Evaluation of Safety and Pharmacokinetic Behavior of Unipeg® in Healthy Human Volunteers

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Abstract: Peginterferon α-2a (20 kDa) derived from Hansenula Polymorpha is a distinct variety of peginterferons (PEG-IFN). A pilot study of this drug was conducted on healthy human subjects to evaluate its safety and pharmacokinetic behavior in local population.

With due approval of the IEC operating under ICH-GCP guidelines; ten healthy male subjects were selected randomly from the Pakistani population after thorough screening and signing of the Informed consent for an open label, single dose study. Each subject received a subcutaneous injection of the drug (180 µg) in abdominal skin and blood samples were collected at 0 and 1, 2, 3, 6, 12, 24, 36, 60, 84, 108, 132 and 156 hours, and analyzed by a validated ELISA method for peginterferon α-2a (20kDa), Unipeg®.

The Mean ± SEM (standard error of mean) PK parameters were found to be: C_{max}: 18.67±2.92 ng/ml (7.05-34.51); $AUC_{0-\infty}$: 1440±113 h.µg/l] (969-2101); Absorption Half-Life: 17.02±2.06 h (10.37-29.26), elimination half life: 41.437±6.21 h (18.51-78.97 h); volume of distribution 8.933±1.72 L (4.81-18.34), clearance: 112.6±8.21 ml/h (71.96–155.96).

The safety of the drug was evaluated by observation of adverse effects and evaluating the change in general health parameters, hematological and biochemical test results during and after the study.

No Sever Adverse Effect was observed however the most common adverse event (AE) was the fever; observed in all volunteers (n=10), headache (6), Fatigue (5), Vomiting (4) and diarrhea, loss of appetite, body ache was observed in 3 volunteers. Three out of ten volunteers demonstrated decrease in WBC and platelets count. Changes observed in hematology returned to normal values within 16 days.

The safety profile of UNIPEG® was found to be very similar to those of reported in literature for unmodified IFNs and other pegylated interferons generally used in therapy. Future clinical trials are recommended to further establish the safety profile and pharmacokinetics.

Keyword: PEG-IFN-α-2a, 20-kDa, Unipeg, Peginterferon alfa-2a, pharmacokinetics, clinical trial, safety.

1. INTRODUCTION

An estimated three percent of the world's population is chronically infected with hepatitis C [1]. A weighted average of hepatitis B antigen prevalence among healthy adults (blood donors and non-donors) was 2.4% (range 1.4-11.0%) and for hepatitis C antibody was 3.0% (range 0.3-31.9%) in Pakistan [2]. According to the Ministry of Health, government of Pakistan the prevalence rate is 3-4% and 5-6% for hepatitis B and C respectively [3]. Incubation period for hepatitis C is 6 to 8 weeks and 6 to 24 weeks for hepatitis B [4].

The standard treatment for hepatitis B and C include interferon alpha [5, 6]. After subcutaneous administration IFN (interferon) is rapidly absorbed (absorption $t_{1/2}$ 2.3 h) and reaches peak plasma levels within one to eight hours. Plasma levels then fall rapidly (elimination half life ($t_{1/2}$) 3-8 h) and not detectable after 24 h.

Patients treated with the standard thrice weekly IFN regimen experience a sub-therapeutic antiviral response for most of the time they are being treated, coupled with adverse effects during times of peak drug exposure [7]. Pegylating standard IFN α-2a (interferon alfa-2a) has optimized the pharmacological activity of the protein such that efficacy is enhanced, adverse effects minimized, and patient compliance and quality of life are improved [7].

The slow clearance of PEG-IFN alpha maintains viral replication inhibitory concentrations longer time, leading to more effectiveness and fewer administrations. On the other hand, the circulating IFN peak levels are much lower; therefore less intense adverse reactions are induced [8,9]. Interferons with polyethylene glycol chain of different molecular weights are available in market; having different

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WHO Trial Registration Data Set: http://apps.who.int/trialsearch/Trial.aspx?Trial ID=IRCT201111027978N1

pharmacokinetic behaviors and almost similar adverse event profiles.

Recently, a new conjugate of IFN α-2a with 20-kDa (Kilodalton) branched PEG is registered and marketed to cope with national needs in Pakistan under the brand name of Unipeg®. The product is produced biosynthetically using recombinant DNA (Deoxyribonucleic acid) technology of a cloned human leukocyte interferon gene inserted into and expressed in Hansenula Polymorpha. In Unipeg® a single linear PEG chain of 20 kDa is attached to interferon α-2a while 40kDa Peginterferon α-2a (Pegasys®), contains a branched PEG moiety of 40kDa [7]. Unipeg has the attachment of a single PEG chain at the N-terminal of the interferon, while in the case of Pegasys a single PEG chain is attached to one of the 9 possible sites of the interferon molecule.

The molecular weight of the PEG moiety, structure (linear or branched), the number and location of PEG moieties attached to the protein, as well as the chemical method of attachment determine the physicochemical and consequently pharmacological properties of the resulting protein conjugate [7, 10].

The purpose of this pilot study is to determine the pharmacokinetic parameters and to assess the safety of the above mentioned 20-kDa linear PEG interferon α-2a (Unipeg®) in healthy human volunteers in Pakistani population.

2. CLINICAL TRIAL

Investigational Drug Product

Each one ml ampule of the Investigational drug; Unipeg® contained 20kDA Peginterferon α-2a 180 µg/ml, besides the active ingredient the product also contained sodium chloride, acetic acid, sodium acetate, benzyl alcohol, tween 80, and water for injection as excipients.

Human Experimental Protocol

Subjects

The study was conducted on ten healthy human volunteers with due approval of Independent Ethics Committee in compliance to the Helsinki Declaration and ICH-GCP guidelines. The demographic data is reported in Table **1**.

Table 1: Demographic and Baseline Characteristics of Subjects

Gender	All Male
Age (years)	25.2±5.33 (20-32)
Height (Cm)	166(160-170)
Weight (kg)	59.60±7.71 (60-74)
BMI (Kg/m^2)	21.65±2.71 (18.0-25.5)
Race	South Asians (Pakistani)
Mean Hb(gm)	14.45
Mean WBC	$8X10^9/L$
Mean Absolute Neutrophil Count	$4500/mm^3$
Mean Platelets Count	$250X10^9/L$

Ten healthy, male volunteers, with an age: years 25.2±5.33 (20-32); weight: Kg 59.60±7.71 (60-74); BMI: Kg/m^2 21.65±2.71 (18.0-25.5) participated in the study after giving their written informed consent for participation. For participation in the study only those individuals were considered healthy who had no history of chronic diseases, did not suffer any acute illness in the previous 30 days, had no untoward symptoms or signs revealed through physical examination and laboratory tests, and were negative to HIV and hepatitis B and C virus. Subjects were not included if they had received treatment with IFN with in last one year or had donated blood in the previous 2 months. Individuals with low blood counts and hematology results outside the normal range were not included. Absolute Neutrophil Count (ANC) less than $1500/mm^3$ and platelet count less then 50,000/ mm^3 were exclusion criteria.

All volunteers completed the study without any severe adverse event.

Study Design

An open label, single dose study was conducted on ten healthy volunteers. 180µg of Peginterferon α-2a (20 kD) (Batch No. DV003H09, Exp: Date August 2011) was injected in abdominal skin of the human volunteers.

During the study, participants remained indoor in the clinical facility for first 24 hours after the injection under strict medical supervision. Blood sampling and adverse reactions monitoring continued ambulatory until 156 hours. Antipyretic medication was given orally after observing the raise in body temperature after

PEG-IFN injection and every 6 hours thereafter, up to 24 hours or more if needed, in order to mitigate the expected IFN-dependent flu-like syndrome.

Safety was monitored by complete physical and medical examination with clinical laboratory testing and scheduled vital signs surveillance. Hemoglobin, ALT (Alanine transaminase), Total WBC (White blood cells), Neutrophile % and absolute neutrophil count was conducted at screening and the values were taken as base line. Afterwards on fifth day of the drug administration and after two weeks at follow up the tests were repeated and the results were compared with the base line values.

Sample Collection

Blood samples for serum PEG-IFN concentration determinations were collected by direct venipuncture from forearm vein directly in sterile plain red top serum Vacutainer; manufactured by BD Franklin Lakes NJ, USA. The samples were collected before and 1, 2, 3, 6, 12, 24, 36, 60, 84, 108, 132and 156 hours after the subcutaneous injection.

Clinical and Laboratory Evaluation

Hematological (hemoglobin, hematocrit, platelet, and total and differential leukocyte counts) and biochemical (transaminases) determinations were taken as safety variables. Vitals were checked at all sampling times as mentioned above from 0 (pre- dose) to 156 hours and when ever felt necessary by the Physicians. Volunteers were regularly checked for adverse effect symptoms and for any unusual feeling during the whole study. ANOVA (Analysis of variance) was performed to determine the significance of variance in lab tests.

Adverse Event monitoring

The study subjects were detailed about all possible AEs and requested to inform immediately the clinical staff on occurrence or feeling of any AEs as soon as possible, no matter it was very tolerable. The Clinical Investigator monitored closely the subjects for AE and took all necessary actions in the best interest of subjects. None of the subjects was excluded or wished to be dropped out from the study because of AEs.

3 ANALYTICAL METHODS

Bioanalytical Methods

Samples collected and stored according to the procedure provided by Clinical Trial Laboratory Sciences (CTLS), UK. Tubes were kept chilled at 2-8 ^{o}C (centigrade) before the initiation of the blood collection. Samples were left to clot in fridge at 2-8 ^{o}C. Thirty minutes after on clotting, the samples were centrifuged at 1000g for10-15 minutes in a refrigerated centrifuge. Serum was separated immediately after centrifugation in pre-labeled micro- tubes and stored at -20 ^{o}C.

For safety evaluation blood samples were collected according to the standard procedures of PCMD (Dr. Panjwani center for molecular medicine and drug research) diagnostic and clinical research lab of International Center for Chemical and Biological Sciences, University of Karachi, Pakistan.

Bioanalysis of Peginterferon α-2a (20kDa)

Serum samples were analyzed by validated Enzyme Linked Immunosorbant Assay (ELISA) method for Unipeg®. The assay with a dynamic range of 900 to 7pg/ml gave an inter assay mean accuracy of 98.31% and mean precision of 7.9% (n=18). The linearity graph is shown in Figure **1**.

Data Analysis

Statistical Analysis of Safety Data

As described earlier adverse events were monitored and recorded during the whole study. Frequency and severity of every adverse event was observed and recorded. Vital signs and Clinical lab tests results before drug administration and afterwards were processed for evaluation of any statistically significant change by computing the ANOVA (F-value) and performing t tests. Simple statistics were employed in

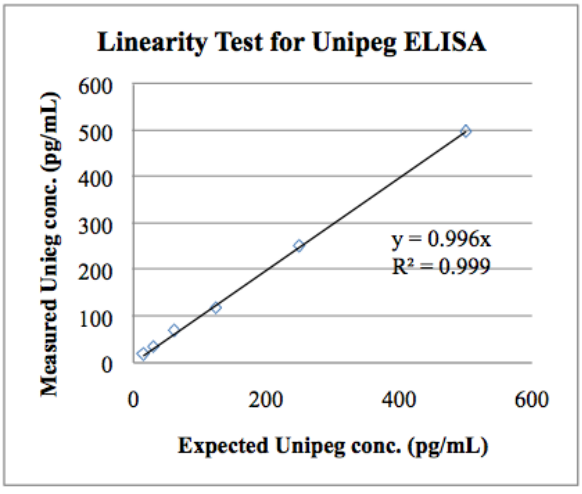

Figure 1: Showing the Linearity of a high sample 5000pg/ml of Unipeg® diluted to10X to500pg and further Sequential dilutions

the computation, in summary the statistical formulas employed are:

Mean is calculated by $\bar{x} = \sum \frac{x}{n}$, SEM by $= \frac{\delta_{n-1}}{\sqrt{n}}$, Variance ratio; $F = \frac{\delta^2_{n-1}}{\delta^2_{n-1}}$, in ANOVA F is determined by $\frac{MS_{treat}}{MS_{error}}$ and for paired t-test t is calculated by $\frac{\bar{d}}{\delta_{dn-1}\sqrt{n}}$

Pharmacokinetic Analysis

The pharmacokinetic analysis of every subject's plasma level data set was performed by a non compartmental model through PK Solution® computer software system. Area under the serum concentration-time curve from 0 to 156 hours ($AUC_{0\text{-}156}$) was calculated using the linear trapezoidal method. The first order rate constant associated with the curve terminal (log linear) portion was taken as elimination rate constant which is utilized for calculation of half life and also for $AUC_{t\text{-}\infty}$ in log linear trapezoidal rule. The formulas for different PK parameters utilized by the system are as follows:

Absorption half life; $ta_{\frac{1}{2}} = \frac{\ln(2)}{k_a}$; Elimination half life $t_{\frac{1}{2}} = \frac{\ln(2)}{\lambda_a}$;

$$AUC_{0-t} = \sum_{i=1}^{k} \left(\frac{C_{i-1} + C_i}{2}\right)(t_i - t_{i-1}); \; AUC_{Q-\infty} = AUC_{0-t} + \frac{\widehat{C_k}}{\lambda_k};$$

$$AUMC_{0-t} = \sum_{i=1}^{k} \left(\frac{C_{i-1} * t_{i-1} + C_i * t_i}{2}\right)(t_i - t_{i-1});$$

$$MRT(expo) = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}}$$

$$MRT(expo) = \sum \frac{1}{\lambda_n};$$

4. RESULTS AND DISCUSSION

Safety of Peginterferon α-2a (20kDa)

Throughout the whole study adverse events were recorded to evaluate the safety profile of the test product. Every subject suffered at least with three adverse events, generally of mild nature from which most of them recovered within few hours and rest recovered before the follow-up visit. Figure **2** shows the number of subjects suffered from different mild to moderate short term adverse events.

Fever was the most frequent event with the drug product found in all (100%) of the subjects. Next to the fever second most common was headache to which 60% of the subjects suffered; the third was Asthenia, which was found in 50% followed by vomiting and nausea in 40% of the subjects. Most of the adverse events were mild; few moderate and subjects showed an early trend of recovery. Table **2** reports the frequency and recovery- time of the most common adverse events during the study.

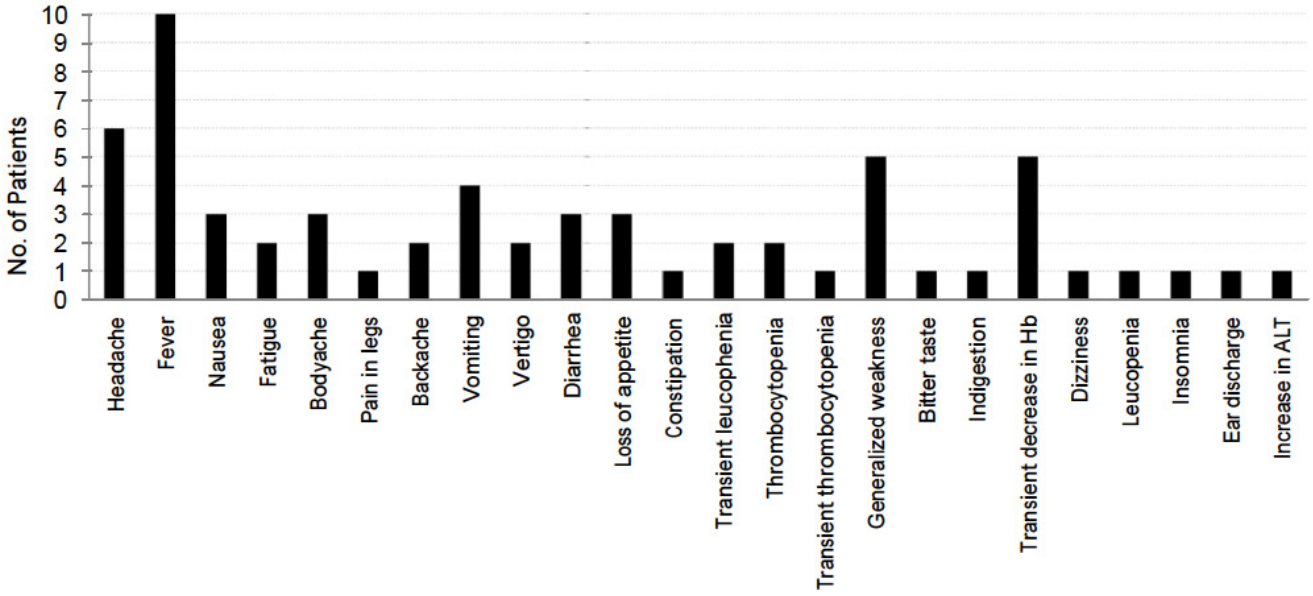

Figure 2: Number of Subjects suffered with different Mild to Moderate Short term Adverse Events.

Table 2: Occurrence-Frequency and Recovery-Time of the Most Common Adverse Events

Adverse event	Severity of Adverse Events			Recovery Time		
	Severe	Moderate	Mild	Within 24 hours	Within 48 hrs	Within 60-96 hrs
Fever	10%	10%	80%	All	-	-
Headache	0%	10%	50%	All	-	-
Asthenia	0%	0%	50%	20%	10%	20%
Vomiting	0%	0%	40%	All	-	-

All the ten volunteers had fever within 2-4 hours after the drug administration. Fever was in range of 99-103 ^{o}F (37.1-39.5 ^{o}C). Six volunteers had headache but it was also resolved. Other reported AEs includes; nausea, fatigue, myalgia (Body-ache), arthralgia (pain in legs), vomiting, vertigo, Diarrhea, constipation, earache etc.

During interferon therapy to encounter the fever and pain paracetamol tablets are administered to the patients before the injection. In present study we did not follow as we observed it in 100 percent of the subjects, we endorse and recommend the practice of paracetamol administration prior to the injection of any PEG-IFN.

On day five, 1.40% to 5.88% drop in hemoglobin level from its base line was found in eight volunteers. However, the hemoglobin level in any of the subject was not clinically significant. During the therapy with Unipeg® we strongly recommend hemoglobin monitoring as it can go to clinically significant low level in weak patients and physician has to take the remedial steps.

On day-5 statistically very significant changes were noticed in Total WBC, Absolute Neutrophils Count, Platelets and Lymphocytes at 1% level of significance and at 5% level changes occurred in neutrophils, monocytes and eosinophil counts. On day sixteen on follow-up, except WBC and Absolute Neutrophils Count all parameters returned to normal and one month after these two were also normal. ANOVA results for these parameters are given in Table **3**.

Only one subject had a leucopenia and two volunteers had thrombocytopenia even after sixteen days of test formulation administration.

Table 3: Analysis of Variance and p-Value for Clinical Lab Results

Parameter	DURING STUDY ON Day FIVE				ON FOLLOW UP (After two weeks)			
	F-value	p value	Sig at 1% level of significance	Sig at 5% level of significance	F- value	p value	Sig at 1% level of significance	Sig at 5% level of significance
Haemoglobin (14-18g/dl)	0.6164	0.4426	ns	ns	1.5480	0.2290	Ns	ns
Total WBC 10^9 /L	21.7185	0.0002	√	√	7.6050	0.0130	√	√
Neutrophils%	5.4706	0.0311	ns	√	0.4120	0.5290	Ns	ns
Absolute Neutrophils Count	15.7624	0.0009	√	√	5.1260	0.0360	Ns	√
Platelates 10^9 /L	9.4769	0.0065	√	√	0.3010	0.5900	Ns	ns
ALT	2.8238	0.1101	ns	ns	-	-	Ns	ns
RBC (red blood cells)	0.0592	0.8105	ns	ns	0.2730	0.6080	Ns	ns
PCV% (Packed cell volume)	0.7848	0.3874	ns	ns	1.0460	0.3200	Ns	ns
MCV (mean corpuscular volume)	0.2148	0.6486	ns	ns	0.1120	0.7420	Ns	ns
Lymphocytes (20-45%)	9.4967	0.0064	√	√	1.0130	0.3280	Ns	ns
Monocytes (1-10 %)	5.1984	0.0350	ns	√	3.5100	0.0770	Ns	ns
Eosinophil (1-5%)	6.2155	0.0226	ns	√	1.9630	0.1780	Ns	ns

On day 5 after drug administration the drop in the total WBCs count was in the range of 27.4% to 60.97%. But, all these were within normal limits of WBC count (i.e. 4.0-11.0X109/L); except for three volunteers who had leucopenia with a drop of 33.33%, 47.69% and 51.61% respectively. The recovering trend towards baseline value of total leucocytes count was observed on day sixteen of drug administration; except for one volunteer who still had leucopenia.

On day 5; 1.88% to 38.46% drop in neutrophil count was also observed for all ten volunteers but, all these were within normal clinical limits. On day sixteen; recovering trend towards baseline values for neutrophil count was very much evident.

Absolute neutrophil count (ANC) also dropped from 24.42% to 75.98% on 5th day. But it remained above 1500/mm3. Again on day16, recovering trend towards baseline value was observed in all the subjects. In seven volunteers, at follow-up; drop in ANC was 2.04% to 24.97% while it was 42.58%, 52.65% and 68.98% in remaining three volunteers; although the drop is marked but, clinically it is not significant.

Transit thrombocytopenia was recorded in one volunteer while mild thrombocytopenia was also observed in one another volunteer. The recovering trend was observed for platelets count.

Concerning safety, flu-like symptoms and hematological count reductions were reported. All the local, systemic and laboratory alterations recorded in this study have been reported under the treatment of PEG IFN alpha-2 [6, 9, 10].

In summary the clinical lab findings do not reveal any significant episode except one of leukopenia. All remaining the adverse events were mild or moderate which disappeared in short span of the single dose study. It must also be noted that the changes in the hematology and biochemistry lab results after drug administration are not clinically very significant in healthy subjects but the changes are statistically significant and must be carefully monitored while treating the patients with challenged health parameters.

To conclude the safety of Unipeg® in the present work it is found that it is equally safe like other pegylated interferons available and on the basis of risk and benefit ratio its therapeutic benefit is outweighing than any risk.

Pharmacokinetics

Besides the evaluation of the safety of the investigational product in the local population, the present study very first time also reports the pharmacokinetics of 20kDa PEG-IFN alfa 2a (Unipeg®) after subcutaneous administration of 180µg of the drug in Pakistani inhabitants. Many studies in past has reported pharmacokinetics of different pegylated interferons [11-14]. In present work all subjects complied with the protocol and to the instruction given to them. The mean profile of the drug is shown in Figure **3**.

The Maximum plasma concentration; C_{max} was observed at 12 hours for Unipeg® and found to be 18.67±2.92 [ng.ml-1] (7.05-34.51). It is higher than the reported values for other brands of 40kDa PEG-IFN alfa 2a; all estimated PK parameters are given in Table **4**.

It is very evident that the observed value for C_{max} is significantly higher than the reported C_{max} of the drug while CL (clearance) and Vd (volume of distribution) are smaller than the reported values (Table **4**).

Being a bio-similar to other pegylated alfa 2a Peg-interferons, one can expect similar PK values but as the 20kDa chain is different one naturally may also expect little differences, this is what we can observe in the present pilot study on a small sample size; future studies on larger sample size on local patient-population will increase our PK knowledge of the 20 kDa drug.

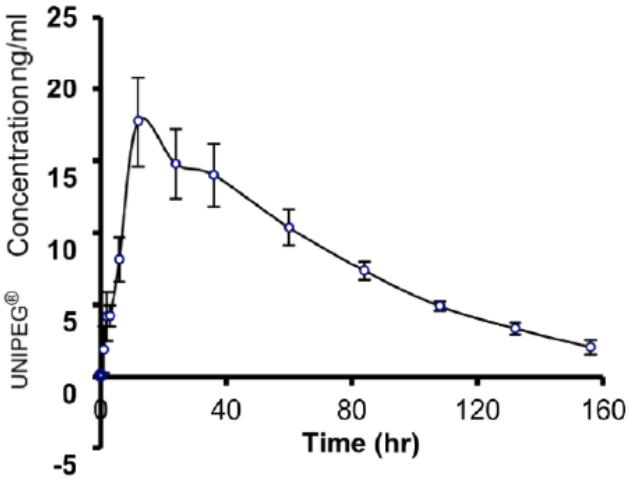

Figure 3: Mean UNIPEG® [PEG INTERFERON] ALFA 2a (20kDa) serum levels.

Table 4: PK Parameters of 20 kDa Peginterferon α-2a (Unipeg®) After Single Subcutaneous Dose of 180 µg in Abdominal Skin in Healthy Human Volunteers

Pharmacokinetic Parameter [units]	Mean ± SEM (Min - Max), CV
Absorption Half-Life, ta½; [h]	17.021±2.060 (10.37-29.26), 38.19
Elimination Half-Life, t½; [h]	41.437±6.210 (18.51-78.97), 47.39
Area Under the Curve up to t, AUC_{0-t} [obs Area]; [h.pg.l-1]	1278.015±119.770 (736-2086), 29.64
Area Under the Curve up to infinity, $AUC_{0-\infty}$ [area]; [h.pg.l-1]	1439.700±113.040 (969-2101), 24.83
Area Under the Curve up to infinity, $AUC_{0-\infty}$ (expo); [h.pg.l-1]	2779.827±303.390 (1738-4839), 34.51
Area Under the Moment Curve up to t, $AUMC_{(0-t)}$; [h2.pg.l-1]	69622.470±4523.860 (51254-91008), 20.55
Mean Residence Time, MRT (area); [h]	76.748±9.920 (44.47-144.40), 40.86
Mean Residence Time, MRT (expo); [h]	84.358±11.690 (46.50-156.18), 43.83
Peak Serum Concentration, C_{max}(obs); [ng.ml-1]	18.670±2.920 (7.05-34.51), 49.46
Minimum Serum Concentration, C_{min} (obs); [ng.ml-1]	0.894±0.190 (0.10-2.11), 66.40
T_{max}; [h]	36.773±4.870 (22.90-66.61), 41.84

CONCLUSION

The safety profile of Unipeg® (20 kDa Pegylated Interferon alfa-2a) after 180µg subcutaneous dose was found to be very similar to those reported in literature for unmodified IFNs and other pegylated interferons generally used in therapy. The PK parameters of Unipeg® correlate very well with those single dose injections found for other pegylated IFN generally used in therapy.

Future clinical trials are recommended to further confirm the investigated safety profile and to explore multiple dose pharmacokinetics in patients.

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