In vivo and in vitro palatability testing of a new paediatric formulation of valaciclovir

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AIMS

The palatability of a new paediatric formulation of valaciclovir was assessed in children and their parents: non-inferiority of the new paediatric formulation (test formulation) compared to the reference formulation was investigated.

METHODS

In vivo palatability testing was performed in a randomized, two-period, multicentre, cross-over study. Children and their parents scored the liking of the new paediatric valaciclovir formulation and the reference formulation on a 100 mm visual analogue scale (VAS). To support formulation development and palatability testing, electronic tongue measurements were applied.

RESULTS

The electronic tongue measurement indicated taste-masking capabilities for three different formulations in the developmental phase. A glycerol-based formulation was further tested and compared to the reference formulation prepared out of crushed and suspended tablets. The mean difference (95% CI) in VAS scores between both formulations, as indicated by the children (n = 20), was 2.4 (−8.5, 13) mm, in favour of the new paediatric valaciclovir formulation. The mean (95% CI) difference in VAS scores indicated by the parents (n = 20) was −0.9 (−12, 9.8) mm.

CONCLUSION

The palatability of the new paediatric valaciclovir formulation was considered non-inferior to the reference formulation prepared out of crushed tablets. We were able to optimize the study design and number of children to be included in the palatability testing by using electronic tongue measurements.
WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Acceptable drug formulations for children are often lacking. Valaciclovir is a drug for which there is a need for an appropriate paediatric formulation.
- Palatability is a key characteristic for acceptability of oral drug formulations and compliance, especially in children.
- Experience to test the acceptability of drug formulations in children is limited.

WHAT THIS STUDY ADDS

- This is the first study in which results from palatability testing in children and adults, as well as results from an electronic tongue assessment, are simultaneously available.
- The number of children needed for a comparative taste assessment can be lowered by application of an electronic tongue measurement during the development of a new paediatric formulation.
- The palatability of the new paediatric valaciclovir formulation was non-inferior to the reference formulation prepared out of crushed tablets.

Introduction

The palatability of oral drug formulations is a key characteristic for the acceptability and compliance to drug therapy, especially for children [1–3]. This aspect is emphasized by the regulatory authorities in the ‘Guideline on pharmaceutical development of medicines for paediatric use’, in which a verification of the acceptability of a new paediatric formulation prior to its approval is demanded [3]. In addition to this, the Paediatric Regulation of 2006 requests the development of appropriate formulations for children, but without performance of unnecessary clinical trials in children [4]. Palatability testing is best performed in the paediatric target population due to high differences in taste preferences between adults and children, and also between healthy and sick children [2]. However, it is debatable when a drug formulation can be considered acceptable, and how acceptability should best be tested in children [5]. Research is needed to determine which methods are best to test for acceptability of different formulations, for different diseases and for children of different ages and stages of development. Experience in testing the acceptability of drug formulations in children is still limited [6–10]. General considerations for performing taste trials in children are included in the EMA reflection paper: “Formulations of choice for the paediatric population” [2]. The validity of the methods used for sensory evaluation varies with the age of the children. A facial hedonic scale and/or a visual analogue scale are commonly used in taste assessments of drug formulations in young children [10]. Also, the forced-choice tracking procedure and rank-order method can be used to assess taste.

In general, palatability testing of drug formulations with human taste panels is reluctantly chosen and hampered by ethical concerns, toxicological aspects, high costs and poor reproducibility [11]. Taking all regulatory, ethical and statistical requirements into account, use of in vitro methods for the taste assessment of oral drug formulations might be a favourable alternative.

The electronic tongue is a promising tool for use in in vitro taste assessments [9]. These instruments are commonly equipped with a sensor array and based on electrochemical measurement principles including potentiometry, voltammetry and amperometry [12–14]. Most of the used electronic tongue sensors are potentiometric membrane electrodes following the Nernst law and their membrane potentials are correlated to at least one reference electrode [11–13]. The sensor responses are caused by interactions of the sample molecules with incorporated components of the electrode membrane. Currently, two commercially available electronic tongue systems are employed for the taste assessment of drug formulations: the α-Astree (AlphaMOS, Toulouse, France) and the taste sensing systems TS-5000Z and SB402B (Insent Inc., Atsugi-Shi, Japan) [13–15]. In the case of the TS-5000Z and SB402B, different sensors are dedicated to different tastes, such as bitterness and sourness. The α-Astree and non-commercially available electronic tongues work cross-selectively, meaning that one sensor is dedicated to a combination of different tastes [15]. Even though electronic tongues are commonly used tools in the development of properly taste-masked drug formulations, the obtained results are only a relative interpretation of taste [9]. A relationship between electronic tongue measurements and human taste has been demonstrated to some extent in adults, but not in children [12, 14, 16–18].

Valaciclovir is used for the treatment and prophylaxis of herpes simplex virus and varicella zoster virus infections [19]. However, in Europe, its use is off-label in children below the age of 12 years. The US Food and Drug Administration (FDA) label information describes the preparation of an oral liquid formulation from crushed tablets, but this formulation has to be discarded after 28 days [20]. To overcome practical problems associated with the formulation prepared out of crushed tablets, such as the short shelf-life and obstruction of feeding tubes, we developed a new extemporaneous paediatric valaciclovir formulation, as described previously [21].

The aim of this study was to investigate the palatability of this new extemporaneous valaciclovir formulation, compared with the frequently used extemporaneous formulation from crushed and suspended valaciclovir tablets. In vivo palatability testing of the new paediatric valaciclovir formulation was performed in children and their parents. The electronic tongue was applied for the formulation development as well as for the in vitro taste assessment of the new formulation.

Methods

Materials

Electronic tongue. For the preparation of the standard and washing solutions for the electronic tongue, potassium
chloride (Gruessing, Filsum, Germany), potassium hydroxide (Gruessing, Filsum, Germany), tartaric acid (AppliChem, Darmstadt, Germany), hydrochloric acid (Merck, Germany) and absolute ethanol (VWR international, Darmstadt, Germany) were used. The measurements were performed with a sensor array consisting of eight commercially available sensors (Insent Inc., Atsugi-Shi, Japan), each dedicated to a defined taste: SB2AAE: umami; SB2CT0: saltiness; SB2AE1: astringency; SB2CA0: sourness; SB2AC0: bitterness (cationic substances); SB2AN0: bitterness (cationic substances); SB2BT0: bitterness (cationic substances); SB2C00: bitterness (anionic substances).

Valaciclovir formulations. Valaciclovir formulations were prepared based on valaciclovir hydrochloride monohydrate (Duchefa Farma, Haarlem, The Netherlands), glycerol (Spruyt Hillen, IJsselstein, The Netherlands), maltodextrin (Kleptose® Linecaps, Roquette, France), citric acid (Duchefa Farma, Haarlem, The Netherlands), disodium hydrogenphosphate (Spruyt Hillen, IJsselstein, The Netherlands), OraSweet® SF (Paddock Laboratories LLC, Minneapolis, US) and purified water. Samples for the formulation development comprised valaciclovir in three different vehicles, named formulations A, B and C. Formulation A contained glycerol as main excipient, formulation B maltodextrin, and formulation C contained both glycerol and maltodextrin as excipients (see Table 1).

The test formulation for the in vivo palatability assessment was chosen based on the results of the first electronic tongue measurement combined with the results of pharmaceutical testing (including stability). The reference formulation was derived from the extemporaneous liquid made from crushed innovator tablets as described in the FDA label information with OraSweet® SF as suspension vehicle [20, 22].

**Electronic tongue measurement protocol and sample preparation**

Electronic tongue measurements were performed using the taste sensing system SA402B (Insent Inc.) and the measurement protocol according to Woertz et al. [23]. Two electronic tongue measurements were performed: (a) one in the developmental phase and (b) one to support the in vivo palatability testing. The most reliable use of electronic tongue measurements for drug formulation development requires a concentration-dependent behaviour of the applied sensors. Therefore, the behaviour of the sensors to different concentrations of valaciclovir in only water (as valaciclovir hydrochloride monohydrate, Duchefa Farma, Haarlem, The Netherlands) was determined prior to evaluating the drug formulations. For this purpose, calibration samples containing 0, 0.2, 2, 20 and 50 mg ml⁻¹ valaciclovir were analysed.

Samples with 0, 20 and 50 mg ml⁻¹ valaciclovir of the formulations A, B and C were tested for the formulation development. The samples for the taste assessment of the newly developed formulation [21] comprised 20 mg ml⁻¹ and 50 mg ml⁻¹ valaciclovir in the chosen vehicle, or 25 mg ml⁻¹ and 50 mg ml⁻¹ in OraSweet® SF (Table 1).

**Table 1**
Composition of formulations tested by the electronic tongue: (a) in the developmental phase and (b) to support the in vivo palatability testing.

<table>
<thead>
<tr>
<th>Composition of the formulation</th>
<th>Abbreviation</th>
<th>Valaciclovir concentration (mg ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Formulations developmental phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formulation A: water, glycerol (42.5%), citric acid, disodium hydrogenphosphate</td>
<td>A1/A2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Val20_A</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Val50_A</td>
<td>50</td>
</tr>
<tr>
<td>Formulation B: water, maltodextrin (0.5:1 mol/mol valaciclovir), citric acid, disodium hydrogenphosphate, sorbic acid</td>
<td>B1/B2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Val20_B</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Val50_B</td>
<td>50</td>
</tr>
<tr>
<td>Formulation C: water, glycerol (25.5%), maltodextrin (0.5:1 mol/mol valaciclovir), citric acid, disodium hydrogenphosphate</td>
<td>C1/C2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Val20_C</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Val50_C</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Val20</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Val50</td>
<td>50</td>
</tr>
<tr>
<td>Water</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Formulations for in vivo palatability assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test (formulation A): water, glycerol (42.5%), citric acid, disodium hydrogenphosphate</td>
<td>Test</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Val20_test</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Val50_test</td>
<td>50</td>
</tr>
<tr>
<td>Reference: OraSweet SF®: water, glycerin, sorbitol, sodium saccharin, xanthan gum, citric acid, sodium citrate methylparaben, potassium sorbate, propylparaben, citrus-cherry flavour.</td>
<td>Reference</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Val25_ref</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Val50_ref</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Val20</td>
<td>20</td>
</tr>
<tr>
<td>Water</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Data analysis of the electronic tongue

Data obtained by electronic tongue measurements were evaluated using Microsoft Excel®, OriginPro 9.0G and Simca 13.0.2 (Umetrics, Sweden) for univariate and multivariate data analysis. The sensor responses were corrected with an external standard solution of 0.5 mM quinine hydrochloride dihydrate (Buchler GmbH, Germany). Each sample was measured four times, and the last three measurements were used to calculate the mean values and standard deviations. The sensor response pattern of the vehicles (formulations without valaciclovir) was used as a positive reference for taste-masking efficiency (i.e. the best taste possible to achieve with the vehicle). Conversely, the pure drug solutions with 20 mg ml⁻¹ and 50 mg ml⁻¹ valaciclovir in water were used as a negative taste reference. For example, if one of the bitter sensors detects a reduced sensor signal for a drug formulation compared to the pure drug solution, a taste-masking effect of the excipients can be assumed [9, 12, 13, 24, 25]. This indicates taste-masking efficiency of the excipients.

To perform the multivariate statistical analysis, a principal component analysis (PCA) was performed to objectively compare the drug formulations, the pure drug solutions (20 mg ml⁻¹ and 50 mg ml⁻¹ valaciclovir in water) and the vehicles. To individually quantify the differences in the taste pattern of the tested samples of the test and reference formulations, the Euclidean distances were calculated using the formula:

\[
d(p,q) = \sqrt{\sum_{i=1}^{n} (p_i - q_i)^2}
\]

where \(p\) and \(q\) are the sensor responses of the different sensors and samples being compared.

In vivo palatability testing

Study population. Children were eligible if aged at least 4 and less than 12 years and having received (val)aciclovir in the past, using valaciclovir as prophylaxis at that time, or had a high probability of future use, such as children with primary immune deficiency or recipients of haematopoietic stem cell transplantation. Children and one of their parents attending the outpatient clinic of the Leiden University Medical Centre, Radboud University Medical Centre or the University Medical Centre Utrecht in The Netherlands, were asked for their participation. Children with a sensitivity or idiosyncrasy to medicinal products or excipients were excluded, as were children with any condition that influences taste sensation (such as upper respiratory infection, mucositis or use of medication that influences taste perception).

The Central Committee on Research Involving Human Subjects (CCMO) provided ethical approval for performance of the assessment (NCT01682109). The trial conformed to the principles of the Declaration of Helsinki and regulations concerning clinical trials, as well as the ‘Code of conduct relating to expressions of objection by minors participating in medical research’ (http://www.ccmo.nl/en/codes-of-conduct).

Study design of the palatability testing. The palatability assessment was a randomized, two-period, multicentre, cross-over study. The design of the study was based on the EMA Reflection Paper and description of conducting taste assessment trials in children [2, 6–8, 26]. The main outcome was based on liking indicated by the subjects on a 100 mm visual analogue scale (VAS) combined with five smiley faces (Figure 1). Prior to the start of the study, signed informed consent was given by the legal guardian(s) for participation of the child. If the parent also participated, signed informed consent was given for their own participation. Only after all the child agreed to participate in the assessment were study procedures started.

Figure 1

Applied combined 100 mm visual analogue/facial hedonic scale

Correlating the results of an electronic tongue measurement with results from a human taste panel increases the value of the information from both measurements. Since the ability to describe basic tastes develops during the first decade of a child’s life, not the children but the parents were asked to describe the basic tastes of the different valaciclovir formulations [28, 29]. Parents could report all the tastes that were applicable: bitter, sweet, salt, sour or other, regardless of the intensity of taste.

With an expected difference between VAS scores of the formulations of 10 mm (see electronic tongue measurements in Results section), a standard deviation of the within-subject differences of about 30 mm and a non-inferiority margin of 10 mm, a total of 20 children was needed to reach a power of 80% to demonstrate non-inferiority of the test formulation compared to the reference formulation.

**Results**

**Electronic tongue measurement as support for the formulation development**

Concentration-dependent sensor responses towards valaciclovir were observed for all applied sensors. Sensors SB2CT0 (saltiness), SB2AE1 (stringency) and SB2BT0 (bitterness of cationic substances) were found to be most sensitive, showing the best concentration dependency towards the pure drug substance indicated by the largest slope. (Slopes (mean ± SD): SB2BT0: 54.1 ± 0.2; SB2CT0: −43.8 ± 0.3; SB2AE1: −43.4 ± 0.3; SB2AN0: 28.0 ± 0.3; SB2CO0: −22.7 ± 0.3; SB2CA0: 19.1 ± 0.5; SB2AC0: 17.6 ± 0.2; SB2AAE: 8.8 ± 0.3).

The three different drug-containing formulations (formulation A, B and C, Table 1), each with different concentrations of valaciclovir, were analysed by the employed sensor array. The PCA was based on the first two principal components explaining 92% of the information given by the sensor responses (principal component 1: 71.1%, principal component 2: 20.9%, Figure 2). In this case, the first principal component defines the bitterness of the investigated sample: samples located on the left side of the map (vehicles) are less bitter than those located on the right side of the map (drug-containing formulations). Merging sensorial information in such a map helps to assess how different samples are detected by the sensors. For example, it indicates a similar taste for the drug formulations ‘Val20_A’ and ‘Val20_C’ (Figure 2). In general, taste-masking of valaciclovir was observed in all investigated drug formulations. As the formulations containing maltodextrin had an inferior physical stability (pharmaceutical testing, unpublished data), formulation A was selected for further investigations.

**Electronic tongue measurement to evaluate the formulations for in vivo palatability testing**

The in vitro taste-masking capability of the test formulation (formulation A) was compared to the reference formulation (Table 1). The obtained sensor responses were initially evaluated by multivariate data analysis by performing a PCA with two principal components (Figure 3). The first principal component described 88.2% of the sensor information. No differentiation as mentioned above (right side: bitter; left side: less bitter) was possible. In this case the main information along the x-axis differentiates the two vehicles. Based on observations during sample handling, this was most probably due to the different fluidity of the samples, indicating different viscosities. Interpreting the map, more viscous samples are located on the left side and less viscous on the right side. Bitterness might be differentiated along the y-axis. The small distances between samples ‘Val20_test’ and ‘test’ demonstrate a good taste-masking effect of the vehicle.

**Figure 2**

PCA map for the formulation development of valaciclovir (mean, $n = 3$, $R^2 = 0.920$, $Q^2 = 0.508$): Val20/50: valaciclovir in water (20 and 50 mg ml$^{-1}$); A1/2, B1/2 and C1/2: vehicles; Val20/50_A/B/C: valaciclovir in vehicles A, B and C (20 and 50 mg ml$^{-1}$).
Conversely, the test sample containing 50 mg ml$^{-1}$ valaciclovir (Val50_test) was located close to the pure drug solution (Val20), indicating only a minor taste-masking effect. The reference formulations (Val25_ref and Val50_ref) were located close to each other but further away from their corresponding vehicle (reference). This indicated differences in taste sensation.

The calculated Euclidean distances are shown in Figure 4 and Table 2. For the test and reference formulations, the samples containing 20 mg ml$^{-1}$ and 25 mg ml$^{-1}$ valaciclovir demonstrated an improved taste-masking efficiency indicated by higher distances between the drug formulations to the pure drug solution and lower distances to their corresponding vehicles. Both calculated Euclidean distances of the reference formulations were higher than those of the test formulations (Table 2), indicating that the reference formulations were less similar in the taste pattern to either the pure drug solution or the reference vehicle. Due to this contradictory outcome, the test formulation was assumed to better taste-mask valaciclovir than the reference formulation. As a result, a difference between liking of the test and reference formulation of approximately 10 mm on the 100 mm VAS score in favour of the new paediatric formulation was expected for the palatability assessment in children.

### In vivo palatability testing

Twenty-one children and 20 parents were included in the taste assessment. One child tasted only two formulations, and the parents of another child were not able to attend. Therefore, VAS scores of all three liquids from 20 children and 20 parents (19 child–parent pairs) could be included in the analysis. Characteristics of the subjects and VAS scores are displayed in Table 3. For the children, mean (95% CI) VAS scores were 26 mm (18, 34) for the test formulation and 24 mm (16, 32) for the reference formulation and a mean difference (95% CI) of 2.4 (−8.5, 13) mm, in favour of the test formulation. The test formulation can therefore be considered non-inferior to the reference formulation. Based on the VAS scores of the formulations, seven children (35%) preferred the test formulation, four (20%) the reference formulation and nine (45%) children indicated a difference of 10 mm or less between the formulations. Inclusion of the interaction of period by formulation as a fixed effect did not have a significant effect ($P = 0.871$) and therefore no carryover effects were observed.

For the parents, mean (95% CI) VAS scores were 45 (36, 54) mm for the test formulation and 46 (37, 55) mm for the reference formulation and a mean difference (95% CI) of −0.9 (−12, 9.8) mm, in disadvantage of the test formulation. Based on the VAS scores of the formulations, six parents (30%) preferred the test formulation, seven (35%) the reference formulation and seven (35%) indicated a difference of
Table 3
Baseline characteristics and results from scores on the visual analogue scale (VAS score)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Children n = 20</th>
<th>Parents n = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median, range)</td>
<td>8.7 (6.3, 11.9)</td>
<td>41 (34, 54)</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>6/14</td>
<td>11/9</td>
</tr>
<tr>
<td>Underlying condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary immune deficiency</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Stem cell transplantation</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>VAS scores (mm) (mean, 95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test formulation</td>
<td>26 (18, 34)</td>
<td>45 (36, 54)</td>
</tr>
<tr>
<td>Reference formulation</td>
<td>24 (16, 32)</td>
<td>46 (37, 55)</td>
</tr>
<tr>
<td>Test – reference formulation</td>
<td>2.4 (–8.5, 13)</td>
<td>−0.9 (–12, 9.8)</td>
</tr>
</tbody>
</table>

10 mm or less between formulations. The test for the interaction of period by formulation showed a P-value of 0.074 and therefore carryover effects cannot be ruled out for the parents. When only the results from the first period are analysed: eleven parents tasted the test formulation and nine the reference formulation. In this way, the mean (95% CI) difference between the VAS scores of the formulations was 12 (–4.5, 28.6) in favour of the test formulation.

VAS scores of the children and the parents did not show a correlation (correlation coefficient = −0.03, P = 0.91). Predictions made by 18 parents as to which formulation would be preferred by their child showed six (33%) correctly predicting their child’s preference and ten (56%) choosing a different formulation. Two children were not able to show a preference.

**Combined electronic tongue and taste testing results**

Nineteen parents assigned basic tastes to the formulations. The predominantly chosen basic tastes by the parents for both the reference and the test formulation were bitterness and sweetness. Twelve parents (63%) thought the reference formulation had a bitter taste and eight parents (42%) thought the test formulation had a bitter taste. The high percentage of parents tasting bitter corresponds to the results found by the electronic tongue, in which the bitter sensor (SB2BT0) was the most distinctive for valaciclovir, together with sensor signals of the saltiness and astringency receptor. The parents did not predominantly choose the saltiness taste. Twelve parents (63%) indicated the reference formulation as being sweet and eleven parents (58%) thought the test formulation was sweet.

**Discussion**

The palatability of the newly developed paediatric valaciclovir formulation was non-inferior to the reference formulation in children. No significant differences were found between the liking of the new paediatric formulation of valaciclovir, compared to crushed and suspended tablets. Non-inferiority was shown for the children, but not for the parents, as the lower margin of the 95% CI was just below −10% (−11.6%). This can be explained by the higher mean VAS score of the reference formulation compared to the test formulation, and the somewhat higher variance in VAS scores of the parents, compared with the children. Variability in preference of the test or reference formulation was also observed between the subjects: 35% of the children and 30% of the parents preferred the test formulation and 20% of the children and 35% of the parents preferred the reference formulation. No carryover effects were observed for the children, but carryover effects for the parents could not be ruled out. When only the results from the first period are analysed, non-inferiority of the reference formulation was observed, also for the parents. When carryover effects are observed, an alternative for an AB crossover design should be chosen [31]. However, this would imply a possible larger burden of the assessment such as a longer assessment, more visits or more subjects, which are undesirable in studies involving paediatric patients.

No correlation was found between the liking of the formulations by the children and their parents. Only a minority of the parents were able to correctly predict the preferred formulation for their child. This confirms that taste assessments of (new) paediatric formulations should be performed in children [2].

This is the first study in which results from palatability testing in children and adults as well as results from an electronic tongue assessment are simultaneously available. Based on the results from the electronic tongue measurement, it was expected that the test formulation would have a slightly better palatability than the reference formulation. Without the use of the electronic tongue in the palatability testing, no difference in VAS scores would be expected and the number of children to be included would have been more than 3.5-fold higher. The expected difference of 10 mm in VAS score between the formulations could not be confirmed, nor ruled out. An explanation could be the complexity of tastes of both formulations. The pure active pharmaceutical ingredient valaciclovir has a bitter taste. The test and reference formulation both contain citric acid, which has a sour taste, and both contain sweet tasting substances. However, sensors to capture the complexity of sweetness were not available, which is a limitation of this study. Sweetness could thus not be measured with the electronic tongue. Children especially mostly like sweetness, but it is generated by substances with a wide molecular diversity. Sweetness sensors for selected sweet-tasting substances have recently been developed and development is extended to more complicated molecules [12, 32, 33]. Validated sensors to measure sweetness are needed for optimal in vitro evaluation of paediatric drug formulations. Besides the complexity of tastes of the formulations, also the use of a non-trained taste panel influences the precision of the results. To develop a taste-masking strategy during formulation development, more precise results are desirable, encouraging the application of electronic tongues. Aspects such as texture, smell and appearance of a formulation can influence acceptability [2, 3], but were neither scored...
nor measured during the assessment. However, for acceptability, solutions are generally preferred over suspensions [34]. The new formulation of valaciclovir is a solution, which, for that reason, would be preferred over the suspension prepared out of crushed tablets.

One of the strengths of this study is that we were able to perform palatability testing in a paediatric target population using valaciclovir or with a high probability of future use. A different paediatric population who could benefit from the new paediatric formulation of valaciclovir are (premature) neonates. Because of the possible burden of the trial assessments and the lack of experience with methods for acceptability testing of drug formulations in neonates, they were not included in the study.

The difference in palatability concentration between the test and reference formulation (20 vs. 25 mg ml\(^{-1}\), respectively) is debatable. As was shown with the electronic tongue measurement, a higher concentration of palatability in water results in a higher sensor signal and an assumed more bitter-tasting formulation, which would be unfavourable for the reference formulation. However, the choice was made to use concentrations that would be used in clinical practice. The concentration for the test formulation was based on pharmaceutical stability testing and expected ease of calculation of the volume to be administered. The concentration of the reference formulation was as included in the FDA label information, and would thus be used in daily practice.

In conclusion, we found that in children, the palatability of the new paediatric valaciclovir formulation was non-inferior to the reference formulation prepared out of crushed tablets. Next to a longer shelf-life than crushed and suspended tablets combined with a comparable exposure as tablets, the results of this palatability study further support the use of the new extemporaneous paediatric formulation as an alternative formulation for (crushed and suspended) valaciclovir tablets. By applying an electronic tongue measurement during the development and as screening for the in vivo palatability testing, we were able to optimize effort and number of children to be included in a clinical trial.

Competing Interests
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Contributors
All authors made a substantial contribution to the design of the study, the acquisition and/or interpretation of the data and approved the final article to be submitted.

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