Population PKTE analysis of ocular and systemic data for intravitreal BI 764524 in patients with diabetic macular ischemia from the HORNBILL study

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Objective

- To develop a pharmacokinetic–target engagement (PKTE) model for BI 764524 based on data from the single rising dose (SRD) and multiple dose (MD) parts of the HORNBILL study to support selection of dosing regimens for the Phase IIb study

Poster summary

- **A model was developed to characterise the pharmacokinetics (PK) and target engagement (TE) of BI 764524 after intravitreal administration of BI 764524 in adult patients with diabetic macular ischemia (DMI) using data from the HORNBILL study**
- **The model provided an adequate description of the observed data and may be used to support selection of dosing regimens for the Phase IIb study**

What was known?

- Diabetic retinopathy is characterised by retinal non-perfusion (RNP), which, if located centrally, can lead to DMI[1]
- Binding of Semaphorin 3A (Sema3A) to its receptor causes angiogenesis dysregulation and increased retinal permeability, which may be linked to the development of RNP in patients with diabetic retinopathy[2–4]
- BI 764524, an anti-Sema3A antibody, showed good tolerability, safety and early pharmacodynamic data in patients with DMI in the HORNBILL Phase I/IIa study[5]

What is new?

- A PKTE model was developed for BI 764524 that consisted of three connected one-compartment target-mediated drug disposition (TMDD) submodels in the vitreous humour (VH), aqueous humour (AH) and serum

Methods

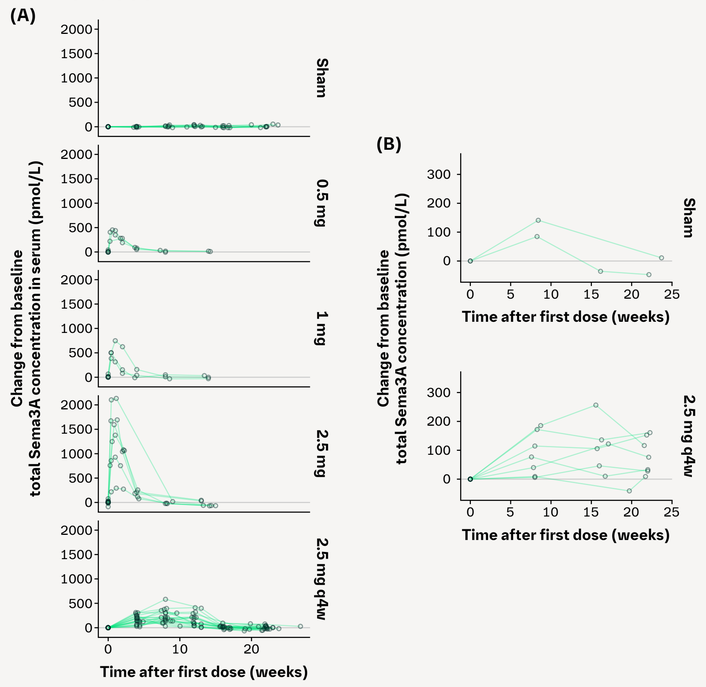
- HORNBILL was a two-part Phase I/IIa study of intravitreal BI 764524 in US and UK patients with DMI[5]
  - Part 1 was non-randomised, open-label and SRD (0.5, 1.0 or 2.5 mg)
  - Part 2 was randomised, masked, sham-controlled and MD (2.5 mg on Day 1 and Weeks 4 and 8)
- Optional AH samples were collected in the MD part (Day 1 and Weeks 8, 16 and 22) in addition to serum samples from the SRD part (Days 1 and 4 and Weeks 1, 2, 4, 8 and 14) and MD part (Day 1 and Weeks 4, 8, 12, 16 and 22)
- PKTE analysis was performed using NONMEM version 7.5
- The joint-sequential population PK parameters and data (PPPD) approach was used to consider the AH data preferentially before the serum data were included
- The overall PKTE model structure was based on the retina–VH–AH model for ranibizumab developed by Hutton-Smith *et al*[6]
- Potential covariate–parameter relationships were evaluated using the stepwise covariate model building procedure with adaptive scope reduction

Results

PKTE data

- The number of observations and number of participants in the PKTE analysis data set were, respectively:
  - 15 and 7 for the total BI 764524 concentrations in AH
  - 36 and 10 for the total Sema3A concentrations in AH
  - 214 and 32 for the total BI 764524 concentrations in serum
  - 260 and 42 for the total Sema3A concentrations in serum
- An increase in the total Sema3A concentration following the BI 764524 treatment was observed in both serum and AH (**Figure 1**), suggesting that the binding of BI 764524 to Sema3A protects Sema3A from its natural rapid elimination
  - This indicates drug-mediated target disposition and offers an indirect characterisation of TE

Figure 1. Individual observed change from baseline of total Sema3A concentration in serum (A) and AH (B) vs time after the first dose



Change in total Sema3A concentration from baseline in the serum (A) and in the AH (B) in participants in the PKTE analysis data set, stratified by treatment group. Data points from the same individual are connected by lines. Data are presented on a linear scale.
AH, aqueous humour; PKTE, pharmacokinetic-target engagement; q4w, every 4 weeks; Sema3A, Semaphorin 3A.

Final VH–AH–serum PKTE model

- Using the joint-sequential PPPD approach, a model was first developed based on data from AH only, and the estimated parameters were fixed when the final PKTE model was developed based on all data
  - The first-order elimination rate constant of BI 764524 from the VH to the AH ($k_{vit\text{-}aq,D}$) was 0.153 day^{-1} with a relative standard error (RSE) of 40.7%. The first-order elimination rate constant of Sema3A from the VH to the AH ($k_{vit\text{-}aq,S}$) was 0.788 day^{-1} with an RSE of 32.2%
  - The Sema3A concentration at baseline in the AH ($S_{0_{aq}}$) was 177 pmol/L with an RSE of 10.5%. The Sema3A concentration at baseline in the serum ($S_{0_{sys}}$) was 248 pmol/L with an RSE of 8.41% for the SRD part and 181 pmol/L with an RSE of 6.36 % for the MD part
- The final PKTE model consisted of three connected one-compartment TMDD submodels describing the PK and TE of BI 764524 in the VH, AH and serum (**Figure 2**)

Figure 2. Schematic of the final VH–AH–serum PKTE model for BI 764524

Solid arrows represent mass balance relationships and rectangles represent compartments. Variables written in blue are estimated parameters. Variables written in green are parameters fixed to a value greater than zero, and variables written in red are parameters that are not considered and fixed to zero. Variables written in yellow are derived variables based on parameter values: $S_{0_{vit}} = S_{0_{aq}} \cdot k_{aq\text{-}sys,S}/k_{vit\text{-}aq,S}$; $R_{in,vit} = S_{0_{vit}} \cdot (k_{deg,vit} + k_{vit\text{-}aq,S})$; $R_{in,sys} = S_{0_{sys}} \cdot k_{deg,sys} - S_{0_{aq}} \cdot k_{aq\text{-}sys,S}$.
AH, aqueous humour; D, free BI 764524; DS, BI 764524–Sema3A complex; $k_{aq\text{-}sys,D}$, first-order elimination rate constant of BI 764524 from the AH to the serum; $k_{aq\text{-}sys,S}$, first-order elimination rate constant of Sema3A from the AH to the serum; $k_{deg,aq}$, first-order Sema3A degradation rate constant in the AH; $k_{deg,sys}$, first-order Sema3A degradation rate constant in the serum; $k_{deg,vit}$, first-order Sema3A degradation rate constant in the VH; k_{off}, first-order dissociation rate constant for BI 764524-Sema3A complex; k_{on}, second-order association rate constant for BI 764524 and Sema3A; $k_{vit\text{–}aq,D}$, first-order elimination rate constant of BI 764524 from the VH to the AH; $k_{vit\text{–}aq,S}$, first-order elimination rate constant of Sema3A from the VH to the AH; $k_{vit,D}$, first-order elimination rate constant of BI 764524 in the VH; $k_{vit,S}$, first-order elimination rate constant of BI 764524-Sema3A complex(es) in the VH; PKTE, pharmacokinetic-target engagement; $R_{in,aq}$, zero-order Sema3A production rate in the AH; $R_{in,sys}$, zero-order Sema3A production rate in the serum; $R_{in,vit}$, zero-order Sema3A production rate in the VH; S, free Sema3A; $S_{0_{aq}}$, Sema3A concentration at baseline in the AH; $S_{0_{sys}}$, Sema3A concentration at baseline in the serum; $S_{0_{vit}}$, Sema3A concentration at baseline in the VH; SDS, Sema3A-BI 764524-Sema3A complex; $V_{aq,D}$, volume of distribution of BI 764524 in the AH; $V_{aq,S}$, volume of distribution of Sema3A in the AH; VH, vitreous humour; $V_{sys,D}$, volume of distribution of BI 764524 in the serum; $V_{sys,S}$, volume of distribution of Sema3A in the serum; V_{vit}, volume of distribution of BI 764524 and Sema3A in the VH.

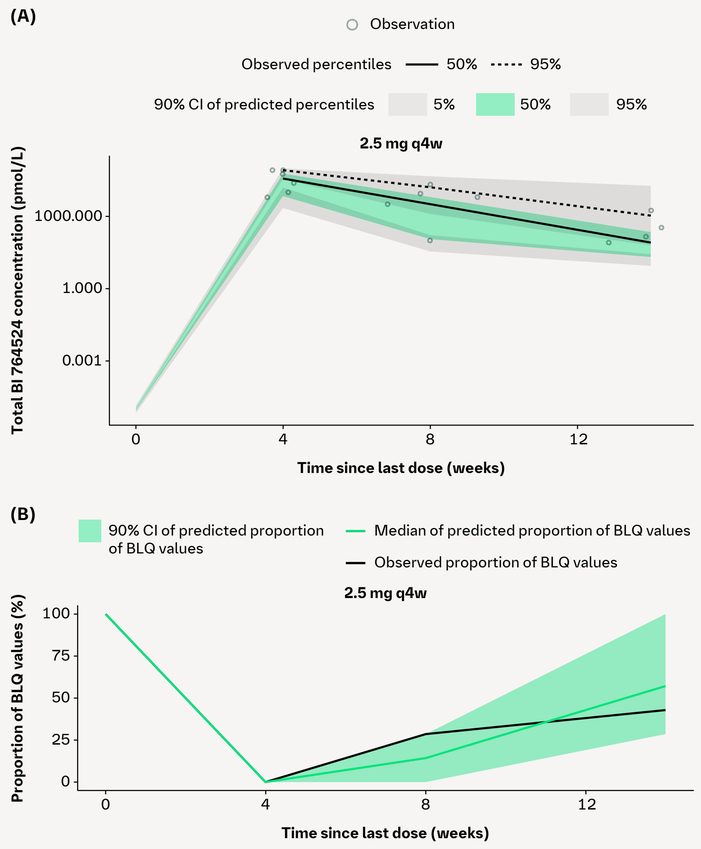
Results (cont.)

- The model described:
  - The association and disassociation of BI 764524 with one or two Sema3A molecules in the VH, AH and serum
  - The elimination of free BI 764524 (D), free Sema3A (S), BI 764524–Sema3A complex (DS) and Sema3A–BI 764524–Sema3A complex (SDS) from VH to AH and from AH to serum
- Key assumptions in the final PKTE model were:
  - The turnover of all analytes (D, S, DS, SDS) in AH is negligible, because the residence time in VH is known to be longer than the residence time in AH
  - Only 1:1 (DS) and 2:1 (SDS) bindings are possible
  - Binding of one Sema3A to BI 764524 does not alter the binding affinity of the second Sema3A
  - Volume of distribution of BI 764524 and Sema3A in the VH (V_{vit}) equals 4.85 mL
  - Second-order association rate constant for BI 764524 and Sema3A (k_{on}) equals 0.240 $(pmol/L \cdot day)^{-1}$
  - First-order dissociation rate constant for DS (k_{off}) equals 6.96 day^{-1}
- The stepwise covariate model was performed for the base model developed based on all data, and none of the parameter–covariate relationships were identified to be significant

Model diagnostics

- Visual predictive checks (VPCs) were generated using the final PKTE model. One key VPC, shown in **Figure 3**, indicated that the performance of the model was satisfactory in predicting longitudinal total BI 764524 concentrations and the proportion below the limit of quantification in AH

Figure 3. VPC of total BI 764524 concentrations (A) and percent BLQ (B) in the AH vs time since last dose using the final PKTE model



Data are shown for the MD part of the study in the PKTE analysis data set. Time points associated with BLQ observations were included in the VPC. BLQ values were censored for the observed data and are plotted only for the simulated data.
AH, aqueous humour; BLQ, below limit of quantification; CI, confidence interval; MD, multiple dose; PKTE, pharmacokinetic-target engagement; q4w, every 4 weeks; VPC, visual predictive check.

Study limitations

- The joint-sequential PPPD approach used precluded covariate analysis for the AH PKTE model, and key parameters (i.e. $k_{vit\text{–}aq,D}$ and $k_{vit\text{–}aq,S}$) were estimated using limited AH data; therefore, any inference drawn based on the final PKTE model developed using AH data only should be interpreted with caution
- The small size and limited number of observations overall is a limitation of this analysis

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Disclosures

Qing Xi Ooi reports consultancy for Boehringer Ingelheim and employment with Pharmetheus. **Anyue Yin** reports employment with Pharmetheus. **Bartlomiej Krawczyk**, **Martin Gliem**, **Khaled Nassar**, **Stefan Wölke**, **Gudrun Simons**, **Michel Wagner** and **Ronald Niebecker** report employment with Boehringer Ingelheim. **David Brown** reports consultancy for AffaMed, Alcon, Alexion, Allergan, Amgen, Annexon, Apellis, Astellas, Bayer, BIRC, Boehringer Ingelheim, Chengdu Kanghong, Clearside, Eyebiotech, EyePoint, Gemini, Genentech, Graybug Vision, Gyroscope, Heidelberg, i-Lumen, IONIS, Kodiak, LumiThera, MeiraGTx, Mylan, NGM, Novartis, Ocular Therapeutix, Ocuphire, OcuTerra, Opthea, Optos, Outlook Therapeutics, Oxular, Regeneron, RegenXBio, Rezolute, Roche, SamChunDang, Samsung, Sandoz, Santen, SciFluor, Senju, Shanghai Henlius, Stealth, Taiwan Liposome Company, ThromboGenics, Xbrane and Zeiss; and financial support from Adverum, Clearside, Ocuphire and Optos. **Chirag Jhaveri** reports consultancy for Iveric Bio and Regeneron; financial support from Boehringer Ingelheim, ONL Therapeutics, Novartis, RegenXBio, Gyroscope Therapeutics, Kodiak Sciences, Iveric Bio and Genentech; and receipt of gifts, honoraria, travel reimbursement, patent royalties, or any other financial compensation in any amount from Iveric Bio and Regeneron. **Victor H. Gonzalez** has nothing to disclose. **Charles Wykoff** reports consultancy for 4DMT, AbbVie, ADARx, Adverum, Aerie, Alcon, Alimera, Alkeus, Allgenesis, AMC Sciences, Annexon, Apellis, Asclepix, Aviceda, Bausch + Lomb, Bayer, BioCryst, Bionic Vision, Boehringer Ingelheim, Chengdu Kanghong, Curacle, Emmecell, Eyebiotech, EyePoint, Frontera, Genentech, InGel, IVERIC Bio, Janssen, Kiora, Kodiak, Kowa, Merck, Merit, Nanoscope, Neurotech, NGM, Novartis, Oak Bay Bio, Ocular Therapeutix, Ocuphire, Ocuterra, Ollin, ONL, Opthea, Osanni, Oxular, Palatin, Perceive Bio, Perfuse, Ray, RecensMedical, Regeneron, RegenXBio, RetinAl, Roche, Sandoz, Sanofi, Santen, SciNeuro, Skyline, Stealth, Suzhou Raymon, Sylentis, TCG Crossover, Thea, Therini, VH401 (Valo), Visgenx and Zeiss; financial support from 4DMT, AbbVie, Adverum, AffaMed, Alexion, Alimera, Allgenesis, Amgen, Annexin, Annexon, Apellis, Ascidian, Asclepix, Aviceda, Avirmax, Bayer, Beacon (formerly AGTC), Boehringer Ingelheim, Chengdu Origen, Clearside, Curacle, Eluminex, Eyebiotech, EyePoint, Genentech, Gyroscope, IONIS, IVERIC bio, Janssen, Kalaris, Kodiak, Kyoto DDD, Kyowa Kirin, Nanoscope, Neurotech, NGM, Novartis, Ocugen, Ocular Therapeutix, Oculis, Ocuphire, OcuTerra, Opthea, Outlook Therapeutics, Oxular, Oxurion, Oyster Point, Perceive Bio, Privunt, Pykus, Regenxbio, RegenXBio, Rezolute, Roche, Shanghai Henlius, Stealth, Skyline and Valo; and personal financial interest in InGel, ONL, Osanni, Panther, PolyPhotonix, RecensMedical, TissueGen, Visgenx and Vitranu. **Sobha Sivaprasad** reports consultancy for AbbVie, Amgen, Apellis, Bayer, Biogen, Boehringer Ingelheim, Novartis, Eyebiotech, Eyepoint Pharmaceuticals, Janssen Pharmaceuticals, Novo Nordisk, Optos, Ocular Therapeutix, Kriya Therapeutics, OcuTerra, Roche, Stealth Biotherapeutics and Sanofi; financial support from AbbVie, Bayer, Boehringer Ingelheim, Novartis, Janssen Pharmaceuticals and Roche; and receipt of gifts, honoraria, travel reimbursement, patent royalties or any other financial compensation in any amount from Bayer and Roche. **Quan Dong Nguyen** reports consultancy for Boehringer Ingelheim, Genentech, Regeneron and Rezolute; and lectures, presentations, speaker bureaus or educational events for Acelyrin, Belite Bio, Boehringer Ingelheim, Oculis and Privunt.

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The drug discussed in this poster is not currently approved for use.

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