Introduction

Today, the spectrum of phytopharmaceutical preparations ranges from immediate release tablets, capsules, and lozenges to effervescent tablets, solutions, syrups, and teas. It is noticeable that modified release or sustained release dosage forms obviously do not play a significant role in phytotherapy, although therapeutically, they could provide a good benefit, especially in some chronic indications [1, 2]. Looking at herbal cold preparations, products for the treatment of sinusitis/rhinosinusitis and acute or chronic bronchitis dominated the market in Germany in 2020 [3]. The two top-selling cold remedies (R05C class) in pharmacies were Sinupret extract (BNO 1016) and Gelomyrtol forte (ELOM-080), with around 3 million packs sold. They are both also marketed in-
formulation has been proven for BNO 1016, an immediate release coated tablet formulation, in early clinical and phase II studies. In clinical trials, BNO 1016 has been shown to activate mucociliary clearance, which is clinically relevant, especially in critically ill patients. Moreover, nonclinical data have demonstrated its potential slight delay of 0.5 h under fed conditions. The rate and extent of exposure (C_{max}, AUC(0-t_{last})) of verbenalin decreased after the intake of food (ratio of geometric means fed/fasted: 0.48 and 0.69, respectively), whereas that of the further marker analyte gentiopicroside was nearly unchanged (ratio fed/fasted: 0.75 and 1.04, respectively). Geometric mean ratios of C_{max} and AUC(0-t_{last}) values of gentiopicroside were slightly increased with 1.13 and 1.33, respectively. Mean apparent elimination half-times of the three analytes lay in the range of 0.96–1.78 h (fasted) and 1.30–2.05 h (fed), suggesting that elimination kinetics are unchanged (see Table 1). Overall, a relevant food effect could not be observed after administration in dogs.

Individual overlays of the ELOM-080 analytes in the fasted state also showed an overall similar picture in the three dogs (Fig. 2). Interestingly, lag times of up to 2 h p. a. could be observed for at least two of the three analytes, reflecting a longer residence time of the formulations in the dogs’ stomach until drug liberation in the intestine. Corresponding t_{max} values lay in the range of 3 to 4 h p. a. The individual overlays after the administration of the high-fat diet show two major peaks. This occurred in two of the three animals. A sigmoidal course after administration can be observed for all three analytes detected. Curves showed the typical sigmoidal course after single dose administration (Fig. 1). There was no lag time under fasting and only an expected slight delay of 0.5 h under fed conditions. The rate and extent of exposure (C_{max}, AUC(0-t_{last})) were similar for all three analytes, reflecting an overall similar picture in the three dogs (Fig. 2).

### Results

Overlays of individual plasma concentration vs. time curves of dogs receiving BNO 1016 under fasting and fed conditions are given in Fig. 1 and of dogs receiving ELOM-080 in Figs. 2a, b. The corresponding mean curves are depicted in Figs. 3 and 4 and the pharmacokinetic evaluation is given in Table 1.

In general, the three analytes determined for BNO 1016 demonstrated a similar course in the fasted as well as in the fed state by the visual impression. Typical characteristics of an immediate release drug formulation with a rapid increase until C_{max} with median t_{max} values of 1 h in the fasted and 2 h in the fed state could be observed for all three analytes detected. Curves showed the typical sigmoidal course after single dose administration (Fig. 1). There was no lag time under fasting and only an expected slight delay of 0.5 h under fed conditions. The rate and extent of exposure (C_{max}, AUC(0-t_{last})) of verbenalin decreased after the intake of food (ratio of geometric means fed/fasted: 0.48 and 0.69, respectively), whereas that of the further marker analyte was nearly unchanged (ratio fed/fasted: 0.75 and 1.04, respectively). Geometric mean ratios of C_{max} and AUC(0-t_{last}) values of gentiopicroside were slightly increased with 1.13 and 1.33, respectively. Mean apparent elimination half-times of the three analytes lay in the range of 0.96–1.78 h (fasted) and 1.30–2.05 h (fed), suggesting that elimination kinetics are unchanged (see Table 1). Overall, a relevant food effect could not be observed after administration in dogs.

### Modified release or enteric-coated oral dosage forms, however, are at risk of pharmacokinetic interactions affecting the absorption process, especially in the case of concomitant food intake [13–15]. Such food effects are often not predictable from the in vitro characteristics of a dosage form. Several investigations have demonstrated a high probability of food interactions for formulations with pH-dependent release properties, such as enteric-coated formulations [16], which present a quite sizeable, indigestible solid particle. Passage of such particles through the pylorus occurs normally during phase III of the migrating motor complex. Food intake interrupts the migrating motor complex and can thereby delay the passing of enteric-coated formulations from the stomach into the duodenum [17,18]. Therefore, an in vivo food interaction might also be suggested to occur with the intake of ELOM-080 enteric-coated capsules.

In the present exploratory pilot study, we compared possible effects of food intake on ELOM-080 enteric-coated capsules and BNO 1016 immediate release coated tablets in male beagle dogs. Beagle dogs are considered a standard model to predict possible food effects of drug formulations [18,19].
Fig. 1 Overlay of individual plasma concentration vs. time curves of gentiopicroside, verbenalin, and a further marker analyte in dogs (n = 3) after administration of BNO 1016 under fasting (a) and fed (b) conditions. For graphical presentation, all concentrations of BLOQ are set to “0”.

Fig. 2 Overlay of individual plasma concentration vs. time curves of 1,8-cineole, perillic acid, and limonene in dogs (n = 3) after administration of ELOM-080 under fasting (a) and fed (b) conditions. For graphical presentation, all concentrations of BLOQ are set to “0”.

Fig. 3 Mean plasma concentration vs. time curves (± SD) of gentiopicroside, verbenalin, and a further marker analyte in dogs (n = 3) after administration of BNO 1016 under fasting (a) and fed (b) conditions. For graphical presentation, all concentrations of BLOQ are set to “0”.
lay in the range from 2.98 to 3.51 h (fasted) and 1.97 to 3.09 h (fed). Although \( t_{1/2} \) of limonene could not be derived properly, the data suggest that elimination kinetics are not altered by food intake, as expected (see Table 1).

**Table 1** Pharmacokinetic parameters after administration of ELOM-080 and BNO 1016 in the fasted and fed states.

<table>
<thead>
<tr>
<th></th>
<th>ELOM-080</th>
<th></th>
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<th>BNO 1016</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasted state</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>AUC(0-t_last)</strong> Geom. mean (CV%) [hng/mL]</td>
<td>7996.87 (52.11)</td>
<td>123.77 (194.23)</td>
<td>8329.68 (19.98)</td>
<td>160.44 (39.98)</td>
<td>75.91 (69.34)</td>
</tr>
<tr>
<td><strong>C_{max}</strong> Geom. mean (CV%) [ng/mL]</td>
<td>2791.06 (32.08)</td>
<td>213.90 (357.61)</td>
<td>1500.42 (64.69)</td>
<td>65.84 (23.13)</td>
<td>40.69 (65.07)</td>
</tr>
<tr>
<td><strong>t_{max}</strong> Median (range) [h]</td>
<td>3 (3–4)</td>
<td>4 (3–6)</td>
<td>4 (4–4)</td>
<td>1 (1–1)</td>
<td>1 (1–1)</td>
</tr>
<tr>
<td><strong>t_{lag}</strong> Median (range) [h]</td>
<td>1.02 (1.02–2)</td>
<td>2 (2–2)</td>
<td>2 (2–2)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td><strong>t_{1/2}</strong> Mean (SD) [h]</td>
<td>3.51 (1.25)</td>
<td>–</td>
<td>2.98 (0.28)</td>
<td>1.09 (0.11)</td>
<td>0.96 (3.34)</td>
</tr>
<tr>
<td><strong>Fed state</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>AUC(0-t_last)</strong> Geom. mean (CV%) [hng/mL]</td>
<td>8963.18 (82.49)</td>
<td>2890.91 (45.14)</td>
<td>7478.24 (190.63)</td>
<td>213.18 (7.88)</td>
<td>52.08 (7.71)</td>
</tr>
<tr>
<td><strong>C_{max}</strong> Geom. mean (CV%) [ng/mL]</td>
<td>2566.48 (80.36)</td>
<td>1234.14 (123.21)</td>
<td>1373.78 (171.89)</td>
<td>74.62 (29.61)</td>
<td>19.38 (18.45)</td>
</tr>
<tr>
<td><strong>t_{max}</strong> Median (range) [h]</td>
<td>4 (1–6)</td>
<td>1 (1–6)</td>
<td>4 (1–8)</td>
<td>2 (2–3)</td>
<td>2 (1–2)</td>
</tr>
<tr>
<td><strong>t_{lag}</strong> Median (range) [h]</td>
<td>0.5 (0.5–3)</td>
<td>0.5 (0.5–4)</td>
<td>0.5 (0.5–4)</td>
<td>0.5 (0.5–0.5)</td>
<td>0.5 (0.5–0.5)</td>
</tr>
<tr>
<td><strong>t_{1/2}</strong> Mean (SD) [h]</td>
<td>3.09 (1.11)</td>
<td>–</td>
<td>1.97 (0.26)</td>
<td>1.30 (0.23)</td>
<td>2.05 (1.574)</td>
</tr>
<tr>
<td><strong>Ratio fed/fasted</strong> AUC(0-t_last)</td>
<td>1.12</td>
<td>23.36</td>
<td>0.90</td>
<td>1.33</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>C_{max}</strong></td>
<td>0.92</td>
<td>5.77</td>
<td>0.92</td>
<td>1.13</td>
<td>0.48</td>
</tr>
</tbody>
</table>

**Discussion**

The present pilot study investigated the pharmacokinetics of BNO 1016 and ELOM-080 with special attention to (1) the absorption and (2) the occurrence of a food effect depending on preceding conditions.
Feed intake in male beagle dogs. This was an exploratory pilot study and therefore a sample size calculation for a confirmatory trial did not take place. We chose three Beagle dogs as from a 3R perspective: the use of larger sample sizes would not be ethically acceptable, i.e., if results can be obtained from smaller sample sizes. Both herbal medicinal products are widely used in Germany and Europe for the treatment of acute rhinosinusitis. BNO 1016 is available as an immediate release formulation (coated tablet) and ELOM-080 is contained in an enteric-coated soft gelatin capsule. It can be assumed that absorption of APIs from BNO 1016 occurs fast and therefore, results also in a fast onset of treatment effects. The purpose of an enteric coating is to delay dissolution and the release of APIs from the drug formulation until it has reached the intestine. Therefore, it might be suggested that the retention time of an enteric-coated soft gelatin capsule in the stomach is influenced when food has been consumed prior to ingestion or immediately afterwards. The time indigestible solid particles are retained in the stomach usually depends on the diameter of the dosage form and the frequency of food intake, as well as on the composition and caloric density of an administered meal [20, 21]. Consequently, food effects most frequently manifest themselves in a relevant in vivo change in liberation from the dosage form associated with a change in the onset of absorption ($t_{\text{lag}}$), i.e., in pharmacokinetic parameters that are strongly formulation dependent. Furthermore, the extent and rate of bioavailability can be influenced (AUC$_{0-t_{\text{last}}}$, $C_{\text{max}}$, $t_{\text{max}}$). Conceivable, but less probable, is the influence on distribution and elimination. However, in the case of sudden large increases in dosage, e.g., in the case of a dose-dumping phenomenon [22], changes due to saturation phenomena of eliminating enzymes and transporters are also possible. As a consequence, the EMA guidelines on the pharmacokinetic and clinical evaluation of modified release dosage forms [23] also require the verification of unexpected release characteristics.

In humans, published data show that single unit enteric-coated dosage forms may remain in the stomach for 10 h or even longer when coadministered with a high-fat breakfast followed by several meals over the course of the day [24]. Moreover, it is known that gastric emptying of drugs may be even delayed for up to 30 h in non-fasted animals [25].

In this first pilot study, we chose beagle dogs as the standard model to study food effects [18]. Based on our previous experience with the analytical detectability of analytes in plasma from rats and dogs, we chose to administer the 5-fold equivalent of the recommended human daily dose assuming that the physiological performance of the single formulations will not change with the dosage administered. Plasma samples were withdrawn until 30 h p. a. to avoid missing possible late-occurring absorption processes. In general, the analytes determined for BNO 1016 demonstrated a similar course of the individual plasma concentrations vs. time curves in the fasted as well as in the fed state by the visual impression. Lag times of the absorption process lay in the expected range of 0–0.5 h p. a. for an immediate release formulation with corresponding median $t_{\text{max}}$ values of 1–2 h. A relevant food effect could be ruled out. For the enteric-coated formulation of ELOM-080, however, we observed lag times of the absorption up to 2 h p. a. even in the fasted state, reflecting longer gastric residence times of the formulations in the dogs. In the fed state, a pronounced food effect could be noticed, with median lag times up to 3–4 h p. a. and a splitting into two major peaks in plasma curves in two of the three dogs. The cause of this double peak phenomenon is unknown. Neither the inspection of the laboratory journals nor the direct questioning of the staff gave any indications of misadministration, e.g., dogs biting capsules etc.

While according to the respective SmPC [4], the intake of ELOM-080 is recommended before meals, a truly empty stomach in humans can usually only be expected in the mornings after overnight fasting. The consumption of meals and snacks throughout the day might practically lead to a closed pylorus sphincter over long time distances during the day [26]. A respective food effect in humans for ELOM-080 should not lead to severe safety-relevant side effects. However, if this finding in dogs translates to humans, some of the frequently observed gastrointestinal side effects, like stomach and upper abdominal complaints [4], might be explained. Most certainly, a precise dosing with a rapid release and onset of action does not seem likely based on the data obtained in the present study. Therefore, it seems quite valuable to verify these findings in a further pharmacokinetic study in humans, considering that patients suffering from respiratory tract disorders take ELOM-080 with the expectation of a fast relief of their complaints.

In conclusion, our pilot study provides evidence that, in contrast to the immediate release medicine BNO 1016 with fast and similar absorption characteristics, absorption of ELOM-080 from an enteric-coated capsule might be substantially affected by food intake in humans. Consequently, a faster and more precise onset of action in humans can be assumed for BNO 1016.

### Materials and Methods

#### Test items and dose selection

For the experiments, commercially available Sinupret extract coated tablets (Batch No.: 0000144647) and Gelomyrtol forte soft gelatin capsules (Batch No.: 260248) containing BNO 1016 or ELOM-080, respectively, were purchased in a public pharmacy. A coated tablet of Sinupret extract contains 160.00 mg dry extract (3:6:1) of gentian root, cowslip flowers, sorrel herb, elderflower, and verbena (1:3:3:3:3); extraction solvent: ethanol 51% (m/m). One enteric-coated soft gelatine capsule of Gelomyrtol forte contains 300 mg distillate from a mixture of rectified eucalyptus oil, rectified sweet orange oil, sweet orange oil, rectified myrtle oil, and rectified lemon oil (66:32:1:1). Previous experiments on BNO1016 showed that the single equivalent human dose is not sufficient for the reliable bioanalytical detection of the lower concentrated analytes. Therefore, doses were chosen as high as necessary and as low as possible and the dosage of ELOM-80 was adapted accordingly.

The 5-fold equivalent of the recommended human daily dose was chosen [BNO 1016: 5 tablets per animal, i.e., 72 (± 2.2) mg/kg, ELOM-080: 6 capsules per animal, i.e., 162 (± 5.0) mg/kg] to ensure bioanalytical detectability of the selected analytes in plasma.
Study design and animal treatment

The study protocol was approved by the Avogadro LS Animal Ethics Committee on July 7, 2020, according to the reference number approval 2017021409405658 (id 062) authorized by the French Ministry for higher education and research. Animal housing and care complied with the recommendations of Directive 2010/63/EU.

Three non-naïve male adult beagle dogs [mean age 42 (+8.7) months; Marshall BioResources] weighing 10.9 to 11.4 kg, collectively housed in pens, were used in the study, which was performed according to a 4-period, 4-treatment within-design. Animals received all treatments under both fasted (periods 1 and 3) and fed (periods 2 and 4) conditions. They were fasted overnight in each period for at least 8 h prior to dosing. In periods 1 and 3, a high-fat diet was given about 3 h after administration (fasted state).

The high-fat diet consisted of the following ingredients: 2 large eggs, 50 g of bacon, 130 g of bread, 15 g of sunflower oil, 15 g of butter, and 190 g of tap water. The ingredients were homogenized in a laboratory blender. Diet was prepared and then stored in 50 g aliquots at ca. −20 °C and used within 1 month maximum. Aliquots were defrosted overnight at ca. +5 °C before use. Composition of the high-fat diet was as follows: 17% fat, 11% protein, and 18% carbohydrate (on a fresh matter basis). In periods 2 and 4, the same high-fat diet was given approximately 10 min prior to dosing. Then, regular feeding (Teklad 2027, Envigo Teklad Diets) was given about 12 h post-drug administration (p. a.) in each period. Water was offered ad libitum. Treatments were separated for at least 7 treatment-free days to guarantee a sufficient washout of the drugs.

Test items were administered orally directly into the back of the throat of the animals. Ten mL of water was added directly into the mouth during administration to ensure good esophageal transit and then 50 mL was administered by gavage using a gastroesophageal tube to mimic ingestion with liquid in humans as recommended.

Blood sampling

Blood samples (2.5 mL) were withdrawn into lithium heparin tubes from the jugular vein. Samples were collected at the following time points: pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 26, 28, and 30 h p. a. Real blood sampling times were noted.

Bioanalytics and pharmacokinetics

After withdrawal, blood samples were immediately centrifuged at 2500 × g for 10 min at +5 °C and plasma obtained was cooled in dry ice. Samples were set on dry ice and stored at ≤ −70 °C until measurement. A maximum period of 8 weeks elapsed from blood withdrawal to measurement. Reliably detectable and representative ingredients or metabolites were selected for measurement: 1,8-cineole, limonene, and its metabolite perillic acid were determined for ELOM-80, and gentiopicroside, verbenaolin, and a further marker analyte for BNO 1016. This further analyte is considered a standard marker substance for BNO 1016 but shall not be described in more detail in here for internal company reasons.

The monoterpene metabolite perillic acid as well as gentiopicroside, verbenaolin, and the further marker analyte were determined after protein precipitation by LC-MS/MS. For sample preparation, 50 µL plasma samples were mixed with internal standard solution (200 ng/mL methylparaben (for perillic acid), 30 ng/mL amarogentin (for gentiopicroside, verbenaolin), 40 ng/mL eriocitrin (for the further marker analyte) in 1% formic acid in acetonitrile in a 96-well filter plate (Ostro Protein Precipitation & Phospholipid Removal Plate, Waters). The filter plate was placed in the test tube shaker for 5 min at 800 rpm (pulsating) and subsequently centrifuged for 5 min at 2000 × g.

Chromatographic separation was performed on a UHPLC system (1290 Infinity series, Agilent). For the determination of gentiopicroside, verbenaolin, and the further marker analyte, a Phenomenex Kinetex C18 column (50 × 2.1 mm, 1.7 µm) was used. The injection volume was 1 µL and the flow rate was set to 0.7 mL/min. For the chromatographic separation, a gradient was run using 0.5% acetic acid in water (solvent A) and acetonitrile (solvent B). For the determination of perillic acid, a Zorbax RRHD Eclipse C18 column (50 × 2.1 mm, 1.8 µm; Agilent) was used. The injection volume was 2 µL and the flow rate was set to 0.6 mL/min. For the chromatographic separation, a gradient was run using 0.1% formic acid in water (solvent A) and acetonitrile (solvent B). Detection was performed using a triple quadrupole mass spectrometer (Triple Quad 6500 or API 4000, Sciex) in MRM mode. Measurements were carried out in the positive electrospray ionization mode. The system was controlled using Analyst 1.7.1 software (Sciex).

For monoterpene analysis, 300 µL plasma samples were processed by solid-phase extraction. 1,8-Cineole and limonene were quantitatively determined by GC-MS. For sample preparation, plasma samples were added to the internal standard solution (2.0 µg/mL menthol in methanol) in Eppendorf tubes. Afterwards, SPE cartridges (C18 cartridge; Waters) were equilibrated with methanol, then with water. Samples mixed with the internal standard were loaded onto the cartridge. The eluate was collected and loaded onto the cartridge twice more, then the cartridge was washed three times with water. Finally, the analytes were eluted with a mixture of ethylacetate/hexane. A sample vial was filled with the upper phase and used for the GC-MS measurement. The separation was carried out on a gas chromatograph 7890A from Agilent using an Agilent HP-innowax capillary column (30 m × 320 µm × 0.25 µm). The injection volume was 1.5 µL. A temperature gradient of the column oven was run. Detection was performed using a mass spectrometer (5975C, Agilent with electron impact ionization in selected ion monitoring mode).

Limonene (purity 99.6% by GC), perillic acid (purity 99.4% by titration), menthol (purity ≥ 98% by GC), and methylparaben (content ≥ 99%) were purchased from Sigma-Aldrich, eriocitrin (content 88.8%) was from HWI Analytik GmbH, and amarogentin (content 91%), 1,8-cineole (content 99%), gentiopicroside (content 96%), and verbenaolin (content 100%) were from PhytoLab.

Calibration ranges were 20–10 000 ng/mL for 1,8-cineole and 20–5000 ng/mL for limonene. Perillic acid had a range of 100–9000 ng/mL, gentiopicroside and verbenaolin a range of 5–1000 ng/mL, and the further marker analyte had a range of 2–400 ng/mL. The lowest concentration indicated for each concentration range represents the respective LLOQ. Calibration ranges covered the plasma concentrations of all study samples. Calibra-
tion and quality control samples were prepared in canine plasma. The analytical method used for the quantification of gentiopicroside, verbenalin, and the further marker analyte was fully validated in compliance with relevant EMA guidelines for bioanalytical method validation [27]. The performance of all analytical methods used was controlled via QC samples.

For the LC-MS/MS methods, correlation coefficients of 0.9996 (perillic acid, verbenalin), 0.9997 (further marker analyte), and 0.9998 (gentiopicroside) were obtained. Accuracies of the calibration samples were in the range of 93.17–104.8% (perillic acid), 93.94–105.2% (verbenalin), 94.82–107.1% (gentiopicroside), and 94.18–112.3% (further marker analyte). QC sample accuracies ranged between 83.43–95.79% (perillic acid), 93.08–109.9% (gentiopicroside), 91.94–108.6% (verbenalin), and 88.89–115.0% (further marker analyte).

For the GC-MS methods, correlation coefficients ranged between 0.9996–0.9998 (1,8-cineole) and 0.9981–0.9997 (limonene). For the calibration samples, accuracies were in the range of 91.26–117.8% (1,8-cineole) and 89.35–116.5% (limonene). QC sample accuracies ranged between 84.95–109.3% (1,8-cineole) and 83.01–143.8% (limonene).

Pharmacokinetic parameters derived were determined model independently by non-compartmental analysis using Certara Phoenix 64 WinNonlin software (version 8.2.0.4383). Plasma concentrations below LLOQ were set to “0” before Cmax and afterwards omitted. Cmax and tmax values were read directly from the observed concentration-time points. Areas under the curves were calculated according to the linear/log trapezoidal rule, which uses linear data obtained during the absorption phase up to Cmax and logarithmically transformed concentrations thereafter. Although not the focus of this work, the apparent terminal elimination half-life was calculated using nonlinear regression on data points visually assessed to be on the terminal phase of concentration curves. Half-life times were only determined when meaningful, i.e., when at least three measured values above LLOQ were available in the elimination phase. The lag time was taken as the time interval from dosing to the sampling time point for the first quantifiable concentration of an analyte. For graphical presentations, all plasma concentrations below LLOQ were set to “0”.

Contributors’ Statement


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Conflict of Interest

Financial: Jan Seibel and Meinolf Wonnemann are employees of Bionorica SE, Germany. Financial: Astrid Neumann and Anne Müller are employees of Bionorica research GmbH, Austria.

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