2. CLINICAL STUDY SYNOPSIS

<table>
<tr><td>Name of Company:
Intercell AG</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

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Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
IXIARO®</td></tr>
<tr><td>Name of Active Ingredient:
Japanese Encephalitis Vaccine</td></tr>
<tr><td colspan="3">Title of Study:
An Open-Label, Uncontrolled Phase 4 Study To Assess The Safety and Immunogenicity of The Japanese Encephalitis (JE) Vaccine IXIARO® (IC51) in an Elderly Population</td></tr>
<tr><td colspan="3">Protocol Number: IC51-315</td></tr>
<tr><td colspan="3">Principal Investigators:
Site 01: Dr. Tomas Jelinek
Site 02: Prof. Dr. Gerd-Dieter Burchard
Site 03: Prof. Emil Reisinger
Site 04: Prof. Bernd Jilma
Site 05: Prof. Dr. Herwig Kollaritsch</td></tr>
<tr><td colspan="3">Study Sites:
Five sites (3 in Germany and 2 Austria) were active during this study and have enrolled at least one subject.</td></tr>
<tr><td colspan="3">Publication (reference):</td></tr>
<tr><td colspan="2">Study Dates:
First Subject In: 28 June 2010
First Subject Treated: 05 July 2010
Last Subject Out: 11 October 2011</td><td>Phase of Development:
Phase 4</td></tr>
<tr><td colspan="3">Objectives:
Primary:
▪ To assess the safety profile of the purified inactivated JE vaccine IXIARO® in an elderly (≥ 65 years of age) population
Secondary:
• To assess the immunogenicity of the purified inactivated JE vaccine IXIARO® in an elderly population using SCRs at Day 70. SCR (Seroconversion Rate) is defined as the rate of subjects with a PRNT titer of ≥1:10
• To assess the immunogenicity of the purified inactivated JE vaccine IXIARO® in an elderly population using GMTs for JEV neutralizing antibodies determined by PRNT at Day 70</td></tr>
<tr><td colspan="3">Methodology:
Open-label, uncontrolled, multi-center, phase 4 study.</td></tr>
<tr><td colspan="3">Number of subjects (planned and analyzed)
Planned: 200 subjects enrolled
Actual: 249 screened, 200 enrolled (i.e. first vaccination administered)</td></tr>
</table>

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Diagnosis and Main Criteria for Inclusion:

- Male and female subjects aged ≥ 65 years at the time of first vaccination and good general health status including subjects with pharmacologically controlled conditions like hypocholesterolemia, hypertension, cardiovascular disease or non insulin-dependent diabetes mellitus
- Weight ≥45.5 kg and ≤150 kg at Visit 0 (Screening Visit)
- White blood cells ≥2,500/mm^3 and <11,000/mm^3 at Visit 0
- Absolute neutrophil count within normal limits at Visit 0
- Platelets within normal limits at Visit 0
- Written informed consent obtained from the subject prior to any study-related procedures

Test Product, Dose and Mode of Administration, Batch Number:

IXIARO® with aluminium hydroxide (Alum), 0.5ml (6µg). Intramuscular (i.m.) injection on Days 0 and 28.

IXIARO® Batch No: JEV09K33A

Duration of Treatment:

Subjects received IXIARO® 0.5ml (6 µg) i.m. injection on Day 0 and Day 28.
Study duration per subject: 7-8 months.

Reference Therapy, Dose, and Mode of Administration, Batch Number:

Not applicable

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Criteria for Evaluation:

Primary:

- Rate of subjects with serious adverse events (SAEs) and medically attended adverse events (AEs) during the vaccination period until Day 70 after the first vaccination

Secondary:

- Rate of subjects with SAEs and medically attended AEs during the vaccination period and up to 6 months after the second vaccination
- Rate of subjects with unsolicited AEs up to Day 70 after the first vaccination
- Rate of subjects with unsolicited AEs up to six months after the second vaccination
- Rate of subjects with abnormal safety laboratory parameters(hematology, clinical chemistry, urinalysis) up to Day 70 after the first vaccination
- Rate of subjects with solicited local (injection site pain, itching (pruritus), tenderness, hardening (induration), swelling (edema), redness (erythema)) and solicited systemic (headache, muscle pain, fever, flu-like symptoms, nausea, vomiting, rash excessive fatigue) AEs assessed with a subject diary for 7 consecutive days after each vaccination
- GMTs and SCRs for JEV neutralizing antibodies determined by PRNT at Day 70

Statistical Methods:

Immunogenicity analysis:

The primary immunogenicity analysis investigated the GMT at Day 70 in the intention-to-treat (ITT) population. Only descriptive statistics including two-sided 95% CIs were used to analyze and report the results. Additionally, the GMT at Day 70 within the per-protocol (PP) population was calculated.

Further immunogenicity analysis included a calculation of the SCR and the corresponding two-sided 95% CIs for Day 70 in the ITT and PP populations. Immunogenicity results were also stratified for age (≥65 to 74 years vs. ≥75 years of age) and for recent TBE vaccination (TBE vaccination within the past 5 years vs. no TBE vaccination within the past 5 years). Fisher´s Exact Test or Wilcoxon Test, respectively were used to determine group differences. Furthermore, non-parametric correlation analysis (Spearman) has been performed for age versus GMT and logistic regression analysis for age versus SCR.

Safety analysis:

All subjects who received at least one vaccination were included in the safety analysis. Descriptive statistics were used to analyze the number and percentage of subjects with SAEs and medically-attended AEs, any AE and any AE assessed as being related to the vaccine. All AEs are presented by system organ class and preferred term. Changes in safety laboratory parameters (hematology, clinical chemistry and urinalysis) until Day 70 after the first vaccination and during follow-up until Day 208 were analyzed descriptively. Safety analyses were performed for four separate time periods, including 4 weeks after first vaccination, 4 weeks after second vaccination, up to Day 70 and up to Day 208. Safety analysis was also stratified for the age groups ≥65 to 74 years and ≥75 years of age and differences were compared with Fisher's exact test.

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Summary of Immunogenicity Results:

- Seroconversion (i.e. a JE neutralizing antibody titer of ≥1:10 in a 50% Plaque Reduction Neutralization Test) at Visit 3 (Day 70) was observed in 65.0% of subjects (N=197) compared to 4.0% of subjects at Visit 1 (Day 0, N=200).
- GMT at Visit 3 (Day 70) was 37.4, with a 95% CI 29.2, 47.8 and a range of 5.0 to 10856.0.
- GMT and SCR at Day 70 were comparable between subjects aged 65 to 74 years at enrolment (N=173) and subjects aged ≥75 years at enrolment (N=23), with GMTs of 37.2 and 42.2 and SCRs of 65.3% and 65.2%, respectively (p=n.s.).
- The lack of obvious differences between age groups for SCR and GMT was confirmed by logistic regression analysis on age versus seroconversion at Visit 3 (Day 70) which did not demonstrate a significant influence of age on seroconversion (Likelihood ratio test: p=0.2626). Correlation analysis of age versus GMT at Visit 3 (Day 70) showed a very weak (correlation coefficient of 0.1890) positive correlation of age and GMT at Visit 3 (Day 70) (p=0.0078) which may be a chance observation as not supported by the other findings.
- Statistically significant differences were observed between the TBE groups at Visit 3 (Day 70) with a GMT of 65.0 and a SCR of 89.7% in subjects with recent TBE vaccinations (TBE vaccination within the last 5 years prior to study enrolment, N=29) vs. a GMT of 34.0 and a SCR of 60.7% in subjects with no recent TBE vaccinations (N=168) ($p<0.05$ for comparisons of both SCR and GMT).
- Generally, PP analysis results confirmed ITT results.

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Summary of Safety Results:

- 200 subjects received the first dose of IXIARO® and 193 subjects received the second dose of IXIARO®. Mean age was 69.5 years. The most frequently reported medical condition was Vascular Disorders reported by 82 subjects (41.0%); in this SOC 81 subjects (40.5%) reported hypertension. Consequently, the most frequently reported concomitant medications were antihypertensive, antithrombotic or beta-blocking agents, with agents acting on the renin-angiotensin system as the most common concomitant medication reported in 63 subjects (31.5%).
- The rate of subjects with serious or medically attended AEs up to Day 70 (primary endpoint) was 19.0% (38 subjects, 95% CI: 14.2 to 25.0).
- A total of 6.5% of subjects reported SAEs: a total of 14 SAEs were reported in 13 subjects, none of which were related to IXIARO® vaccination. Five subjects reported SAEs in the period up to Day 70 (2.5%) and 13 subjects reported SAEs in the period up to Month 7 (6.5%).
- A total of 24.0% of subjects (48 subjects) reported medically attended AEs; none of them were related to IXIARO® vaccination. Thirty-eight subjects (19.0%) reported AEs in the period up to Day 70 and 48 subjects (24.0%) reported AEs in the period up to Month 7.
- No significant differences in the frequency of AEs were observed between age groups. AEs were reported in 108 subjects (61.7%) in the 65-74 years age group (N=175) and in 17 subjects (70.8%) in the ≥75 years age group (N=24).
- Solicited and unsolicited AEs were reported in 126 subjects (63.0%) up to Month 7. 94 subjects (47.0%) experienced an AE assessed as related to IXIARO® vaccination. A total of 4 subjects (2.0%) reported severe AEs (solicited and unsolicited) which were assessed as related to IXIARO® vaccination. No related AEs (solicited and unsolicited) were medically attended.
- No subjects were withdrawn from the study due to unsolicited or solicited AEs.
- 2 subjects (1.0%) did not receive the second vaccination due to AEs: two subjects experienced a total of four unsolicited AEs (Subject 15102033 had a medically attended, moderate AE of "diabetes mellitus inadequate control" which was assessed as not related to IXIARO® vaccination as well as a moderate AE of "arthralgia", which was assessed as unlikely related to IXIARO® vaccination. Subject 15103050 had a medically attended mild AE of "urticaria", which was assessed as unlikely related to IXIARO® vaccination and a second AE of mild "urticaria" which was assessed as unlikely related to IXIARO® vaccination.)
- A total of 5 subjects (2.5%) had unsolicited AEs of special interest; in a total of 2 subjects (1.0%) these AEs of special interest were considered related to IXIARO® vaccination by the investigator.

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- A total of 67 subjects (33.5%) reported a solicited local AE during the study. A total of 51 subjects (25.5%) reported grade 1 solicited local AEs, 13 subjects (6.5%) reported grade 2 solicited local AEs and 3 subjects (1.5%) reported grade 3 solicited local AEs. The most frequently reported solicited local AEs were injection site pain (13.0%), tenderness (26.0%) and redness (10.5%).
- A total of 54 subjects (27.0%) reported a solicited systemic AE during the study. A total of 39 subjects (19.5%) reported grade 1 solicited systemic AEs, 14 subjects (7.0%) reported grade 2 solicited systemic AEs and 1 subject (0.5%) reported grade 3 solicited systemic AEs. The most frequently reported solicited systemic AEs were headache (18.0%) and myalgia (9.5%).
- No deaths occurred during the study period.
- Evaluation of laboratory parameters did not indicate any safety issues.

Conclusions:

- IXIARO® is generally well tolerated in elderly, and the safety profile is largely comparable with younger adults.
- The SCR of 65% and GMT of 37 are lower compared to younger adults, but SCR is in the range of seroconversion reported in elderly for other vaccines (e.g. Tick-borne Encephalitis Virus, Hepatitis Virus A and B, Influenza Virus).
- The difference in SCR and GMT from younger to elderly adults is in the range of other vaccines.
- Subject age in the elderly population studied (65 to 83 years) had no obvious effect on GMT and SCR.
- In this trial, previous TBE vaccination during the past 5 years led to a higher SCR and GMT.

Date of Report: FINAL 1.0 – 04 May 2012