Article: Treatment

Monotherapy with the once-weekly GLP-1 analogue dulaglutide for 12 weeks in patients with Type 2 diabetes: dose-dependent effects on glycaemic control in a randomized, double-blind, placebo-controlled study

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Abstract

Aims Evaluate dose-dependent effects of once-weekly dulaglutide, a glucagon-like peptide-1 analogue, on glycaemic control in patients with Type 2 diabetes treated with lifestyle measures with or without previous metformin.

Methods This 12-week, double-blind, placebo-controlled, dose–response trial randomized 167 patients who were antihyperglycaemic medication-naïve or had discontinued metformin monotherapy [mean baseline HbA1c 59 ± 8 to 61 ± 8 mmol/mol (7.6 ± 0.7 to 7.8 ± 0.8%)] to once-weekly injections of placebo or dulaglutide (0.1, 0.5, 1.0 or 1.5 mg).

Results A significant dose-dependent reduction in HbA1c (least squares mean ± se) was observed across doses (P < 0.001). HbA1c reductions in the 0.5, 1.0 and 1.5 mg dulaglutide groups were greater than in the placebo group [−10 ± 1, −11 ± 1 and −11 ± 1 vs. 0 ± 1 mmol/mol (−0.9 ± 0.1, −1.0 ± 0.1 and −1.0 ± 0.1 vs. 0.0 ± 0.1%), respectively, all P < 0.001]. Dose-dependent reductions in fasting plasma glucose were also observed [least squares mean difference (95% CI) ranging from −0.43 (−1.06 to 0.19) mmol/l for dulaglutide 0.1 mg to −1.87 (−2.56 to −1.19) mmol/l for dulaglutide 1.5 mg, P < 0.001]. Dose-dependent weight loss was demonstrated across doses (P = 0.009), but none of the groups were different from placebo. The most common adverse events were nausea and diarrhea.

Conclusions The observed dulaglutide dose-dependent reduction in HbA1c and its acceptable safety profile support further clinical development for treatment of Type 2 diabetes.


Keywords fasting blood glucose, GLP-1 receptor agonist, glucagon-like peptide-1, HbA1c, homeostasis model assessment 2

Abbreviations DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HOMA2-%B, homeostasis model assessment of β-cell function; HOMA2-%S, homeostasis model assessment of insulin sensitivity

Introduction

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that causes increases in glucose-dependent insulin secretion, inhibition of glucagon secretion, slowing of gastric emptying, and increased satiety [1]. Several GLP-1 analogues have been developed or are in development for treatment of Type 2 diabetes [2–7]. Dulaglutide (Dula; LY2189265; XXXXX, XXXXX), a long-acting GLP-1 analogue, consists of two GLP-1 peptides covalently linked by a small peptide to a human IgG4-Fc heavy chain (Fig. 1). The GLP-1 moieties contain amino acid substitutions that protect from inactivation by dipeptidyl peptidase-4 (DPP-4), while the linker peptide maintains the potency of the GLP-1 peptide. The IgG4-Fc is modified by substituting several amino acids to reduce interaction with high-affinity Fc receptors, cytotoxicity and immunogenicity [8]. The large molecule size is expected to limit renal clearance. The resulting half-life is approximately 4 days and time to peak concentration is 12–72 h [9].
Dose-dependent reductions in fasting plasma glucose, postprandial glucose and HbA1c were previously reported in patients with Type 2 diabetes (n = 43) receiving once-weekly dulaglutide (doses ranging from 0.05 to 8 mg) for 5 weeks [9]. The objective of this Phase 2 study was to assess the dose–response relationship with respect to HbA1c across a narrower range of doses and a longer 12-week treatment period.

**Research design and methods**

**Study design**

This 12-week, double-blind, placebo-controlled, dose–response study assessed the safety and efficacy of dulaglutide in patients with Type 2 diabetes (n = 167). The study was conducted between November 2008 and January 2010 in 44 sites in seven countries. Eligible patients were anti-hyperglycaemic medication-naïve or on metformin monotherapy. Inclusion criteria were: age ≥ 18 and ≤ 75 years; BMI ≥ 23 to ≤ 40 kg/m² for patients native to and residents of South and/or East Asia; ≥ 25 to ≤ 40 kg/m² for all other patients; stable weight for 3 months before screening; and HbA1c ≥ XX to ≤ XX mmol/mol ≥ 7.0 to ≤ 9.5% for anti-hyperglycaemic medication-naïve patients and > XX to ≤ XX mmol/mol > 6.5 to ≤ 9.0% [> XX to ≤ XX mmol/mol > 6.0 to ≤ 8.5% prior to a protocol amendment] for patients who were taking metformin. Exclusion criteria included treatment with any oral anti-diabetes drug other than metformin within 3 months or other GLP-1 analogue within 6 months prior to screening, prior use of insulin for long-term glycaemic control, serious cardiovascular condition, liver disease, history of pancreatitis or serum creatinine ≥ 1.5 mg/dl (men) or ≥ 1.4 mg/dl (women).

Study periods included: 2-week screening, 4- to 8-week lead-in (8-week washout after discontinuing metformin was required prior to obtaining the qualifying HbA1c); 12-week treatment period; and 4-week safety follow-up. After lead-in, an HbA1c value ≥ XX to ≤ XX mmol/mol ≥ 6.5 to ≤ 9.5% [≥ XX to ≤ XX mmol/mol ≥ 7.0 to ≤ 9.5%] prior to protocol amendment]] was required for randomization. Patients were randomized (block sizes of 5) to one of five treatment arms: placebo, 0.1 mg, 0.5 mg, 1.0 mg or 1.5 mg dulaglutide (Dula 0.1, Dula 0.5, Dula 1.0 and Dula 1.5) in a 1:1:1:1:1 ratio via an interactive voice-response system. In the original design, patients were randomized to placebo, 0.1 mg, 0.5 mg, 1.0 mg or 3.0 mg dulaglutide. Based on recommendations from the data monitoring committee of another dulaglutide study, the Dula 3.0 arm was discontinued in May 2009 and the protocol was amended to replace the Dula 3.0 arm with the Dula 1.5 arm. A total of 17 patients had been randomized prior to protocol amendment; the three patients on the Dula 3.0 dose were discontinued and the other 14 patients continued on randomized treatment.

Patients were stratified for randomization by country, BMI and pre-study therapy (metformin use or not). Study drug was administered once weekly; as this was a placebo-controlled study, the use of additional oral anti-diabetes drugs was permitted only when needed for rescue therapy (according to pre-specified criteria). If rescued, patients continued to administer the study drug until the last on-treatment visit. Other GLP-1 agonists and DPP-4 inhibitors were not allowed at any time.

A common protocol was approved at each site by an institutional review board and was performed in accordance with the principles of the Declaration of Helsinki. Prior to participation, all patients provided written informed consent.

**Study endpoints**

The primary efficacy measure was change from baseline in HbA1c at 12 weeks. Additional measures included changes in fasting plasma glucose (central laboratory), 7-point self-monitored plasma glucose, β-cell function and insulin sensitivity using the homeostasis model assessment 2 (HOMA2-%B and HOMA2-%S, respectively), body weight and proportion of patients achieving HbA1c < XX or ≤ XX mmol/mol (< 7 or ≤ 6.5%). Safety assessments included cardiovascular (pulse rate, blood pressure, electrocardiogram) and laboratory parameters, reported adverse events and anti-dulaglutide antibodies. Electrocardiograms were recorded in triplicate and tracings were over-read by a cardiologist at a centralized vendor (Biomedical Systems Corporation, XXXXX, XXXXX, XXX); this report was used for analysis. Referencing the American Diabetes Association definition, hypoglycaemia was defined as plasma glucose ≤ 3.9 mmol/l (≤ 70 mg/dl) and/or symptoms and/or signs attributable to hypoglycaemia. Severe hypoglycaemia was defined as an episode requiring the assistance of another person to actively administer therapy [10]. Patients with at least one paneled enzyme measurement ≥ 3 times the upper limit of normal underwent a standardized diagnostic examination.

Plasma analytes and HbA1c were quantified by Quintiles Laboratories (Smyrna, GA, USA). Electrochemiluminescence immunosorbent assay was used for detection of anti-dulaglutide antibodies (Millipore, XXXX, XXXX, XXX);
positive samples were titrated for titres. Fasting plasma glucose and insulin concentrations were used for HOMA2 calculations [11].

Statistical analysis
The target sample size of 36 patients per group was calculated to provide 90% power for detecting a linear dose–response, excluding the placebo group, with a 0.60 slope in change from baseline HbA\(_1c\) for each 1-mg change in dose. Assumptions included residual standard deviation (SD) of 1.2%, 0.61 mg SD of the doses, 2-sided 0.05 significance level and 20% dropout rate. With this sample size, a 0.9% difference in change from baseline in HbA\(_1c\) could be detected between any dulaglutide group and the placebo group with 80% power.

The primary and secondary analyses were performed on the intention-to-treat population \((n = 167)\), defined as all randomized patients who received study therapy, including patients from the discontinued Dula 3.0 mg arm \((n = 3)\). Changes from baseline were reported as least-squares mean and standard error (least-squares mean \pm se), although summary statistics were not provided for the discontinued Dula 3.0 arm because of the small number.

A mixed-effects model for repeated measures (MMRM) was used for analyses of continuous variables. To evaluate the dose–response relationship on the change in HbA\(_1c\) at 12 weeks, the model included: country, dose, pre-study therapy (metformin yes/no), visit and dose-by-visit interaction as the fixed effects; baseline BMI and/or baseline HbA\(_1c\) as a covariate; and patient as a random effect. If baseline BMI and baseline HbA\(_1c\) were significantly correlated at the 0.10 alpha level, the model included the one that had a higher correlation with the change in HbA\(_1c\) at 12 weeks. Orthogonal contrasts considering the unequal spacing between doses were used to examine the linear and log linear dose–response without placebo at 12 weeks. The contrast with the smaller se, representing the better fit, was reported. Dunnett’s test was used to control the type I error when comparing placebo to the individual doses.

A Cochran–Armitage trend test was used to assess categorical data, and a one-way ANOVA on the ranks with treatment as a fixed effect was conducted for laboratory data. All statistical analyses were performed using the SAS System® version 8.2 or higher (SAS Institute, Cary, NC, USA).

Results

Patients
In total, 460 patients were screened; most frequent reasons for screen failure were not fulfilling inclusion/exclusion criteria \((n = 244)\), patient decision \((n = 36)\) and physician decision \((n = 12)\). The three patients randomized to Dula 3.0 were discontinued at 1, 64 and 72 days post-randomization; 164 patients were randomized to the other five treatment arms and 153 completed the 12-week treatment (Fig. 2). Twelve patients discontinued before the last safety follow-up visit (Table 1 and Fig. 2). Three patients received rescue therapy (two in the placebo group and one in the Dula 1.0 group). Patient characteristics at entry were well balanced with no significant differences between groups (Table 1).

![Figure 2](image-url)  
**FIGURE 2** Patient disposition from entry to completing safety period throughout the study.
Primary endpoint
At randomization, baseline HbA1c (mean ± SD) was comparable among groups [60 ± 9, 60 ± 8, 59 ± 8, 61 ± 8 and 60 ± 7 mmol/mol (7.7 ± 0.8, 7.6 ± 0.7, 7.6 ± 0.7, 7.8 ± 0.8 and 7.6 ± 0.7%)] for placebo, Dula 0.1, Dula 0.5, Dula 1.0 and Dula 1.5, respectively (Fig. 3a). Dose-dependent reductions in HbA1c were observed across the dulaglutide groups (P < 0.001) at endpoint. Reductions in HbA1c were greater than placebo for each of the dulaglutide doses (P < 0.001) except the Dula 0.1 group (P = 0.069); least-squares mean difference (95% CI): Dula 0.1, −0.43 (−1.06 to 0.19) mmol/l; Dula 0.5, −1.47 (−2.12 to −0.83) mmol/l; Dula 1.0, −1.66 (−2.31 to −1.02) mmol/l; and Dula 1.5, −1.87 (−2.56 to −1.19) mmol/l (Fig. 3d); change in the placebo group was least-squares mean ± SE: −0.21 ± 0.25 mmol/l. Dose-dependent reductions in mean pre-meal and postprandial plasma glucose from 7-point self-monitored plasma glucose were observed at endpoint in response to treatment with dulaglutide (P ≤ 0.003, data not shown). Additionally, decreases in mean pre-meal and postprandial plasma glucose in Dula 0.5, Dula 1.0 and Dula 1.5 groups were significantly greater than placebo (data not shown).

There was an increasing trend across groups in the per cent of patients achieving HbA1c < 53 mmol/mol (< 7.0%) at...

Secondary endpoints
At endpoint, dose-dependent reductions in mean daily plasma glucose and fasting plasma glucose were observed across all doses (P < 0.001) (Fig. 3c and d). Changes in fasting plasma glucose were greater than placebo for each of the doses (P < 0.001), except for the Dula 0.1 group (P = 0.456); least-squares mean difference (95% CI): Dula 0.1, −0.43 (−1.06 to 0.19) mmol/l; Dula 0.5, −1.47 (−2.12 to −0.83) mmol/l; Dula 1.0, −1.66 (−2.31 to −1.02) mmol/l; and Dula 1.5, −1.87 (−2.56 to −1.19) mmol/l (Fig. 3d); change in the placebo group was least-squares mean ± SE: −0.21 ± 0.25 mmol/l. Dose-dependent reductions in mean pre-meal and postprandial plasma glucose from 7-point self-monitored plasma glucose were observed at endpoint in response to treatment with dulaglutide (P ≤ 0.003, data not shown). Additionally, decreases in mean pre-meal and postprandial plasma glucose in Dula 0.5, Dula 1.0 and Dula 1.5 groups were significantly greater than placebo (data not shown).

There was an increasing trend across groups in the per cent of patients achieving HbA1c < 53 mmol/mol (< 7.0%) at...
FIGURE 3 Glycaemic control in patients with Type 2 diabetes (intent-to-treat population, \( n = 164 \)) in response to treatment with placebo (\( n = 32 \)), Dula 0.1 (\( n = 35 \)), Dula 0.5 (\( n = 34 \)), Dula 1.0 (\( n = 34 \)) or Dula 1.5 mg (\( n = 29 \)). (a) HbA\(_1c\) by study visit (mean ± sd); (b) least-squares mean change from baseline in HbA\(_1c\) by study visit (least-squares mean ± st); (c) least-squares mean change in mean 7-point self-monitored plasma glucose by visit; (d) least-squares mean change from baseline in fasting plasma glucose by study visit; (e) percentage of patients achieving HbA\(_1c\) targets of < 53 mmol/mol (< 7.0%) and ≤ 48 mmol/mol (≤ 6.5%) at week 12. Statistically significant dose effect is observed for both targets, \( P < 0.001 \) by Cochran–Armitage trend exact test; and (f) least-squares mean change in HOMA2-%B by visit. Glucose values in mg/dl were converted to mmol/l by dividing by 18. *\( P < 0.05 \) vs. placebo; †\( P < 0.05 \) vs. placebo.

Changes in body weight at week 12 (least-squares mean ± se) were −1.4 ± 0.5 kg for placebo, −0.2 ± 0.4 kg for Dula 0.1, −0.3 ± 0.4 kg for Dula 0.5, −1.1 ± 0.4 kg for Dula 1.0 and −1.5 ± 0.5 kg for Dula 1.5. Dose-dependent reductions in body weight were observed across the dulaglutide groups at week 12 (\( P = 0.009 \)), but were not significant when compared with placebo. This outcome may be partially related to two patients in the placebo group who experienced weight loss of 11.2 and 11.3 kg as a result of haemorrhagic pancreatitis and participation in a weight-loss programme, respectively.

Safety and tolerability

Overall, 51.8% (\( n = 85 \)) of patients reported ≥ 1 treatment-emergent adverse event during the treatment period, with no significant trend across groups (see also Supporting Information, Table S1). The most frequent treatment-emergent adverse
events were nausea, diarrhoea, and nasopharyngitis, with overall incidences of 7.9% (n = 13), 6.1% (n = 10) and 5.5% (n = 9), respectively; there was no significant trend across groups (Table S1). Four patients (2.4%) discontinued because of adverse events (Table 1).

Investigators reported four cases of serious adverse events (2.4%). Two were considered possibly related to study drug: haemorrhagic pancreatitis associated with cholelithiasis (placebo) and abdominal pain/distension (Dula 1.5). The other two cases were breast cancer (Dula 0.5), diagnosed based on a mammogram completed 6 months prior to study enrolment, and atrial flutter (Dula 1.0). No deaths occurred during the study.

There were no severe hypoglycaemic events reported. The overall incidence of hypoglycaemia was not different among groups (P = 0.822); placebo, 3.1% (n = 1/32); Dula 0.1, 5.7% (n = 2/35); Dula 0.5, 8.8% (n = 3/34); Dula 1.0, 5.9% (n = 2/34); and Dula 1.5, 10.3% (n = 3/29).

Systolic and diastolic blood pressures were not different between dulaglutide groups and placebo. Changes from baseline in electrocardiogram-derived heart rate were not different between dulaglutide groups and placebo (see also Supporting Information, Table S2).

There were no significant differences between the groups in levels of pancreatic enzymes (lipase, pancreatic amylase and total amylase) at endpoint. Two patients (Dula 1.5 mg) demonstrated increases >3 times the upper limit of normal on consecutive testing during the study; both underwent computed tomography (CT) scans and results were within normal range. Administration of study drug was not interrupted and both patients showed improvement or normalization of laboratory findings during the trial.

A treatment-emergent anti-dulaglutide antibody was reported in one patient in the Dula 1.0 group (4-fold or greater increase in antibody titre from baseline); antibody titre 1:64 at week 4 and 1:8 at week 12. One patient (Dula 0.1) reported treatment-emergent skin rash and skin exfoliation (anti-dulaglutide antibody negative).

Discussion

This dose–response study assessed the effect of a range of doses of dulaglutide, a once-weekly administered GLP-1 analogue, on HbA1c over a 12-week treatment period. The results of the study demonstrate a significant dose–response effect on change in HbA1c from baseline to 12-week endpoint.

The trial involved patients earlier in the course of disease, supported by the relatively short mean duration of diabetes and the relatively modest increase in mean HbA1c level at the end of the lead-in period after discontinuation of metformin. This population was selected because a less advanced β-cell secretory deficit and modest hyperglycaemia were characteristics suitable for a monotherapy, placebo-comparator study. The HbA1c-lowering effect of the higher dulaglutide doses was clinically relevant [up to −11 ± 1 mmol/mol (−1.0 ± 0.1%) in the Dula 1.5 group]. The magnitude of this effect, when compared with that reported for other GLP-1 analogues in similar patient populations, suggests that this compound is effective in reducing elevated glucose levels [2,7,12]. No significant difference in glucose lowering between the three higher dose groups (0.5, 1.0 and 1.5 mg) was observed, but relatively lower baseline HbA1c levels and near-normal levels at endpoint in all three groups may have decreased the ability to fully differentiate the effect of increasing doses. As maximal reductions in average and fasting plasma glucose were not observed until 2–4 weeks of completed treatment (Fig. 3c and d), it is also possible that a longer treatment period (>12 weeks) is needed for the full effect on haemoglobin glycosylation to be demonstrated [13].

Treatment with dulaglutide increased β-cell function as measured by the increase in HOMA2-%B. Caution must be taken in the interpretation of this observation because this is a short study. The increase in HOMA2-%B may just reflect GLP-1 agonist-mediated increase in insulin secretion and may not translate into long-term improvement in β-cell function. These observations are consistent with the previous 16-week, Phase-2, placebo-controlled trial showing that treatment with dulaglutide caused significant decreases in HbA1c and blood glucose, and improvement in β-cell function in patients with Type 2 diabetes treated with two other oral anti-diabetes drugs [14].

The effect of exenatide, liraglutide, albiglutide and exenatide once weekly on body weight has been studied as a secondary objective in several large clinical trials. When compared with placebo or other glucose-lowering agents, these medications are, on average, associated with no weight gain or with weight loss [2,3,5,7,12]. In this study, dulaglutide was associated with dose-dependent reductions in body weight similar to other GLP-1 analogues; however, no difference was observed in comparison with placebo. One possible reason for this outcome is the large change in body weight in two patients in the placebo group. An exploratory, post-hoc analysis that excluded outliers from all treatment groups (+3 SD) indicated that these two patients could explain, to a significant extent, the body weight reductions observed in the placebo group and the lack of difference between the placebo arm and each dulaglutide dose. More comprehensive assessments will be conducted in larger, ongoing, Phase 3 studies.

The most commonly reported treatment-emergent adverse events were nausea and diarrhoea, consistent with the adverse event profile of other agents in this class [2,15,16]. The incidence of these events in dulaglutide-treated patients was not different from that in placebo-treated patients and the severity infrequently resulted in discontinuation (one patient from Dula 0.5; two patients from Dula 1.5), indicating acceptable gastrointestinal tolerability.

Because of previously reported cases of acute pancreatitis in conjunction with the use of marketed GLP-1 analogues, measurements of serial pancreatic enzymes were included to assess the predictive value for pancreatic adverse events. As mild increases in these laboratory parameters, without any known clinical association, frequently occur in patients with Type 2
diabetes [17], patients with greater changes (≥ 3 times the upper limit of normal) were of special interest. The six patients who were noted to have enzyme elevations above this threshold were in the Dula 1.0 and Dula 1.5 groups, but none presented with clinical symptoms. In only two patients was an increase in pancreatic enzymes hyperenzymemia confirmed on subsequent testing (both had a normal CT scan of the pancreas). These laboratory findings did not require change in treatment regimen. Importantly, the majority (four patients) demonstrated increased pancreatic enzyme levels before randomization. Of note, the patient who presented with acute haemorrhagic pancreatitis shortly after randomization to the placebo-treated group had normal pancreatic enzymes at baseline. Therefore, the observed changes in pancreatic enzymes do not appear to be predictive of clinical outcomes and their relevance in this setting remains to be determined.

Changes in heart rate have been reported with the use of marketed GLP-1 analogues [16,18]. Administration of dulaglutide did not result in any significant difference in heart rate in comparison with non-exposed individuals. Similar to the assessment of the effects of dulaglutide on heart rate, no significant changes in systolic and diastolic blood pressures were observed. There were no significant changes observed in lipid values associated with dulaglutide treatment (see also Supporting Information, Table S3).

In conclusion, once-weekly administration of dulaglutide for 12 weeks in patients with Type 2 diabetes (who were anti-hyperglycemic medication-naïve or had previously been treated with metformin monotherapy) resulted in dose-dependent improvement in glycemic control, with a significant increase in β-cell function. Dose-dependent decrease in body weight was observed; however, the decrease in body weight in the placebo group attenuated the significance of this analysis. In this study, dulaglutide displayed an acceptable safety and tolerability profile. Further studies are needed to fully characterize the effects of dulaglutide on safety and efficacy parameters, and clinical investigation is ongoing in the large Phase 3 Assessment of Weekly Administration of LY2189265 in Diabetes (AWARD) programme.

Competing interests

GG has commonality of interest with Eli Lilly and Company, Amylin, Mercck, Novo Nordisk, GSK, Takeda, Merck, Sanofi-Aventis, AstraZeneca, AZ, BMS, by the nature of research grants and/or speaking engagements. GGs has commonality of interest with Eli Lilly and Company, Amylin, Xoma, Takeda and Roche by the nature of research grants. FTB, RB and ZM are employees and shareholders of Eli Lilly and Company. AC has nothing to declare.

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References


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**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

- Table S1. Treatment-emergent adverse events observed in ≥ 3% of patients until the end of treatment period.
- Table S2. Baseline values and changes from baseline to week 12 in heart rate, systolic and diastolic blood pressures after treatment with placebo or dulaglutide.
- Table S3. Baseline values and changes from baseline to week 12 in triglycerides, cholesterol, HDL and LDL after treatment with placebo or dulaglutide.

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     - Select the stamp you want to use. (The Approved stamp is usually available directly in the menu that appears).
     - Click on the proof where you’d like the stamp to appear. (Where a proof is to be approved as it is, this would normally be on the first page).

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7. **Drawing Markups** Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

   - Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks.

   - **How to use it**
     - Click on one of the shapes in the Drawing Markups section.
     - Click on the proof at the relevant point and draw the selected shape with the cursor.
     - To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
     - Double click on the shape and type any text in the red box that appears.

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For further information on how to annotate proofs, click on the Help menu to reveal a list of further options: