Bioequipotency of idraparinux and idrabiotaparinux after once weekly dosing in healthy volunteers and patients treated for acute deep vein thrombosis

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Idrabiotaparinux is a synthetic biotinylated derivative of the activated factor X (FXa) inhibitor, idraparinux pentasaccharide. Idrabiotaparinux can be administered subcutaneously once weekly and biotinylation enables reversal of the anticoagulant effect with a 30 min intravenous infusion of avidin. Idraparinux was previously investigated in a large clinical trial in patients with deep vein thrombosis (DVT), and once weekly subcutaneous injection had similar efficacy and safety to standard therapy consisting of heparin plus a vitamin K antagonist. The EQUINOX phase III trial investigated the potential use of 6 months of once weekly treatment with idrabiotaparinux, and showed a similar efficacy and safety profile as treatment with idraparinux for the prevention of recurrent venous thromboembolism in patients with acute DVT.

WHAT THIS STUDY ADDS

- The bioequipotency between idrabiotaparinux and idraparinux based on their pharmacodynamic anti-FXa activity was demonstrated in the targeted patient population, confirming that the addition of a biotin moiety did not appear to affect the potency of idraparinux to inhibit FXa. This study provides support to substitute idraparinux with idrabiotaparinux once weekly dosing in the treatment of venous thromboembolism. The EQUINOX study suggests that a bioequipotency approach for compounds with similar pharmacological activity could be used to extrapolate clinical trial results from one compound to another.

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AIM

To assess the bioequipotency of equimolar doses of idraparinux (2.5 mg) and idrabiotaparinux (3.0 mg).

METHOD

In a phase I study, 48 healthy male volunteers were randomized to a single subcutaneous injection of idrabiotaparinux or idraparinux, followed by plasma sampling over 27 days. In a prospective substudy of the phase III EQUINOX trial, 228 patients treated for acute symptomatic deep vein thrombosis received idrabiotaparinux or idraparinux once weekly for 6 months. Plasma sampling was performed within 5 days following the last injection. The primary pharmacodynamic endpoint was the inhibition of activated factor X (FXa) activity. Maximal anti-FXa activity ($A_{\max}$) and area under anti-FXa activity vs. time curve (AAUC) were calculated. Safety and tolerability were also assessed.

RESULTS

In both studies, pharmacodynamic anti-FXa vs. time profiles of idrabiotaparinux and idraparinux were superimposable. Ratio estimates (90% confidence intervals [CIs]) for idrabiotaparinux : idraparinux were 0.96 (0.89, 1.04) for $A_{\max}$ and 0.95 (0.87, 1.04) for AAUC in the phase I study, and 1.11 (1.00, 1.22) for $A_{\max}$ and 1.06 (0.96, 1.16) for AAUC at month 6 in the EQUINOX substudy. Idrabiotaparinux and idraparinux were considered bioequipotent because 90% CIs were within the pre-specified interval (0.80, 1.25). Study treatments were well tolerated.

CONCLUSION

Pharmacodynamic parameters reported after single dose in healthy volunteers and after repeated once weekly dosing in patients demonstrated the bioequipotency of idrabiotaparinux and idraparinux based on FXa inhibition. These outcomes support the use of an idrabiotaparinux dose bioequipotent to an idraparinux dose in large clinical trials, and the possibility to substitute idrabiotaparinux to idraparinux for the treatment of venous thromboembolism.

Introduction

Idraparinux is a long acting synthetic pentasaccharide that specifically inhibits activated factor X (FXa) via selective antithrombin binding [1]. Idraparinux shows predictable pharmacokinetics (PK) with complete bioavailability after subcutaneous (s.c.) administration and a long terminal half-life (~66 days), which allows once weekly fixed dosing [1–3]. As such, idraparinux offers the potential for improved convenience and compliance in long term out-patient anticoagulant treatment of venous thromboembolism (VTE), with the following advantages: no requirement for coagulation monitoring, stable therapeutic levels of anticoagulation and fewer drug or food interactions.

Idrabiotaparinux is identical to idraparinux, but with the addition of a biotin moiety covalently bound through a linker to the pentasaccharide molecule (Figure 1). The biotin moiety of idrabiotaparinux is devoid of any pharmacological effect, such as prothrombotic activity. Neither biotin nor the linker placement interfere with the interaction of the idraparinux portion of the idrabiotaparinux molecule with antithrombin, thus resulting in the same range of binding constant to antithrombin and of pharmacological activity as idraparinux alone, as measured by anti-FXa activity in animal models [4]. Idraparinux was previously investigated in a large clinical trial in patients with deep vein thrombosis (DVT), and once weekly s.c. had similar efficacy and safety to standard therapy consisting of heparin plus a vitamin K antagonist [5]. In the phase III EQUINOX trial, a 6-month treatment course with equimolar amounts of idrabiotaparinux or idraparinux in patients with acute symptomatic DVT showed comparable efficacy with a trend towards less bleeding with idrabiotaparinux

[6]. In addition, biotinylation of idraparinux allows anti-FXa activity to be rapidly and specifically reversed by a 30 min intravenous (i.v.) infusion of avidin [7]. Immediate and specific reversal of anti-FXa activity is important for the clinical use of anticoagulant agents, especially long acting ones, as patients may urgently require reversal of anticoagulation, for example in the event of an emergency surgical procedure, bleeding or overdose.

Before concluding that idrabiotaparinux could substitute for idraparinux to treat DVT, a direct comparison of the two drugs is needed to demonstrate their equivalence based on pharmacodynamic (PD) anti-FXa activities, i.e. bioequipotency, and confirm that their efficacy and safety profiles are similar. This manuscript reports the results of the bioequipotency of idraparinux and idrabiotaparinux, using a bioequivalence statistical approach after single, equimolar, s.c. dosing in healthy volunteers in a phase I study, and after multiple once weekly s.c. dosing in patients being treated for acute symptomatic DVT in a substudy of the EQUINOX trial.

Methods

Study design, volunteers and patients

A single dose, open label, randomized, parallel group phase I study compared the PD, PK, and safety profiles of idraparinux and idrabiotaparinux in healthy volunteers receiving s.c. equimolar dose of either idraparinux (2.5 mg) or idrabiotaparinux (3.0 mg). This study included healthy men aged 18 to 45 years, with a body mass index of 18 to 28 kg m⁻², a weight range of 60 to 90 kg, normal coagulation status (defined as international normalization ratio

Figure 1

Chemical structures of idraparinux and idrabiotaparinux

Figure 2

Study design schema of the EQUINOX trial and substudies. DVT, deep vein thrombosis

[INR] < 1.3) and an activated partial thromboplastin time of ≤ 6 s above normal control values.

The phase III EQUINOX trial was an international, double-blind, randomized, parallel group study in patients with acute symptomatic DVT treated with either idrabiotaparinux or idraparinux. Patients were enrolled in the EQUINOX bioequipotency substudy (ClinicalTrials.gov identifier: Substudy of NCT00311090 EQUINOX trial) if they were aged > 18 years and had a confirmed diagnosis of acute symptomatic DVT of the lower limb. The first stage of the EQUINOX trial comprised, after a first randomization, of 26 s.c. weekly injections of equimolar doses of idraparinux (2.5 mg) or idrabiotaparinux (3.0 mg) over a 6 month period to assess the efficacy, safety, PD and PK profiles of each drug (Figure 2). On day 183, at the 6 month visit, eligible patients were then randomized to one of two substudies, one substudy assessing the reversal effect of avidin on idrabiotaparinux [7] and the present substudy evaluating bioequipotency (Figure 2). Patients randomized to the bioequipotency substudy received one additional s.c. injection of either idrabiotaparinux or idraparinux on day 183, stratified according to their previous treatment. Plasma samples were taken at 0, 0.5, 4, 48 and 120 h for PK and PD analysis. The blood sampling time points for the bioequipotency assessment were selected according to the theoretical requirements of an optimal population model building balanced by the feasibility constraints of conducting such a study in general hospitals/clinics.

Both studies were conducted in accordance with the Declaration of Helsinki and in compliance with the requirements of Good Clinical Practice. The study protocols (and amendments) received approval from the relevant institu-

tional review boards including local ethics committees in any participating country. Written informed consent was obtained from all volunteers and patients before their enrolment into the studies.

Bioequipotency assessment

Bioanalytical methods

Pharmacokinetic assessment Idraparinux and idrabiotaparinux plasma concentrations of healthy volunteers were measured by a fully validated biological chromogenic assay that used the antithrombin-mediated FXa inhibitory activity of each compounds (Stachrom Heparin kit: Diagnostica Stago, Inc., Parsippany, NJ, USA) with an excess of exogenous antithrombin. The excess of antithrombin aimed to ensure that all the compound present in the plasma collection was bound to antithrombin, thus maximizing the inhibition. Therefore, the anti-FXa activity measured reflected the total amount of circulating oligosaccharide without being influenced by the presence of any endogenous factor in the sample. The lower limit of quantification (LLOQ) was $0.047 \mu\text{mol l}^{-1}$ for both compounds. Taking the LLOQ to be the lowest validation concentration with precision and accuracy within 20%, the current assay has been validated from 0.047 to $0.46 \mu\text{mol l}^{-1}$, for both compounds in human plasma. The results of between batch variability fulfilled the acceptance criteria ($\pm 15\%$) for precision and accuracy. Due to the difference in molecular weight between both compounds (Figure 1), concentrations were expressed in molar units to allow a direct comparison.

During non-clinical idrabiotaparinux metabolism studies and repeated dose toxicokinetic studies, a

debiotinylated metabolite of idrabiotaparinux (loss of the biotin moiety, but with the linker) was observed and identified *in vivo* as an equipotent active metabolite (SSR115771) based on anti-FXa activity and likely to be present in human plasma after repeated s.c. administration. The chemical structure of the metabolite is closely related to those of idraparinux and idrabiotaparinux (structure in-between idraparinux and idrabiotaparinux).

A physicochemical method was subsequently developed and validated for the simultaneous quantitative analysis of idrabiotaparinux and its debiotinylated metabolite in human plasma, using protein precipitation followed by ion-pairing liquid chromatography (LC) with tandem electrospray mass spectroscopy (MS/MS) detection, with a LLOQ of $0.027 \mu\text{mol l}^{-1}$ similar to that obtained with the previous chromogenic method. The assay has been validated from 0.027 to $1.35 \mu\text{mol l}^{-1}$, and results demonstrated that the accuracy, repeatability and intermediate precision evaluated at the LLOQ and on quality-control samples fulfilled the acceptance criteria for idrabiotaparinux and its debiotinylated metabolite. This specific method was used in the EQUINOX trial. The LC-MS/MS and anti-FXa methods have been cross-validated using spiked quality control samples and clinical samples from a single dose phase I study (data not shown).

Pharmacodynamic assessment The primary PD variable assessed for both study drugs was the inhibition of FXa activity measured using a validated chromogenic enzyme assay without addition of exogenous antithrombin. The molar PD activities of idraparinux and idrabiotaparinux were similar *in vitro*, as demonstrated by superimposed calibration curves of both compounds. Therefore, idraparinux was used as a calibrator for the PD assessments of both compounds. Without plasma sample dilution and addition of exogenous antithrombin, this method is expected to preserve the initial oligosaccharide–antithrombin complex formed *in vivo* and can, thus, be considered to reflect optimally complex-mediated anti-FXa activity in subjects. Inhibition of FXa activity was expressed as a percentage, with 0% representing no FXa inhibition in the absence of oligosaccharide and 100% representing maximal FXa inhibition in the presence of oligosaccharide amounts in excess, vs. endogenous concentrations of antithrombin on a molar basis ($\sim 3 \mu\text{M}$). The LLOQ for this anti-FXa assay was 0.808%. The results of between batch variability fulfilled the acceptance criteria ($\pm 15\%$) for precision and accuracy. There was no difference in PD activity between idraparinux and idrabiotaparinux. Matrices were without effect on PD quantification and anticoagulants did not affect the calculation. No automated carry-over was observed.

Pharmacokinetic and pharmacodynamic exposure parameters for bioequipotency

Pharmacokinetics In the phase I study, the following plasma PK parameters were determined for idrabiotaparinux and idraparinux, using a non-compartmental approach (WinNonlin version 4.0.1 Pharsight Corp., St Louis, MO, USA): maximal concentration (C_{max}) and area under the curve up to the last concentration ($\text{AUC}(0, t_{\text{last}})$) above the LLOQ.

In the phase III substudy, a sparse sampling approach was implemented and PK parameters at month 6 were estimated by non-linear mixed effect modelling (NONMEM® version VI on a Linux cluster, ICON, Elicott City, MD, USA). For each treatment group, a separate population PK model was built with classical steps of population model building, particularly, the selection of structural and statistical models. However, no screening or inclusion of covariates were performed because the primary objective was to compute individual predicted PK exposures at month 6. C_{max} and AUC at month 6 were calculated. LC-MS/MS analysis allowed a demonstration of circulating concentrations of the active debiotinylated metabolite of idrabiotaparinux in patients from the EQUINOX study after repeated administration. As this metabolite has the same anti-FXa PD activity as the parent compound (data not shown), the plasma concentrations of both idrabiotaparinux and its debiotinylated metabolite were added on a molar basis before building the population PK and PD models for the EQUINOX data set.

Pharmacodynamics In the phase I study, the following plasma PD parameters were determined from the anti-FXa activity of idrabiotaparinux and idraparinux, using a non-compartmental approach (WinNonlin version 4.0.1, Pharsight Corp.): maximal activity (A_{max}) and area under the anti-FXa activity vs. time curve above the LLOQ ($\text{AAUC}(0, t_{\text{last}})$). As mentioned above, the non-compartmental approach was not appropriate for the phase III substudy as a result of sparse sampling.

In the EQUINOX substudy, once the respective final population PK models for idrabiotaparinux and idraparinux were obtained, two separate population PK and PD models were built using the predicted PK data and observed PD values. As for PK values, no screening and inclusion of covariates was performed because the primary objective of the PK and PD modelling was to compute individual predicted PD parameters at month 6 and assess the interindividual variability with minimal shrinkage for both compounds. For both treatments, this two-step approach using PK and PD relationships allowed the calculation of individual predicted PD vs. time profiles, which were used to estimate the individual predicted PD exposure parameters at the exact week of the observations for each patient at month 6. The following individual PD exposure parameters were determined and used to assess bioequipotency: A_{max} at month 6 and AAUC at month 6 over the 7 day dosing interval.

Safety evaluation In the phase I study, safety assessments included reporting all treatment-emergent adverse events

(TEAEs, defined as adverse events occurring at any time between treatment administration and 28 days post-treatment), monitoring of vital signs, electrocardiograms (ECGs), recording of local tolerability data, and laboratory analysis of clinical chemistry, haematology and coagulation parameters.

In the phase III substudy, safety assessments included reporting of death, bleeding (numbers and percentages of patients with clinically-relevant bleeding within 6 months, from first study drug administration up to day 182), and TEAEs (defined as any event that started or worsened in intensity or became serious after first study drug administration, and up to the end of study).

Statistical methods Standard descriptive statistics were computed for the individual PD endpoints in the phase I and III studies and plotted graphically. A standard bioequivalence approach was used to assess bioequipotency in both studies. PD exposure parameters of $A_{\max}$ and $AAUC(0, t_{\text{last}})$ from the phase I study, and individual model-derived PD values for $A_{\max}$ and $AAUC$ at month 6 from the phase III substudy were log-transformed and the 90% confidence interval (CI) of the differences of mean log values between treatment groups was estimated. The corresponding 90% CI and point estimate of the ratios of geometric means were obtained by exponential transformation. Bioequipotency was considered demonstrated if the 90% CI of the ratios for both $A_{\max}$ and $AAUC$ were included in the bioequivalence reference interval (0.80–1.25) as proposed by international guidance [8, 9]. The log-normality of the distribution of model-derived PD exposure parameters and the presence of outliers were graphically assessed. The bioequivalence approach was retained as an adequate methodology for demonstrating the bioequipotency, as it is the only recognized method by regulatory authorities for assessing similarity between two products. Moreover, the (0.80–1.25) reference interval means that the point estimate should be lower than 1.25, in order to still conclude a bioequipotency, and such a difference, based on PERSIST data, was not translated in a statistically significant increase of bleeding risk (data not shown).

At the time of the bioequipotency assessment (month 6), idraparinux and idrabiotaparinux exposure had not completely achieved steady-state. Therefore, the population PK and PD models were used to compute predicted individual PD profiles at steady-state. The corresponding PD exposure parameters at steady state ($A_{\max}$ and $AAUC$) were derived and the respective 90% CI of the geometric mean ratios between both compounds were compared with the bioequivalence acceptance interval.

Finally, the anti-FXa activity PD profiles of idrabiotaparinux and idraparinux during the whole time course of the EQUINOX study were compared using observed A_{trough} values (pre-dose activity) obtained on days 15, 36, 57, 92 and 183.

The same calculations as for PD in the phase I and EQUINOX substudy analyses were performed on the individual PK exposure parameters ($C_{\max}$ and AUC). The point estimate and 90% CI of the geometric mean ratio for $C_{\max}$ and AUC were obtained.

Results

In the phase I study, 55 healthy male volunteers, aged 18 to 41 years, were enrolled and comprised the safety population. There were seven premature withdrawals, one due to poor compliance with the protocol, one at the request of the volunteer and five volunteers were lost to follow-up. A total of 48 volunteers (24 per treatment group) had complete PD measurements for the whole study period and comprised the evaluable PD analysis population.

In total, 131 idrabiotaparinux-treated patients and 130 idraparinux-treated patients were allocated to the bioequipotency EQUINOX substudy after a 6 month treatment period. Sixteen patients in the idrabiotaparinux group and 17 in the idraparinux group were excluded from the bioequipotency substudy analysis because they did not meet pre-defined criteria (no PD samples, lack of PD sample before the last injection, only one to two PD samples drawn after the last injection, and insufficient numbers of injections or not regularly spaced). Therefore, 228 patients were eligible for inclusion in the bioequipotency substudy analysis population (114 patients per group). Overall, 63% and 52% of patients were male with 98% and 95% Caucasian in the idrabiotaparinux and idraparinux groups, respectively. The median age of patients was 56.5 years (range 19–95 years) in the idrabiotaparinux group and 60.0 years (range 19–91 years) in the idraparinux group. Other parameters that may impact on the PKs of idrabiotaparinux and idraparinux, such as weight or baseline creatinine clearance, were also similar between the groups.

Pharmacodynamic profiles

After a single s.c. administration of equimolar doses of idraparinux and idrabiotaparinux in the phase I study, the mean PD anti-FXa time profiles were superimposable (Figure 3). Mean $A_{\max}$ and $AAUC(0, t_{\text{last}})$ values were similar between both groups (Table 1). Ratio estimates (90% CI) were 0.96 (0.89, 1.04) for $A_{\max}$ and 0.95 (0.87, 1.04) for $AAUC(0, t_{\text{last}})$. Therefore, idrabiotaparinux and idraparinux were considered bioequipotent as the 90% CIs were within the pre-specified bioequivalence interval (0.80, 1.25).

In the EQUINOX substudy, the mean predicted PD FXa inhibition time profiles at month 6 for idraparinux and idrabiotaparinux were also superimposable in patients with DVT after a 6 month repeated once weekly s.c. treatment (Figure 4).

Moreover, mean observed anti-FXa data collected at the pre-specified time points and used to develop

Figure 3

Mean pharmacodynamic anti-factor Xa activity vs. time profiles of idrabiotaparinux (3.0 mg) and idraparinus (2.5 mg) after single subcutaneous equimolar dosing in healthy volunteers ($n = 24$ per treatment group). LLOQ, lower limit of quantification. —○—, idrabiotaparinux; —■—, idraparinus

population models and derive predicted data were superimposed between both compounds and with predicted data (Figure 4). Mean $A_{\max}$ and AAUC values at month 6 were similar between groups. Ratio estimates (90% CI) were 1.11 (1.00, 1.22) for $A_{\max}$ and 1.06 (0.96, 1.16) for AAUC (Table 1). Consistent with the study in healthy volunteers, idrabiotaparinux and idraparinus were again considered bioequivalent as the 90% CIs were within the pre-specified bioequivalence interval.

At the time of bioequivalency assessment (month 6), steady-state was not completely achieved for both compounds. Therefore, the PK and PD models were used to compute predicted individual PD parameters at steady-state. They showed similar mean predicted $A_{\max}$ and AAUC values between groups with 90% CIs within the pre-specified bioequivalence interval (Table 1).

Of note, the mean PD FXa inhibition profiles of idraparinus and idrabiotaparinux were also superimposable in patients with DVT during the 6 months of treatment because they were similar in the two treatment groups for each time point at pre-dose (Figure 5).

Pharmacokinetic profiles

After a single administration of equimolar doses of idraparinus and idrabiotaparinux in the phase I study, the mean PK profiles were superimposable for both compounds (Figure 6). Mean $C_{\max}$ and $AUC(0, t_{\text{last}})$ values were similar between the idrabiotaparinux and the idraparinus groups. Ratio estimates (90% CI) were 0.92 (0.87, 0.98) for $C_{\max}$ and 0.94 (0.83, 1.07) for $AUC(0, t_{\text{last}})$ (Table 2).

In the EQUINOX substudy, the mean PK profiles of idraparinus and the sum of idrabiotaparinux and its debiotinylated metabolite were also superimposable in patients

after treatment for 6 months (Figure 7). It was initially planned to compare the PK parameters for the idrabiotaparinux parent compound with those of idraparinus. However, because SSR115771 (the debiotinylated metabolite) was observed in patients after repeated administration and showed an anti-FXa activity similar on a molar basis to that of idrabiotaparinux and idraparinus, the PK model building of idrabiotaparinux was performed using the sum of observed active entities at each time point. Mean $\pm$ SD predicted idraparinus and idrabiotaparinux plus SSR115771 plasma concentrations at month 6 were superimposable in patients after treatment (Figure 7).

Mean $C_{\max}$ and AUC values at month 6 were determined for both groups and were similar, with ratio estimates (90% CI) of 1.06 (1.00, 1.11) for $C_{\max}$ and 1.04 (0.98, 1.10) for AUC (Table 2).

Thereafter, a preliminary population PK model was developed to characterize concomitantly the PK of the two active circulating entities independently from available EQUINOX data (up to 6 months). Based on this model, data showed that steady-state of unchanged idrabiotaparinux was reached 2 weeks after initiation of treatment, and its elimination half-life was around 4 days. In contrast, the debiotinylated metabolite (SSR115771) showed an accumulation profile similar to idraparinus, with a steady-state reached within the same period of time (6–8 months) (Figure 8). The elimination half-life of the debiotinylated metabolite has been estimated at 52 days, of the same order of magnitude as the terminal phase of elimination of idraparinus [3]. The PK difference between unchanged idrabiotaparinux and its debiotinylated metabolite is supported by the distribution characteristics of idrabiotaparinux [10]. After s.c. administration of idrabiotaparinux, a fraction was eliminated unchanged via the renal route and the remaining fraction was distributed in peripheral tissues where most of it was debiotinylated. The resulting debiotinylated metabolite was slowly released via the lymphatic system into the vascular compartment, as idraparinus, before being cleared via the renal route.

Safety

In the phase I study, the number of volunteers presenting with at least one TEAE was similar in the idrabiotaparinux (20/27 volunteers) and idraparinus groups (21/28 volunteers). Most TEAEs were mild in intensity. Three patients in the idraparinus group had haemoglobin decreases from baseline of more than 2 g dl^{-1} which were not associated with bleeding. No potentially clinically significant decreases in haemoglobin were recorded in the idrabiotaparinux group. There were no other relevant changes in biochemistry coagulation parameters, vital signs or ECGs in either treatment group. Local tolerance of both treatments was good.

In the EQUINOX substudy, a 6 month treatment period with idrabiotaparinux compared with idraparinus in patients with DVT showed a trend for less bleeding. There

Table 1

Pharmacodynamic parameters and ratio estimates of idrabiotaparinux vs. idraparinux after subcutaneous equimolar dosing in healthy volunteers ($n = 24$ per treatment group) or patients in the EQUINOX bioequipotency substudy ($n = 114$ per treatment group)

Parameter*	Idrabiotaparinux (3.0 mg***)	Idraparinux (2.5 mg***)	Ratio (90% CI)** idrabiotaparinux vs. idraparinux
After single dosing in healthy volunteers			
A_{max} (%)	9.93 $\pm$ 1.64 (17) [9.79]	10.1 $\pm$ 2.03 (20) [9.95]	0.96 (0.89, 1.04)
AAUC(0, t_{last}), (% h)	359 $\pm$ 69.5 (19) [352]	369 $\pm$ 84.4 (23) [359]	0.95 (0.87, 1.04)
After repeated dosing in patients in EQUINOX substudy at month 6			
A_{max} (%)	18.8 $\pm$ 8.84 (47) [17.16]	17.6 $\pm$ 9.77 (56) [15.52]	1.11 (1.00, 1.22)
AAUC (% h)	1213 $\pm$ 670 (55) [1086]	1135 $\pm$ 566 (50) [1027]	1.06 (0.96, 1.16)
After repeated dosing in patients in EQUINOX substudy at steady-state			
A_{max} (%)	20.0 $\pm$ 10.7 (53) [17.9]	19.2 $\pm$ 11.1 (58) [16.8]	1.07 (0.96, 1.19)
AAUC (% h)	1286 $\pm$ 800 (62) [1130]	1261 $\pm$ 672 (53) [1133]	1.00 (0.90, 1.10)

*All values are quoted in mean $\pm$ SD (%CV) [Geometric mean]. **Calculated using log transformed values. ***Equimolar dose of idraparinux and idrabiotaparinux. AAUC, area under the anti-Xa activity vs. time over the dosing interval; AAUC(0, t_{last}), AAUC from time 0 to the time corresponding to the last concentration above the limit of quantification; A_{max} , maximal activity; CI, confidence interval; SD, standard deviation.

Figure 4

Pharmacodynamic anti-factor Xa activity vs. time profiles of idrabiotaparinux (3.0 mg) and its debiotinylated metabolite (SSR115771) vs. idraparinux (2.5 mg) after repeated subcutaneous equimolar dosing in patients with deep vein thrombosis in the EQUINOX bioequipotency substudy at month 6 ($n = 114$ per treatment group). —, idrabiotaparinux and debiotinylated metabolite, mean predictions; —, idraparinux, mean predictions; ○, idrabiotaparinux and debiotinylated metabolite, mean observed data; ○, idraparinux, mean observed data

was less clinically-relevant bleeding (20 [5.2%] vs. 27 [7.3%]) and less major bleeding (3 [0.8%] vs. 14 [3.8%]) with idrabiotaparinux than with idraparinux, respectively [6]. Similar results were observed for TEAEs and mortality in the idraparinux and idrabiotaparinux groups.

Figure 5

Pharmacodynamic anti-factor Xa activity vs. time profiles of idrabiotaparinux (3.0 mg) vs. idraparinux (2.5 mg) after repeated subcutaneous equimolar dosing in patients with deep vein thrombosis over the time course of the study. LLOQ, lower limit of quantification. —○—, idrabiotaparinux; —●—, idraparinux

Discussion

Idraparinux was the first long acting synthetic pentasaccharide to enter clinical development [1]. In the PERSIST and van Gogh DVT studies, standard duration regimens of idraparinux, given as a fixed once weekly dose, were effective as secondary prophylaxis to prevent recurrent VTE and

Figure 6

Mean pharmacokinetic concentration vs. time profiles of idrabiotaparinux (3.0 mg) and idraparinux (2.5 mg) after single subcutaneous equimolar dosing in healthy volunteers ($n = 24$ per treatment group). LLOQ, lower limit of quantification. $\circ$ —, idrabiotaparinux; $\blacksquare$ —, idraparinux

were associated with a potentially lower risk of bleeding than vitamin K antagonists (VKAs) [2, 5].

The EQUINOX study confirms the bioequipotency of the biotinylated molecule, idrabiotaparinux vs. idraparinux following multiple once weekly s.c. dosing in the targeted patient population with acute DVT, which was previously demonstrated in healthy subjects after a single s.c. administration, because the 90% CIs of PD anti-FXa exposure parameters were within the pre-specified bioequivalence interval (0.80, 1.25). The mean anti-FXa time profiles after each treatment were superimposable highlighting their very similar PD activities. Furthermore, mean pre-dose levels of FXa activity were identical in the treatment groups throughout the 6 month study period.

These bioequipotency data suggest that results observed with idraparinux in the PERSIST and van Gogh trials may be extrapolated to idrabiotaparinux, potentially indicating that idrabiotaparinux has a similar efficacy to VKAs in secondary VTE prevention. In line with the bioequipotency data, the efficacy of idrabiotaparinux and idraparinux was found to be similar after the 6 month treatment period of the core EQUINOX study [6]. Rates of recurrent VTE (9 [2.3%] vs. 12 [3.2%]) and of fatal or non-fatal PE (6 [1.6%] vs. 7 [1.8%]); were similar with idrabiotaparinux and idraparinux, respectively [6]. Of note, in this limited sample of patients lower rates of clinically-relevant bleeding were observed with idrabiotaparinux than idraparinux (5.2% vs. 7.3%) as well as less major bleeding (0.8% vs. 3.8%) [6]. The safety and efficacy profiles of idrabiotaparinux were confirmed in the Cassiopea trial with 3203 patients where once weekly idrabiotaparinux after an initial course of low molecular weight heparin was an effective, safe and straightforward treatment for patients with acute pulmonary embolism and can effectively replace VKAs [11].

For ethical and feasibility reasons related to the PK characteristics of the study drugs (long elimination half-lives) it was not possible to demonstrate bioequipotency in healthy volunteers after repeated administration. As a consequence the demonstration of bioequipotency was performed in two steps: in a phase I study in volunteers after single dose administration; and then confirmed after repeated administration at month 6 in patients. For both studies a parallel group design was selected due to the long half-lives of the study drugs. Moreover, a major advantage of the EQUINOX substudy was to demonstrate the bioequipotency in the target patient population. Even if patients were sparsely sampled, as in many clinical circumstances, population models are appealing and can be used to derive PK and PD parameters for subsequent comparisons using statistical evaluations. The approach applied in the EQUINOX study could be envisaged in other circumstances in late stage clinical development to address a need in drug development for assessing PK similarity between different compounds, formulations or populations, allowing reduction in the time of clinical development by avoiding additional clinical studies. Regarding limitations, it was not directly possible to demonstrate bioequipotency at steady-state. However, bioequipotency was demonstrated at 6 months because this is the most usual treatment duration in patients with VTE. Furthermore, additional analyses based on predictions indicated that bioequipotency was also demonstrated in the same subset of patients at steady-state. A possible limitation of the bioequipotency assessment is that patients with severe renal impairment were not included in the studies. Additional investigations are required to ascertain if idrabiotaparinux dose adjustments are required in such patients.

A debiotinylated metabolite (SSR115771) has been observed after repeated dosing. During the EQUINOX study, the debiotinylated metabolite showed a slow increase in plasma concentrations over the 6 month duration of the study, with a flat profile over the dosing interval (Figure 8), most likely corresponding to a slow metabolism and release of this compound from the peripheral compartment to the blood compartment. Similar to idraparinux, the slow release from tissues observed during preclinical distribution studies would be responsible for the long elimination phase of the debiotinylated metabolite [10]. However, in the Cassiopea study, treatment with idrabiotaparinux was associated with fewer bleeding events than treatment with warfarin during the treatment period (6 months). This was also observed in the 6 month follow-up period after treatment cessation, indicating that the slow release of the debiotinylated metabolite from tissues into the systemic circulation was not associated with safety issues [11]. The presence of the debiotinylated metabolite observed after a 30 min i.v. infusion of avidin 100 mg in a second substudy of EQUINOX, may explain the remaining anti-FXa activity observed after the large reversibility of idrabiotaparinux anti-FXa activity [7].

Table 2

Pharmacokinetic parameters and ratio estimates of idrabiotaparinux vs. idraparinux after subcutaneous equimolar dosing in healthy volunteers ($n = 24$ per treatment group) or patients in the EQUINOX bioequipotency substudy at month 6 ($n = 114$ per treatment group)

Parameter*	Idrabiotaparinux (3.0 mg***)	Idraparinux (2.5 mg***)	Ratio (90% CI)** idrabiotaparinux vs. idraparinux
After single dosing in healthy volunteers			
C_{max} ($\mu\text{mol l}^{-1}$)	0.368 ± 0.0257 (7) [0.367]	0.401 ± 0.0513 (13) [0.397]	0.92 (0.87, 0.98)
$AUC(0, t_{last})$ ($\mu\text{mol l}^{-1} \text{ h}$)	21.8 ± 3.87 (18) [21.5]	23.9 ± 6.57 (27) [22.9]	0.94 (0.83, 1.07)
After repeated dosing in patients in the EQUINOX substudy at month 6			
C_{max} ($\mu\text{mol l}^{-1}$)	0.525 ± 0.152 (29) [0.505]	0.544 ± 0.107 (20) [0.534]	1.06 (1.00, 1.11)
AUC ($\mu\text{mol l}^{-1} \text{ h}$)	50.2 ± 14.3 (29) [48.4]	51.6 ± 13.2 (26) [50.1]	1.04 (0.98, 1.10)

*All values are quoted in mean $\pm$ SD (%CV) [Geometric mean]. **Calculated using log transformed values. ***Equimolar dose of idraparinux and idrabiotaparinux. AUC, area under the curve; $AUC(0, t_{last})$, AUC up to the last concentration; CI, confidence interval; C_{max} , maximal concentration; SD, standard deviation.

Figure 7

Pharmacokinetic concentrations vs. time profiles of idrabiotaparinux (3.0 mg) and its debiotinylated metabolite (SSR115771) vs. idraparinux (2.5 mg) after repeated subcutaneous equimolar dosing in patients in the EQUINOX bioequipotency substudy at month 6 ($n = 114$ per treatment group). —▲—, idrabiotaparinux and debiotinylated metabolite; —●—, idraparinux

As idrabiotaparinux and its debiotinylated metabolite show similar pharmacological activities, concentrations of both molecular entities were considered all together in the PK and PD relationship. However, a full population PK model of idrabiotaparinux and of its debiotinylated metabolite that includes all phase III data should be developed in order to characterize appropriately of the PKs of the parent and metabolite compounds in the patient population, as well as relevant covariates that may explain the compounds variability.

In conclusion, the addition of a biotin moiety did not appear to affect the potency of idraparinux to inhibit FXa and idrabiotaparinux was well tolerated. The PD param-

Figure 8

Predicted concentrations of idrabiotaparinux (3.0 mg) and its debiotinylated metabolite (SSR115771) vs. idraparinux (2.5 mg) after repeated subcutaneous equimolar dosing in patients over a 6 month treatment period. —, idrabiotaparinux; —, debiotinylated metabolite; ···, idraparinux

eters reported after a single s.c. dose in healthy volunteers and repeated once weekly s.c. dosing in patients demonstrated the bioequipotency of idrabiotaparinux and idraparinux. These outcomes support the use of an idrabiotaparinux dose bioequipotent to an idraparinux dose in large clinical trials, and the possibility to substitute idrabiotaparinux for idraparinux for the treatment of VTE.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf

(available on request from the corresponding author). All authors are employed by Sanofi and may receive company stock as part of their incentive packages and declare no support from any other organizations for the submitted work; no financial relationships with any other organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.'

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