

**Information Sheet for Participants
Screening Participants**

Protocol No. PR-21005	Version No. 2.0	Date: 05/04/2021
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Protocol Title: Tebipenem-pivoxil as an alternative to ceftriaxone for clinically non-responding children with shigellosis: a randomized non-inferiority trial

ClinicalTrials.gov Registration: NCT05121974

Investigator's name: Dr Sharika Nuzhat

Organization: International Centre for Diarrhoeal Disease Research, Bangladesh

Purpose of the research

Background

Shigellosis is the second leading cause of diarrheal deaths worldwide. The World Health Organization (WHO) recommends antibiotic therapy for children with *Shigella* dysentery. Azithromycin is used as a first line therapy with ceftriaxone (second-line) reserved for the most severe cases. Approximately 20% of *Shigella* isolates are resistant to azithromycin suggesting a substantial number of children will require second-line therapy. Though Bangladesh has a low resistance of 5% to ceftriaxone, the potential for rapid emergence of antibiotic resistance to this third-generation cephalosporin and ceftriaxone's resource-intensive delivery method underscore the need for evidence-based alternative antibiotic regimens for multidrug resistant *Shigella* infections. Oral tebipenem-pivoxil could provide a therapeutic option for children with shigellosis that have failed first-line treatment options. This drug established safety record in pediatrics treating respiratory tract infections.

We are conducting a study to evaluate the response to tebipenem-pivoxil in pediatric patient population (24-59 months) with Shigellosis who failed 1st line drug therapy and comparing the effectiveness with Ceftriaxone. GlaxoSmithKline (GSK), a pharmaceutical company is supporting this study from a technical perspective.

Why invited to participate in the study?

To fulfil the aim of our research study, we need to collect stool samples of your child, we assume that s/he has shigella we might need to change her/his antibiotic. For this purpose, we will provide her/him either oral Tebipenam-pivoxil or inj. Ceftriaxone or oral Azithromycin and will monitor the response and for this we need to collect stool sample for investigations.

This information, if available, will help the doctors to improve the management of shigellosis bypassing use of injectable drugs. This is why we are requesting you to help us by giving your permission to include your child in our study.

Methods and procedures [What is expected from the participants of the research study?]

If you allow participation of your child in our study, you may expect the followings:

- The doctors, nurses and other staff of this hospital will provide the usual good care and treatment to your child. Participating in this study will not change the standard treatment of this hospital in any way, and the laboratory investigations if required for management of your child, will also be done according to the policy and guidelines of this hospital.
- We would ask you some questions related to your child's illness and perform thorough physical examinations on admission day
- On each day of hospitalization during 1st line antibiotic for shigellosis, we will assess the progress of illness (improvement or deterioration).
- We would collect stool sample of the baby on admission day
- Your co-operation for the study activities is essential

Risk and benefits

Anticipated potential risks:

There is no major risk involved in participation of your child in the study. We would provide treatment for shigellosis at the Dhaka Hospital of icddr,b as per hospital guideline with oral azithromycin.

Anticipated potential benefits:

Your infant will not directly benefit from participating in the study. However, your infant may be able to contribute to our understanding to develop alternate effective treatments for shigellosis. In the long term, the results of this study could benefit other children in Bangladesh and elsewhere, by helping us to understand the effects of tebipenem-pivoxil in shigellosis. The goal is to identify the alternate oral treatment for management of Shigellosis.

Privacy, anonymity and confidentiality

We do hereby state that privacy, anonymity and confidentiality of data/information identifying your child will strictly be maintained. We would keep all medical information, description of treatment, and results of the laboratory tests performed on your child confidential, under lock and key, and none other than our research staff will have an access to this information. No one other than this group of investigators, regulatory authorities and the Ethical Review Committee (a group of experts which protects the interest of study participants) of icddr,b and investigators sponsor of this study would have access to such information. Your child's name and identity will not be disclosed while analysing or publishing the results of this study.

Future use of information

In the case of future use of the information collected from this study, privacy, anonymity and confidentiality of information will be maintained. We will store the stool sample in a way that your child's identity will not be recognised, and use the samples for performing tests that are modified in the near future for superior results, as well as new tests for studying the pathogen and drug response. No

further consent will be requested for such studies. The future use of the information collected through the study will not be of a commercial nature.

Right not to participate and withdraw

Your child's participation in the study is voluntary, and you have the sole authority to decide for or against your patient's participation. You would also be able to withdraw your child's participation any time during the study, without showing any cause. If you decide to withdraw from the study after enrolment the samples/data that are already collected up to that point will be kept and used anonymously for future analysis. Refusal to take part in or withdrawal from the study will involve no penalty or loss of care, benefits or attention.

Principle of compensation

Treatment at this hospital is free for all patients, and your child will not be an exception. Similarly, we will not pay money for participation in our study.

Consent Form for Participants
Screening Participants

Protocol No. PR-21005	Version No. 2.00	Date: 05-04-2021
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Protocol Title: Tebipenem-pivoxil as an alternative to ceftriaxone for clinically non-responding children with shigellosis: a randomized non-inferiority trial

Investigator's name: Dr Sharika Nuzhat

Organization: International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)

If you agree to our proposal for enrolling you/your patient in our study, please put √ mark on appropriate box(es) of the following and finally sign on the specified place for you:

I have read the participant's information sheet version 2.00 dated 05 April 2021, have had the opportunity to ask question, discuss the study, and received satisfactory answers.

Yes No

I understand that I am free to leave the study without giving any reason.

Yes No

I agree to the collection of stool/faecal material

Yes No

I understand that the information I give is confidential.

Yes No

I agree to my identifiable data being used for future ethically approved studies

Yes No

I agree to being contacted in the future for studies related to this research.

Yes No

I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the sponsor and by regulatory authorities, where it is relevant to my taking part in this research. I give my permission for those individuals to have access to my records.

Yes No

I give my consent to take part in the study.

Yes No

Signature or left thumb impression of
Parent/ Guardian/ Attendant

Date

Signature or left thumb impression of the witness

Date

Signature of the PI or his/her representative

Date

Communication:

If you have any question you can ask me right now or at any time later to the below mentioned personnel:

Purpose of contact	Name and address	Address for communication
For any question related to the study, or any problem	Dr Sharika Nuzhat Associate Scientist & Principal Investigator of the study	Address: Dhaka Hospital, icddr,b, Mohakhali, Dhaka-1212 Mobile: 01552365270
To know the rights or benefits or to log any complain or dissatisfaction	M A Salam Khan (IRB Coordinator)	IRB Secretariat, Research Administration, icddr,b, Mohakhali, Dhaka-1212 Phone: (+88-02) 9827084 or Mobile: 01711428989

Thank you for your cooperation.

Information Sheet for Participants Main Trial Participants

Protocol No. PR-21005	Version No. 2.0	Date: 05/04/2021
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Protocol Title: Tebipenem-pivoxil as an alternative to ceftriaxone for clinically non-responding children with shigellosis: a randomized non-inferiority trial

ClinicalTrials.gov Registration: NCT05121974

Investigator's name: Dr Sharika Nuzhat

Organization: International Centre for Diarrhoeal Disease Research, Bangladesh

Purpose of the research

Background

Shigellosis is the second leading cause of diarrheal deaths worldwide. The World Health Organization (WHO) recommends antibiotic therapy for children with *Shigella* dysentery. Azithromycin is used as a first line therapy with ceftriaxone (second-line) reserved for the most severe cases. Approximately 20% of *Shigella* isolates are resistant to azithromycin suggesting a substantial number of children will require second-line therapy. Though resistance to ceftriaxone is low in Bangladesh at 5%, the potential for rapid emergence of antibiotic resistance to this third-generation cephalosporin and ceftriaxone's resource-intensive delivery method, underscore the need for evidence-based alternative antibiotic regimens for multidrug resistant *Shigella* infections. Oral tebipenem-pivoxil could provide a therapeutic option for children with shigellosis that have failed first-line treatment options. This drug established safety record in pediatrics treating respiratory tract infections.

We are conducting a study to evaluate the response to tebipenem-pivoxil in pediatric patient population (24-59 months) with Shigellosis who failed 1st line drug therapy and comparing the effectiveness with Ceftriaxone. To confirm the safety profile and pharmacokinetics of tebipenem in this study population we have enrolled and collected biological samples from first 15 children with tebipenem-pivoxil and confirmed prior to the full trial. GlaxoSmithKline (GSK), a pharmaceutical company is supporting this study from a technical perspective.

Why invited to participate in the study?

To fulfil the aim of our research study, 64 children are going to be enrolled in either Inj Ceftriaxone or oral tebipenem-pivoxil arm. As your child has shigellosis and there is no clinical improvement, we assume that s/he has failed 1st line antibiotic Azithromycin. For this purpose, we will provide her/him either Inj. Ceftriaxone or oral Tebipenem-pivoxil and will monitor the response and for this we need to collect blood and stool sample for investigations.

This information, if available, will help the doctors to improve the management of shigellosis bypassing use of injectable drugs. This is why we are requesting you to help us by giving your permission to include your child in our study.

Methods and procedures [What is expected from the participants of the research study?]

If you allow participation of your child in our study, you may expect the followings:

- The doctors, nurses and other staff of this hospital will provide the usual good care and treatment to your child. Participating in this study will not change the standard treatment of this hospital in any way, and the laboratory investigations if required for management of your child, will also be done according to the policy and guidelines of this hospital.
- We would ask you some questions related to your child's illness, and perform thorough physical examinations on the enrolment day in the study and on each day of hospitalization to assess the progress of illness (improvement or deterioration).
- We would provide either Inj. Ceftriaxone I/V once daily or oral Tebipenem thrice daily for 3 days. This study drugs are safe as mentioned earlier.
- We would collect stool sample of the baby on the day of enrolment and subsequently with regular intervals on day 3, 7, 30.
- We would also collect 3 ml blood samples on day 3. In addition, 3 ml of blood will be collected from the participants at day 0, day 7 and day 30 of follow-up. Blood samples will be collected via the traditional method of venipuncture (cubital vein) by needle and syringe.
- After completion of treatment, the doctors of this hospital will discharge your child from the hospital, according to the policy and guidelines of this hospital. What it means is that the management of your child and her/his discharge will not be influenced by participation of your child in our study.
- After discharging the patient from hospital, we would provide regular follow up of the baby day 7 and day 30 in a pre-specified schedule. For this purpose, you need to visit our hospital according to the schedule.
- Your co-operation for the study activities is very necessary.

Risk and benefits

Anticipated potential risks:

There is no major risk involved in participation of your child in the study. Possible adverse events may be vomiting, diarrhea, skin rash, urticaria. Despite taking precautions, if your child develops any symptoms due to this study procedure, we would provide appropriate treatment at the Dhaka Hospital of icddr,b. Your child may experience little discomfort or pain while providing the blood samples. There is no major risk involved in giving blood samples.

Anticipated potential benefits:

Your infant will not directly benefit from participating in the study. However, your infant may be able to contribute to our understanding to develop alternate effective treatments for shigellosis. In the long term, the results of this study could benefit other children in Bangladesh and elsewhere. by helping us to understand the effects of tebipenem-pivoxil in shigellosis. The goal is to identify the alternate oral treatment for management of Shigellosis.

Privacy, anonymity and confidentiality

We do hereby state that privacy, anonymity and confidentiality of data/information identifying your child will strictly be maintained. We would keep all medical information, description of treatment, and results of the laboratory tests performed on your child confidential, under lock and key, and none other than our research staff will have an access to this information. No one other than this group of investigators, regulatory authorities and the Ethical Review Committee (a group of experts which

protects the interest of study participants) of icddr,b and investigators sponsor of this study would have access to such information. The biological samples will be sent abroad for further analysis. Your child's name and identity will not be disclosed while analysing or publishing the results of this study.

Future use of information

In the case of future use of the information collected from this study, privacy, anonymity and confidentiality of information will be maintained. We will store the stool and blood sample in a way that your child's identity will not be recognised, and use the samples for performing tests that are modified in the near future for superior results, as well as new tests for studying the pathogen and drug response. No further consent will be requested for such studies. The future use of the information collected through the study will not be of a commercial nature.

Right not to participate and withdraw

Your child's participation in the study is voluntary, and you have the sole authority to decide for or against your patient's participation. You would also be able to withdraw your child's participation any time during the study, without showing any cause. If you decide to withdraw from the study after enrolment the samples/data that are already collected up to that point will be kept and used anonymously for future analysis. Refusal to take part in or withdrawal from the study will involve no penalty or loss of care, benefits or attention.

Principle of compensation

Treatment at this hospital is free for all patients, and your child will not be an exception. Similarly, we will not pay money for participation in our study. If your child has a study related injury s/he will receive standard care at the Dhaka Hospital (Cholera Hospital) in Mohakhali, Dhaka. For the purpose of the research reimbursement of cost of transportation during follow up in the study will be considered for each and every patient enrolled into the study. However, the amount should be equivalent to the actual cost for two-way travel incurred by you to bring your child to the hospital and then back home.

Consent Form for Participants
Main Trial Participants

Protocol No. PR-21005	Version No. 2.00	Date: 05-04-2021
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Protocol Title: Tebipenem-pivoxil as an alternative to ceftriaxone for clinically non-responding children with shigellosis: a randomized non-inferiority trial

Investigator's name: Dr Sharika Nuzhat

Organization: International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)

If you agree to our proposal for enrolling you/your patient in our study, please put √ mark on appropriate box(es) of the following and finally sign on the specified place for you:

I have read the participant's information sheet version 2.00 dated 05 April 2021, have had the opportunity to ask question, discuss the study, and received satisfactory answers. Yes No

I understand that I am free to leave the study without giving any reason. Yes No

I agree to the collection of up to 3 ml of blood. Yes No

I agree that anonymised blood samples can be sent to abroad for analysis Yes No

I agree to the collection of stool/faecal material Yes No

I understand that the information I give is confidential. Yes No

I agree to my identifiable data being used for future ethically approved studies Yes No

I agree to being contacted in the future for studies related to this research. Yes No

I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the sponsor and by regulatory authorities, where it is relevant to my taking part in this research. I give my permission for those individuals to have access to my records. Yes No

I give my consent to take part in the study. Yes No

Signature or left thumb impression of
Parent/ Guardian/ Attendant

Date

Signature or left thumb impression of the witness

Date

Signature of the PI or his/her representative

Date

Communication:

If you have any question you can ask me right now or at any time later to the below mentioned personnel:

Purpose of contact	Name and address	Address for communication
For any question related to the study, or any problem	Dr Sharika Nuzhat Associate Scientist & Principal Investigator of the study	Address: Dhaka Hospital, icddr,b, Mohakhali, Dhaka-1212 Mobile: 01552365254
To know the rights or benefits or to log any complain or dissatisfaction	M A Salam Khan (IRB Coordinator)	IRB Secretariat, Research Administration, icddr,b, Mohakhali, Dhaka-1212 Phone: (+88-02) 9827084 or Mobile: 01711428989

Thank you for your cooperation.



**Information Sheet for Participants
Pharmacokinetic Study and Pilot Trial for Efficacy Participants**

Protocol No. PR-21005	Version No. 2.0	Date: 05/04/2021
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Protocol Title: Tebipenem-pivoxil as an alternative to ceftriaxone for clinically non-responding children with shigellosis: a randomized non-inferiority trial

ClinicalTrials.gov Registration: NCT05121974

Investigator's name: Dr Sharika Nuzhat

Organization: International Centre for Diarrhoeal Disease Research, Bangladesh

Purpose of the research

Background

Shigellosis is the second leading cause of diarrheal deaths worldwide. The World Health Organization (WHO) recommends antibiotic therapy for children with *Shigella* dysentery. Azithromycin is used as a first line therapy with ceftriaxone (second-line) reserved for the most severe cases. Approximately 20% of *Shigella* isolates are resistant to azithromycin suggesting a substantial number of children will require second-line therapy. Though resistance to ceftriaxone is low in Bangladesh at 5%, the potential for rapid emergence of antibiotic resistance to this third-generation cephalosporin and ceftriaxone's resource-intensive delivery method, underscore the need for evidence-based alternative antibiotic regimens for multidrug resistant *Shigella* infections. Oral tebipenem-pivoxil could provide a therapeutic option for children with shigellosis that have failed first-line treatment options. This drug established safety record in pediatrics treating respiratory tract infections.

We are conducting a pilot study to evaluate the response to tebipenem-pivoxil in pediatric patient population (24-59 months) with Shigellosis and comparing the efficacy with Azithromycin. To confirm the safety profile and pharmacokinetics of tebipenem in this study population we are enrolling and collecting biological samples from 15 children with tebipenem-pivoxil and safety is going to be confirmed prior to the full trial. GlaxoSmithKline (GSK), a pharmaceutical company is supporting this study from a technical perspective.

Why invited to participate in the study?

To fulfil the aim of our research study, we need to enrol 30 children in oral tebipenem-pivoxil arm and 15 children in Azithromycin arm. As your child has shigellosis and she/he will be randomized to any of the treatment arms. For this purpose, we will provide her/him either oral Tebipenem-pivoxil or oral Azithromycin and will monitor the response and for this we need to collect blood and stool sample for investigations.

This information, if available, will help the doctors to improve the management of shigellosis bypassing use of injectable drugs. This is why we are requesting you to help us by giving your permission to include your child in our study.

Methods and procedures [What are expected from the participants of the research study?]

If you allow participation of your child in our study, you may expect the followings:

- The doctors, nurses and other staff of this hospital will provide the usual good care and treatment to your child. Participating in this study will not change the standard treatment of this hospital in any way, and the laboratory investigations if required for management of your child, will also be done according to the policy and guidelines of this hospital.
- We would ask you some questions related to your child's illness, and perform thorough physical examinations on the enrolment day in the study and on each day of hospitalization to assess the progress of illness (improvement or deterioration).
- We would provide oral Tebipenem thrice daily for 3 days or oral Azithromycin once daily for 3 days. This new study drug tebipenem is safe as mentioned earlier.
- If your child is randomized to Tebipenem arm she/he will be included in pharmacokinetic study of tebipenem.
- For pharmacokinetic analysis we would collect blood samples 6 times on day 1 and 3 of oral Tebipenem (Pre-Dose: 0 hours, Post-Dose 1:0.5 hours (± 6 minutes), 1 hour (± 6 minutes), 2 hours (± 12 minutes), Post-dose 2: 1-2 hours after second dose, Post-dose 3:1-2 hours after third dose. Each sample will contain 0.5 ml of blood which will be collected via the traditional method of venipuncture (cubital vein) by needle and syringe.
- On day 2 of Tebipenem we would collect sample for 3 times, Pre-Dose: 0 hours, Post-Dose 2: 1-2 hours after second dose, Post-Dose 3: 1-2 hours after third dose. Each sample will contain 0.5 ml of blood which will be collected via the traditional method of venipuncture (cubital vein) by needle and syringe.
- For any of the arms we would collect stool sample of the baby on the day of enrolment and subsequently with regular intervals on day 3, 7, 30. We would also collect 3 ml blood samples on day 3. In addition, 3 ml of blood will be collected from the participants at day 0, day 7 and day 30 of follow-up. Blood samples will be collected via the traditional method of venipuncture (cubital vein) by needle and syringe.
- After completion of treatment, the doctors of this hospital will discharge your child from the hospital, according to the policy and guidelines of this hospital. What it means is that the management of your child and her/his discharge will not be influenced by participation of your child in our study.
- After discharging the patient from hospital, we would provide regular follow up of the baby day 7 and day 30 in a pre-specified schedule. For this purpose, you need to visit our hospital according to the schedule.

- Your co-operation for the study activities is very necessary.

Risk and benefits

Anticipated potential risks:

There is no major risk involved in participation of your child in the study. Possible adverse events may be vomiting, diarrhoea, skin rash, urticaria. Despite taking precautions, if your child develops any symptoms due to this study procedure, we would provide appropriate treatment at the Dhaka Hospital of icddr,b. Your child may experience little discomfort or pain while providing the blood samples. There is no major risk involved in giving blood samples.

Anticipated potential benefits:

Your infant will not directly benefit from participating in the study. However, your infant may be able to contribute to our understanding to develop alternate effective treatments for shigellosis. In the long term, the results of this study could benefit other children in Bangladesh and elsewhere. The goal is to identify the alternate oral treatment for management of Shigellosis.

Privacy, anonymity and confidentiality

We do hereby state that privacy, anonymity and confidentiality of data/information identifying your child will strictly be maintained. We would keep all medical information, description of treatment, and results of the laboratory tests performed on your child confidential, under lock and key, and none other than our research staff will have an access to this information. No one other than this group of investigators, regulatory authorities and the Ethical Review Committee (a group of experts which protects the interest of study participants) of icddr,b and investigators sponsor of this study would have access to such information. The biological samples will be sent to abroad for further analysis. Your child's name and identity will not be disclosed while analyzing or publishing the results of this study.

Future use of information

In the case of future use of the information collected from this study, privacy, anonymity and confidentiality of information will be maintained. We will store the stool and blood sample in a way that your child's identity will not be recognised, and use the samples for performing tests that are modified in the near future for superior results, as well as new tests for studying the pathogen and drug response. No further consent will be requested for such studies. The future use of the information collected through the study will not be of a commercial nature.

Right not to participate and withdraw

Your child's participation in the study is voluntary, and you have the sole authority to decide for or against your patient's participation. You would also be able to withdraw your child's participation any time during the study, without showing any cause. If you decide to withdraw from the study after enrolment the samples/data that are already collected up to that point will be kept and used anonymously for future analysis. Refusal to take part in or withdrawal from the study will involve no penalty or loss of care, benefits or attention.

Principle of compensation

Treatment at this hospital is free for all patients, and your child will not be an exception. Similarly, we will not pay money for participation in our study. If your child has a study related injury s/he will receive standard care at the Dhaka Hospital (Cholera Hospital) in Mohakhali, Dhaka. For the purpose of the research reimbursement of cost of transportation during follow up in the study will be considered for each and every patient enrolled into the study. However, the amount should be equivalent to the actual cost for two-way travel incurred by you to bring your child to the hospital and then back home.

Consent Form for Participants
Pharmacokinetic Study and Pilot Trial for Efficacy Participants

Protocol No. PR-21005	Version No. 2.00	Date: 05-04-2021
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Investigator's name: Dr Sharika Nuzhat

Organization: International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)

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I have read the participant's information sheet version 2.00 dated 05 April 2021, have had the opportunity to ask question, discuss the study, and received satisfactory answers. Yes No

I understand that I am free to leave the study without giving any reason. Yes No

I agree to the collection of up to 3 ml of blood. Yes No

I agree that anonymised blood samples can be sent to abroad for analysis Yes No

I agree to the collection of stool/faecal material Yes No

I understand that the information I give is confidential. Yes No

I agree to my identifiable data being used for future ethically approved studies Yes No

I agree to being contacted in the future for studies related to this research. Yes No

I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the sponsor and by regulatory authorities, where it is relevant to my taking part in this research. I give my permission for those individuals to have access to my records. Yes No

I give my consent to take part in the study. Yes No

Signature or left thumb impression of
Parent/ Guardian/ Attendant

Date

Signature or left thumb impression of the witness

Date

Signature of the PI or his/her representative

Date

Communication:

If you have any question you can ask me right now or at any time later to the below mentioned personnel:

Purpose of contact	Name and address	Address for communication
For any question related to the study, or any problem	Dr Sharika Nuzhat Associate Scientist & Principal Investigator of the study	Address: Dhaka Hospital, icddr,b, Mohakhali, Dhaka-1212 Mobile: 01552365270
To know the rights or benefits or to log any complain or dissatisfaction	M A Salam Khan (IRB Coordinator)	IRB Secretariat, Research Administration, icddr,b, Mohakhali, Dhaka-1212
		Phone: (+88-02) 9827084 or Mobile: 01711428989

Thank you for your cooperation.