An increasing number of reports suggest that inhibitors of the dipeptidyl-peptidase IV (DPP4i) are implicated in the development of bullous pemphigoid (BP) [1–8]. We investigated BP patients diagnosed in our center (Department of Dermatology and Venereology, Lausanne University Hospital Centre, Lausanne, and Department of Dermatology, Inselspital – Bern University Hospital, Bern, Switzerland; Centro Studi GISED, Bergamo, Italy). We searched the database of the laboratory of dermatopathology with the keyword “bullous pemphigoid” between January 2007 and July 2013. We next identified patients with a definite diagnosis of BP with or without adult onset diabetes mellitus (AODM). The diagnosis of BP was based on typical or consistent clinical features, typical or compatible histological findings, and positive immunopathological studies, including direct and indirect immunofluorescence microscopy, and enzyme-linked immunosorbent assays (ELISA) for BP180 and BP230. If serum was not available for testing, diagnosis was based on the presence of 3 of 4 well-established clinical criteria for BP in patients having linear deposits of C3 and/or IgG along the epidermal basement membrane as delineated by the en/113 men) were selected, with a mean age of 76.5 years. Use of DPP4i for each patient was assessed according to the antidiabetic treatment(s). The association between BP development and the intake of DPP4i for each patient was assessed according to the World Health Organization and Uppsala Monitoring Centre (WHO-UMC) scale, a standardized causality assessment scale of adverse drug reactions [11], to allow direct comparison with the aforementioned study [1].

The control group consisted of 170 patients with AODM, selected by year of birth, who were followed up by the endocrinology outpatient clinic between 2012 and 2014. The patients’ files were reviewed concerning treatment for diabetes, specifically the use of DPP4i. Both groups were compared for gender, treatment with DPP4i, age, and calendar year of consultation with a 2-sample t test. The χ² test and the Wilcoxon rank-sum test were used for categorical and continuous variables, respectively. We compared exposure to DPP4i in both groups with adjustment for confounders such as age, gender, and calendar year of visit with multiple logistic regression models. Effect of exposure was expressed in terms of odds ratios (OR) along with their 95% confidence intervals (CI).

Between January 2007 and July 2013, we identified 93 BP patients. Among these, 23 (24.7%; 12 women/11 men) were diabetic, 9 of whom were treated with DPP4i. The mean age at inclusion in the case series was 77.6 years (68–93 years). The average follow-up was 55.3 months (32–73 months) (Table 1). Patients developed BP between 5 months and over 4 years after the introduction of DPP4i. Of the 9 patients, 5 were on vildagliptin + metformin, 3 were on sitagliptin + metformin, and 1 was on vildagliptin/metformin (later replaced by sitagliptin/metformin) combination. In 7 cases, the association between drug intake and BP onset was classified as “possible,” which represents a probability of less than 50% for DPP4i to have caused the disease. Two cases (patients 3 and 7) developed BP more than 48 months after the first use of DPP4i and were classified as unlikely.

A total of 170 nondermatological control patients (57 women/113 men) were selected, with a mean age of 76.5 years. Use of DPP4i was found in 9 out of 23 (39.1%) BP patients with AODM and in 57 out of 170 (33.5%) diabetic control patients. The crude OR for DPP4i use in diabetic BP patients was 1.27 (95% CI, 0.52–3.12, p = 0.596). When the effect of gender, age, and calendar year was accounted for, the adjusted OR increased to 2.48 (95% CI, 0.75–8.3, p = 0.137).

An increasing number of patients who developed BP during treatment with DPP4i has been reported, raising the question about a causal relationship [3–10]. In France, there has been an average of 10 cases of possible DPP4i-induced BP cases per year from 2008 to 2012 [12, 13].

We observed a prevalence of 39% of DPP4i in cases and 33% in controls. When the effect of gender, age, and year was accounted for, there was a nonsignificant trend towards more use of DPP4i in BP patients. Most diabetic patients with BP had a history of vildagliptin use, a molecule already incriminated in a previous study [1].

A total of 24.7% of the BP patients were diabetic, with a similar proportion of women and men (25 and 24.4% respectively), whereas in the general Swiss population aged 75 years or older, the prev-
The prevalence of AODM is approximately 15% in men and 11% in women [14]. Our findings support previous reports suggesting an association between AODM and BP [15, 16].

This is the first study to investigate the potential role of DPP4i in triggering BP in the Swiss population. Based on the available data, an association between the onset of BP and the use of DPP4i cannot be shown. Further prospective studies are needed to validate our findings.

Key Message
Our retrospective case-control study raises the awareness that BP might be a potential side effect of DPP4i.

Disclosure Statement
The authors have no conflicts of interest to disclose.

Table 1. Demographics and characteristics of the BP cases with type-2 diabetes treated with DPP-4 inhibitors

<table>
<thead>
<tr>
<th>Patient/gender/age, years</th>
<th>Glaptin type</th>
<th>Glaptin at onset (yes/no)</th>
<th>Glaptin intake prior to BP onset, months</th>
<th>BP outcome</th>
<th>Glaptin at last follow-up (yes/no)</th>
<th>Comorbidities/other therapies (9–11)</th>
<th>Causality drug induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/70</td>
<td>Vildagliptin&lt;sup&gt;a&lt;/sup&gt; Saxagliptin/metformin&lt;sup&gt;b&lt;/sup&gt; Vildagliptin&lt;sup&gt;c&lt;/sup&gt; Sitagliptin/metformin</td>
<td>Yes</td>
<td>12</td>
<td>Relapse at 39 months after the initial episode, currently on MTX 15 mg/week 45 months of follow-up</td>
<td>Yes</td>
<td>–</td>
<td>Possible</td>
</tr>
<tr>
<td>2/F/84</td>
<td>Sitagliptin/metformin</td>
<td>Yes</td>
<td>36</td>
<td>Remission after doxycycline and nicotinamide Occasional itch 48 months of follow-up</td>
<td>No</td>
<td>–</td>
<td>Possible</td>
</tr>
<tr>
<td>3/M/73</td>
<td>Vildagliptin</td>
<td>Yes</td>
<td>&gt;48</td>
<td>Remission after topical corticosteroids 52 months of follow-up</td>
<td>No</td>
<td>–</td>
<td>Unlikely</td>
</tr>
<tr>
<td>4/F/70</td>
<td>Vildagliptin/metformin</td>
<td>Yes</td>
<td>5</td>
<td>Last relapse at 78 months after the initial episode, 3 relapses in total treated with topical corticosteroid courses 45 months of follow-up</td>
<td>Yes</td>
<td>–</td>
<td>Possible</td>
</tr>
<tr>
<td>5/M/68</td>
<td>Vildagliptin&lt;sup&gt;d&lt;/sup&gt; Sitagliptin/metformin</td>
<td>Yes</td>
<td>30</td>
<td>Remission on MTX 10 mg/week and dermocorticoids 32 months of follow-up</td>
<td>No</td>
<td>Dementia</td>
<td>Possible</td>
</tr>
<tr>
<td>6/M/80</td>
<td>Sitagliptin</td>
<td>No, stopped 24 months before</td>
<td>48</td>
<td>Remission after topical corticosteroids Occasional itch 63 months of follow-up</td>
<td>No</td>
<td>–</td>
<td>Possible</td>
</tr>
<tr>
<td>7/M/85</td>
<td>Vildagliptin/metformin</td>
<td>Yes</td>
<td>&gt;48</td>
<td>Remission after topical corticosteroids 68 months of follow-up</td>
<td>Yes</td>
<td>Spironolactone intake</td>
<td>Unlikely</td>
</tr>
<tr>
<td>8/M/93</td>
<td>Vildagliptin</td>
<td>Yes</td>
<td>21</td>
<td>Remission after topical corticosteroids 72 months of follow-up</td>
<td>Yes</td>
<td>–</td>
<td>Possible</td>
</tr>
<tr>
<td>9/M/76</td>
<td>Sitagliptin</td>
<td>Yes</td>
<td>10–11</td>
<td>Remission after topical corticosteroid courses with relapse 73 months of follow-up</td>
<td>Yes</td>
<td>Dementia</td>
<td>Possible</td>
</tr>
</tbody>
</table>

BP, bullous pemphigoid; F, female; M, male; MTX, methotrexate. <sup>a</sup> Switched to saxagliptin/metformin after 36 months. <sup>b</sup> Switched to vildagliptin again after 24 months. <sup>c</sup> Switched to sitagliptin/metformin after 14 months. <sup>d</sup> Switched to sitagliptin/metformin after 31 months.

References