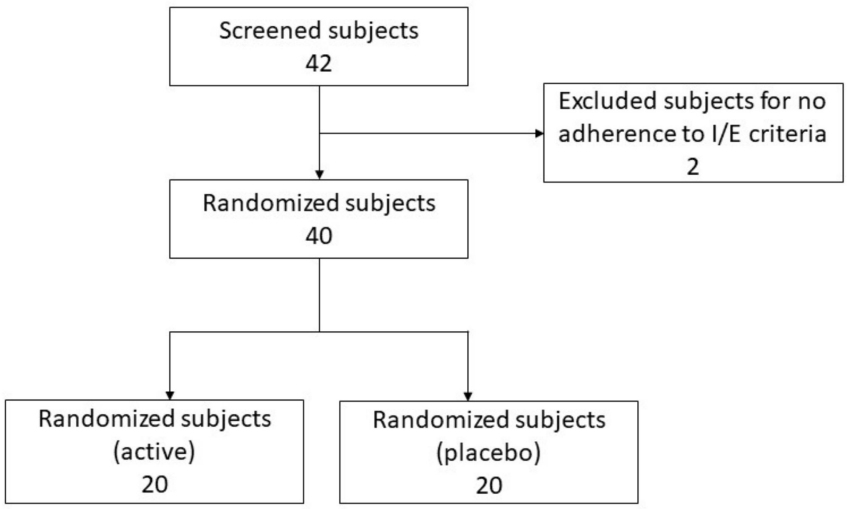


Figure 1. Study flow chart.

Thirty-nine (39) subjects concluded the study while one subject from the placebo group was lost at the final visit.

Demographics and baseline characteristics of subjects enrolled in the study are shown in Table 2. Gender, age, and body mass index did not differ at the baseline between the treatment groups. There was no significant past disease history and no co-morbid conditions were found in any subjects. None of the subjects was on any concomitant medication at the time of enrolment. Vital signs, physical examination, and haematological parameters were regular in all subjects.

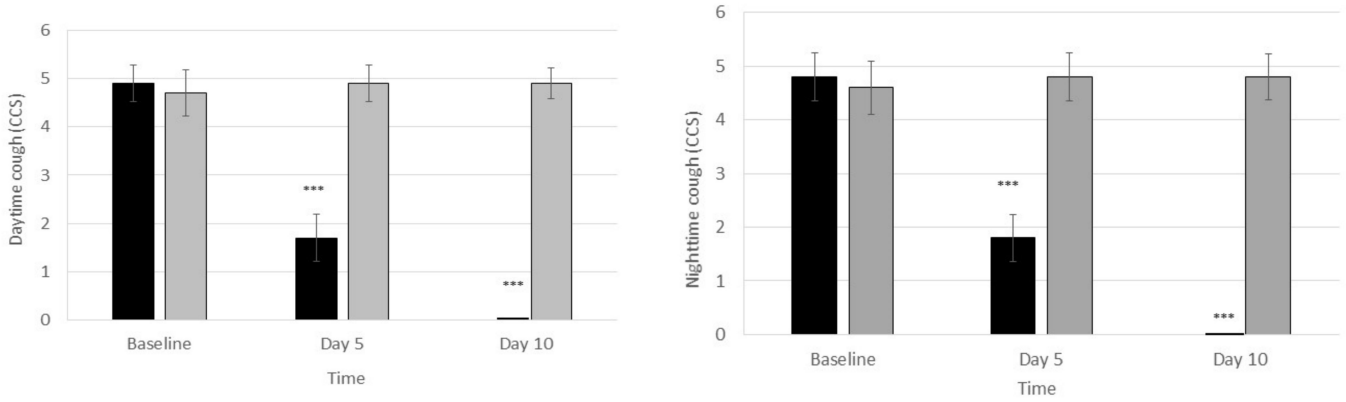
Table 2. Baseline demographic characteristics.

	Active	Placebo	*p*-Value
Number	20	20	
Age (years); mean (SD)	53.2 (6.98)	42.1 (13.74)	0.613
Gender (M/F)	8/12	11/9	0.216
BMI (kg/m^2); mean (SD)	26.89 (2.74)	25.46 (2.28)	0.701

Treatment compliance was ≥99% in all subjects that completed the study.

3.1. Primary Endpoint

Daytime cough and nighttime cough scores were significantly improved following the treatment with the active product. Results of the Cough Clinical Score (CCS) are shown in Figure 2. The administration of the active product resulted in a significant reduction of both daytime cough and nighttime cough already after 5 days of treatment ($p < 0.001$) with a complete resolution after 10 days ($p < 0.001$). An improvement of at least 2 scores (CCS) was found in all subjects treated with the investigational product. In particular, the mean CCS at baseline for the active group was 4.9 for daytime cough score and 4.8 for nighttime cough score. After 5 days of treatment (visit 3), the mean score decreased to 1.7 for daytime cough and 1.8 for nighttime cough, respectively. At the end of treatment (visit 4/day 10) both daytime and nighttime cough scored 0.



(**a**) (**b**)

Figure 2. Cough Clinical Score (CCS). (**a**) Daytime cough CCS; (**b**) Nighttime cough CCS. Black bars: active; grey bars: placebo. *** $p < 0.001$ active vs. placebo.

On the contrary, the mean CCS at baseline for subjects on the placebo was 4.7 for daytime cough score and 4.6 for nighttime cough score. After 5 days, in the placebo group, the mean CCS reached 4.9 for daytime cough ($p = 0.89$) and 4.8 for nighttime cough ($p = 0.324$) remaining unchanged at the end of the study. No significant reduction was observed for CCS in the placebo group at the end of the treatment ($p = 0.573$ for daytime; $p = 0.347$ for nighttime).

3.2. Secondary Endpoint

LCQ was assessed at baseline, day 5 and at the end of treatment (day 10). LCQ scores are shown in Table 3. Significant improvements of the overall score on each domain were recorded in the active group after 5 days as well as at the end of treatment ($p < 0.0001$). No change in LCQ score was observed in the placebo group at any time during the study ($p > 0.05$).

At baseline, a cough severity VAS >9 was recorded in both arms. After 5 days of treatment with the investigational product, the cough severity improved significantly ($p < 0.0001$) with a VAS score of 0.9 while reaching zero at day 10. On the contrary, the VAS score did not change ($p = 1.0$ day 5 vs. baseline; $p = 0.563$ day 10 vs. baseline) in the placebo arm during the whole study (always >9).

Table 3. LCQ core (mean ± SD).

	Active					Placebo					*p*-Value		
	Baseline	**Day 5**	***p*-Value vs. Baseline**	**Day 10**	***p*-Value vs. Baseline**	**Baseline**	**Day 5**	***p*-Value vs. Baseline**	**Day 10**	***p*-Value vs. Baseline**	**Active vs. Placebo at Baseline**	**Active vs. Placebo at Day 5**	**Active vs. Placebo at Day 10**
Total score	3.7 ± 0.17	13.6 ± 0.32	$p < 0.0001$	20.8 ± 0.18	$p < 0.0001$	3.7 ± 0.17	3.7 ± 0.18	0.983	3.7 ± 0.18	0.995	1.000	$p < 0.0001$	$p < 0.0001$
Physical score	1.2 ± 0.06	4.5 ± 0.20	$p < 0.0001$	6.9 ± 0.07	$p < 0.0001$	1.2 ± 0.06	1.2 ± 0.06	0.958	1.2 ± 0.06	0.935	1.000	$p < 0.0001$	$p < 0.0001$
Psychological score	1.4 ± 0.07	4.6 ± 0.13	$p < 0.0001$	7.0 ± 0.04	$p < 0.0001$	1.4 ± 0.07	1.4 ± 0.06	1.000	1.4 ± 0.07	0.991	1.000	$p < 0.0001$	$p < 0.0001$
Social score	1.1 ± 0.13	4.5 ± 0.29	$p < 0.0001$	6.9 ± 0.14	$p < 0.0001$	1.1 ± 0.12	1.1 ± 0.13	1.000	1.1 ± 0.13	0.980	1.000	$p < 0.0001$	$p < 0.0001$

At baseline, sleep quality was affected in both groups most of the time due to frequent coughing. Subjects receiving the active product showed a significant reduction of nocturnal cough ($p < 0.001$) after both 5 and 10 days of treatment. This was associated with a significant improvement of sleep quality assessed by a daily questionnaire filled by subjects using a scoring scale ranging from 0 (no disturbing) to 6 (extremely disturbing). In particular, subjects in the active group showed a mean score of 5.8 at baseline, which significantly decreased to 2.3 after 5 days and was zero at the end of treatment (day 10). On the contrary, in the placebo group, the mean score remained unchanged from baseline to day 5 (5.8) ($p = 0.750$) and at the end of treatment (5.7) ($p = 0.983$).

SF-36 was used to assess the quality of life in subjects treated with either the active treatment or placebo. The study results showed that at the end of the study all items were ameliorated significantly in patients receiving the active treatment, while no significant improvement ($p = 0.268$) was reported by patients from the placebo arm. These findings corroborate the data from LCQ confirming that the investigational active product is effective in improving the perception of a better quality of life in subjects with a cough.

All participants (100%) in the active arm reported a positive perception about the treatment and were very happy or happy about the treatment itself.

Tolerability was rated by the investigator as excellent, good, fair and poor. Both study arms showed an excellent tolerability profile and no side effects were recorded during the entire study. Haematological parameters, biochemistry, and vital signs were not affected by treatments and were within the physiological ranges both at baseline and at the end of the study.

4. Discussion

The cough is a common and troublesome symptom both in adults and children, which often requires a medical consultation. From the survey by Del Negro et al. [6], it appeared that a cough becomes a concern for patients when it lasts more than one week and mainly when children are affected; as a result, patients seek medical advice for an appropriate therapy. Cough management usually involves the use of medications and over-the-counter (OTC) drugs, which block the cough reflex or improve sputum removal.

Nowadays, a wide array of products are available over the counter for cough and colds, primarily antitussive, expectorants, mucolytic products that provide temporary relief of symptoms such as coughing and chest congestion. Notably, the majority of products are in form of liquid syrup which despite containing a high amount of sugar are not very palatable because of the bitterness of pharmaceutically active compounds. Among the OTC medications, symptomatic drugs (antitussives and mucolytic) are very popular either used as self-medication or as a prescribed treatment after medical consultation.

The current clinical study was performed to assess both the effectiveness and safety of a novel gummy formulation for relieving acute cough.

The product object of the current double blind, randomized, placebo-controlled, pilot clinical investigation is registered in the EU as a medical device (class IIa according to MDD 93/42/CEE) acting through a mechanical mechanism of action by forming a protective layer on the oropharyngeal mucosa due to the mucoadhesive properties of its functional compounds including acacia honey, mallow polysaccharides and Arabic gum as a base. The protective layer limits the contact of tissue with exogenous irritant agents such as smoking and environmental exposure to dust, smog, etc., which are known for exacerbating the cough reflex and causing local irritation on the oropharyngeal mucosa [24].

The results of the current study showed that IP significantly reduced both nighttime and daytime cough after 5 days of administration. Such significant effect was maintained until the end of treatment (day 10). In particular, sleep disturbances were completely resolved following the treatment with IP, thus ameliorating sleep quality and duration as a direct consequence of decreased nocturnal cough in subjects who took the IP compared to those in the placebo arm. This finding was also confirmed by results from the SF-36

questionnaire assessing patients' quality of life, which was significantly improved at the end of the treatment with fewer cough-related discomforts.

A fundamental clinical goal when treating a cough is to improve the patients' quality of life. In fact, a cough negatively affects the quality of life of both adults and children. Recently, HRQL has become a key focus in clinical practice as an effective tool for supporting physicians' decisions and therapeutic approaches [24]. In our study, the QoL of all subjects was severely impaired at the baseline due to the high cough frequency. The functional effect of the investigated active product was clearly recorded at the end of treatment as all the domains and items of SF-36 were significantly improved compared to the placebo treatment. Moreover, sleep quality and duration assessed by LCQ were also significantly improved in the active treatment group.

Other authors showed that treating a cough (either acute or persisting) with OTC or herbal preparations significantly contributes to improving symptoms and restoring sleep disorders [25]. A mixture of plants, including *M. sylvestris*, has been found to ease cough in asthmatic subjects already after 3 days of administration [26].

Regarding the non-pharmacological approach for relieving cough, most published studies found that patients may benefit from *P. sidoides* consumption. Several clinical studies have been carried out in order to assess the efficacy of *Pelargonium sidoides* root extract in relieving respiratory symptoms, such as a cough, mainly associated with respiratory infections. Gokce et al. [27] showed that *P. sidoides* root extract significantly improved URTI symptoms in children, such as dry cough and cough frequency after 3 days of administration compared to the placebo. In a multicenter, prospective, randomized, double blind, parallel group, placebo-controlled study, *P. sidoides* resulted as effective in reducing the severity of symptoms and shortening the duration of the common cold symptoms, including cough, compared to the placebo [28].

Similar results were found in children: a syrup containing acacia honey and specific plant-derived substances, such as resins, polysaccharides, and sugars, appeared superior to the placebo in the treatment of a cough and significantly improved sleep of both children and their parents by reducing nighttime cough [23,29]. The authors explained the results supposing that honey and the other plant components, although without any specific pharmacological properties, may form a layer with a mechanical barrier effect thus limiting the local irritation by external noxious stimulus, i.e., bacteria and pollutants, and inhibit nervous stimulation resulting in a soothing effect and cough relief.

Treatment compliance was nearly 100% confirming that gummies are a convenient dosage form not only in children but also in adults. It can be speculated that gummies enable higher compliance due to superior sensory experience.

The current randomized clinical study has some limitations; first, the small sample size, although the statistical calculation confirmed the total number of the recruited subjects was enough for rejecting the null hypothesis. Second, albeit validated LCQ and VAS were used, the questionnaire for nocturnal cough and sleep assessment was not validated.

5. Conclusions

In conclusion, the current randomized, double blind, placebo-controlled, pilot clinical study confirmed the effectiveness of the IP in relieving an acute cough and ameliorating sleep and quality of life. More specifically, the intake of the IP after 5 days attains significant relief from cough symptoms in adults. As a result of these findings, the IP may be recommendable to adults who experience cough symptoms.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethical Committee of the Rajalakshmi Hospital, Bangalore, India (protocol code GLI_SCRS_SSCS_2020 and date of approval: 30 August 2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The TMF is stored in the Sponsor's archive.

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Conflicts of Interest: R.R. is employed by IHS. The other authors declare no conflict of interest. The funder had no role in the collection, analyses, or interpretation of data or in the writing of the manuscript.

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