CONVENIO MODIFICATORIO 2, AL CONVENIO CONCERTACION, NÚMERO INCMN/301/08/PI/11/16 DE FECHA 26 DE ENERO DE 2016 Y ENMENDADO EL 05 DE ABRIL DE 2017, EN ADELANTE **"EL CONVENIO PRINCIPAL"**, QUE CELEBRAN POR UNA PARTE, EL INSTITUTO NACIONAL DE CIENCIAS MÉDICAS Y NUTRICIÓN SALVADOR ZUBIRÁN, REPRESENTADO POR EL DOCTOR DAVID KERSHENOBICH STALNIKOWITZ, EN SU CARÁCTER DE DIRECTOR GENERAL, A QUIEN EN ADELANTE SE LE DENOMINARÁ COMO **"EL INSTITUTO"** Y POR UNA SEGUNDA PARTE MERCK SHARP & DOHME COMERCIALIZADORA S DE R.L. DE C.V ACTUANDO POR SU PROPIDO DERECHO A SOLICITUD DE MERCK SHARP & DOHME CORP., A QUIEN EN LO SUCESIVO SE LE DENOMINARÁ **"EL PATROCINADOR"**, REPRESENTADA EN ESTE ACTO POR LA DRA. ALEXANDRA GUADALUPE BARAJAS OLIVAS, EN SU CARÁCTER DE REPRESENTANTE LEGAL, Y COMO INVESTIGADOR RESPONSABLE, EN SU CARÁCTER DE **"INVESTIGADOR PRINCIPAL"** EL DR. LUIS ALFREDO PONCE DE LEON GARDUÑO, A QUIENES EN CONJUNTO SE LES DENOMINARÁ COMO **"LAS PARTES"**, SUJETÁNDOSE AL TENOR DE LAS SIGUIENTES DECLARACIONES Y CLÁUSULAS: **ANTECEDENTES** 1. **EL INSTITUTO** formalizó **EL CONVENIO PRINCIPAL** con **EL PATROCINADOR** el 26 de Enero de 2016 con el objeto de desarrollar dentro de las instalaciones de **EL INSTITUTO** el proyecto de investigación en materia de infección bacteriana, titulado **"Una prueba clínica de fase III, randomizada, en doble ciego, controlada con comparador activo para estimar la eficacia y seguridad de**	AMENDMENT 2 TO THE COOPERATION AGREEMENT NUMBER INCMN/301/08/PI/11/16 DATED ON JANUARY 26, 2016 AND AMENDED ON APRIL 5, 2017, "**THE AGREEMENT**" BY AND AMONG INSTITUTO NACIONAL DE CIENCIAS MEDICAS Y NUTRICION SALVADOR ZUBIRAN, REPRESENTED BY DAVID KERSHENOBICH STALNIKOWITZ, MD., AS GENERAL DIRECTOR HEREINAFTER CALLED **"THE INSTITUTE"** AND A SECOND PART MERCK SHARP & DOHME COMERCIALIZADORA, S DE R.L. DE C.V ACTING FOR ITS PROPOSED RIGHT TO APPLICATION OF MERCK SHARP & DOHME CORP., TO WHICH SUCCESSIVE IT WILL BE NAMED **"THE SPONSOR"**, REPRESENTED IN THIS ACT BY DRA. ALEXANDRA GUADALUPE BARAJAS OLIVAS, IN THE CHARACTER OF LEGAL PRESENTATIVE AND AS RESPONSIBLE INVESTIGATOR, IN ITS CHARACTER OF**"THE "PRINCIPAL INVESTIGATOR"** LUIS ALFREDO PONCE DE LEON GARDUÑO, MD.; A JOINT WHO ARE REFERRED AS **"THE PARTIES"**,, SUBJECTING TO THE TENOR OF THE FOLLOWING DECLARATIONS AND ARTICLES: **BACKGROUND** 1. **THE INSTITUTE**, formalized **THE AGREEMENT** with **THE SPONSOR** on January 26, 2016, in order to develop within the facilities of **THE INSTITUTE** the research project on bacterial infection, entitled **"A phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial to Estimate the Efficacy and Safety of Imipenem/Cilastatin/Relebactam**

Imipenem/Cilastatina /Relebactam (MK-7655A) frente a Colistimetato Sódico + Imipenem/Cilastatina en participantes con infección bacteriana resistente a Imipenem", en adelante **"EL PROTOCOLO".**	**(MK7655a) versus Colistimethathe Sodium + Imipenem/Cilastatin in subjects with Imipenem-Resistant Bacterial Infection"**, hereinafter **"THE PROTOCOL ".**
2. **EL CONVENIO PRINCIPAL** continua vigente, ya que **EL PROTOCOLO** de Investigación no ha concluido, tal y como se encuentra estipulado en el **EL CONVENIO PRINCIPAL** en la CLÁUSULA CUARTA.	2. **THE AGREEMENT** is still in force, as the **THE PROTOCOL** has not been concluded, as stipulated in the **THE AGREEMENT** in ARTICLE FOUR.
3. En la Cláusula VIGESIMA OCTAVA, **LAS PARTES** acuerdan que para modificar el presente Convenio, deberá llevarse a cabo mediante Convenio Modificatorio por escrito y firmado por **LAS PARTES**, el cual iniciará su vigencia a partir de la fecha de la firma, sin este requisito no será válido ninguna modificación.	3. In the TWENTY-EIGHT Article, **THE PARTIES** agree that in order to amend this Agreement, it shall be carried out by means of a Modifying Agreement in writing and signed by **THE PARTIES**, which shall be effective as of the date of signature. Without this requirement no modification will be valid.
DECLARACIONES	**STATEMENTS**
I. Declara EL INSTITUTO a través de su Director General que:	**I. THE INSTITUTE states through its General Director:**
I.1. Que es un Organismo Público Descentralizado de la Administración Pública Federal con personalidad jurídica y patrimonio propio, que dentro de sus facultades se encuentran las de coadyuvar al funcionamiento y consolidación del Sistema Nacional de Salud, así como la de proporcionar consulta externa y atención hospitalaria a la población que requiera atención en su área de especialización y afines, en las instalaciones que para el efecto disponga, con criterios de gratuidad fundada en las condiciones socioeconómicas de los usuarios, sin que las cuotas de recuperación desvirtúen su función social, mediante la prestación de servicios profesionales de medicina, hospitalarios, de	**I.1.** It is a Decentralized Public Organization of the Federal Public Administration, and its powers include to contribute to the operation and consolidation of the National Health System, as well as to provide external consultation and hospital care to the population that requires medical attention in the area of specialization and related, in facilities available for that purpose, with criteria for gratuity based on the socioeconomic conditions of the users, establishing recovery fees which do not retract them from its social function by providing professional medical services, hospital, laboratory and clinical studies and therefore, to carry out scientific research in the field of Health, in

laboratorios y estudios clínicos y por ello realiza actividades de investigación científica en el campo de la Salud, de conformidad con los artículos 1° y 45 de la Ley Orgánica de la Administración Pública Federal; 14 y 15 de la Ley Federal de las Entidades Paraestatales; 1°; 2, fracciones III. IV, VII y IX; 6° fracciones I y II; 7° fracción I; 9 fracción V; 37, 39 fracción IV y 41 de la Ley de los Institutos Nacionales de Salud y de los Artículos 3 fracciones I, II y XIV y 34 fracción I del Estatuto Orgánico del Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", así como, lo que estable la NORMA Oficial Mexicana NOM-012-SSA3-2012, que establece los criterios para la ejecución de proyectos de investigación para la salud en seres humanos.	accordance with Articles 1 and 45 of the Organic Law of the Federal Public Administration; 14 and 15 of the Federal Law of Public Enterprises; 1, 2, fraction III, IV, VII and IX; 6 fraction I and II; 7 fraction I; 9 fraction V; 37, 39 fraction IV and 41 of the Law of the National Institutes of Health and Articles 3 sections I, II and XIV and 34 fraction I of the Organic Statute of the National Institute of Medical Sciences and Nutrition "Salvador Zubirán", and the Guidelines for the Administration of Third Party Resources Intended to Finance Research Projects of the National Institutes of Health.
I.2. Que tiene facultades para representar en este acto a **EL INSTITUTO** y suscribir la presente Enmienda, de conformidad con lo dispuesto en el artículo 19 fracción I de la Ley de los Institutos Nacionales de Salud, y acredita su personalidad conforme a la Protocolización de su Nombramiento, el cual consta en el Acta número ciento treinta y siete mil doscientos treinta y dos, otorgada ante la fe del Lic. Ignacio Soto Borja y Anda, Titular de la Notaria Pública No. 129 del Distrito Federal; facultades que a la fecha no le han sido revocadas, limitadas o modificadas en forma alguna.	**I.2.** That it has the power to represent the INSTITUTE in this act and to subscribe to this Amendment, in accordance with the provisions of article 19, section I of the National Institutes of Health Act, and proves its personality in accordance with the Protocol of Appointment; which is recorded in the Act number one hundred and thirty-seven thousand two hundred and thirty-two, granted before the faith of Mr. Ignacio Soto Borja y Anda, Holder of the Notary Public No. 129 of the Federal District; Faculties that to date have not been revoked, limited or modified in any way.
II. Declara EL PATROCINADOR a través de su Representante legal que:	**II.THE SPONSOR STATES THROUGH ITS LEGAL REPRESENTATIVE**
II.1. Que su representada es una sociedad constituida conforme a las Leyes de la República Mexicana, lo cual tiene constancia en la Escritura Pública número 50,185, de fecha 19 de Agosto de 2004, otorgada ante la fe del Licenciado Ignacio Soto Sobreyra y Silva, Notario Público número 13, de la Ciudad de México, cuyo primer testimonio quedó debidamente inscrito en el Registro Público de Comercio del Distrito Federal.	**II.1.** THE SPONSOR is a corporation incorporated under the Laws of Mexico, which is recorded in the Deed number 50185 dated 19TH August, 2004, granted before Ignacio Soto Sobreyra y Silva. Notary Public number 13, City of Mexico, whose first testimony was duly registered with the Public Registry of Commerce of Mexico City.
II. 2. Que el objeto social de su representada es la compra, venta, adquisición, exportación y comercialización de todo tipo de productos	**II.2.** That the business purpose of it's represented is the purchase, sale, acquisition, export and merchandising of all kinds of

químicos, medicinales, farmacéuticos, biológicos y nutricionales, entre otros, el cual tiene constancia en la escritura indicada, descrita en el inciso anterior.	chemical, medical, pharmaceutical, biological and nutritional products, among others, which is recorded in the specified script, described in the preceding paragraph.
II.3. Que **EL CONVENIO PRINCIPAL** fue formalizado por la Dra. Yvonne Aboitiz Slim, en su calidad de representante legal, sin embargo, el presente **CONVENIO MODIFICATORIO** será formalizado por la C. Alexandra Guadalupe Barajas Olivas, en su carácter de apoderada general, quien acredita su personalidad con la Escritura Pública número 91,872 de fecha 04 de mayo de 2018, otorgada ante la fe del C. Lic. Mauricio Gálvez Muñoz, Notario Público Número 39 del Distrito Federal, hoy Ciudad de México, documento en el cual constan las facultades suficientes y necesarias para su formalización.	**II.3.** That THE MAIN AGREEMENT was formalized by Dr. Yvonne Aboitiz Slim, as legal representative; however, this MODIFICATORY AGREEMENT will be formalized by DRA. Alexandra Guadalupe Barajas Olivas, in her capacity as general attorney, who proves her personality with Public Deed number 91,872 dated May 4, 2018, granted before the faith of C. Lic. Mauricio Gálvez Muñoz, Public Notary Number 39 of the Federal District, today Mexico City, document in which sufficient and necessary faculties are recorded for its formalization.
III. DECLARA EL INVESTIGADOR PRINCIPAL, POR SU PROPIO DERECHO.	**III. "THE RESEARCHER" STATES, IN ITS OWN RIGHT.**
III.1. Que **EL INVESTIGADOR** es una persona física con conocimientos, habilidades y destrezas para celebrar el presente Convenio.	**III.1.** That **THE RESEARCHER** is a natural person with knowledge, abilities and skills to hold this AGREEMENT.
III.2 Que **EL INVESTIGADOR** actualmente ejerce la profesión de Médico Cirujano, en la especialidad de Infectología de Adultos, y cuenta con los conocimientos necesarios para llevar a cabo el Proyecto o Protocolo de Investigación, en los términos que más adelante se señalan.	**III.2.** That **THE RESEARCHER** currently practices the profession of Surgeon Doctor, in the specialty of Adult Infectology, and has the necessary knowledge to carry out the Project or Research PROTOCOL, under the terms as outlined below.
III.3. EL INVESTIGADOR declara y garantiza que ninguna acción, demanda, reclamo, investigación o procedimiento legal o administrativo está pendiente o amenaza con respecto a la inhabilitación de **EL INVESTIGADOR** y la prohibición del ejercicio de su profesión. **EL INVESTIGADOR** acuerda informar inmediatamente y por escrito a **EL PATROCINADOR**, en caso de que exista o se prevea el comienzo de una acción, demanda, reclamo, investigación o procedimiento legal o administrativo que amenace o inicie la inhabilitación de **EL INVESTIGADOR** o la prohibición para ejercer su profesión.	**III.3. THE RESEARCHER** represents and warrants that no action, suit, claim investigation or legal or administrative proceeding is pending or threatened relating to **THE RESEARCHER**'s debarment and the prohibition to exercise it's profession and **THE RESEARCHER** agrees to immediately inform **THE SPONSOR** in writing if any such action, suit, claim, investigation or legal or administrative proceeding is threatened or commenced for **THE RESEARCHER**'s debarment or prohibition to exercise it's profession.

IV. DECLARAN LAS PARTES.	**IV. "THE PARTIES" STATE**
IV.1. Que han negociado de buena fe los términos y condiciones del presente Convenio, a través de sus representantes debidamente acreditados, y que tienen pleno conocimiento de sus implicaciones jurídicas.	**IV.1.** That they have negotiated in good faith the terms and conditions of this AGREEMENT, through their duly authorized representatives, and have full knowledge of its legal implications.
Expuesto lo anterior, **"LAS PARTES"** se reconocen la personalidad con que comparecen a la celebración del presente Convenio Modificatorio, sujetándose a las siguientes:	Exposed the above, **"THE PARTIES"** recognize the personality with which they appear at the celebration of this Modifying Agreement, subject to the following:
CLAUSULAS	**CLAUSES**
PRIMERA OBJETO DE LAS PARTES. Las partes convienen en sustituir en su totalidad el Anexo C por el Anexo C.2	**FIRST OBJECT OF THE PARTIES.** Parties agree to substitute the Exhibit C by Exhibit C.2|
SEGUNDA. Salvo el contenido expreso en este documento, continúan rigiendo para **LAS PARTES**, todas y cada una de las condiciones originales establecidas en **EL CONVENIO PRINCIPAL** y sus anexos.	**SECOND.** Except as expressly provided in this document, each and every one of the original conditions established in **THE AGREEMENT** and Exhibits shall continue to apply to both **PARTIES**.
TERCERA. Ambas partes reconocen que el presente convenio modificatorio, no constituye novación de las obligaciones contenidas en el convenio y que no existe dolo, error ni violencia o algún vacío del consentimiento en la solución del presente instrumento, por lo que están de acuerdo en todas y cada una de sus declaraciones y cláusulas que lo integran.	**THIRD.** Both parties acknowledge that this modifying agreement does not constitute a novation of the obligations contained in the agreement and that there is no fraud, error or violence or any void of consent in the solution of this instrument, so they agree on each and every one of its declarations and clauses that integrate it.
El presente convenio modificatorio se firma por triplicado en la Ciudad de México a los 12 días del mes de Julio de 2018.	This Amendment is signed in triplicate in Mexico City on July 12th, 2018.

INSTITUTO NACIONAL DE CIENCIAS MÉDICAS Y NUTRICIÓN SALVADOR ZUBIRÁN

BY/POR: _____

NAME/NOMBRE: DR. DAVID KERSHENOBICH STALNIKOWITZ

TITLE/CARGO: GENERAL DIRECTOR / DIRECTOR GENERAL

DATE/FECHA: 30-agosto-18

DR. LUIS ALFREDO PONCE DE LEON GARDUÑO

BY/POR: _____

TITLE/CARGO: PRINCIPAL INVESTIGATOR / INVESTIGADOR PRINCIPAL

DATE/FECHA: 17/AUG/2018

MERCK SHARP & DOHME COMERCIALIZADORA S DE R.L. DE C.V.

BY/POR: _____

NAME/NOMBRE: DRA. ALEXANDRA GUADALUPE BARAJAS OLIVAS

TITLE/CARGO: LEGAL REPRESENTATIVE / REPRESENTANTE LEGAL

DATE/FECHA: 10-Aug-2018

GLOBAL AGREEMENTS Virginia Gilbert

6-iul-18

PID:521669

SiteNo:1202

MSD Study Site Budget
MK-7655A-013-00

PI Name: Alfredo Ponce de Leon Garduno

Institution (Site): Instituto Nacional de Ciencias Medicas y Nutricion "Salvador Zubiran"

The target number of patients for your site is __3___. For the purpose of trial planning and management, this Budget encompasses an enrollment range between _3____ and _3____. However, as you approach your target of _3____, if you wish to continue to enroll, you must be proactive & contact the CRA for approval to continue enrolling up to __3___. If you wish to continue to enroll beyond _3_, a Budget Amendment will be issued to finalize the authorization of any potential increase in subject numbers beyond __3___. The budget will be adjusted if the study design is modified and has a financial impact. Sponsor reserves the right to decrease or increase the number of patients at any time during the enrollment period without renegotiating based on the costs listed in this budget. Such notification shall be in writing from a person authorized by the Sponsor.

Mexico Arms & Cohorts: No Arms										
Procedure	**Qty**	**OH**	**Budget**	**V1Scr**	**V2D1**	**V3D3**	**V4EOT**	**V5EFU**	**V6D28**	**V7SFU**
Informed consent	1	✓	1,005.00	1,005.00						
Genomics consent; DNA consent	1	✓	392.00	392.00						
Inclusion/Exclusion Criteria	1	✓	452.00	452.00						
Initial medical history only	1	✓	968.00	968.00						
Prior and Concomitant medications	7	✓	284.00	284.00	284.00	284.00	284.00	284.00	284.00	284.00
Intravenous (IV) infusion for therapy, prophylaxis or diagnosis (IMI or IMI/REL)	8	✓	618.00		2,472.00	2,472.00				
Intravenous (IV) infusion for therapy, prophylaxis or diagnosis (CMS or placebo)	4	✓	887.00		1,774.00	1,774.00				
Acute Physiology and Chronic Health Evaluation II (APACHE II)	1	✓	555.00	555.00						
Initial physical examination only	1	✓	1,182.00		1,182.00					
Directed Physical examination: Includes a problem focused interval medical history, vital signs, height and weight	5	✓	753.00			753.00	753.00	753.00	753.00	753.00
AE, local infusion monitoring, review infection	6	✓	262.00		262.00	262.00	262.00	262.00	262.00	262.00
Phlebotomy specimen collection with lab handling and shipping; Complex - may include a pregnancy blood draw	6	✓	910.00		910.00	910.00	910.00	910.00	910.00	910.00
Collection of Urine	2	✓	84.00		84.00		84.00			
PK samples; collection, lab handling & shipping	3	✓	202.00	202.00	404.00					
Clinical Response Assessment	4	✓	146.00			146.00	146.00	146.00	146.00	
Procedure Sub Total				Mex$ 3,858.00	Mex$ 7,372.00	Mex$ 6,601.00	Mex$ 2,439.00	Mex$ 2,355.00	Mex$ 2,355.00	Mex$ 2,209.00

Non Procedure	**Qty**	**OH**	**Budget**	**V1Scr**	**V2D1**	**V3D3**	**V4EOT**	**V5EFU**	**V6D28**	**V7SFU**
Physician, Complex (e.g. Initial visit, final visit) - Per Visit	7	✓	1,598.00	1,598.00	1,598.00	1,598.00	1,598.00	1,598.00	1,598.00	1,598.00
Study Coordinator, Complex (e.g. Initial visit, final visit) - Per Visit	7	✓	968.00	968.00	968.00	968.00	968.00	968.00	968.00	968.00
Electronic Data Capture (EDC) - Per Hour	14	✓	329.00	658.00	658.00	658.00	658.00	658.00	658.00	658.00
Pharmacist Complex	5	✓	778.00		1,945.00	1,945.00				
Interactive Voice Response System (IVRS) - Per Hour	1	✓	300.00		150.00	150.00				
Nurse - Per Hour	5	✓	432.00		1,080.00	1,080.00				
Patient Reimbursement, Expenses, Patient Travel - Per Visit	1	✓	302.00							302.00
Non Procedure Sub Total				Mex$ 3,224.00	Mex$ 6,399.00	Mex$ 6,399.00	Mex$ 3,224.00	Mex$ 3,224.00	Mex$ 3,224.00	Mex$ 3,526.00
Sub Total				Mex$ 7,082.00	Mex$ 13,771.00	Mex$ 13,000.00	Mex$ 5,663.00	Mex$ 5,579.00	Mex$ 5,579.00	Mex$ 5,735.00
Overhead 20% (selected costs)				Mex$ 1,416.40	Mex$ 2,754.20	Mex$ 2,600.00	Mex$ 1,132.60	Mex$ 1,115.80	Mex$ 1,115.80	Mex$ 1,147.00
Total Cost Per Visit(Mex$)				Mex$ 8,498.40	Mex$ 16,525.20	Mex$ 15,600.00	Mex$ 6,795.60	Mex$ 6,694.80	Mex$ 6,694.80	Mex$ 6,882.00

Total / Patient
Mex$ 87,680.80
3
Mex$ 263,042.40

Total Estimated number of Randomized Patients

Total Per Patient Visit Cost based on Estimated Patients

Georgina Castillo

27 JUN 2018

Alexandra Barajas Olivas, MD
Exec.Clinical Research Director
GCTO-Mexico

28 Jun 2018

- The Per Patient Visit Cost includes study-related costs for each patient as required in the Protocol, including procedure costs, site personnel fees (including electronic data entry), administrative fees during performance of the study (copying, shipping preparation, labels, etc.), lab draws, patient stipends (if elected), and indirect costs and overhead. All of the study related costs are included in the costs outlined above. The Per Patient Visit Costs section of the budget represents procedures required to be performed on every patient. The Site Costs are outlined below and include: Additional procedures which are required by the Protocol for specific events and approved by the Sponsor, procedures that are required by the Protocol for a sub-set of patients, and costs which may be incurred by the Site in support of initiating and supporting the study at the Site until completion of all patients and documentation.

- Supplies sourced from Sponsor (or at the Sponsor's expense) that are licensed or have a value greater than USD $100 per Sponsor calculations at study close-out will be either returned to Sponsor or purchased at current market value, or disposition as instructed by Sponsor.

- For randomized patients who do not complete the study, the Site will be paid according to the per visit schedule noted above for those completed visits documented by electronic data capture or other approved data input.

SITE COSTS *	TOTAL NOT TO EXCEED:	Mex$ 2,701,737.30

*** Site Costs will be paid upon receipt of an invoice with documentation from the third party, when applicable, or upon receipt of other acceptable documentation.**

	Quantity	Per Occurrence	NOT TO EXCEED
Study Start-Up Fee/Site Set-Up Fee	1	18,042	Mex$ 18,042.00
Sponsor agrees to reimburse the site a Study Start-up Fee upon execution of the contract agreement.			
Chart Review / Data Mining - Per Hour*	570	429	Mex$ 244,530.00
Screen Failures:	2	6,374	Mex$ 12,747.60
The Sponsor agrees to reimburse the site for screen failures at a rate of 1:2 in accordance with the number of randomized patients. For example, if the Screen Failure Ratio is 1:4, the site will be paid 1 screen failure for every 4 randomized patients. The site may be paid 2 screen failures when 8 patients are randomized. For each screen failure, your site will be paid $6,373.80 at V1; A screen failure is a patient who has entered the study with a signed consent form and was not randomized into the active treatment period due to failure to meet the inclusion/exclusion criteria as specified in the protocol. If the site has been given written permission by a member of the Sponsors Clinical Team to enroll more patients, screen failures will be paid accordingly			
Pharmacy: Set-Up Fee (montly 1,500 m.n. January 2016 to May 2017*	1	33,000	Mex$ 33,000.00
Sponsor agrees to reimburse the site an Initial Pharmacy Fee, upon receipt of an invoice.			
Contingency Allotment, Patient*	1	20,000	Mex$ 20,000.00
Sponsor agrees to pay for unexpected costs for the patient upon prior approval by Sponsor and upon receipt of an invoice or acceptable documentation			

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Sponsor agrees to pay for unexpected costs for the patient upon prior approval by Sponsor and upon receipt of an invoice or acceptable documentation

Serious adverse events (SAE) per report*	6	681	Mex$ 4,086.00
Sponsor agrees to reimburse the site for providing documentation and reports related to Serious Adverse Events for patients at your site upon receipt of invoice. Costs will be reviewed and approved through Sponsor.			
Unscheduled Visits*	6	2,930	Mex$ 17,580.00
Sponsor agrees to reimburse the site for each unscheduled visit upon receipt of an invoice and appropriate documentation. Costs will be reviewed and approved through Sponsor.			
Visits (Day 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20)*	78	14,291	Mex$ 1,114,729.20
Sponsor agrees to reimburse the site for each unscheduled visit upon receipt of an invoice and back up documentation. Costs will be reviewed and approved through Sponsor.			
Visits (Day 6, 9, 12, 15, 18)*	30	15,383	Mex$ 461,502.00
Sponsor agrees to reimburse the site for each unscheduled visit upon receipt of an invoice and back up documentation. Costs will be reviewed and approved through Sponsor.			
Chest Xray*	6	854	Mex$ 5,124.00
Interpretation and Report; Chest Xray*	6	308	Mex$ 1,848.00
Oxygen saturation via pulse oximetry*	24	380	Mex$ 9,120.00
PaO2, FiO2 and O2 saturation are HABP/VABP only*	24	824	Mex$ 19,776.00
Urine pregnancy test; by visual color comparison methods*	3	155	Mex$ 465.00
Blood draw, phlebotomy, pregnancy test*	3	168	Mex$ 504.00
IMS code: Re-consent, Informed consent performed again with the same patient (3 per patient)*	9	710	Mex$ 6,390.00
Collection of HABP/VABP, cIAI Specimen for Culture and Susceptibility, as clinically indicated*	12	363	Mex$ 4,356.00

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Culture, bacterial; HABP/VABP, cIAI with isolation and presumptive identification of isolates; as clinically indicated*	12	431	Mex$ 5,172.00
Collection of cUTI samples*	24	431	Mex$ 10,344.00
cUTI Culture, bacterial;with isolation and presumptive identification of isolates*	24	299	Mex$ 7,176.00
Susceptibility/sensitivity studies, antibiotic; microdilution or agar dilution, minimum lethal concentration (MLC), each plate - testing on study samples*	50	287	Mex$ 14,350.00
Susceptibility/sensitivity studies, antibiotic; testing on pre-screening samples*	1500	286	Mex$ 429,000.00
Archived Tumor Specimen Retrieval*	3	2,500	Mex$ 7,500.00
Site Validation*	1	7,448	Mex$ 7,447.50
Office Supplies/Admin Supplies -January 2016 to may 2017*	22	1,500	Mex$ 33,000.00
Daily Facility Charge Complex - Per day*	63	3,396	Mex$ 213,948.00
Total Estimated Budget:			Mex$ 2,904,809.70

Sponsor agrees to reimburse the site validation fee upon receipt of the site validation form. The amount listed is the maximum amount. Actual reimbursement will be calculated upon receipt of the site validation form.

PAYMENT SCHEDULE: Per patient visit costs shall be due and payable as follows:

Payments will be made in monthly installments based on the number of completed visits per randomized patient. Patient visit data is obtained in-house according to information provided by the Electronic Data Capture System (EDC). The final payment will be withheld from the monthly installments until study completion.

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Georgina Castillo

27 JUN 2018

Study Start-Up Fee / Site Set-Up Fee (listed above in the Site Costs).	Mex$ 18,042.00	Payment will be made upon agreement execution.
Final Payment: a withheld amount of the Total Per Patient Visit Costs.	Mex$ 20,307.24	Final payment will be sent to Site upon receipt by Sponsor of all completed case report forms and transferred data, and study database lock.

Remittance for the applicable amount is generally issued by Sponsor within 60 days.

Invoice Submissions:

Please direct all invoices and invoice inquiries to the Sponsor Payment Coordinator assigned to this study. On all submissions and inquiries, please include Study #, Site # and Principal Investigator Name in the subject line of your email and on the invoice.

Institution shall submit invoices to Sponsor within 90 days of work performed. Invoices submitted beyond 90 days may be subject to additional verification by Sponsor which may delay payment.

The final invoice from Institution must be submitted to Sponsor within 90 days after the study close-out visit.

Sponsor Payment Coordinator

Name:	**Beatriz Rodriguez Esquivel**
Phone #	**54819600 ext. 19550**
Fax #:	**54841622**
e-mail:	beatriz_rodriguez@merck.com
Address	**Av. San Jeronimo No. 369, Col. La Otra Banda, C.P. 01090 México, D.F.**

Payee Details

Payee Name :	Instituto Nacional de Ciencias Medicas y Nutrición "Salvador Zubiran"
Payee Address :	Vasco de Quiroga No. 15
	Sección XVI
	C.P. 14000
	Professional License # (US only):
	State of License (US only):
	Mexico
Attention	Dr. Alfredo Ponce de León

GCTO-Mexico/COM
Georgina Castillo

27 JUN 2018

Alexandra Barajas Olivas, MD
Exec.Clinical Research Director
GCTO-Mexico

- The Per Patient Visit Cost includes study-related costs for each patient as required in the Protocol, including procedure costs, site personnel fees (including electronic data entry), administrative fees during performance of the study (copying, shipping preparation, labels, etc.), lab draws, patient stipends (if elected), and indirect costs and overhead. All of the study related costs are included in the costs outlined above. The Per Patient Visit Costs section of the budget represents procedures required to be performed on every patient. The Site Costs are outlined below and include: Additional procedures which are required by the Protocol for specific events and approved by the Sponsor, procedures that are required by the Protocol for a sub-set of patients, and costs which may be incurred by the Site in support of initiating and supporting the study at the Site until completion of all patients and documentation.

- Patient Reimbursement for travel is included in the cost of each clinic visit in the amount of $_302.00 Visit FU

- Patient Reimbursement, Stipend is included is the cost of specified visits in the amount of $_____: (NOTE: list visits here)

- A Central Laboratory will be used for this study. No processing fees will be incurred by the Site other than lab collection fees already contained in the budget.

- Supplies sourced from Sponsor that are licensed or have a value greater than USD $100 per Sponsor calculations at study close-out will be either returned to Sponsor or purchased at current market value, or disposition as instructed by Sponsor.

- For randomized patients who do not complete the study, the Site will be paid according to the per visit schedule noted above for those completed visits documented by electronic data capture or other approved data input.

SITE COSTS *	TOTAL NOT TO EXCEED:		Mex$ 2,493,687.30
* Site Costs will be paid upon receipt of an invoice with documentation from the third party, when applicable, or upon receipt of other acceptable documentation.			
	Quantity	Per Occurrence	NOT TO EXCEED
Study Start-Up Fee/Site Set-Up Fee Sponsor agrees to reimburse the site a Study Start-up Fee upon execution of the contract agreement.	1	18,042.00	Mex$ 18,042.00 ✓
Chart Review / Data Mining - Per Hour*	120 (530)	429.00	Mex$ 51,480.00
Screen Failures The Sponsor agrees to reimburse the site for screen failures at a rate of __1:2_____ in accordance with the number of randomized patients. For example, if the Screen Failure Ratio is 1:4, the site will be paid 1 screen failure for every 4 randomized patients. The site may be paid 2 screen failures when 8 patients are randomized. For each screen failure, your site will be paid 6,373.80 at V1; A screen failure is a patient who has entered the study with a signed consent form and was not randomized into the active treatment period due to failure to meet the inclusion/exclusion criteria as specified in the protocol. If the site has been given written permission by a member of the Sponsors Clinical Team to enroll more patients, screen failures will be paid accordingly. Refer to Budget Notes for specific details.	2 (6,374)	6,373.80	Mex$ 12,747.60 $12,747.60
Contingency Allotment, Patient* Sponsor agrees to pay for unexpected costs for the patient upon prior approval by Sponsor and upon receipt of an invoice or acceptable documentation	1	20,000.00	Mex$ 20,000.00 ✓
Site Validation* Sponsor agrees to reimburse the site validation fee upon receipt of the site validation form. The amount listed is the maximum amount. Actual reimbursement will be calculated upon receipt of the site validation form.	1	7,447.50	Mex$ 7,447.50
Serious adverse events (SAE) per report* Sponsor agrees to reimburse the site for providing documentation and reports related to Serious Adverse Events for patients at your site upon receipt of invoice. Costs will be reviewed and approved through Sponsor.	6	681.00	Mex$ 4,086.00 ✓
Unscheduled Visits* Sponsor agrees to reimburse the site for each unscheduled visit upon receipt of an invoice and appropriate documentation. Costs will be reviewed and approved through Sponsor.	6	2,930.00	Mex$ 17,580.00 ✓
Visits (Day 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 18, 20)* Sponsor agrees to reimburse the site for each unscheduled visit upon receipt of an invoice and back up documentation. Costs will be reviewed and approved through Sponsor.	78	14,291.40	Mex$ 1,114,729.20 ✓
Visits (Day 6, 9, 12, 15, 18)*	30	15,383.40	Mex$ 461,502.00 ✓

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Sponsor agrees to reimburse the site for each unscheduled visit upon receipt of an invoice and back up documentation Costs will be reviewed and approved through Sponsor.

Chest Xray*	6	854.00	Mex$ 5,124.00	✓
Interpretation and Report: Chest Xray*	6	308.00	Mex$ 1,848.00	✓
Oxygen saturation via pulse oximetry*	24	380.00	Mex$ 9,120.00	✓
PaO2, FiO2 and O2 saturation are HABP/VABP only*	24	824.00	Mex$ 19,776.00	✓
Urine pregnancy test; by visual color comparison methods*	3	155.00	Mex$ 465.00	✓
Blood draw, phlebotomy, pregnancy test*	3	168.00	Mex$ 504.00	✓
Collection of HABP/VABP, cIAI Specimen for Culture and Susceptibility, as clinically indicated*	12	363.00	Mex$ 4,356.00	✓
Culture, bacterial; HABP/VABP, cIAI with isolation and presumptive identification of isolates; as clinically indicated*	12	431.00	Mex$ 5,172.00	✓
Collection of cUTI samples*	24	431.00	Mex$ 10,344.00	✓
cUTI Culture, bacterial;with isolation and presumptive identification of isolates*	24	299.00	Mex$ 7,176.00	✓
Susceptibility/sensitivity studies, antibiotic; microdilution or agar dilution, minimum lethal concentration (MLC), each plate - testing on study samples* pay according 1 panel with 4 isolates per panel, amount = 1 panel	50	287.00	Mex$ 14,350.00	✓
IMS code: Re-consent, informed consent performed again with the same patient (3 per patient)*	9	710.00	Mex$ 6,390.00	✓
Susceptibility/sensitivity studies, antibiotic; testing on pre-screening samples* pay acording 1 panel with 4 isolates per panel, amount = 1 panel	1500 1100	286.00	Mex$ 314,600.00	$ 424,000.00
Susceptibility/sensitivity studies, antibiotic; testing on pre-screening samples* pay acording 1 panel with 4 isolates per panel, amount = 40 monthly= $ 11,440.00 (January to May 2017)	400	285.00	Mex$ 114,400.00	
Archived Tumor Specimen Retrieval*	3	2,500.00	Mex$ 7,500.00	✓
Office Supplies since January 2016 to May 2017	22 17	1,500.00	Mex$ 25,500.00	$ 33,000.00
Pharmacy Fee	1 17	1,500.00	Mex$ 25,500.00	$ 33,000.00
There is a monthly fee of $1,500.00 m.n. plus every month			33,000	
Daily Facility Charge Complex, per day	63	3,396.00	Mex$ 213,948.00	

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Total Estimated Budget: Mex$ 2,696,759.70

Budget Notes:

Budget Notes: Notes: This budget is built with a max of 6 ptsScreen Fail cost = 75% of V1. Screen Fail ratio: 1:2. 1 SF to be paid per every 2 randomized patients.Subject identification card built into Study Coordinator time.Vital signs, height and weight built into physical exam daysBlood for FBR is built into normal safety blood draw.Patient Reimbursement for travel assumes 2 per pt Infection Site and Blood Specimen for Culture and Susceptibility and Chest X-Rays pro-rated based on infection typeBronchoscopy and Laparoscopy may be included in pass-through costs if not part of Standard of Care proceduresInfection Site and Blood Specimen for Culture and Susceptibility HABP/VABP, cIAI assumes 2 per ptInfection Site and Blood Specimen for Culture and Susceptibility cUTI assumes 4 per pt Chest X-ray and Interpretation assumes 2 per ptGases, blood, arterial blood gases (any combination of pH, pCO2, pO2, CO2, HCO3) assumes 5 per ptThe PaO2, FIO2 and O2 saturation are HABP/VABP only; assumes 5 per ptArchived Specimen retrieval - sites will not be collecting an infection site specimen but will be using a prior specimen to provide to our central lab. For this, the site would need to have the lab locate the isolate(s), prepare a pure culture and ship to the central labSusceptibility testing on pre-screened samples estimate based on the following - Per site: ~50/day x 20 days/mo x 15 mo (divided by 4; 4 isolates per panel)Merck will reimburse site for reasonable meal expenses not to exceed $20/per person (inclusive of tax and tip) that occur during the conduct of Study Start Up/Study Initiation Investigator Meetings. The number of attendees must be approved by your Clinical Research Associate. Payment will be made upon receipt of actual invoice. Pharmacy fees are included in the ppcVisit days 2, 4, 5/7 to 21 located in site costs and reimburseable through invoice Should a subject come in early for a discon visit, the site will complete all procedures for the next regularly scheduled visit.

PAYMENT SCHEDULE: Per patient visit costs shall be due and payable as follows:

Payments will be made in monthly installments based on the number of completed visits per randomized patient. Patient visit data is obtained in-house according to information provided by the Electronic Data Capture System (EDC). The final payment will be withheld from the monthly installments until study completion.

Study Start-Up Fee / Site Set-Up Fee (listed above in the Site Costs).	Mex$ 18,042.00	Payment will be made upon agreement execution. ✓
Final Payment: a withheld amount of the Total Per Patient Visit Costs.	Mex$ 20,307.24	Final payment will be sent to Site upon receipt by Sponsor of all completed case report forms and transferred data, and study database lock. ✓

Remittance for the applicable amount is generally issued by Sponsor within 60 days.

Invoice Submissions:

Please direct all invoices to the Sponsor Payment Coordinator assigned to this study.

Institution shall submit invoices to Sponsor within 90 days of work performed. Invoices submitted beyond 90 days may be subject to additional verification by Sponsor which may delay payment.

Sponsor Payment Coordinator	
Name:	Beatriz Rodriguez Esquivel ✓
Phone #	54819600 ext. 19550 ✓
Fax #:	54841622 ✓
e-mail:	beatriz_rodriguez@merck.com ✓
Address	Av. San Jeronimo No. 369, Col. La Otra Banda, C.P. 01090 México, D.F. ✓

Payee Details

Payee Name :	Instituto Nacional de Ciencias Medicas y Nutrición "Salvador Zubiran" ✓
Payee Address :	Vasco de Quiroga No. 15 ✓
	Sección XVI ✓
	C.P. 14000 ✓
	Professional License # (US only): ✓
	State of License (US only): ✓
	Mexico ✓
Attention	Dr. Alfredo Ponce de León ✓

11/Ene/2017

Yvonne Aboitiz Slim, MD
Global Clinical Trial Operations
Director-México

10 Ene 17

PID:521669

SiteNo:1202

Merck/MSD Study Site Budget
MK-7655A-013-00

PI Name: Alfredo Ponce de Leon Garduno

Institution (Site): Instituto Nacional de Ciencias Medicas y Nutricion "Salvador Zubiran"

The target number of patients for your site is __3___. For the purpose of trial planning and management, this Budget encompasses an enrollment range between _3___ and _3___. However, as you approach your target of _3___, if you wish to continue to enroll, you must be proactive & contact the CRA for approval to continue enrolling up to __3___. If you wish to continue to enroll beyond _3_, a Budget Amendment will be issued to finalize the authorization of any potential increase in subject numbers beyond __3___. The budget will be adjusted if the study design is modified and has a financial impact. Sponsor reserves the right to decrease or increase the number of patients at any time during the enrollment period without renegotiating based on the costs listed in this budget. Such notification shall be in writing from a person authorized by the Sponsor.

Mexico Arms & Cohorts: No Arms

Procedure	Qty	OH	Budget	V1Scr	V2D1	V3D3	V4EOT	V5EFU	V6D28	V7SFU
Informed consent	1	✓	1,005.00	1,005.00						
Genomics consent; DNA consent	1	✓	392.00	392.00						
Inclusion/Exclusion Criteria	1	✓	452.00	452.00						
Initial medical history only	1	✓	968.00	968.00						
Prior and Concomitant medications	7	✓	284.00	284.00	284.00	284.00	284.00	284.00	284.00	284.00
Intravenous (IV) infusion for therapy, prophylaxis or diagnosis (INI or INI/REL)	8	✓	618.00		2,472.00	2,472.00				
Intravenous (IV) infusion for therapy, prophylaxis or diagnosis (CMS or placebo)	4	✓	887.00		1,774.00	1,774.00				
Acute Physiology and Chronic Health Evaluation II (APACHE II)	1	✓	555.00	555.00						
Initial physical examination only	1	✓	1,182.00		1,182.00					
Directed Physical examination: Includes a problem focused interval medical history, vital signs, height and weight. T	5	✓	753.00			753.00	753.00	753.00	753.00	753.00
AE, local infusion monitoring, review infection	6	✓	262.00		262.00	262.00	262.00	262.00	262.00	262.00
Phlebotomy specimen collection with lab handling and shipping; Complex - may include a pregnancy blood draw if r	6	✓	910.00		910.00	910.00	910.00	910.00	910.00	910.00
Collection of Urine	2	✓	84.00		84.00		84.00			
PK samples; collection, lab handling & shipping	3	✓	202.00	202.00	404.00					
Clinical Response Assessment	4	✓	146.00			146.00	146.00	146.00	146.00	
Procedure Sub Total				Mex$ 3,858.00	Mex$ 7,372.00	Mex$ 6,601.00	Mex$ 2,439.00	Mex$ 2,355.00	Mex$ 2,355.00	Mex$ 2,209.00

Non Procedure	Qty	OH	Budget	V1Scr	V2D1	V3D3	V4EOT	V5EFU	V6D28	V7SFU
Physician, Complex (e.g. initial visit, final visit) - Per Visit	7	✓	1,598.00	1,598.00	1,598.00	1,598.00	1,598.00	1,598.00	1,598.00	1,598.00
Study Coordinator, Complex (e.g. initial visit, final visit) - Per Visit	7	✓	968.00	968.00	968.00	968.00	968.00	968.00	968.00	968.00
Electronic Data Capture (EDC) - Per Hour	14	✓	329.00	658.00	658.00	658.00	658.00	658.00	658.00	658.00
Pharmacist Complex	5	✓	778.00		1,945.00	1,945.00	1,945.00			
Interactive Voice Response System (IVRS) - Per Hour	1	✓	300.00		150.00	150.00	150.00			
Nurse - Per Hour	5	✓	432.00		1,080.00	1,080.00	1,080.00			
Patient Reimbursement, Expenses, Patient Travel - Per Visit	1	✓	302.00							302.00
Non Procedure Sub Total				Mex$ 3,224.00	Mex$ 6,399.00	Mex$ 6,399.00	Mex$ 3,224.00	Mex$ 3,224.00	Mex$ 3,224.00	Mex$ 3,526.00
Sub Total				Mex$ 7,082.00	Mex$ 13,771.00	Mex$ 13,000.00	Mex$ 5,663.00	Mex$ 5,579.00	Mex$ 5,579.00	Mex$ 5,735.00
Overhead 20% (selected costs)				Mex$ 1,416.40	Mex$ 2,754.20	Mex$ 2,600.00	Mex$ 1,132.60	Mex$ 1,115.80	Mex$ 1,115.80	Mex$ 1,147.00
Total Cost Per Visit(Mex$)				Mex$ 8,498.40	Mex$ 16,525.20	Mex$ 15,600.00	Mex$ 6,795.60	Mex$ 6,694.80	Mex$ 6,694.80	Mex$ 6,882.00

Total / Patient
Mex$ 67,690.80
3
Mex$ 203,072.40

Total Estimated number of Randomized Patients

Total Per Patient Visit Cost based on Estimated Patients

11/ENE/2017

Yvonne Aboitiz Slim, MD
Global Clinical Trial Operations
Director-México

10-Ene-17