APPENDIX 3
Statistical analysis plan for non-primary outcomes

Two secondary, three exploratory, and two safety outcomes have been included in the protocol. Subjects will be analyzed in all analyses according to the randomized treatment allocation. Secondarily, per-protocol analyses will be conducted only including children who reported full adherence to the antibiotic therapy.

Nominal p-values will be presented for secondary and exploratory analyses, but no statistical significance will be asserted. For safety analyses, a p-value of less than 5% will be considered statistically significant. Clinically relevant, statistically non-significant differences will be addressed.

Secondary outcomes
3. Absence from school or daycare due to illness within 28 days after randomization
We will use the fraction of days the child is absent from school or daycare due to illness, calculated as the number of days the child is absent from school or daycare due to illness divided by the sum of the number of days the child is present at school or daycare plus the number of days the child is absent from school or daycare due to illness. The two randomized groups will be compared using the Wilcoxon-Mann-Whitney test. The population-level summary measure will be the difference between the means of the fractions with two-sided 95% confidence limits (CLs) based on the normal approximation for the estimated mean difference. Children not assigned to a school or daycare will be excluded from the analysis. In case of death, we will use the highest fraction observed in the trial as the outcome for the child. In a secondary analysis, we will exclude the children who died.

4. Recurrent UTI regardless of the pathogen or death of any cause within 100 days after the end of treatment
The population-level summary measure will be the risk difference (RD), calculated as the proportion in the intervention group minus the proportion in the control group, with the upper one-sided 97.5% CL. Inferiority will be rejected if the upper one-sided 97.5% CL for the RD shows a difference of less than the non-inferiority limit of 10 percentage points. If more than 5% of data is missing, data will be imputed based on available knowledge of the patient and the observations of the other patients in the same randomized group. In case of deaths unrelated to infection and with no previous recurrent UTI, we will present analyses i) excluding these children; and ii) imputing that each child did not have recurrent UTI, respectively.

Exploratory outcomes
5. Number of hospital days related to UTI symptoms within 28 days after the end of treatment
The two randomized groups will be compared using the Wilcoxon-Mann-Whitney test. Treatment effects will be evaluated as the difference between the number of days with two-sided 95% CLs based on the normal approximation for the estimated mean difference.
6. Number of days with a physical or virtual (phone or online) consultation during antibiotic therapy for the baseline infection.

The two randomized groups will be compared using the Wilcoxon-Mann-Whitney test. Treatment effects will be evaluated as the difference between the number of days with two-sided 95% CLs based on the normal approximation for the estimated mean difference.

7. Recurrent infection with a bacterium resistant to the antibiotic given for the baseline infection within 100 days after the end of treatment

The population-level summary measure will be the RD, calculated as the proportion in the intervention group minus the proportion in the control group, with two-sided 95% CLs. Recurrent infections with a bacterium sensitive to the antibiotic given for the baseline infection will not lead to censoring.

Safety outcomes

8. Antibiotic-related non-serious adverse events within 28 days after randomization (see in the “Outcome” section for the definition)

As the outcome for each child, we will use the fraction of days the child is affected by one or more non-serious adverse events, calculated as the number of days the child is affected by one or more non-serious adverse events divided by the number of days observed. The two randomized groups will be compared using the Wilcoxon-Mann-Whitney test. The population-level summary measure will be the difference between the means of the fractions with two-sided 95% CLs based on the normal approximation for the estimated mean difference.

In addition, we will for each randomized group present the total number of non-serious adverse events, the number of children who had one or more non-serious adverse events, the number of non-serious adverse events per person-year at risk, and the total number of days with one or more non-serious adverse event. The same outcome measures will also be presented separately for each type of non-serious adverse event.

9. Serious adverse events within 100 days after randomization (see in the “Outcome” section for the definition)

For each randomized group, we will present the total number of serious adverse events and the number of children with one or more serious adverse events. The same outcome measures will also be presented separately for each type of serious adverse event.