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Research Article

Racecadotril for Acute Diarrhea in Infants, Children and Adolescents: An Open-Label Clinical Study in Russia

Andrey P. Prodeus[1]*, Olga Vasilievna Shamsheva[2], Vasiliy F. Uchaykin[2], Irina Solnyshkina[3], and Suntje Sander-Struckmeier[3]

[1]*Department of Moscow Healthcare, G.N. Speransky Pediatric City Clinical Hospital, Russia*

[2]*LLC Diagnostics and vaccines, Russia*

[3]*Abbott Laboratories GmbH, Germany*

***Corresponding author**

Andrey P. Prodeus, Moscow State Budgetary Healthcare Institution "G.N. Speransky Pediatric City Clinical Hospital #9 of the Moscow Healthcare department" / Moscow SBHI, Russia, Tel: 7-499-259-5867; Email: prodeus@mail.ru

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Keywords

- Racecadotril
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Abstract

Objectives: This study evaluated the efficacy and safety of racecadotril together with oral rehydration solution (ORS) compared to ORS alone in infants (>3 months), children and adolescents with acute diarrhea. ClinicalTrials.gov Identifier: NCT03463512.

Methods: A controlled, open-label, parallel-group multicentre study in which a total of 124 children and adolescents aged 3 months to <18 years (n=62 per treatment group), were randomized to treatment with oral racecadotril (1.5 mg/kg), t.i.d. for a maximum of 5 days plus ORS (RACE+ORS) or ORS alone. The primary endpoint was duration of diarrhea from the start of treatment until final diarrheal/watery stool before recovery or end of study treatment.

Results: The median duration of diarrhea was statistically significantly shorter with RACE+ORS compared to ORS (16.8 h vs 40.6 h; p<0.0001). The overall mean number of stools during the study decreased with RACE+ORS compared with ORS (5.9 vs 8.3), as did the mean number of watery stools (4.2 vs 6.5). All subjects (62/62; 100%) in the RACE+ORS group recovered by Day 6 compared to 58/62 (93.5%) with ORS. The median time to recovery was statistically significantly shorter with RACE+ORS compared with ORS (29.3 h vs 58.2 h; p<0.0001). The median duration of treatment was shorter with RACE+ORS (49.50 h) compared with ORS (67.08 h). No treatment emergent adverse events were reported in either treatment group.

Conclusions: Racecadotril plus ORS was significantly more effective for the treatment of acute diarrhea than ORS alone in children aged 3 months to <18 years and was well tolerated.

ABBREVIATIONS

b.w.: Body Weight; CI: Confidence Interval; FA: Full Analysis; GPA: Global Physician Assessment; ORS: Oral Rehydration Solution; PP: Per Protocol; RACE: Racecadotril; SD: Standard Deviation; t.i.d.: Three Times Daily; WGO: World Gastroenterology Organization.

INTRODUCTION

Acute diarrhea is the most frequent gastroenterological disorder, and the main cause of dehydration, in childhood. Acute diarrhea typically lasts less than 7 days and usually not longer than 14 days [1]. It mainly occurs in children until five years of age and particularly in neonates in the second half-year and children until three years of age. As dehydration and negative nutritive balance are the main complications of acute diarrhea, the compensation of lost body fluids and adequate diet form the basis of treatment [2]. The ESPGHAN guidelines 2014 [1], and World Gastroenterology Organization (WGO) guidelines 2013 [3], state that the gold standard of treatment of acute diarrhea in pediatric population is ORS.

Racecadotril is a pure intestinal antisecretory active substance. It is a prodrug of thiorphan and is converted rapidly by nonspecific, blood-borne esterases and acts to decrease the intestinal hypersecretion of water and electrolytes but has no effect on basal secretory activity and does not modify the duration of intestinal transit [4-13]. Racecadotril has been shown to be effective and well tolerated for the symptomatic treatment of acute diarrhea in pediatric subjects older than 3 months [14,15]. Racecadotril has the potential to help optimize treatment of acute diarrhea by decreasing the time to recovery, reducing the required dose of ORS and other efficacy parameters, while not increasing the burden of adverse events. The use of racecadotril may also lead to savings to healthcare systems [15].

This study was conducted to assess the efficacy and safety profile of racecadotril in Russian pediatric and adolescent subjects with acute diarrhea.

MATERIALS AND METHODS

Study design

This was a controlled, open-label, non-blinded, parallel-group study evaluating the efficacy and safety of racecadotril in infants, children and adolescents with acute diarrhea and was conducted in seven investigational sites in Russia from 29 March 2018 to 15 June 2018. Subjects were randomized to a treatment group by the assignment of a 5-digit randomization number to each subject according to a randomization scheme. The medication was identified using 6-digit kit randomization numbers.

Subjects

Children and adolescents of both genders from age 3 months to <18 years were included with confirmed diagnosis of acute diarrhea (defined as the passage of three or more unformed or liquid stools within the last 24 h and lasting for <3 d), as well as age-appropriate informed consent as per local requirements. Exclusion criteria included known allergy to racecadotril or any of its ingredients; renal or hepatic impairment; need for treatment for acute diarrhea other than ORS alone; fever >39°C; bloody and/or purulent stools; presence of antibiotic-associated diarrhea, chronic diarrhea or iatrogenic diarrhea. During the study, participants were not allowed to be treated with additional treatments with potential to affect the gastrointestinal system.

Written approval of the study was obtained from the Independent Ethics Committee / Institutional Review Board that complies with the local regulatory requirements prior to the study being implemented. The study was conducted in compliance with Good Clinical Practice and the applicable national regulations to assure that the rights, safety, and well-being of the participating study subjects were protected consistent with the ethical principles that have their origin in the Declaration of Helsinki. Voluntary written informed consent was obtained from one parent/caregiver of each subject prior to performing any study-related procedures.

Treatments and schedule

Subjects were randomized to treatment with oral racecadotril (Hidrasec® Infants: Granules for Oral Suspension 10 mg; Hidrasec® Children: Granules for Oral Suspension 30 mg; Hidrasec®: 100 mg capsules; Abbott Laboratories GmbH), three times daily (t.i.d.), according to the body weight dose requirement (i.e., 1.5 mg/kg b.w.; infants <9 kg: one 10 mg sachet t.i.d., in infants 9-<13 kg: two 10 mg sachets t.i.d., children 13-27 kg: one 30 mg sachet t.i.d, children >27 kg: two 30 mg sachets t.i.d., children or adolescents ≥ 60 kg: 100 mg capsule t.i.d.) on an out-patient or in-patient basis for a maximum of 5 days in addition to ORS (Rehydron® [dextrose + potassium chloride + sodium chloride + sodium citrate] powder for solution for oral administration) (RACE+ORS), or with ORS alone. Standard treatment was ORS according to the registered local label and the instruction of the investigator.

The study plan included two visits and a follow-up phone call. Subjects presenting with acute diarrhea underwent a physical examination including vital signs, a review of their medical history, and concomitant medication. The dehydration level of the subject was also assessed as mild, moderate, or severe. If the subjects were eligible, demographics, number of stools during the last 24 h were assessed as baseline values. Included subjects who started study treatment on Day 1.

Treatment was continued until recovery to a maximum of 5 d. Parents/caregivers were instructed to stop treatment when the patient recovered. Recovery was defined by the evacuation of the first of two consecutive normal stools (i.e., defined as the stool consistency the subject had before diarrhea). In the evening of each day, the parent(s)/caregiver(s) filled in diaries, documenting the date and time of each individual stool, the stool consistency of each stool, ORS amount and the study drug intake. Adverse events were reported on an ongoing basis. Treatment was stopped at recovery or after the morning dose of Day 6, if not recovered. The last dose of study drug intake was the morning dose of Day 6, if not recovered earlier. The parent(s)/caregiver(s) visited the site for the end of study visit of the child and data on vital signs, adverse events, physical examination and concomitant medication were collected. The parent(s)/caregiver(s) returned the diaries and unused medication. For the safety follow-up, a phone call was performed 5-7 d after the end of the treatment period or recovery for the safety follow-up.

Endpoints

The primary efficacy endpoint was duration of diarrhea (in hours), with RACE+ORS compared with ORS alone in infants, children and adolescents with acute diarrhea. Duration of diarrhea was defined from start of treatment until date and time of the evacuation of the final watery/diarrheal stool before recovery derived from the daily diary (maximum of 5 d of treatment). Secondary endpoints included number of recovered subjects per treatment group; time until recovery per treatment group with time to recovery defined by date and time of the evacuation of the first of two consecutive normal stools or no stool within 12 h; Global Physician Assessment (GPA), at the end of treatment (where treatment success = GPA score of 1 or 2); and, for toilet trained children and adolescents, number of stools per day and number of watery stools per day from start of treatment until end of study treatment. Safety endpoints included adverse events, vital signs, physical examination.

Statistical methods

The sample size of this study was based on the results obtained in a randomized, double-blind study with racecadotril in the treatment of hospitalized children aged 3-60 months suffering from acute watery diarrhea [16], showing a recovery probability of 84.2% (measured by duration of diarrhea until final watery/diarrheal stool) in the racecadotril group and a 59.4% probability of recovery in the placebo group after a treatment duration of 72 hours. Using these assumptions, 55 subjects per group would have at least 80% power to show a difference between the treatment groups.

The full analysis (FA), set was used for the analysis of the efficacy data. Primary efficacy results analysis was repeated on the per protocol (PP) set as the sensitivity analysis. A Kaplan-Meier plot was generated to compare the two treatment groups for the primary efficacy parameter. The log-rank test at two-sided significance level 5% was used to test whether the observed

difference of the duration of diarrhea between two treatment groups was statistically significant. Time until recovery was assessed in a similar way.

The safety sample was used for the analysis of the safety and tolerability data and consisted of all subjects who were in the all subjects allocated to treatment sample and had at least one dose of study medication administered. The FA set consisted of all subjects who were included in the safety sample and had data for at least one post-baseline assessment of any efficacy measurement. The per protocol (PP) set consisted of all subjects who were included in the FA set and did not present any major protocol violation.

RESULTS

Disposition

A total 124 subjects were consented, enrolled and randomized non-blinded into the study; 62 were randomized to receive racecadotril in addition to ORS and 62 to receive ORS alone. Subject disposition is described in Figure 1. No subjects withdrew from the study for any reason. The study population was represented by all age subgroups (in order to reflect as close as possible real-world clinical practice): subgroup A (3 to <24 months), consisted of 20 subjects (n=14 RACE+ORS; n=6 ORS), subgroup B (≥ 2 to <12 years), consisted of 87 subjects (n=39; n=48), and subgroup C (12 to <18 years), consisted of 17 subjects (n=9; n=8). All subjects (124/124, 100%), were included in each analysis set. Analysis by age was pre-planned per protocol as a descriptive subgroup analysis.

Demographic and baseline characteristics

Demographic data are presented in Table 1. Gender distribution was close to equal with slightly more males (67/124, 54.0%), than females (57/124, 46%). Subjects were predominantly white (120/124, 96.8%). Subjects were aged from 2 years to 11 years (87/124, 70.2%), with a mean age of 6.5 years. Both treatment groups were well balanced with respect to demographic and other baseline characteristics. Medical history findings most commonly involved gastrointestinal disorders (124/124, 100%). At baseline, the mean number of stools in the previous 24 h was 5.0 in the RACE+ORS group and 4.8 in the ORS group. In both groups, the majority of subjects had mild dehydration at screening (59.7% in the RACE+ORS group and 58.1% in the ORS group).

Efficacy

The median duration of diarrhea (primary endpoint) was 16.8 h (95% confidence interval [CI]: 13.8-23.4 h) in the RACE+ORS group and 40.6 h (95% CI: 24.1-49.4 h), in the ORS group, a difference that was statistically significant (p<0.0001) (Figure 2).

At Day 6 all subjects 62/62 (100%), recovered with RACE+ORS compared with 58/62 (93.5%) with ORS. The overall mean (standard deviation [SD]) number of stools recorded during the study was 5.9 (2.9), with RACE+ORS and 8.3 (4.4), with ORS and was 4.2 (2.7), and 6.5 (4.3), for watery stools, respectively. The median time to recovery was 29.3 h (95% CI: 25.3-34.9), with RACE+ORS and 58.2 h (95% CI: 48.4-68.2), with ORS. Based on an additional Cox regression analysis, the relative risk RACE+ORS vs ORS was 4.13 (95% CI: 2.69-6.35; p<0.0001).

For all of the weight subgroups evaluated, the duration of diarrhea and time to recovery was significantly shorter with RACE+ORS compared to ORS alone, except for subjects with body weight ≥60 kg (n=9); there was a tendency towards a quicker time to recovery with RACE+ORS treatment, but not for median duration of diarrhea (Table 2). Across all age subgroups, RACE+ORS showed better efficacy results than ORS alone consistent with the main analysis (i.e., duration of diarrhea; Table 3). GPA success (i.e., complete relief + marked improvement) at the end of treatment was reported for all subjects (62/62, 100%) treated with RACE+ORS and 60 (60/62, 96.8%) treated with ORS (p=0.4959).

In the RACE+ORS group, the mean number of watery stools decreased from 3.2 (Day 1), to 0.1 (Day 3), and no watery stools

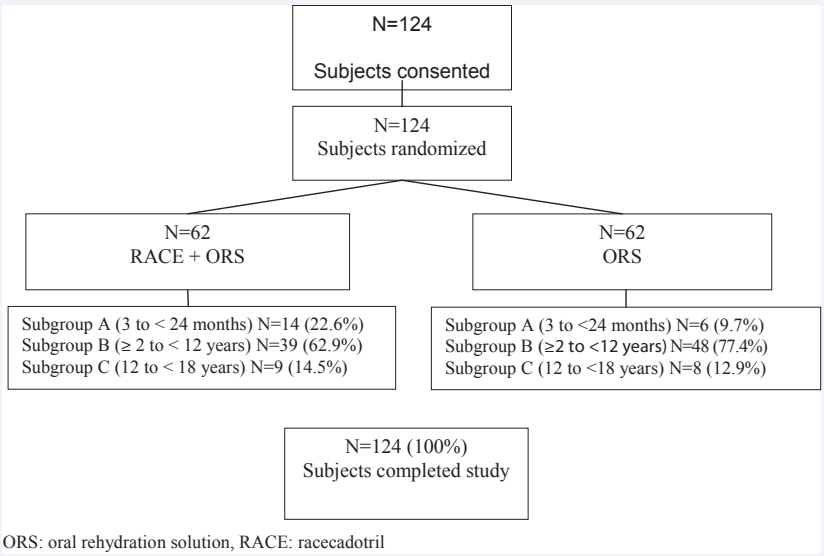
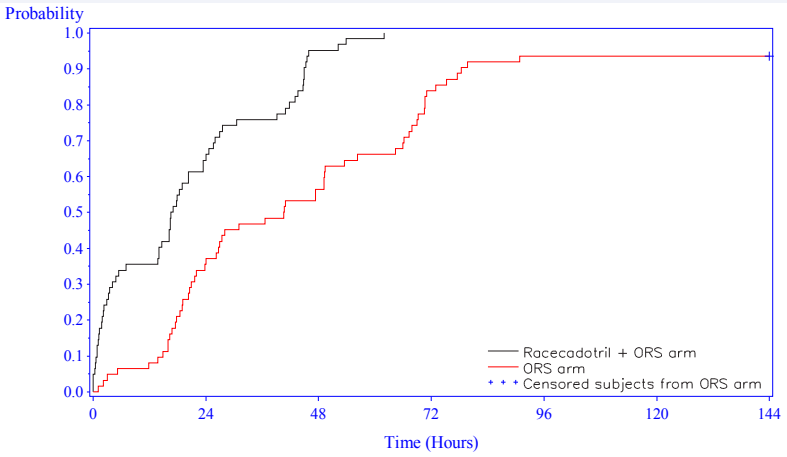


Figure 1 Subject disposition.

Table 1: Baseline characteristics of main diagnosis (Safety Sample).

Characteristic	Statistics	RACE+ORS (N=62)	ORS (N=62)	Total (N=124)
Number of stools during the last 24 hours	n Mean (SD) Median Minimum/Maximum	62 5.0 (1.5) 5.0 3/11	62 4.8 (1.2) 5.0 3/8	124 4.9 (1.4) 5.0 3/11
Dehydration level	n No dehydration, n (%) Mild dehydration, n (%) Moderate dehydration, n (%)	62 21 (33.9%) 37 (59.7%) 4 (6.5%)	62 23 (37.1%) 36 (58.1%) 3 (4.8%)	124 44 (35.5%) 73 (58.9%) 7 (5.6%)

ORS: oral rehydration solution, RACE: Racecadotril, SD: standard deviation



Treatment group	Number of subjects	Censored N (%)	Median (95% CI)
RACE+ORS	62	0 (0.0)	16.8 (13.8 – 23.4)
ORS	62	4 (6.5)	40.6 (24.1 – 49.4)

For all censored subjects censoring occurred at 144 h.

CI: confidence interval, ORS: oral rehydration solution, RACE: Racecadotril; SD: Greenwood's estimator of standard deviation of Kaplan-Meier estimator

Number of recovered subjects (last diarrheal/watery stool before recovery) cumulatively by days (Kaplan-Meier analysis) (FA subject sample)

Day	RACE+ORS (n=62)	ORS (n=62)
Day 1	40 (64.5%)	22 (35.5%)
Day 2	59 (95.2%)	35 (56.5%)
Day 3	62 (100.0%)	52 (83.9%)
Day 4	62 (100.0%)	58 (93.5%)
Day 5	62 (100.0%)	58 (93.5%)
Day 6	62 (100.0%)	58 (93.5%)

Based on the Kaplan-Meier estimates

Figure 2 Kaplan-Meier plot of duration of diarrhea (FA subject sample).

were reported on Day 4 and Day 5. Age-subgroup analysis showed the last episode of watery stool was reported on Day 2 for subgroups of 3 to <24 months and 12 to <18 years old (each n=9), and on Day 3 for subgroup of ≥ 2 to <12 years old (n=39). In the ORS group, mean numbers of watery stools changed from 4.1 (Day 1) to 0.1 (Day 5). The last episode of watery stool was reported on Day 2 for subgroup of 3 to <24 months old (n=1), on Day 4 for subgroup of ≥2 to <12 years old (n=48), and on Day 5 for 12 to <18 years olds (n=8).

Exposure and safety

All randomized subjects (124/124, 100%), received at least one dose of study medication and were included in the safety analysis (Safety subject sample). The completion of the study by all participants was facilitated by the maximum of 5 days of treatment. Overall, the median duration of treatment was shorter in the RACE+ORS group (49.50 h), as compared to the ORS group (67.08 h). The mean cumulative dose of racecadotril was 12.2 mg/kg b.w. (13.1 mg/kg b.w. in 3 to <24 months age subgroup;

Table 2: Duration of diarrhea (hours) by weight/dosing subgroups (FA set).

Weight/dosing subgroup	Statistics	RACE+ORS	ORS	p-value*
Infants <9 kg	n Mean (SD) Median (95%CI)	2 19.8 (19.3) 19.8 (0.5-39.2)	2 49.3 (0.1) 49.3 (49.2-49.3)	0.0896
Infants 9 kg to <13 kg	n Mean (SD) Median (95%CI)	11 10.0 (3.6) 2.9 (0.7-25.6)	9 39.1 (7.5) 40.7 (16.0-70.7)	0.0027
Children 13 kg to 27 kg	n Mean (SD) Median (95%CI)	34 23.7 (3.0) 18.7 (16.2-27.0)	33 46.9 (5.0) 47.4 (21.7-67.8)	<0.0001
Children >27 kg to 60 kg	N Mean (SD) Median (95%CI)	10 18.0 (5.3) 17.1 (0.0-24.7)	14 42.3 (6.9) 34.3 (20.3-66.0)	0.0082
Children or adolescents ≥60 kg	n Mean (SD) Median (95%CI)	5 20.8 (10.1) 14.0 (0.0-44.8)	4 18.8 (10.3) 12.9 (2.2-47.3)	0.5920

ORS: oral rehydration solution, RACE: Racecadotril CI: confidence interval, N: number of subjects in weight/dosing subgroup, SD: standard deviation
*log-rank test.

Table 3: Duration of diarrhea (hours) by age subgroups (FA set).

Age subgroup	Statistics	RACE+ORS	ORS	p-value*
3 to <24 months	n Mean (SD) Median (95%CI)	14 14.8 (4.1) 10.4 (0.7-26.0)	6 42.7 (8.4) 45.1 (17.8-75.3)	0.0085
≥2 to <12 years	n Mean (SD) Median (95%CI)	39 22.1 (2.8) 17.8 (14.1-24.0)	48 44.5 (3.9) 40.6 (22.0-64.3)	<0.0001
12 to <18 years	n Mean (SD) Median (95%CI)	9 19.2 (6.7) 14.0 (0.0-44.8)	8 33.5 (9.3) 27.0 (2.2-69.3)	0.1033

ORS: oral rehydration solution, RACE: Racecadotril, CI: confidence interval, N: number of subjects in age subgroup, SD: standard deviation
*log-rank test.

12.3 mg/kg b.w. in ≥ 2 to <12 years age subgroup; 10.6 mg/kg b.w. in 12 to <18 years age subgroup). There was a tendency toward lower mean cumulative dose of ORS in the RACE+ORS group (52.4 mg/kg b.w.) compared to the ORS group (68.6 mg/kg b.w.).

No treatment emergent adverse events were reported during the study and no deaths, serious or other significant adverse events. In both treatment groups, mean results for vital signs were within normal range, with minimum changes from screening to end of treatment. There were no subjects with dehydration at the end of RACE+ORS treatment, while there were 2 (2/62, 3.2%), subjects with mild dehydration at the end of therapy with ORS (aged 11.8 and 12.0 years).

DISCUSSION

A major aspect of treatment of acute diarrhea in pediatrics is to prevent and correct dehydration. The only response to this significant clinical problem, as stated by the World Health Organization, is an accurate intake of ORS, as no available drug was (at the time of the recommendation) able to antagonize intestinal hypersecretion [17,18]. A physician has limited options for anti-diarrheal/add-on treatments on top of ORS for the infant/pediatric population. The use of loperamide is now discouraged and smectite (i.e., following ANSM, French Health Authority, France) may no longer be used in children <2 years of age [19]. Furthermore, the results with probiotics are strain-dependent and duration of diarrhea is, on average, reduced by one day. Therefore, investigations into potential options in addition to ORS may help to meet the unmet clinical need for improved symptoms and outcomes.

Clinical study data demonstrate that the addition of racecadotril to ORS substantially reduces duration of diarrhea. In adults, racecadotril has been shown to be more effective than placebo in randomized, double-blind clinical studies of patients with acute diarrhea [20]. Cojocaru et al. (2002), demonstrated the efficacy of racecadotril as adjuvant therapy to oral and intravenous rehydration in the treatment of acute diarrhea in 166 children (aged 3 months to 3 years), and noted fewer emergency department second visit before recovery [21]. The findings of a 2011 meta-analysis indicated that, as an adjunct to oral rehydration solution, racecadotril has a clinically relevant effect in reducing diarrhea (duration, stool output and stool number), irrespective of baseline conditions (dehydration, Rotavirus or age), treatment conditions (inpatient or outpatient studies) or geographic location [22].

The current study confirmed the efficacy and positive benefit-

risk-profile for racecadotril that has been demonstrated in previous clinical studies. These results also confirm those obtained from a randomized, double-blind study with racecadotril in the treatment of hospitalized children aged 3-60 months suffering from acute watery diarrhea [16]. This study included 135 boys, rehydrated with an ORS, in addition to racecadotril (1.5 mg/kg), or placebo orally every 8 h. The mean (± standard error) 48-h stool output was 92±12 g/kg body weight in the racecadotril group and 170 ± 15 g/kg in the placebo group ($p<0.001$), representing a 46% reduction with racecadotril. Children in the racecadotril group recovered after about one day (median: 28 h), compared with two days for those in the placebo group who were rotavirus-negative (median: 52 h), and three days for those in the placebo group who were rotavirus-positive (median: 72 h) ($p<0.001$). The intake of ORS was significantly lower with racecadotril compared with placebo ($p<0.001$), and racecadotril was well tolerated. Interestingly, based on three cost-efficacy analyses performed on data from the United Kingdom, Thailand and Malaysia, the addition of racecadotril to ORS can be more cost-efficient than ORS treatment alone, leading to savings to the healthcare systems up to 900 Euros/patient [15].

The present study showed for most of the weight subgroups evaluated, the results for key efficacy endpoints were consistent with that for the overall analysis, except for the nine children or adolescents of ≥ 60 kg (who received the 100 mg capsule t.i.d.), for which no tendency towards a quicker recovery with RACE+ORS treatment could be seen only for time to recovery, but not for median duration of diarrhea. Across age subgroups, the efficacy results indicated a similar level of clinical benefit on diarrhea resolution as shown for the main analysis. The physician's global evaluations were comparable for both treatment groups: the GPA success at the end of treatment was reported for all subjects (100%), treated with RACE+ORS and 60 subjects (96.8%), treated with ORS ($p=0.4959$).

Treatment with RACE+ORS led to faster decrease in daily stool numbers compared with ORS alone. The median duration of treatment was shorter with RACE+ORS (49.50 h) compared with ORS (67.08 h). The mean cumulative dose of racecadotril was 12.2 mg/kg b.w.. There was a tendency toward lower mean cumulative dose of ORS with RACE+ORS (52.4 ml/kg) compared to ORS (68.6 ml/kg), that is explained by the faster recovery and shorter treatment duration needed with RACE+ORS.

There were no subjects with dehydration at the end of RACE+ORS treatment, whereas there were two still dehydrated subjects (aged 11.8 and 12.0 years), at the end of ORS therapy. There were no treatment-emergent adverse events reported in both treatment groups. Racecadotril was well tolerated by all subjects, these results confirm those of other studies in adult and pediatric populations [20,21]. This is also the first study to have evaluated racecadotril 100 mg capsules (t.i.d.), in adolescents.

Limitations of the study include the relatively low number of subjects in the age group 12 to <18 years (principally due to the dosing groups being per kg body weight and not per age), for the 100 mg (where kg of body weight is not always consistent with age), and the difference in sample size for the two treatment groups in the 3 to <24 months subgroup. No stratification for age was done because dosing is by body weight. Despite this, the efficacy results favoured RACE+ORS compared with ORS. The mean age of 6.5 years was relatively high for this treatment compared to other studies. This was intentional in order to reflect real-world clinical practice as close as possible. Whereas the established method to confirm the antidiarrheic effect of a drug is to measure stool weight, the endpoints assessed in the present study (duration of diarrhea) provided an indirect measure of effect but also facilitated the collection of data. An additional potential limitation is the relatively low number of subjects weighing less than 9 kg, where a trend towards improved outcomes with RACE+ORS compared with ORS alone was observed.

CONCLUSION

The study results showed that racecadotril added to standard treatment with ORS was significantly more effective than ORS alone in children and adolescents aged 3 months to <18 years with acute diarrhea. As an adjunct to ORS, oral racecadotril (1.5 mg/kg b.w. t.i.d.), reduced the duration of acute diarrhea and shortened recovery time, the difference vs ORS alone was highly significant ($p<0.0001$). The racecadotril treatment effect was generally consistent across the age and weight subgroups. Treatment with racecadotril was well tolerated. This study confirms that racecadotril is effective and well tolerated as an adjuvant therapy in the treatment of acute diarrhea in infants, children and adolescents. The findings of the subgroup analyses can help inform appropriate treatment of children and adolescents with acute diarrhea in real-world clinical practice.

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CONFLICT OF INTEREST

None. Funding for the study was provided by Abbott Laboratories GmbH. Abbott Laboratories GmbH had no influence in designing and writing the protocol, collection of data, performing the analysis of the study results and writing of the manuscript. The authors are investigators in this study. Following careful consideration of relevant guidelines, International Committee of Medical Journal Editors authorship criteria were fully met by each author.

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