Development of *in vitro* models to demonstrate the ability of PecSys®, an *in situ* nasal gelling technology, to reduce nasal run-off and drip

Jonathan Castile, Yu-Hui Cheng, Ben Simmons, Michael Perelman, Alan Smith, and Peter Watts

Archimedes Development Ltd, Albert Einstein Centre, Nottingham Science Park, University Boulevard, Nottingham, UK

**Abstract**

Many of the increasing number of intranasal products available for either local or systemic action can be considered sub-optimal, most notably where nasal drip or run-off give rise to discomfort/tolerability issues or reduced/variable efficacy. PecSys, an *in situ* gelling technology, contains low methoxy (LM) pectin which gels due to interaction with calcium ions present in nasal fluid. PecSys is designed to spray readily, only forming a gel on contact with the mucosal surface. The present study employed two *in vitro* models to confirm that gelling translates into a reduced potential for drip/run-off: (i) Using an inclined TLC plate treated with a simulated nasal electrolyte solution (SNES), mean drip length (±SD, n = 10) was consistently much shorter for PecSys (1.5 ± 0.4 cm) than non-gelling control (5.8 ± 1.6 cm); (ii) When PecSys was sprayed into a human nasal cavity cast model coated with a substrate containing a physiologically relevant concentration of calcium, PecSys solution was retained at the site of initial deposition with minimal redistribution, and no evidence of run-off/drip anteriorly or down the throat. In contrast, non-gelling control was significantly more mobile and consistently redistributed with run-off towards the throat. **Conclusion:** In both models PecSys significantly reduced the potential for run-off/drip ensuring that more solution remained at the deposition site. In *vivo*, this enhancement of retention will provide optimum patient acceptability, modulate drug absorption and maximize the ability of drugs to be absorbed across the nasal mucosa and thus reduce variability in drug delivery. **Keywords:** Nasal drug delivery, pectin, formulation, no-drip, gels, *in situ* gelling, inclined plate, anatomical nasal cast, *in vitro* models, mucosal drug delivery.
degree of esterification above 50% and LM pectins have a degree of esterification up to 50%\(^4\). The LM pectin employed in PecSys gels in the presence of divalent cations, notably Ca\(^{2+}\) which is a component of mucosal secretions. Calcium causes LM pectin to gel by linking adjacent pectin chains; ionic bonds are formed between a divalent calcium cation and the carboxyl group of two separate pectin chains resulting in an ordered three-dimensional network cross-linked by calcium ions\(^5\) (Figure 1). This allows the formulation to spray readily as a finely dispersed plume before forming a gel on contact with the mucosal surface.

PecSys is utilized in Fentanyl Pectin Nasal Spray (FPNS), marketed as PecFent\(^\circledR\)/Lazanda\(^\circledR\) by Archimedes Pharma, an intranasal fentanyl spray used for managing breakthrough pain in cancer. PecSys technology is primarily employed in FPNS to attenuate the peak plasma concentration (\(C_{\text{max}}\)) while allowing an early time to that peak (\(T_{\text{max}}\)), as demonstrated in pharmacokinetic studies\(^6,7\). This modulated absorption profile of fentanyl is intended to match the profile of a typical breakthrough pain episode\(^2,6,7\). In situ gelling also has the potential to reduce run off and drip associated with conventional nasal spray formulations\(^8\).

Clinical studies specifically evaluating sensory attributes of nasal sprays such as odor, taste, run-off and drip have been reported in the literature\(^8,9\); these typically involve a large number of subjects and rely on patient questionnaires. Although such studies are unquestionably valuable and instructive, limitations such as the subjective nature of the measurements, sample size and diversity of the subject population are acknowledged by study investigators\(^9\). Extensive clinical data for FPNS in patients have demonstrated good nasal tolerability and low incidences of nasal symptoms such as running and drip\(^10-13\). It is accepted that such sensory attributes, being largely subjective, are difficult to quantify accurately especially in an efficacy study where they are peripheral to the main study objective, namely the treatment of breakthrough pain in cancer in the case of FPNS.

Our laboratory has developed two in vitro methods to evaluate the in situ gelling performance of PecSys with the aim of demonstrating objectively and quantitatively that the gelling characteristics translate into a reduced potential for run-off and drip which is likely to improve the consistency and tolerability of drugs delivered nasally. One model is based on an inclined plate and the second utilizes a more anatomically relevant cast of the human nasal cavity. The authors consider that these in vitro models will generate valuable data to quantitatively support clinical findings, particularly for FPNS which exhibits identical in vitro gelling and spray properties to drug-free PecSys solution (data on file). Furthermore, such models could have potential utility in facilitating the development/optimization of future novel in situ gelling formulations.

An inclined plate has been employed in a number of published studies, typically employing excised mucosal tissue, to evaluate adhesive/retentive properties of drug delivery technologies when subjected to a controlled gravitational force\(^14-16\). These principles were applied in the present study to develop an in vitro model using an inclined TLC plate treated with a simulated nasal electrolyte solution (SNES) containing calcium, sodium and potassium ions at concentrations equivalent to those present in human nasal fluid\(^17,18\); the model was used to quantify the ability of PecSys to reduce drip compared with a non-gelling control in a simulated nasal environment. The inclined plate model will demonstrate any differences between gelling performance of the formulations quantitatively, based on a single measurement (drip length), and as such should be readily comprehensible.

The authors are, however, cognizant that the inclined plate model does not take into account any influence of nasal anatomy. Recent studies by Kundoor and Dalby\(^19,20\) employed an anatomical cast of the human nasal cavity to evaluate in vitro the deposition properties of different nasal spray products. The studies investigated the effect of a comprehensive range of formulation factors such as viscosity, application method (conventional nasal spray pump versus nebulizer), and administration-related

![Figure 1. Schematic illustration of the gelling mechanism of LM pectin in the presence of calcium ions.](image-url)
variables such as head position, dosing angle and nasal spray insertion depth. Deposition pattern was determined by coating the nasal cast with a water-sensitive indicator. These principles have been employed in the present study to assess the deposition and gelling characteristics of PecSys. The unique challenge was to simulate the ionic conditions of the nasal cavity by fixing a physiologically relevant concentration of calcium onto the surface of the nasal cast model. Such a model could be envisaged to have utility in objectively quantifying the ability of PecSys to reduce nasal run-off and drip compared with a conventional non-gelling formulation.

Materials and methods

Materials

Polygram® SIL G Thin-layer chromatography (TLC) plates were supplied by Machery-Nagel (Germany). Potassium chloride and Fast Green FCF dye were supplied by Sigma-Aldrich (USA). Sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride and calcium chloride dihydrate were purchased from Fisher Scientific (UK). The silicone anatomical cast of a human nasal cavity was supplied by Koken Co. (Japan). Medical lubricant (KY®-Jelly water-based lubricant containing propylene glycol, sorbitol and hydroxyethyl cellulose) was obtained from Johnson & Johnson. PecSys (LM-pectin based aqueous) solution was prepared in-house at Archimedes Development Ltd. All chemicals were used without further purification.

Methods

Preparation of test solutions

PecSys solution was prepared by dissolving 10 mg/mL LM pectin and 41.5 mg/mL mannitol (to adjust tonicity) in ultrapure water. Phosphate buffer (0.1 M) solution was prepared at pH 6.6 by dissolving sodium dihydrogen phosphate dihydrate and disodium phosphate dihydrate in ultrapure water. Fast Green FCF dye was included in PecSys and 0.1 M phosphate buffer (control) solutions as a visualization agent. The respective solutions were filled into glass bottles and a metered-dose (0.1 mL) nasal spray pump (Aptar Pharma, Germany) was then secured onto each bottle. Before use, spray bottles were primed in an upright orientation by actuating the nasal spray pump according to the manufacturer’s instructions.

Evaluation of test solutions using inclined plate model

The principle of the experimental technique was to apply a calcium-containing electrolyte solution onto a solid surface able to retain the liquid while orientated into a downwards direction. The test solutions were applied onto this wetted surface using the nasal spray pump, deposition visualized and the dripping characteristics evaluated. A significant number of preliminary experiments were performed to define optimal experimental conditions: Parameters such as plate coating solution, coating technique and incline angle, spray nozzle distance and orientation were optimized during method development.

Each TLC plate was prepared by full immersion for 10 min in a simulated nasal electrolyte solution (SNES) comprising an aqueous solution containing 8.77 mg/mL sodium chloride, 2.98 mg/mL potassium chloride and 0.59 mg/mL calcium chloride dihydrate. Excess coating solution was carefully removed from the plate using laboratory tissue. The plate was then secured facing upwards at 45° from vertical onto a poly(methylmethacrylate) backing plate. The dosing nozzle was positioned perpendicularly to the surface of the plate. The distance of the nozzle tip from the plate surface was 1.5 cm and 3 cm for the control and PecSys spray bottles respectively to produce comparable deposition areas. The delivered dose volume of each spray was confirmed by weight to ensure an acceptable dose volume had been delivered (limits of 0.085–0.115 mL were applied). Plates were left for 5 min before being examined for evidence of run-off/drip. Run-off/drip was quantified by measuring the distance of travel of the test solution down the plate from the lower edge of the original spray. Ten replicate plates were assessed for each of the PecSys and control solutions.

As an additional control, the experiment was repeated using TLC plates treated with ultrapure water in place of SNES to confirm any differences were due to in situ gelling rather than physical differences between un-gelled PecSys and the non-gelling phosphate buffer control (n = 10).

Evaluation of test solutions using anatomical nasal cast model

The principle of the experimental technique was to apply substrate (medical lubricant) incorporating the physiologically relevant electrolyte (calcium) to the interior surface of the nasal cast. At the concentrations found in human nasal fluid, monovalent cations have no appreciable effect on PecSys gelling properties and were omitted in order to avoid potential interactions with other ingredients of the coating substrate. Initial method development studies were performed to optimize parameters such as the coating substrate, actuator nozzle insertion and cast incline angle. Fixed weights of the substrate were applied evenly on the interior surface of one-half of the silicone cast (3 g) and Plexiglas septum (0.4 g); the cast was then positioned on a flat surface at a slight backward incline (10°) from horizontal. The dosing nozzle was inserted approximately 1 cm into the nostril and pointed towards the bridge of the nose (approximately 45° from horizontal) as would be the case in man. The nasal pump was then actuated by hand to deliver a single spray into the nasal cavity. The delivered dose volume of each spray was confirmed by weight to ensure a consistent dose volume had been delivered (limits of 0.085–0.115 mL were applied). Ten replicate samples were assessed for each measurement. The experimental arrangement is shown in Figure 2 with annotations to illustrate the key anatomical regions of the cast.

A digital video recording (1280 × 720 pixels; 25 fps) was captured before and then up to at least 120 s after
spray actuation using a Nikon D3100 digital SLR camera under standardized photographic conditions with respect to lighting, camera position and magnification. Still images were extracted at baseline and 120 s after actuation. The deposition pattern in each image was quantified using Adobe® Photoshop®. Linear and area measurements were determined using an average measurement scale which was stored within the Photoshop software. The average measurement scale was calculated by determining the average pixel length of a 2 cm marker which was attached to the septum of the cast and thus captured on all deposition images. Although there were some minor variations resulting from changes in the camera-to-cast distances between images, the maximum variation seen in the marker length in any two images was only 0.3 mm.

Deposition pattern assessment

Deposition pattern assessment was carried out according to the principles of the method described by Kundoor and Dalby19,20. For area quantification using Photoshop, the image size was first adjusted to 20 x 11.25 cm with a resolution of 100 pixels per cm. The 2000 x 1125 pixels image contrast was automatically adjusted using Auto Contrast and the colored deposition pattern was emphasized compared with the background using Hue and Saturation tools. After setting the Tolerance level, the Color Range tool, in combination with the Similar and Grow commands, was used to select the entire deposition area. Using the previously stored average measurement scale, the area of the selected deposition pattern was calculated using the Record Measurements command. For combined area quantification, initial and 120 s deposition patterns were overlaid using the Paste in Place command with any necessary adjustments made using the Move tool. The area of the combined pattern was then calculated using the average measurement scale and the Record Measurements command. Linear distance measurements were determined using the average measurement scale and the Ruler tool. A fixed measurement point (see Figure 2) was set within the throat of the cast on all images and this point was used to determine the distance of the closest point of the deposition pattern to the throat.

Data were analyzed using the following metrics:

- Run-off into the throat: For the purpose of these experiments, the throat was defined as starting at the point where the palate intersected the nasopharynx (see Figure 2). A visual assessment was made of whether the spray solution was present in the throat.
- Distance to the throat: For images in which the solution had not reached the throat, the distance (cm) of the leading edge of the deposition profile to a fixed point in the throat was measured. Note: Where solution had reached the throat the distance was recorded as 0 cm.

- Difference between deposition area at 0 s and 120 s (cm²): Calculated by subtracting the initial deposition area from the deposition area at 120 s. This reflected only a change in surface area occupied by the spray solution; it did not capture any redistribution associated with no change in area (see below).
- Area of new coverage (cm²) after 120 s: This signified redistribution within the nasal cast, including movements that were not associated with a change in surface area, and was calculated by subtracting the initial deposition area from the total area of coverage when the initial deposition pattern was overlaid onto the deposition pattern at 120 s. As an example, if the surface area of the deposited spray was 5 cm² at both 0 and 120 s but the area occupied had moved from the turbinate region to the nasopharynx, the area change would be 0 cm² but the area of new coverage would be 5 cm².

To confirm that any differences seen between the behavior of gelling and non-gelling solutions were solely due to PecSys and not differences in deposition or formulation properties, a control experiment was conducted in which the cast was coated with the same weight of medical lubricant without added calcium. PecSys solution and control solution, each containing dye, were tested and the change in total deposition area after 120 s quantified as above to establish the degree of deposition movement within the cast. The increase in total area of the respective deposition patterns after 120 s was comparable (58.8 ± 5.1% for PecSys and 53.0 ± 10.4% for non-gelling control) indicating that the behavior of the two solutions within the cast was similar in the absence of calcium.

Results

Inclined plate model

A typical image showing PecSys and non-gelling control solutions sprayed onto an inclined TLC plate treated with SNES is shown in Figure 3 (arrows and data summary added for illustrative purposes). Individual drip length data are provided in Table 1.

Figure 2. Set-up of the nasal cast model (annotated with key anatomical features).
The mean drip length for PecSys was 1.5 ± 0.4 cm (range 1.0–2.2 cm). This was consistently much shorter than for the non-gelling control where the mean length was 5.8 ± 1.6 cm (range 3.9–8.7 cm). The difference in drip length between the two test solutions was statistically significant ($p < 0.001$; unpaired $t$-test).

Conversely, in the control experiment where PecSys and non-gelling control solutions were sprayed onto an inclined TLC plate treated with water (no calcium), mean drip length for PecSys and non-gelling control were comparable at 7.2 ± 1.9 cm (range 4.2–9.5 cm) and 7.4 ± 1.9 cm (range 3.9–10.2 cm) respectively (image provided in Figure 4 and data in Table 2). The differences in drip length for PecSys and control solution were not statistically significant ($p = 0.88$; unpaired $t$-test). It should be noted that mean drip length for the control was slightly longer on the water-treated plate compared with the SNES-treated plate but the difference was not statistically significant ($p = 0.06$; unpaired $t$-test).

**Anatomical nasal cast model**

Typical photographs for PecSys and non-gelling control are shown in Figure 5. On spraying into the cast both PecSys and non-gelling control were typically deposited over similar areas of the nasal cavity, particularly at the front and middle of the turbinate region. Observations during the course of the experiment indicated that PecSys was retained at the site of deposition with minimal evidence of redistribution within the cast, and no evidence of run-off or drip. In contrast, the non-gelling control consistently appeared to rapidly drip to the base ( palate) with run-off towards the throat. Inspection of still images at baseline (0 s) and 120 s supported this assessment.

These findings were confirmed when deposition patterns were enhanced using Photoshop software: A significant difference between the retention profiles of PecSys and non-gelling control solution was clearly observed; typical images are provided in Figures 6 and 7. The initial deposition patterns of PecSys and control were comparable with no evidence of immediate deposition into the throat for any sample of either solution. At the end of the 120 s observation period, 4 out of 10 non-gelling control sprays had dripped into the throat region of the cast, whereas the PecSys formulation did not reach the throat for any of the replicate sprays tested.

**Table 1.** Drip length determined 5 min after non-gelling control and PecSys were sprayed onto inclined TLC plates treated with SNES.

| Sample | Control (cm) | PecSys (cm) |
|--------|--------------|-------------|
| 1      | 5.9          | 1.4         |
| 2      | 6.8          | 1.6         |
| 3      | 8.7          | 1.1         |
| 4      | 3.9          | 1.1         |
| 5      | 4.2          | 2.2         |
| 6      | 5.8          | 1.0         |
| 7      | 7.8          | 2.0         |
| 8      | 5.7          | 1.4         |
| 9      | 4.2          | 2.0         |
| 10     | 4.6          | 1.5         |
| Mean   | 5.8          | 1.5         |
| SD     | 1.6          | 0.4         |

**Table 2.** Drip length determined 5 min after non-gelling control and PecSys were sprayed onto inclined TLC plates treated with water.

| Sample | Control (cm) | PecSys (cm) |
|--------|--------------|-------------|
| 1      | 6.5          | 6.7         |
| 2      | 3.9          | 9.2         |
| 3      | 5.6          | 8.7         |
| 4      | 8.3          | 8.7         |
| 5      | 7.4          | 9.5         |
| 6      | 10.2         | 6.5         |
| 7      | 8.0          | 7.7         |
| 8      | 9.6          | 6.4         |
| 9      | 6.0          | 4.2         |
| 10     | 8.0          | 4.6         |
| Mean   | 7.4          | 7.2         |
| SD     | 1.9          | 1.9         |
The distance to the throat from the leading edge of the spray deposition pattern at 0 s and 120 s was also determined. Example images illustrating how this measurement was performed are provided in Figure 8 and results are presented in Table 3. In initial deposition patterns (0 s), there was no significant difference in distance from the leading edge of the pattern to the throat \((p = 0.24; \text{unpaired } t\text{-test})\), with values of 3.4 ± 0.4 cm and 3.2 ± 0.5 cm for PecSys and control respectively. After 120 s the mean distance from the throat for PecSys remained relatively unchanged at 2.7 ± 0.7 cm (range 1.9–3.8 cm) whereas the non-gelling control had decreased considerably to 0.7 ± 0.8 cm (range 0.0–2.0 cm); the difference between these values was significant \((p < 0.001; \text{unpaired } t\text{-test})\).

The area of initial deposition for PecSys (4.1 ± 0.7 cm²) was slightly lower than control (5.2 ± 1.3 cm²); after 120 s the PecSys area had increased marginally by 0.4 ± 0.1 cm² whereas a significantly greater increase of 1.5 ± 0.5 cm² was observed for the non-gelling control \((p < 0.001; \text{unpaired } t\text{-test})\) (Table 4). The area of new coverage at 120 s for PecSys was 1.1 ± 0.2 cm² (27.1 ± 5.5% increase) compared with 2.4 ± 0.4 cm² (48.9 ± 13.5% increase) for non-gelling control (Table 5); this represents a significant increase in additional area due to movement for control compared with PecSys \((p < 0.001; \text{unpaired } t\text{-test})\).
The nose has many advantages over other routes of drug delivery in terms of speed and efficiency of absorption; for example, nasally-absorbed drugs avoid the first pass effect, thus maximizing bioavailability. Some of the same benefits may also be achieved through the oral mucosa but it is difficult to retain the drug in the oral cavity; any swallowed drug is exposed to the extreme conditions of the gastrointestinal tract and, if absorbed, subject to first pass metabolism. For example, in the case of fentanyl a number of reviews suggest that up to 50% of buccally administered drug is swallowed, resulting in a prolonged absorption profile and reduced overall bioavailability. Simply substituting buccal dosing with nasal dosing will not solve this problem, unless the drug can be sufficiently retained in the nasal cavity, given most nasal liquid formulations are associated with run-off and post-nasal drip. It has been concluded that patients are less likely to adhere to a nasal treatment regime when they perceive sensory attributes such as run-off/drip to be unfavorable.

Whilst clinical studies have demonstrated the advantages of minimizing run-off and drip, as stated earlier, quantifying these formulation attributes is difficult. Quantitative data are likely to prove invaluable in the effective optimization of nasal spray formulations. The two in vitro models described herein succeed in...
quantifying run-off and drip in an environment that simulates the ionic conditions found at the nasal mucosal surface.

In our studies, the models were used to discriminate between a PecSys formulation and non-gelling control: In the inclined plate model, the use of PecSys significantly reduced drip length compared with a non-gelling control solution. It is evident that the significantly shorter drip length for PecSys compared with non-gelling control is due to the ability of PecSys to gel on contact with calcium ions present in the simulated nasal environment rather than differences in physical properties between the two solutions since there was no difference in behavior when the PecSys and non-gelling solutions were applied to a calcium-free (water-treated) plate. The results also provide evidence that the interaction between PecSys and calcium is effectively instantaneous given the shortness of the observed drip length.

In the anatomical nasal cast model, the initial deposition area of PecSys and control solutions was comparable with that obtained by Kundoor and Dalby, who reported values of around 3.8 to 5.8 cm² when 0.1 mL of water was sprayed from a range of different nasal spray devices. Both the visual inspection of the images and the quantified changes in deposition over time demonstrated that the PecSys technology reduced run-off/drip and consistently retained the solution within the nasal cavity in contrast to the non-gelling control. These results also demonstrate that even with a small volume of solution (0.1 mL) administered as a finely dispersed plume of droplets, rapid run-off and drainage from the nasal cavity may occur for simple solutions, hence emphasizing the advantages of using “no-drip” formulation technologies.

Direct comparison of the gelling properties of PecSys with other in situ gelling formulations is difficult due to differences in the mechanism of action. Nevertheless, with appropriate modifications reflecting the individual gelling mechanism (e.g. thermal conditions or chemical interaction), it is envisaged that the models described in this paper would facilitate the screening of other formulations to investigate their potential to reduce nasal run-off and drip. For example, models could be devised to ascertain whether gel formation in thermoresponsive gelling systems is sufficiently rapid to improve nasal retention. Thermoreversible gelling systems based on poloxamer 407 (P407), a pharmaceutically acceptable block copolymer surfactant, have received significant attention. Whether the phase transition of P407 would be sufficiently rapid in vivo to avoid nasal run-off and drip is in need of confirmation. Gelling systems based on the ionic interaction of gellan gum with nasal fluid have also been reported. Gellan gum has also been investigated for use in locally-acting formulations intended to treat oral candidiasis and vaginitis. Also noteworthy is an ocular nanoparticulate system which gels due to the sensitivity of cellulose acetate phthalate to changes in pH.

Other potential uses for the inclined plate model as a development tool include evaluating effects of changes in formulation parameters such as the concentration of PecSys or other excipients, or delivery device characteristics. For example, a reduction in pectin concentration would be expected to decrease gel strength with a corresponding increase in drip length. Clearly, the inclined plate could also be readily adapted to be used as an in vitro model for other mucosal surfaces (e.g. eye, vagina) by substituting SNES with the relevant ionic solutions or incorporating other agents such as mucin and represents a potentially more accessible alternative to inclined plate models that utilize excised mucosal tissue.

The anatomical nasal cast model could also be adapted and employed to investigate the effect of changing formulation parameters or determining the effect of dosing factors such as inspiration, angle of head tilt (upright, backwards or forwards) or positioning of the nasal spray during administration. While the authors acknowledge that a nasal cast model is not able to fully describe physiological conditions such as mucociliary clearance that would be experienced in vivo, its ability to allow isolation of the impact of factors relating to formulation and dose administration in an anatomically relevant setting creates a useful development tool. A nasal cast model has been used to determine the effect of breathing patterns on nasal deposition profiles. Changes in breathing profile were found not to affect spray deposition whereas formulation variables such as viscosity generated clear differences; results correlated well with in vivo human data.

In this regard, the results from our in vitro investigations correlate with and provide a rational basis for the pharmacokinetic findings in man seen with FPNS. Human studies have shown that PecSys is able to modulate fentanyl absorption compared with non-gelling nasal solutions and enhance absorption (shortened Tmax and enhanced Cmax with a small incremental increase in AUC0-∞) compared with buccally administered fentanyl products. The results also provide an explanation for the high efficacy and patient satisfaction seen in Phase 3 clinical trials.

**Conclusions**

Two in vitro models were successfully developed to investigate the potential advantages of in situ gelling. As demonstrated in both models, by forming a gel in situ due to a reaction with calcium ions in nasal fluid, PecSys may significantly reduce run-off/drip compared with a simple, non-gelling solution and has the potential to provide longer retention in the nasal cavity. In vivo, this enhancement of retention may modulate drug absorption and, by keeping drug at absorption site, maximize the ability of drugs to be absorbed across the nasal mucosa. This is likely to reduce variability in drug delivery and maximize efficacy and patient acceptability. The results of the study are valuable in providing further insight to support clinical findings on nasal tolerability of FPNS.
Declaration of interest
All of the authors are employees of Archimedes Pharma and receive salary and other compensation from the company.

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