

Physicochemical stability of the bevacizumab biosimilar, ABP 215, after preparation and storage in intravenous bags

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Study Objectives: To evaluate extended in-use stability of bevacizumab biosimilar, ABP 215, after dilution into intravenous bags, extended storage, and simulated infusion to enable advanced preparation and storage.

Methods: Two lots of ABP 215 were diluted to high- (16.5 mg/mL) and low- (1.4 mg/mL) dose concentrations in two types of intravenous bag under ambient light conditions. Dosed intravenous bags were stored at 2°C–8°C for 35 days, followed by 30°C for 2 days, and each bag was infused on Day 37. Analysis of purity and physicochemical stability was performed using size-exclusion high-performance liquid chromatography (SE-HPLC), cation-exchange high-performance liquid chromatography (CEX-HPLC), reduced capillary electrophoresis-sodium dodecyl sulphate (rCE-SDS), subvisible particle detection assays, visual inspection, and by measuring protein concentration and potency.

Results: No meaningful changes were seen in ABP 215 purity when analysed by SE-HPLC, CEX-HPLC and rCE-SDS following dilution, storage and infusion of two lots, bags, and doses. Protein concentration remained consistent throughout the study for all samples and no significant loss in potency was detected. No potentially proteinaceous particles or increases in subvisible particles were observed.

Discussion: This study investigated the in-use stability of ABP 215 following dilution, extended storage, and infusion, that represent worst-case handling conditions. ABP 215 exhibited consistent product quality and activity, with no significant degradation observed under the conditions tested.

Conclusion: ABP 215 retains physicochemical stability after dilution over the recommended dosing concentrations, extended storage, and simulated infusion. This supports the advance preparation and storage of ABP 215 in intravenous bags for infusion.

Keywords: ABP 215, administration, bevacizumab, biosimilar, infusion, stability

Introduction/Study objectives

Bevacizumab (Avastin®) is a humanized monoclonal antibody targeting vascular endothelial growth factor A (VEGF-A) [1]. It binds to VEGF-A, preventing it from interacting with endothelial cell surface receptors, thus affecting the formation of new blood vessels and endothelial cell proliferation [1]. Bevacizumab was approved in the US in 2004 [2], and EU in 2005 [3] for the treatment of a variety of advanced solid tumours including: colorectal cancer, non-small cell lung cancer (NSCLC), renal cell cancer, epithelial ovarian, fallopian tube or primary peritoneal cancer, cervical cancer, recurrent glioblastoma (US only), and breast cancer (EU only) [4, 5].

ABP 215 (MVASI™), a bevacizumab biosimilar, was licensed for use in the US in September 2017 and was the first approved biosimilar to bevacizumab [6, 7]. Subsequently, approval was granted for use of ABP 215 in the EU in January 2018 [8]. ABP 215 is approved in combination with other agents for the treatment of metastatic colorectal cancer; unresectable, locally advanced, recurrent or metastatic non-squamous NSCLC; metastatic renal cell carcinoma; and persistent, recurrent, or metastatic cervical cancer [9, 10]. Similar to reference bevacizumab, ABP 215 is also approved in the US for the treatment of recurrent glioblastoma [9]. In the EU, it has additional indications, in combination with chemotherapy, for metastatic breast cancer; advanced or recurrent epithelial ovarian, fallopian tube and primary peritoneal cancer; and unresectable, advanced, recurrent or metastatic NSCLC other than that of predominantly squamous cell histology [10].

The structural and functional similarity, including, for example, primary and higher order structure, biological activity and thermal forced degradation of ABP 215 compared with reference bevacizumab (from both US and EU sources), have previously been demonstrated [11]. The pharmacokinetic (PK) profile of ABP 215 and bevacizumab were initially demonstrated to be similar during phase I clinical studies performed in healthy males [12, 13]. The clinical efficacy, safety, PKs and immunogenicity of ABP 215 and bevacizumab were subsequently confirmed to be similar in a phase III study in patients with advanced NSCLC [14].

ABP 215 is supplied commercially as a liquid drug product in single-use vials at a concentration of 25 mg/mL. It is administered by intravenous (IV) infusion after dilution in a pre-filled infusion bag. The administered dose of ABP 215 is weight-based and ranges from 5 mg/kg to 15 mg/kg, depending on the indication [9, 10]. The recommended final IV bag concentration range is 1.4 mg/mL to 16.5 mg/mL [10].

In Europe and other regions, IV bags may be routinely prepared at centralized hospital pharmacy locations using aseptic techniques and then distributed to clinical oncology sites for patient administration. The practice of dose banding allows for the advance preparation of specific doses of drugs with sufficient stability [15, 16]. Standardization of chemotherapy doses through dose banding has been shown to decrease drug spending [17] and improve overall safety in drug ordering [18]. Other

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potential benefits include a reduction in medication preparation errors, patient waiting times and drug wastage [19]. Dose banding of bevacizumab currently takes place in hospital pharmacies in Europe [20, 21] and the US [18]. Extended physicochemical stability of ABP 215 under in-use conditions would enable flexibility in administration, by ensuring efficacy during handling conditions not covered by the standard stability studies performed previously [11].

Here we evaluate the extended storage (at 2°C–8°C for 35 days and then at 30°C for 48 hours) and simulated infusion of ABP 215 in IV bags. The extended in-use chemical and physical stability of ABP 215 in IV bags was evaluated for two different drug product lots, diluted at two different protein concentrations.

Methods

IV bag preparation and sample collection

Two different IV bag models were used in the study, B Braun partial additive bag (PAB) S8004-5264 (polyolefin, free of latex, polyvinyl chloride (PVC) and DEHP (bis[2-ethylhexyl] phthalate)) and Baxter Viaflex bag 2B1302 (PVC), and are referred to throughout as PAB and PVC, respectively, see Figure 1. The PAB bags are used pre-filled and contain 109 ± 4 mL of saline (0.9% sodium chloride) at pH 5.5; the PVC bags are used pre-filled and contain 110 ± 5 mL of saline (0.9% sodium chloride) at pH 5. ABP 215 is supplied at a concentration of 25 mg/mL in 51 mM sodium phosphate, 60 mg/mL α,α-trehalose dihydrate, 0.040% w/v polysorbate 20 at pH 6.2. Two drug product lots were tested in this study, with both lots being approximately 18 months old at study end, see Figure 1.

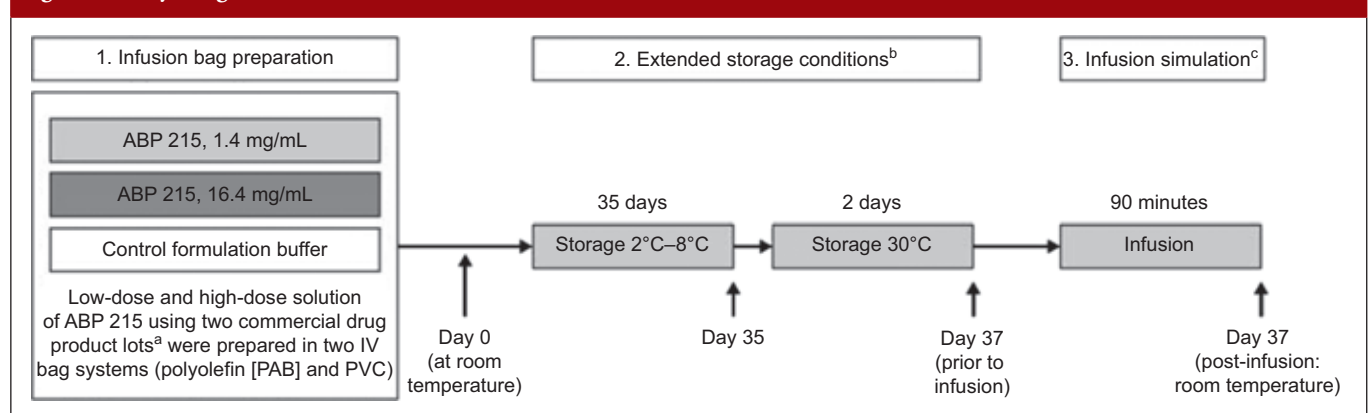
ABP 215 was diluted into 100 mL saline IV bags, which resulted in the final concentration targets of 1.4 mg/mL (low dose) and 16.5 mg/mL (high dose), for both drug product lots. An

additional study arm IV bag was prepared containing ABP 215 formulation buffer (preparation simulated the high-dose bag dosing) and was used as a control for the visual inspection and high-accuracy light obscuration (HIAC) analyses.

The prepared IV bags were stored at 2°C–8°C for 35 days, followed by storage at 30°C for 2 days (to represent the worst-case storage conditions at the patient administration site). IV infusion was simulated for each bag on Day 37. Infusion was set to simulate a nominal 100 mL bag volume infusion over 90 minutes (the slowest recommended clinical infusion duration for the worst-case product contact assessment within the infusion system), with a resulting infusion rate of 67 mL/hour. The infused contents were collected in a sterile polyethylene terephthalate copolyester, glycol modified bottle. Preparation of the IV bags, sampling throughout the study, and infusion took place at facility room temperature under ambient light conditions, in line with clinical practice.

Samples were collected at the following timepoints, see Figure 1: T = 0, after IV bag dosing (at facility room temperature), Days 14, 30 and 35 (during storage at 2°C–8°C), Days 36 and 37 (during storage at 30°C), and T = final (Day 37) after infusion (at facility room temperature). The samples collected on Days 14 and 30 (2°C–8°C) and Day 36 (30°C) were retention samples for size-exclusion high-performance liquid chromatography (SE-HPLC), cation-exchange high-performance liquid chromatography (CEX-HPLC), reduced capillary electrophoresis-sodium dodecyl sulphate (rCE-SDS) and potency analysis, and were collected for testing only if required to assess observed potential trends. Due to the inherent variability of HIAC data, this assay was performed on Day 14 as an additional confirmatory data point for each study arm. In general, samples were collected into cryo vials and frozen prior to analysis, with visual inspection and HIAC samples collected into 20 cc clear glass vials and analysed on the same day.

Figure 1: Study design



Note: Additional testing on retention samples (size-exclusion high-performance liquid chromatography, cation-exchange high-performance liquid chromatography, reduced capillary electrophoresis-sodium dodecyl sulphate, and/or potency analysis) was going to be performed on Days 14 and 30 (2°C–8°C) and Day 36 (30°C) if needed to assess observed potential data trends.

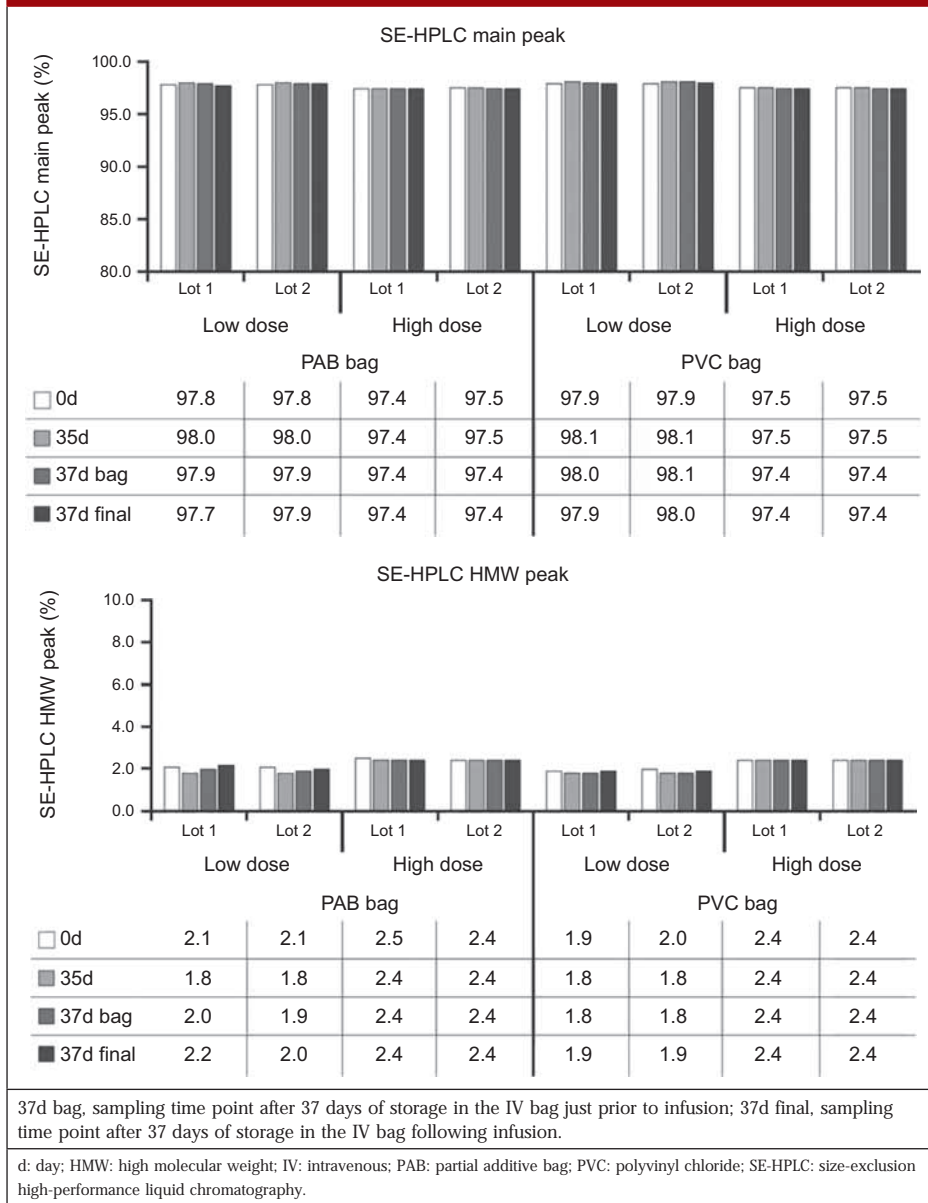
^aLot 1: 100 mg stock keeping unit, 18 months old at end of study; Lot 2: 400 mg stock keeping unit, 18 months old at end of study.

^bThe bags were stored at 2°C–8°C for 35 days, followed by 2 days at 30°C to simulate worst-case storage conditions at the patient administration site.

^cSimulation involved a 100 mL bag volume infusion (infusion rate was 67 mL/hour) over 90 minutes using an infusion pump to collect pre- and post-infusion samples.

PAB: partial additive bag; PVC: polyvinyl chloride.

Figure 2: SE-HPLC main and HMW peak results



with a flow rate of 0.5 mL/min using an HPLC system running Empower software. Ultraviolet (UV) absorbance at 280 nm was used to monitor the analytes. The peak area of each species was determined as a percentage of the total peak area to evaluate the purity of the sample [11]. During the study, high molecular weight (HMW) species were resolved from the main peak.

CEX-HPLC was used to assess the charge heterogeneity of ABP 215. Charged variants within the ABP 215 samples were separated on a Dionex ProPac WCX-10 analytical column using a Waters HPLC system. Briefly, 50 µg of each sample was injected onto the column and eluted with a gradient from 20 mM sodium phosphate, pH 6.3 to 20 mM sodium phosphate, 500 M sodium chloride, pH 6.3 using an HPLC system running Empower software. Fractions were eluted using a salt gradient and monitored by UV absorbance at 280 nm. To evaluate purity of the sample, the peak area of each separately eluting charge variant group (main, basic and acidic peaks) was determined as a percentage of the total peak area [11].

The relative amount of size variants based on protein hydrodynamic size, including heavy chain (HC) and light chain (LC) variants, was assessed using rCE-SDS, an orthogonal molecular sizing method. Denatured protein size variants were separated under reduced conditions. SDS and β-mercaptoethanol (reduction buffer) were used to denature and reduce samples of ABP 215, respectively. Samples were incubated in the reducing buffer at 70°C for 10 minutes. Denatured samples were then injected onto a 57 cm, 50 µm internal diameter Beckman Coulter bare, fused silica capillary. An electric field was applied using a Beckman Coulter capillary electrophoresis system, which resulted in the separation of samples based on hydrodynamic size, with the time taken to migrate for smaller size proteins inversely related to their overall size. UV absorbance at 220 nm was used to monitor analytes, and the purity of the sample was evaluated by determining the peak area of each species as a percentage of the total peak area [11].

Protein concentration and recovery

The amount of protein loss due to surface contact binding was assessed by measuring the protein concentration. The protein concentration in the solution was determined by UV absorbance using variable pathlength technology [11]. Protein recovery was calculated as the ratio of the final 37-day post-infusion

Assessment of physical and chemical stability of ABP 215

The following were methods chosen to assess ABP 215 as they are indicative of drug product stability and pharmaceutical quality. The purity assays, potency and subvisible particle testing are sensitive to higher order structure changes, conformational changes, biological activity and aggregation.

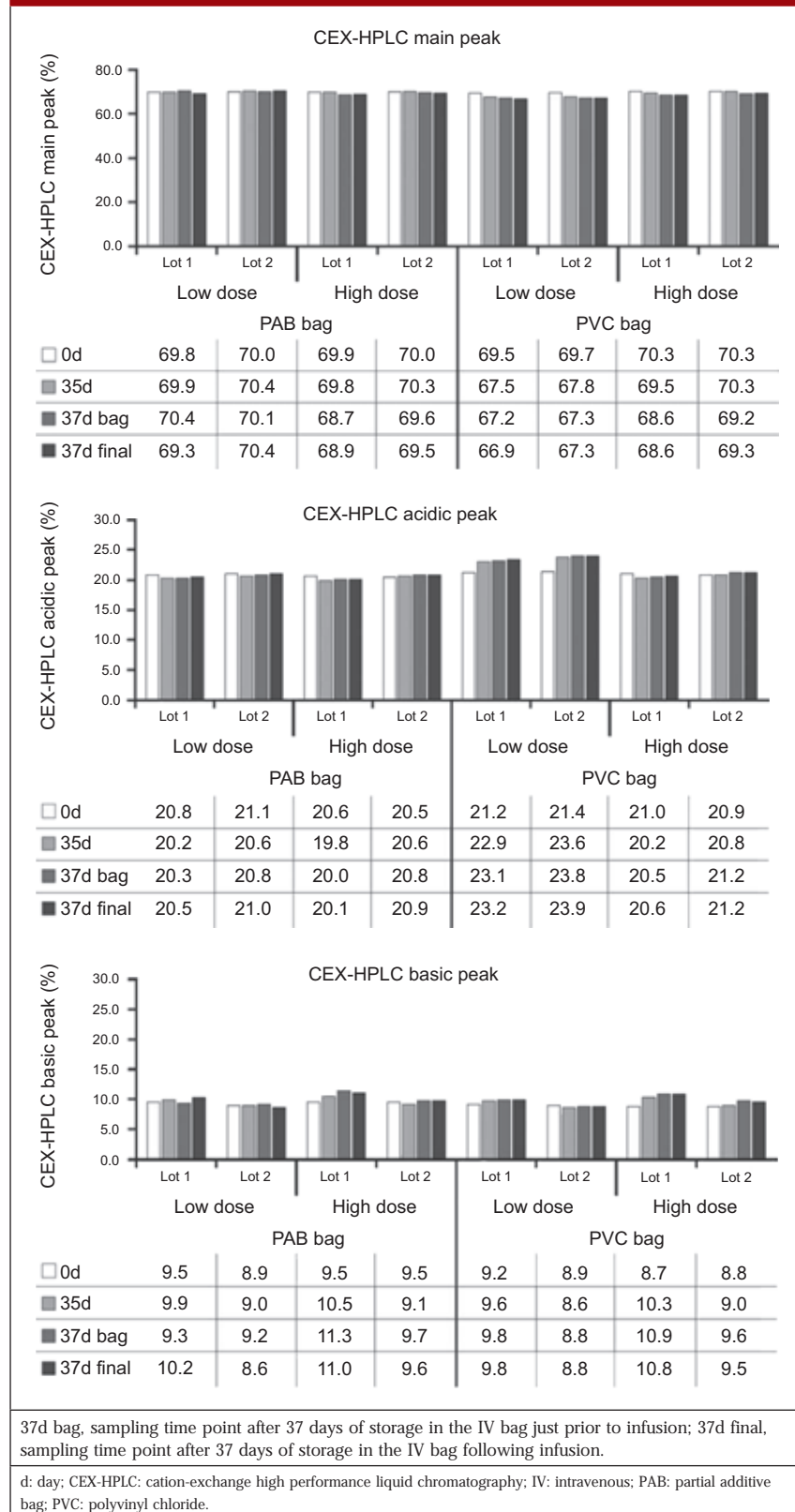
Purity

SE-HPLC was used to evaluate the size heterogeneity of native or non-denatured ABP 215. SE-HPLC measurements were made on an Agilent HPLC system using a Tosoh Bioscience TSK-GEL G3000SWXL column. Briefly, 300 µg of each sample was injected onto the column and eluted isocratically over 35 minutes with 100 mM sodium phosphate, 250 mM sodium chloride, pH 6.8,

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Figure 3: CEX-HPLC main peak (top graph), acidic peak (middle graph) and basic peak (bottom graph) results



(T = final) protein concentration over the initial time 0 (T = 0) measurement and was expressed as a percentage.

Potency

The biological activity of ABP 215 was evaluated using a quantitative, cell-based proliferation inhibition bioassay. The dose-dependent inhibitory effects of ABP 215 on the proliferation of vascular endothelial growth factor receptor-expressing human umbilical vein endothelial cells (HUVEC) were measured. HUVEC express both VEGF-R1 and VEGF-R2 receptors, which interact with and bind VEGF resulting in endothelial cell proliferation. HUVEC were incubated with a constant concentration of VEGF and varying concentrations of ABP 215 reference standard, control and test samples. Following a timed incubation, an adenosine triphosphate (ATP)-specific luminescent reagent was added to the assay plates, resulting in cell lysis and generation of luminescence signal that was proportional to the amount of ATP present. The quantity of ATP was directly proportional to the number of viable cells and inversely proportional to the ABP 215 concentration in tested samples. The sample response relative to the reference standard was determined using a 4-parameter logistic model fit. Results are reportable by meeting assay acceptance criteria and sample acceptance criteria for parallelism between test samples and the reference standard curve. Results were reported as per cent relative potency values [11].

Visual inspection and subvisible particle count

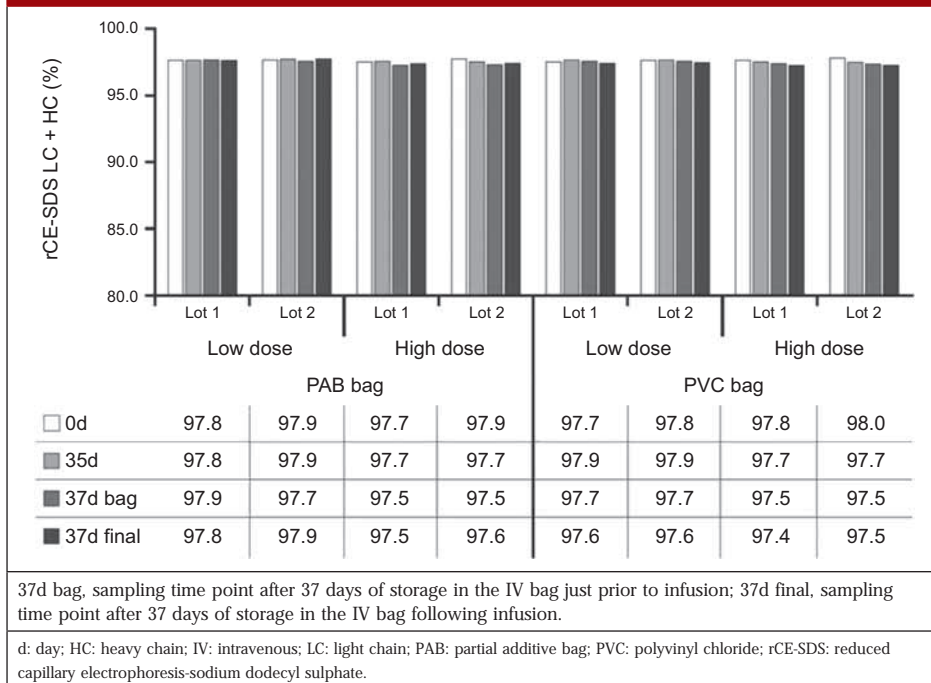
The presence and any trends in potentially proteinaceous particles were evaluated by visual inspection, and HIAC was used to assess subvisible particle trends. A HIAC liquid particle counting system (HACH 9703+) equipped with a light obscuration sensor was used to assess the presence of subvisible particles [11]. The average and standard deviation of the subvisible particles in the $\geq 10 \mu\text{m}$ and $\geq 25 \mu\text{m}$ range were determined. Results were reported as the average of three measurements with the standard deviation indicated on the graph for each result.

Results

Purity

For all three purity assays (SE-HPLC, CEX-HPLC and rCE-SDS), no meaningful changes were seen. SE-HPLC analysis of low- and high-dose ABP 215 from both lots and types of IV bag demonstrated that the percentage of main peak ranged between 97.4% and 98.1%. The HMW peak values for all lots, bags and doses ranged

Figure 4: rCE-SDS heavy and light chain results



low- and high-dose ABP 215 from both lots and types of IV bag ranged between 66.9% and 70.4%. The acidic and basic peak results for both doses and lots in each IV bag model, ranged between 19.8% and 23.9%, and 8.6% and 11.3%, respectively, see Figure 3. On rCE-SDS, the percentage of heavy chain and light chain in all samples ranged between 97.4% and 98.0%, see Figure 4.

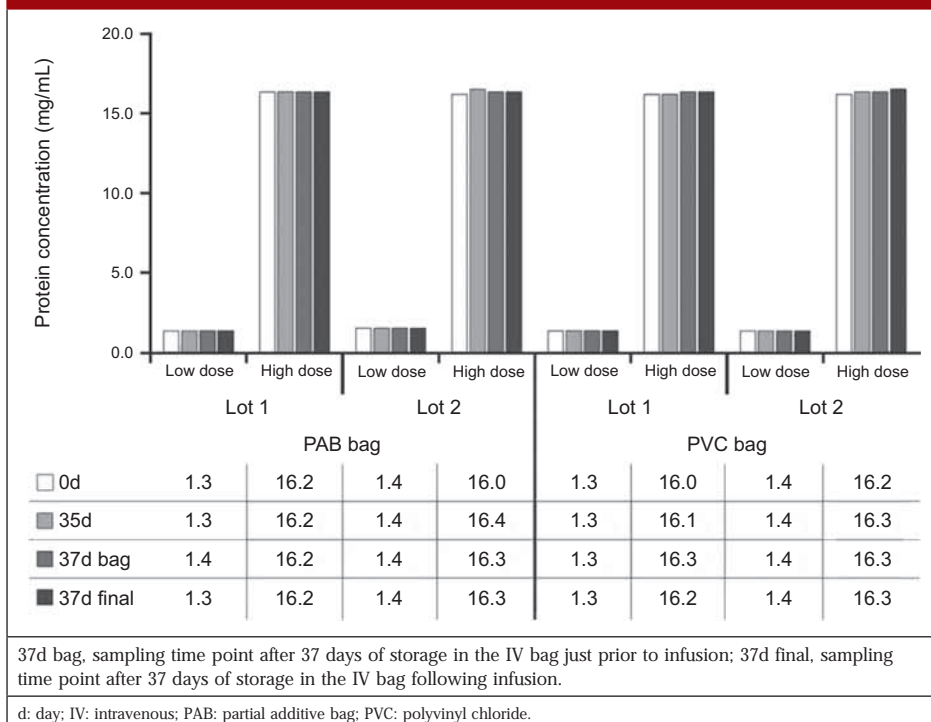
Protein concentration and recovery

No meaningful changes were observed in protein concentration for either ABP 215 lots or doses throughout the duration of exposure to the IV bags and infusion system materials, see Figure 5. For the low and high doses, ABP 215 concentrations ranged from 1.3 mg/mL to 1.4 mg/mL, and 16.0 mg/mL to 16.4 mg/mL, respectively. Across samples, protein recovery ranged from 99.4% to 101.7%.

Potency

In the proliferation inhibition assay, there were no practically significant losses in potency over the study duration, see Figure 6. The tested samples had relative potencies between 83% and 120%.

Figure 5: Protein concentration results



Visual inspection and subvisible particle count

Throughout the study no potentially proteinaceous particles were observed by visual inspection. For both types of IV bag, both ABP 215 doses and lots, and the control formulation buffer samples, there were no consistent trends over time seen in the subvisible particle analysis, see Appendix Figure 1. In the ABP 215 samples, particle counts/mL ranged between 9 and 64 for particles $\geq 10 \mu\text{m}$, and between 0 and 4 for particles $\geq 25 \mu\text{m}$.

Discussion

This study investigated the in-use stability of ABP 215, a bevacizumab biosimilar, after dilution into two types of IV bag. This type of study builds on the standard stability studies conducted to fulfil regulatory licensing requirements and more closely reflects the conditions encountered in a real-world, hospital pharmacy setting.

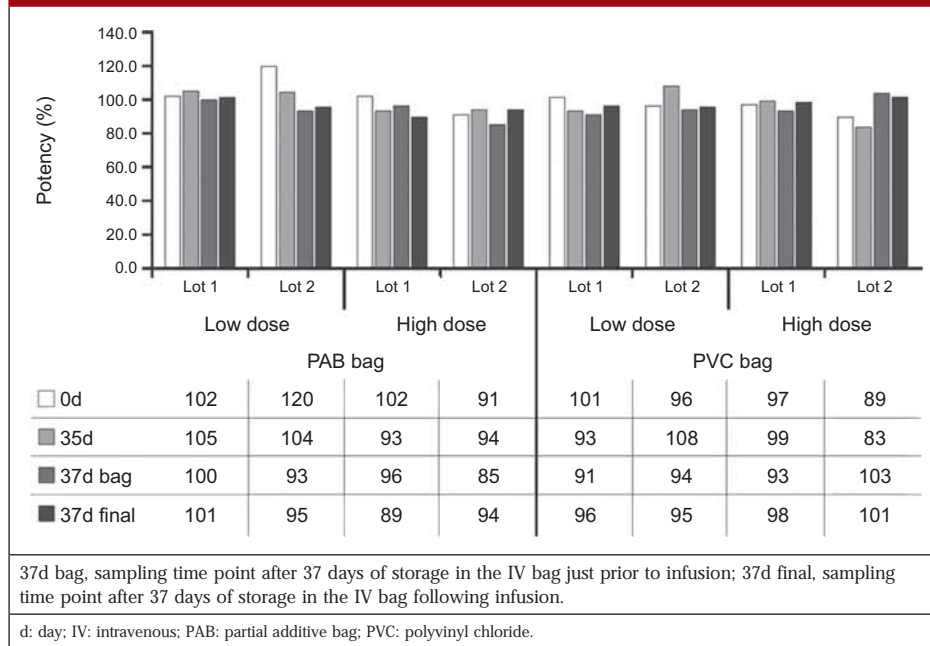
between 1.8% and 2.5%. For SE-HPLC, there were lower levels of HMW species in the low-dose samples compared with the high-dose samples, with corresponding changes seen in the main peak, see Figure 2. The main peak results from the CEX-HPLC analysis of

The effect of extended storage and simulated infusion on the physical and chemical stability of ABP 215 was assessed for two separate ABP 215 lots, diluted to two different protein concentrations. The high (16.5 mg/mL) and low (1.4 mg/mL) ABP 215

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Figure 6: Potency results: proliferation inhibition bioassay



doses used here represent the concentration limits used in clinical practice. The IV bags containing ABP 215 were prepared in ambient light conditions, stored at 2°C–8°C for 35 days and 30°C for an additional 2 days, and finally infused over 90 minutes, at an infusion rate of 67 mL/hour. This is the slowest recommended infusion rate, thereby providing worst-case duration of product contact with the infusion system. Under these dilution, storage and infusion conditions, including worst-case handling conditions, ABP 215 demonstrated consistent product quality and activity across a robust set of stability-indicating assays, including size and charge variants, fragmentation, particulate formation, protein concentration, and potency. No significant ABP 215 degradation was observed across the tested conditions. Although we acknowledge that higher order structural determination is important in the development of any pharmaceutical product [22], we did not use spectroscopy-based techniques to assess the impact of extended storage and infusion on the secondary or tertiary structure of ABP 215 in this study. However, the combination of chromatographic and biological techniques used provide a reliable indication of the structural integrity of the molecule. Furthermore, the higher order structure of ABP 215 compared with reference bevacizumab has previously been reported using Fourier-transform infrared spectroscopy and UV circular dichroism, while the thermal stability of the two products was previously compared using differential scanning calorimetry [11]. These results demonstrate that ABP 215 is physically and chemically stable in 0.9% saline diluent for IV administration for up to 35 days at 2°C–8°C, followed by 2 days storage at 30°C, and is compatible with commonly used IV bags and tubing assembly materials. Analysis of ABP 215 by SE-HPLC indicated that the levels of HMW species present in the low-dose samples (1.4 mg/mL) were lower than in the high-dose samples (16.5 mg/mL). This is due to a reduction of the reversible self-association of ABP 215, and thus a lower level of HMW species, in the diluted low-

dose samples and so does not reflect a difference in stability of ABP 215 drug product when diluted at different concentrations.

The ABP 215 drug product lots utilized in this study were both commercial lots manufactured using two different commercial drug product lots. The drug product lots were approximately 18 months old when the study was initiated. A potential limitation of this study was that non-major degradation pathways were not included.

These data support the advance preparation of ABP 215 in IV bags at concentrations of 1.4 mg/mL–16.5 mg/mL and storage at 2°C–8°C for up to 35 days, followed by storage at room temperature (up to 30°C) for up to 2 days. This allows for ABP 215 IV bags to be prepared in a central pharmacy and stored refrigerated until needed, and then transported at room temperature to clinical oncology sites

for administration to the patient. This flexibility could benefit pharmacists and nurses, allow for use of dose-banding, and potentially reduce drug wastage. It might also benefit patients by reducing waiting times and providing them with the possibility of receiving ABP 215 treatment in satellite clinics closer to their homes.

To the best of our knowledge, this is the first study to investigate the extended in-use stability of a bevacizumab biosimilar (ABP 215). The originator product, bevacizumab, has been shown to be stable after dilution when stored at 2°C–8°C for 30 days, followed by 48 hours at 2°C–30°C [4]. The physicochemical properties of another bevacizumab biosimilar were also shown to be similar to reference bevacizumab following dilution and storage at 2°C–8°C for 24 hours [23]. Extended stability studies have also been performed on biosimilars of rituximab, infliximab and trastuzumab [24–27]. Biosimilars to rituximab and infliximab demonstrated stability when diluted and stored at 2°C–8°C for 14 or 30 days, followed by 24 hours at room temperature, and when stored at 4°C and 25°C for 7 days, respectively [24, 27]. The trastuzumab biosimilars, CT-P6 and ABP 980, exhibited stability following dilution and storage at 2°C–8°C for 1 month, followed by 24 hours at room temperature, and storage at 2°C–8°C or 30°C for 5 weeks, followed by 48 hours at 30°C, respectively [25, 26].

Conclusion

Using a range of stability-indicating assays, this study showed that ABP 215 was physically and chemically stable when diluted to both low- and high-dose concentrations for IV administration, stored for up 35 days at 2°C–8°C, followed by 2 days at 30°C, and subsequent worst-case infusion duration. These in-use stability data build on the available stability data for the originator product, bevacizumab [4] and for other bevacizumab biosimilars

[23], and support the feasibility of the preparation and distribution of ABP 215 from centralized hospital pharmacies.

For patients

Drugs administered intravenously, such as cancer treatments, are prepared in an infusion bag at the specific dose needed by the patient. The quality of the drug needs to be maintained if these prepared infusion bags are to be stored for a period of time prior to use. This study tested whether the stability of the cancer drug MVASI™ (also called ABP 215, a drug that is essentially the same as Avastin® [bevacizumab]) is affected following dilution and storage for a length of time and at a range of temperatures similar to those used during real-world treatment. The results of this study show that the quality and stability of both high and low doses of MVASI™ were maintained after being stored in two different types of infusion bag in the refrigerator for around a month, followed by storage at room temperature for 2 days, and finally following simulated infusion. This means that specific doses of MVASI™ can be prepared in advance in hospital pharmacies and stored in a refrigerator as needed before distribution to the clinic ready for administration to the patient. This advance preparation could save the hospital time and money and reduce patient waiting times.

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Prior presentations

An abstract reporting these data was originally submitted to the 25th Congress of the European Association of Hospital Pharmacists, which was due to be held in March 2020, but was subsequently postponed due to the coronavirus pandemic. The associated poster will now be presented at the rescheduled meeting, which will be held on 24–26 March 2021 in Vienna, Austria.

Competing interests

All authors are employees and stockholders of Amgen Inc.

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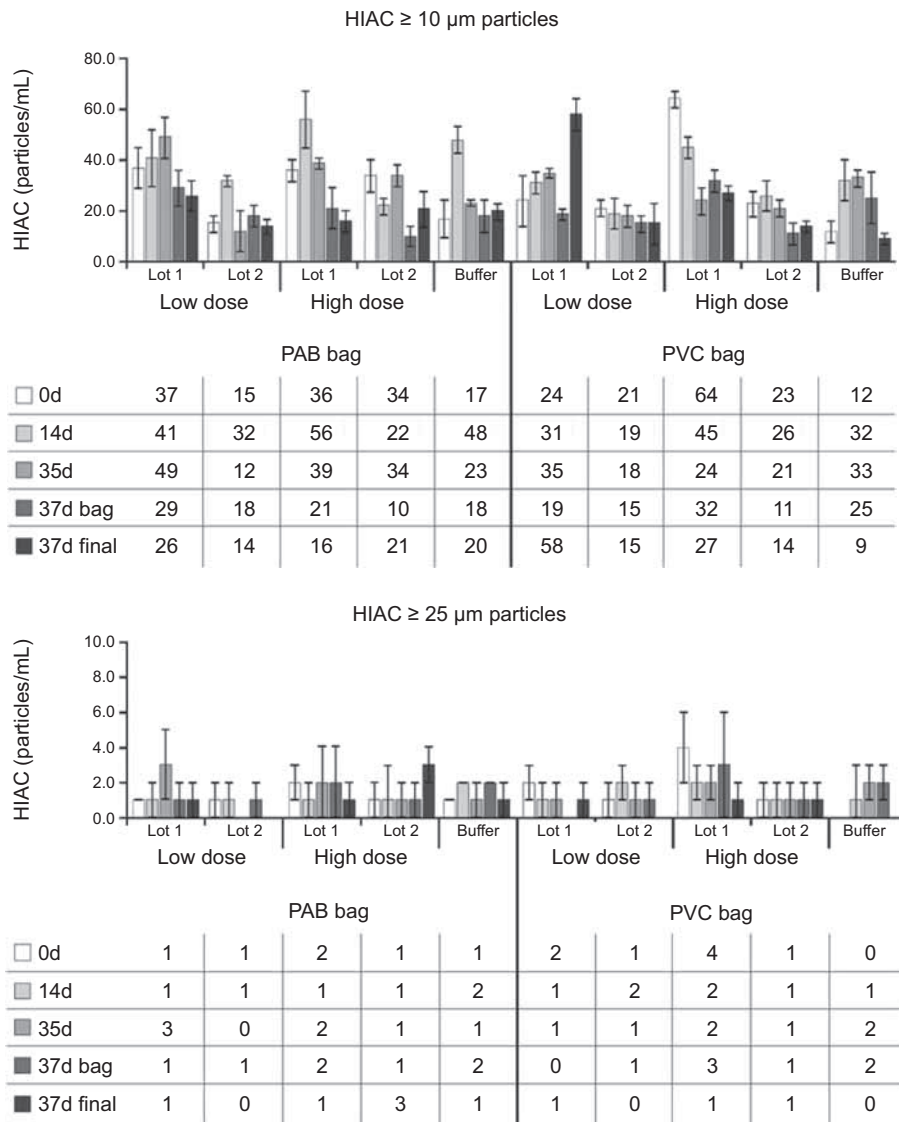
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Appendix Figure 1: Subvisible particles testing results



Data are presented as the mean of triplicate measurements with the standard deviation of each sample shown as error bars. 37d bag, sampling time point after 37 days of storage in the IV bag just prior infusion; 37d final, sampling time point after 37 days of storage in the IV bag following infusion.

d: day; HIAC: high-accuracy light obscuration; IV: intravenous; PAB: partial additive bag; PVC: polyvinyl chloride.