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In reply please  
refer to: P5-447-3/OG/PD

Your reference:

Dr Padma GM Rao  
Director - BA/BE  
Manipal AcuNova KH  
Clinical Research Centre  
4th Floor, Shirdi Sai Baba Cancer Hospital  
576 104 Manipal  
Inde

8 May 2008

Dear Dr Rao,

**WHO Prequalification of Medicines Programme  
Inspection of Contract Research Organization (CRO)  
Manipal AcuNova KH Clinical Research Centre, Manipal, India, 22 and 23 January 2008**

Referring to the above-mentioned inspection, please find enclosed the World Health Organization (WHO) Final Conclusion.

We should like to take this opportunity to thank you for your collaboration.

Yours sincerely,

Dr Raul Kiivet  
Manager  
Prequalification Programme  
Quality Assurance and Safety: Medicines

ENCL.

### Inspection Report of a Contract Research Organization Final conclusion

The report is the property of the organization responsible for performing the inspection.

#### Part 1: General information

Name of organization	Manipal AcuNova KH Clinical Research Centre
Physical address	4 <sup>th</sup> floor, Shirdi Sai Baba Cancer Hospital 576 104 Manipal, India
Postal address	Same as above
Telephone number	00 91 820 257 1201 / 2 2553
Fax number	00 91 820 257 1999
Summary of activities	Performance of clinical studies, including bioequivalence trials (clinical and bio-analytical parts)
<b>WHO reference number</b> Study	<b>HA 396</b> # 021 - 06 A randomized, open label, balanced, two treatment, two periods, two sequences, single dose, crossover bioequivalence study in 26 healthy human adult male subjects, under fasting condition with 21 days of washout period between doses.
Start and stop dates for each phase of the clinical study	Period 1 : 14 October 2006 to 18 October 2006 Period 2 : 04 November 2006 to 08 November 2006
Investigational Products	Nevirapine 200 mg Tablet Manufactured by : Matrix Laboratories Limited, F-4 & F-12, Malegaon, MIDC, Sinnar- 422 113, Nashik District, Maharashtra State, India. Batch number : A536003 Manufacturing date : July 2006
Reference Products	Viramune <sup>®</sup> (Nevirapine 200mg) Tablet Boehringer Ingelheim Pharmaceuticals Inc, USA Batch number : 558027A
<b>WHO reference number</b> Study	<b>HA 410</b> # 033-06 A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Tenofovir disoproxil fumarate 300 mg tablets (Matrix Laboratories Ltd, India) with Viread <sup>®</sup> (Tenofovir disoproxil fumarate) 300 mg tablets, manufactured for Gilead Sciences, Inc. USA, in 32 healthy human adult male subjects under fed conditions.



Start and stop dates for each phase of the clinical study	Period 1 : 20 January 2007 to 24 January 2007 Period 2 : 30 January 2007 to 3 February 2007
Investigational Products	Tenofovir disoproxil fumarate 300 mg Tablet Manufactured by: Matrix Laboratories Limited, F-4 & F-12, Malegaon, MIDC, Sinnar- 422 113, Nashik District, Maharashtra State, India. Batch number : TDF A536001 Manufacturing date: Nov. 2006.
Reference Products	Viread® (Tenofovir disoproxil fumarate 300 mg) Tablet Manufactured by Gilead Sciences, Foster city, CA 94404. Batch No: FDB023
Sponsor	Matrix Laboratories Limited, India
Contact person	Dr. Padma GM Rao      padma.rao@acunovalife.com
Personnel met	Dr. Padma GM Rao, Director - BA/BE Dr R. Rajesh, Sr. QA Associate Umesh B A, Chief Quality Officer (Bangalore) Dr Srinivas Shenoy B, Clinical Pharmacologist Dr. Ayaaz Hussain Khan, Chief Scientific Officer Arun TS Quality Assurance Associate. <u>From Matrix</u> Ramakrishna Bangaru, Vice President Biopharmaceutics
Names of inspectors:	Dr. Philippe Panouillot for WHO Dr. Olivier Gross ,WHO Dr. Daniela Vieira dos Reis Coordination of Inspection in Pharmaceutical Equivalence and Bioequivalence Centres - CIBIO General Office of Medicines - GG MED Brazilian Health Surveillance Agency - ANVISA Dr. Kelen Soares. Coordination of Inspection in Pharmaceutical Equivalence and Bioequivalence Centres - CIBIO General Office of Medicines - GG MED Brazilian Health Surveillance Agency - ANVISA
Date of inspection:	22 and 23 January 2008
Project (if any):	Prequalification Programme : Priority Essential Medicines

**2. Comments on the satisfactoriness of the corrective actions proposed**

We acknowledge receipt of your responses dated 15th of April 2008 to the World Health Organization (WHO) report.

An assessment of the information provided in relation to each observation has revealed that the corrective actions proposed by the sponsor and the CRO are acceptable.

### 3. Conclusions

#### Initial conclusion (January 2008) .

Based on the people met and the documents reviewed, and considering the findings of the inspection, reflected in the observations listed in the inspection report, the studies inspected :

**For the clinical part were considered to have been conducted at an acceptable level of compliance** with WHO Good Clinical Practices (GCP) and Good Laboratory Practices (GLP), by Manipal AcuNova KMC Clinical Pharmacology Unit located in Manipal, India.

**For the bio-analytical part can not be considered at that stage to have been conducted at an acceptable level of compliance** with WHO Good Clinical Practices (GCP) and Good Laboratory Practices (GLP), by Manipal AcuNova KMC Clinical Pharmacology Unit located in Manipal, India. **In several runs, more than 50% of Quality Controls of the same level of concentration failed although the corresponding batches were accepted (8 runs for HA 410 and 1 run for HA 396). The WHO assessors will evaluate if bioequivalence is still demonstrated after exclusion of the invalid runs or if a reanalysis of those samples is necessary. If WHO assessors give finally their approval, WHO inspectors will have no more objections for these studies.**

The observations (non-compliances with the WHO guidelines) listed below need to be addressed by the company and verified through evaluation of the documentation of the corrective actions (planned and implemented) submitted by the Research Organization.

#### Definitive conclusion (April 2008)

Based on the people met and the documents reviewed, and considering the findings of the inspection , the corrective actions proposed, and the conclusion of the assessors :

*Worku, Wondiyfraw, 07 March 2008 :*

*the justifications presented by the CRO to keep the validity of the BE reports are acceptable. The BE parameters were recalculated by excluding those volunteers whose analytical data were mistakenly accepted. The re-calculated parameters demonstrated the Bioequivalence of the test product. In addition, re-determination of the within study precision and accuracy values also considered the rejected runs and the values are still shown to be within the acceptance limits.*

the studies inspected can be considered to be a proof of bioequivalence between test products HA 396 and HA 410 and the respective relevant comparators.

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WHO  
Dr Olivier Gross  
(on behalf of the inspection team)

08/05/08  
\_\_\_\_\_  
Date