609

SHIGATEC Trial: A Phase II Study Assessing Monoclonal Antibodies Against Shiga Toxin 1 and 2 in Shiga Toxin-producing *E. coli*-infected Children

Eduardo L. López[1], Thomas G. Cleary [2], Didier Reymond[3] and the Shigamabs Clinical Trial Network*

[1] Ricardo Gutierrez Children's Hospital, Buenos Aires, Argentina; [2] University of Texas Medical School, Houston, TX, USA ; [3]Thallion Pharmaceuticals Inc., Montreal, QC, Canada

49th IDSA Annual Meeting

Boston, USA

October 20-23, 2011

Background

Shiga toxin-producing *E. coli* (STEC) are the main pathogens responsible for causing hemolytic uremic syndrome (HUS). There are no approved therapies to prevent the development of HUS or its associated complications, only supportive care.

Shigamabs[#], is comprised of two chimeric monoclonal antibodies against Shiga toxin 1 and Shiga toxin 2, respectively (Figure 1).

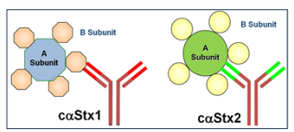

Figure 1: Shigamabs binding to toxins

Shigamabs has been shown active in preclinical animal models and well tolerated in four Phase I studies in healthy adults (Table 1).

Clinical Phase (sponsor)	Antibody	Number of Subjects	SAE
Phase I (DMID)	cαStx2	17	None
Phase I (DMID)	cαStx1	7	None
Phase I (Thallion)	cαStx1 + cαStx2 individually	16	None
Phase I (Thallion)	cαStx1 + cαStx2 concomitantly	10	none

Table 1: Four Phase I Studies

Methods

A randomized, double blind, placebo-controlled Phase II study (Figure 2) was initiated in November 2010. The study consists of two arms: A) standard of care + Shigamabs, or B) standard of care + placebo, randomized 2:1.

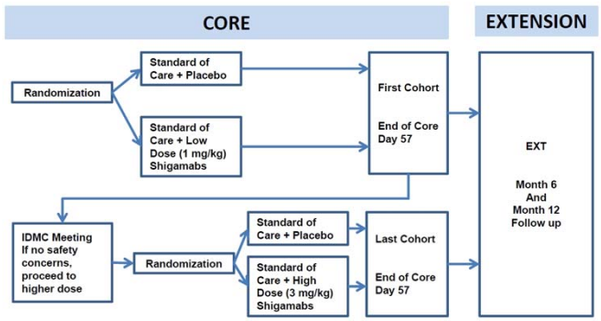

Figure 2: SHIGATEC Study Design

Two doses of Shigamabs (1 and 3 mg/kg) are being tested in two sequential cohorts of 21 children, aged 6 months to 18 years, presenting with bloody diarrhea and testing positive for Shiga toxins using two commercial diagnostic kits (Meridian Premier EHEC Assay and/or the ImmunoCard STAT! *E. coli* O157 Plus test).

Shigamabs (or placebo) is infused over one hour as a single infusion. Patients are followed during a two-month core phase, then an extension phase for a total of one year.

Primary endpoints are safety and tolerability; secondary endpoints are efficacy and pharmacokinetics. An Independent Data Monitoring Committee (IDMC) oversees the safety aspects of the study.

The study is being conducted entirely in South America, with the largest number of clinical centers in Argentina, as this country has the highest incidence of STEC infections and HUS in the world. The Shigamabs Clinical Trial Network* comprises a total of 17 centers distributed in Argentina, Chile and Peru.

Results

Data are reported for the low dose cohort, recruited between November 2010 and February 2011. The study is still ongoing (high dose cohort) and the data remain blinded.

A total of 305 patients were screened. Twenty-two patients were enrolled in the low dose cohort with a mean age of 3½ years old (10 months – 11 years) and 68% of children less than 4 years old (Table 2).

One patient progressed to HUS, the only SAE reported in this cohort and deemed not related to study-drug. Overall 13 patients had a total of 34 adverse events (AEs), with 9 patients having no AEs. All reported AEs were mild and none were deemed drug related (Table 3). Vital signs during and up to 4 hours after infusion were unremarkable. Hematology and biochemistry parameters did not show any significant anomalies.

Central microbiology laboratory results confirmed the presence of Shiga toxin-producing *E. coli* in samples from 14 patients, six of them being O157 and eight non O157 strains, with a predominance of Shiga toxin 2 producers.

Preliminary pharmacokinetics show a typical profile for a single IV antibody infusion with mean peak levels at ~ 1 hour (Figure 3). Cmax was similar between the two antibodies with cαStx1 levels declining more quickly, a finding previously observed in the Phase I studies in healthy adults. These results will be compared to the higher dose (3mg/kg) upon completion of the ongoing cohort.

Category	Variable	Results
Age	mean	3 years and 4 months
	median	20 months
	Min-max	7 months – 11 years
Gender	male	12
	female	10
Weight	mean	14
	median	11
	Min-max	8 - 35
Country	Argentina	16
	Chile	6
	Peru	0

Table 2: Patient Demographics

Adverse Events	N	%
Pharyngitis	5	22.7
Diarrhea	4	18.2
Vomiting	3	13.6
Pyrexia	2	9.1

Table 3: Adverse Events (> 5%)

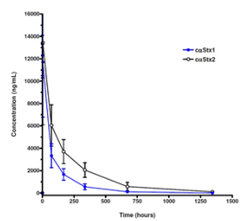

Figure 3: cαStx1 and cαStx2 PK

A preliminary assessment of the development of Human Anti-Chimeric Antibody (HACA) responses over time was conducted (Table 4). Overall, a similar number of patients tested positive for HACA against each of cαStx1 and cαStx2, however, no response progression over time can be concluded based on these early data. At most time points where responses were observed and measurable, the HACA titers were low, the exception being the 6 month time point with cαStx2 where some of the titers were relatively higher. The incidence and progression of HACA per individual patient and the clinical relevance of these findings will be evaluated more fully once the study is completed and the data are unblinded.

Timepoint	Number of Patients Tested	cαStx1		cαStx2	
		HACA Positive	Titer Range**	HACA Positive	Titer Range**
Day 1 (Pre-Dose)	22	1	NA	0	
Day 15	21	4	7 - 12	3	6 - 14
Day 29	17	1	4	0	
Day 57	20	1	11	1	NA
EXT Month 6	17	0		4	115 - >512

EXT: Extension Study; NA: Not Available ** Dilution Factor

Table 4: Preliminary HACA Results

***Shigamabs Clinical Trial Network**

Argentina:

Dr. S. González Ayala, Hospital Sor María Ludovica, La Plata; Dr. G. Ezcurra, Hospital San Roque, Paraná; Dr. A. Falaschi, Hospital Pediátrico "Dr. Humberto Notti", Mendoza; Dr. J. Ferraris, Hospital Italiano de Buenos Aires, Buenos Aires; Dr. R. Galindez, Hospital Pediatrico del Niño Jesus, Córdoba; Dr. E. Inchaurregui, Hospital de Niños de La Santísima Trinidad, Córdoba; Dr. E. López, Hospital de Niños Ricardo Gutiérrez, Buenos Aires; Dr. M. Mastruzzo, Hospital Boccalandro, Buenos Aires; Dr. S. Miceli, Sanatorio San Lucas, Tucumán; Dr. E. Teplitz, Hospital Italiano Regional del Sur, Bahia Blanca

Chile:

Dr. M. Acuña, Hospital Roberto del Rio, Santiago; Dr. L. Twele, Hospital Regional Guillermo Grant Benavente, Concepción; Dr. R. Vergara, Hospital Carlos Van Buren, Valparaiso; Dr. R. Villena, Hospital de Niños "Dr. E. González Cortés", Santiago

Peru:

Dr. L. Huicho, Instituto de Salud del Niño, Lima; Dr. I. Reyes, Hospital de Emergencias Pediatricas, Lima; Dr. C. Ugarte Taboada, Hospital Nacional Cayetano Heredia, Lima

Shigamabs Steering Committee Members:

Dr. M. Bitzan, Canada, Dr. T. Cleary, USA (Chairman); Dr. E. López, Argentina; Dr. T. Ochoa, Peru; Dr. V. Prado, Chile; Dr. M. Taylor, UK

Conclusion

The SHIGATEC trial is the first clinical study testing Shigamabs for its safety and potential benefits in the prevention of disease and complications caused by Shiga toxin-producing bacteria in infected children. In the first 22 patients enrolled, Shigamabs was well tolerated with no drug related AEs. The SHIGATEC IDMC reviewed the core data from the low dose cohort and concluded the lack of any observed safety issue, therefore recommending to proceed with the high dose cohort.

[#] Shigamabs is being developed through a development and commercialization partnership established between Thallion and LFB Biotechnologies SAS (Les Ulis, France)